Development of Copper-Catalyzed Enantioselective Alkene Difunctionalization Reactions via Radical Intermediates

By

Rong Zhu

B.Sc. Chemistry
Peking University – 2010

Submitted to the Department of Chemistry in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY IN ORGANIC CHEMISTRY

at the
Massachusetts Institute of Technology

February 2015

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Submitted to the Department of Chemistry on Jan 14, 2015 in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Organic Chemistry at the Massachusetts Institute of Technology

Abstract

Chapter 1

A mild, versatile, and convenient method for the efficient oxytrifluoromethylation of unactivated alkenes based on a copper-catalyzed ligand-assisted difunctionalization strategy has been developed. This method provides access to a variety of classes of synthetically useful CF_3-containing building blocks from simple starting materials.

Chapter 2

A method for the efficient enantioselective oxytrifluoromethylation of alkenes has been developed using a copper catalyst system inspired by the ligand dependence observed in the racemic reaction. Mechanistic studies are consistent with a metal-catalyzed redox radical addition mechanism, in which a C–O bond is formed via the copper-mediated enantioselective trapping of a prochiral alkyl radical intermediate derived from the initial trifluoromethyl radical addition.

Chapter 3

A general and versatile method for the catalytic enantioselective oxyfunctionalization of alkenes has been developed based on a key Cu-mediated enantioselective C–O bond forming process of prochiral alkyl radical intermediates. A wide range of radicals were found to participate this type of reaction, including azidyl, arylsulfonyl, aryl, acyloxyl and alkyl radicals. This method provides rapid access to a broad spectrum of interesting enantiomerically enriched lactones through tandem C–N/C–O, C–S/C–O, C–$C_{aryl/alkyl}$/C–O or C–O/C–O bond formation, in good yields and enantiomeric excesses with good functional group compatibility.

Thesis Supervisor: Stephen L. Buchwald
Title: Camille Dreyfus Professor of Chemistry

Acknowledgements

"Time flies like an arrow, fruit flies like a banana." It is not until I started writing my thesis that I became realized that how fast my time at MIT has passed. Today I can still remember the second half of my first class in the graduate school, which was Prof. Greg Fu's organic chemistry tutorial, because I overslept the first half of it.

As I looked back at the past four and half years, I found graduate study is somewhat like doing catalysis: a project starts - an idea input - a preliminary result - problem solving - paper writing - a project finished. Every time such a turnover is achieved, an idea is consumed and some new chemistry is produced. Just like the chemical catalysis, such turnovers would never be possible without the catalysts: the guidance, support and generosity of others. Although I would take great pleasure in acknowledging every person individually who has had an impact on me, I unfortunately do not have the space. So thank you all, who have helped to "catalyze" the my graduate school reaction, for which I am really, really grateful.

I would like to start by thank my advisor, Steve Buchwald. Steve has always been extremely supportive, and has taught me a lot, about both chemistry and life. One thing I would like to thank Steve the most for is the freedom along with the guidance that I have been enjoying in developing and working on my own projects. Without that I would never be able to discover the interesting copper chemistry, and I believe this research experience will be extremely useful for my future career development.

Along with Steve I would like to thank other faculty members who have helped me during my time here. I would like to thank my thesis committee chair Tim Swager, who have offered valuable advice and guidance for my career, and I am fortunate to have the opportunity to continue the next phase of my research work in his group. I would also like to thank Tim Jamison, Greg Fu and Mohammed Movassaghi for their kind help and support.

In Steve's group, I have had the great pleasure of working with the most brilliant postdoc researchers from all over the world. When I first began, Tom, Jun and Wei helped me getting used to the life in the lab. I want to thank Tom for helping me with the preparation of my first paper, of which I can never overemphasize the importance for my later research. Wei not only taught me lab techniques, but also shared thousands of funny jokes over the four years we worked together. I learned a lot from the discussion with Pengfei, Xiaoxing, Elliot and Tim. When I finished my rookie year, Donghui and Xinyan became my good friends, who I always liked to hang out with, and the best memory comes from the camping trip to Acadia. I need to thank Christine for her excellent work helping the big group keep running as well as keeping (almost) everyone drinking in the party. I would like to give my special thanks to Andrew P. for his fascinating work that set the ground for my later research. As I became a senior graduate student, I benefited a lot from the helpful discussion everyday with Mao, Dawen, Yiming, Yifeng, Shiliang, Shaolin, Ye, Erhad, Vasu, Aaron, Wenliang, Hong Geun, Daniel, Laurent, Yong, Eun Jin, J. B., Takashi, Alex S., Alex D., Nate, Edward, Chi Wai, Tom. B., Matthias, Meredeth, and Robb. Dawen and Yifeng, it is unbelievably amazing that we grew up in the same town and met together here at MIT.

Next, I would like to thank all the graduate students that I have worked with. Mingjuan is the nicest person I have ever met and it was always a pleasure working or hanging out with her.

She was always ready to help me on everything, and I would have missed thirty-four deadlines and forgotten twenty-two assignments in my first semester without her. Yang and Yuxuan, my collegemates from PKU full of potential, are the smartest graduate students I have ever met. I believe you will become famous chemists in the future. Nootaree, Katya, Phil, Nick, Jim, Nathan, Brett, Pedro, Paula, Spencer, Johannes, Stig, Billy, Jeff, Saki, Bryan, Anthony and Zack, thank you all for your help and support over the years.

Additionally, I would like to thank all the people who helped me before I came to MIT. The two-month experience in John Wolfe's group is invaluable. Without John's support I would not have the chance to get into MIT or Steve's group. I need to thank Prof. Yang and Prof. Chen, who were extremely supportive during my time as an undergrad in their lab. Today I still benefit from the training received as well as the friendship developed in the Yang group.

This leaves me to thank all my family and friends. My special thanks go to Fei and Chao, my two great friends. We may be going to have our families and careers in different countries, but we are always best friends forever. Many thanks to my CSSA teammates and friends from the Riversbasketball who shared numerous cheering moments as well as funny stories with me, both on and off the court.

I would like to thank the people who have the biggest impact on my life and personality, and have been continuously supporting me unconditionally with their best efforts since I was born, my father and mother. I can really find no word to fully express my thankfulness for my parents.

I would like to save the most important acknowledgment in the end, for my dear Bing. I cannot imagine how hard it would be for me to make through my graduate school without her support, accompany, love and everything. I am so lucky to have you, Bing, the catalyst of my life. Everything we have been through together, some happy, some sad, all become cherished memories that we share, which I would like to tell our sons and daughters with you by my side.

Preface

This thesis has been adapted from the following published articles co-written by the author:

"Copper-Catalyzed Oxytrifluoromethylation of Unactivated Alkenes." Rong Zhu, Stephen L. Buchwald *J. Am. Chem. Soc.* **2012**, *134*, 12462.

"Enantioselective Functionalization of Radical Intermediates in Redox Catalysis: Copper-Catalyzed Asymmetric Oxytrifluoromethylation of Alkenes." Rong Zhu, Stephen L. Buchwald *Angew. Chem. Int. Ed.* **2013**, *52*, 12655.

Respective Contributions

The author carried out all the experiments, collected and analyzed all the data presented in this thesis except for crystal structures depicted in Chapter 2, Figure 1 and Chapter 3, Scheme 9 which were solved by Dr. Peter Müller at MIT.

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Introduction

Alkene difunctionalization encompass mechanistically diverse transformations that result in the overall addition of two functional groups across a carbon–carbon double bond.[1] The first examples of alkene difunctionalization include the classic electrophilic halogenation reactions that were discovered over a century ago. Since then, this class of reactions has been the subject of intense investigation by organic chemists, in part due to their ability to rapidly increase molecular complexity through the simultaneous construction of multiple carbon–carbon/carbon–heteroatom bonds and stereogenic centers. Indeed, more recently developed examples of diastereo- and enantioselective alkene difunctionalizations such as the Sharpless dihydroxylation have proven to be highly versatile and widely used synthetic transformations.

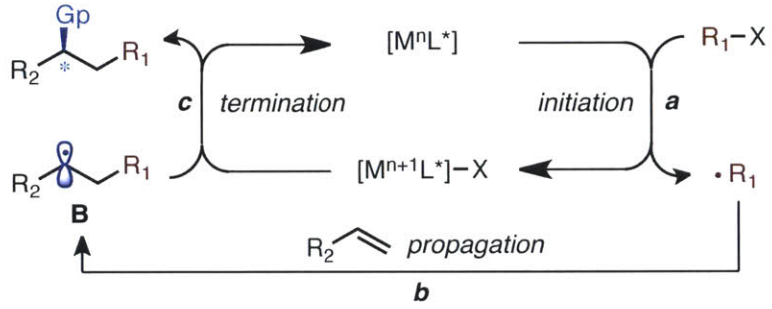
During the past several decades, the development of asymmetric catalysis has brought new opportunity for incorporating new reactivity and selectivity into traditional alkene difunctionalization reactions. Many new methods based on metal- or organo-catalysts have been developed in this field, leading to efficient enantioselective syntheses of structurally diverse molecules.[2] However, catalytic asymmetric methods for the difunctionalization reactions that proceed by the atom transfer radical addition mechanism, which accounts for a significant portion of alkene difunctionalization reactions currently practiced, remain elusive.[3] As shown in Scheme 1a, the major challenge lies in the catalyst-controlled enantioselective functionalization of the prochiral alkyl radical intermediate **A** (termination step).

While attempts involving Lewis acid complexation and chiral chain-transfer catalysts with some highly activated alkene substrates have been made,[4] a potentially more general solution involves the use of a chiral transition metal complex as the redox catalyst for a radical reaction (Scheme 1b). Here, the chiral metal complex is proposed to play a dual role: 1) initiate radical formation when in the lower oxidation state (step **a**) and 2) mediate the enantioselective bond forming process via prochiral radical **B** when in the higher oxidation state (step **c**). While a variety of redox catalysts based on different transition metals are capable of mediating step **a**, a catalyst delivering effective enantioselectivity in step **c** is still unknown.[5]

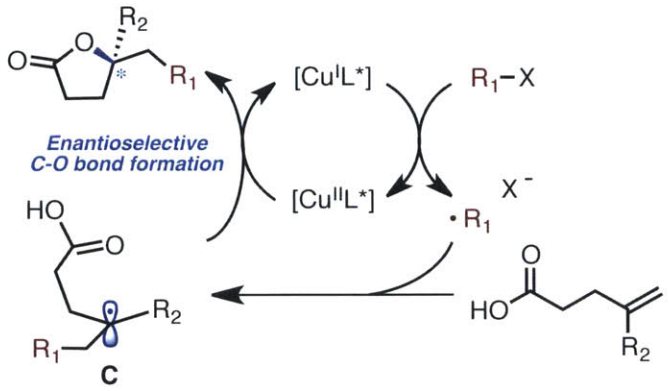
***Scheme 1**. Background of the Cu-catalyzed enantioselective radical alkene difunctionalization.*

a) Elementary steps in atom transfer radical addition

b) Atom transfer radical addition catalyzed by a chiral transition metal complex



c) Cu-Catalyzed enantioselective radical difunctionalization



Aiming at addressing the aforementioned challenge, the results presented herein focus on: 1) the discovery of a copper-based redox catalyst enabling efficient enantioselective C–O bond formation via the interception of alkyl radical intermediates in an atom transfer radical addition type reaction (Scheme 1c; Chapter 1 and 2); 2) the development of a general and versatile method for the enantioselective oxyfunctionalization of alkenes based on this key C–O bond forming process (Chapter 3). It should be noted that although the development of a racemic reaction is described in chapter 1, the identification of the crucial ligand effect in this study set the ground for the later discovery of the related enantioselective process.

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[1] Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083.

[2] Selected reviews: (a) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981; (b) Shimizu, Y.; Kanai, M. *Tetrahedron Lett.* **2014**, *55*, 3727; (c) Chemler, S. R.; Bovino, M. T. *ACS Catal.* **2013**, *3*, 1076; (d) MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

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[4] Selected reviews: (a) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263; (b) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163; (c) Zimmerman, J.; Sibi, M. P. *Top. Curr. Chem.* **2006**, *263*, 107; (d) Bar, G.; Parsons, A. F. *Chem. Soc. Rev.* **2003**, *32*, 251.

[5] (a) Murai, S.; Sugise, R.; Sonoda, N. *Angew. Chem. Int. Ed.* **1981**, *20*, 475; (b) Kameyama, M.; Kamigata, N.; Kobayashi, M. *J. Org. Chem.* **1987**, *52*, 3312; (c) Brunner, H.; Bluchel, C.; Doyle, M. P. *J. Organomet. Chem.* **1997**, *541*, 89.

Chapter 1.

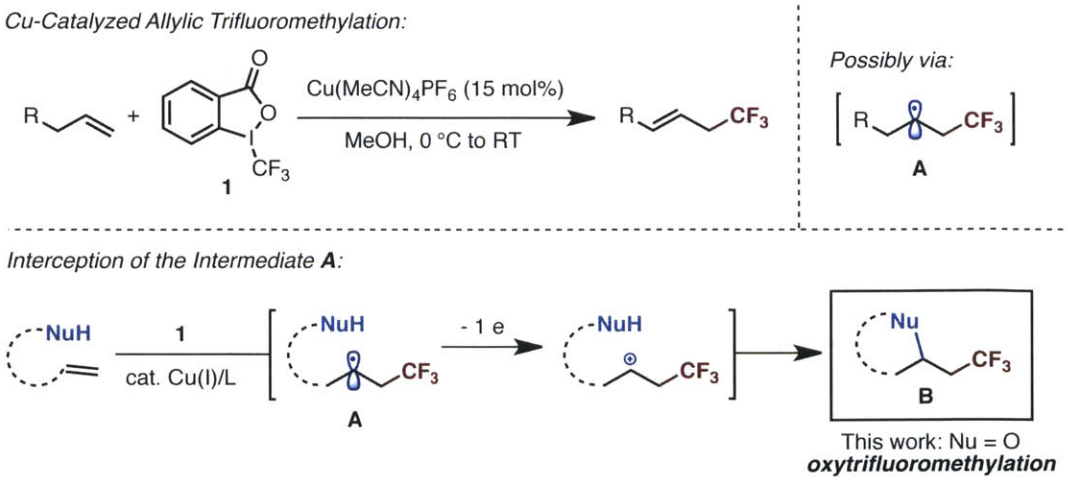
Cu-Catalyzed Ligand-Assisted Alkene Oxytrifluoromethylation:
a Versatile Method to Access Trifluoromethyl-Containing Building Blocks

1.1 Introduction

The incorporation of fluoroalkyl groups and particularly the trifluoromethyl (CF_3) group in pharmaceutically and agrochemically relevant molecules has a significant impact on their physical and biological properties, mainly because of the unique metabolic stability, lipophilicity, and electron-withdrawing nature of the trifluoromethyl substituent.[1] The importance of CF_3-containing compounds provides a continuing driving force for the development of more efficient and versatile trifluoromethylation methods.[2] Our research group has focused on the development of new fluorination[3] and trifluoromethylation[4] reactions using transition metal catalysis. Herein we report a mild and versatile copper-catalyzed oxytrifluoromethylation reaction of unactivated alkenes that allows rapid access to a variety of CF_3-containing building blocks from simple starting materials.

In 2011, our group, as well as those of Liu and Wang, independently reported the copper-catalyzed allylic trifluoromethylation of unactivated alkenes (Scheme 1).[4d,5] During the course of our studies, we proposed that this transformation might involve an α-CF_3-alkyl radical (**A**) that subsequently undergoes elimination to afford the allylic trifluoromethyl product. We became interested in the possibility of intercepting this putative intermediate **A**, as a means of synthesizing of a number of structurally diverse CF_3-containing building blocks in a step-economical fashion.

Scheme 1. *Copper-Catalyzed Trifluoromethylation of Unactivated Alkenes.*

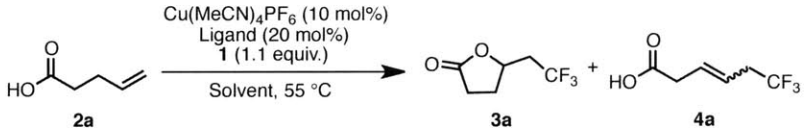


We envisioned that the oxidative difunctionalization of unactivated alkenes involving tandem C–CF_3 and C–Nu bond formation could be achieved based on this strategy.[6,7] It was hypothesized that a single electron oxidation of the radical intermediate followed by trapping the resulting carbocation would lead to the desired difunctionalization product **B**.[8] The success of this strategy lies in the identification of a catalyst system that is efficient for both the C–CF_3 bond formation and the subsequent functionalization steps as well as the ability to inhibit the competitive elimination pathway. Herein we describe a copper(I)/2,2'-biquinoline catalytic system that incorporates these qualities with oxygen-based nucleophiles.

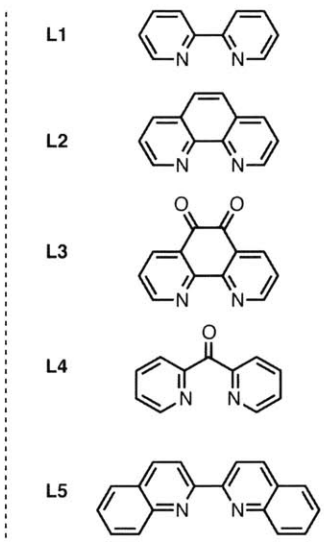
1.2 Results and Discussion

We began our study by examining the reaction of 4-pentenoic acid (**2a**) in the presence of Togni's reagent **1**[9] and a catalytic amount of $Cu(MeCN)_4PF_6$ in methanol. Only the allylic trifluoromethylated product **4a** was observed in this case, suggesting elimination to be the major pathway (Table 1, entry 1). After examining the effects of solvents and additives, we found that switching to acetonitrile, in the presence of a catalytic amount of 2,2'-bipyridyl (**L1**), afforded the desired oxytrifluoromethylation product **3a** in 10% yield (entry 3).

Table 1. *Ligand effect.* [a]



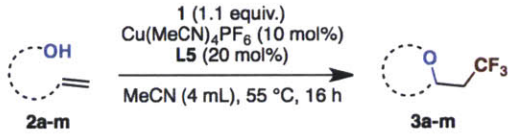
Entry	Solvent	Ligand	Yield (%)[b] 3a	Yield (%)[b] 4a
1	MeOH	-	< 5	46
2	MeCN	-	< 5	< 5
3	MeCN	**L1**	10	18
4	MeCN	**L2**	12	11
5	MeCN	**L3**	11	< 5
6	MeCN	**L4**	86	5
7	MeCN	**L5**	89	< 5
8[c]	MeCN	**L5**	< 5	< 5



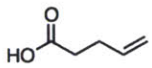
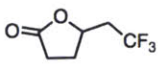
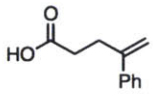
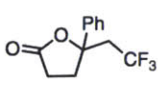
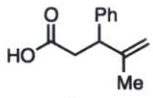
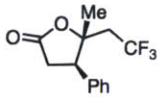
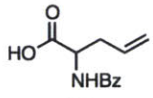
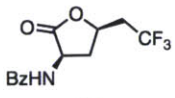
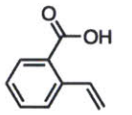
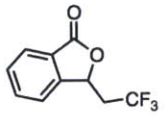
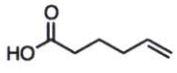
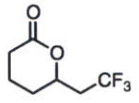
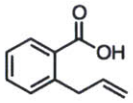
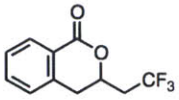
[a] Reaction conditions: $Cu(MeCN)_4PF_6$ (10 mol %), ligand (20 mol %), **2a** (0.10 mmol, 1.0 equiv), **1** (1.1 equiv), solvent (1.0 mL), 55 °C, 16 h. [b] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [c] Without $Cu(MeCN)_4PF_6$.

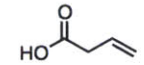
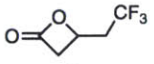
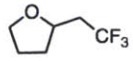
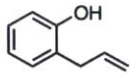
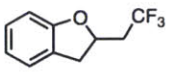
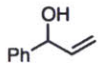
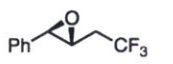
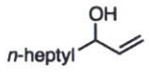
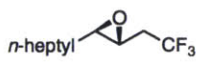
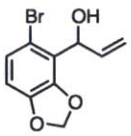
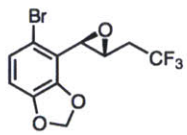
Encouraged by this result, we evaluated a series of different pyridine-based bidentate ligands, which finally led to the identification of di-2-pyridyl ketone (**L4**) and 2,2'-biquinoline (**L5**) as optimal (entry 6 and 7). A nearly 90% yield of **3a** could be obtained in the presence of either **L4** or **L5**, with only trace of **4a** observed. Both the copper salt and ligand proved to be essential for the oxytrifluoromethylation reaction to take place, as no **3a** was observed in the absence of either of these components (entries 2 and 8).

Table 2. *Substrate scope of the Cu-catalyzed oxytrifluoromethylation.* [a]



2a-m **3a-m**

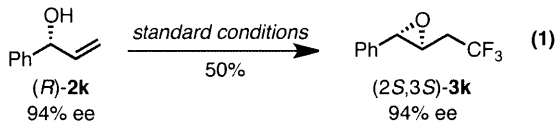
Entry	Substrate	Product	yield (%)[b]
1	 **2a**	 **3a**	76
2	 **2b**	 **3b**	81
3	 **2c**	 **3c**	94 (dr 2.2:1)
4	 **2d**	 **3d**	74 (dr 2.8:1)
5[c]	 **2e**	 **3e**	64
6	 **2f**	 **3f**	71
7	 **2g**	 **3g**	77

Entry	Substrate	Product	yield (%)[b]
8[c]	 **2h**	 **3h**	42[e]
9	 **2i**	 **3i**	73[e]
10[d]	 **2j**	 **3j**	35
11[c,f]	 **2k**	 **3k**	50 (dr 10:1)
12	 **2l**	 **3l**	70 (dr 4:1)
13[c]	 **2m**	 **3m**	64 (dr > 20:1)

[a] Reaction conditions: $Cu(MeCN)_4PF_6$ (10 mol %), 2,2'-biquinoline (20 mol %), **2** (0.50 mmol, 1.0 equiv), **1** (1.1 equiv), MeCN (4 mL), 55 °C, 16 h. [b] Isolated yields, average of two runs. Diastereomeric ratio determined by ^{19}F NMR and ^{1}H NMR spectroscopic analysis. Structures of the major diastereomers are shown. [c] $Cu(MeCN)_4PF_6$ (20 mol %) and 2,2'-biquinoline (30 mol %) were used. [d] $Cu(MeCN)_4PF_6$ (20 mol %) and di-2-pyridyl ketone (30 mol %) were used. [e] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [f] The reaction did not go to full conversion.

With an optimized protocol in hand, we next explored the scope of this oxytrifluoromethylation reaction. Illustrative examples are shown in Table 2. A series of unsaturated aliphatic and aromatic carboxylic acids were found to undergo the desired transformation to give the corresponding trifluoromethylated lactones in good yields (entries 1-8). With regard to the scope of alkene moiety, monosubstituted and geminal disubstituted alkenes were excellent substrates for this reaction.[10] Alkyl and aryl substituents on the carbon–carbon double bond were well-tolerated. In terms of the size of the ring formed, δ-, γ-, and even β-lactones proved to be accessible.

Next, we sought to expand the scope of the nucleophile to include other common oxygen-based functional groups. It was found that primary alcohols (Table 2, entry 9) and phenols (entry 10) also served as viable nucleophiles for this reaction.[11] Allylic alcohols (Table 2, entry 11-13) are an especially interesting class of substrates because their oxytrifluoromethylation reactions give rise to 3-trifluoromethyl-1,2-epoxides, which are highly versatile CF_3-containing intermediates. It was found that both aryl- (**2k**, **2m**) and alkyl-substituted (**2l**) allylic alcohols furnished the desired products in moderate to good yields. When the enantiomerically enriched **2k** was subjected with the standard protocol, **3k** was produced with no erosion of the enantiomeric excess (eq. 1).



(*R*)-**2k**
94% ee

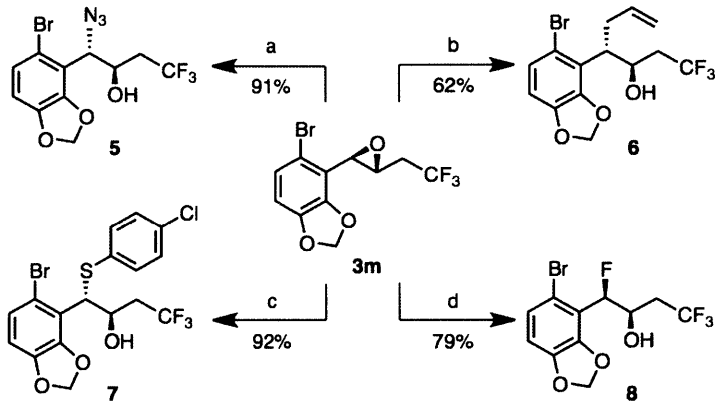
(2*S*,3*S*)-**3k**
94% ee

(1)

To demonstrate further the synthetic utility of the products derived from this method, oxytrifluoromethylation product **3m** was shown to undergo epoxide opening in good yields in the presence of a number of different nucleophiles, including an azide, a Grignard reagent, a thiol, and a fluoride (Scheme 2). A series of highly functionalized CF_3-containing building blocks (**5**-**8**) that are otherwise difficult to access, were easily prepared from the simple allylic alcohol **2m** in two steps.

While the mechanistic details of this copper-catalyzed oxytrifluoromethylation reaction remain unclear at this point, the use of a copper(I)/bidentate pyridine-based ligand system is suggestive of an atom transfer-type radical addition pathway.[8b,12] Further, the oxytrifluoromethylation reaction was found to be completely inhibited by addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a known radical scavenger.[13]

Scheme 2. *Versatile transformations of the oxytrifluoromethylation product* ***3m***. [a]



[a] Reaction conditions: (a) NaN_3 (3 equiv), NH_4Cl (2 equiv), H_2O/MeOH, 80 °C, 3 h; (b) Allylmagnesium bromide (3 equiv), Et_2O, RT, 2 h; (c) *p*-ClC_6H_4SH (2 equiv), NaOH (2 equiv), dioxane/H_2O, 65 °C, 2 h; (d) BF_3•Et_2O (0.33 equiv), DCM, -15 °C, 5 min.

1.3 Conclusion

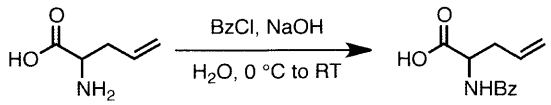
In conclusion, a mild, versatile and convenient method for the efficient oxytrifluoromethylation of unactivated alkenes based on a copper(I)/2,2'-biquinoline catalytic system has been developed. Carboxylic acids, alcohols, and phenols all serve as suitable nucleophiles under the conditions developed. The reaction conditions are compatible with a range of functional groups including amides, β-lactones, epoxides, and aryl bromides. All of the reactions were carried out using simple, user-friendly bench-top setup. This methodology allows rapid access to a variety of synthetically useful building blocks such as CF_3-containing lactones, cyclic ethers, and epoxides from simple starting materials. We are continuing work to gain insight into the reaction mechanism and expand the scope of this copper-catalyzed alkene difunctionalization strategy.

1.4 Experimental

General considerations. All reactions were carried out with dry solvents under anhydrous conditions, unless otherwise noted. Anhydrous acetonitrile was purchased from Aldrich. Tetrakis(acetonitrile)copper(I) hexafluorophosphate was purchased from Strem and stored in a dry box. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. All chemicals were weighed on the bench top, in the air. All reactions were set up using standard Schlenk techniques. 1-Trifluoromethyl-1,2-benziodoxol-3-(*1H*)-one (Togni trifluoromethylating reagent, **1**) was prepared according to the literature procedure.[4d] Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All yields of the copper-catalyzed oxytrifluoromethylation reactions stated are the average of at least two experiments. Reactions were monitored by ^{19}F NMR spectroscopy and thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as a visualizing agent and phosphomolybdic acid in ethanol or $KMnO_4$ solution and heat as developing agents. Flash silica gel chromatography was performed using Silicycle SiliaFlashP60 (230-400 mesh) silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer and were calibrated using residual solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR; CD_3CN: 1.94 ppm for ^{1}H NMR and 1.32 ppm for ^{13}C NMR). ^{19}F NMR spectra were recorded on a varian 300 MHz spectrometer and were calibrated using $CFCl_3$ as an external reference (0 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, at = apparent triplet, ad = apparent doublet. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer (iD5 ATR). HPLC analyses were performed on an Angilent 1100 series system with Daicel Chiralcel® columns (4.6 mm x 250 mm) in hexanes/*i*-PrOH mixtures. Melting points (m.p.) were obtained on a Mel-Temp capillary melting point apparatus. Gas chromatographic analyses were performed on an Agilent 6890 gas chromatograph. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

Synthesis and characterization of non-commercial substrates. 4-Phenylpent-4-enoic acid (**2b**),[14] 4-methyl-3-phenylpent-4-enoic acid (**2c**),[15] 2-vinylbenzoic acid (**2e**),[16] 2-allylbenzoic acid (**2g**),[17] were prepared according to literature procedures.

(±)-*N*-benzoyl-allylglycine (**2d**) Adapted from a previously reported procedure.[18] In a 50 mL round-bottom-flask equipped with a Teflon-coated magnetic stir bar racemic allylglycine (230

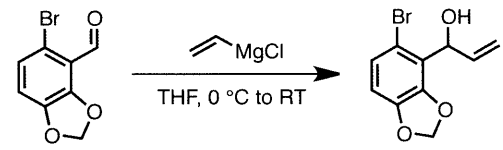


2d

mg, 2.0 mmol) was dissolved in 0.2 M aqueous sodium hydroxide solution (20 mL, 4.0 mmol) at 0 °C. At the same temperature, benzoyl chloride (280 mg, 2.0 mmol) was added to the flask via syringe dropwise. The resulting mixture was stirred at room temperature overnight and diluted with ethyl acetate (20 mL) and acidified with 6N HCl (pH<2). The aqueous phase was separated and extracted with ethyl acetate (20 mL×3). The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. Recrystallization of the residue from ethyl ether afforded racemic *N*-benzoyl-allylglycine (211 mg, 48 %) as a colorless crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 2 H), 7.54, (m, 1 H), 7.45 (m, 2 H), 6.70 (d, J =7.2 Hz, 1 H), 5.81 (m, 1 H), 5.24 (d, J =8.4 Hz, 1 H), 5.20 (s, 1 H), 4.88 (m, 1 H), 2.74 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 167.9, 133.5, 132.3, 132.1, 128.9, 127.3, 120.1, 52.11, 36.2; IR (film) ν_{max} 3064, 1716, 1628, 1526, 1488, 1201, 920 cm^{-1} ; Anal. Calcd. For $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98. Found: C, 65.71; H, 6.04. m. p. 103-105 °C.

(±)-1-(5-bromobenzo[*d*][1,3]dioxol-4-yl)prop-2-en-1-ol (**2m**) An oven-dried 20 × 150 mm Fisher Scientific re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with 5-bromobenzo[*d*][1,3]dioxole-4-carboxaldehyde (460 mg, 2.0 mmol). The reaction tube was sealed with a septum screw-cap (10/90, Teflon/SIL, National Scientific) and connected to a Schlenk line. The tube was then briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). Anhydrous THF (5 mL) was added to the tube followed by vinylmagnesium chloride (1.6 M solution in THF, 1.9 mL, 3.0 mmol) via syringe at 0 °C and the argon pressure was removed. After stirring at room temperature for 12 h the mixture



2m

was diluted with ethyl ether (5 mL) and saturated aqueous ammonium chloride solution (5 mL). The aqueous layer was separated and extracted with ethyl acetate (5 mL×3), and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (EtOAc/hexane = 8:1 to 3:1) afforded **2m** (489 mg, 95 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* =8.3 Hz, 1 H), 6.59 (d, *J* =8.3 Hz, 1 H), 6.12 (m, 1 H), 5.95 (d, *J* =6.6 Hz, 2 H), 5.51 (m, 1 H), 5.27 (add, *J* =17.0 Hz, 1.2 Hz, 1 H), 5.16 (dd, *J* =10.4 Hz, 1.2 Hz, 1 H), 3.11 (d, *J* =8.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 145.9, 137.3, 125.7, 123.9, 115.6, 113.1, 108.9, 101.8, 73.1; IR (film) ν_{max} 3416, 1452, 1405, 1237, 1050, 1011, 997, 932 cm^{-1} ; Anal. Calcd. For $C_{10}H_9BrO_3$: C, 46.72; H, 3.53. Found: C, 46.90; H, 3.41. m. p. 75-76 °C.

General procedure and characterization for the Cu-catalyzed oxytrifluoromethylation of unactivated alkenes.

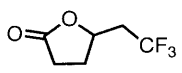
General Procedure A: Ligand Effect (Table 1)

An oven-dried 13×100 mm Fisher Scientific re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (3.7 mg, 0.01 mmol, 0.10 equiv.), ligand (0.02 mmol, 0.20 equiv.), 1-trifluoromethyl-1,2-benziodoxol-3-(*1H*)-one **1** (Togni's reagent, 34.8 mg, 0.11 mmol, 1.1 equiv.). The reaction tube was sealed with a septum screw-cap (Thermo Scientific ASM PHN CAP w/PTFE/SIL, cat. #03388316) and connected to a Schlenk line. The tube was then briefly evacuated and backfilled with argon (this sequence was repeated a total of four times). 4-pentenoic acid **2a** (10.0 mg, 0.10 mmol, 1.0 equiv.) was added to the tube via syringe followed by anhydrous solvent (1.0 mL). The argon pressure was removed and the sealed tube was placed in a pre-heated 55 °C oil bath. After stirring at the same temperature for 16 h the mixture was allowed to cool to room temperature and α,α,α-trifluorotoluene (internal standard, 14.6 mg, 0.10 mmol, 1.0 equiv.) was added. The crude reaction mixture was then analyzed by ^{19}F NMR spectroscopy.

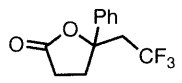
General Procedure B: Substrate Scope (Table 2)

An oven-dried 20 × 150 mm Fisher Scientific re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (18.6 mg, 0.050 mmol, 0.10 equiv.), 2,2'-biquinoline (25.6 mg, 0.10 mmol, 0.20 equiv.), 1-trifluoromethyl-1,2-benziodoxol-3-(*1H*)-one **1** (Togni's reagent, 174 mg, 0.55 mmol, 1.1 equiv.) and alkene substrate (0.50 mmol, 1.0 equiv. for non-liquid substrates). The reaction tube was sealed with a septum screw-cap (10/90, Teflon/SIL, National Scientific) and connected to a Schlenk line. The tube was then briefly evacuated and backfilled with argon (this sequence was repeated a total of four times). Alkene substrate (0.50 mmol, 1.0 equiv. for liquid

substrates) was added to the tube via syringe followed by anhydrous acetonitrile (4.0 mL) to afford a purple solution. The argon pressure was removed and the sealed tube was placed in a pre-heated 55 °C oil bath. After stirring at the same temperature for 16 h the mixture was allowed to cool to room temperature, diluted with diethyl ether (10 mL), and washed with saturated aqueous sodium bicarbonate solution (4 mL). The aqueous layer was separated and extracted with diethyl ether (4 mL×3). The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (EtOAc/hexane or Et_2O/pentane, UV light as a visualizing agent and phosphomolybdic acid in ethanol and heat as developing agents) to afford the oxytrifluoromethylation product. [Note: Some of the oxytrifluoromethylation products are somewhat volatile and should not be placed under vacuum for extended periods of time]

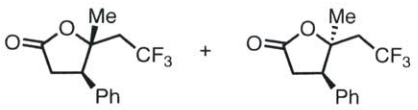


(±)-5-(2,2,2-trifluoroethyl)dihydrofuran-2(3*H*)-one (3a) Following general procedure B, the title compound was synthesized from 4-pentenoic acid (**2a**) (50.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (pentane: ethyl ether = 3:1 to 0:1, GC-MS was used to help identifying product-containing fractions) to afford **3a** (64.2 mg, 76 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (dddd, J =8.8 Hz, 6.4 Hz, 6.4 Hz, 6.3 Hz, 1 H), 2.65 (m, 1 H), 2.56 (m, 2 H), 2.52-2.35 (m, 2 H), 1.99 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 125.1 (q, J_{CF} = 275 Hz), 73.9 (q, J_{CF} = 3 Hz), 39.6 (q, J_{CF} = 28 Hz), 28.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.2 (at, J = 10.3 Hz); IR (film) ν_{max} 2922, 1776, 1364, 1255, 1131, 1113, 1025, 919 cm^{-1}; Anal. Calcd. For $C_6H_7F_3O_2$: C, 42.87; H, 4.20. Found: C, 43.03; H, 4.14.



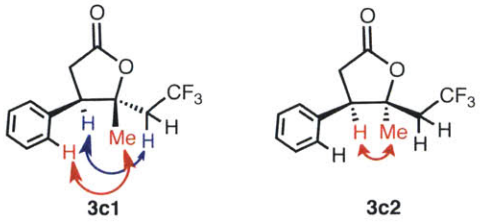
(±)-5-phenyl-5-(2,2,2-trifluoroethyl)dihydrofuran-2(3*H*)-one (3b) Following general procedure B, the title compound was synthesized from 4-phenyl-4-pentenoic acid (**2b**) (88.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 8:1 to 3:1) to afford **3b** (98.7 mg, 81 %) as a colorless crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.32 (m, 5 H), 2.87 (dq, J =15.6 Hz, 10.4 Hz, 1 H), 2.80 (dq, J =15.6 Hz, 10.4 Hz, 1 H), 2.67-2.57 (m, 3 H), 2.44 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 141.1, 128.9, 128.5, 124.7, 124.7 (q, J_{CF} = 276 Hz), 84.3 (q, J_{CF} = 2 Hz), 45.2 (q, J_{CF} = 27 Hz), 34.3, 28.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.7 (at, J = 10.4 Hz); IR (film) ν_{max} 1775, 1382, 1248, 1198, 1121, 1077, 1046, 928 cm^{-1}; R_f(hexanes: ethyl

acetate = 3:1)= 0.38; Anal. Calcd. For $C_{12}H_{11}F_3O_2$: C, 59.02; H, 4.54. Found: C, 58.97; H, 4.45. m. p. 64-65 °C.



3c1 Major **3c2** Minor

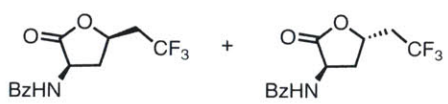
(±)-5-methyl-4-phenyl-5-(2,2,2-trifluoroethyl) dihydrofuran-2(3*H*)-one (3c) Following general procedure B, the title compound was synthesized from 4-methyl-3-phenyl-4-pentenoic acid (**2c**) (95.1 mg, 0.50 mmol). d.r.(**3c1**:**3c2**) = 2.2:1 as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 10:1 to 4:1) to afford an inseparable mixture of **3c1** and **3c2** (125.8 mg, 96 %) as a colorless oil. The relative stereochemistry of **3c1** and **3c2** was assigned by 2D-NOESY experiment (Figure 1). ^1H NMR (400 MHz, $CDCl_3$) **3c1**: δ 7.41-7.18 (m, 5 H), 3.70 (dd, *J* =9.4 Hz, 9.2 Hz, 1 H), 3.01 (dd, *J* =17.8 Hz, 9.9 Hz, 1 H), 2.92 (dd, *J* =17.8 Hz, 8.5 Hz, 1 H), 2.64 (aq, *J* =10.6 Hz, 2 H), 1.15 (s, 3 H); **3c2**: δ 7.41-7.18 (m, 5 H), 3.58 (dd, *J* =8.2 Hz, 8.2 Hz, 1 H), 3.02 (dd, *J* =17.8 Hz, 8.3 Hz, 1 H), 2.92 (dd, *J* =17.8 Hz, 8.5 Hz, 1 H), 2.24 (dq, *J* =15.6 Hz, 10.8 Hz, 1 H), 1.87 (dq, *J* =15.6 Hz, 10.7 Hz, 1 H), 1.71 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) **3c1**: δ 174.4, 135.6, 129.3, 129.1, 128.1, 125.1 (q, J_{CF} = 277 Hz), 84.6 (q, J_{CF} = 2 Hz), 49.4, 43.1 (q, J_{CF} = 28 Hz), 33.5, 21.5; **3c2**: δ 174.7, 136.3, 128.5, 128.4, 127.8, 125.5 (q, J_{CF} = 276 Hz), 84.3 (q, J_{CF} = 2 Hz), 52.1, 40.0 (q, J_{CF} = 28 Hz), 34.3, 25.1; ^{19}F NMR (282 MHz, $CDCl_3$) **3c1**: δ -60.2 (at, *J* = 10.8 Hz); **3c2**: δ -59.9 (at, *J* = 10.7 Hz); IR (film) ν_{max} 1776, 1377, 1264, 1229, 1197, 1123, 1101, 967, 928 cm^{-1}; R_f(hexanes: ethyl acetate = 3:1)= 0.43; Anal. Calcd. For $C_{13}H_{13}F_3O_2$: C, 60.46; H, 5.07. Found: C, 60.71; H, 4.98.



3c1 **3c2**

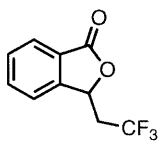
Figure 1. *Strong cross peaks observed in 2D-NOESY experiment.*

(±)-*N*-(2-oxo-5-(2,2,2-trifluoroethyl) tetrahydrofuran-3-yl)benzamide (3d) Following general procedure B, the title compound was synthesized from racemic *N*-benzoyl-allylglycine (**2d**) (109.6 mg, 0.50 mmol).

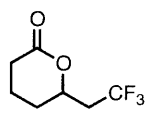


cis-**3d** Major *trans*-**3d** Minor

d.r.(*cis*:*trans*) = 2.8:1 as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. Relative stereochemistry was assigned based on comparison with literature compounds.[19] The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 8:1 to 1:1) to afford an inseparable mixture of *cis*-**3d** and *trans*-**3d** (101.6 mg, 71 %) as a colorless crystalline solid. ^1H NMR (400 MHz, CD_3CN) *cis*-**3d**: δ 7.78 (m, 2 H), 7.56-7.52 (m, 2 H), 7.45 (m, 2 H), 4.73 (m, 2 H), 2.77-2.52 (m, 3 H), 2.18 (m, 1 H); ^{13}C NMR (100 MHz, CD_3CN) *cis*-**3d**: δ 174.9, 167.7, 134.4, 132.9, 129.6, 128.1, 126.8 (q, J_{CF} = 274 Hz), 71.7 (q, J_{CF} = 3 Hz), 50.4, 39.7 (q, J_{CF} = 28 Hz), 34.4; ^{19}F NMR (282 MHz, CD_3CN) *cis*-**3d**: δ -64.2 (at, J = 10.7 Hz); *trans*-**3d**: δ -64.1 (at, J = 10.7 Hz); IR (film) ν_{max} 3411, 1768, 1659, 1525, 1427, 1364, 1254, 1128, 1074, 1000 cm^{-1}; R_f(hexanes: ethyl acetate = 1:1)= 0.33; Anal. Calcd. For $C_{13}H_{12}NF_3O_3$: C, 54.36; H, 4.21. Found: C, 54.22; H, 4.28. m. p. 211-213 °C.

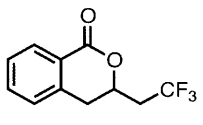


(±)-3-(2,2,2-trifluoroethyl)isobenzofuran-1(3*H*)-one (3e) Following a slightly modified general procedure B, the title compound was synthesized from 2-vinylbenzoic acid (**2e**) (74.1 mg, 0.50 mmol) using tetrakis(acetonitrile)copper(I) hexafluorophosphate (37.3 mg, 0.10 mmol, 0.20 equiv.), 2,2'-biquinoline (38.4 mg, 0.15 mmol, 0.30 equiv.), 1-trifluoromethyl-1,2-benziodoxol-3-(*1H*)-one **1** (Togni's reagent, 174 mg, 0.55 mmol, 1.1 equiv.). The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 12:1 to 3:1) to afford **3e** (70.3 mg, 65 %) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J =7.6 Hz, 1 H), 7.74 (atd, J =7.6 Hz, 1.0 Hz, 1 H), 7.60 (at, J =7.6 Hz, 1 H), 7.52 (d, J =7.6 Hz, 1 H), 5.71 (dd, J =8.4 Hz, 3.7 Hz, 1 H), 2.86-2.54 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 147.6, 134.7, 130.2, 126.2, 125.8, 125.1 (q, J_{CF} = 276 Hz), 122.1, 74.5 (q, J_{CF} = 3 Hz), 39.5 (q, J_{CF} = 29 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.8 (at, J = 10.4 Hz); IR (film) ν_{max} 1768, 1599, 1395, 1327, 1267, 1249, 1136, 1121, 1048 cm^{-1}; R_f(hexanes: ethyl acetate = 3:1)= 0.46; Anal. Calcd. For $C_{10}H_7F_3O_2$: C, 55.56; H, 3.26. Found: C, 55.76; H, 3.12. m. p. 75-76 °C.

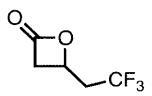


(±)-6-(2,2,2-trifluoroethyl)tetrahydro-2*H*-pyran-2-one (3f) Following general procedure B, the title compound was synthesized from 5-hexenoic acid (**2f**) (57.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (pentane: ethyl ether = 3:1 to 0:1, GC-MS was used to help identifying product-containing fractions) to afford **3f** (66.5 mg, 73 %) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$)

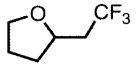
δ 4.58 (m, 1 H), 2.65-2.52 (m, 2 H), 2.49-2.31 (m, 2 H), 2.02-1.84 (m, 3 H), 1.62 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 125.2 (q, J_{CF} = 275 Hz), 74.0 (q, J_{CF} = 3 Hz), 40.0 (q, J_{CF} = 28 Hz), 29.1, 27.8, 18.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.6 (at, J = 10.4 Hz); IR (film) ν_{max} 1732, 1239, 1174, 1140, 1122, 1079, 1056, 1037 cm^{-1}; Anal. Calcd. For $C_7H_9F_3O_2$: C, 46.16; H, 4.98. Found: C, 45.89; H, 5.09.



(±)-3-(2,2,2-trifluoroethyl)isochroman-1-one (3g) Following general procedure B, the title compound was synthesized from 2-allylbenzoic acid (**2g**) (81.1 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 20:1 to 6:1) to afford **3g** (84.7 mg, 74 %) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J =7.6 Hz, 1 H), 7.56 (dd, J =7.3 Hz, 7.2 Hz, 1 H), 7.40 (dd, J =7.6 Hz, 7.4 Hz, 1 H), 7.27 (d, J =7.3 Hz, 1 H), 4.84 (m, 1 H), 3.08 (m, 2 H), 2.78 (m, 1 H), 2.55 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 137.9, 134.2, 130.5, 128.2, 127.6, 125.2 (q, J_{CF} = 275 Hz), 124.7, 72.3 (q, J_{CF} = 3 Hz), 39.3 (q, J_{CF} = 28 Hz), 33.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.5 (at, J = 10.4 Hz); IR (film) ν_{max} 1718, 1606, 1462, 1412, 1289, 1250, 1154, 1111, 1066, 1032 cm^{-1}; R_f(hexanes: ethyl acetate = 3:1)= 0.41; Anal. Calcd. For $C_{11}H_9F_3O_2$: C, 57.40; H, 3.94. Found: C, 57.11; H, 4.00. m. p. 57-58 °C.

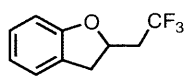


(±)-4-(2,2,2-trifluoroethyl)oxetan-2-one (3h) Following a slightly modified general procedure B, the title compound was synthesized from vinylacetic acid (**2h**) (43.0 mg, 0.50 mmol) using tetrakis(acetonitrile) copper(I) hexafluorophosphate (37.3 mg, 0.10 mmol, 0.20 equiv.), 2,2'-biquinoline (38.4 mg, 0.15 mmol, 0.30 equiv.), 1-trifluoromethyl-1,2-benziodoxol-3-(*1H*)-one **1** (Togni's reagent, 174 mg, 0.55 mmol, 1.1 equiv). The yield of **3h** was 43 % as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture using a,a,a-trifluorotoluene as an internal standard. ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (m, 1 H), 3.74 (dd, J =16.7 Hz, 5.8 Hz, 1 H), 3.33 (dd, J =16.7 Hz, 4.2 Hz, 1 H), 2.89-2.76 (m, 1 H), 2.64-2.57 (m, 1 H); ^{19}F NMR (282 MHz, CD_3CN) δ -64.6 (at, J = 10.7 Hz).

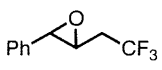


(±)-2-(2,2,2-trifluoroethyl)tetrahydrofuran (3i) Following general procedure B, the title compound was synthesized from 4-penten-1-ol (**2i**) (43.0 mg, 0.50 mmol). The yield of **3i** was 71 % as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture using a,a,a-trifluorotoluene as an internal standard. ^1H NMR (400 MHz, CD_3CN)

δ 4.04 (m, 1 H), 3.81 (ddd, J =8.1 Hz, 7.0 Hz, 6.9 Hz, 1 H), 3.68 (ddd, J =8.0 Hz, 7.9 Hz, 6.1 Hz, 1 H), 2.42-2.31 (m, 2 H), 2.08 (m, 1 H), 1.88 (m, 1 H), 1.54 (m, 1 H); ^{13}C NMR (100 MHz, CD_3CN) δ 127.6 (q, J_{CF} = 274 Hz), 73.5 (q, J_{CF} = 3 Hz), 68.5, 39.8 (q, J_{CF} = 27 Hz), 32.4, 26.0; ^{19}F NMR (282 MHz, CD_3CN) δ -64.0 (at, J = 11.4 Hz).



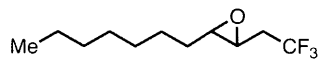
(±)-2-(2,2,2-trifluoroethyl)-2,3-dihydrobenzofuran (3j) Following a slightly modified general procedure B, the title compound was synthesized from 2-allylphenol (**2j**) (67.1 mg, 0.50 mmol) using tetrakis(acetonitrile)copper(I) hexafluorophosphate (37.3 mg, 0.10 mmol, 0.20 equiv.), bi-2-pyridyl ketone (27.6 mg, 0.15 mmol, 0.30 equiv.) and 1-trifluoromethyl-1,2-benziodoxol-3-(*1H*)-one **1** (Togni's reagent, 174 mg, 0.55 mmol, 1.1 equiv.). The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 1:0 to 20:1) to afford **3j** (36.2 mg, 36 %) as a sticky white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.12 (m, 2 H), 6.90-6.80 (m, 2 H), 5.04 (m, 1 H), 3.43 (dd, J =15.6 Hz, 9.0 Hz, 1 H), 3.00 (dd, J =15.6 Hz, 7.6 Hz, 1 H), 2.72 (m, 1 H), 2.47 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 128.5, 125.8, 125.7 (q, J_{CF} = 275 Hz), 125.1, 121.1, 109.8, 76.5 (q, J_{CF} = 3 Hz), 40.1 (q, J_{CF} = 27 Hz), 35.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.0 (at, J = 10.6 Hz); IR (film) ν_{max} 1597, 1481, 1423, 1399, 1256, 1233, 1110, 1074, 872 cm^{-1}; R_f(hexanes: ethyl acetate = 10:1)= 0.50; m. p. 39-41 °C.



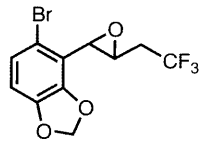
(±)-2-phenyl-3-(2,2,2-trifluoroethyl)oxirane (3k) Following a slightly modified general procedure B, the title compound was synthesized from 1-phenyl-2-propen-1-ol (**2k**) (67.1 mg, 0.50 mmol) using tetrakis(acetonitrile) copper(I) hexafluorophosphate (37.3 mg, 0.10 mmol, 0.20 equiv.), 2,2'-biquinoline (38.4 mg, 0.15 mmol, 0.30 equiv.), 1-trifluoromethyl-1,2-benziodoxol-3-(*1H*)-one **1** (Togni's reagent, 174 mg, 0.55 mmol, 1.1 equiv.). *trans*:*cis* = 10:1 as determined by ^{19}F NMR and ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 1:0 to 20:1) to afford **3k** (52.2 mg, 51 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) *trans*-diastereomer: δ 7.40-7.27 (m, 5 H), 3.74 (d, J =1.9 Hz, 1 H), 3.19 (ddd, J =6.1 Hz, 5.4 Hz, 2.0 Hz, 1 H), 2.58-2.41 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) *trans*-diastereomer: δ 136.1, 128.8, 128.8, 125.7, 125.7 (q, J_{CF} = 275 Hz), 57.6, 55.5 (q, J_{CF} = 4 Hz), 37.6 (q, J_{CF} = 29 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) *cis*-diastereomer: δ -64.4 (at, J = 10.4 Hz); *trans*-diastereomer: δ -64.6 (at, J = 10.3 Hz); IR (film) ν_{max} 1375, 1276, 1250, 1145, 1076, 1036, 887 cm^{-1}; R_f

(hexanes: ethyl acetate = 10:1)= 0.50; Anal. Calcd. For $C_{10}H_9F_3O$: C, 59.41; H, 4.49. Found: C, 59.71; H, 4.59.

Following the same procedure above, enantiomerically enriched **3k** was synthesized from (*R*)-**2k** (94% ee) in 50% yield. Enantiomeric excess (for *trans* diastereomer): 94% ee, determined by chiral HPLC analysis, Chiralcel OD-H 4.6 mm x 250 mm, hexanes: *i*-PrOH = 99.5:0.5, 1.0 mL/min, 210 nm, t_R = 14.5 min (minor) and 19.0 min (major).

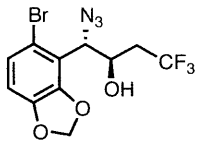


(±)-2-heptyl-3-(2,2,2-trifluoroethyl)oxirane (3l) Following general procedure B, the title compound was synthesized from 1-decen-3-ol (**2l**) (78.1 mg, 0.50 mmol). *trans*:*cis* = 4:1 as determined by ^{19}F NMR and ^1H NMR spectroscopic analysis of the crude reaction mixture. The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 1:0 to 20:1) to afford **3l** (80.9 mg, 72 %) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) *trans*-diastereomer: δ 2.88 (ddd, J =5.9 Hz, 5.8 Hz, 2.1 Hz, 1 H), 2.76 (ddd, J =5.8 Hz, 5.5 Hz, 2.0 Hz, 1 H), 2.43-2.19 (m, 2 H), 1.58-1.26 (m, 12 H), 0.88 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) *trans*-diastereomer: δ 125.9 (q, J_{CF} = 275 Hz), 58.0, 51.4 (q, J_{CF} = 4 Hz), 37.5 (q, J_{CF} = 28 Hz), 31.9, 31.7, 29.4, 29.3, 25.9, 22.7, 14.2; ^{19}F NMR (282 MHz, $CDCl_3$) *cis*-diastereomer: δ -64.7 (at, J = 10.7 Hz); *trans*-diastereomer: δ -64.8 (at, J = 10.7 Hz); IR (film) ν_{max} 2927, 2857, 1466, 1344, 1277, 1250, 1148, 1075 cm^{-1}; R_f(pentane: ethyl ether = 10:1)= 0.63; Anal. Calcd. For $C_{11}H_{19}F_3O$: C, 58.91; H, 8.54. Found: C, 58.64; H, 8.41.

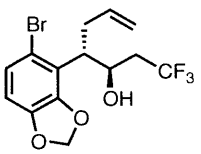


(±)-5-bromo-4-(3-(2,2,2-trifluoroethyl)oxiran-2-yl)benzo[*d*][1,3] dioxole (3m) Following general procedure B, the title compound was synthesized from 1-(5-bromobenzo[*d*][1,3]dioxol-4-yl)prop-2-en-1-ol (**2m**) (128.5 mg, 0.50 mmol). *trans*:*cis* > 20:1 as determined by ^{19}F NMR and ^1H NMR spectroscopic analysis of the crude reaction mixture. The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 1:0 to 8:1) to afford **3m** (109.2 mg, 67 %) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J =8.3 Hz, 1 H), 6.65 (d, J =8.3 Hz, 1 H), 5.98 (m, 2 H), 3.89 (d, J =2.1 Hz, 1 H), 3.67 (m, 1 H), 2.65-2.37 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 146.7, 125.7 (q, J_{CF} = 275 Hz), 125.6, 117.4, 115.1, 109.7, 102.1, 55.3, 52.3 (q, J_{CF} = 4 Hz), 37.5 (q, J_{CF} = 29 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.6 (at, J = 10.4 Hz); IR (film) ν_{max} 1447, 1417, 1368, 1321, 1251, 1235, 1138, 1108, 1065, 1048 cm^{-1}; R_f(hexanes: ethyl acetate = 3:1)= 0.67; Anal. Calcd. For $C_{11}H_8BrF_3O_3$: C, 40.64; H, 2.48. Found: C, 40.59; H, 2.26. m. p. 49-50 °C

Procedures and Characterization for the Derivatization of Oxytrifluoromethylation Product 3m (Scheme 2)

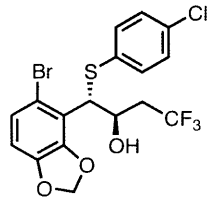


(±)-(1*S*,2*R*)-1-azido-1-(5-bromobenzo[*d*][1,3]dioxol-4-yl)-4,4,4-trifluorobutan-2-ol (5) A mixture of epoxide **3m** (32.5 mg, 0.10 mmol, 1.0 equiv.), sodium azide (19.5 mg, 0.30 mmol, 3.0 equiv.) and ammonium chloride (10.6 mg, 0.20 mmol, 2.0 equiv.) in methanol/water (v/v=1:1, 1.5 mL) was stirred at 80 °C for 3 h before cooling to room temperature. After removing methanol *in vacuo* the mixture was extracted with diethyl ether (1 mL×4). The combined organic phase was concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 10:1 to 4:1) to afford the title compound (33.6 mg, 91 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J =8.3 Hz, 1 H), 6.08 (d, J =1.1 Hz, 1 H), 6.02 (d, J =1.1 Hz, 1 H), 5.05 (d, J =7.4 Hz, 1 H), 4.48 (m, 1 H), 2.61 (dqd, J =15.2 Hz, 11.1 Hz, 1.8 Hz, 1 H), 2.32 (m, 1 H), 2.25 (br, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 146.7, 126.7, 126.4 (q, J_{CF} = 276 Hz), 116.9, 115.7, 110.5, 102.3, 67.2 (q, J_{CF} = 3 Hz), 66.4, 37.7 (q, J_{CF} = 28 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.3 (at, J = 10.7 Hz); IR (film) ν_{max} 2105, 1453, 1237, 1123, 1051, 934 cm^{-1}. R_f(hexanes: ethyl acetate = 3:1)= 0.52.

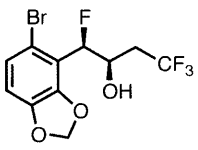


(±)-(3*R*,4*S*)-4-(5-bromobenzo[*d*][1,3]dioxol-4-yl)-1,1,1-trifluorohept-6-en-3-ol (6) An oven-dried 13×100 mm Fisher Scientific re-sealable test tube test tube equipped with a Teflon-coated magnetic stir bar was charged with **3m** (45 mg, 0.14 mmol, 1.0 equiv.). The reaction tube was sealed with a septum screw-cap (Thermo Scientific ASM PHN CAP w/PTFE/SIL, cat. #03388316) and connected to a Schlenk line. The tube was then briefly evacuated and backfilled with argon (this sequence was repeated a total of four times). Anhydrous diethylether (0.5 mL) followed by allylmagnesium bromide solution (1.0 M in diethylether, 0.42 mL, 3.0 equiv.) was added to the tube via syringe at room temperature and the argon pressure was removed. After stirring at room temperature for 3 h the mixture was quenched with saturated aqueous ammonium chloride solution (2 mL). The aqueous layer was separated and extracted with diethyl ether (1 mL×3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 20:1 to 5:1) to afford the title compound (31.4 mg, 62 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J =8.3 Hz, 1 H), 6.65 (d, J =8.3 Hz, 1 H), 6.03 (d, J =1.0 Hz, 1 H), 5.94 (d, J =1.0 Hz, 1 H), 5.68 (m, 1 H), 5.05 (dd, J =17.0 Hz, 3.1

Hz, 1 H), 4.97 (d, J =10.4 Hz, 1 H), 4.36 (m, 1H), 3.49 (m, 1 H), 2.71-2.53 (m, 2 H), 2.44-2.32 (m, 2 H), 2.22-2.11 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 146.0, 135.4, 126.6, 126.6 (q, J_{CF} = 276 Hz), 122.0, 117.8, 117.2, 109.7, 101.3, 68.1, 48.9, 39.5 (q, J_{CF} = 27 Hz), 33.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.5 (at, J = 10.4 Hz); IR (film) ν_{max} 1734, 1445, 1362, 1236, 1123, 1050, 938 cm^{-1}. R_f(hexanes: ethyl acetate = 3:1)= 0.58;



(±)-(1*S*,2*R*)-1-(5-bromobenzo[*d*][1,3]dioxol-4-yl)-1-((4-chlorophenyl)thio)-4,4,4-trifluorobutan-2-ol (7) A mixture of epoxide **3m** (45.0 mg, 0.14 mmol, 1.0 equiv.), sodium hydroxide (11 mg, 0.28 mmol, 2.0 equiv.) and 4-chlorothiophenol (40 mg, 0.28 mmol, 2.0 equiv.) in dioxane/water (v/v=10:1, 1 mL) was stirred at 65 °C for 2 h before cooling to room temperature and diluted with 3 mL diethyl ether. The mixture was washed with 1N NaOH aqueous solution (5 mL) and separated. The organic phase was concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 20:1 to 6:1) to afford the title compound (60.4 mg, 92 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 4 H), 7.10 (d, J =8.3 Hz, 1 H), 6.64 (d, J =8.3 Hz, 1 H), 5.93 (s, 1 H), 5.64 (s, 1 H), 4.57-4.49 (m, 2 H), 2.96 (m, 1 H), 2.48 (br, 1 H), 2.30 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 147.3, 136.3, 135.3, 129.2, 129.2, 126.6, 126.5 (q, J_{CF} = 276 Hz), 119.9, 119.9, 109.4, 101.7, 67.4, 56.7, 39.1 (q, J_{CF} = 27 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.5 (at, J = 10.4 Hz); IR (film) ν_{max} 1475, 1448, 1266, 1236, 1140, 1112, 1092, 1012, 989 cm^{-1}. R_f(hexanes: ethyl acetate = 3:1)= 0.56; Anal. Calcd. For $C_{17}H_{13}BrClF_3O_3S$: C, 43.47; H, 2.79. Found: C, 43.21; H, 2.84.



(±)-(1*R*,2*R*)-1-(5-bromobenzo[*d*][1,3]dioxol-4-yl)-1,4,4,4-tetra fluorobutan-2-ol (8) Adapted from a previously reported procedure,[20] the title compound was synthesized from **3m** (23.3 mg, 0.07 mmol). The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 10:1 to 3:1) to afford **3a** (19.5 mg, 79 %) as a sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, J = 8.3 Hz, 1.3 Hz, 1 H), 6.74 (dd, J = 8.3 Hz, 1.0 Hz, 1 H), 6.05 (d, J = 1.3 Hz, 1 H), 6.03 (d, J = 1.3 Hz, 1 H), 5.73 (dd, J = 46 Hz, 6.3 Hz, 1 H), 4.61 (m, 1 H), 2.62 (br, 1 H), 2.51-2.43 (m, 1 H), 2.24-2.17 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0 (d, J_{CF} = 2 Hz), 147.3(d, J_{CF} = 2 Hz), 126.2, 126.0 (q, J_{CF} = 274 Hz), 116.9 (d, J_{CF} = 21 Hz), 113.5 (d, J_{CF} = 6 Hz), 110.8 (d, J_{CF} = 1 Hz), 102.3, 94.3 (d, J_{CF} = 175 Hz), 67.3 (dq, J_{CF} = 24 Hz, 3 Hz), 36.7 (qd, J_{CF} = 28 Hz, 6 Hz); ^{19}F NMR (282

MHz, $CDCl_3$) δ -63.9 (at, J = 10.4 Hz, 3 F), -192.5 (dd, J = 46.0 Hz, 16.6 Hz, 1 F); IR (film) 3969, 1738, 1456, 1364, 1240, 1151, 1127, 1054, 873 cm^{-1}; R_f(hexanes: ethyl acetate = 3:1)= 0.48; Anal. Calcd. For $C_{11}H_9BrF_4O_3$: C, 38.29; H, 2.63. Found: C, 38.54; H, 2.47.

1.5 References and Notes

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[11] In preliminary experiments, the reactions of substrates containing secondary amides or sulfonamides in place of carboxylic acids gave little or no yield of the desired product.

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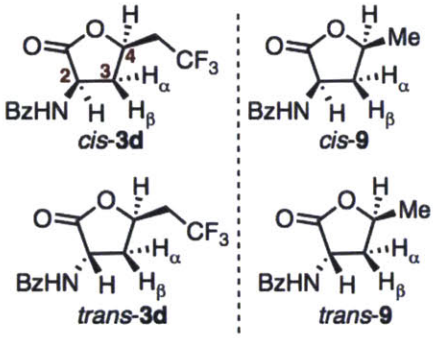

Chemical Shift (ppm) in $CDCl_3$ (10%TFA added)

	cis-**3d**	*trans*-**3d**	*cis*-**9**	*trans*-**9**
$H_{3\alpha}$	3.08	2.70-2.80	2.92	2.98
$H_{3\beta}$	2.28	2.70-2.80	2.05	2.98
C_2	51.3	49.9	51.5	50.2
C_3	35.0	33.2	37.2	34.9
C_4	73.7	74.7	75.7	77.9

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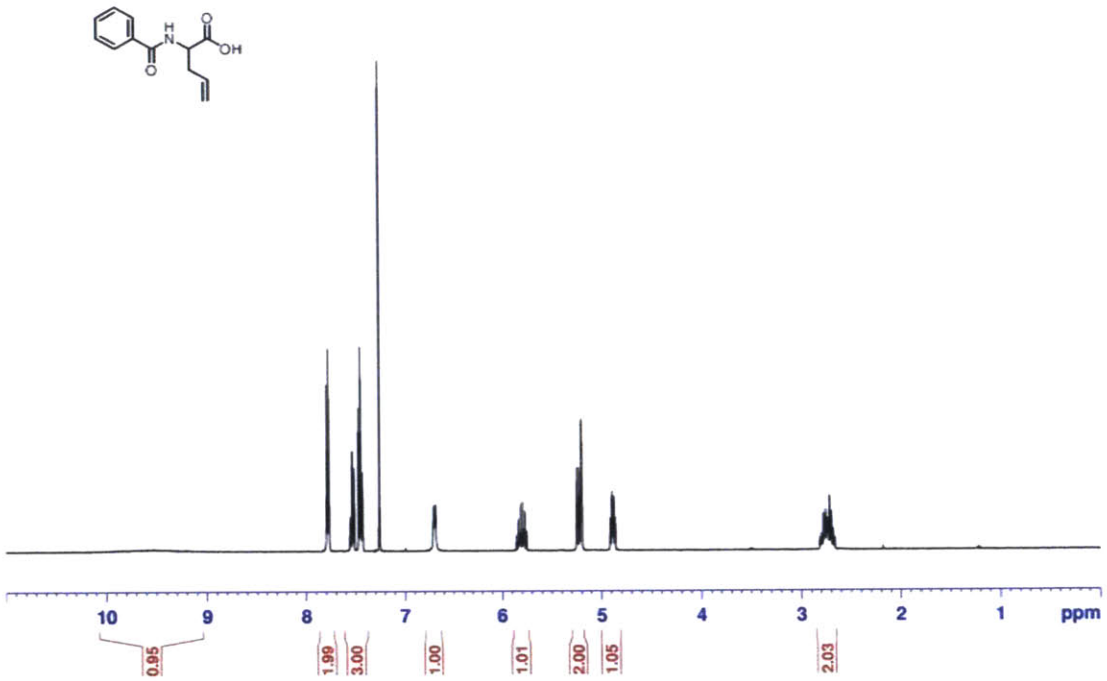
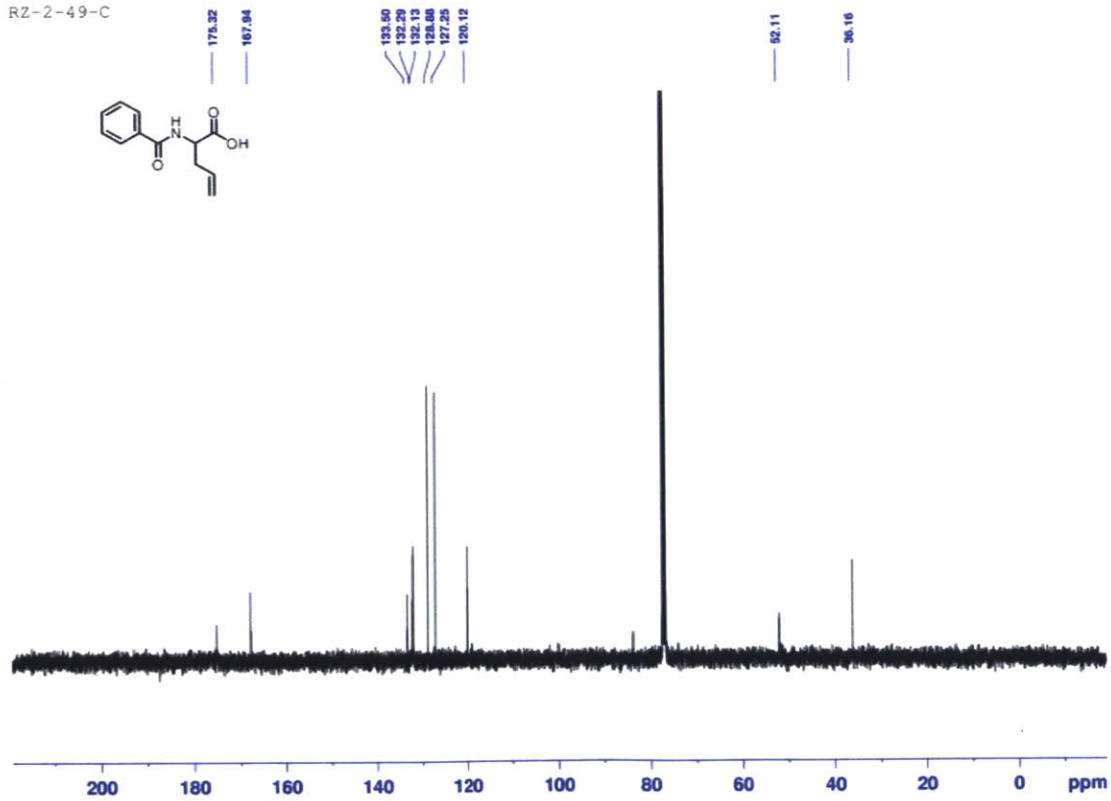
1.6 Spectra and HPLC traces

2d ^{1}H NMR (400 MHz, $CDCl_3$)

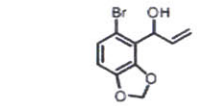


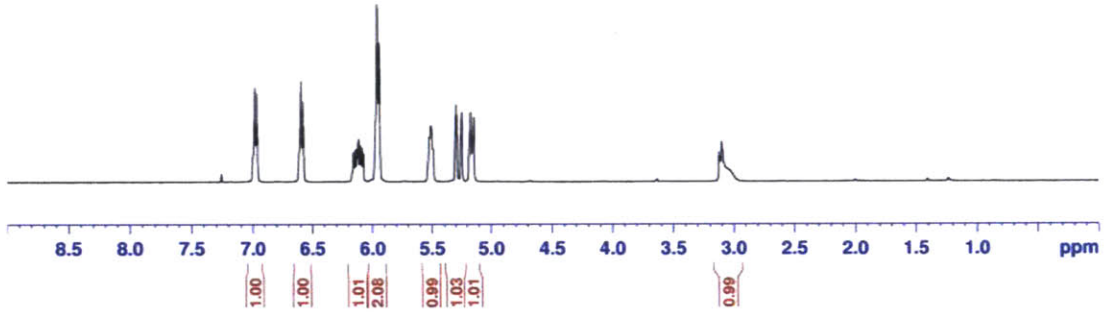
2d ^{13}C NMR (100 MHz, $CDCl_3$)



RZ-2-62D-H

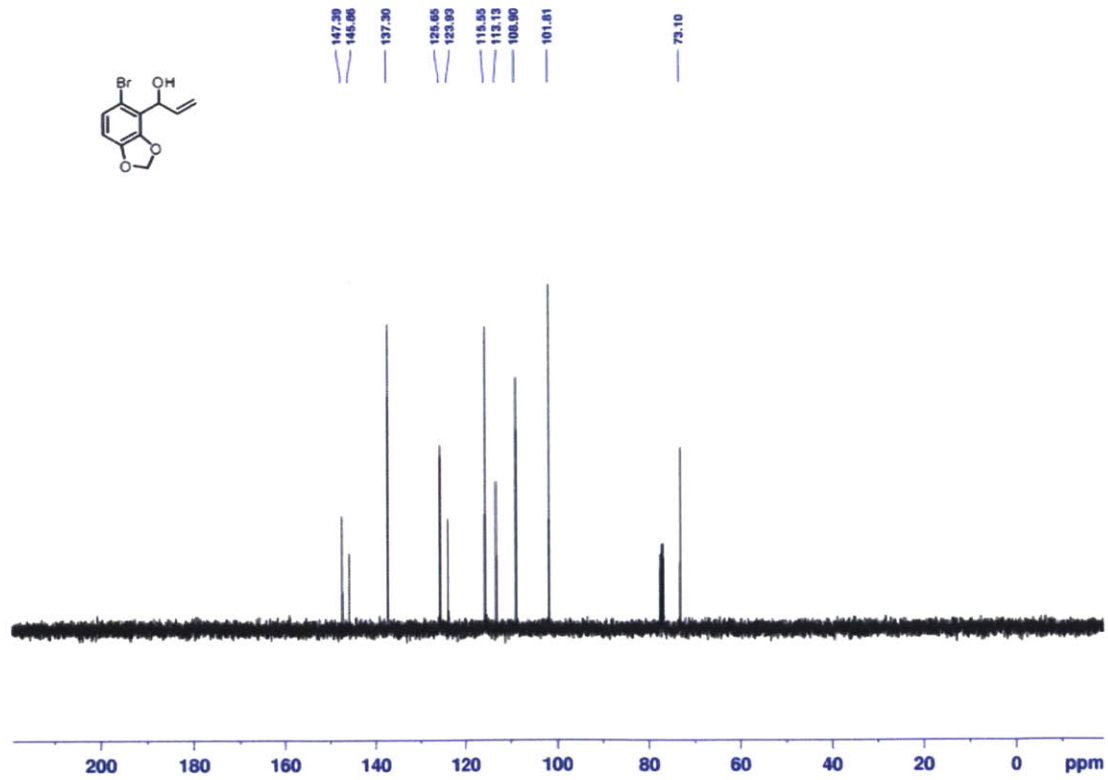
2m ^{1}H NMR (400 MHz, $CDCl_3$)





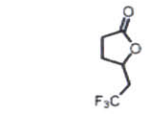
2m ^{13}C NMR (100 MHz, $CDCl_3$)

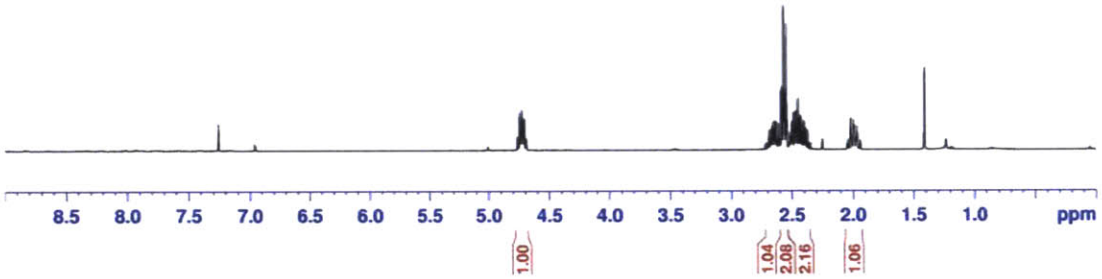
RZ-2-62D-C



RZ-2-44-H

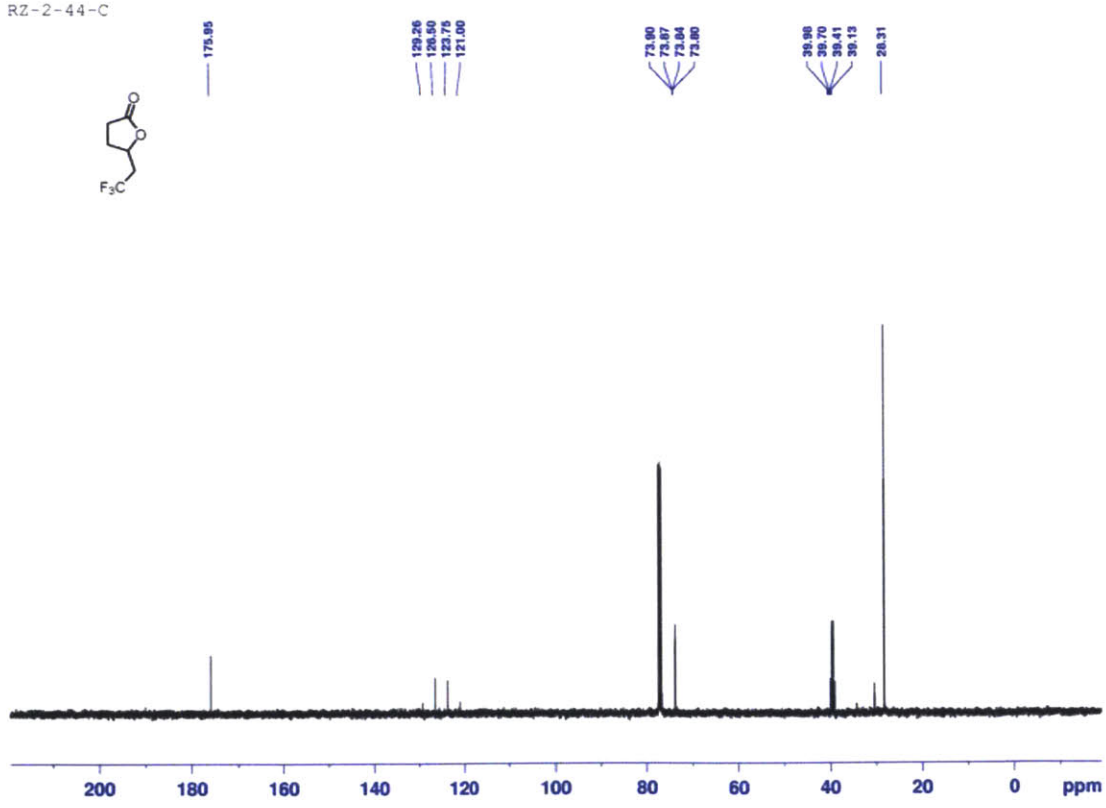
3a ^{1}H NMR (400 MHz, $CDCl_3$)



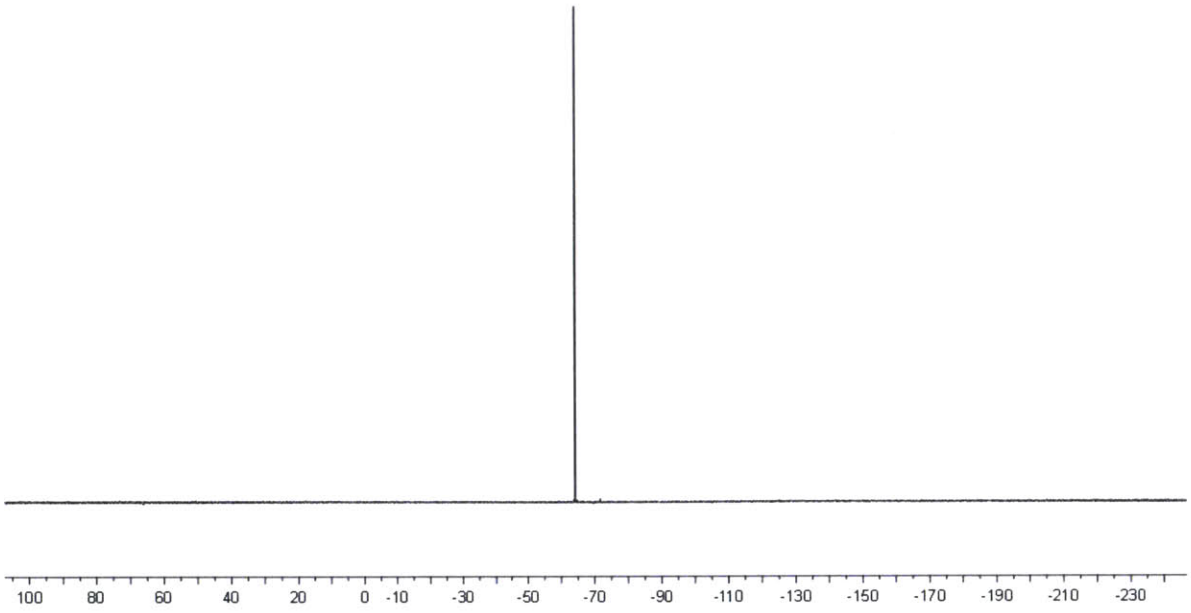


3a ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-2-44-C

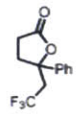


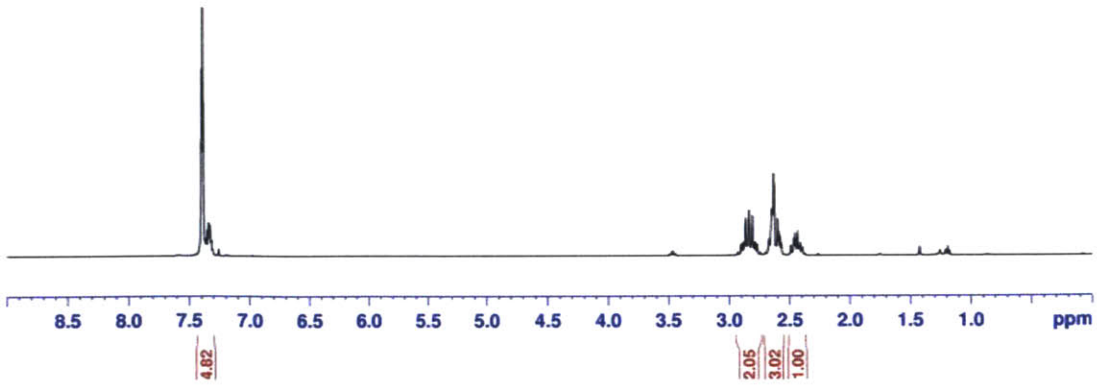
3a ^{19}F NMR (282 MHz, $CDCl_3$)



RZ-2-43-H

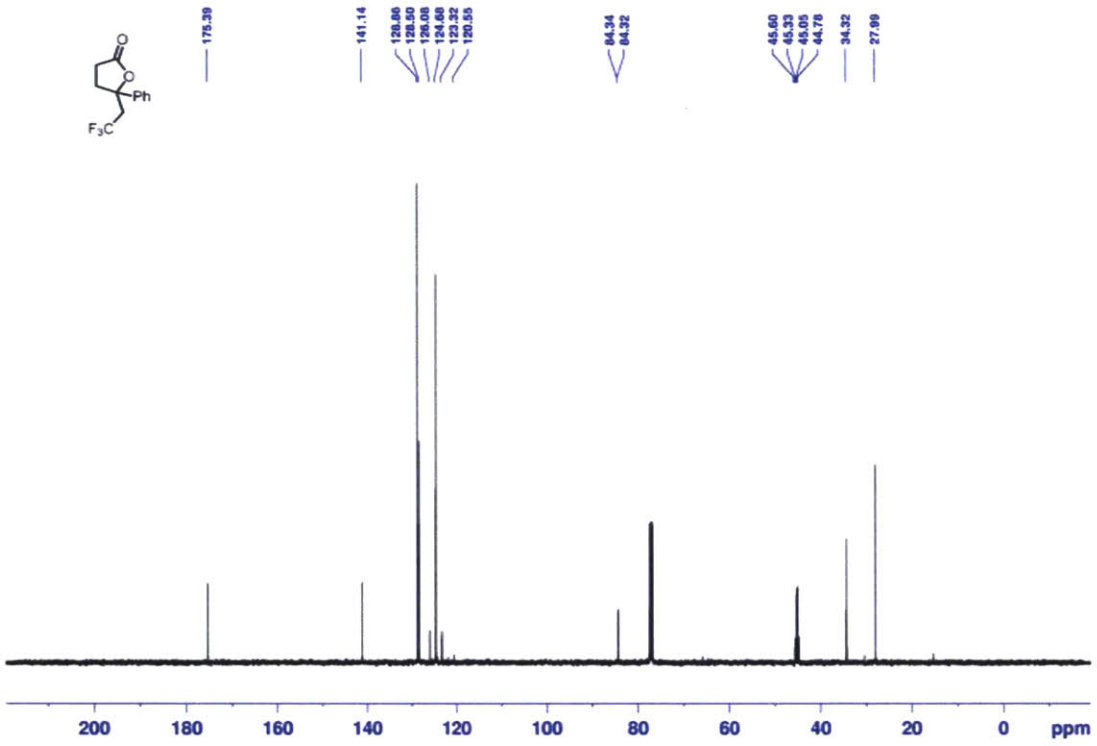
3b ^{1}H NMR (400 MHz, $CDCl_3$)

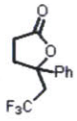




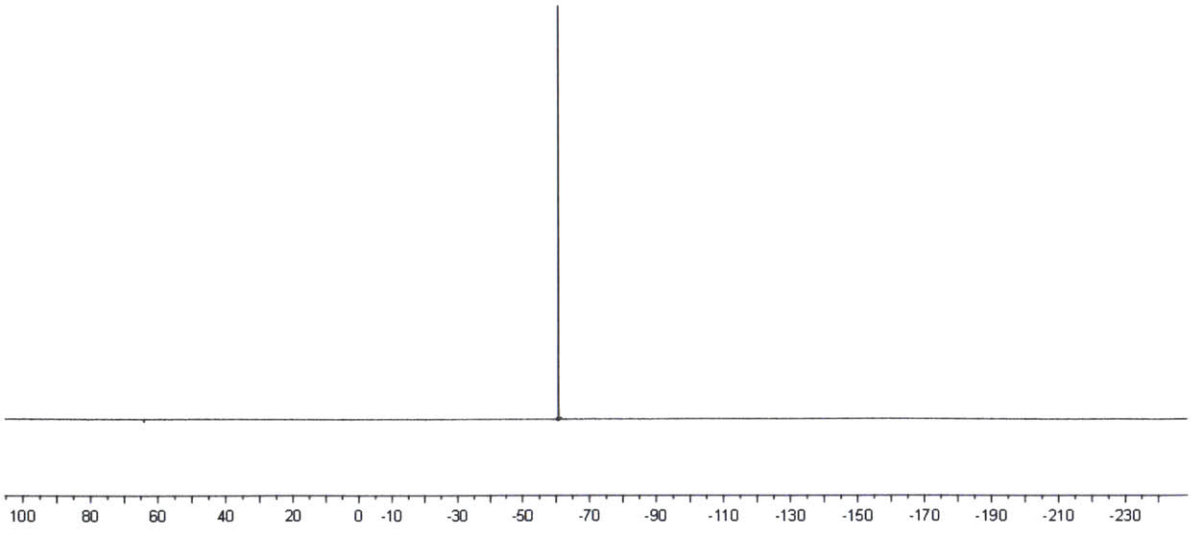
RZ-2-43-C

3b ^{13}C NMR (100 MHz, $CDCl_3$)



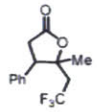


3b ^{19}F NMR (282 MHz, $CDCl_3$)



3c ^{1}H NMR (400 MHz, $CDCl_3$)

RZ-2-46-H



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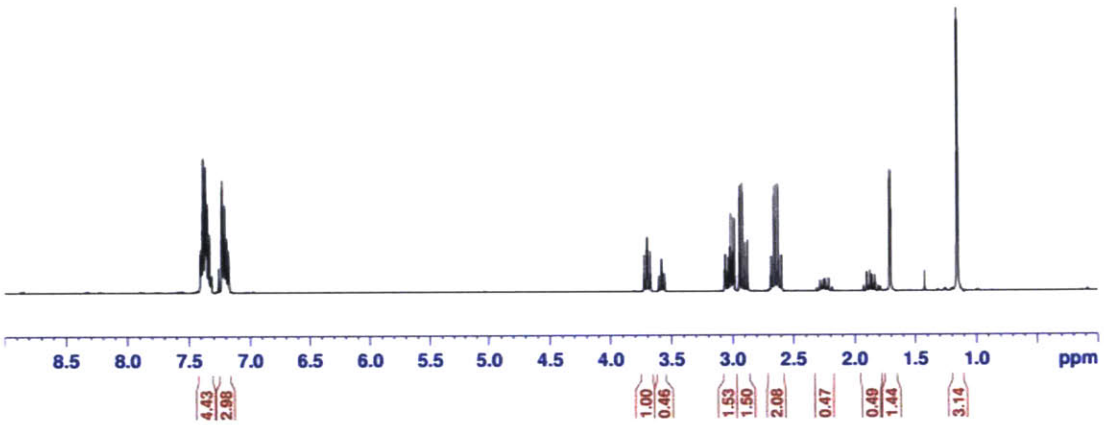
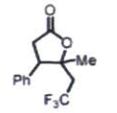


3c ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-2-46-C



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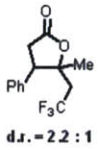
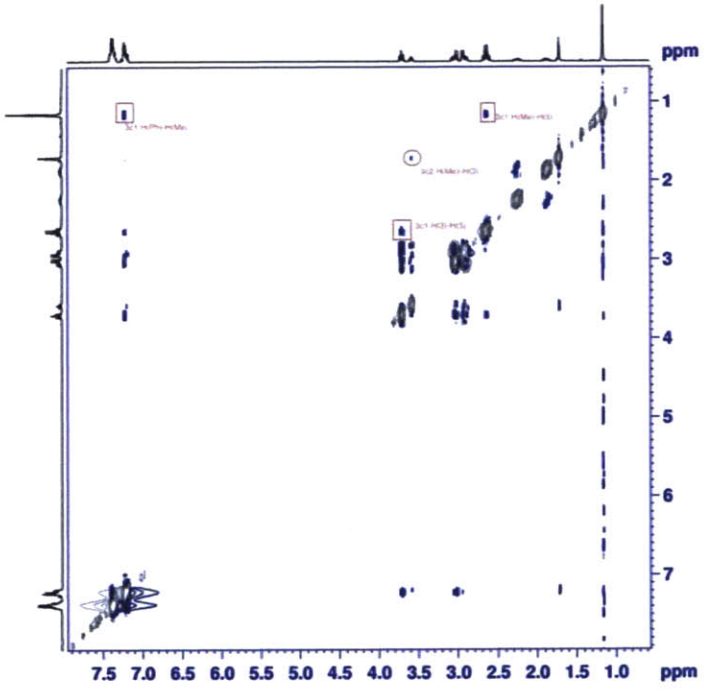


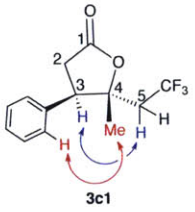
d.r. = 2.2 : 1

3c ^{19}F NMR (282 MHz, $CDCl_3$)

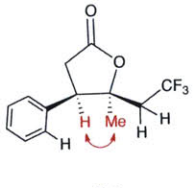
RZ-2-46-2D NOESY

3c 2D NOESY (400 MHz, $CDCl_3$)





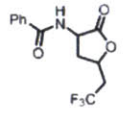
3c1



3c2

RZ-2-54-H-d3-MeCN

3d ^{1}H NMR (400 MHz, CD_3CN)



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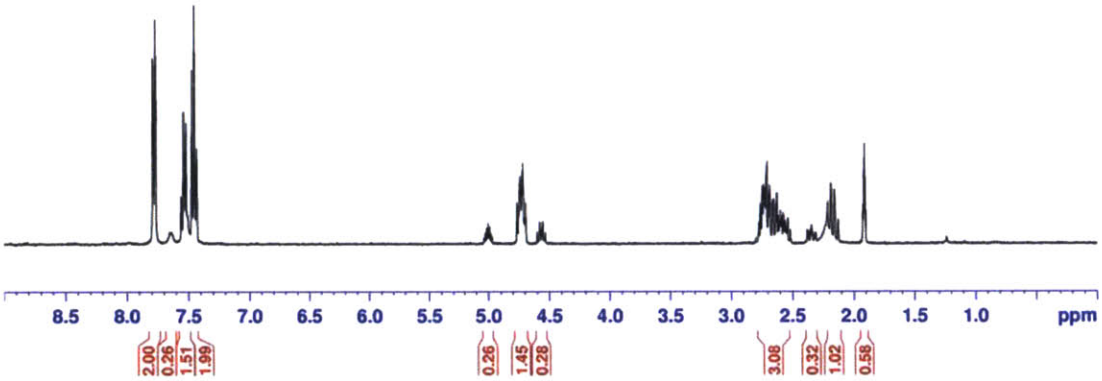
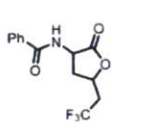


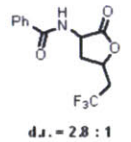
RZ-2-54-C-d3-MeCN

3d ^{13}C NMR (100 MHz, CD_3CN)



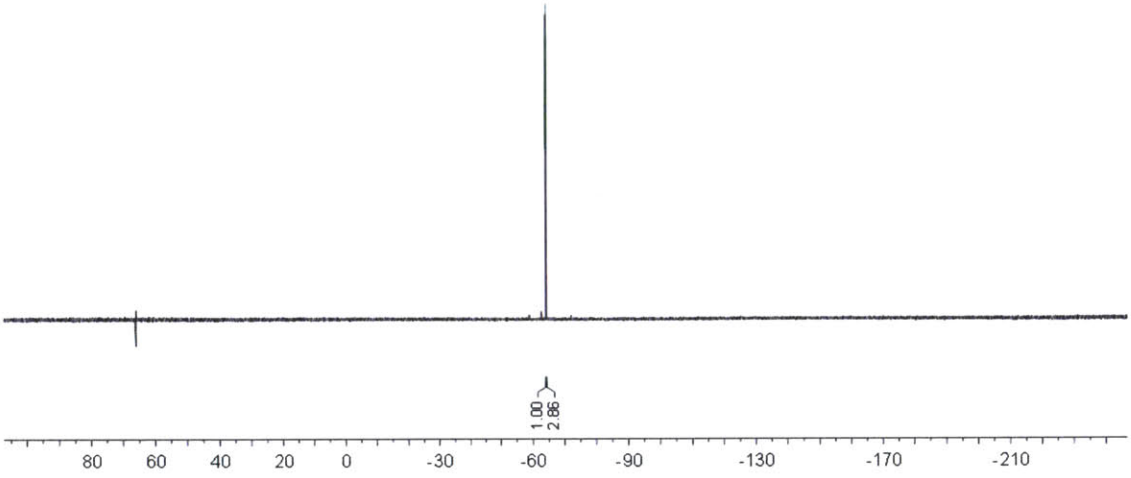
d.r. = 2.8 : 1

RZ-2-54-F



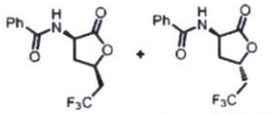
d.r. = 2.8 : 1

3d ^{19}F NMR (282 MHz, CD_3CN)



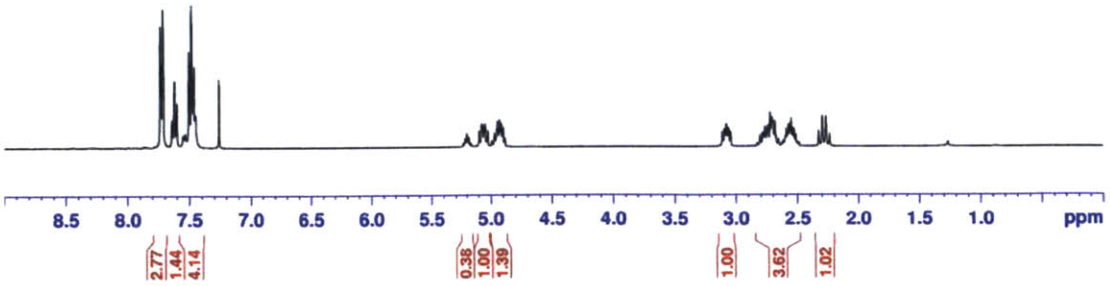
3d ^{1}H NMR (400 MHz, $CDCl_3$ + TFA)

RZ-2-54-CDCl3+TFA



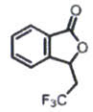
cis(major) trans(minor)

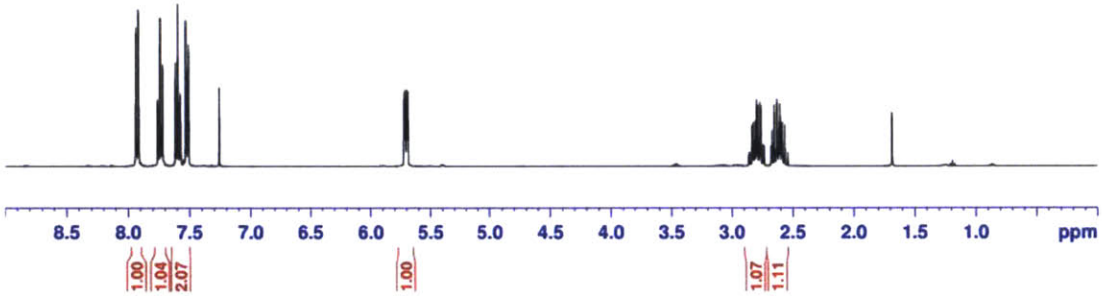
cis:trans=2.8:1



RZ-2-55-H

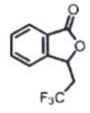
3e ^{1}H NMR (400 MHz, $CDCl_3$)

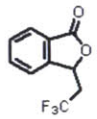




3e ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-2-55-C

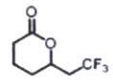


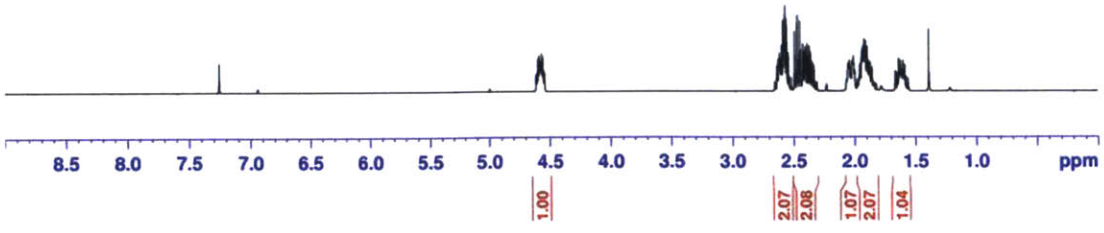


3e ^{19}F NMR (282 MHz, $CDCl_3$)

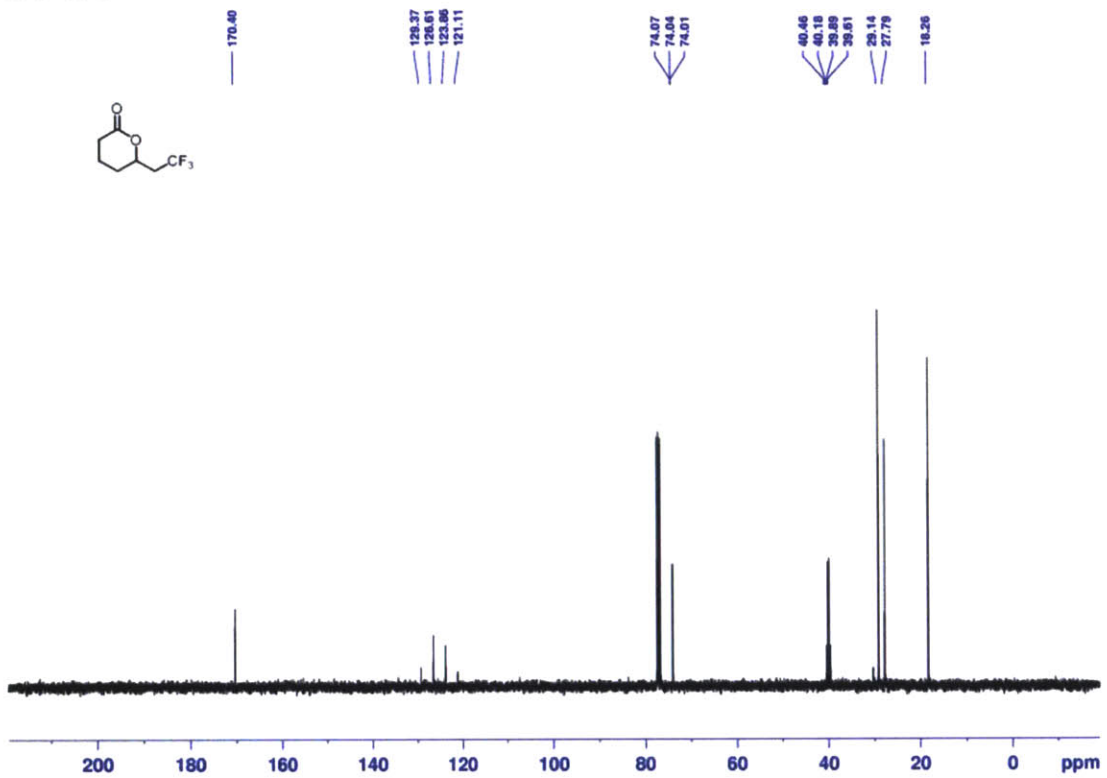
RZ-2-56-H

3f ^{1}H NMR (400 MHz, $CDCl_3$)

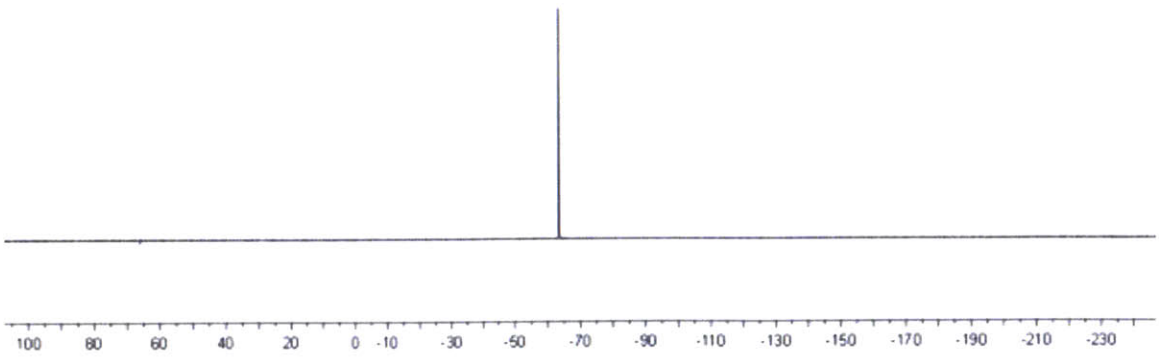




3f ^{13}C NMR (100 MHz, $CDCl_3$)

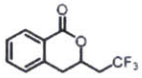


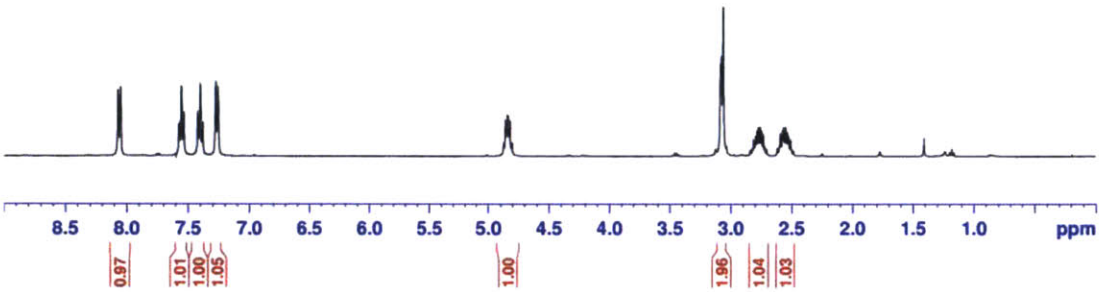
3f ^{19}F NMR (282 MHz, $CDCl_3$)



RZ-2-78-H

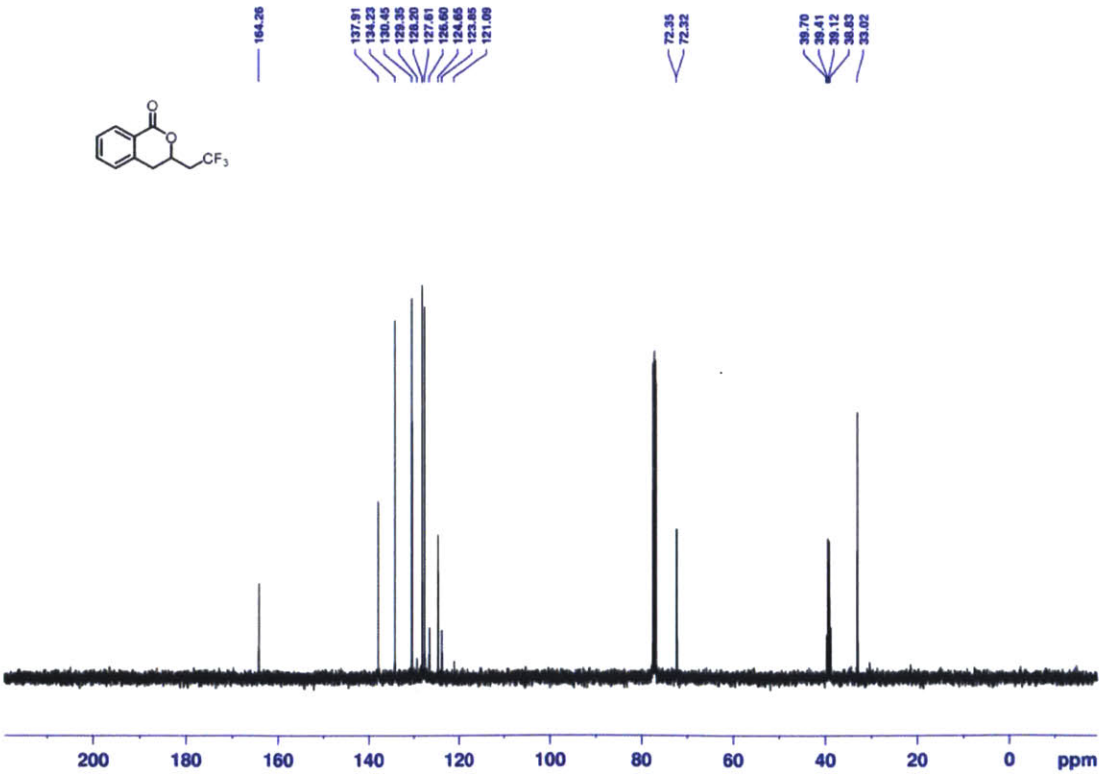
3g ^{1}H NMR (400 MHz, $CDCl_3$)

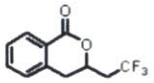




3g ^{13}C NMR (100 MHz, $CDCl_3$)

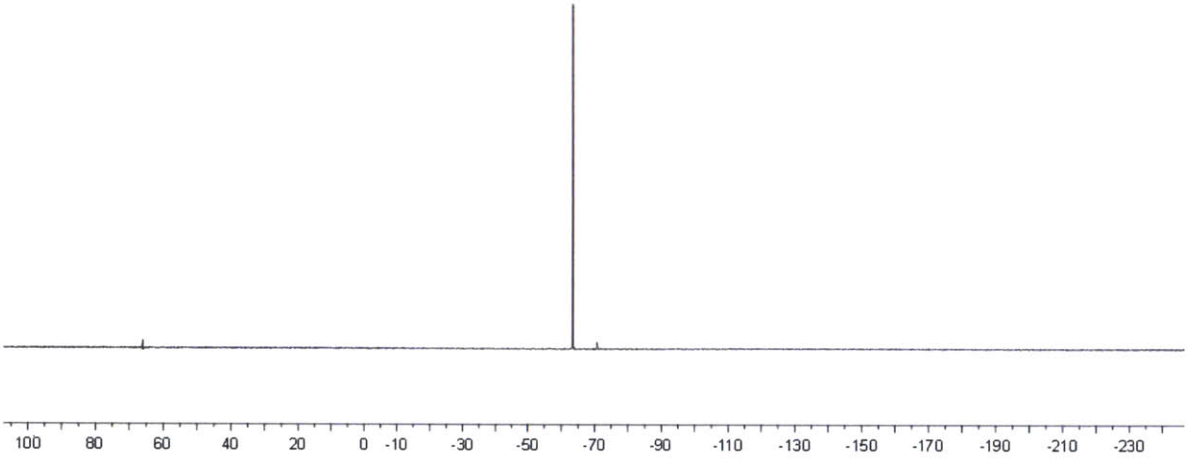
RZ-2-78-C





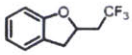
-63.495
-63.532
-63.569

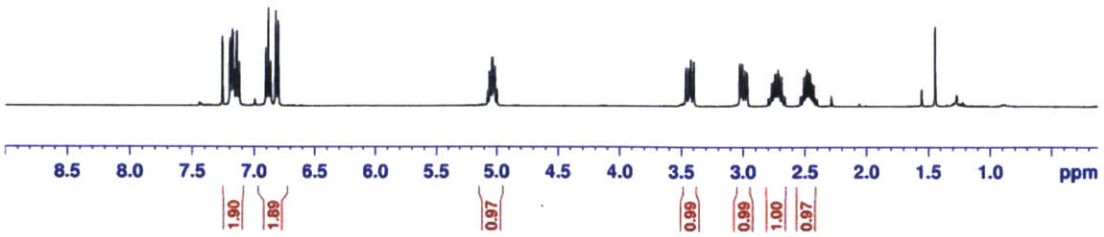
3g ^{19}F NMR (282 MHz, $CDCl_3$)



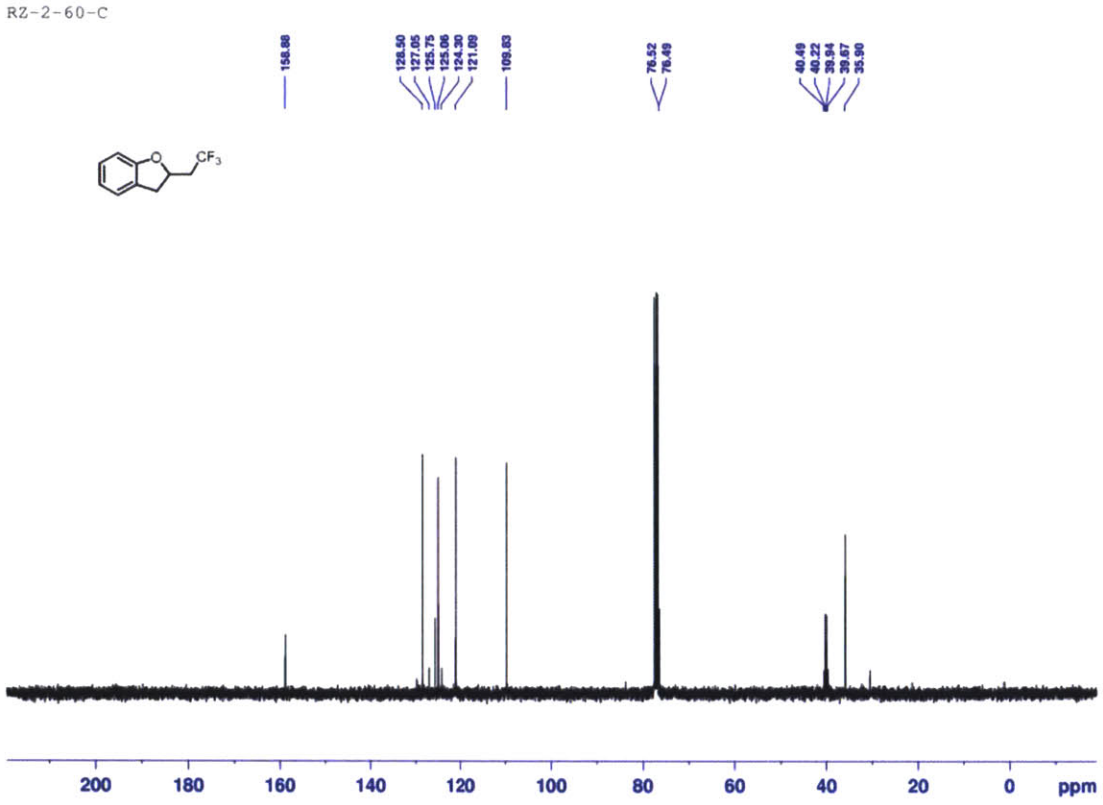
RZ-2-60-H

3j ^{1}H NMR (400 MHz, $CDCl_3$)

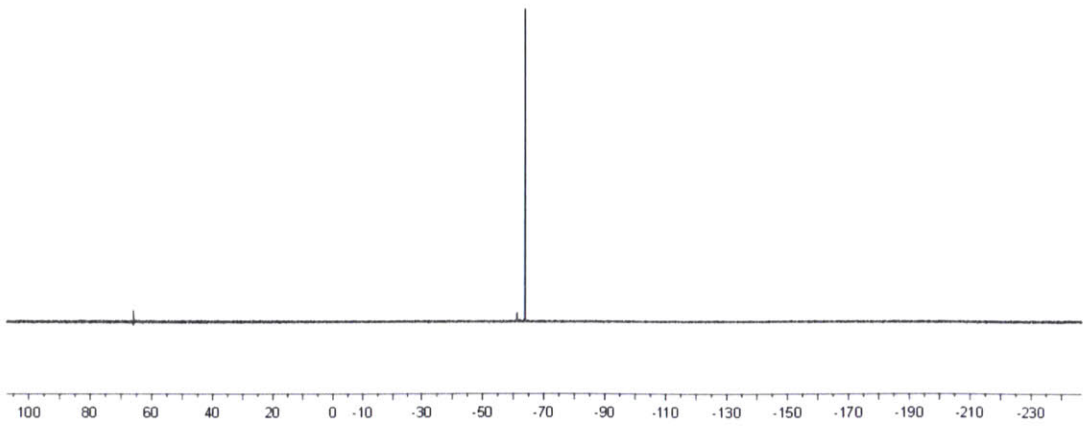




3j ^{13}C NMR (100 MHz, $CDCl_3$)

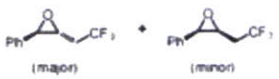


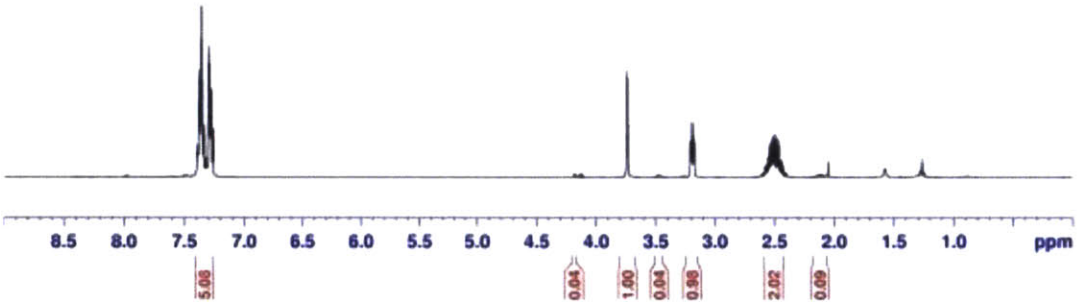
3j ^{19}F NMR (282 MHz, $CDCl_3$)



RZ-2-107-H

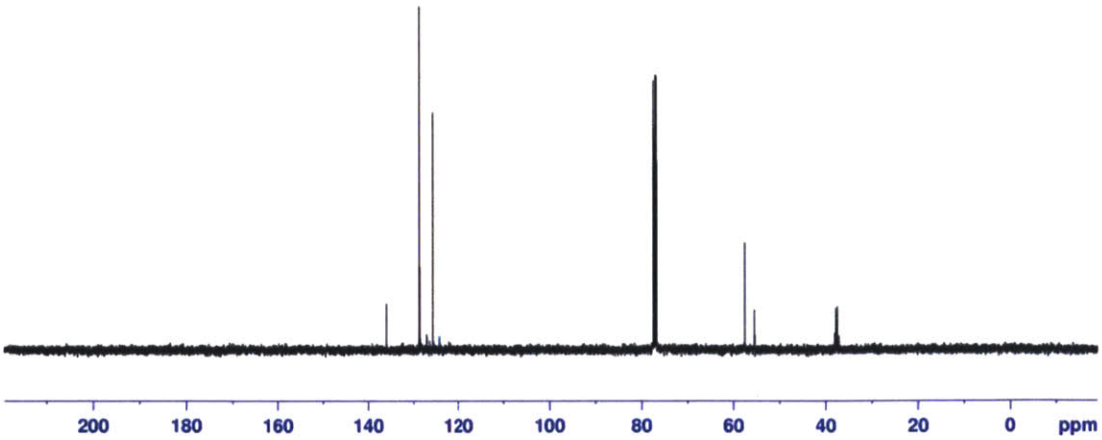
3k ^{1}H NMR (400 MHz, $CDCl_3$)



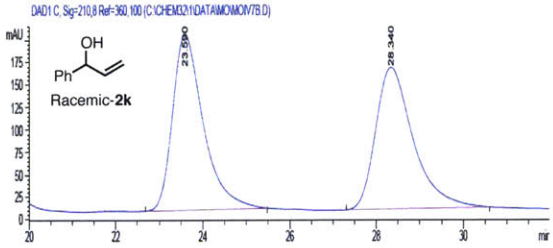


3k ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-2-107-C

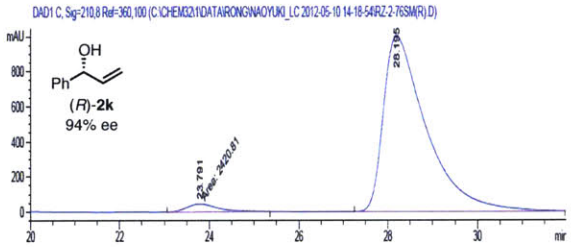


HPLC traces for starting material and product in eq 1



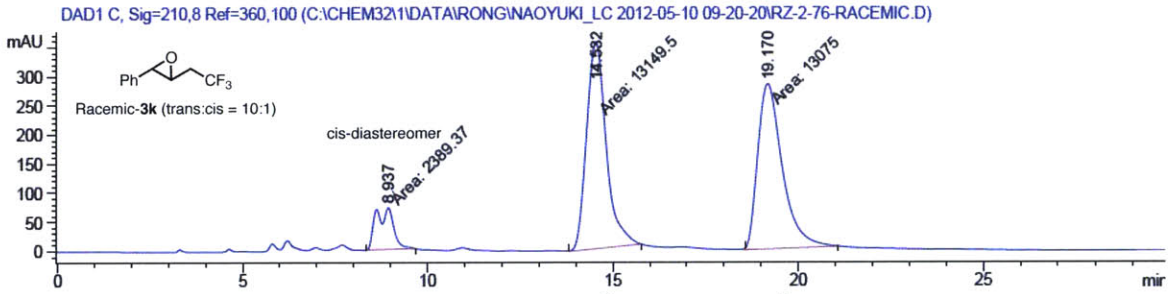
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.590	BB	0.7384	9638.32813	195.08264	50.3036
2	28.340	BB	0.8997	9521.98926	157.87106	49.6964



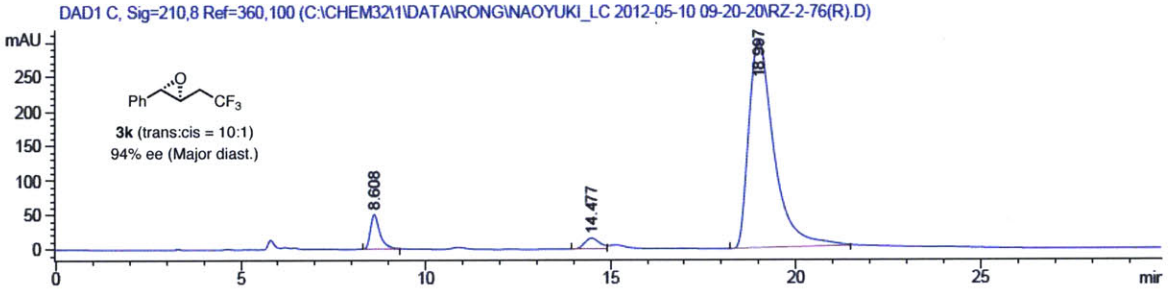
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.791	MM	0.8517	2420.80908	47.37288	3.5103
2	28.195	BB	0.9469	6.65413e4	999.30890	96.4897



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.937	MM	0.5602	2389.37280	71.08680	8.3504
2	14.532	MM	0.6181	1.31495e4	354.54828	45.9548
3	19.170	MM	0.7680	1.30750e4	283.73843	45.6948

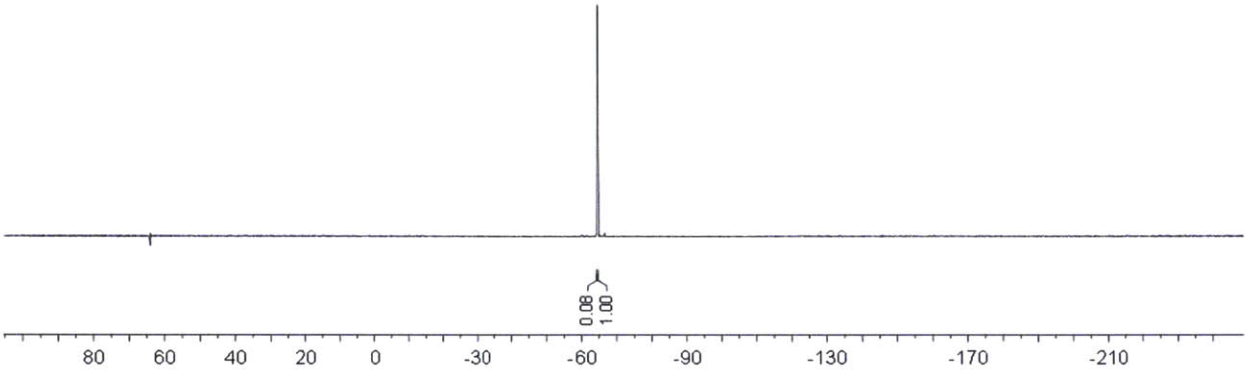


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.608	BB	0.2735	922.68469	50.42570	5.9096
2	14.477	MM	0.4614	403.30606	14.56898	2.5831
3	18.997	BB	0.7227	1.42873e4	301.59232	91.5073

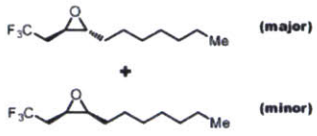
RZ-2-107-F

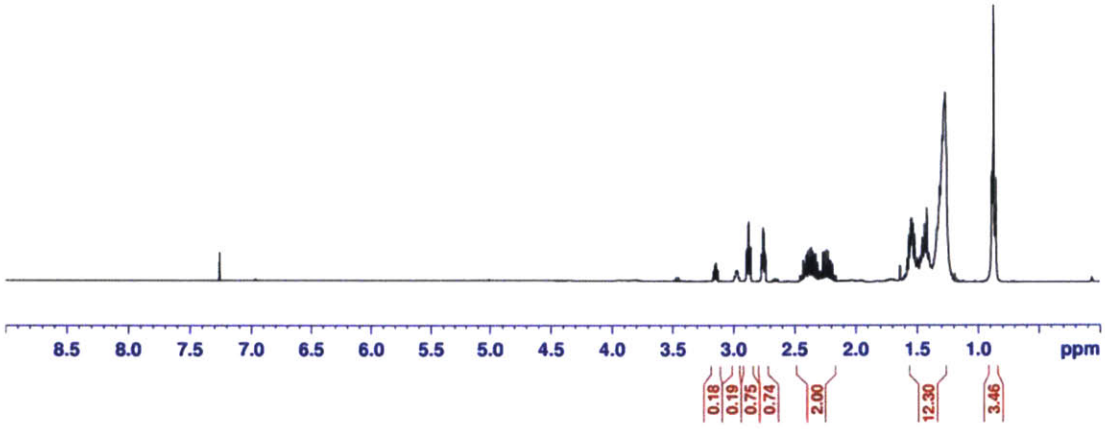
3k ^{19}F NMR (282 MHz, $CDCl_3$)



RZ-2-53-H

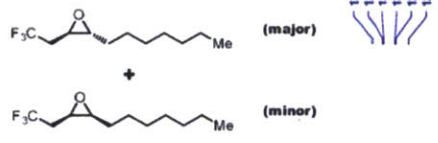
3l ^{1}H NMR (400 MHz, $CDCl_3$)

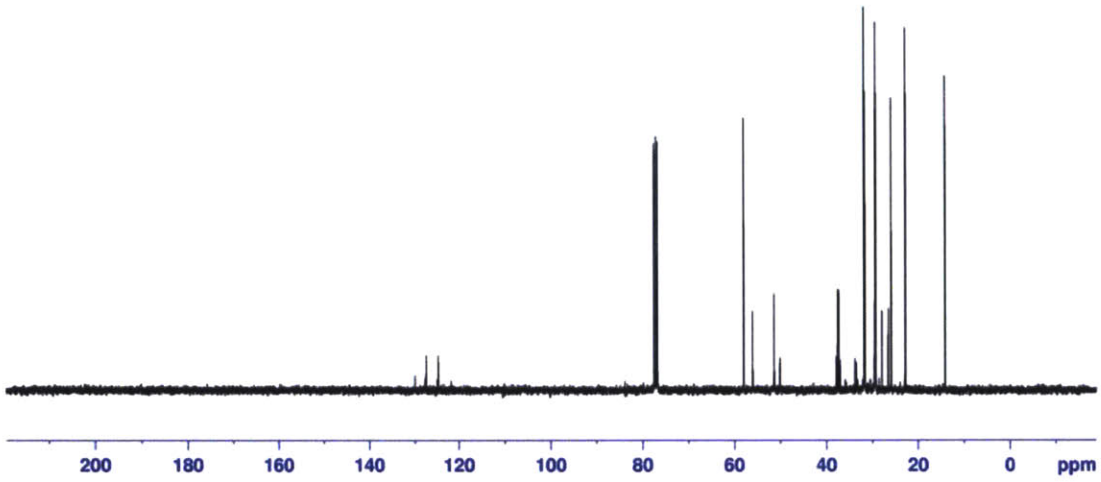




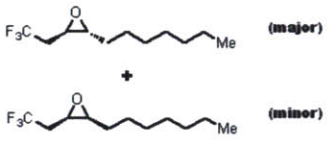
RZ-2-53-C

3l ^{13}C NMR (100 MHz, $CDCl_3$)

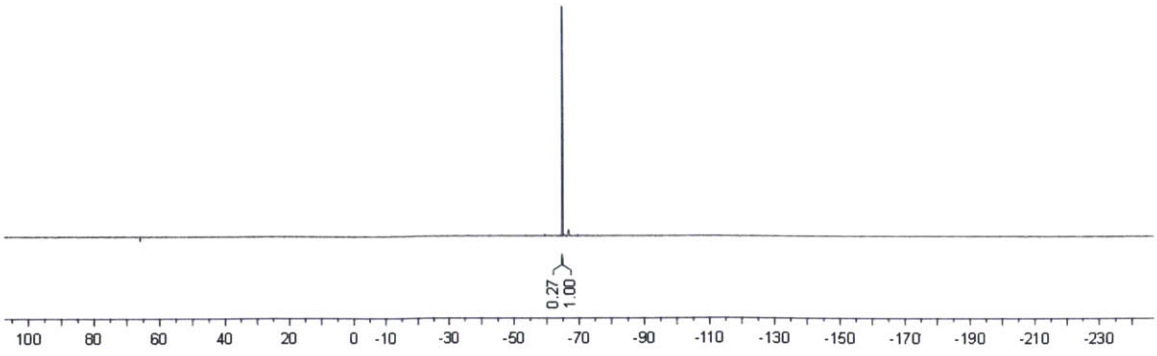




RZ-2-53-F

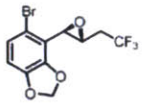


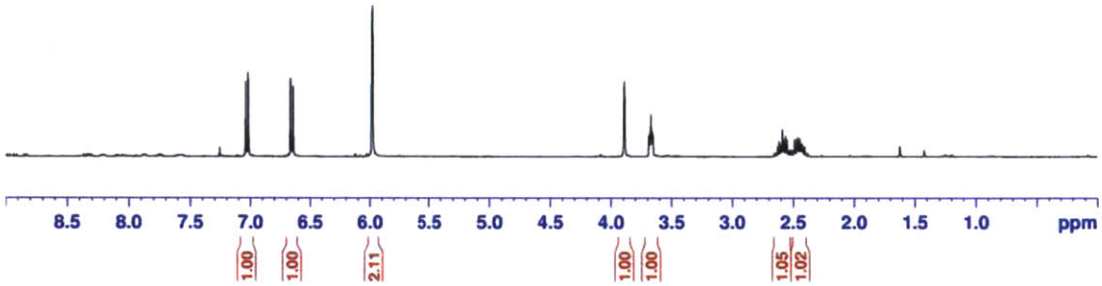
3l ^{19}F NMR (282 MHz, $CDCl_3$)



RZ-2-67-H

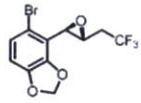
3m ^{1}H NMR (400 MHz, $CDCl_3$)

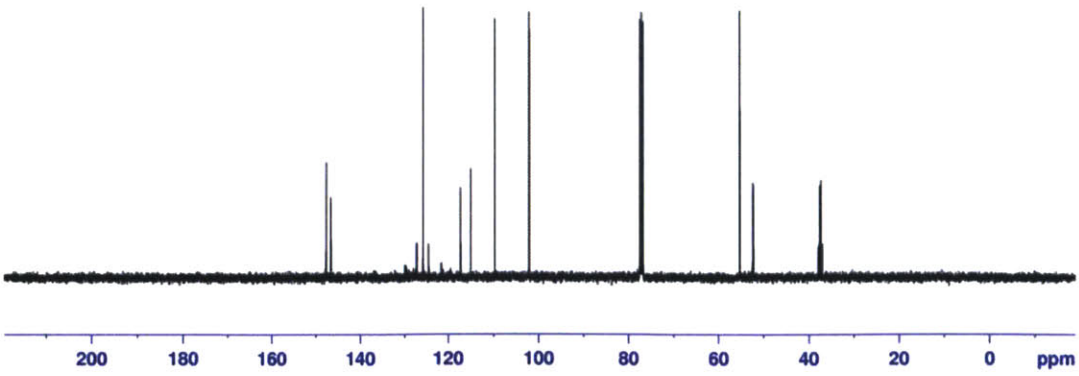




3m ^{13}C NMR (100 MHz, $CDCl_3$)

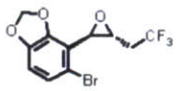
RZ-2-67-C



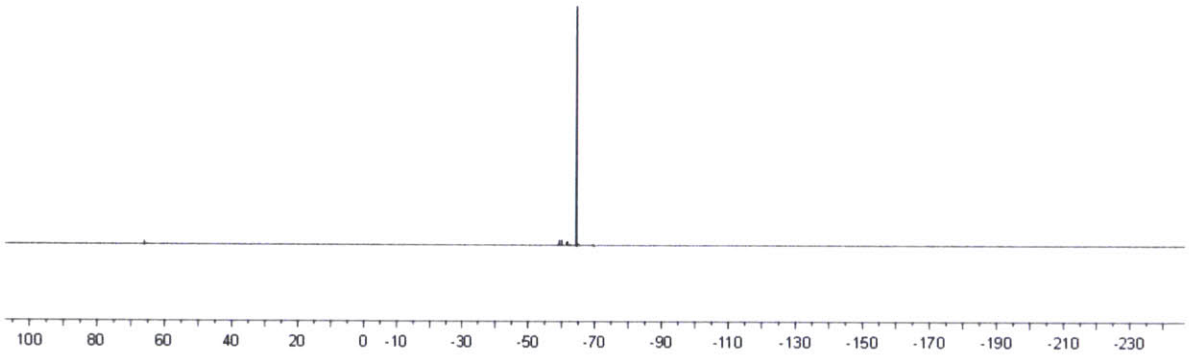


RZ-2-67-F

-64.544
-64.581
-64.618

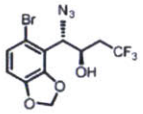


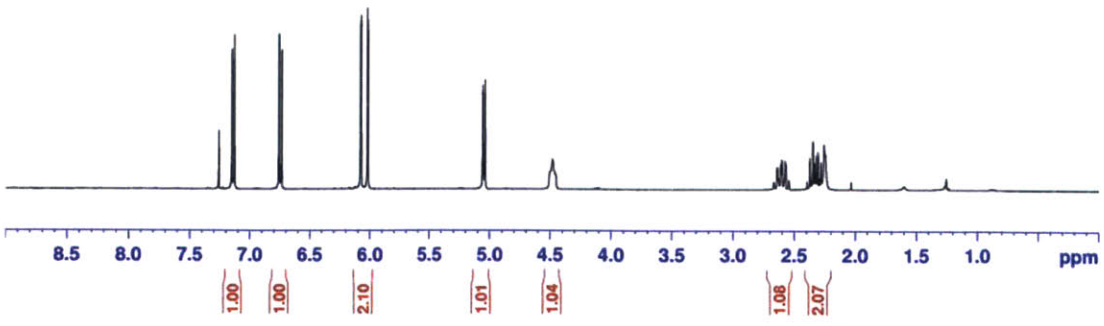
3m ^{19}F NMR (282 MHz, $CDCl_3$)



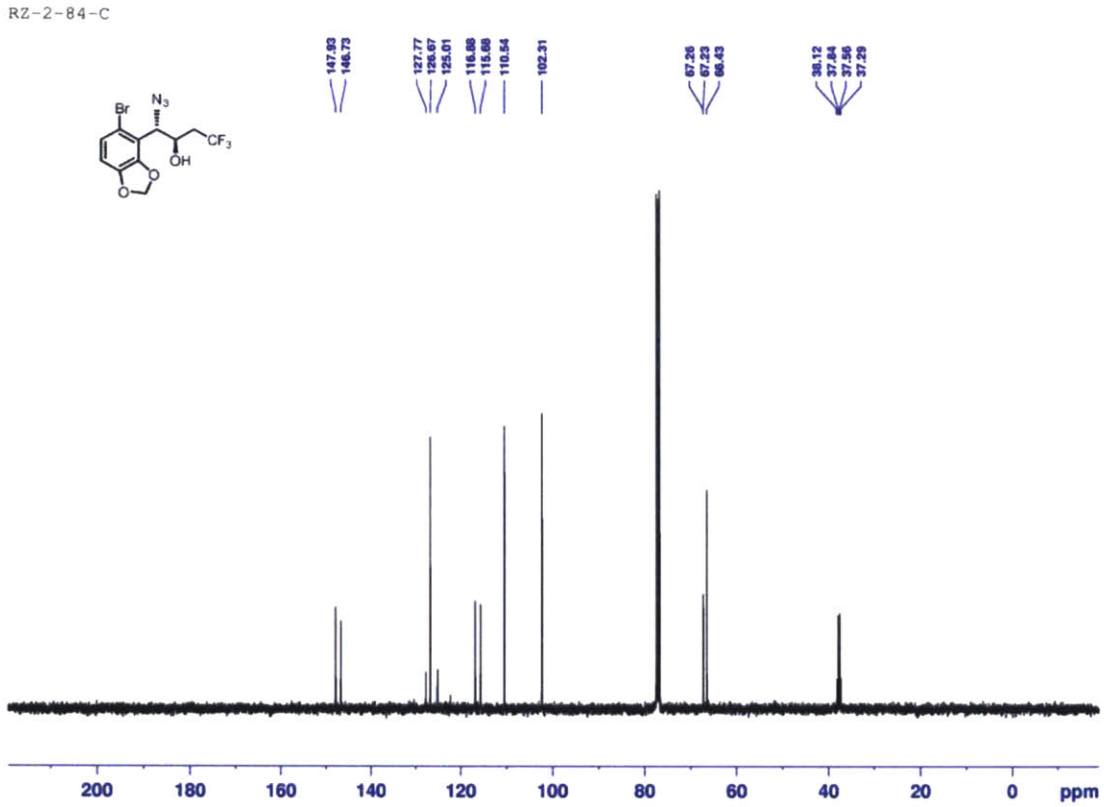
RZ-2-84-H

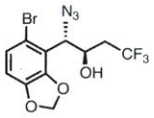
5 ^{1}H NMR (400 MHz, $CDCl_3$)



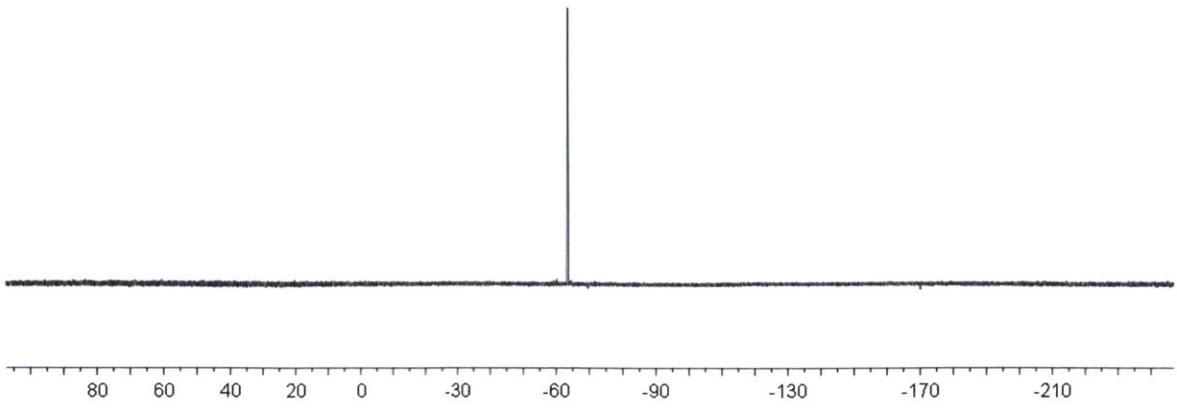


5 ^{13}C NMR (100 MHz, $CDCl_3$)



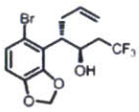


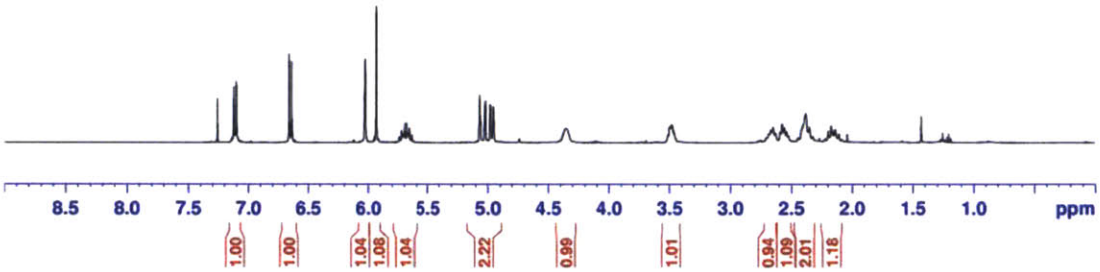
5 ^{19}F NMR (282 MHz, $CDCl_3$)



RZ-2-95A-H

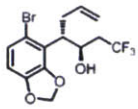
6 ^{1}H NMR (400 MHz, $CDCl_3$)



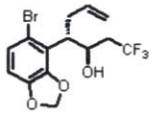


RZ-2-95A-C

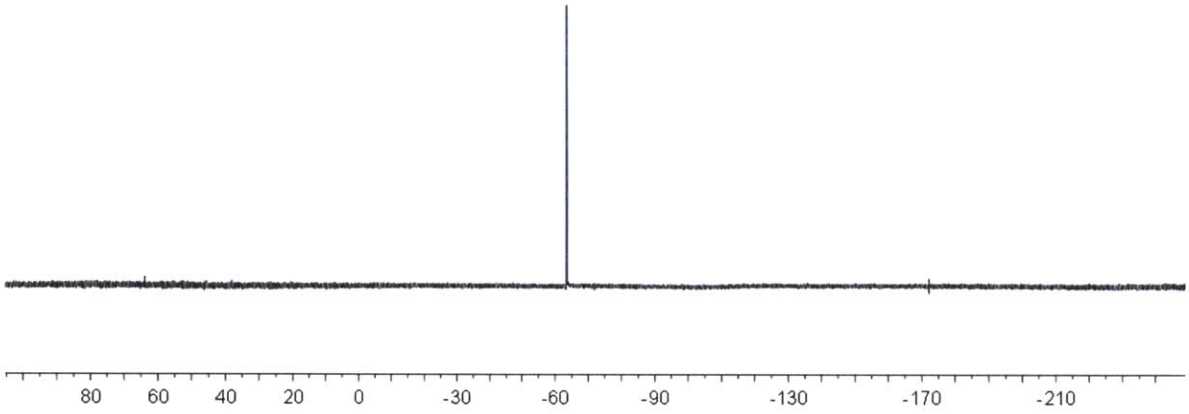
6 ^{13}C NMR (100 MHz, $CDCl_3$)



RZ-2-95A-F

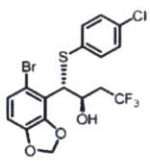


6 ^{19}F NMR (282 MHz, $CDCl_3$)

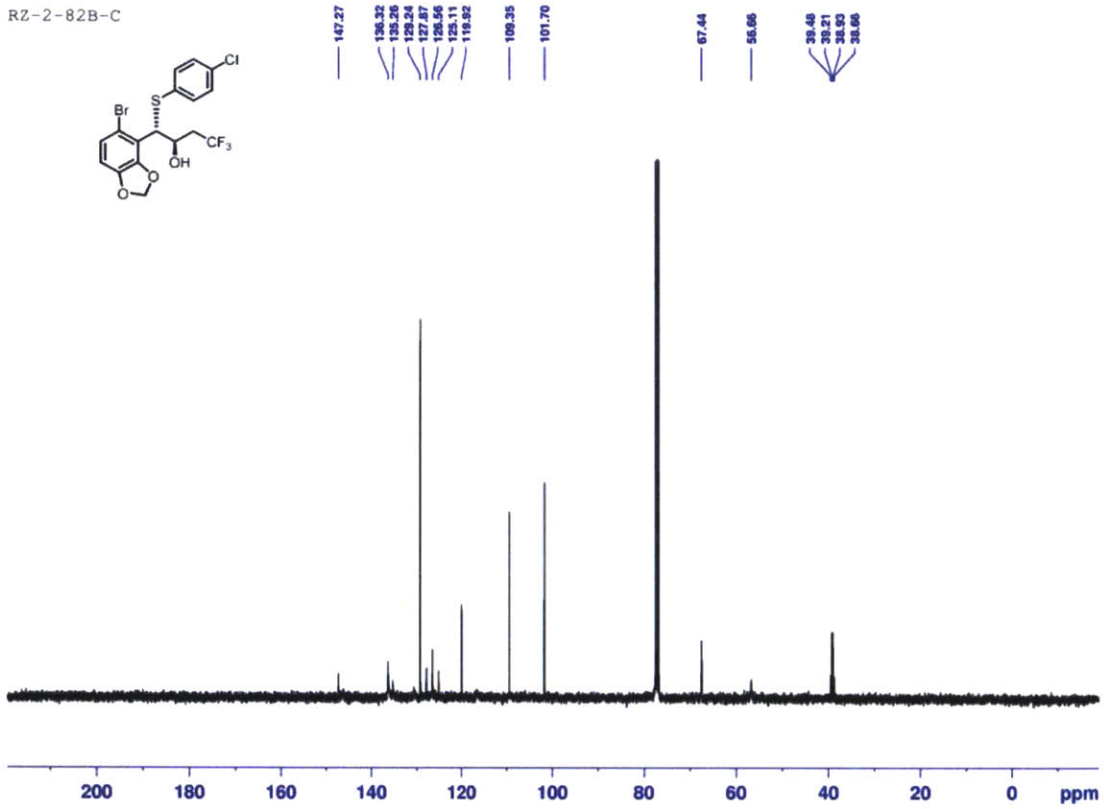


RZ-2-82B-H

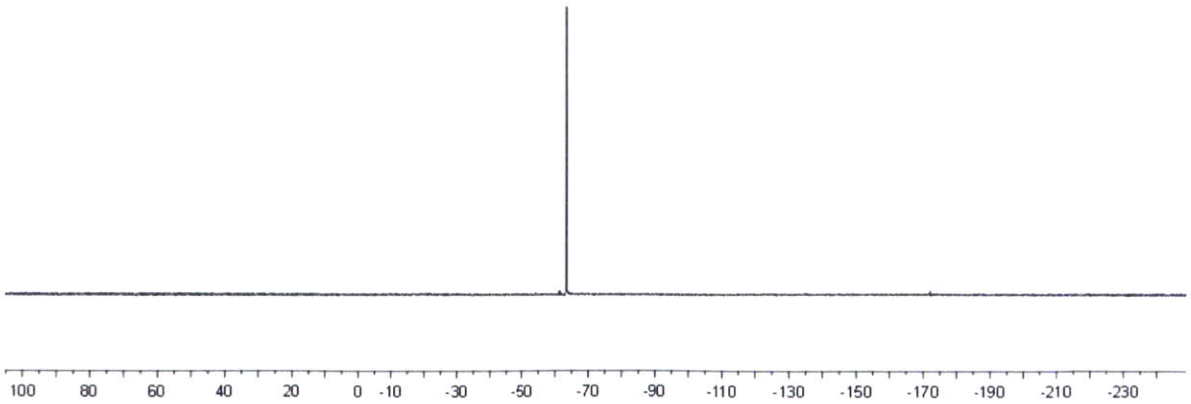
7 ^{1}H NMR (400 MHz, $CDCl_3$)



7 ^{13}C NMR (100 MHz, $CDCl_3$)

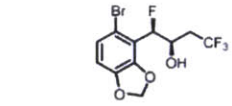


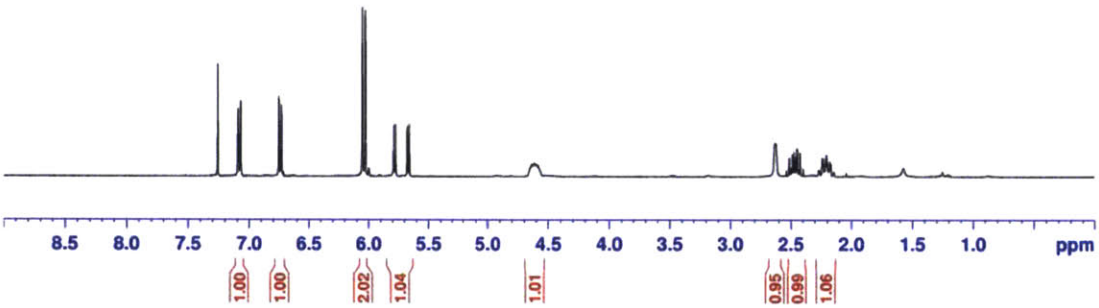
7 ^{19}F NMR (282 MHz, $CDCl_3$)



RZ-2-92-H

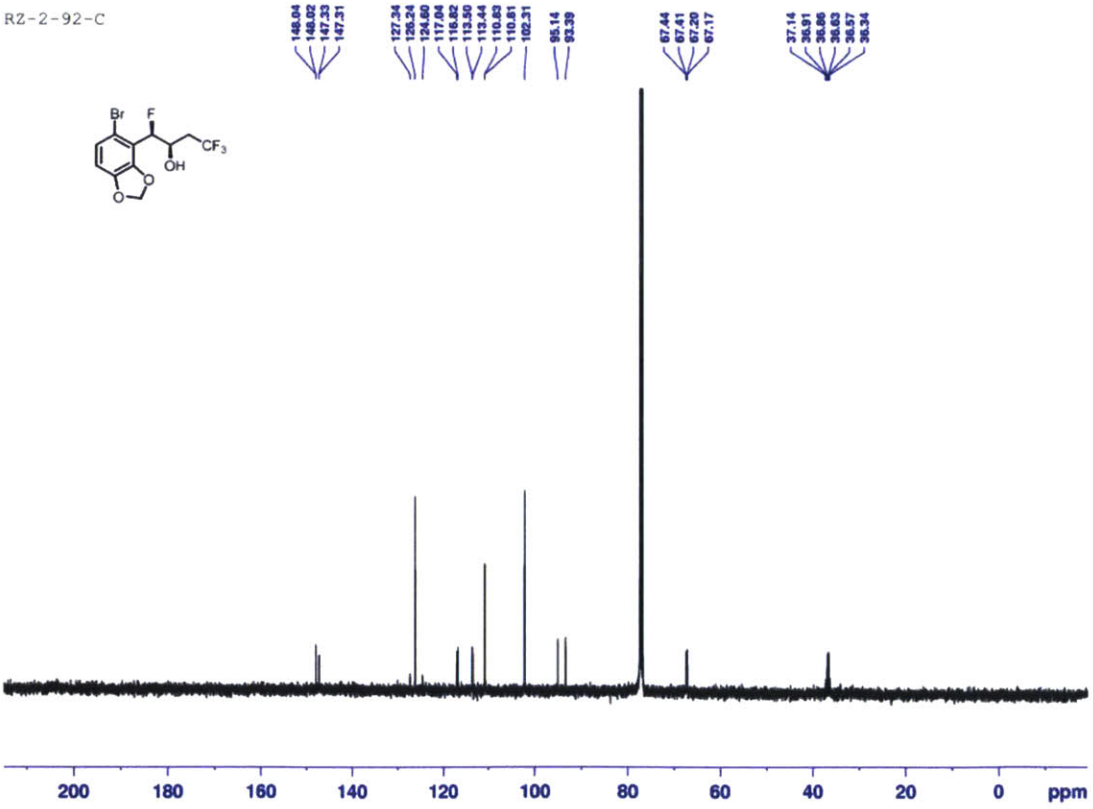
8 ^{1}H NMR (400 MHz, $CDCl_3$)



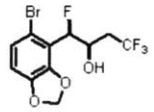


8 ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-2-92-C



RZ-2-92-F



8 ^{19}F NMR (282 MHz, $CDCl_3$)

Chapter 2.

Cu-Catalyzed Enantioselective Alkene Oxytrifluoromethylation:
Discovery of a Cu-Mediated Enantioselective C–O Bond Forming Process
via a Radical Intermediate.

2.1 Introduction

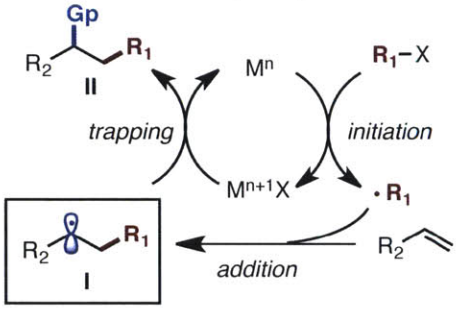
Transition metal-catalyzed alkene difunctionalization represents a versatile and step-economical strategy for the enhancement of molecular complexity, as it accesses multiple carbon–carbon/carbon–heteroatom bonds and stereogenic centers in a single step from simple precursors.[1,2] One of the most synthetically important transformations of this class is the radical addition of alkenes catalyzed by a transition metal redox system.[3] In a typical catalytic cycle (Scheme 1a), a metal-generated radical adds across the alkene to give nascent carbon radical intermediate **I**. Subsequent functionalization of **I** gives rise to **II** while regenerating the metal catalyst. Depending on the nature of the functional group used for trapping, a C–X (X = halogen), C–O, C–N or C–C bond can be incorporated.[4] In contrast to numerous reports on reactions that afford racemic products, catalyst-controlled enantioselective functionalizations of **I**, interesting and potentially useful processes, have been rarely explored. The only disclosure is by Sonoda and Kamigata who reported the use of chiral rhodium and ruthenium complexes as catalysts for the atom transfer radical addition involving carbon–halogen bond formation affording products with 16% ee and 10-40% ee, respectively.[5] Our interest in developing a transition metal-catalyzed asymmetric radical addition reaction via the enantioselective trapping of **I** originated from our recent study on the copper-catalyzed ligand-assisted oxytrifluoromethylation of alkenes.[6] This method provides efficient access to a variety of CF_3-containing building blocks such as lactones, cyclic ethers and epoxides. A redox radical addition mechanism was proposed for this transformation, in which a C–O bond was formed via the copper-mediated trapping of an α-CF_3-alkyl radical species **III** derived from the addition of CF_3 radical (Scheme 1b).[7]

During the course of our study, the use of a bidentate pyridine-based ligand was found to facilitate the C–O bond formation step. This ligand effect prompted us to explore the possibility of achieving asymmetric catalysis in this system by means of enantioselectively trapping the putative intermediate **III**. This strategy represents a mechanistically unique approach to enantioselective C–O bond formation via a radical intermediate. Given the wide range of difunctionalization reactions such radical intermediates can participate in and the lack of methods for exploiting their reactivity in enantioselective transformations, we believed that the study of this transformation could have a significant impact in the broader context of transition metal redox catalysis.

In this report, we disclose the realization of this strategy in the copper-catalyzed enantioselective oxytrifluoromethylation of alkenes. Mechanistic investigations are consistent with a metal-catalyzed redox radical addition mechanism, featuring the enantioselective functionalization of an alkyl radical intermediate.

Scheme 1. *Background of the methodology development.*

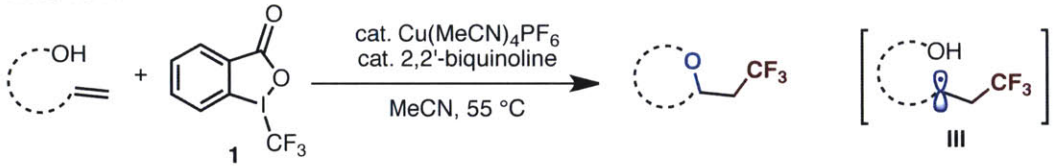
(a) Radical addition catalyzed by a transition metal redox system



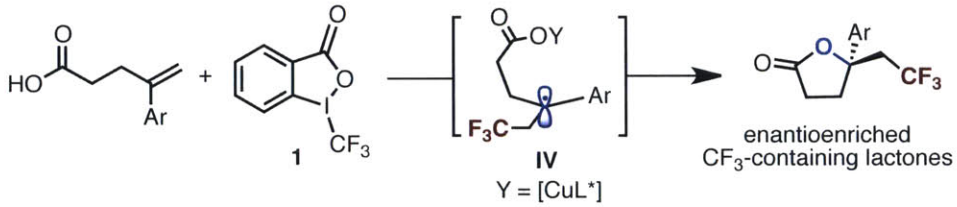
- broad scope
- versatility
- simple starting material
- valuable products

enantioselective transformation: rarely explored

(b) Previous work:



(c) This work: enantioselective radical addition catalyzed by a Cu(I) redox system - oxytrifluoromethylation

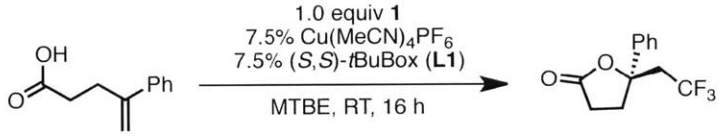


2.2 Results and Discussion

We began our study by examining the reaction of 4-phenyl-4-pentenoic acid (**2a**) with Togni's reagent (**1**)[8] in the presence of a catalytic amount of $Cu(MeCN)_4PF_6$ combined with a series of chiral ligands. The combination of $Cu(MeCN)_4PF_6$ and (*S,S*)-*t*BuBox (**L1**) in methyl *tert*-butyl ether (MTBE) at room temperature furnished the oxytrifluoromethylation product **3a** in 85% yield and 81% ee (Table 1, entry 1). The enantioselectivity showed a significant dependence on the solvent, following the trend: ethereal solvents > ethyl acetate > chloroalkane

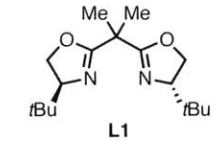
solvents > alcohol solvents > acetonitrile (entries 4-7). Next, the use of a cationic copper(I) precatalyst was found necessary for the desired reaction to take place. Copper(I) iodide was incapable of catalyzing the desired transformation, while the use of copper(I) chloride provided a substantial amount of **3a** with slight selectivity for the opposite enantiomer (entries 8 and 9).[9] The reaction could not be catalyzed by a cationic copper(II) salt (entry 10).[10] In addition, two Lewis acids were tested and **3a** was detected in neither of these cases (entries 11 and 12). This suggested the activation of **1** as an electrophile by means of Lewis acid coordination is not likely involved in the productive pathway.[11]

Table 1. *Effect of reaction parameters.*

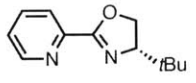


2a standard conditions **3a**

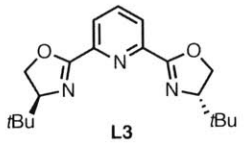
Entry	change from standard conditions	Yield [%][a]	ee [%][b]
1	none	85	81
2	**L2** instead of **L1**	< 2	n.d.
3	**L3** instead of **L1**	< 2	n.d.
4	EtOAc instead of MTBE	82	71
5	CH_2Cl_2 instead of MTBE	84	62
6	MeOH instead of MTBE	57	36
7	MeCN instead of MTBE	80	4
8[c]	CuI instead of $Cu(MeCN)_4PF_6$	< 2	n.d.
9	CuCl instead of $Cu(MeCN)_4PF_6$	66	-21
10	$Cu(OTf)_2$ instead of $Cu(MeCN)_4PF_6$	< 2	n.d.
11	$Zn(OTf)_2$ instead of $Cu(MeCN)_4PF_6$	< 2	n.d.
12	$Sc(OTf)_3$ instead of $Cu(MeCN)_4PF_6$	< 2	n.d.



L1



L2



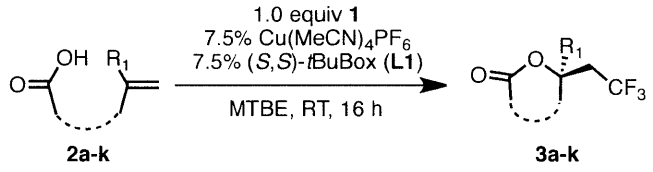
L3

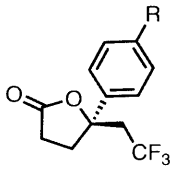
[a] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [b] Determined by HPLC analysis using a chiral stationary phase.

We next explored the scope of the transformation and representative examples are shown in table 2. An array of unsaturated carboxylic acids bearing different aryl groups were found to undergo the desired transformation to give the corresponding trifluoromethylated lactones in good yields and useful enantiomeric excesses. The mild conditions were compatible with a number of functional groups including aryl halides (table 2, **3b-d**) and ketones (**3f**). An

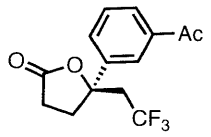
electron-deficient aryl substituent (**3e**) and a 3-thiophenyl substituent (**3h**) on the alkene were also tolerated. The incorporation of a geminal dimethyl group showed little effect on the yield or enantiomeric excess realized (**3i** and **3k**). Incomplete conversion of the starting material and a diminished yield of product was observed when the sterically demanding 1-naphthyl substituent was present, even though a good level of enantiomeric excess was still observed (**3g**). It was found that both γ- and δ-lactones (**3j** and **3k**) were accessible under the standard conditions.[12]

Table 2. *Cu-Catalyzed enantioselective oxytrifluoromethylation.*[a]

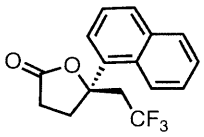




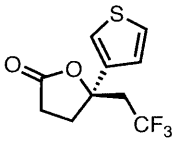
		Yield %	ee %
3a	R = H	88	82
3b	R = Br	78	83
3c	R = Cl	81	81
3d	R = F	80	75
3e	R = CF_3	74	81



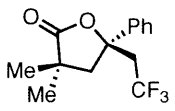
3f
78% yield, 83% ee
(70% yield, 98% ee[b])



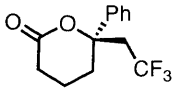
3g
44% yield, 81% ee



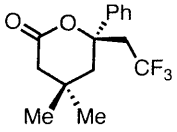
3h
87% yield, 74% ee



3i
70% yield, 80% ee



3j
85% yield, 81% ee



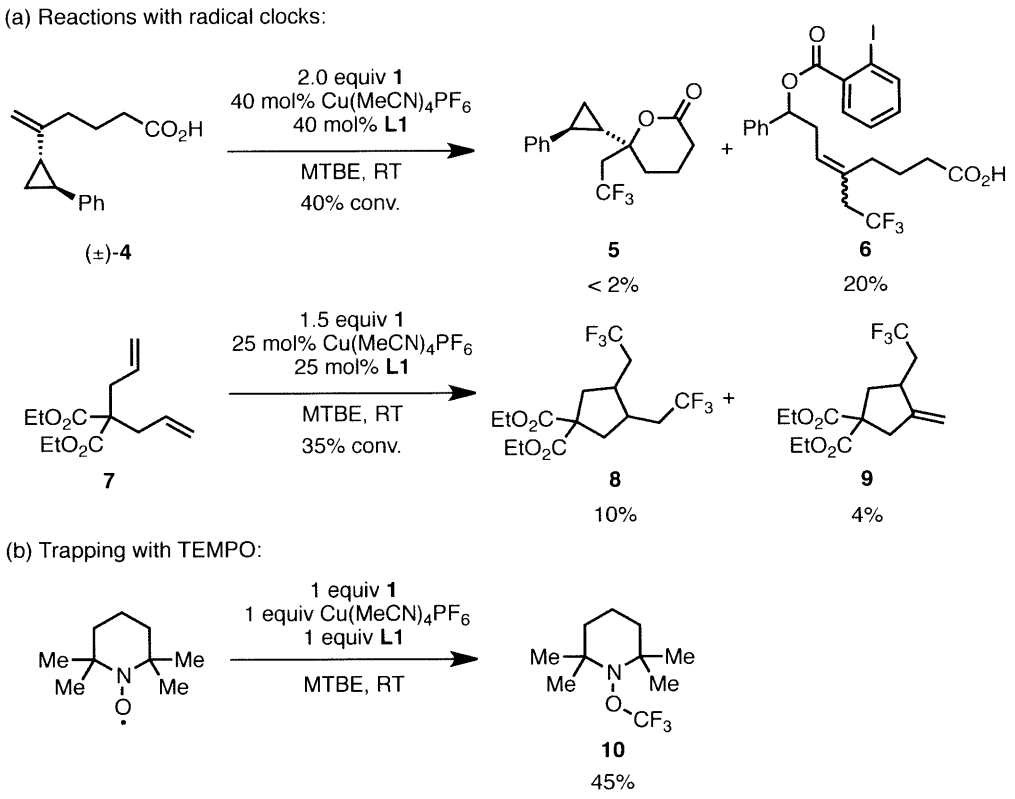
3k
85% yield, 83% ee

[a] Reaction conditions: $Cu(MeCN)_4PF_6$ (7.5 mol %), **L1** (7.5 mol %), **1** (1.0 equiv), **2** (0.50 mmol, 1.0 equiv) in 10 mL MTBE at 25 °C for 16 h. Isolated yields, average of two runs. Enantiomeric excesses were determined by chiral HPLC analysis. [b] The product crystallized from the crude reaction mixture after work-up. For details see the supporting information.

A series of experiments was performed to test our mechanistic hypothesis (Scheme 2a). When cyclopropane radical clock **4** was treated with **1** in the presence of the catalyst system, the oxytrifluoromethylation product **5** was not detected. Instead, a complex mixture of CF_3-containing products resulting from cyclopropane ring opening was observed, the largest component of which was identified to be **6**. Further, the use of diallyl malonate **7** as substrate

provided two 5-*exo*-cyclization products, **8** and **9**.[13] These observations are consistent with a mechanism involving an α-CF_3-alkyl radical intermediate **IV** (Scheme 1c). Next, the reaction between **1** and a radical scavenger TEMPO ((2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) in the presence of the catalyst system afforded the trifluoromethyl-trapping adduct **10** in 45% yield (Scheme 2b).[14]

Scheme 2. *(a) Radical clock experiments. (b) TEMPO trapping experiment.*

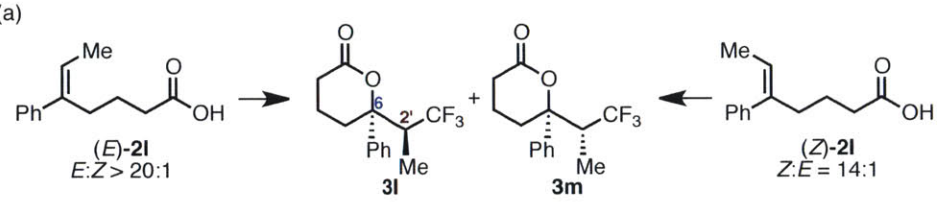


A study of the reaction of trisubstituted alkene substrates provided further insight into the reaction mechanism. As shown in Scheme 3a, both geometric isomers of 5-phenyl-5-heptenoic acid (**2l**) were synthesized and subjected to the standard reaction conditions respectively. It was found that, regardless of the alkene geometry of the substrate, almost the same product diastereomeric ratio (**3l** : **3m** = 1:1.7), and same enantiomeric excess for each diastereomer (92-93% ee for **3l**, 58-59% ee for **3m**) were obtained. This observation excluded a Wacker-like oxycupration mechanism for the C–O bond formation process.[15] Next, from these results we

were able to calculate the ratio of the four stereoisomers **3l** : *ent*-**3l** : **3m** : *ent*-**3m** to be 36:1:50:13. In terms of the CF_3-bearing stereogenic center (C2'), the ratio between the products with a 2'*R* configuration (**3m** and *ent*-**3l**) and those with a 2'*S* configuration (**3l** and *ent*-**3m**) was essentially 1:1. This observation indicated a stepwise mechanism consist of (1) a non-stereoselective C–CF_3 bond-forming step and (2) a diastereoselective C–O bond-forming step, which explains the stereoisomer ratio obtained as illustrated below.

Scheme 3. *(a) Trisubstituted alkenes as mechanistic probes.* [a] *(b) Rationale for the product distribution observed.*

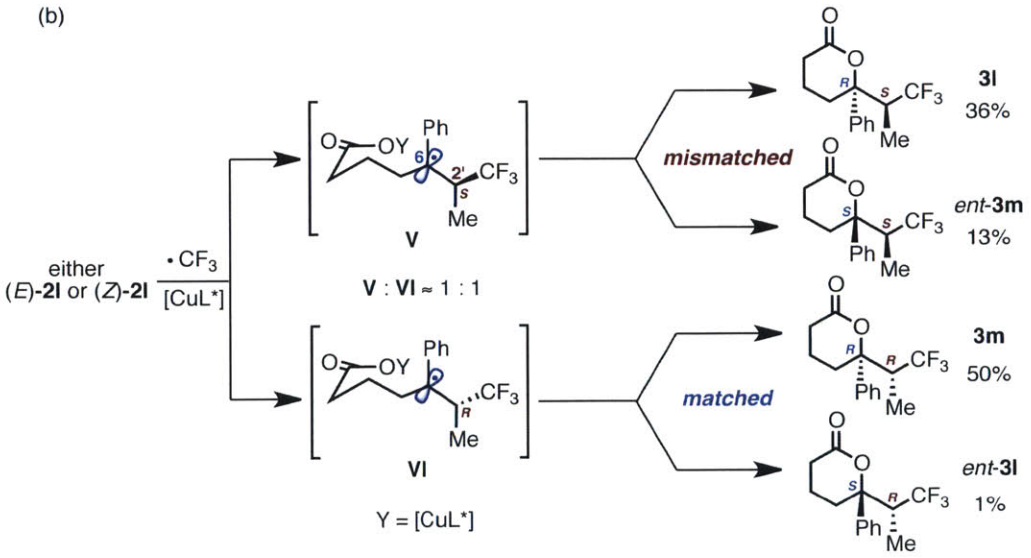
(a)



substrate	3l yield [%][b]	3l ee [%][c]	3m yield [%][b]	3m ee [%][c]	d.r.[b]	ratio of stereoisomers 3l : *ent*-3l : 3m : *ent*-3m
(*E*)-**2l**	28	93	47	58	1 : 1.7	36.3 : 1.3 : 49.3 : 13.1
(*Z*)-**2l**	24	92	40	59	1 : 1.7	35.7 : 1.5 : 49.8 : 13.0

[a] Reaction conidtions: 1.2 equiv **1**, 10 mol% $Cu(MeCN)_4PF_6$, 10 mol% **L1,** MTBE, RT, 22 h. [b] Determined by ^{19}F NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis.

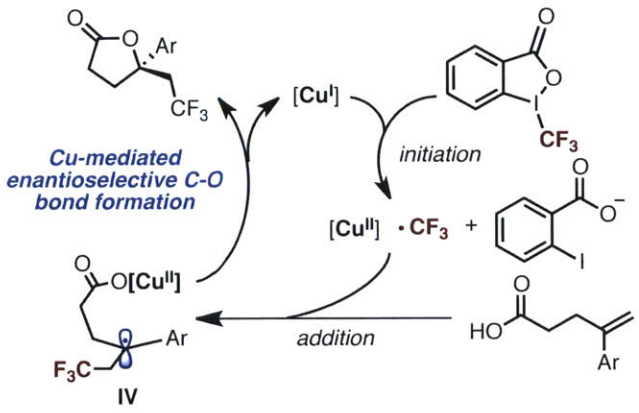
(b)



As shown in Scheme 3b, in the first radical addition step, either (*E*)- or (*Z*)-**2l** reacts with a trifluoromethyl radical to form a C–CF_3 bond in a non-stereoselective fashion, furnishing a pair of enantiomeric α-CF_3-alkyl radicals **V** and **VI** in a ratio close to 1:1. In the C–O bond-forming step, both the copper catalyst system and the already established stereogenic center at the 2' position come into play, providing matched/mismatched scenarios. For **V**, the catalyst-controlled selectivity (6*R* over 6*S*) contradicts the substrate-controlled selectivity (6*S*, 2'*S* over 6*R*, 2'*S*), therefore affording a diminished selectivity (36:13) for the catalyst-controlled product **3l**. For its enantiomer **VI**, the catalyst-controlled selectivity (6*R* over 6*S*) is reinforced by the substrate-controlled selectivity (6*R*, 2'*R* over 6*S*, 2'*R*), leading to an enhanced selectivity (50:1) for **3m**.

A catalytic cycle consistent with the mechanistic study discussed above is proposed (Scheme 4). A single-electron-transfer between **1** and the Cu(I) catalyst generates a CF_3 radical and a Cu(II) complex. The CF_3 radical then adds across the alkene to give **IV**, which undergoes enantioselective C–O bond formation mediated by the Cu(II) species, affording the lactone product while regenerating the Cu(I) catalyst.[16]

Scheme 4. *Mechanistic proposal.*



2.3 Conclusion

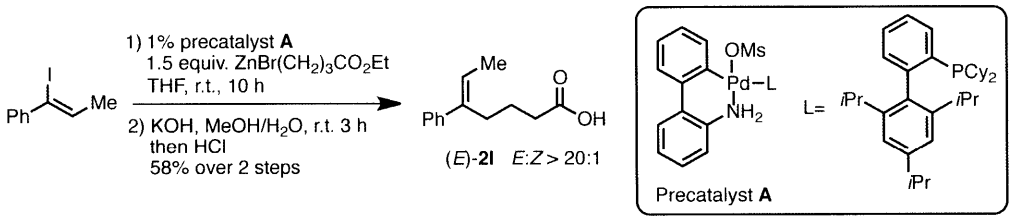
In conclusion, we have developed a simple and mild method for the efficient enantioselective oxytrifluoromethylation of alkenes using a copper-based catalyst system. This method delivers a set of enantioenriched CF_3-containing lactones with good functional group compatibility. Evidence was found in support of a redox radical addition mechanism, in which a C–O bond is enantioselectively formed via a carbon radical intermediate. This method provides

a novel approach to enantioselective C–O bond formation that can potentially be applied to a range of transition metal-catalyzed radical difunctionalization reactions. We are continuing work to expand the scope of this copper-catalyzed enantioselective difunctionalization strategy.

2.4 Experimental

General considerations. All reactions were carried out with dry solvents under anhydrous conditions, unless otherwise noted. Anhydrous methyl *tert*-butyl ether (MTBE) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (99%) were purchased from Aldrich and used as received. Tetrakis(acetonitrile)copper(I) hexafluorophosphate was purchased from Strem and stored in a dry box. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. All chemicals were weighed on the bench top, in the air. 1-Trifluoromethyl-1,2-benziodoxol-3-(*1H*)-one (Togni trifluoromethylating reagent, **1**) was prepared according to the literature procedure.[13] Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All yields of the copper-catalyzed asymmetric oxytrifluoromethylation reactions stated are the average of at least two experiments. Reactions were monitored by ^{19}F NMR spectroscopy and thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as a visualizing agent and phosphomolybdic acid in ethanol or iodine on silica gel as developing agents. Flash silica gel chromatography was performed using Silicycle SiliaFlashP60 (230-400 mesh) silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer and were calibrated using residual solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). ^{19}F NMR spectra were recorded on a Varian 300 MHz spectrometer or a Bruker AMX 400 spectrometer and were calibrated using $CFCl_3$ as an external reference (0 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, at = apparent triplet, ad = apparent doublet. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer (iD5 ATR). HPLC analyses were performed on an Angilent 1100 series system with Daicel Chiralcel® columns (4.6 mm x 250 mm) in hexanes/*i*-PrOH mixtures. Melting points (m.p.) were obtained on a Mel-Temp capillary melting point apparatus. Optical rotations were measured on Jacsco P-1010 polarimeter with a sodium lamp(589 nm) at 24 °C. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

Synthesis and characterization of non-commercial substrates. 4-Phenylpent-4-enoic acid (**2a**),[17] 4-(4-chlorophenyl)pent-4-enoic acid (**2c**),[17] 4-(4-fluorophenyl)pent-4-enoic acid (**2d**),[17] 4-(4-trifuorophenyl)pent-4-enoic acid (**2e**),[17] 4-(1-naphthalenyl)pent-4-enoic acid (**2g**),[18] 5-phenylhex-5-enoic acid (**2j**),[18] 3,3-dimethyl-5-phenylhex-5-enoic acid (**2k**),[18] 4-(4-bromophenyl)pent-4-enoic acid (**2b**),[19] 2,2-dimethyl-4-phenylpent-4-enoic acid (**2i**),[20] 4-(3-thienyl)pent-4-enoic acid (**2h**),[21] 4-(3-acetylphenyl)pent-4-enoic acid (**2f**),[22] (*Z*)-5-phenylhept-5-enoic acid ((*Z*)-**2l**, *Z*:*E* = 14:1 as determined by ^{1}H NMR analysis),[23] were prepared according to literature procedures.



Synthesis of (*E*)-5-phenylhept-5-enoic acid ((*E*)-2l): An oven-dried 20 × 150 mL re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with precatalyst **A** (7 mg, 0.008 mmol, 0.01 equiv). The tube was then sealed with a Teflon screw-cap septum and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). (*Z*)-(1-iodoprop-1-en-1-yl)benzene (0.8 mmol, 195 mg, *Z*:*E* > 20:1)[24] was added to the tube followed by anhydrous THF (1 mL) via syringe. The zinc reagent[25] (1 M in THF, 1.2 mL, 1.5 equiv) was then added to the resulting mixture via syringe dropwise at room temperature to afford a light yellow solution. After stirred at room temperature for 10 h the mixture was diluted with ethyl ether (4 mL) and saturated aqueous ammonium chloride solution (4 mL). The aqueous layer was separated and extracted with ethyl ether (4 mL×3), and the combined organic layers were concentrated *in vacuo*. The residue was dissolved in methanol (3 mL) and treated with aqueous potassium hydroxide solution (1 M, 3 mL, 3.8 equiv). After stirred at room temperature for 3 h, methanol was removed *in vacuo*. The aqueous residue was washed with hexanes (5 mL) and ethyl ether (5 mL) and then acidified (pH < 2). The resulting mixture was extracted with ethyl ether (5 mL×3), and the combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:10 to 1:5) to afford (*E*)-5-phenylhept-5-enoic acid ((*E*)-**2l**, *E*:*Z* > 20:1) as a colorless oil (94 mg, 58% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) *E*:*Z* > 20:1. δ 7.34-7.21 (m, 5 H), 5.81 (q, *J* =6.8 Hz, 1 H), 2.59 (t, *J* =7.6 Hz, 2 H), 2.35 (t, *J* =7.6 Hz, 2 H), 1.80 (d, *J* =6.8 Hz, 3 H), 1.72 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 142.9, 139.8, 128.4, 126.8, 126.4, 124.1, 33.5, 28.5, 23.3, 14.3; IR (film) ν_{max} 2931, 1703, 1409, 1237, 933, 754, 575 cm^{-1}; R_f (hexanes: ethyl acetate = 2:1)= 0.4; Anal. Calcd. For $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.70; H, 7.73.

General Procedure and Characterization for the Copper-Catalyzed Enantioselective Oxytrifluoromethylation of Alkenes

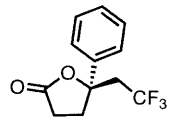
General Procedure A: Effect of Reaction Parameters (Table 1)

Standard conditions: An oven-dried 13×100 mm Fisher Scientific re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (2.8 mg, 0.0075 mmol, 0.075 equiv), 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**L1**, 2.2 mg, 0.0075 mmol, 0.075 equiv), 1-trifluoromethyl-1,2-benziodoxol-3-(*1H*)-one **1** (Togni's reagent, 31.6 mg, 0.1 mmol, 1.0 equiv) and 4-phenyl-4-pentenoic acid (**2a**) (17.6 mg, 0.1 mmol, 1.0 equiv). The tube was then sealed with a septum screw-cap (Thermo Scientific ASM PHN CAP w/PTFE/SIL, cat. #03388316) and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). Anhydrous methyl *tert*-butyl ether (0.5 mL) was added to the tube via syringe. The reaction mixture was stirred at room temperature (25 °C) for 16 h. α, α, α-Trifluorotoluene (internal standard, 12.2 mL, 1 equiv) was added to the reaction mixture via syringe. The crude reaction mixture was then analyzed by ^{19}F NMR spectroscopy. The reaction mixture was then washed with saturated aqueous sodium bicarbonate solution (2 mL). The aqueous layer was separated and extracted with diethyl ether (4 mL × 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by thin-layer chromatography to afford the oxytrifluoromethylation product **3a** which was then analyzed by chiral HPLC (Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 97:3).

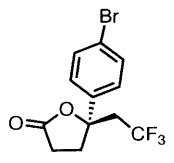
General Procedure B: Substrate Scope (Table 2)

An oven-dried 20 × 150 mm Fisher Scientific re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (14 mg, 0.0375 mmol, 0.075 equiv), 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**L1**, 11

mg, 0.0375 mmol, 0.075 equiv), **1** (158 mg, 0.50 mmol, 1.0 equiv) and unsaturated carboxylic acid (0.50 mmol, 1.0 equiv). The reaction tube was sealed with a septum screw-cap (10/90, Teflon/SIL, National Scientific) and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). Anhydrous methyl *tert*-butyl ether (10 mL) was added to the tube via syringe to afford a blue mixture. The argon pressure was removed and the reaction mixture was stirred at room temperature (25 °C) for 16 h.[26] The reaction mixture was then washed with saturated aqueous sodium bicarbonate solution (12 mL). The aqueous layer was separated and extracted with diethyl ether (4 mL×3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes or Et_2O/hexanes (for compounds that have similar or greater polarity than the chiral ligand recovered), using UV light as a visualizing agent and phosphomolybdic acid in ethanol or iodine on silica gel as developing agents) to afford the oxytrifluoromethylation product.



(*R*)-5-phenyl-5-(2,2,2-trifluoroethyl)dihydrofuran-2(3*H*)-one (3a) Following general procedure B, the title compound was synthesized from 4-phenyl-4-pentenoic acid (**2a**) (88.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 8:1 to 3.5:1) to afford **3a** (105.0 mg, 86% yield, 81% ee) as a pale yellow sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.32 (m, 5 H), 2.87 (dq, J =15.6 Hz, 10.4 Hz, 1 H), 2.80 (dq, J =15.6 Hz, 10.4 Hz, 1 H), 2.67-2.57 (m, 3 H), 2.44 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 141.1, 128.9, 128.5, 124.7, 124.7 (q, J_{CF} = 277 Hz), 84.3 (q, J_{CF} = 2 Hz), 45.2 (q, J_{CF} = 27 Hz), 34.3, 28.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.0 (at, J = 10.4 Hz); IR (film) ν_{max} 1775, 1382, 1248, 1198, 1122, 1077, 1046, 929 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1)= 0.40; Anal. Calcd. For $C_{12}H_{11}F_3O_2$: C, 59.02; H, 4.54. Found: C, 58.74; H, 4.66. $[\alpha]_D^{24}$ = -53.0 (c= 1, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 97:3, 0.8 mL/min, 210 nm, t_R = 26.3 min (major) and 32.2 min (minor).



(*R*)-5-(4-bromophenyl)-5-(2,2,2-trifluoroethyl)dihydrofuran-2(3*H*)-one (3b) Following general procedure B, the title compound was synthesized from 4-(4-bromophenyl)pent-4-enoic acid (**2b**) (127 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: diethyl ether = 3:1

to 1:2.5 to 1:3) to afford **3b** (124.2 mg, 77% yield, 83% ee) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* =8.8 Hz, 2 H), 7.28 (d, *J* =8.8 Hz, 2 H), 2.88-2.75 (m, 2 H), 2.67-2.56 (m, 3 H), 2.50-2.41 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 140.2, 132.1, 126.6, 124.5 (q, J_{CF} = 277 Hz), 122.8, 83.9, 45.2 (q, J_{CF} = 27 Hz), 34.4, 27.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.9 (at, *J* = 10.2 Hz); IR (film) ν_{max} 1786, 1486, 1377, 1259, 1180, 1106, 1046, 1009, 922 cm^{-1}; R_f(hexanes: ethyl acetate = 1.5:1)= 0.5; Anal. Calcd. For $C_{12}H_{10}BrF_3O_2$: C, 44.61; H, 3.12. Found: C, 44.77; H, 3.02. m. p. 48-49 °C. $[\alpha]_D^{24}$ = -36.9 (c= 0.6, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 97:3, 0.8 mL/min, 230 nm, t_R = 30.7 min (major) and 38.2 min (minor).

The absolute configuration of **3b** was determined by X-ray crystallography. The absolute configurations of **3a** and **3c**-**m** were assigned by analogy.

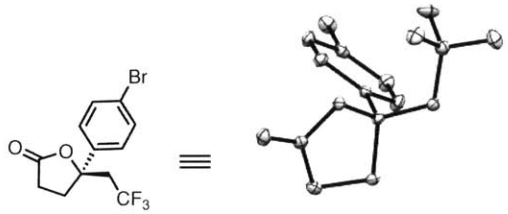
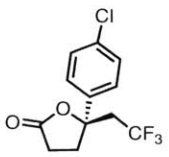
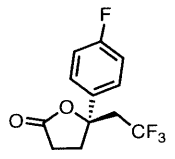


Figure 1. ORTEP representation of **3b**. (thermal ellipsoids shown at 50% probability. Hydrogen atoms are omitted for clarity.)

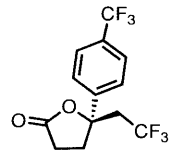


(*R*)-5-(4-chlorophenyl)-5-(2,2,2-trifluoroethyl)dihydrofuran-2(3*H*)-one (3c)

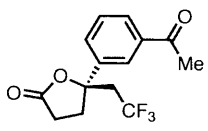
Following general procedure B, the title compound was synthesized from 4-(4-chlorophenyl)pent-4-enoic acid (**2c**) (105 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: diethyl ether = 3:1 to 1:2.5 to 1:3) to afford **3c** (114.6 mg, 82% yield, 82% ee) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* =8.8 Hz, 2 H), 7.33 (d, *J* =8.8 Hz, 2 H), 2.88-2.75 (m, 2 H), 2.67-2.57 (m, 3 H), 2.50-2.41 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 139.6, 134.7, 129.1, 126.3, 124.6 (q, J_{CF} = 277 Hz), 83.9, 45.3 (q, J_{CF} = 27 Hz), 34.4, 28.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -61.0 (at, *J* = 10.3 Hz); IR (film) ν_{max} 1767, 1492, 1393, 1262, 1247, 1118, 1047, 924 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1)= 0.25; Anal. Calcd. For $C_{12}H_{10}ClF_3O_2$: C, 51.72; H, 3.62. Found: C, 51.59; H, 3.72. m. p. 59-60 °C. $[\alpha]_D^{24}$ = -37.6 (c= 0.5, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 97:3, 0.8 mL/min, 230 nm, t_R = 30.2 min (major) and 37.1 min (minor).



(*R*)-5-(4-fluorophenyl)-5-(2,2,2-trifluoroethyl)dihydrofuran-2(3*H*)-one (3d) Following general procedure B, the title compound was synthesized from 4-(4-fluorophenyl)pent-4-enoic acid (**2d**) (97 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: diethyl ether = 3:1 to 1:2.5) to afford **3d** (102.9 mg, 79% yield, 75% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 2 H), 7.08 (m, 2 H), 2.87-2.75 (m, 2 H), 2.69-2.58 (m, 3 H), 2.47-2.40 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 162.6 (d, J_{CF} = 246 Hz), 136.8, 126.8 (d, J_{CF} = 8 Hz), 124.6 (q, J_{CF} = 277 Hz), 115.9 (d, J_{CF} = 22 Hz), 84.0, 45.4 (q, J_{CF} = 27 Hz), 34.4, 28.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.0 (at, J = 10.2 Hz, 3 F), -113.9 (m, 1 F); IR (film) ν_{max} 1779, 1606, 1511, 1379, 1229, 1119, 1036, 925 cm^{-1}; R_f (hexanes: ethyl acetate = 2:1)= 0.33; Anal. Calcd. For $C_{12}H_{10}F_4O_2$: C, 54.97; H, 3.84. Found: C, 55.19; H, 4.16. $[\alpha]_D^{24}$ = -39.8 (c= 1, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 97:3, 0.8 mL/min, 210 nm, t_R = 27.2 min (major) and 32.5 min (minor).



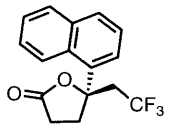
(*R*)-5-(4-trifluoromethylphenyl)-5-(2,2,2-trifluoroethyl)dihydrofuran-2(3*H*)-one (3e) Following slightly modified general procedure B in which the combined organic layers obtained from the extraction were briefly washed with 0.05 M aqueous sodium hydroxide solution (5 mL) to remove the unreacted substrate before concentrated *in vacuo*, the title compound was synthesized from 4-(4-trifluoromethyl phenyl)pent-4-enoic acid (**2e**) (122 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: diethyl ether = 3:1 to 1:4) to afford **3e** (112.9 mg, 72% yield, 81% ee) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J =8.4 Hz, 2 H), 7.54 (d, J =8.8 Hz, 2 H), 2.94-2.78 (m, 2 H), 2.73-2.58 (m, 3 H), 2.51-2.41 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 145.2, 131.0 (q, J_{CF} = 32 Hz), 126.1, 125.4, 124.5 (q, J_{CF} = 277 Hz), 123.8 (q, J_{CF} = 271 Hz), 83.8, 45.2 (q, J_{CF} = 28 Hz), 34.5, 27.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.0 (at, J = 10.2 Hz, 3 F), -63.3 (s, 3 F); IR (film) ν_{max} 1788, 1380, 1324, 1251, 1109, 1069, 926 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1)= 0.33; Anal. Calcd. For $C_{13}H_{10}F_6O_2$: C, 50.01; H, 3.23. Found: C, 50.23; H, 3.17. The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 97:3, 0.8 mL/min, 210 nm, t_R = 27.5 min (major) and 37.1 min (minor).



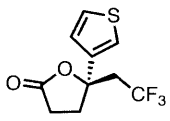
(*R*)-5-(3-acetylphenyl)-5-(2,2,2-trifluoroethyl)dihydrofuran-2(3*H*)-one (3f) Following general procedure B, the title compound was synthesized from 4-(3-acetylphenyl)pent-4-enoic acid (**2f**) (109 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: ethyl ether = 1:1 to 1:7) to afford **3f** (115.5 mg, 81%, 83% ee) as a pale yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 1 H), 7.91 (d, J =7.6 Hz, 1 H), 7.63 (d, J =8.0 Hz, 1 H), 7.50 (at, J =7.6 Hz, 1 H), 2.89 (m, 2 H), 2.71-2.61 (m, 3 H), 2.60 (s, 3 H), 2.44 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 175.0, 142.0, 137.6, 129.4, 129.33, 128.7, 124.6 (q, J_{CF} = 276 Hz), 124.3, 84.0 (q, J_{CF} = 2 Hz), 45.2 (q, J_{CF} = 27 Hz), 34.5, 27.9, 26.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.9 (at, J = 10.2 Hz); IR (film) ν_{max} 1768, 1674, 1389, 1296, 1243, 1119, 1050, 929 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1)= 0.15; Anal. Calcd. For $C_{14}H_{13}F_3O_3$: C, 58.74; H, 4.58. Found: C, 58.70; H, 4.59. The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel IA 4.6 mm x 250 mm, hexanes:*i*-PrOH = 90:10, 0.8 mL/min, 210 nm, t_R = 16.3 min (minor) and 18.4 min (major).

Chromatography-free synthesis of **3f** : An oven-dried 20 × 150 mm Fisher Scientific re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (14 mg, 0.0375 mmol, 0.075 equiv), 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**L1**, 11 mg, 0.0375 mmol, 0.075 equiv), **1** (Togni's reagent, 158 mg, 0.50 mmol, 1.0 equiv) and **2f** (109 mg, 0.50 mmol). The reaction tube was sealed with a septum screw-cap (10/90, Teflon/SIL, National Scientific) and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). Anhydrous methyl *tert*-butyl ether (10 mL) was added to the tube via syringe to afford a blue mixture. The argon pressure was removed and the reaction mixture was stirred at room temperature (25 °C) for 16 h. The reaction mixture was then washed with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous layer was separated and extracted with diethyl ether (4 mL×3). The combined organic layers were dried over Na_2SO_4, filtered though a short plug of silica gel and concentrated *in vacuo* until *ca.* 1.5 mL solvent was left. Crystallization from this solution at -20 °C afforded **3f** (99.8 mg, 70%, 98% ee) as colorless needle-like crystals. m. p. 105-106 °C. $[\alpha]_D^{24}$ = -62.6 (c= 1, $CHCl_3$).

(*R*)-5-(1-Naphthalenyl)-5-(2,2,2-trifluoroethyl)dihydrofuran-2(3*H*)-one (2g) Following slightly modified general procedure B in which the combined organic layers obtained from the extraction

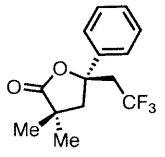


were briefly washed with 0.05 M aqueous sodium hydroxide solution (5 mL) to remove the unreacted substrate before concentrated *in vacuo*, the title compound was synthesized from 4-(1-napthalenyl)-4-pentenoic acid (**2g**) (113 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 6:1 to 4:1) to afford **3g** (67.5 mg, 46% yield, 81% ee) as a sticky colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.86 (m, 3 H), 7.78 (d, *J* =7.2 Hz, 1 H), 7.59 (td, *J* =6.8 Hz, 1.6 Hz, 1 H), 7.53 (td, *J* =6.8 Hz, 1.2 Hz),), 7.48 (d, *J* =8.0 Hz, 1 H), 3.25 (dq, *J* =16.0 Hz, 10.4 Hz, 1 H), 3.11 (dq, *J* =16.0 Hz, 10.4 Hz, 1 H), 3.06 (m, 1 H), 2.94 (m, 1 H), 2.73 (ddd, *J* =18.0 Hz, 10.0 Hz, 5.6 Hz, 1 H), 2.51 (ddd, *J* =18.0 Hz, 10.0 Hz, 8.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 137.0, 134.9, 130.2, 130.1, 128.6, 126.8, 125.8, 125.3, 125.2 (q, J_{CF} = 277 Hz), 123.7, 123.4, 85.0 (q, J_{CF} = 2 Hz), 43.9 (q, J_{CF} = 28 Hz), 32.9, 28.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.2 (at, *J* = 10.5 Hz); IR (film) ν_{max} 1779, 1376, 1260, 1193, 1121, 1058, 930 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1)= 0.42; The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel AD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 97:3, 0.8 mL/min, 210 nm, t_R = 12.8 min (minor) and 15.4 min (major).

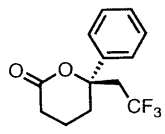


(*R*)-5-(3-thiophenyl)-5-(2,2,2-trifluoroethyl)dihydrofuran-2(3*H*)-one (3h) Following general procedure B, the title compound was synthesized from 4-(3-thiophenyl)pent-4-enoic acid (**2h**) (91 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 8:1 to 3.5:1) to afford **3h** (110.7 mg, 88%, 73% ee) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* =5.2 Hz, 3.2 Hz. 1 H), 7.28 (dd, *J* =3.2 Hz, 1.6 Hz. 1 H), 7.02 (dd, *J* =5.2 Hz, 1.6 Hz. 1 H), 2.83 (m, 2 H), 2.63-2.47 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 142.0, 127.5, 124.8, 124.6 (q, J_{CF} = 277 Hz), 123.2, 83.0 (q, J_{CF} = 2 Hz), 44.8 (q, J_{CF} = 27 Hz), 34.0, 28.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.2 (at, *J* = 10.3 Hz); IR (film) ν_{max} 1776, 1374, 1248, 1191, 1116, 1040, 924 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1)= 0.41; Anal. Calcd. For $C_{10}H_9F_3O_2S$: C, 48.00; H, 3.63. Found: C, 48.17; H, 3.77. $[\alpha]_D^{24}$ = -24.2 (c= 1, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 97:3, 0.8 mL/min, 230 nm, t_R = 32.6 min (major) and 40.4 min (minor).

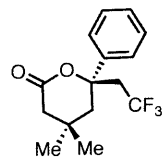
(*R*)-3,3-dimethyl-5-phenyl-5-(2,2,2-trifluoroethyl)dihydrofuran-2(3*H*)-one (3i) Following general procedure B, the title compound was synthesized from 2,2-dimethyl-4-phenylpent-4-enoic acid (**2i**) (102 mg, 0.50 mmol). The product was purified by silica gel flash column



chromatography (hexanes: ethyl acetate = 8:1 to 4:1) to afford **3i** (99.3 mg, 73% yield, 80% ee) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 4 H), 7.31 (m, 1 H), 2.82 (dq, *J* =15.6 Hz, 10.4 Hz, 1 H), 2.76 (dq, *J* =15.6 Hz, 10.4 Hz, 1 H), 2.67 (d, *J* =13.2 Hz, 1 H), 2.57 (d, *J* =13.2 Hz, 1 H), 1.32 (s, 1 H), 0.90 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 142.4, 128.9, 128.4, 124.8, 124.6 (q, J_{CF} = 277 Hz), 81.1, 48.6, 46.8 (q, J_{CF} = 27 Hz), 40.1, 26.4, 25.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.6 (at, *J* = 10.2 Hz); IR (film) ν_{max} 1766, 1379, 1261, 1236, 1131, 1091, 1035, 928 cm^{-1}; R_f(hexanes: ethyl acetate = 3:1)= 0.50; Anal. Calcd. For $C_{14}H_{15}F_3O_2$: C, 61.76; H, 5.55. Found: C, 61.60; H, 5.48. m. p. 61-62 °C. $[\alpha]_D^{24}$ = -19.7 (c= 1, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel IC 4.6 mm x 250 mm, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 210 nm, t_R = 29.1 min (major) and 22.9 min (minor).



(*R*)-6-phenyl-6-(2,2,2-trifluoroethyl)tetrahydro-2*H*-pyran-2-one (3j) Following general procedure B, the title compound was synthesized from 5-phenylhex-5-enoic acid (**2j**) (95 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 8:1 to 3.5:1) to afford **3j** (109.1 mg, 85% yield, 81% ee) as a colorless sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30(m, 5 H), 2.80-2.68 (m, 2 H), 2.51-2.35 (m, 3 H), 2.21 (m, 1 H), 1.82-1.74 (m, 1 H), 1.60-1.48 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 141.4, 129.1, 128.3, 125.0, 124.8 (q, J_{CF} = 277 Hz), 83.5, 46.8 (q, J_{CF} = 27 Hz), 31.2, 29.0, 16.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.3 (at, *J* = 10.3 Hz); IR (film) ν_{max} 1732, 1446, 1384, 1236, 1045, 912 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1) = 0.50; Anal. Calcd. For $C_{13}H_{13}F_3O_2$: C, 60.46; H, 5.07. Found: C, 60.23; H, 5.04. m. p. 61-62 °C. $[\alpha]_D^{24}$ = -20.8 (c= 1.3, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel AD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 97:3, 1.0 mL/min, 210 nm, t_R = 13.6 min (major) and 15.1 min (minor).

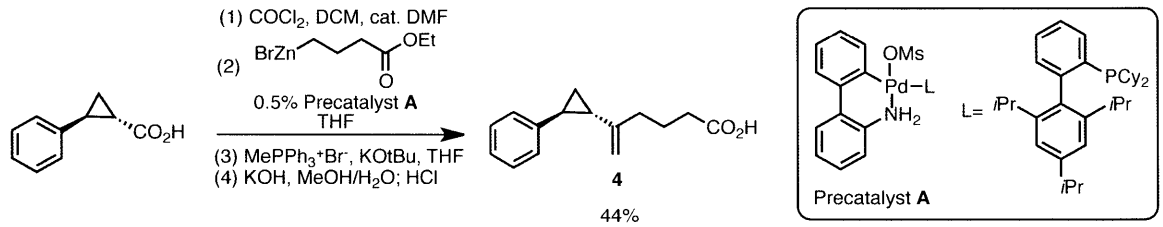


(*R*)-4,4-dimethyl-6-phenyl-6-(2,2,2-trifluoroethyl)tetrahydro-2*H*-pyran-2-one (3k) Following general procedure B, the title compound was synthesized from 3,3-dimethyl-5-phenylhex-5-enoic acid (**2k**) (109 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 8:1 to 5:1) to afford **3k** (119.5 mg, 84% yield, 83% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.27(m, 5 H), 2.68 (aq, *J* =10.4 Hz, 2 H), 2.55 (d, *J* =14.8 Hz, 1 H), 2.19-2.07 (m,

3 H), 1.06 (s, 3 H), 0.77 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 142.0, 128.9, 128.3, 125.1, 124.6 (q, J_{CF} = 277 Hz), 82.5, 48.5 (q, J_{CF} = 27 Hz), 44.0, 43.5, 32.5, 30.6, 29.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.1 (at, J = 10.4 Hz); IR (film) ν_{max} 1741, 1378, 1245, 1115, 1023, 932 cm^{-1}; R_f(hexanes: ethyl acetate = 3:1)= 0.50; Anal. Calcd. For $C_{15}H_{17}F_3O_2$: C, 62.93; H, 5.99. Found: C, 62.80; H, 6.07. $[\alpha]_D^{24}$ = -29.6 (c= 1, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel AD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 97:3, 1.0 mL/min, 210 nm, t_R = 8.4 min (major) and 10.5 min (minor).

Radical Clock and TEMPO Trapping Experiments (Scheme 2)

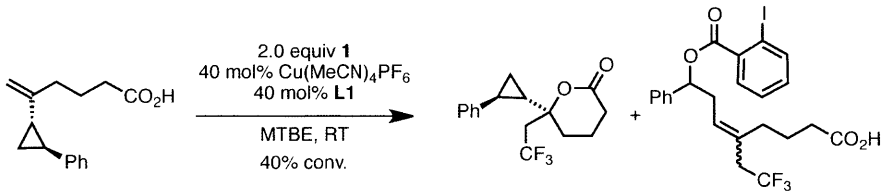
Synthesis of radical clock **4**:



(±)-5-((1*S*,2*S*)-2-phenylcyclopropyl)hex-5-enoic acid (4) An oven-dried 5 mL vial equipped with a Teflon-coated magnetic stir bar was charged with (±)-(1*S*,2*S*)-2-phenylcyclopropanecarboxylic acid (170 mg, 1.05 mmol). The tube was then sealed with a Teflon screw-cap septum and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon. Anhydrous dichloromethane (1 mL) and two drops of anhydrous DMF was added to the vial via syringe and the argon pressure was removed. A venting needle was inserted into the vial. At 0 °C to the reaction mixture was added oxalyl chloride solution (2 M in dichloromethane, 0.75 mL, 1.4 equiv) slowly. The resulting reaction mixture was stirred at room temperature overnight before concentrated *in vacuo*. A mixture of the residue and precatalyst A (4 mg, 0.005 mmol) were dissolved in anhydrous THF (1 mL) under argon. The zinc reagent[25] (1 M in THF, 1.2 mL, 1.2 equiv) was then added to the reaction mixture via syringe dropwise at room temperature. After stirred at room temperature for 1 h the mixture was diluted with ethyl ether (5 mL) and saturated aqueous ammonium chloride solution (5 mL). The aqueous layer was separated and extracted with ethyl ether (5 mL×3), and the combined organic layers were dried over Na_2SO_4, filtered though a short silica gel plug and concentrated *in vacuo*. The crude product was used for next step without further purification.

At 0 °C to a slurry of methyltriphenylphosphonium bromide (464 mg, 1.3 mmol) in anhydrous THF (2 mL) was added KO*t*Bu (140 mg, 1.25 mmol) in one portion. The resulting yellow mixture was stirred at room temperature for 1 h before the crude product from the previous step was introduced. The reaction mixture was further stirred for 4 h at the same temperature before diluted with ethyl ether (5 mL) and 1 M aqueous HCl solution (5 mL). The aqueous layer was separated and extracted with ethyl ether (5 mL×3), and the combined organic layers were concentrated *in vacuo*. The residue was re-dissolved in methanol (4 mL) and treated with 1 M aqueous potassium hydroxide solution (4 mL). After stirred at room temperature for 2 h, methanol was removed *in vacuo*. The aqueous residue was washed with ethyl ether (5 mL×3) and then acidified (pH < 2). The resulting mixture was extracted with ethyl ether (5 mL×3), and the combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (EtOAc/hexane = 1:2) to afford (±)-5-((1*S*,2*S*)-2-phenylcyclopropyl)hex-5-enoic acid **4** (105 mg, 44% from (±)-(1*S*,2*S*)-2-phenylcyclo propanecarboxylic acid) as a pale yellow oil.

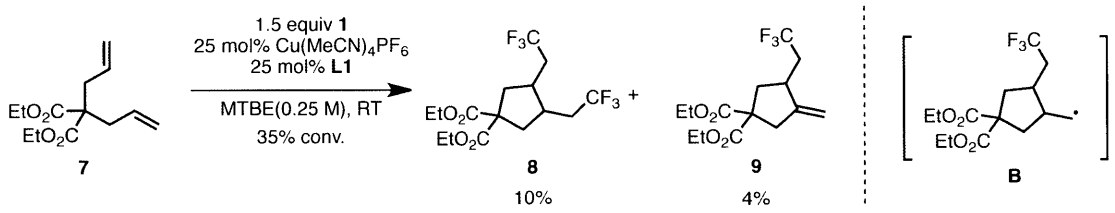
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.66 (br, 1 H), 7.28 (m, 2 H), 7.18 (m, 1 H), 7.10 (m, 2 H), 4.76 (s, 1 H), 4.74 (d, *J* =0.8 Hz, 1 H), 2.40 (t, *J* =7.6 Hz, 2 H), 2.19 (t, *J* =7.6 Hz, 2 H), 1.94-1.82 (m, 3 H), 1.57 (m, 1 H), 1.24 (m, 1 H), 1.15 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 148.7, 142.8, 128.5, 125.9, 125.8, 107.6, 35.8, 33.6, 28.4, 25.7, 23.0, 15.7; IR (film) ν_{max} 2938, 1703, 1641, 1604, 1411, 1246, 906, 732, 695 cm^{-1}; R_f (hexanes: ethyl acetate = 2:1)= 0.6.



Radical clock experiment 1: An oven-dried 13×100 mm Fisher Scientific re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (9 mg, 0.4 equiv), 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**L1**, 7 mg, 0.4 equiv), **1** (38 mg, 2 equiv). The reaction tube was sealed with a septum screw-cap (Thermo Scientific ASM PHN CAP w/PTFE/SIL, cat. #03388316) and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon (this sequence was repeated a

total of three times). **4** (14 mg, 0.06 mmol) was added to the tube via syringe followed by anhydrous methyl *tert*-butyl ether (0.4 mL). The argon pressure was removed and the reaction mixture was stirred at room temperature (25 °C) for 16 h. Solid precipitated from the blue reaction mixture during the course of the reaction. The reaction mixture was then diluted with saturated aqueous ammonium chloride solution (4 mL), ethyl ether (4 mL) and acetic acid (5 drops). The aqueous layer was separated and extracted with diethyl ether (4 mL×3). The combined organic layers were concentrated *in vacuo*. The residue was redissolved in $CDCl_3$ (α, α, α-trifluorotoluene (internal standard, 1 equiv) was added), and analyzed by ^1H NMR, ^{19}F NMR and LC-MS.

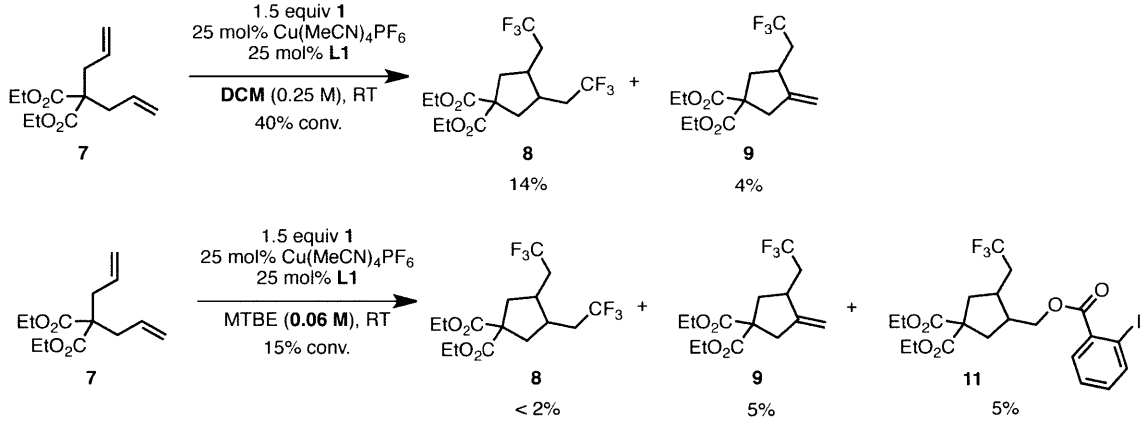
Less than 2% oxytrifluoromethylation product **5** was formed. The reaction produced a complex mixture of CF_3-containing cyclopropane-opening products in *ca.* 40% yield in total. The major product was identified to be **6** (*ca.* 20% yield by ^{19}F NMR, 1.4:1 mixture of alkene geometric isomers). However, this compound was inseparable from some other unidentified CF_3-containing products and 2-iodobenzoic acid (derived from **1**). Therefore ^{19}F NMR yield was given for **6**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8 Hz, 1 H), 7.82 (d, J = 8 Hz, 1 H), 7.42-7.13 (m, 7 H), 6.01 (at, J = 7 Hz, 1 H), 5.56 (major isomer, at, J = 7 Hz) and 5.48 (minor isomer, at, J = 7.6 Hz) (1 H), 2.90-2.63 (m, 4 H), 2.31-2.24 (m, 2 H), 2.17-2.10 (m, 2 H), 1.71 (major isomer, m) and 1.61 (minor isomer, m) (2 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.2 (major isomer, at, J = 10.9 Hz), -65.1 (minor isomer, at, J = 10.9 Hz); ESI/APCI-MS (*m/z*, relative intensity): 569.0 ($[M+Na]^+$, 100), 570.0 (24.6), 571.0 (4.2).



Radical clock experiment 2: An oven-dried 13×100 mm Fisher Scientific re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (9.5 mg, 0.25 equiv), 2,2′-isopropy lidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**L1**, 7.5 mg, 0.25 equiv), **1** (47.5 mg, 1.5 equiv). The reaction tube was sealed with a septum screw-cap (Thermo Scientific ASM PHN CAP w/PTFE/SIL, cat. #03388316) and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). Diethyl diallylmalonate **7** (24 mg, 0.10 mmol) was added to the

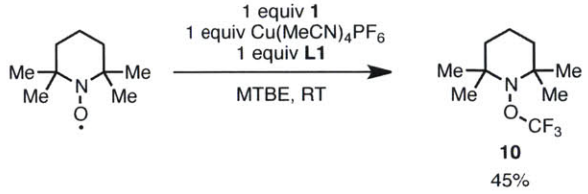
tube via syringe followed by anhydrous methyl *tert*-butyl ether (0.4 mL). The argon pressure was removed and the reaction mixture was stirred at room temperature (25 °C) for 16 h. White solid precipitated from the blue reaction mixture during the course of the reaction. The reaction mixture was then diluted with saturated aqueous sodium bicarbonate solution (4 mL) and ethyl ether (4 mL). The aqueous layer was separated and extracted with diethyl ether (4 mL×3). The combined organic layers were concentrated *in vacuo*. The residue was redissolved in $CDCl_3$ (α, α, α-trifluorotoluene (internal standard, 1 equiv) was added), and analyzed by ^1H NMR, ^{19}F NMR and GC-MS. Cyclization products **8** and **9** (derived from radical intermediate **B**) were observed in 10% and 4% yield based on NMR analysis, respectively.[13]

The product distribution was found dependent on factors such as solvent and concentration. For example, (1) in dichloromethane, an increase in the yield of **8** (presumably via radical-radical coupling of intermediate **B**) was observed; (2) in a more diluted system (0.06 M), **8** was observed in less than 2% yield. Instead, **11** was formed, presumably via a similar C—O bond formation process as in the oxytrifluoromethylation reaction.



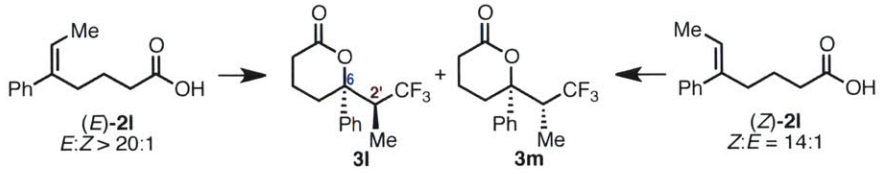
TEMPO trapping experiment: An oven-dried 13×100 mm Fisher Scientific re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (7.5 mg, 1 equiv), 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**L1**, 5.9 mg, 1 equiv), **1** (6.3 mg, 1 equiv). The reaction tube was sealed with a septum screw-cap (Thermo Scientific ASM PHN CAP w/PTFE/SIL, cat. #03388316) and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). A solution of TEMPO (3.1 mg, 1 equiv) in anhydrous methyl *tert*-butyl ether (0.2 mL) was added to the tube via syringe. The argon pressure was removed and the reaction

mixture was stirred at room temperature (25 °C) for 1 h. α, α, α-Trifluorotoluene (internal standard, 1 equiv) was added and the reaction mixture was then diluted with ethyl ether (1 mL) and analyzed by ^{19}F NMR and GC-MS. **10** was observed in 45% yield.[12]



10
45%

Trisubstituted Alkene Substrates as Mechanistic Probes (Scheme 3) [27]



substrate	3l yield [%][b]	3l ee [%][c]	3m yield [%][b]	3m ee [%][c]	d.r.[b]	ratio of stereoisomers **3l** : *ent*-**3l** : **3m** : *ent*-**3m**
(*E*)-**2l**	28	93	47	58	1 : 1.7	36.3 : 1.3 : 49.3 : 13.1
(*Z*)-**2l**	24	92	40	59	1 : 1.7	35.7 : 1.5 : 49.8 : 13.0

Reaction with (*Z*)-2l: An oven-dried 20 × 150 mm Fisher Scientific re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (18.6 mg, 0.05 mmol, 0.10 equiv), 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**L1**, 14.7 mg, 0.05 mmol, 0.10 equiv), **1** (190 mg, 0.60 mmol, 1.2 equiv) and (*Z*)-**2l** (102 mg, 0.50 mmol, 1.0 equiv). The reaction tube was sealed with a septum screw-cap (10/90, Teflon/SIL, National Scientific) and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). Anhydrous methyl *tert*-butyl ether (10 mL) was added to the tube via syringe to afford a blue mixture. The argon pressure was removed and the reaction mixture was stirred at room temperature (25 °C) for 16 h. α, α, α-Trifluorotoluene (internal standard, 61 mL, 1 equiv) was added to the reaction mixture via syringe, and the crude reaction mixture was analyzed by ^{19}F

NMR spectroscopy. The ^{19}F NMR yields for diastereomers **3l** and **3m** were 23.6% and 39.9% respectively (d.r. = 1:1.69).

The crude reaction mixture was then washed with saturated aqueous sodium bicarbonate solution (12 mL). The aqueous layer was separated and extracted with diethyl ether (4 mL×3). The combined organic layers were briefly washed with 0.05 M aqueous NaOH solution (10 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 0:1 to 10:1 to 6:1 to 5.5:1) to give major diastereomer **3m** (R_f = 0.64 (EtOAc/hexanes = 1:2), 45.6 mg, 34% isolate yield, 58.6% ee) and minor diastereomer **3l** (R_f = 0.60 (EtOAc/hexanes = 1:2)). **3l** was further purified by preparative thin-layer chromatography (27.5 mg, 20% yield, 91.9% ee). Stereoisomer ratio calculated: (**3l** + *ent*-**3m**):(**3m** + *ent*-**3l**) = 51:49.

(*R*)-6-phenyl-6-((*R*)-1,1,1-trifluoropropan-2-yl)tetrahydro-2*H*-pyran-2-one (**3m**): colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2 H), 7.32 (m, 3 H), 2.70 (qq, *J* =9.2 Hz, 7.2 Hz, 1 H), 2.50-2.38 (m, 3 H), 2.33 (td, *J* =13.6 Hz, 3.6 Hz, 1 H), 1.74 (m, 1 H), 1.41 (m, 1 H), 1.10 (d, *J* =7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 141.7, 129.1, 128.2, 127.0 (q, J_{CF} = 280 Hz), 125.6, 86.4, 48.7 (q, J_{CF} = 24 Hz), 30.2 (q, J_{CF} = 3 Hz), 29.3, 16.3, 9.2 (q, J_{CF} = 3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.5 (ad, *J* = 9.0 Hz); IR (film) ν_{max} 1738, 1447, 1264, 1204, 1169, 1120, 1027, 985, 760, 702 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1)= 0.64; Anal. Calcd. For $C_{14}H_{15}F_3O_2$: C, 61.76; H, 5.55. Found: C, 61.83; H, 5.70. $[\alpha]_D^{24}$ = -14.0 (c= 0.9, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel IA 4.6 mm x 250 mm, hexanes:*i*-PrOH = 99:1, 0.8 mL/min, 210 nm, t_R = 15.7 min (minor) and 16.7 min (major).

(*R*)-6-phenyl-6-((*S*)-1,1,1-trifluoropropan-2-yl)tetrahydro-2*H*-pyran-2-one (**3l**): colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.32 (m, 5 H), 2.77 (qq, *J* =8.8 Hz, 7.2 Hz, 1 H), 2.65 (dt, *J* =14.4 Hz, 4.0 Hz, 1 H), 2.44 (ddd, *J* =18.4 Hz, 10.0 Hz, 8.0 Hz, 1 H), 2.31 (dddd, *J* =18.4 Hz, 7.6 Hz, 3.2 Hz, 1.2 Hz, 1 H), 2.16 (td, *J* =13.2 Hz, 4.8 Hz, 1 H), 1.84 (m, 1 H), 1.63 (m, 1 H), 1.08 (d, *J* =7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 139.6, 128.8, 128.4, 126.7 (q, J_{CF} = 280 Hz), 126.5, 86.4, 49.1 (q, J_{CF} = 25 Hz), 29.0, 28.3, 16.3, 10.0 (q, J_{CF} = 3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -65.0 (ad, *J* = 9.0 Hz); IR (film) ν_{max} 1739, 1448, 1264, 1205, 1169, 1120, 1028, 760, 703 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1)= 0.60; Anal. Calcd. For $C_{14}H_{15}F_3O_2$: C, 61.76; H, 5.55. Found: C, 61.87; H, 5.59. The enantiomeric excess was determined by chiral

HPLC analysis: Chiralcel IA 4.6 mm x 250 mm, hexanes:*i*-PrOH = 99:1, 0.8 mL/min, 210 nm, t_R = 18.3 min (minor) and 20.7 min (major). The relative stereochemistry of **3m** and **3l** were assigned based on comparison with known compounds.[8] The absolute stereochemistry were assigned based on analogy to **3b**.

Reaction with (*E*)-2l: Following the same procedure for the reaction with (*Z*)-**2l** described above, An oven-dried 20 × 150 mm Fisher Scientific re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (18.6 mg, 0.05 mmol, 0.10 equiv), 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (**L1**, 14.7 mg, 0.05 mmol, 0.10 equiv), **1** (190 mg, 0.60 mmol, 1.2 equiv) and (*E*)-**2l** (102 mg, 0.50 mmol, 1.0 equiv). The reaction tube was sealed with a septum screw-cap (10/90, Teflon/SIL, National Scientific) and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). Anhydrous methyl *tert*-butyl ether (10 mL) was added to the tube via syringe to afford a blue mixture. The argon pressure was removed and the reaction mixture was stirred at room temperature (25 °C) for 16 h. α, α, α-Trifluorotoluene (internal standard, 61 mL, 1 equiv) was added to the reaction mixture via syringe, and the crude reaction mixture was analyzed by ^{19}F NMR spectroscopy. The ^{19}F NMR yields for diastereomers **3l** and **3m** were 28.1% and 46.6% respectively (d.r. = 1:1.66).

The crude reaction mixture was then washed with saturated aqueous sodium bicarbonate solution (12 mL). The aqueous layer was separated and extracted with diethyl ether (4 mL×3). The combined organic layers were briefly washed with 0.05 M aqueous NaOH solution (10 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography and preparative TLC to give **3m** (58.2% ee) and **3l** (93.1% ee). Stereoisomer ratio calculated: (**3l** + *ent*-**3m**):(**3m** + *ent*-**3l**) = 51:49.

2.5 References and Notes

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[16] The details of this enantioselective C–O bond formation step are unclear at this point. Three possible scenarios have been proposed: a) single-electron-oxidation of **IV** to the corresponding carbocation by the Cu(II) complex, followed by nucleophilic trapping; b) single-electron-oxidation of **IV** by the Cu(II) complex and nucleophilic trapping occurring simultaneously in a concerted transition state; c) recombination of **IV** and the Cu(II) complex to afford an alkyl Cu(III) complex, which reductively eliminates to give the C–O bond.

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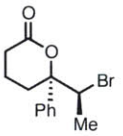
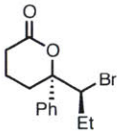
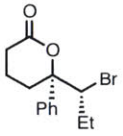
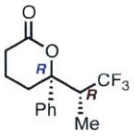
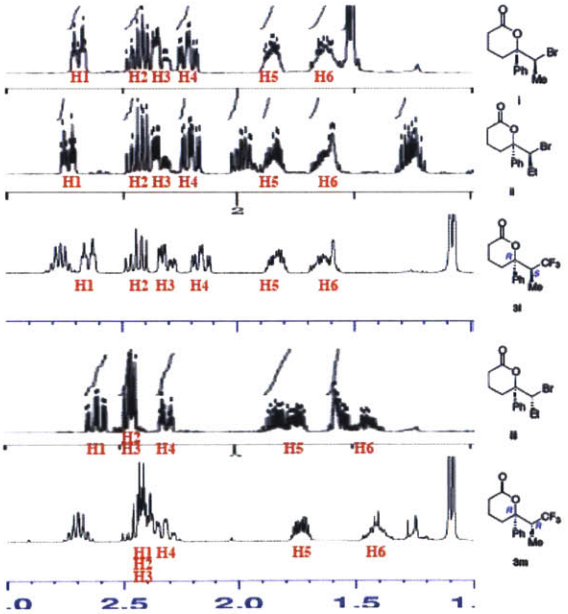
[23] Murai, K.; Nakamura, A.; Matsushita, T.; Shimura, M.; Fujioka, H. *Chem. Eur. J.* **2012**, *18*, 8448. The ^{1}H NMR spectra of **3l** and **3m** were compared to those reported for compound **i**, **ii** and **iii**.

characteristic ^{1}H NMR signals / chemical shift (ppm)	 i	 ii	 **3l**	 iii	 **3m**
H1	2.69	2.73	2.65	2.60	2.40
H2	2.44	2.43	2.44	2.46	2.46-2.44
H3	2.34	2.34	2.31	2.46	2.44-2.42
H4	2.21	2.20	2.16	2.30	2.33
H5	1.86	1.84	1.84	1.75	1.74
H6	1.63	1.60	1.63	1.47	1.42



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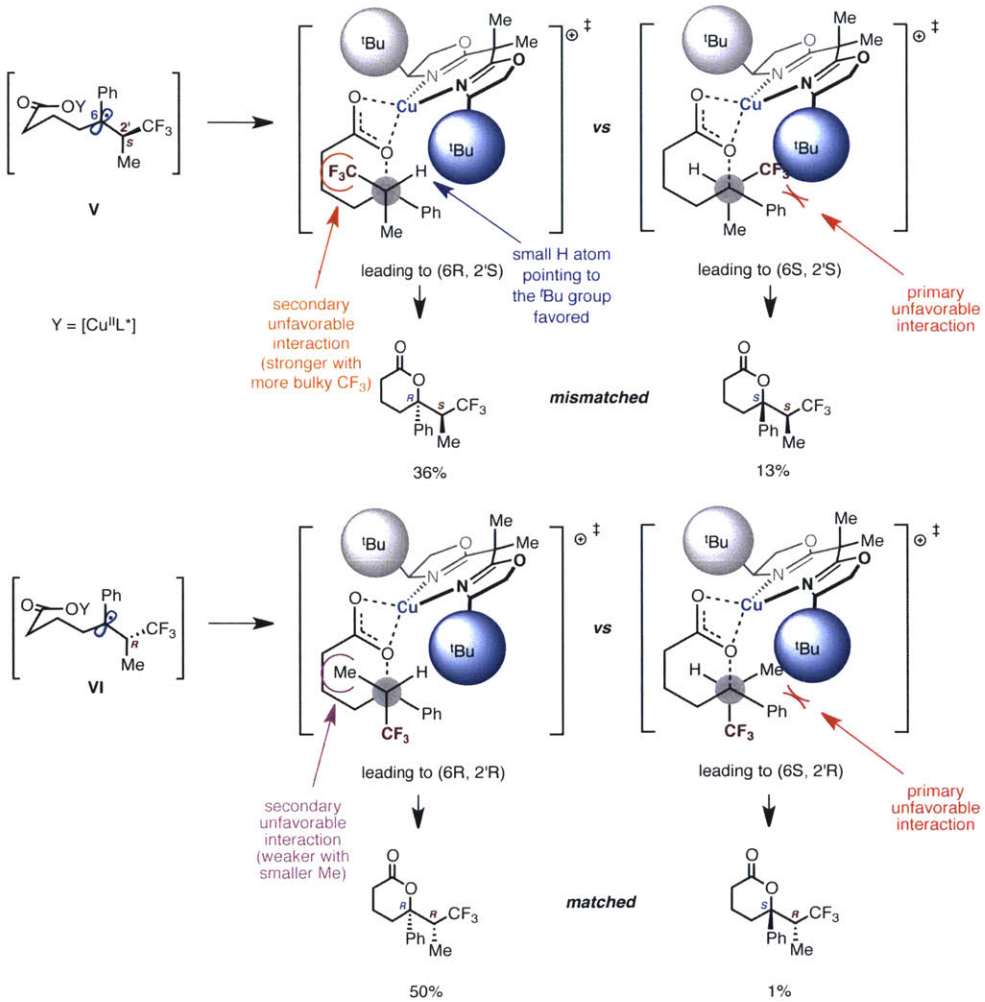
[26] Solids presented in the beginning of the reaction should be mostly dissolved during the course of the reaction, affording a clear blue-green solution. Reaction mixture turning white cloudy usually indicated the failure to exclude oxygen.

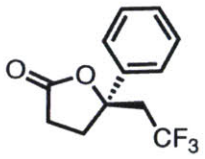
[27] A possible explanation for the stereoselectivity observed: The major unfavorable interaction is between the ^{t}Bu group and the aryl group. A secondary unfavorable interaction is caused by the group overlapping with the carbon ring backbone, which is stronger with a CF_3 and weaker with a Me group. This results in the higher selectivity via intermediate **VI** and lower selectivity via **V**.

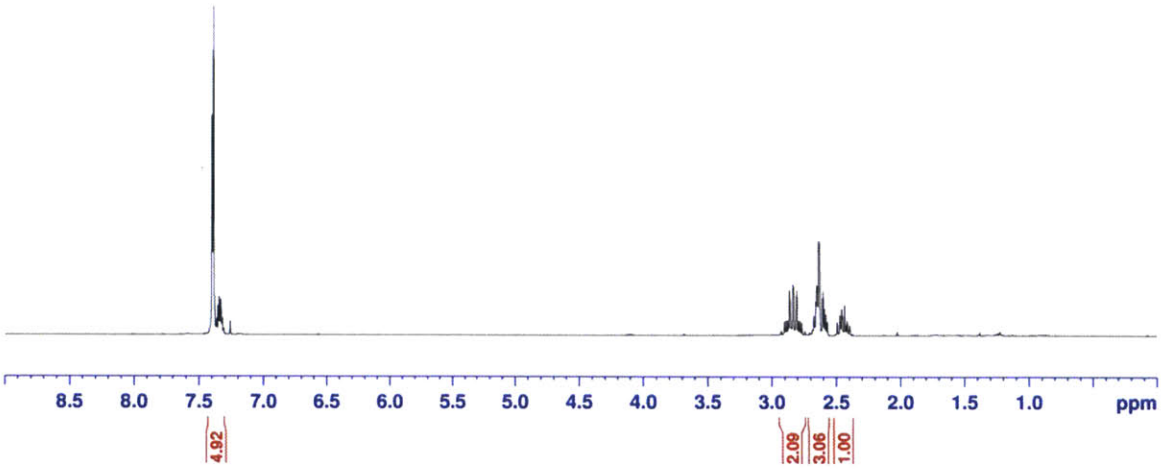


2.6 Spectra and HPLC traces

RZ-3-96-H

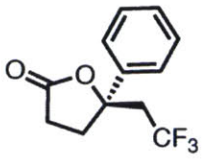
3a ^{1}H NMR (400 MHz, $CDCl_3$)

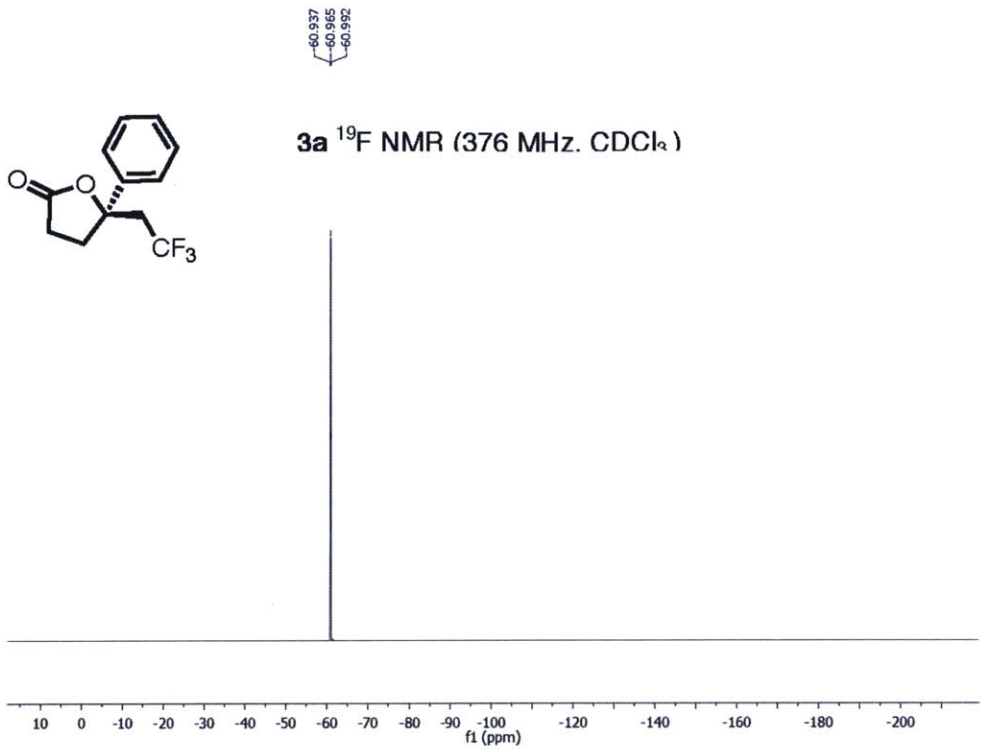




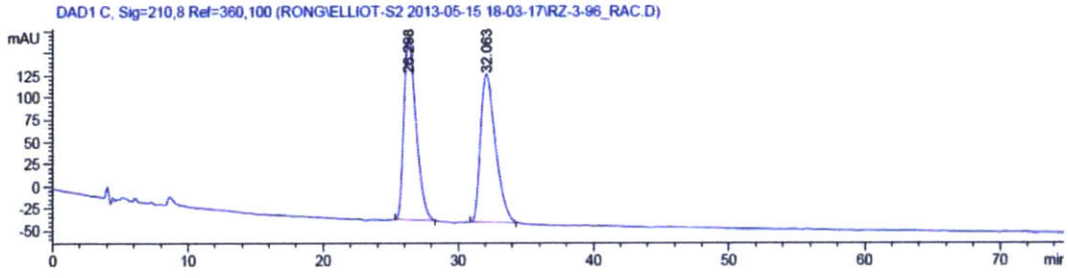
3a ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-3-96-C



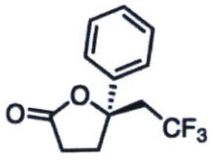


HPLC traces for compound 3a

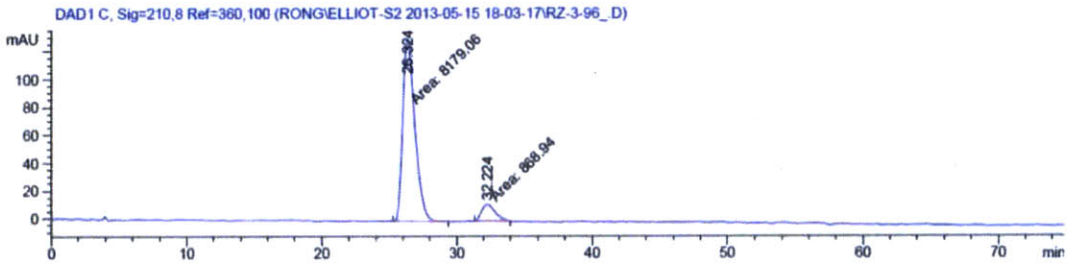


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.298	BB	0.9243	1.28534e4	204.77682	50.0201
2	32.063	BB	1.0662	1.28431e4	167.18340	49.9799
Totals :				2.56966e4	371.96022	

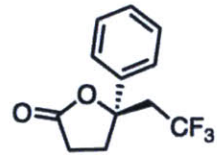


(±)-3a



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

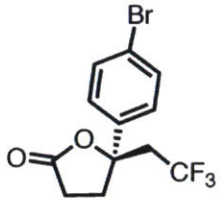
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.324	MM	1.0425	8179.05859	130.76067	90.3963
2	32.224	MM	1.1810	868.94000	12.26282	9.6037
Totals :				9047.99860	143.02349	

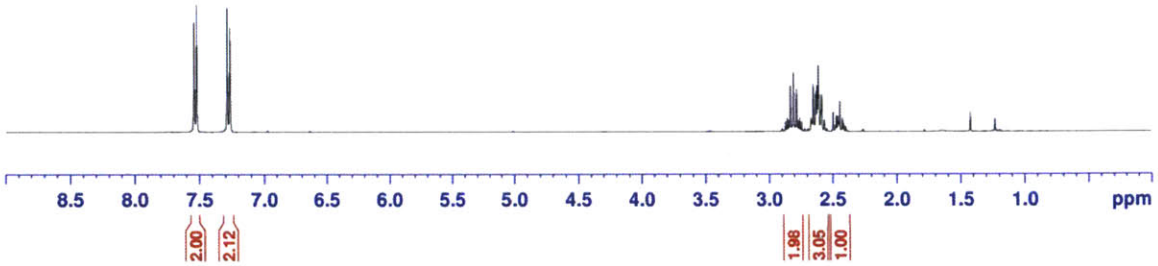


3a

RZ-3-83-H

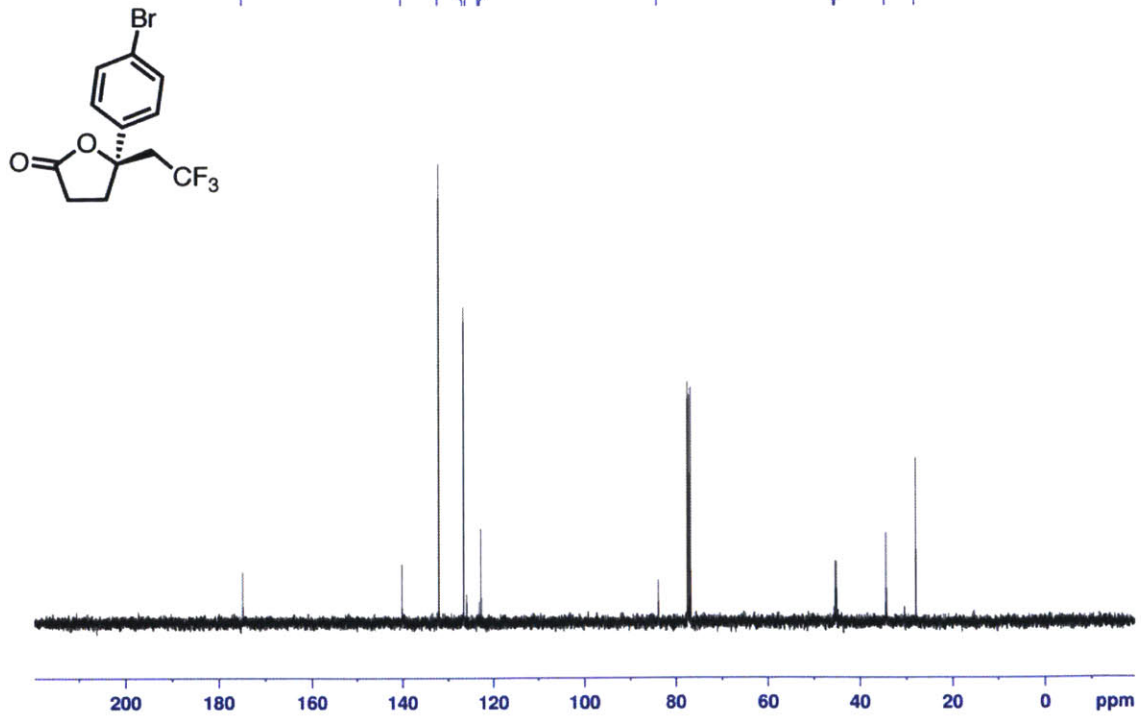
3b ^{1}H NMR (400 MHz, $CDCl_3$)



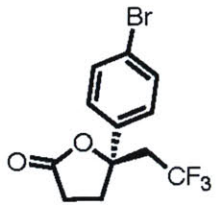


3b ^{13}C NMR (100 MHz, $CDCl_3$)

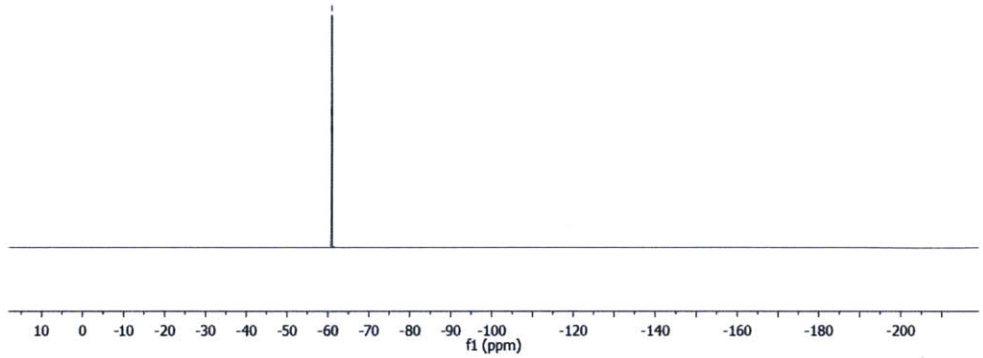
RZ-3-83-C



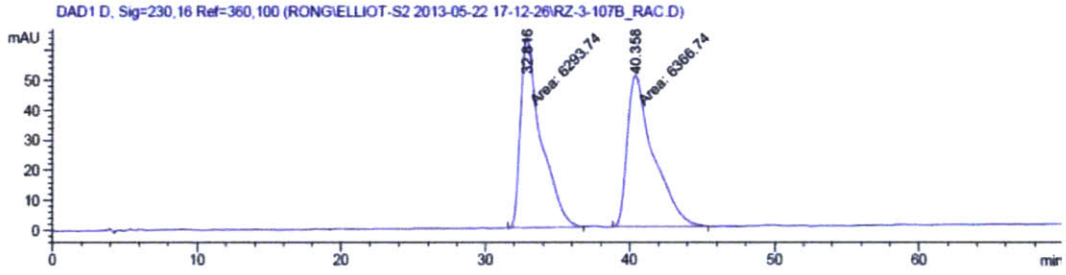
RZ-3-83-F



3b ^{19}F NMR (376 MHz, $CDCl_3$)

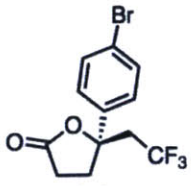


HPLC traces for compound 3b

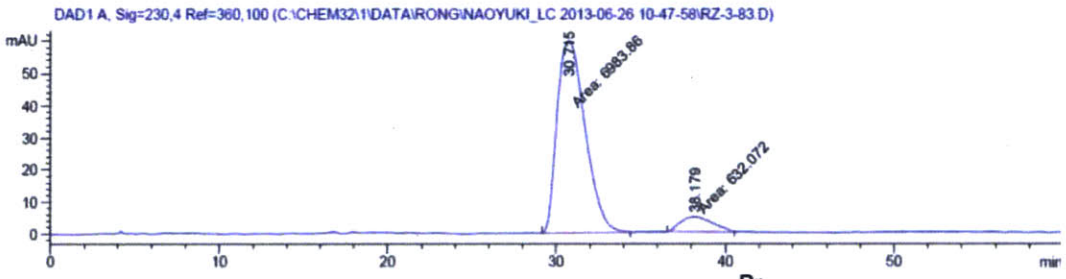


Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.816	MM	1.6638	6293.73926	63.04526	49.7117
2	40.358	MM	2.1021	6366.73535	50.47818	50.2883
Totals :				1.26605e4	113.52344	

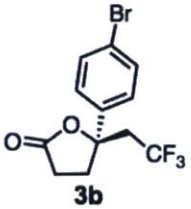


(±)-3b



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

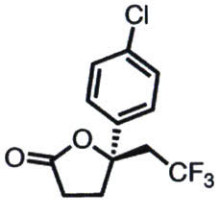
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.715	MM	1.9425	6983.85840	59.92274	91.7007
2	38.179	MM	2.2312	632.07239	4.72152	8.2993
Totals :				7615.93079	64.64426	

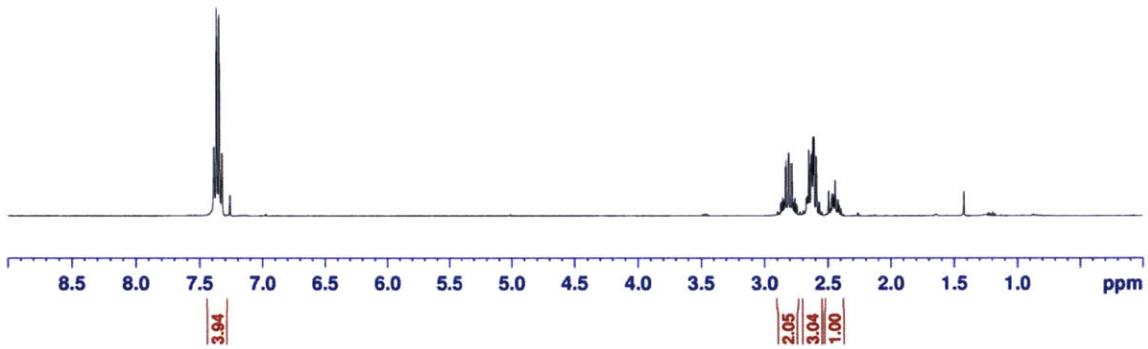


3b

RZ-3-91-H

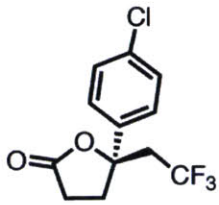
3c ^{1}H NMR (400 MHz, $CDCl_3$)



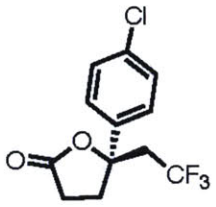


3c ^{13}C NMR (100 MHz, $CDCl_3$)

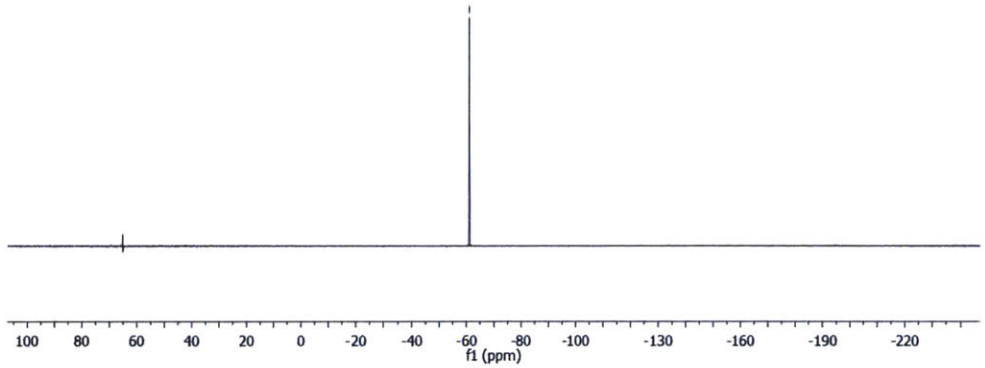
RZ-3-91-C



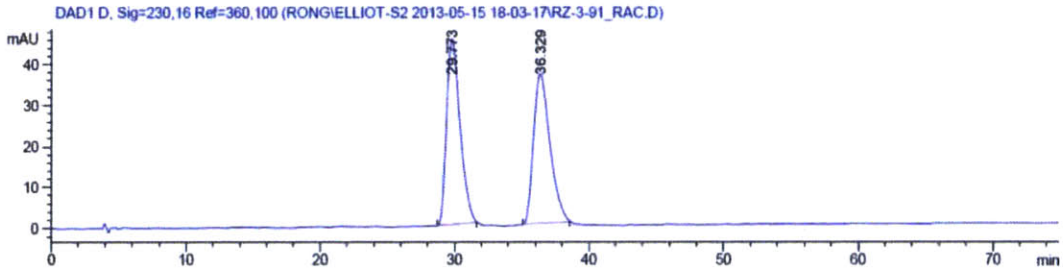
RZ-3-91-F



3c ^{19}F NMR (282 MHz, $CDCl_3$)

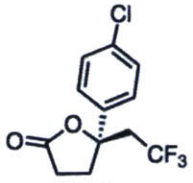


HPLC traces for compound 3c

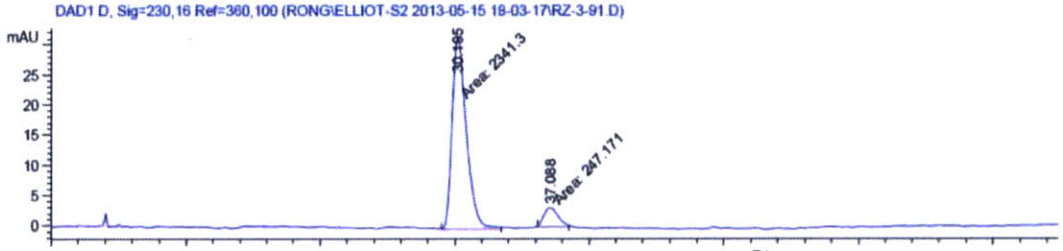


Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.773	BB	1.0518	3180.40503	45.26018	50.2057
2	36.329	BB	1.2432	3154.34155	36.46455	49.7943
Totals :				6334.74658	81.72473	

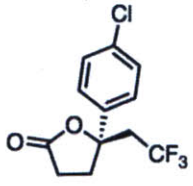


(±)-3c



Signal 4: DAD1 D, Sig=230,16 Ref=360,100

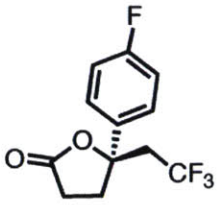
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.195	MM	1.2283	2341.30225	31.76820	90.4511
2	37.088	MM	1.2796	247.17065	3.21925	9.5489
Totals :				2588.47290	34.98745	

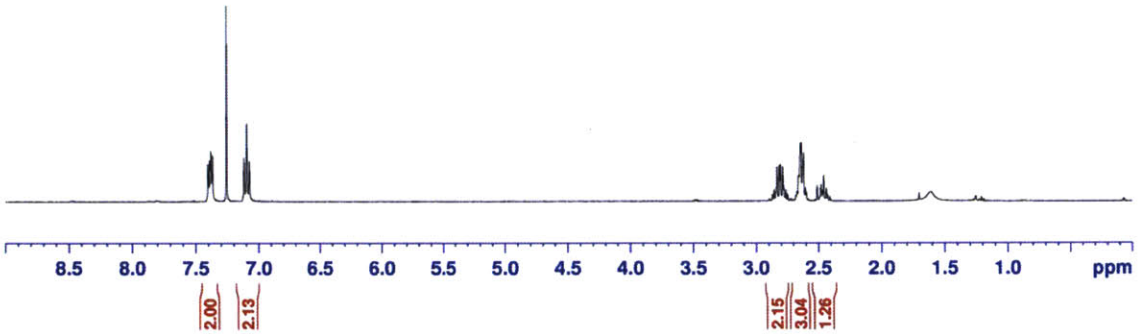


3c

RZ-3-99-H

3d ^{1}H NMR (400 MHz, $CDCl_3$)

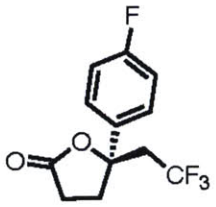




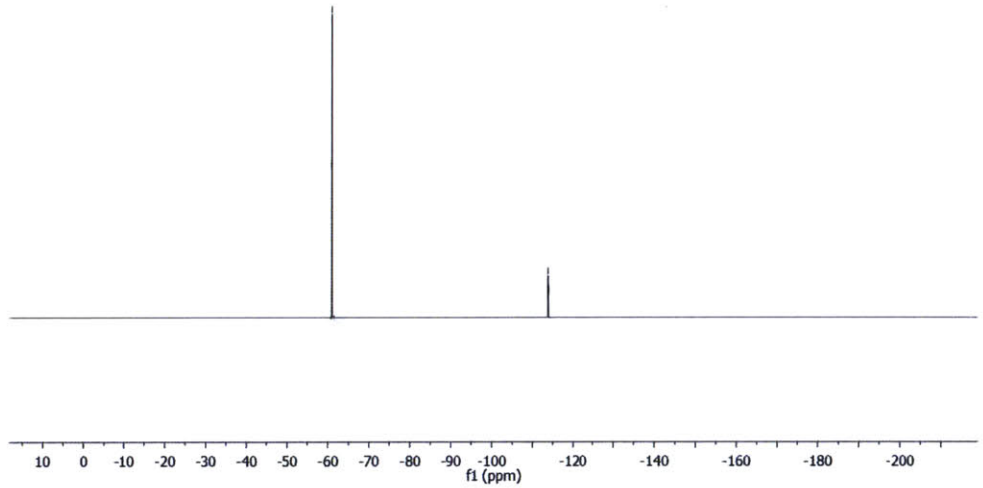
3d ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-3-99-C

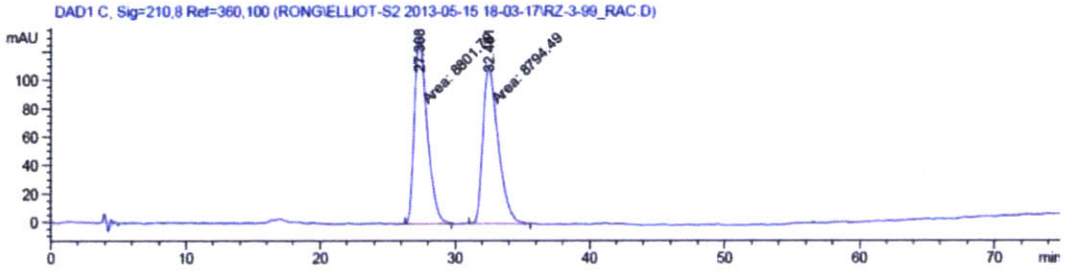
RZ-3-99-F



3d ^{19}F NMR (376 MHz, $CDCl_3$)

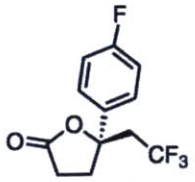


HPLC traces for compound 3d

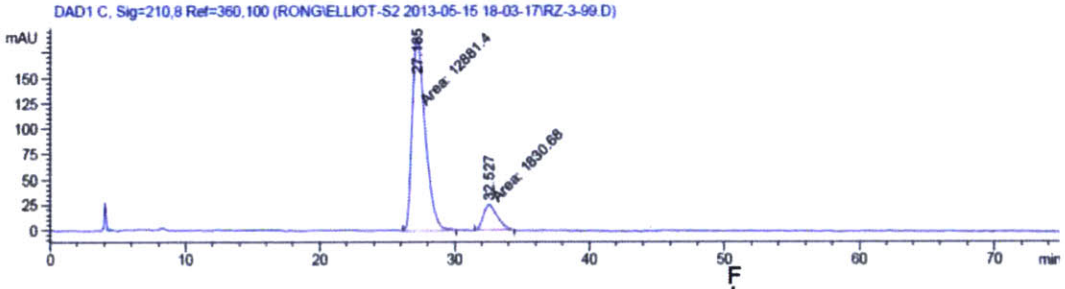


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.308	MM	1.1151	8801.79395	131.55710	50.0207
2	32.481	MM	1.3331	8794.49219	109.95344	49.9793
Totals :				1.75963e4	241.51054	

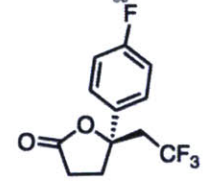


(±)-3d



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

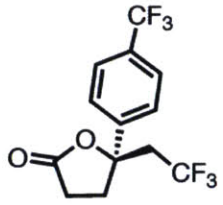
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.185	MM	1.1291	1.28814e4	190.14659	87.5566
2	32.527	MM	1.2081	1830.68152	25.25463	12.4434
Totals :				1.47121e4	215.40122	

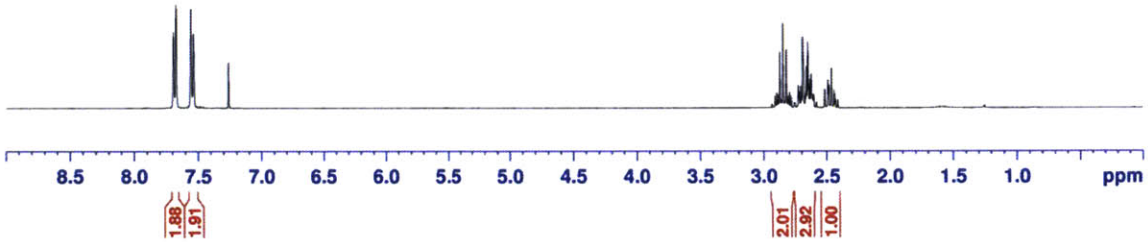


3d

RZ-3-104A-H

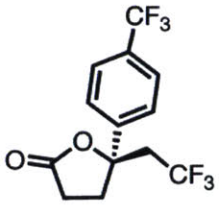
3e ^{1}H NMR (400 MHz, $CDCl_3$)



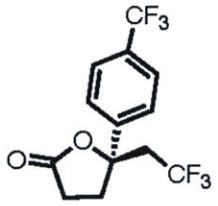


3e ^{13}C NMR (100 MHz, $CDCl_3$)

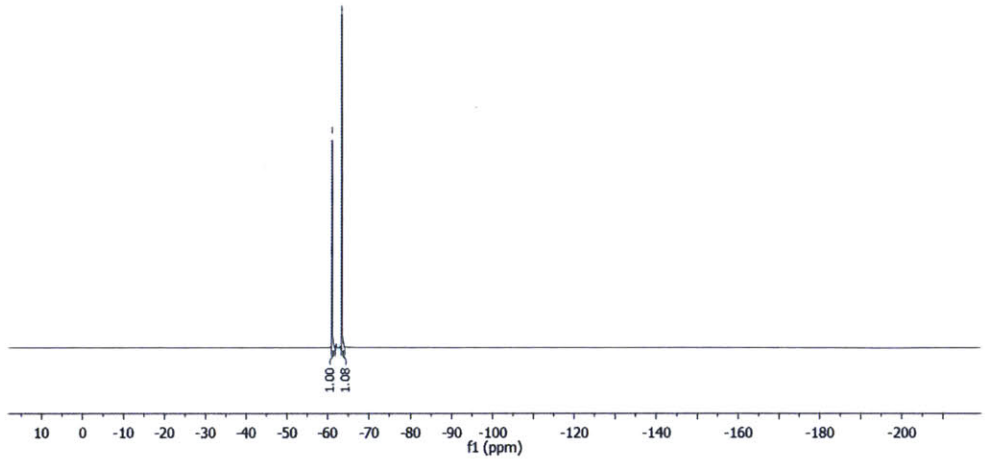
RZ-3-104A-C



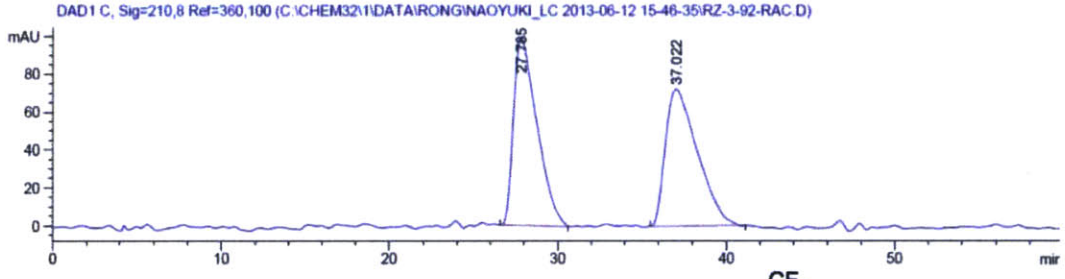
RZ-3-104A-F



3e ^{19}F NMR (376 MHz, $CDCl_3$)

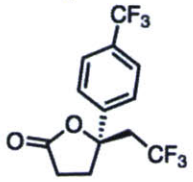


HPLC traces for compound 3e

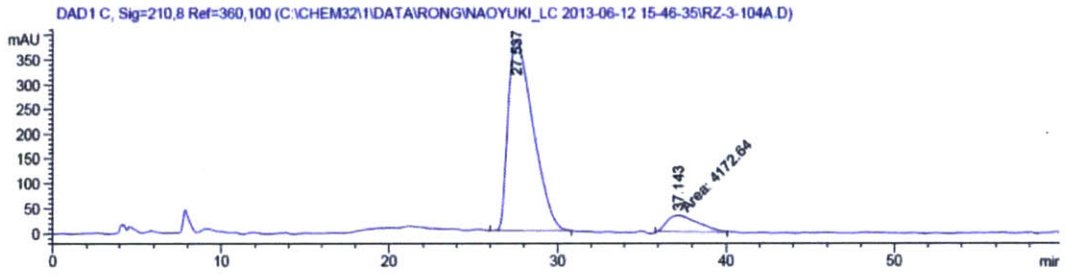


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.785	BB	1.2249	9620.12891	99.42204	50.3609
2	37.022	BB	1.5402	9482.25098	72.48448	49.6391
Totals :				1.91024e4	171.90652	

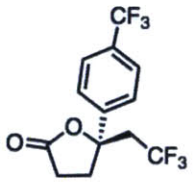


(±)-3e



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

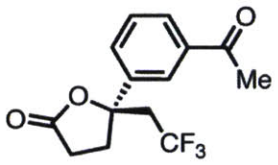
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.537	BB	1.4283	3.97673e4	385.25488	90.5038
2	37.143	MM	2.1067	4172.64258	33.01132	9.4962
Totals :				4.39400e4	418.26620	

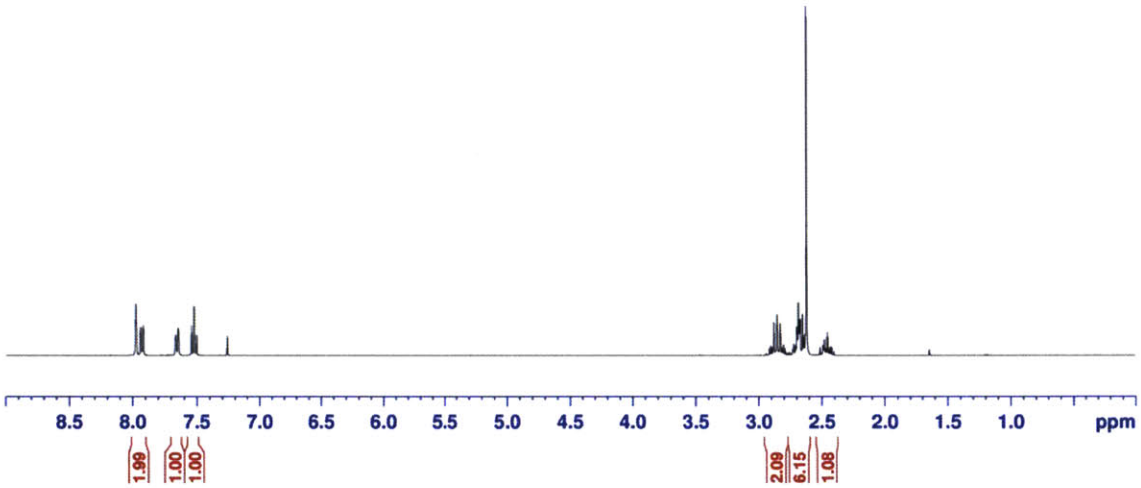


3e

RZ-3-112-H

3f ^{1}H NMR (400 MHz, $CDCl_3$)

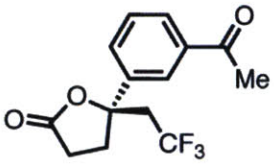


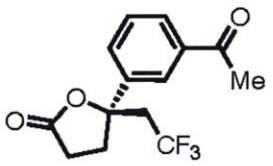


RZ-3-112-C

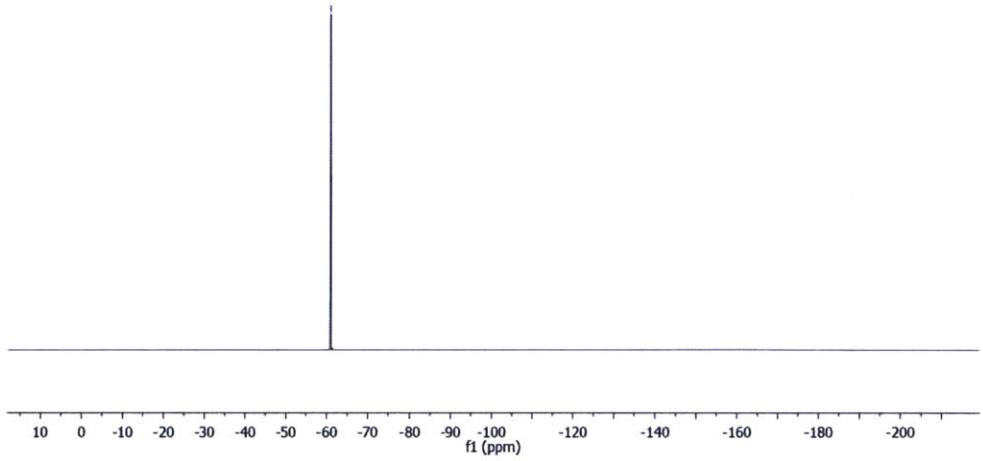
3f ^{13}C NMR (100 MHz, $CDCl_3$)

197.57
174.92
142.04
137.70
129.46
129.39
128.76
125.96
124.35
123.19
83.99
45.47
45.20
34.43
27.99
26.83

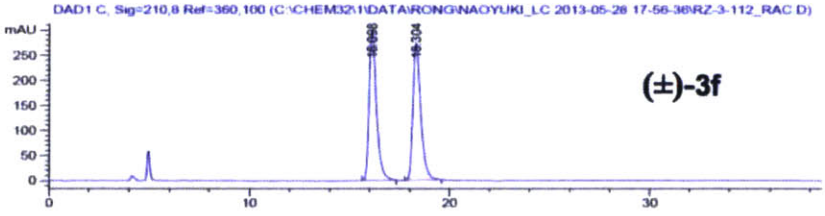




3f ^{19}F NMR (376 MHz, $CDCl_3$)

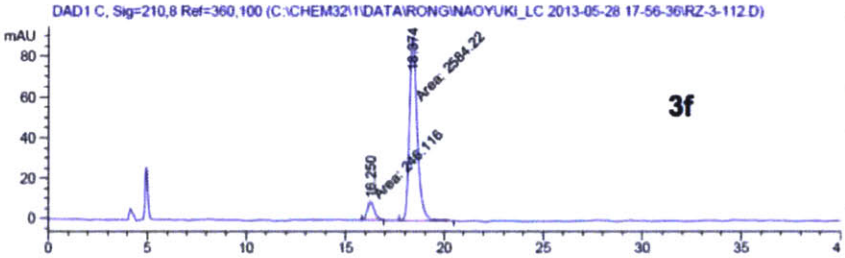


HPLC traces for compound 3f



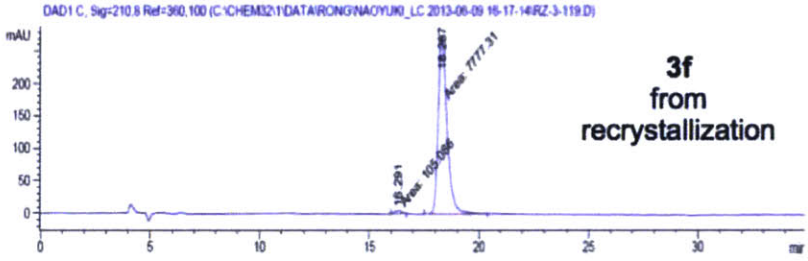
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.098	BB	0.3890	7659.92334	298.86264	50.0167
2	18.304	BB	0.4250	7654.79346	273.10046	49.9833
Totals :				1.53147e4	571.96310	



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.250	MM	0.4377	246.11610	9.37206	8.6956
2	18.374	MM	0.4727	2584.22192	91.11408	91.3044
Totals :				2830.33803	100.48614	

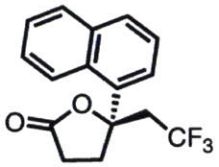


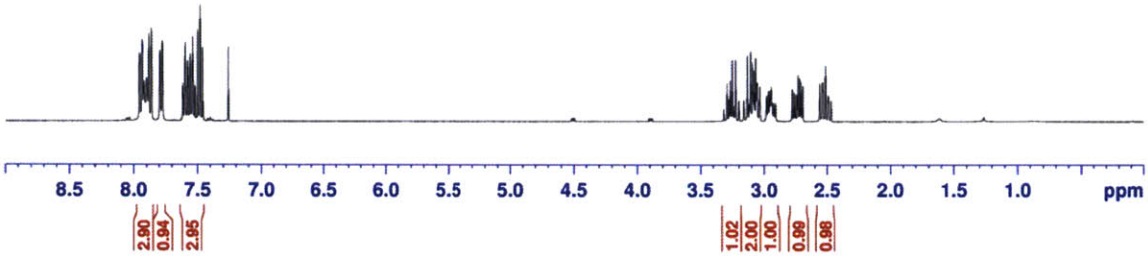
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.291	MM	0.3536	105.08598	4.95301	1.3332
2	18.287	MM	0.4716	7777.30908	274.82693	98.6668
Totals :				7882.39506	279.77995	

RZ-3-105-H

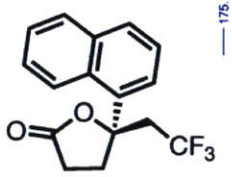
3g ^{1}H NMR (400 MHz, $CDCl_3$)



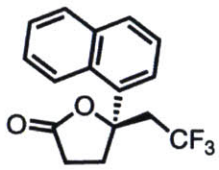


3g ^{13}C NMR (100 MHz, $CDCl_3$)

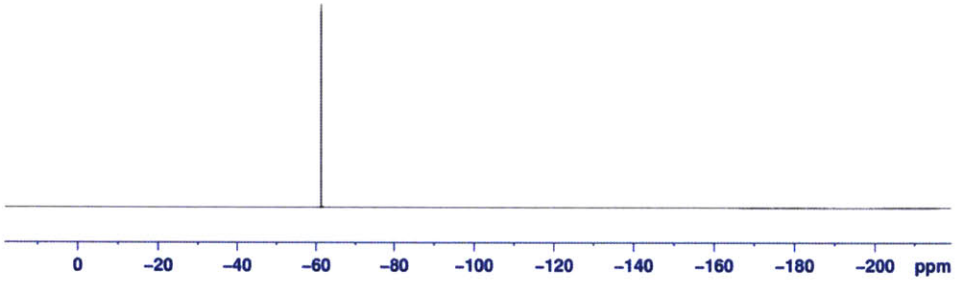
RZ-3-105-C



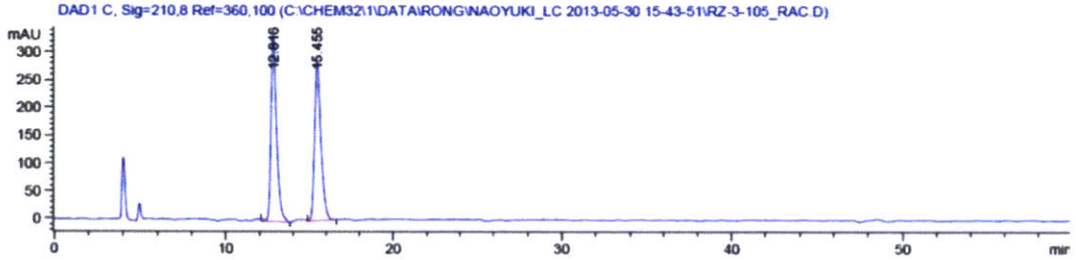
RZ-3-105-F



3g ^{19}F NMR (376 MHz, $CDCl_3$)

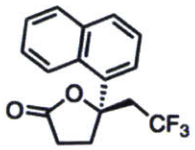


HPLC traces for compound 3g

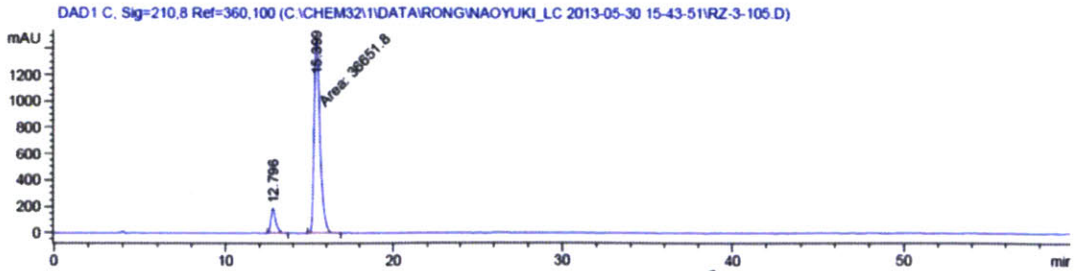


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.816	VV	0.3525	7923.84033	334.39627	50.7680
2	15.455	VB	0.4041	7684.10449	287.23532	49.2320
Totals :				1.56079e4	621.63159	

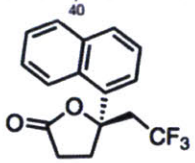


(±)-3g



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

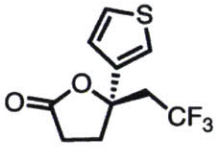
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.796	BB	0.3031	3795.40283	188.32103	9.3836
2	15.399	MM	0.4145	3.66518e4	1473.60706	90.6164
Totals :				4.04472e4	1661.92809	

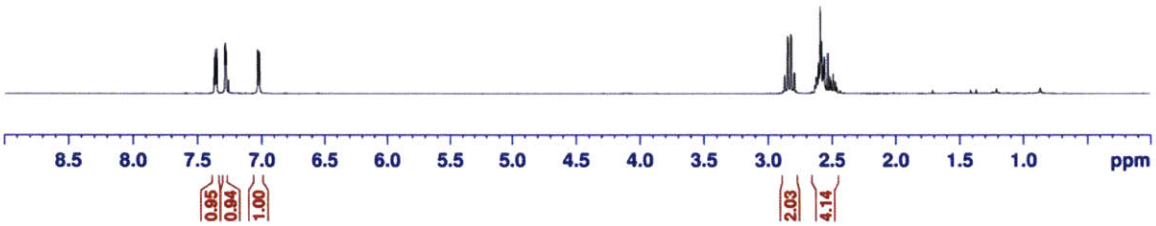


3g

RZ-3-94-H

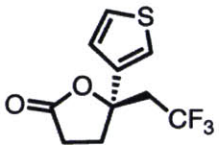
3h ^{1}H NMR (400 MHz, $CDCl_3$)



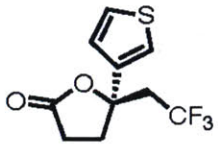


3h ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-3-94-C

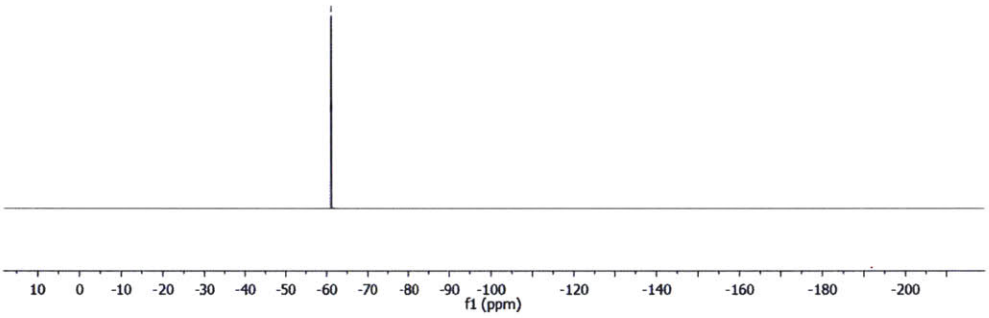


RZ-3-94-F

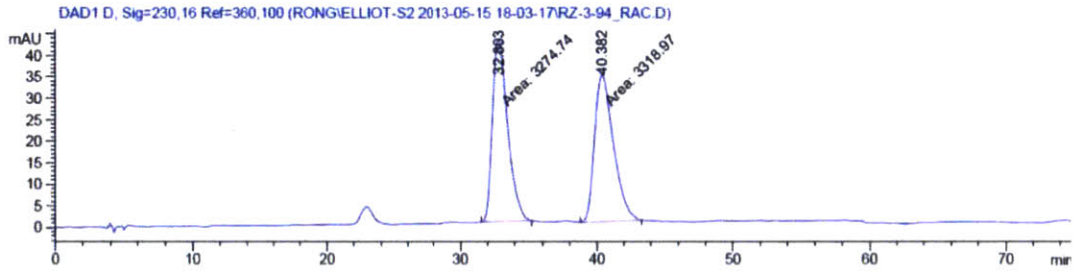


61.182
61.210
61.237

3h ^{19}F NMR (376 MHz, $CDCl_3$)

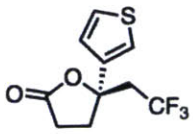


HPLC traces for compound 3h

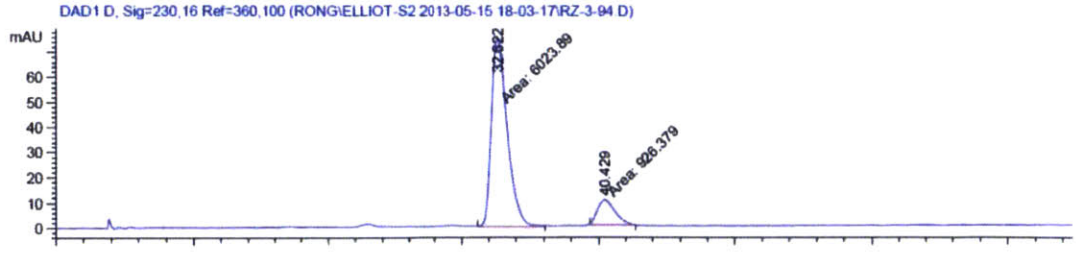


Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.803	MM	1.2874	3274.74146	42.39560	49.6646
2	40.382	MM	1.6127	3318.96899	34.30114	50.3354
Totals :				6593.71045	76.69675	

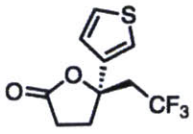


(±)-3h



Signal 4: DAD1 D, Sig=230,16 Ref=360,100

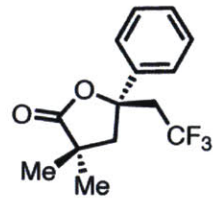
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.622	MM	1.3294	6023.88574	75.52219	86.6713
2	40.429	MM	1.5247	926.37915	10.12656	13.3287
Totals :				6950.26489	85.64876	

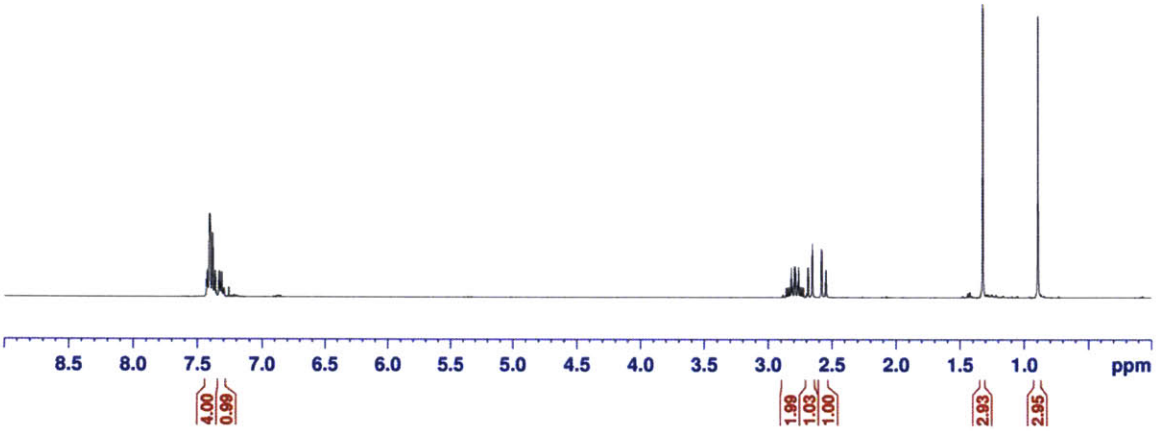


3h

RZ-3-95-H

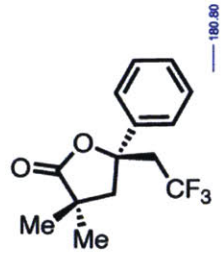
3i ^{1}H NMR (400 MHz, $CDCl_3$)

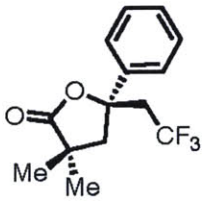




3i ^{19}C NMR (100 MHz, $CDCl_3$)

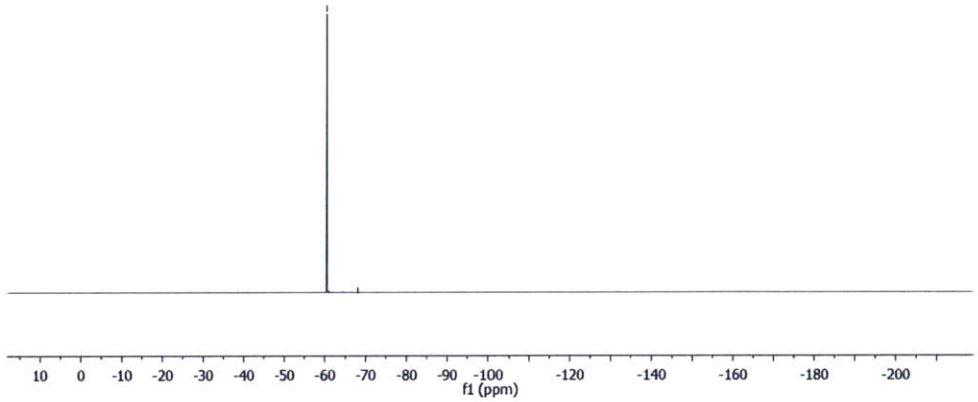
RZ-3-95-C



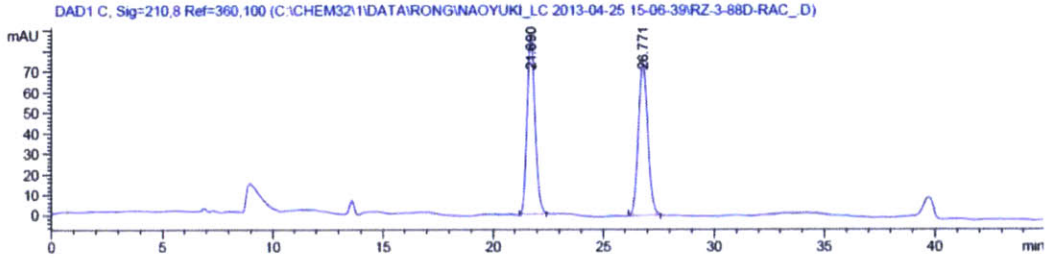


-60.576
-60.603
-60.630

3i ^{19}F NMR (376 MHz, $CDCl_3$)

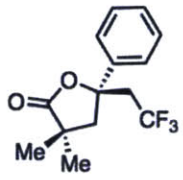


HPLC traces for compound 3i

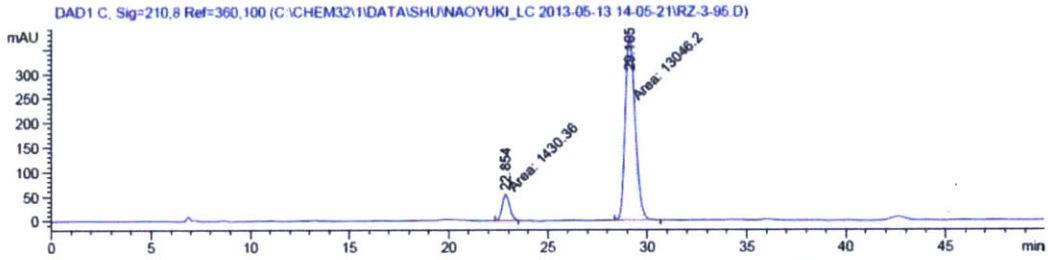


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.690	BB	0.4011	2229.55005	86.97044	49.8795
2	26.771	BB	0.4747	2240.31958	74.10431	50.1205
Totals :				4469.86963	161.07475	

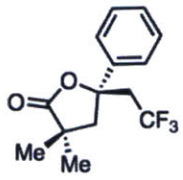


(±)-3i



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

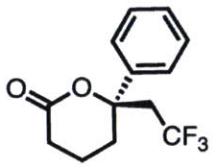
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.854	MM	0.4478	1430.36121	53.24110	9.8805
2	29.105	MM	0.5810	1.30462e4	374.21735	90.1195
Totals :				1.44766e4	427.45845	

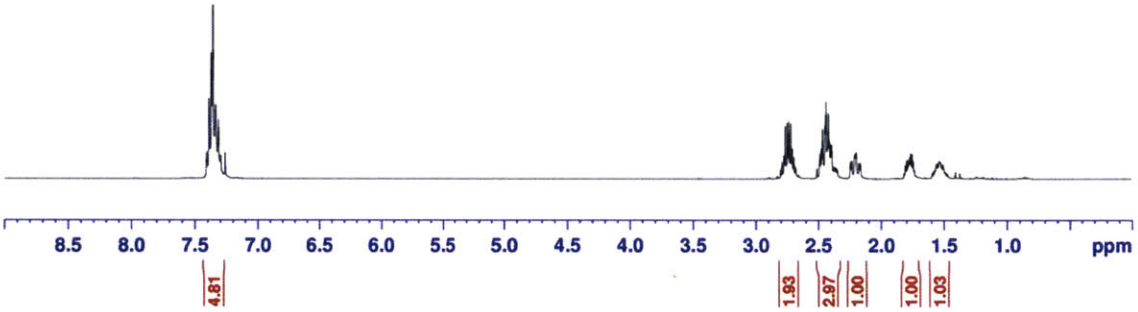


3i

RZ-3-89-H

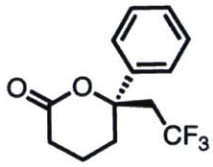
3j ^{1}H NMR (400 MHz, $CDCl_3$)



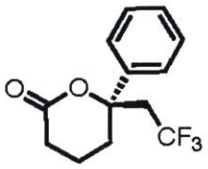


RZ-3-89-C

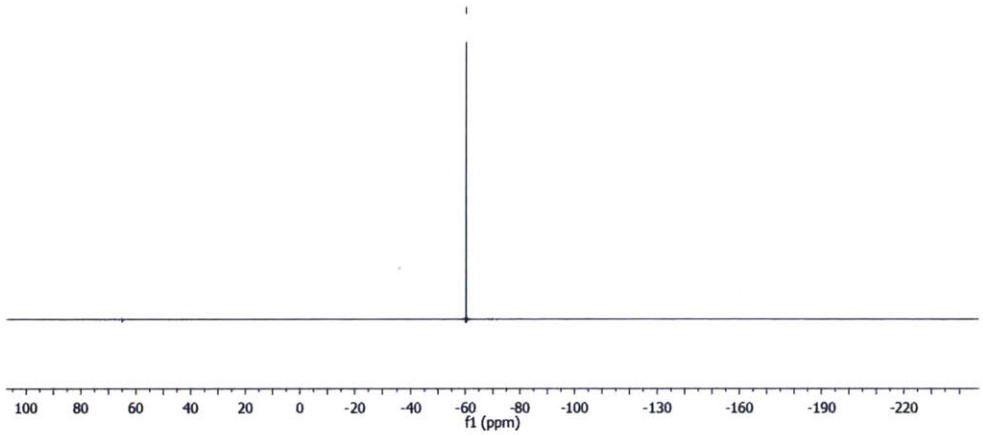
3j ^{13}C NMR (100 MHz, $CDCl_3$)



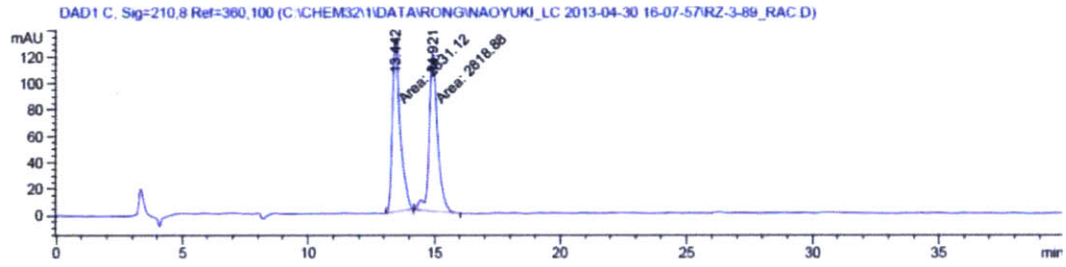
RZ-3-89-F



3j ^{19}F NMR (282 MHz, $CDCl_3$)

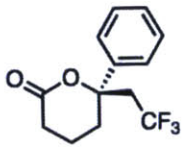


HPLC traces for compound 3j

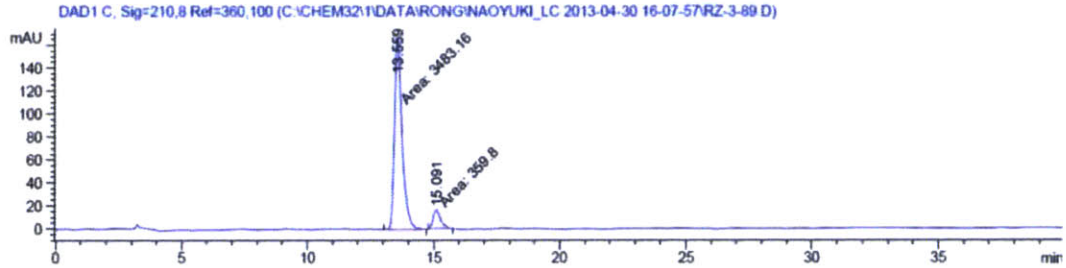


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.442	MM	0.3592	2831.11816	131.36601	50.1083
2	14.921	MM	0.3939	2818.88452	119.28081	49.8917
Totals :				5650.00269	250.64682	

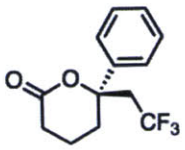


(±)-3j



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

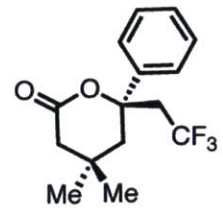
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.559	MM	0.3478	3483.15918	166.91127	90.6374
2	15.091	MM	0.3607	359.80008	16.62308	9.3626
Totals :				3842.95926	183.53435	

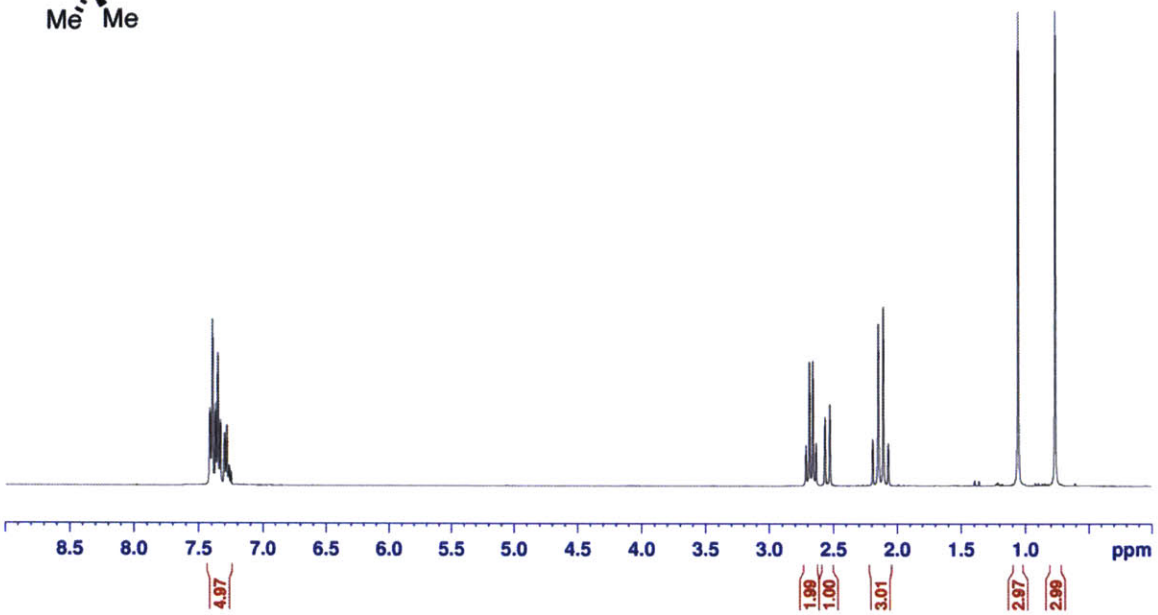


3j

RZ-3-90-H

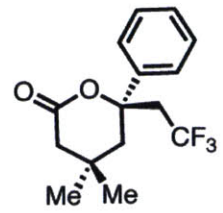
3k ^{1}H NMR (400 MHz, $CDCl_3$)



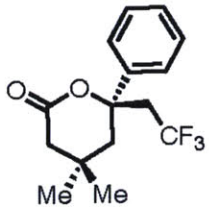


RZ-3-90-C

3k ^{13}C NMR (100 MHz, $CDCl_3$)

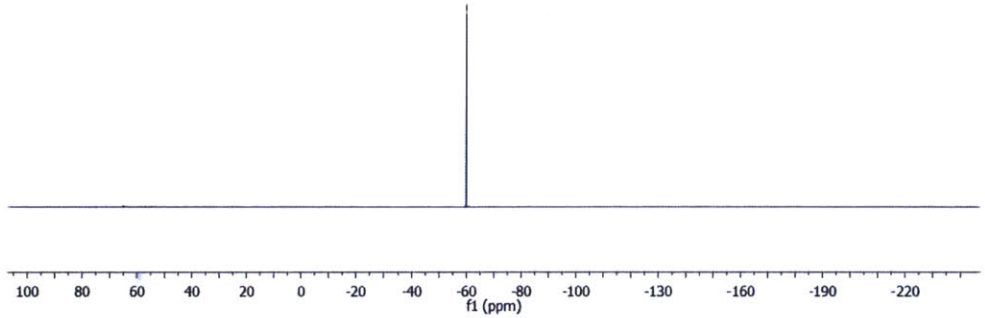


RZ-3-90-F

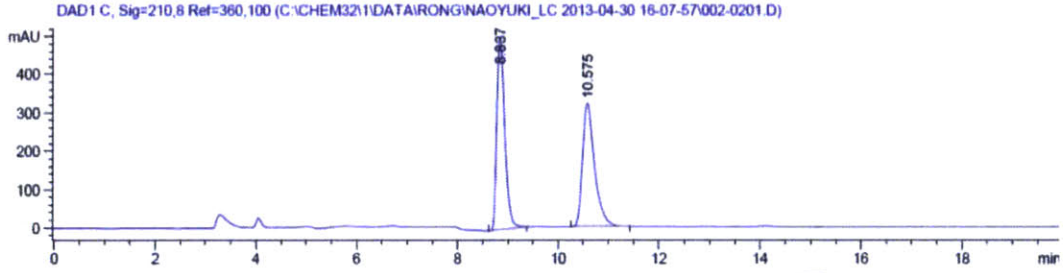


-60.022
-60.059
-60.096

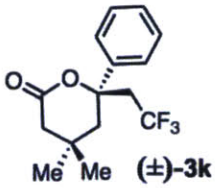
3k ^{19}F NMR (282 MHz, $CDCl_3$)



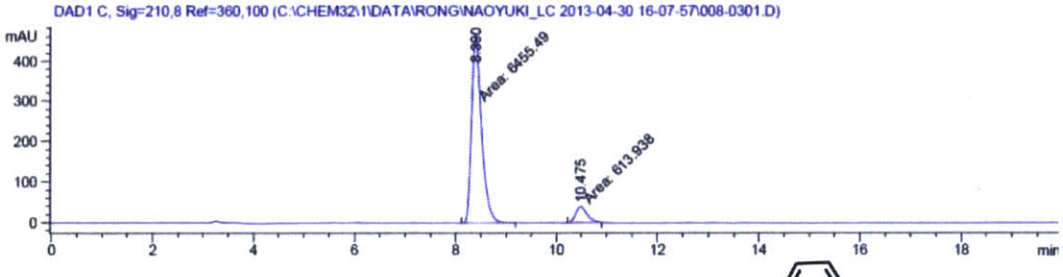
HPLC traces for compound 3k:



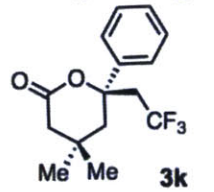
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.837	BB	0.1706	5531.95752	501.89572	50.7018
2	10.575	BB	0.2509	5378.82129	321.92737	49.2982
Totals :				1.09108e4	823.82309	



(±)-3k



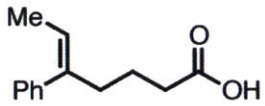
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.390	MM	0.2333	6455.49316	461.21140	91.3156
2	10.475	MM	0.2581	613.93805	39.64419	8.6844
Totals :				7069.43121	500.85558	



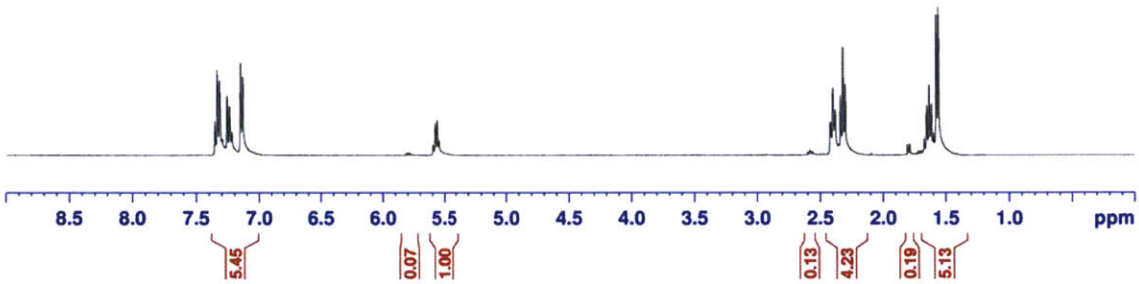
3k

RZ-3-124r3

(*Z*)-**2l** ^{1}H NMR (400 MHz, $CDCl_3$)

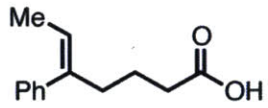


(*Z*)-**2l**
Z:*E* = 14:1

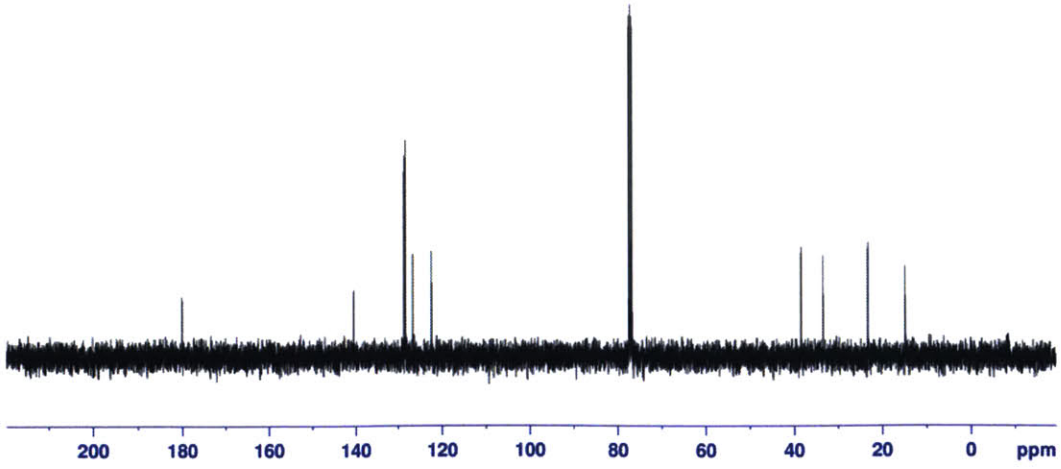


(*Z*)-**2l** ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-3-124r3

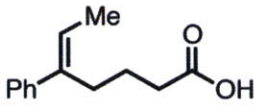


(*Z*)-**2l**
Z:*E* = 14:1

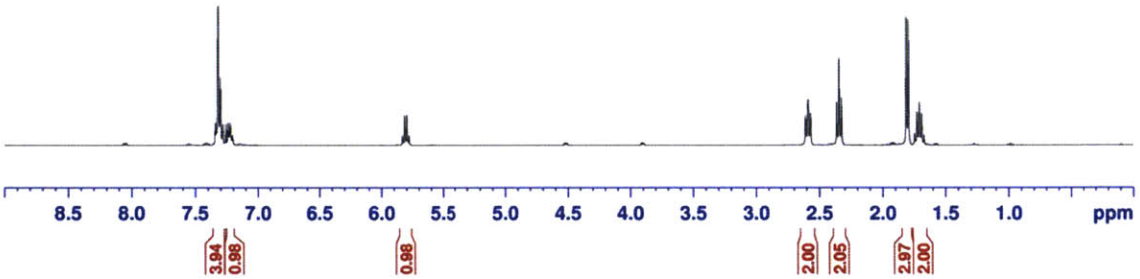


RZ-3-120r2-H

(*E*)-**2l** ^{1}H NMR (400 MHz, $CDCl_3$)

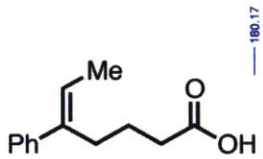


(*E*)-**2l**
E:*Z* > 20:1



(*E*)-**2l** ^{13}C NMR (100 MHz, $CDCl_3$)

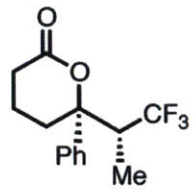
RZ-3-120r2-C

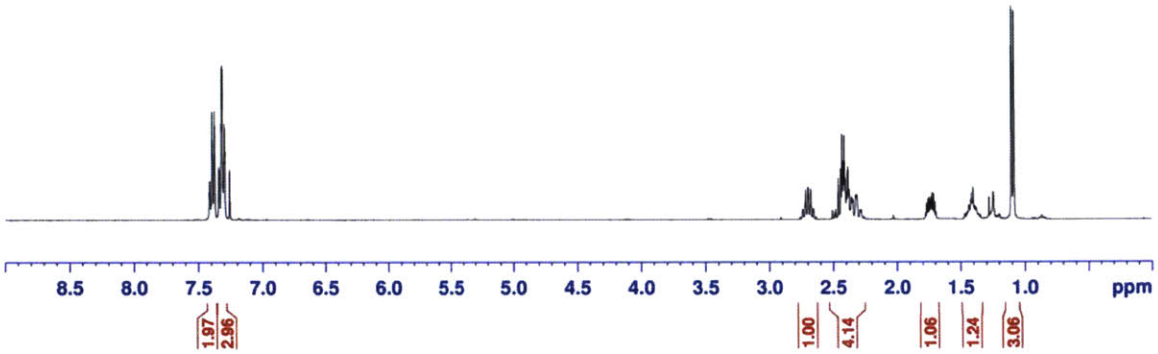


(*E*)-**2l**
E:*Z* > 20:1

RZ-3-129-MajorDiastereomer

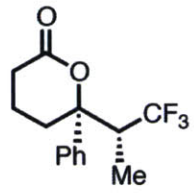
3m ^{1}H NMR (400 MHz, $CDCl_3$)

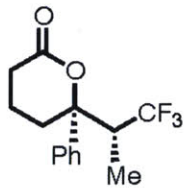




3m ^{13}C NMR (100 MHz, $CDCl_3$)

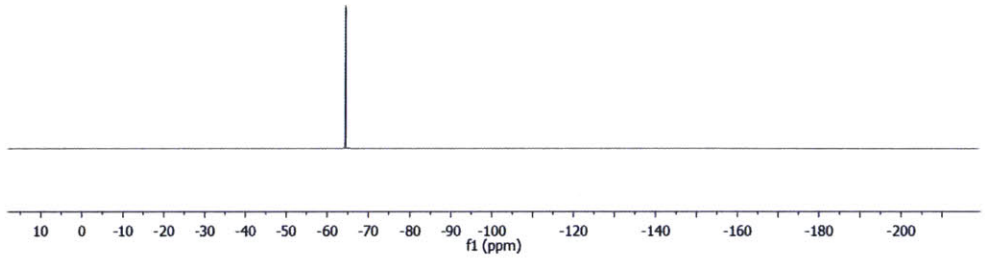
RZ-3-129-MajorDiastereomer



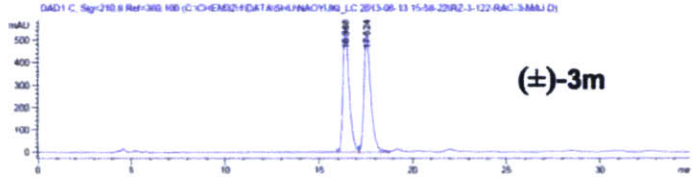


-64.515
-64.539

3m ^{19}F NMR (376 MHz, $CDCl_3$)



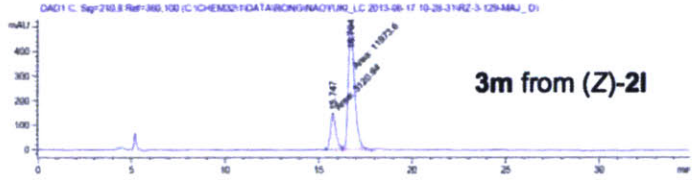
HPLC traces for compound 3m



(±)-3m

Signal 3: DAD1 C, Sig=210,8 Ref=360,100

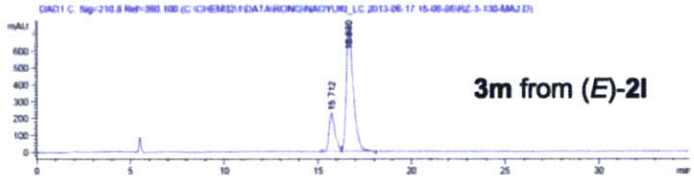
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.388	BV	0.3503	1.30560e4	563.56586	49.3965
2	17.524	VB	0.3830	1.33750e4	525.45898	50.6035
Totals :				2.64311e4	1089.02484	



3m from (*Z*)-2l

Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.747	MM	0.3440	3120.94092	151.19560	20.6759
2	16.704	MM	0.3958	1.19736e4	504.16827	79.3241
Totals :				1.50946e4	655.36388	



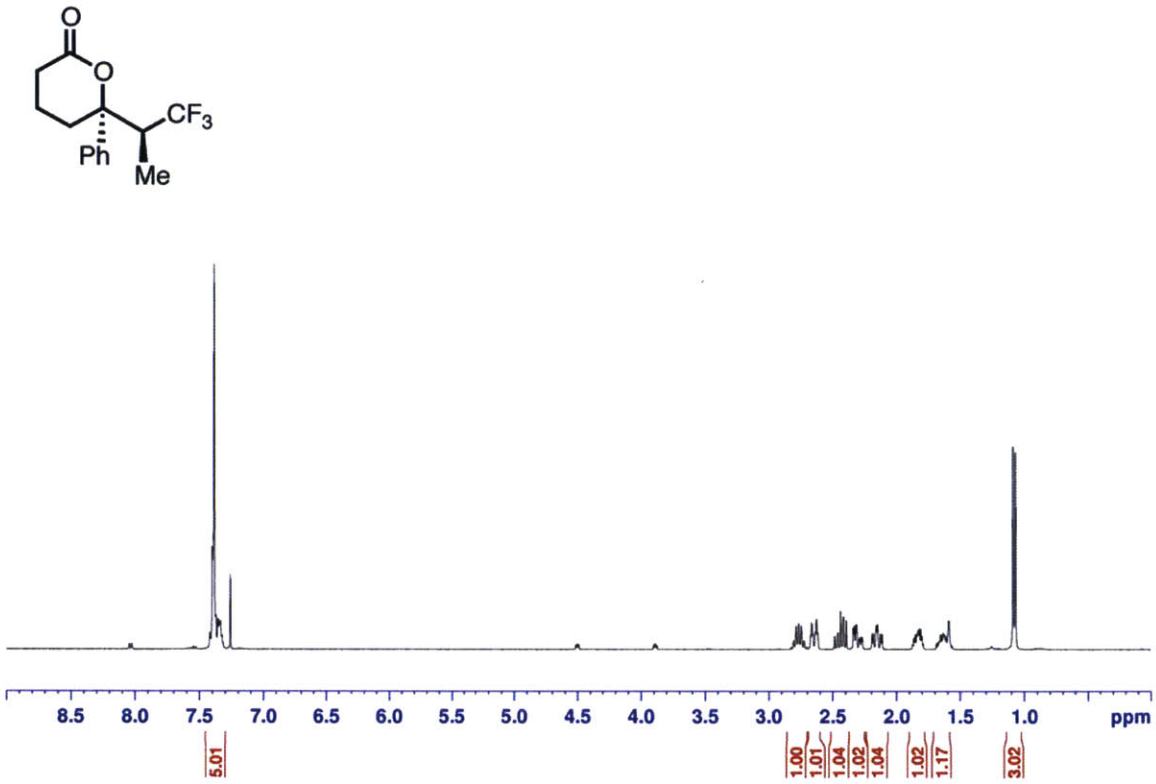
3m from (*E*)-2l

Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.712	BV	0.3480	5173.37012	225.23352	20.9105
2	16.630	VB	0.3985	1.95671e4	739.92780	79.0895
Totals :				2.47405e4	965.16132	

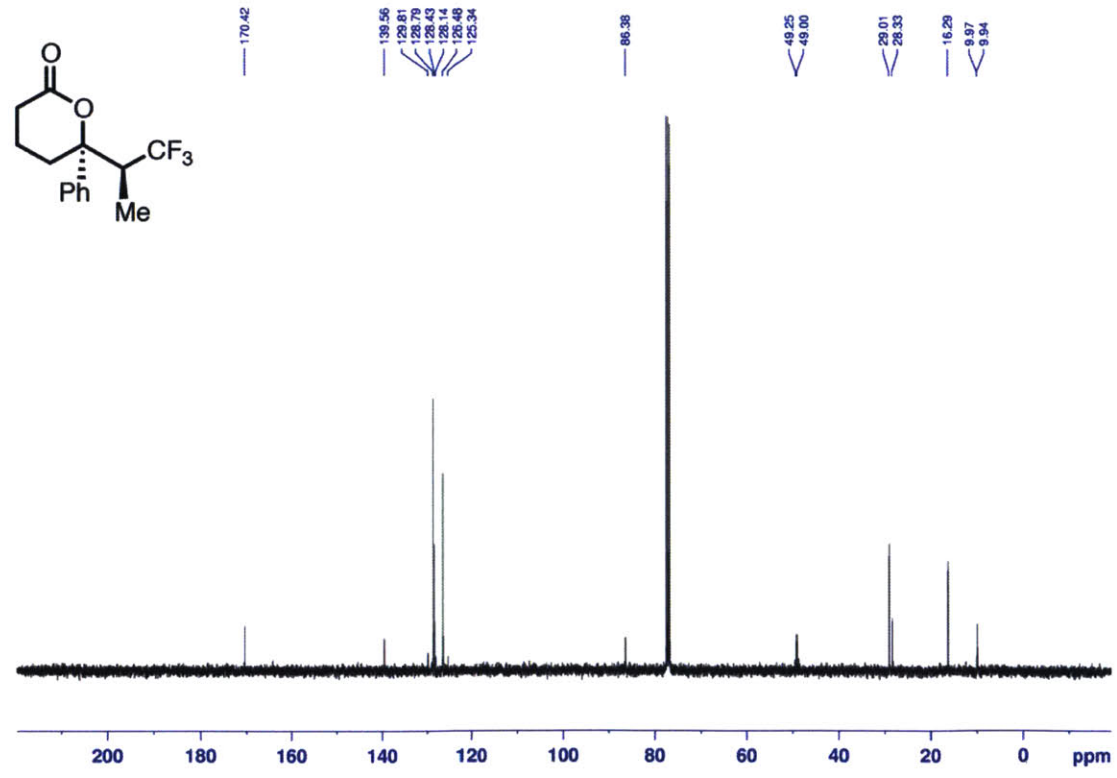
RZ-3-129-MinorDiastereomer

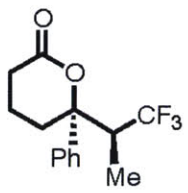
3l ^{1}H NMR (400 MHz, $CDCl_3$)



3l ^{13}C NMR (100 MHz, $CDCl_3$)

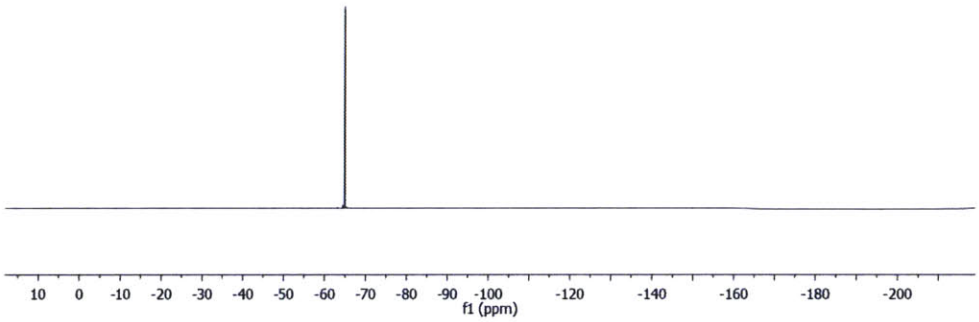
RZ-3-129-MinorDiastereomer



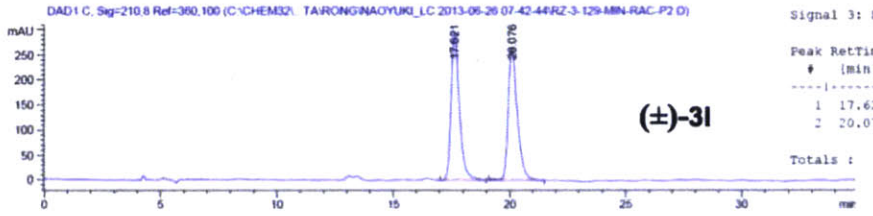


-65.006
-65.030

3l ^{19}F NMR (376 MHz, $CDCl_3$)

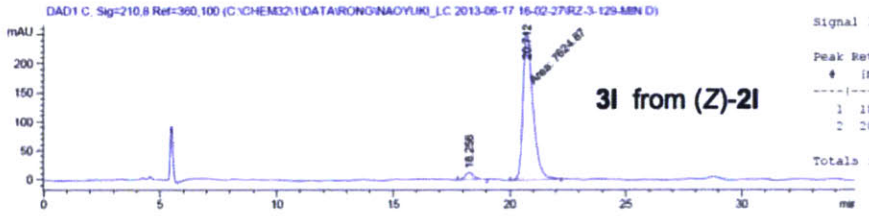


HPLC traces for compound 3l



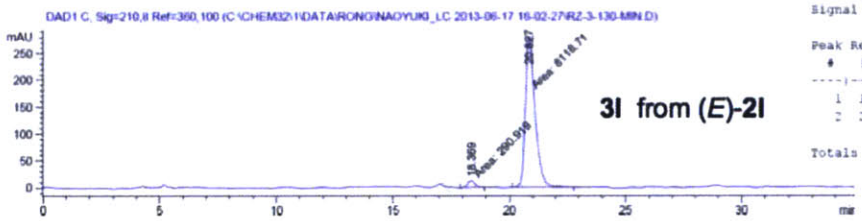
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.621	VB	0.3778	7482.86768	297.09979	50.5319
2	20.076	BB	0.4188	7325.33691	264.73019	49.4681
Totals :				1.48082e4	561.82999	



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.256	BB	0.3821	321.77927	12.85207	4.0492
2	20.712	MM	0.4986	7624.87158	254.85289	95.9508
Totals :				7946.65085	267.70496	

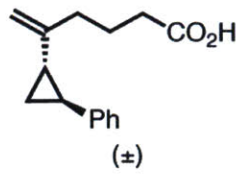


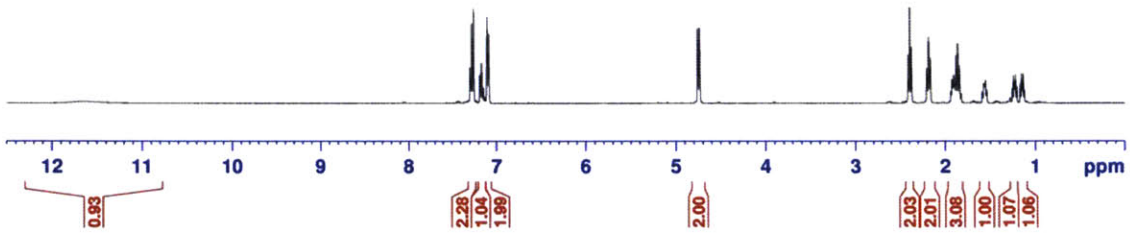
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.369	MM	0.3721	290.91943	13.02949	3.4594
2	20.827	MM	0.4844	8118.70752	279.35886	96.5406
Totals :				8409.62695	292.38835	

RZ-3-133r4

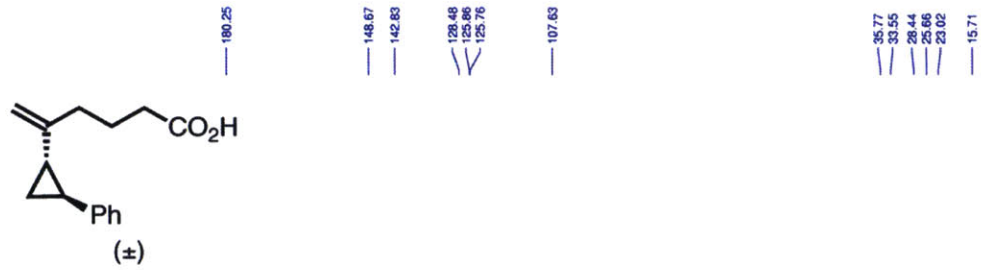
4 ^{1}H NMR (400 MHz, $CDCl_3$)

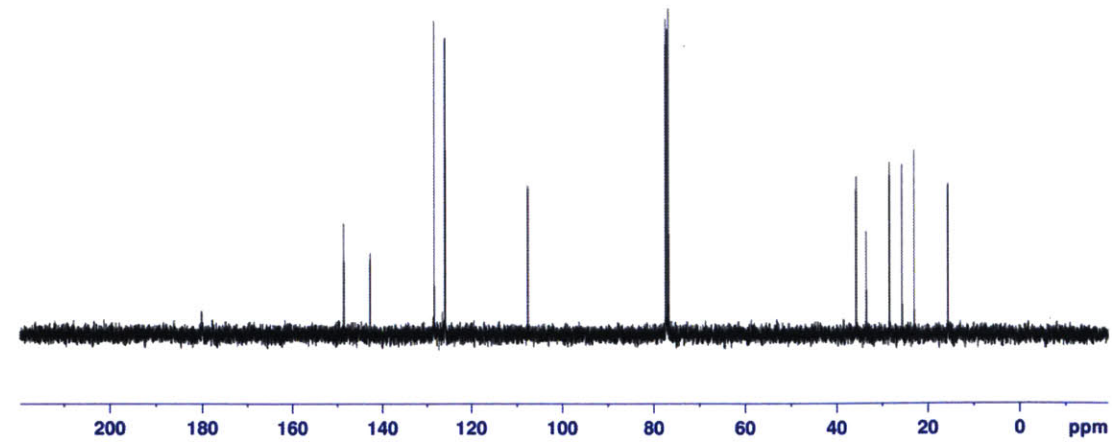




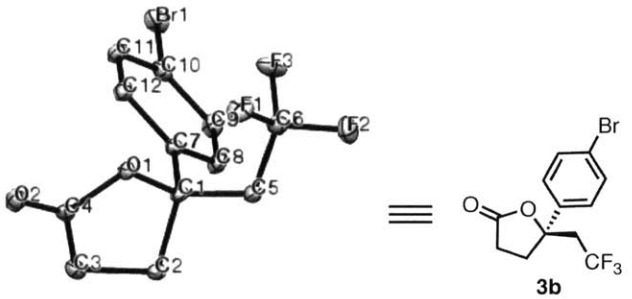
4 ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-3-133r4





X-Ray crystallography information (compound 3b)



3b

Crystal data and structure refinement for x13071

Identification code	x13071	
Empirical formula	C12 H10 Br F3 O2	
Formula weight	323.11	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 14.1070(4) Å	α= 90°.
	b = 5.7880(2) Å	β= 107.5980(10)°.
	c = 15.4036(4) Å	γ = 90°.
Volume	1198.86(6) $Å^3$	
Z	4	
Density (calculated)	1.790 Mg/m^3	
Absorption coefficient	3.458 mm^{-1}	
F(000)	640	
Crystal size	0.250 x 0.150 x 0.100 mm^3	
Theta range for data collection	1.514 to 30.506°.	
Index ranges	-20<=h<=19, -8<=k<=8, -21<=l<=22	
Reflections collected	56400	
Independent reflections	7213 [R(int) = 0.0288]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7213 / 1 / 325	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2sigma(I)]	R1 = 0.0177, wR2 = 0.0430	
R indices (all data)	R1 = 0.0189, wR2 = 0.0432	
Absolute structure parameter	0.0159(19)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.307 and -0.265 e.$Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for x13071. (U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.)

	x	y	z	U(eq)
Br(1)	-800(1)	4920(1)	748(1)	19(1)
F(1)	4346(1)	11753(2)	1403(1)	21(1)

F(2)	4476(1)	9403(2)	364(1)	25(1)
F(3)	3047(1)	10001(2)	564(1)	23(1)
O(1)	3774(1)	9794(2)	2842(1)	12(1)
O(2)	4019(1)	11019(2)	4268(1)	17(1)
C(1)	3639(1)	7612(3)	2357(1)	12(1)
C(2)	4110(2)	5807(3)	3100(1)	14(1)
C(3)	3923(1)	6864(3)	3938(1)	15(1)
C(4)	3926(1)	9424(3)	3756(1)	13(1)
C(5)	4229(1)	7732(3)	1667(1)	14(1)
C(6)	4010(1)	9716(4)	1002(1)	15(1)
C(7)	2536(1)	7102(3)	1933(1)	12(1)
C(8)	2259(1)	5033(4)	1466(1)	17(1)
C(9)	1272(2)	4400(3)	1116(1)	18(1)
C(10)	544(1)	5866(3)	1233(1)	15(1)
C(11)	790(2)	7948(3)	1687(1)	16(1)
C(12)	1789(1)	8561(3)	2038(1)	15(1)
Br(2)	11875(1)	2243(1)	4347(1)	22(1)
F(4)	7042(1)	199(3)	348(1)	35(1)
F(5)	6927(1)	-2047(2)	1408(1)	41(1)
F(6)	8296(1)	-343(3)	1524(1)	45(1)
O(3)	6868(1)	-113(2)	3002(1)	13(1)
O(4)	6089(1)	-1171(3)	3998(1)	19(1)
C(21)	7286(1)	1980(3)	2734(1)	12(1)
C(22)	6770(2)	3948(3)	3097(1)	15(1)
C(23)	6619(2)	2853(3)	3948(1)	16(1)
C(24)	6472(1)	350(3)	3696(1)	14(1)
C(25)	6982(1)	1992(3)	1691(1)	14(1)
C(26)	7315(1)	-48(4)	1251(1)	19(1)
C(27)	8406(1)	2027(3)	3174(1)	12(1)
C(28)	8919(1)	241(3)	3725(1)	16(1)
C(29)	9951(1)	317(3)	4094(1)	17(1)
C(30)	10467(1)	2181(4)	3900(1)	16(1)
C(31)	9973(2)	4004(4)	3365(1)	18(1)
C(32)	8947(2)	3926(3)	3016(1)	16(1)

Bond lengths [Å] and angles [°] for x13071.

Br(1)-C(10)	1.8958(19)	C(8)-C(9)	1.382(3)
F(1)-C(6)	1.349(2)	C(8)-H(8)	0.9500
F(2)-C(6)	1.349(2)	C(9)-C(10)	1.385(3)
F(3)-C(6)	1.332(2)	C(9)-H(9)	0.9500
O(1)-C(4)	1.376(2)	C(10)-C(11)	1.384(3)
O(1)-C(1)	1.451(2)	C(11)-C(12)	1.394(3)
O(2)-C(4)	1.195(2)	C(11)-H(11)	0.9500
C(1)-C(7)	1.523(2)	C(12)-H(12)	0.9500
C(1)-C(5)	1.537(2)	Br(2)-C(30)	1.8949(17)
C(1)-C(2)	1.544(2)	F(4)-C(26)	1.334(2)
C(2)-C(3)	1.523(2)	F(5)-C(26)	1.333(3)
C(2)-H(2A)	0.9900	F(6)-C(26)	1.330(2)
C(2)-H(2B)	0.9900	O(3)-C(24)	1.374(2)
C(3)-C(4)	1.508(3)	O(3)-C(21)	1.461(2)
C(3)-H(3A)	0.9900	O(4)-C(24)	1.198(2)
C(3)-H(3B)	0.9900	C(21)-C(27)	1.519(2)
C(5)-C(6)	1.507(3)	C(21)-C(25)	1.533(2)
C(5)-H(5A)	0.9900	C(21)-C(22)	1.544(2)
C(5)-H(5B)	0.9900	C(22)-C(23)	1.528(2)
C(7)-C(8)	1.391(3)	C(22)-H(22A)	0.9900
C(7)-C(12)	1.398(2)	C(22)-H(22B)	0.9900

C(23)-C(24)	1.499(3)
C(23)-H(23A)	0.9900
C(23)-H(23B)	0.9900
C(25)-C(26)	1.506(3)
C(25)-H(25A)	0.9900
C(25)-H(25B)	0.9900
C(27)-C(28)	1.393(2)
C(27)-C(32)	1.401(3)
C(28)-C(29)	1.395(3)
C(28)-H(28)	0.9500
C(29)-C(30)	1.384(3)
C(29)-H(29)	0.9500
C(30)-C(31)	1.390(3)
C(31)-C(32)	1.384(3)
C(31)-H(31)	0.9500
C(32)-H(32)	0.9500

C(4)-O(1)-C(1)	110.37(13)
O(1)-C(1)-C(7)	110.34(14)
O(1)-C(1)-C(5)	107.64(14)
C(7)-C(1)-C(5)	114.17(13)
O(1)-C(1)-C(2)	104.29(13)
C(7)-C(1)-C(2)	109.97(14)
C(5)-C(1)-C(2)	109.95(14)
C(3)-C(2)-C(1)	102.16(14)
C(3)-C(2)-H(2A)	111.3
C(1)-C(2)-H(2A)	111.3
C(3)-C(2)-H(2B)	111.3
C(1)-C(2)-H(2B)	111.3
H(2A)-C(2)-H(2B)	109.2
C(4)-C(3)-C(2)	103.07(15)
C(4)-C(3)-H(3A)	111.2
C(2)-C(3)-H(3A)	111.2
C(4)-C(3)-H(3B)	111.2
C(2)-C(3)-H(3B)	111.2
H(3A)-C(3)-H(3B)	109.1
O(2)-C(4)-O(1)	120.49(17)
O(2)-C(4)-C(3)	129.93(16)
O(1)-C(4)-C(3)	109.56(15)
C(6)-C(5)-C(1)	117.49(15)
C(6)-C(5)-H(5A)	107.9
C(1)-C(5)-H(5A)	107.9
C(6)-C(5)-H(5B)	107.9
C(1)-C(5)-H(5B)	107.9
H(5A)-C(5)-H(5B)	107.2
F(3)-C(6)-F(1)	106.64(16)
F(3)-C(6)-F(2)	107.11(14)
F(1)-C(6)-F(2)	105.68(15)
F(3)-C(6)-C(5)	114.01(16)
F(1)-C(6)-C(5)	112.54(14)
F(2)-C(6)-C(5)	110.37(16)
C(8)-C(7)-C(12)	118.43(16)
C(8)-C(7)-C(1)	118.68(16)
C(12)-C(7)-C(1)	122.79(16)
C(9)-C(8)-C(7)	121.50(17)
C(9)-C(8)-H(8)	119.3
C(7)-C(8)-H(8)	119.3
C(8)-C(9)-C(10)	119.07(17)
C(8)-C(9)-H(9)	120.5
C(10)-C(9)-H(9)	120.5
C(11)-C(10)-C(9)	121.12(18)
C(11)-C(10)-Br(1)	121.24(15)
C(9)-C(10)-Br(1)	117.64(14)
C(10)-C(11)-C(12)	119.17(18)
C(10)-C(11)-H(11)	120.4
C(12)-C(11)-H(11)	120.4
C(11)-C(12)-C(7)	120.70(17)
C(11)-C(12)-H(12)	119.6
C(7)-C(12)-H(12)	119.6
C(24)-O(3)-C(21)	110.60(14)
O(3)-C(21)-C(27)	110.11(13)
O(3)-C(21)-C(25)	106.87(14)
C(27)-C(21)-C(25)	113.01(14)
O(3)-C(21)-C(22)	103.58(13)
C(27)-C(21)-C(22)	111.50(15)
C(25)-C(21)-C(22)	111.25(14)
C(23)-C(22)-C(21)	101.99(14)
C(23)-C(22)-H(22A)	111.4
C(21)-C(22)-H(22A)	111.4
C(23)-C(22)-H(22B)	111.4
C(21)-C(22)-H(22B)	111.4
H(22A)-C(22)-H(22B)	109.2
C(24)-C(23)-C(22)	102.86(14)
C(24)-C(23)-H(23A)	111.2
C(22)-C(23)-H(23A)	111.2
C(24)-C(23)-H(23B)	111.2
C(22)-C(23)-H(23B)	111.2
H(23A)-C(23)-H(23B)	109.1
O(4)-C(24)-O(3)	119.74(17)
O(4)-C(24)-C(23)	130.79(17)
O(3)-C(24)-C(23)	109.47(15)
C(26)-C(25)-C(21)	116.23(15)
C(26)-C(25)-H(25A)	108.2
C(21)-C(25)-H(25A)	108.2
C(26)-C(25)-H(25B)	108.2
C(21)-C(25)-H(25B)	108.2
H(25A)-C(25)-H(25B)	107.4
F(6)-C(26)-F(5)	106.05(19)
F(6)-C(26)-F(4)	106.77(16)
F(5)-C(26)-F(4)	106.12(17)
F(6)-C(26)-C(25)	113.23(17)
F(5)-C(26)-C(25)	113.41(15)
F(4)-C(26)-C(25)	110.75(17)
C(28)-C(27)-C(32)	118.58(17)
C(28)-C(27)-C(21)	122.46(16)
C(32)-C(27)-C(21)	118.96(16)
C(27)-C(28)-C(29)	120.71(17)
C(27)-C(28)-H(28)	119.6
C(29)-C(28)-H(28)	119.6
C(30)-C(29)-C(28)	119.29(16)
C(30)-C(29)-H(29)	120.4
C(28)-C(29)-H(29)	120.4
C(29)-C(30)-C(31)	121.18(17)
C(29)-C(30)-Br(2)	119.87(14)
C(31)-C(30)-Br(2)	118.94(15)
C(32)-C(31)-C(30)	118.93(18)
C(32)-C(31)-H(31)	120.5
C(30)-C(31)-H(31)	120.5

C(31)-C(32)-C(27)	121.25(17)	
C(31)-C(32)-H(32)	119.4	Symmetry transformations used to generate
C(27)-C(32)-H(32)	119.4	equivalent atoms:

Anisotropic displacement parameters ($Å^2 \times 10^3$) for x13071. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U1^2]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	13(1)	26(1)	17(1)	0(1)	2(1)	-4(1)
F(1)	23(1)	14(1)	26(1)	0(1)	9(1)	-3(1)
F(2)	30(1)	29(1)	21(1)	2(1)	15(1)	2(1)
F(3)	14(1)	27(1)	23(1)	10(1)	0(1)	2(1)
O(1)	15(1)	10(1)	11(1)	-2(1)	2(1)	1(1)
O(2)	15(1)	20(1)	15(1)	-6(1)	2(1)	1(1)
C(1)	12(1)	9(1)	12(1)	-1(1)	2(1)	1(1)
C(2)	16(1)	12(1)	13(1)	2(1)	2(1)	4(1)
C(3)	15(1)	17(1)	12(1)	2(1)	2(1)	1(1)
C(4)	7(1)	18(1)	12(1)	-1(1)	1(1)	0(1)
C(5)	13(1)	13(1)	14(1)	-1(1)	4(1)	3(1)
C(6)	14(1)	17(1)	15(1)	-1(1)	4(1)	1(1)
C(7)	12(1)	12(1)	10(1)	0(1)	2(1)	1(1)
C(8)	15(1)	16(1)	20(1)	-6(1)	4(1)	2(1)
C(9)	18(1)	16(1)	18(1)	-5(1)	3(1)	-2(1)
C(10)	12(1)	19(1)	11(1)	2(1)	2(1)	-2(1)
C(11)	12(1)	18(1)	19(1)	-1(1)	6(1)	3(1)
C(12)	15(1)	13(1)	15(1)	-2(1)	4(1)	2(1)
Br(2)	11(1)	28(1)	24(1)	-1(1)	3(1)	0(1)
F(4)	59(1)	34(1)	14(1)	1(1)	13(1)	13(1)
F(5)	80(1)	19(1)	34(1)	-9(1)	33(1)	-14(1)
F(6)	26(1)	58(1)	48(1)	-28(1)	6(1)	16(1)
O(3)	14(1)	12(1)	15(1)	2(1)	7(1)	0(1)
O(4)	15(1)	24(1)	20(1)	6(1)	7(1)	0(1)
C(21)	12(1)	10(1)	14(1)	1(1)	5(1)	1(1)
C(22)	16(1)	13(1)	18(1)	2(1)	9(1)	4(1)
C(23)	19(1)	17(1)	15(1)	1(1)	8(1)	4(1)
C(24)	8(1)	19(1)	12(1)	2(1)	1(1)	3(1)
C(25)	16(1)	15(1)	13(1)	2(1)	4(1)	3(1)
C(26)	23(1)	19(1)	15(1)	-1(1)	6(1)	1(1)
C(27)	12(1)	13(1)	12(1)	0(1)	4(1)	1(1)
C(28)	17(1)	14(1)	18(1)	4(1)	6(1)	1(1)
C(29)	16(1)	16(1)	18(1)	4(1)	4(1)	4(1)
C(30)	10(1)	21(1)	17(1)	-1(1)	4(1)	1(1)
C(31)	18(1)	18(1)	19(1)	2(1)	7(1)	-3(1)
C(32)	18(1)	14(1)	17(1)	4(1)	5(1)	1(1)

Hydrogen coordinates ($x 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for x13071.

	x	y	z	U(eq)
H(2A)	3781	4285	2952	17
H(2B)	4831	5628	3186	17
H(3A)	3274	6360	3997	18
H(3B)	4456	6442	4500	18
H(5A)	4945	7786	2013	16

H(5B)	4113	6277	1313	16
H(8)	2760	4032	1385	21
H(9)	1095	2979	799	22
H(11)	285	8948	1758	20
H(12)	1964	9986	2352	18
H(22A)	7199	5336	3251	18
H(22B)	6127	4373	2650	18
H(23A)	7210	3081	4486	20
H(23B)	6028	3504	4079	20
H(25A)	6248	2085	1457	17
H(25B)	7251	3412	1494	17
H(28)	8561	-1041	3851	19
H(29)	10297	-898	4474	20
H(31)	10334	5284	3241	22
H(32)	8603	5184	2662	20

Chapter 3.

General Cu-Catalyzed Enantioselective
Alkene Oxyfunctionalization via Radical Intermediates

3.1 Introduction

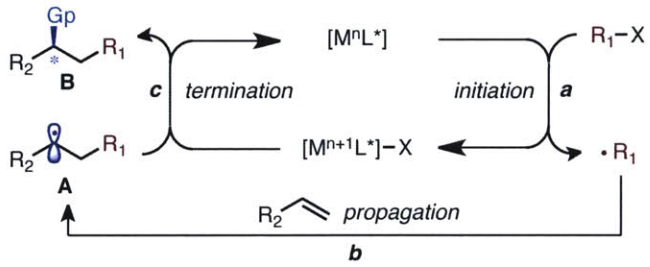
Transition metal-catalyzed enantioselective alkene difunctionalization has emerged as a powerful tool for the synthesis of complex chiral molecules from simple starting materials.[1] Studies in this field have been focused on the development of new strategies to expand the scope of the accessible bond types and structures. While most of the existing strategies have been developed based on two electron processes, the difunctionalization reactions involving alkyl radical intermediates render especially attractive as they could offer different reactivity and selectivity, and potentially lead to more efficient and versatile syntheses.

In this context, we turned our attention to the atom transfer radical addition of alkenes, one of the most important and commonly used methods to generate such alkyl radicals.[2] While the alkyl radical intermediates involved in this type of reaction have been shown to be readily intercepted to form new carbon–carbon/carbon–heteroatom bonds in a racemic fashion,[3] enantioselective functionalization remains challenging.[4] Pioneering work by Porter[5a] and Sibi[5b] made use of a Lewis acid-substrate complexation strategy to achieve enantioselectivity. Additionally, a few reports have shown that chiral chain-transfer catalysts could be used for enantioselective hydrogen atom transfer.[6,7] These approaches are mainly limited to C–C or C–H bond formation from alkyl radicals derived from highly electronically activated alkenes such as α,β-unsaturated carbonyl derivatives. However, to enable the use of less activated alkene substrates and achieve enantioselective carbon–heteroatom bond formation, a new strategy is required.

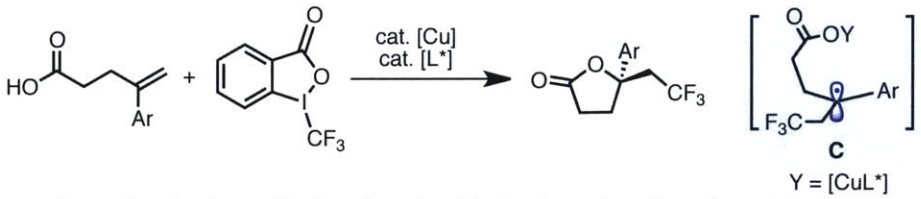
To achieve the desired enantioselective difunctionalization, we hoped to take advantage of a chiral transition metal redox catalyst (Scheme 1a). The chiral metal complex would serve two functions: 1) initiate radical formation when in the lower oxidation state (step **a**) and 2) mediate the enantioselective bond forming process via prochiral radical **A** when in the higher oxidation state (step **c**). While a variety of redox catalysts based on different transition metals are capable of mediating step **a**,[8] a catalyst delivering effective enantioselectivity in step **c** remains elusive. The only efforts to develop such catalysts were reported by Sonoda,[9a] Kamigata,[9b] and Brunner,[9c] who used chiral ruthenium, rhodium and copper complexes to catalyze the atom transfer radical addition reactions involving carbon–halogen bond formation to afford products in 16% ee, 10-40% ee, and 9-20% ee, respectively.

Scheme 1. *Mechanistic hypothesis and development of a copper-catalyzed enantioselective difunctionalization.*

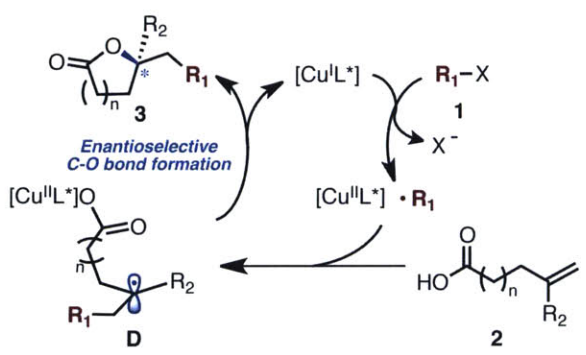
a) Alkene radical addition catalyzed by a chiral transition metal complex redox system



b) Previous work: Cu-catalyzed enantioselective oxytrifluoromethylation via a radical intermediate



c) General enantioselective radical oxyfunctionalization based on Cu-redox catalysis



This work:

R_1—	
N_3—	*Oxyazidation*
$ArSO_2$—	*Oxysulfonylation*
Ar—	*Oxyarylation*
RCO_2—	*Diacyloxylation*

R_2 = aryl, alkynyl, H
n = 1, 2

Our interest in developing a new redox catalyst system for the enantioselective functionalization of radical intermediate **A** originated from our recent study on the copper-catalyzed enantioselective alkene oxytrifluoromethylation reaction (Scheme 1b).[10] During the course of our investigation, we found this transformation likely proceeds by a radical addition mechanism involving a copper-mediated enantioselective C–O bond forming process, through which a tetrasubstituted carbon stereogenic center is produced from tertiary alkyl radical **C**.

Given the stepwise nature of this radical addition/interception mechanism, we envisioned that this enantioselective C–O bond forming process could potentially serve as a general

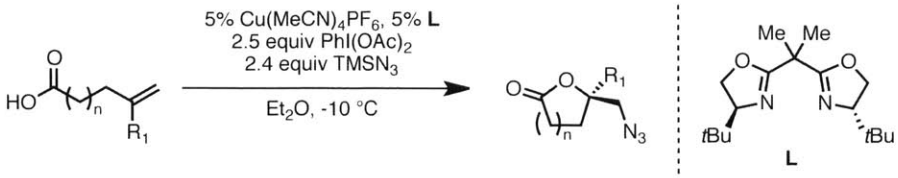
strategy en route to a class of new alkene enantioselective difunctionalization reactions involving the addition of a set of different radicals. (Scheme 1c) The intrinsic versatility associated with this strategy could potentially lead to more efficient and straightforward syntheses of a diverse collection of useful enantiomerically enriched structures starting from simple starting materials. In this report, we present a general copper-catalyzed method for the enantioselective oxyfunctionalization of alkenes, including: oxyazidation ($R_1 = N_3$), oxysulfonylation ($R_1 = ArSO_2-$), oxyarylation ($R_1 = Ar$), and diacyloxylation ($R_1 = RCO_2-$).

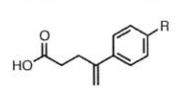
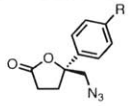
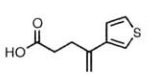
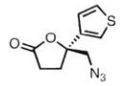
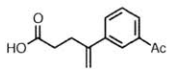
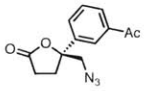
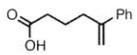
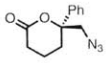
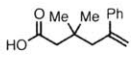
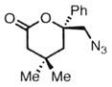
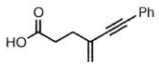
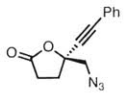
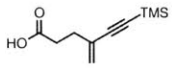
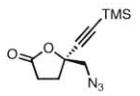
3.2 Results and Discussion

We began our investigation by applying this general strategy to the catalytic enantioselective alkene oxyazidation reaction ($R_1 = N_3$), [11,12] in part, because it yields a straightforward yet rarely explored approach to enantiomerically enriched 1,2-aminoalcohol derivatives, which are useful synthetic building blocks and are found in many biologically relevant compounds.[13] To evaluate the proposed transformation, we examined the reaction of 4-phenyl-4-pentenoic acid (**2a**) with a combination of two simple commercially available reagents, (diacetoxyiodo)benzene as the oxidant and trimethylsilyl azide as the azidyl radical precursor.[14] It was found that, in the presence of a catalytic amount of $Cu(MeCN)_4PF_6$ and (*S,S*)-^{t}BuBox (**L**), the desired oxyazidation product **4a** could be obtained in 63% yield and 89% ee (Table 1, entry 1). The use of preformed azido-iodine(III) reagents did not yield detectable amount of desired product.[15]

We next explored the scope of this transformation and representative examples are summarized in Table 1. A series of unsaturated carboxylic acids bearing different aryl substituents on the alkene were found to undergo the desired oxyazidation reaction to afford the corresponding azidolactones in good enantioselectivity (**4a-j**). Electron-neutral and -deficient aryl substituents were well tolerated (**4a-e**), while slightly lower enantioselectivity was observed with substrates containing a very electron-rich *p*-methoxyphenyl substituent (**4f**). The mild reaction conditions were compatible with a range of functional groups including aryl halides (**4b**, **4c**), nitriles (**4d**), ketones (**4h**), and 3-thiophenyl groups (**4g**). In addition, both γ- and δ-lactones (**4i**, **4j**) proved accessible under the standard reaction conditions. The incorporation of a geminal dimethyl group in the substrate showed little effect on the enantioselectivity obtained.

Table 1. *Cu-Catalyzed enantioselective alkene oxyazidation.*[a]



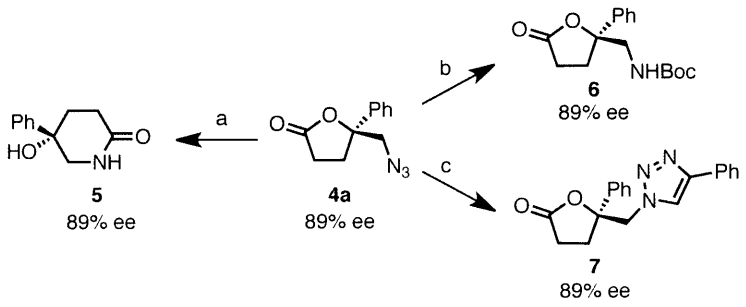
Entry	Substrate		Product	Yield [%][b]	ee [%][c]
					
1	R = H	2a	4a	63	89
2	R = Br	2b	4b	55	89
3	R = Cl	2c	4c	56	89
4	R = CN	2d	4d	50	90
5[e]	R = CF_3	2e	4e	46	91
6	R = OMe	2f	4f	68	75
7[d]		2g	 4g	69	82
8[e]		2h	 4h	53	90
9		2i	 4i	62	89
10		2j	 4j	68	92
11[e]		2k	 4k	50	72
12[e,f]		2l	 4l	44	82

[a]Reaction conditions: $Cu(MeCN)_4PF_6$ (5 mol%), **L** (5 mol%), **2** (0.50 mmol, 1.0 equiv), $PhI(OAc)_2$ (2.5 equiv), $TMSN_3$ (2.4 equiv), in 30 mL Et_2O at -10 °C for 16 h. [b]Yields of isolated products are an average of two runs. [c]Determined by HPLC analysis using a chiral stationary phase. [d]Additional 2,6-di-*tert*-butylpyridine (1.1 equiv) was added. [e]$Cu(MeCN)_4PF_6$ (8 mol%) and **L** (8 mol%) was used. [f]Enantiomeric excess was determined by HPLC analysis of the derivatized product, see the Supporting Information.

We next sought to apply this protocol to substrates without a styrenyl unit (**2k** and **2l**). Substrates containing a 1,3-enyne structure are especially interesting because further transformation of the alkyne group in the product would give access to a more diverse class of structures. It was found that the oxyazidation of these substrates proceeded smoothly to furnish the enantiomerically enriched lactone product in moderate yields and moderate to good enantiomeric excesses (**4k**, **4l**). Notably, a silyl protecting group on the alkyne was tolerated which allows for further elaboration of the product (**4l**).

The azide group in the lactone product can be easily converted to a number of useful nitrogen-containing functional groups in good yields (Scheme 2). For example, palladium-catalyzed hydrogenation of lactone **4a** in methanol afforded chiral tertiary alcohol-containing *d*-lactam **5** via an azide reduction/translactamization cascade. Conversely, hydrogenation of **4a** in the presence of di-*tert*-butyl dicarbonate furnished the Boc-protected aminolactone **6**. The azide group could also undergo [3+2] cycloaddition with phenylacetylene to give a triazole derivative **7**. No erosion of enantiomeric excess was observed in any of these cases.

Scheme 2. *Derivatization of the oxyazidation product* ***4a***.[a]

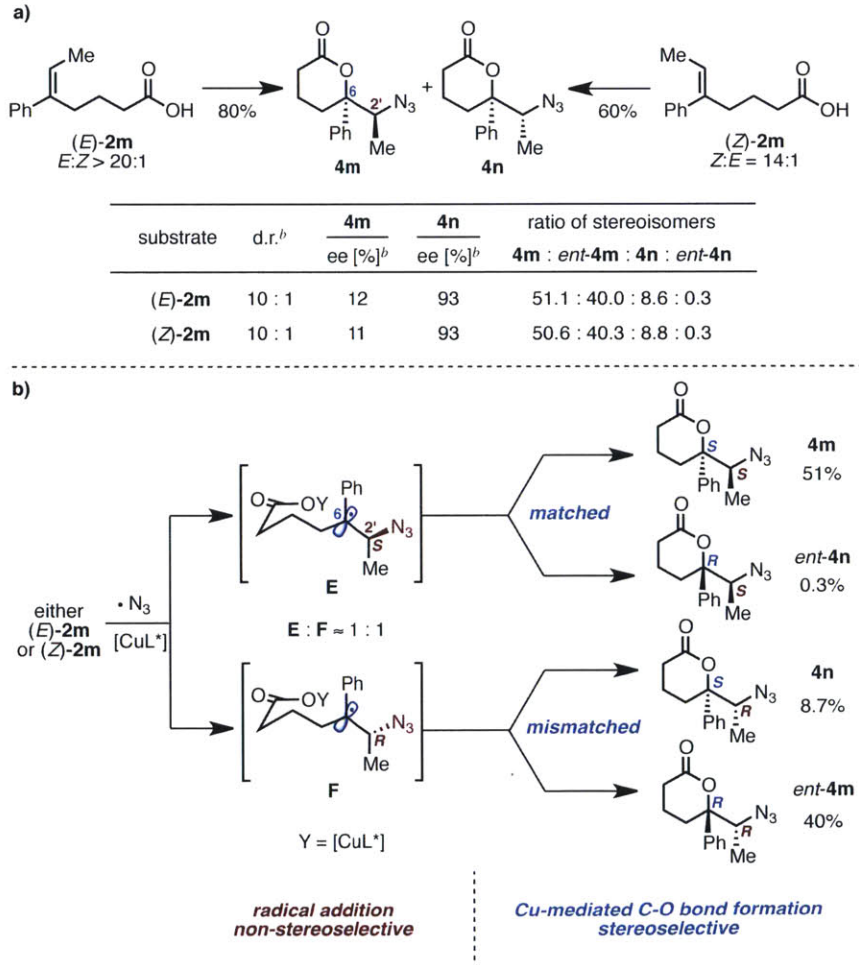


[a]Reaction conditions: (a) Pd/C, H_2 (balloon), MeOH, RT; then DMAP (10 mol%), RT, 78%; (b) Pd/C, H_2 (balloon), Boc_2O, THF, RT, 88%; (c) Sodium ascorbate (0.8 equiv), $CuSO_4 \cdot 5H_2O$ (0.4 equiv), phenylacetylene (1.1 equiv), ^{t}BuOH/H_2O, RT, 96%.

To provide further evidence for our mechanistic hypothesis, oxyazidation reactions with trisubstituted alkene substrates were examined. As shown in Scheme 3a, both geometric isomersuscis of 5-phenyl-5-heptenoic acid ((*E*)-and (*Z*)-**2m**) were synthesized and subjected to the standard reaction conditions. It was found that, regardless of the alkene geometry of the substrate (*E* or *Z*), the same product diastereomeric ratio (**4m**:**4n** = 10:1) and same enantiomeric excess for each diastereomer were obtained (**4m**: 11 and 12% ee, **4n**: 93 and 93% ee). This observation was consistent with the radical addition type mechanism proposed in

Scheme 1c. The fact that the sum of products **4m** and *ent*-**4n** (~51%) equals that of **4n** and *ent*-**4m** (~49%) suggests the formation of a pair of enantiomeric radical intermediates **E** (2'*S*) and **F** (2'*R*) in a 1:1 ratio from a non-stereoselective azidyl radical addition process. Since both the chiral copper catalyst and the already established stereogenic center C2' in intermediates **E** and **F** would have an impact on the stereoselectivity of the C–O bond forming process, the final product distribution could be explained by a substrate-control/catalyst-control competition model demonstrated in Scheme 3b. For **E**, the substrate-controlled selectivity (6*S*, 2'*S* over 6*R*, 2'*S*) is reinforced by the catalyst-controlled selectivity (6*S* over 6*R*), therefore giving a high selectivity (51:0.3) favoring **4m** over *ent*-**4n**. For **F**, a low selectivity (40:8.7) for *ent*-**4m** over **4n** was observed as a result of the opposing substrate-controlled (6*R*, 2'*R* over 6*S*, 2'*R*) and catalyst-controlled (6*S* over 6*R*) selectivities.[16]

Scheme 3. *Cu-Catalyzed oxyazidation of trisubstituted alkenes.*[a]

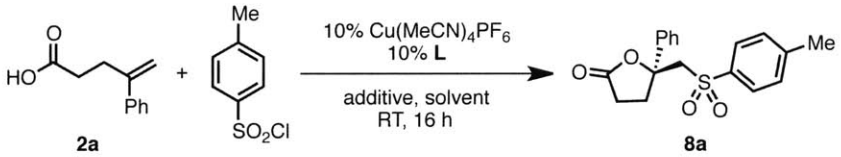


substrate	d.r.[b]	**4m** ee [%][b]	**4n** ee [%][b]	ratio of stereoisomers **4m** : *ent*-**4m** : **4n** : *ent*-**4n**
(*E*)-**2m**	10 : 1	12	93	51.1 : 40.0 : 8.6 : 0.3
(*Z*)-**2m**	10 : 1	11	93	50.6 : 40.3 : 8.8 : 0.3

[a]Reaction conditions: $Cu(MeCN)_4PF_6$ (10 mol%), **L** (10 mol%), **2m** (0.10 mmol, 1.0 equiv), $PhI(OAc)_2$ (2.5 equiv), $TMSN_3$ (2.4 equiv), in 6 mL Et_2O at -10 °C for 16 h. [b]Determined by HPLC analysis using a chiral stationary phase.

With these results in hand, the copper-catalyzed enantioselective oxysulfonylation involving the addition of a sulfonyl radical was next attempted. This transformation would furnish enantiomerically enriched β-hydroxy sulfone derivatives, which are found in many biologically relevant molecules.[17] Molecules containing this structure are also frequently used as intermediates in the synthesis of a variety of natural products.[18] Traditional synthesis of chiral β-hydroxyl sulfones typically involves the asymmetric reduction of β-ketosulfones,[19] which does not provide access to β-sulfonyl tertiary alcohol derivatives. We hypothesized this could be addressed by our copper-catalyzed strategy.

Table 2. *Selected optimizations for the Cu-catalyzed enantioselective alkene oxysulfonylation.*[a]



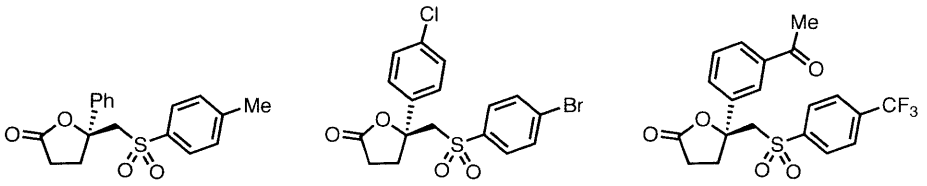
Entry	Base	Solvent	Yield [%][b]	ee [%][c]
1	-	EtOAc	12	28
2	NaOAc (1.1 equiv)	EtOAc	37	18
3	AgOAc (1.1 equiv)	EtOAc	62	74
4	Ag_2CO_3 (0.55 equiv)	EtOAc	95	74
5	Ag_2CO_3 (0.55 equiv)	MTBE	31	66
6	Ag_2CO_3 (0.55 equiv)	Et_2O	48	38

[a]Reaction conditions: $Cu(MeCN)_4PF_6$ (10 mol%), **L** (10 mol%), **2a** (0.10 mmol, 1.0 equiv), tosyl chloride (1.1 equiv), base (x equiv), in 2 mL solvent at RT for 16 h. [b]Yields were determined by ^1H NMR spectroscopic analysis using a internal standard. [c]Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

In order to test this hypothesis, we studied the reaction of **2a** with tosyl chloride as the sulfonyl radical precursor in the presence of the Cu(I) catalyst and **L** (Table 2). The original reaction in ethyl acetate provided the oxysulfonylation product **8a** in 12% yield and 28% ee (entry 1). It was found that the yield of **8a** could be improved by the addition of a base to neutralize the acid generated during the course of the reaction (entry 2). With respect to the observed low enantioselectivity, we reasoned that the enantioselectivity might be adversely affected by the chloride ion generated from the reduction of tosyl chloride via catalyst coordination. Based on this analysis, the reaction was carried out in the presence of silver

acetate as both an acid and a chloride scavenger, and a significant increase in yield and enantioselectivity was observed (entry 3). After evaluation of a series of silver salts, silver carbonate was identified as optimal, leading to an excellent yield of the desired product with over 70% ee (entry 4). The use of methyl *tert*-butyl ether or ethyl ether as the solvent was found to be inferior compared to ethyl acetate with regard to both the yield and enantioselectivity (entry 5 and 6).

***Scheme 4**. Examples of the Cu-catalyzed enantioselective oxysulfonylation.*[a]



8a 92% yield, 74% ee

8b 95% yield, 77% ee

8c 68% yield, 80% ee

[a]Reaction conditions: $Cu(MeCN)_4PF_6$ (10 mol%), **L** (10 mol%), **2** (0.50 mmol, 1.0 equiv), arylsulfonyl chloride (1.1 equiv), silver carbonate (0.60 equiv), in 8 mL ethyl acetate at RT for 16 h. Yields are of isolated products (average of two runs). Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

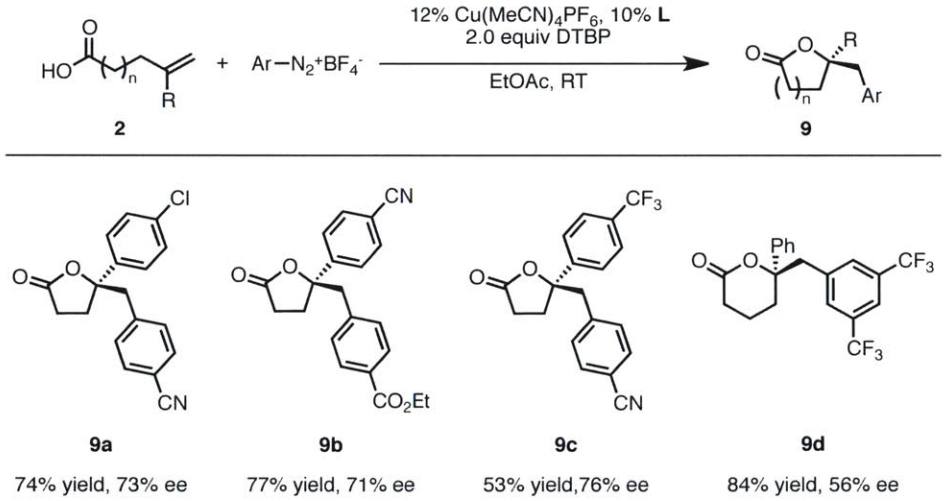
Representative examples of the enantioselective oxysulfonylation are shown in Scheme 5. In general, this method delivers enantiomerically-enriched sulfonylated lactones in good to high yields and good enantioselectivity. The readily availability of arylsulfonyl chlorides allows the quick access to chiral building blocks containing a diverse collection of arylsulfonyl groups using this method.

Next, we sought to expand the scope of this method further to include not only C–N and C–S bond formation but also C–C bond formation, such as C–Aryl bond formation. The enantioselective alkene oxyarylation initiated by the addition of an aryl radical is a potentially powerful reaction for the facile synthesis of chiral alcohol derivatives bearing different α-aryl substituents.[20] We proposed that this transformation could be achieved through the merger of our copper redox catalysis strategy and the classic Meerwein arylation conditions using aryl diazonium salts.

It was found that in the presence of the copper chiral catalyst and 2,6-di-^{t}Bupyridine (DTBP) as an acid scavenger, a series of unsaturated carboxylic acids with electron-neutral and

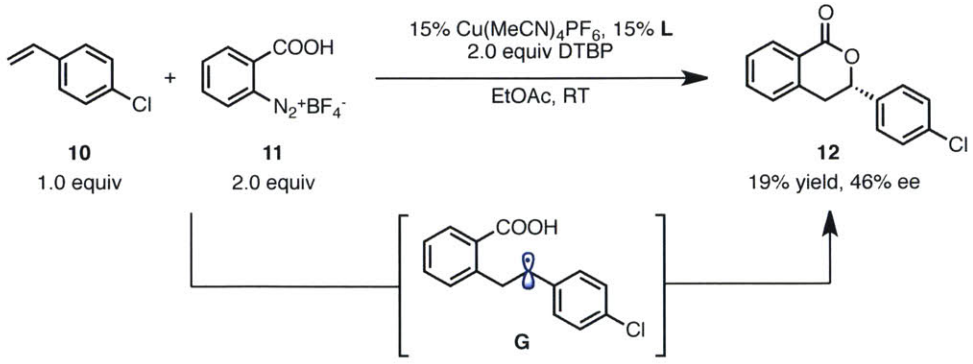
-deficient aryl groups reacted with aryl diazonium salts to furnish the desired oxyarylation products in good yields with moderate to good enantioselectivity (Scheme 5, **9a**-**9d**). A number of common functional groups were found to be compatible with the reaction conditions, such as an aryl chloride (**9a**), an ethyl benzoate (**9b**) and a nitrile group (**9c**). In addition, a δ-unsaturated carboxylic acid afforded the corresponding arylated δ-lactone in good yield, albeit with a lower ee (**9d**).

Scheme 5. *Examples of the Cu-catalyzed enantioselective oxyarylation.*[a].



[a]Reaction conditions: $Cu(MeCN)_4PF_6$ (12 mol%), **L** (10 mol%), **2** (0.50 mmol, 1.0 equiv), aryl diazonium tetrafluoroborate (2.0 equiv), 2,6-di-^{t}Bupyridine (2.0 equiv), in 8 mL ethyl acetate at RT for 16 h. Yields are of isolated products (average of two runs). Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

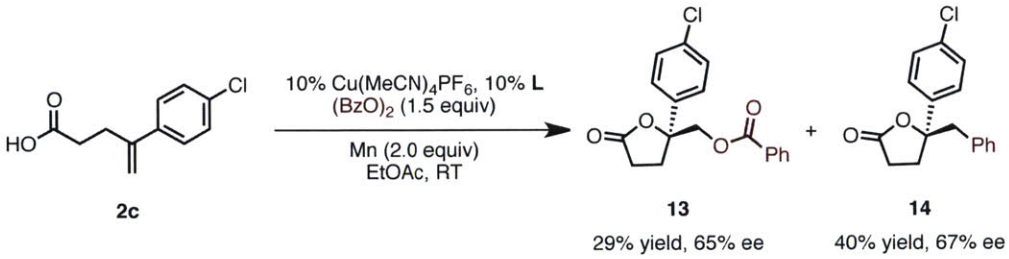
Scheme 6*. An enantioselective formal [4+2] annulation via Cu-catalyzed radical oxyarylation.*[a]



[a]Reaction conditions: $Cu(MeCN)_4PF_6$ (15 mol%), **L** (15 mol%), **10** (0.50 mmol, 1.0 equiv), **11** (2.0 equiv), 2,6-di-^{t}Bupyridine (2.0 equiv), in 8 mL ethyl acetate at RT for 16 h. Yields are of isolated products (average of two runs). Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase.

Taking advantage of this oxyarylation reaction developed, we were able to probe the reactivity and selectivity of mono-substituted alkenes in the copper-catalyzed enantioselective radical oxyfunctionalization, as demonstrated by the copper-catalyzed formal [4+2] annulation reaction described in Scheme 6. We expected 2-carboxybenzenediazonium tetrafluoroborate (**11**) to serve as the precursor for an aryl radical incorporating an adjacent nucleophile. Under the reaction conditions, this radical could add onto 4-chlorostyrene (**10**) to give a secondary benzyl radical intermediate **G**, which might undergo the Cu-mediated C–O bond formation process. We were able to isolate isochromanone derivative **12** produced by this reaction in 19% yield and 46% ee. This suggested that a mono-substituted alkene is capable of participating in the copper-catalyzed enantioselective radical oxyfunctionalization reaction, although much less efficiently than the 1,1-disubstituted alkene substrates. In addition, despite the low selectivity, the Cu-mediated enantioselective C–O bond forming process that proceeded via a secondary benzyl radical intermediate was demonstrated to be viable.

Scheme 7. *Preliminary results on the Cu-catalyzed radical diacyloxylation.*[a]



2c | **13** 29% yield, 65% ee | **14** 40% yield, 67% ee

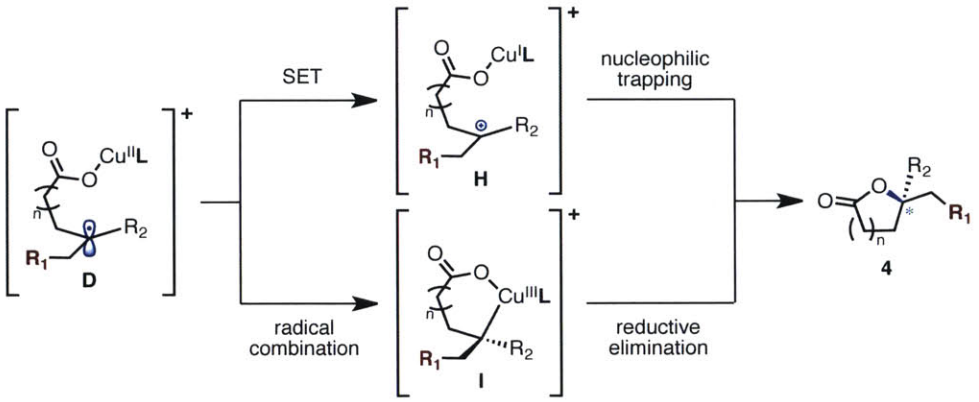
[a]Reaction conditions: $Cu(MeCN)_4PF_6$ (10 mol%), **L** (10 mol%), **2c** (0.50 mmol, 1.0 equiv), dibenzoyl peroxide (1.5 equiv), manganese powder (2.0 equiv), in 8 mL ethyl acetate at RT for 16 h. Yields were determined by ^{1}H NMR analysis using an internal standard. Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

In addition to nitrogen-, sulfur- and carbon-centered radicals, we would like to also explore the use of oxygen-centered radical species in the Cu-catalyzed enantioselective radical oxyfunctionalization, which could lead to the new syntheses of chiral 1,2-diol derivatives.

Preliminary results are described in Scheme 7. The treatment of **2c** with dibenzoyl peroxide in the presence of the chiral catalyst afforded two products: the desired diacyloxylation product **13** (29% yield, 65% ee) and an unexpected oxyarylation product **14** (40% yield, 67% ee). This observation clearly suggested the involvement of benzoyloxyl radicals in the reaction, which in part underwent decarboxylation to give phenyl radicals that led to the oxyarylation process.

Details of the enantioselective C–O bond forming process remains unclear. At this point, we propose two mechanistic possibilities. The first one involves the one-electron oxidation of the tertiary radical **D** to a carbocation **H** by the Cu(II) species, which is immediately trapped intramolecularly by the carboxylate group. In the other scenario which is mechanistically related to the Kharasch oxidation,[21] the combination of the Cu(II) species and the tertiary radical affords a Cu(III) complex **I**, which undergoes reductive elimination to form the C–O bond. Currently neither possibility can be excluded based on the experimental evidence in hand.

***Scheme 8**. Possible pathways for the enantioselective C–O bond forming process.*



3.3 Conclusion.

In conclusion, we have developed a general and versatile method for the catalytic enantioselective oxyfunctionalization of alkenes based on a Cu-mediated enantioselective C–O bond forming process of prochiral alkyl radical intermediates. A wide range of radicals were found to participate this type of reaction, including azidyl, arylsulfonyl, aryl, acyloxyl and alkyl radicals. This method provides rapid access to a broad spectrum of interesting enantiomerically enriched lactones through tandem C–N/C–O, C–S/C–O, C–$C_{aryl/alkyl}$/C–O or C–O/C–O bond formation, in good yields and enantiomeric excesses with good functional group compatibility.

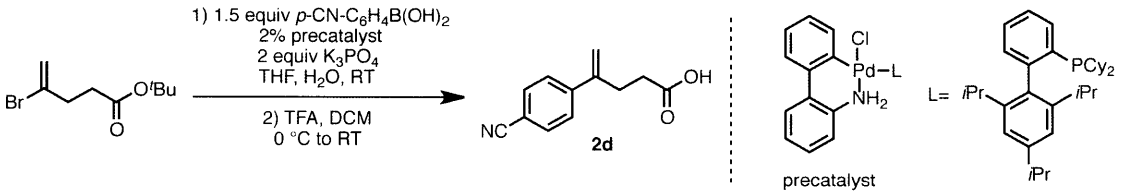
We are continuing the work to expand the scope of this new difunctionalization strategy to include other radical species[22] and nucleophiles, as well as to gain more insight in the key enantioselective functionalization process.

3.4 Experimental

General considerations. All reactions were carried out with dry solvents under anhydrous conditions, unless otherwise noted. Anhydrous ethyl acetate (EtOAc), methyl *tert*-butyl ether (MTBE) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (99%) were purchased from Aldrich and used as received. Tetrakis(acetonitrile)copper(I) hexafluorophosphate was purchased from Strem and stored in a dry box. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. All chemicals were weighed on the bench top, in the air. Reactions were monitored by ^{1}H NMR spectroscopy and thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as a visualizing agent and phosphomolybdic acid in ethanol or iodine on silica gel as developing agents. Flash silica gel chromatography was performed using Silicycle SiliaFlashP60 (230-400 mesh) silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer and were calibrated using residual solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). ^{19}F NMR spectra were recorded on a Varian 300 MHz spectrometer or a Bruker AMX 400 spectrometer and were calibrated using $CFCl_3$ as an external reference (0 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, at = apparent triplet, ad = apparent doublet. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer (iD5 ATR). HPLC analyses were performed on an Angilent 1100 series system with Daicel Chiralcel® columns (4.6 mm x 250 mm) in hexanes/*i*-PrOH mixtures. Melting points (m.p.) were obtained on a Mel-Temp capillary melting point apparatus. Optical rotations were measured on Jacsco P-1010 polarimeter with a sodium lamp(589 nm) at 24 °C. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. HRMS (DART or ESI) spectra were recorded on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). Test b

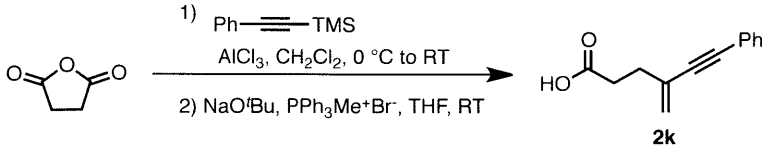
Synthesis and Characterization of non-Commercial Substrates

4-Phenylpent-4-enoic acid (**2a**),[10a] 4-(4-bromophenyl)pent-4-enoic acid (**2b**), [10a] 4-(4-chlorophenyl)pent-4-enoic acid (**2c**), [10a] 4-(4-trifluoromethylphenyl)pent-4-enoic acid (**2e**), [10a] 4-(4-methoxyphenyl)pent-4-enoic acid (**2f**),[23] 4-(3-thienyl)pent-4-enoic acid (**2g**), [10a] 4-(3-acetylphenyl)pent-4-enoic acid (**2h**), [10a] 5-phenylhex-5-enoic acid (2i), [10a] 3,3-dimethyl-5-phenylhex-5-enoic acid (**2j**), [10a] (*Z*)-5-phenylhept-5-enoic acid ((*Z*)-**2m**, *Z*:*E* = 14:1 as determined by ^{1}H NMR analysis), [10a] (*E*)-5-phenylhept-5-enoic acid ((*E*)-**2m**, *Z*:*E* < 1:20 as determined by ^{1}H NMR analysis), [10a] were prepared according to literature procedures.



4-(4-cyanophenyl)pent-4-enoic acid (**2d**) : An oven-dried 100 mL round-bottom-flask equipped with a magnetic stir bar was charged with 4-cyanophenyl boronic acid (1.5 equiv, 0.96 g, 6.5 mmol) and precatalyst (80 mg, 0.02 equiv). The flask was sealed with a rubber septum and connected to a Schlenk line though a needle. The flask was then evacuated and backfilled with argon (This sequence was repeated a total of three times). *tert*-Butyl 4-bromopent-4-enoate (1.02 g, 4.3 mmol, 1.0 equiv),[24] followed by anhydrous tetrahydrofuran (10 mL) and potassium phosphate aqueous solution (2 equiv, 1.84 g in 17 mL degassed water) was added via syringe. The resulting mixture was stirred at room temperature for 48 h before diluted with water (50 mL) and ethyl ether (50 mL). The aqueous phase was separated and extracted with ethyl ether (50 mL × 3). The combined organic layers was concentrated *in vacuo*. The residue was passed through a short plug of silica gel (1 cm × 4 cm) and eluted with hexanes/ethyl ether until all the coupling product was eluted as detected by TLC. The elute was concentrated *in vacuo* and redissolved in dichloromethane (20 mL), to which at 0 °C was added 6.5 mL (20 equiv) trifluoroacetic acid slowly. The resulting mixture was stirred at room temperature for 48 h before concentrating *in vacuo* to remove the solvents and excess trifluoroacetic acid. The residue was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 5:1 to 1:1) followed by one recrystallization to afford **2d** (0.35 g, 40% yield) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.8 Hz, 2 H), 7.51 (d, J = 8.8 Hz, 2 H), 5.42 (s, 1 H), 5.25 (s, 1 H), 2.84 (t, J = 7.6 Hz, 2 H), 2.53 (t, J = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 145.2, 145.2, 132.4, 126.9, 118.9, 116.0, 111.4, 32.8, 29.7; IR (film) ν_{max} 2970, 2232, 1739, 1699, 1627, 1365, 1217, 905, 839 cm^{-1}; R_f(hexanes: ethyl acetate = 1:1)= 0.25; m. p. 101 °C. HRMS: $[M+NH_4]^+$ Calcd. For $C_{12}H_{15}N_2O_2$: 219.1128; Found: 219.1128.



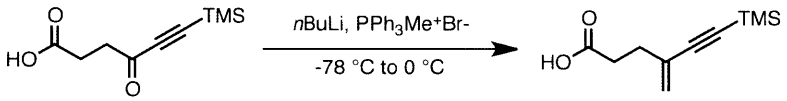
2k

4-Methylene-6-phenylhex-5-ynoic acid (**2k**): Adapted from a previously reported procedure:[25] Powered anhydrous $AlCl_3$ (3.7 g, 28 mmol, 1.75 equiv) was added in portions to an ice-cold mixture of succinic anhydride (2.4 g, 24 mmol, 1.5 equiv) and 1-phenyl-2-trimethylsilylacetylene (3.1 mL, 16 mmol, 1.0 equiv) in 200 mL anhydrous CH_2Cl_2. The mixture was stirred at 0 °C for 2 h and then at room temperature for 16 h. The dark brown mixture was carefully quenched with 1 N HCl at 0 °C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL x 2). The combined organic phase was washed with 1 N HCl, water and brine, and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by passing through a short silica gel column to afford the crude product 4-oxo-6-phenylhex-5-ynoic acid as a brown solid (1.6 g, 50 % yield) which was used in the next reaction without further purification.

An oven-dried 200 mL round-bottom-flask equipped with a magnetic stir bar was charged with methyltriphenylphosphonium bromide (3.7 g, 10.4 mmol, 1.3 equiv) and anhydrous THF (100 mL). The mixture was stirred at 0 °C and sodium *tert*-butoxide (2.0 g, 20.6 mmol, 2.6 equiv) was added in portions. The resulting yellow slurry was stirred at room temperature for 45 min before being cooled to 0 °C. At 0 °C, 4-oxo-6-phenylhex-5-ynoic acid (1.6 g, 8 mmol, 1.0 equiv) was added slowly to the reaction mixture. The resulting mixture was stirred at room temperature for 16 h before concentrating *in vacuo*. The residue was diluted with 200 mL 0.5 N aqueous sodium hydroxide and washed with CH_2Cl_2 (30 mL x 3). The aqueous layer was cooled to 0 °C, acidified (pH < 2), and extracted with Et_2O (100 mL x 3). The combined organic layers were washed with water (30 mL x 3) and brine (30 mL), dried over sodium sulfate, and

concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography to afford **2k** as a yellow solid (0.77 g, 54% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.43 (m, 2 H), 7.31 (m, 3 H), 5.47 (s, 1 H), 5.38 (d, J = 1.2 Hz, 1 H), 2.68 (t, J = 7.6 Hz, 2 H), 2.59 (t, J = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 131.8, 129.6, 128.5, 128.4, 123.1, 122.3, 90.2, 88.7, 33.0, 32.2; IR (film) ν_{max} 2970, 1737, 1706, 1610, 1489, 1442, 1373, 1217, 901, 754, 689 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1)= 0.50; m. p. 74 °C. Anal. Calcd. For $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.81; H, 6.05.



2l

4-Methylene-6-(trimethylsilyl)hex-5-ynoic acid (**2l**): An oven-dried 200 mL round-bottom-flask equipped with a magnetic stir bar was charged with methyltriphenylphosphonium bromide (12.8 g, 36 mmol, 2.4 equiv). The flask was sealed with a rubber septum and connected to a Schlenk line though a needle. The flask was briefly evacuated and backfilled with argon (this sequence was repeated a total of 3 times). Anhydrous THF (100 mL) was added via syringe. At -78 °C to the stirring mixture was added *n*-butyl lithium solution (2.5 M in hexane, 22 mL, 54 mmol, 3.6 equiv) dropwise. The reaction mixture was moved to a 0 °C bath and stirred at the same temperature for 0.5 h before being cooled to -78 °C. At -78 °C, a solution of 4-oxo-6-(trimethylsilyl)hex-5-ynoic acid[26] (3.1 g, 15 mmol, 1.0 equiv) in anhydrous THF (2 M) was added slowly to the reaction mixture via syringe. The resulting mixture was stirred at -78 °C for 0.5 h, then 0 °C for 2 h, and finally warmed to room temperature and stirred overnight. The reaction mixture was quenched at 0 °C by the addition of 70 mL 1 M HCl, 50 mL saturated aqueous NH_4Cl and 50 mL brine. The aqueous layer was separated and extracted with ethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography to afford **2l** as a colorless oil. (1.34 g, 42% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.67 (br, 1 H), 5.41 (s, 1 H), 5.32 (s, 1 H), 2.61 (t, J = 7.6 Hz, 2 H), 2.48 (t, J = 7.6 Hz, 2 H), 0.19 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 129.6,

123.1, 104.4, 95.2, 32.8, 31.9, 0.0; IR (film) ν_{max} 2960, 2145, 1709, 1608, 1411, 1250, 904, 838, 759 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1)= 0.70; HRMS: $[M-H]^-$ Calcd. For $C_{10}H_{15}O_2Si$: 195.0847; Found: 195.0854.

General Procedure and Characterization for the Copper-Catalyzed Enantioselective Oxyfunctionalization of Alkenes

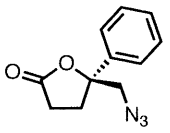
Enantioselective Oxyazidation:

General procedure A for the Cu-catalyzed enantioselective oxyazidation (Table 1):

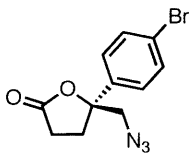
Caution: This reaction should be carried out behind a blast shield. It should be noted that while no incident occurred during this study, azides are potentially hazardous compounds and adequate safety measures should be taken.

An oven-dried 100 mL round bottom flask equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (9.3 mg, 0.025 mmol, 0.05 equiv), 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (7.4 mg, 0.025 mmol, 0.05 equiv) and unsaturated carboxylic acid **2** (0.50 mmol, 1.0 equiv). The flask was sealed with a rubber septum and connected to a Schlenk line though a needle. The flask was briefly evacuated and backfilled with argon (this sequence was repeated a total of two times). The septum was removed, (diacetoxyiodo)benzene (403 mg, 1.25 mmol, 2.5 equiv, dried under high vacuum for 2 h in advance.) was quickly added into the flask and the flask was sealed again with the septum. The flask was connected to a Schlenk line though a needle. The reaction flask was then briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). The reaction flask was cooled to -78 °C. At the same temperature, without stirring, anhydrous diethyl ether (30 mL) was added to the flask via syringe followed by trimethylsilyl azide (158 µL, 1.20 mmol, 2.4 equiv). After cooled at -78 °C for 2 min, the argon pressure was removed and the reaction mixture was moved to a -10 °C bath and stirred at the same temperature for 16 h. The reaction mixture was quenched carefully with saturated aqueous sodium bicarbonate solution (20 mL). The aqueous layer was separated and extracted with diethyl ether (15 mL×3). The combined organic layers was concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes/toluene, using UV light

as a visualizing agent and phosphomolybdic acid in ethanol or iodine on silica gel as developing agents) to afford the oxyazidation product **4**.

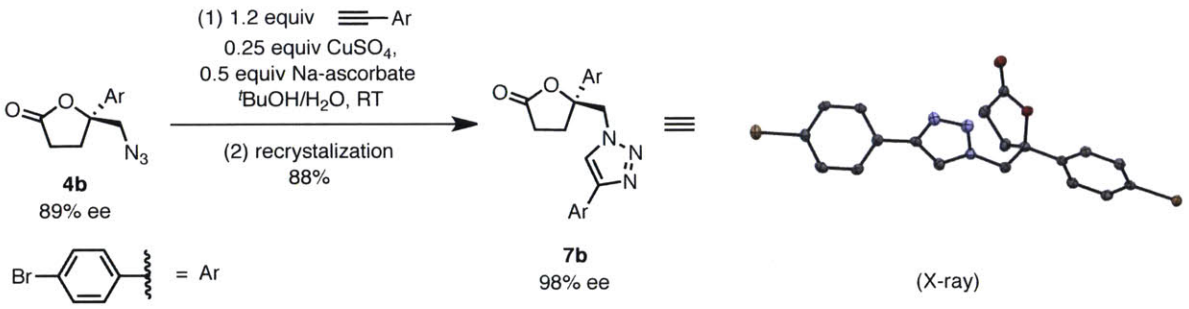


(*S*)-5-(azidomethyl)-5-phenyldihydrofuran-2(3H)-one (4a) Following general procedure A, the title compound was synthesized from 4-phenyl-4-pentenoic acid (**2a**) (88.0 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: toluene: ethyl acetate = 1:0:0 to 0:1:0 to 0:12:1 to 0:8:1) to afford **4a** (66.9 mg, 62% yield, 89% ee) as a pale yellow sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.33 (m, 5 H), 3.67 (d, *J* = 13.2 Hz, 1 H), 3.53 (d, *J* = 13.2 Hz, 1 H), 2.78-2.65 (m, 2 H), 2.55-2.40 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 140.6, 128.9, 128.6, 124.7, 87.7, 60.0, 31.4, 28.7; IR (film) ν_{max} 2096, 1772, 1739, 1448, 1365, 1196, 1062, 935 cm^{-1}; R_f(toluene: ethyl acetate = 4:1)= 0.6; Anal. Calcd. For $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10. Found: C, 61.11; H, 5.18. $[\alpha]_D^{24}$ = -28.1 (c= 0.8, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm, t_R = 20.6 min (major) and 26.3 min (minor).

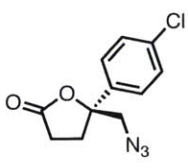


(*S*)-5-(azidomethyl)-5-(4-bromophenyl)dihydrofuran-2(3H)-one (4b) Following general procedure A, the title compound was synthesized from 4-(4-bromophenyl)pent-4-enoic acid (**2b**) (127.5 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: toluene: ethyl acetate = 1:0:0 to 10:0:1 to 6:1:1 to 4:2:1) to afford **4b** (82.6 mg, 56% yield, 89% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 3.65 (d, *J* = 13.2 Hz, 1 H), 3.51 (d, *J* = 13.2 Hz, 1 H), 2.80-2.64 (m, 2 H), 2.52 (m, 1 H), 2.39 (m, 1 H), ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 139.7, 132.1, 126.6, 122.9, 87.2, 59.9, 31.5, 28.7; IR (film) ν_{max} 2097, 1738, 1365, 1229, 1217, 1007cm^{-1}; R_f(hexanes: toluene: ethyl acetate = 2:2:1)= 0.4; Anal. Calcd. For $C_{11}H_{10}N_3O_2Br$: C, 44.62; H, 3.40. Found: C, 44.90; H, 3.54. $[\alpha]_D^{24}$ = + 4.8 (c= 1, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm, t_R = 24.6 min (major) and 31.4 min (minor).

***Scheme 9**. Synthesis and ORTEP presentation of **7b**. (thermal ellipsoids shown at 50% probability. Hydrogen atoms are omitted for clarity.)*



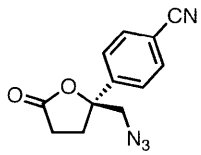
Derivatization of 4b: **(*S*)-5-(4-bromophenyl)-5-((4-(4-bromophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)dihydrofuran-2(3H)-one** (**7b**) To a mixture of **4b** (1.0 equiv, 25 mg, 0.08 mmol), 4-bromophenylacetylene (1.2 equiv, 18 mg, 0.10 mmol) in H_2O/^{t}BuOH (1 mL/1 mL) was added $CuSO_4$□$5H_2O$ (0.25 equiv, 5 mg) and sodium ascorbate (0.5 equiv, 8 mg). The resulting mixture was stirred at room temperature for 20 h before diluted with ethyl acetate (5 mL), saturated aqueous EDTA solution (0.2 mL) and water (5 mL). The aqueous layer was extracted with ethyl acetate (5 mL×3). The combined organic layers were dried over Na_2SO_4, filtered through a short silica gel plug, and concentrated *in vacuo*. The residue was triturated with hexanes, and then recrystallized in CH_2Cl_2/EtOAc to afford **7b** as a colorless crystalline solid (35.4 mg, 88% yield, 98% ee). ^{1}H NMR (400 MHz, $CDCl_3$,) δ 7.86 (s, 1 H), 7.68 (d, *J* = 8.8 Hz, 2 H), 7.57 (m, 4 H), 7.31 (d, *J* = 8.8 Hz, 2 H), 4.84 (d, *J* = 14.8 Hz, 1 H), 4.68 (d, *J* = 14.8 Hz, 1 H), 2.71 (ddd, *J* = 13.2, 9.6, 8.0 Hz, 1 H), 2.50 (ddd, *J* = 13.2, 10.0, 5.2 Hz, 1 H), 2.40 (ddd, *J* = 17.2, 9.6, 8.0 Hz, 1 H), 2.12 (ddd, *J* = 17.2, 9.6, 5.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 147.6, 138.6, 132.5, 132.2, 129.1, 127.5, 126.6, 123.4, 122.6, 121.5, 86.5, 58.3, 31.4, 28.0; IR (film) ν_{max} 1738, 1455, 1365, 1229, 1217, 1000, 922, 831, 817 cm^{-1}; R_f (hexanes : ethyl acetate = 1:1) = 0.5; Anal. Calcd. For $C_{19}H_{15}N_3O_2Br_2$: C, 47.83; H, 3.17. Found: C, 47.78; H, 3.09. $[\alpha]_D^{24}$ = +51.0 (c= 0.5, CH_2Cl_2). m. p. 235-236 °C. The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel IA 4.6 mm x 250 mm, hexanes:*i*-PrOH = 80:20, 1.0 mL/min, 254 nm, t_R = 37.0 min (major) and 21.6 min (minor). The absolute stereochemistry of **7b** was assigned by X-ray crystallography, based on which the absolute stereochemistry of **4b** was assigned. The absolute stereochemistry of **4a-c**, **4e-n**, **8a-c**, **9a-d**, **13**, **14** were assigned based on analogy to **4b**.



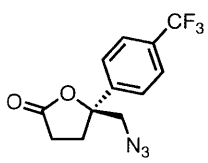
(*S*)-5-(azidomethyl)-5-(4-chlorophenyl)dihydrofuran-2(3H)-one **(4c)**

Following general procedure A, the title compound was synthesized from 4-(4-

chlorophenyl)pent-4-enoic acid (**2c**) (105 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: toluene: ethyl acetate = 1:0:0 to 0:1:0 to 0:12:1 to 0:7:1) to afford **4c** (65.7 mg, 52% yield, 89% ee) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 9.0 Hz, 2 H), 7.32 (d, *J* = 9.0 Hz, 2 H), 3.65 (d, *J* =12.8 Hz, 1 H), 3.52 (d, *J* =12.8 Hz, 1 H), 2.80-2.65 (m, 2 H), 2.52 (m, 1 H), 2.39 (m, 1 H), ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 139.2, 134.7, 129.2, 126.2, 87.2, 59.9, 31.5, 28.7; IR (film) ν_{max} 2097, 1774, 1492, 1277, 1175, 1068, 1011, 935 cm^{-1}; R_f(toluene: ethyl acetate = 4:1)= 0.3; Anal. Calcd. For $C_{11}H_{10}N_3O_2Cl$: C, 52.50; H, 4.01. Found: C, 52.35; H, 4.11. $[\alpha]_D^{24}$ = +1.3 (c= 0.9, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm, t_R = 20.0 min (major) and 24.6 min (minor).

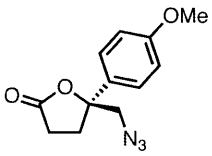


(*S*)-5-(azidomethyl)-5-(4-cyanophenyl)dihydrofuran-2(3H)-one (4d) Following a slightly modified general procedure A in which the combined organic layers after ethyl ether extraction was briefly washed with Na_2CO_3 aqueous solution (0.02 M, 10 mL×2) before concentrating *in vacuo*, the title compound was synthesized from 4-(4-cyanophenyl)pent-4-enoic acid (**2d**) (100 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: toluene: ethyl acetate = 1:0:0 to 0:1:0 to 0:10:1 to 0:6:1) to afford **4d** (56.5 mg, 47% yield, 90% ee) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 3.66 (d, *J* =13.2 Hz, 1 H), 3.57 (d, *J* = 13.2 Hz, 1 H), 2.84-2.69 (m, 2 H), 2.53 (m, 1 H), 2.40 (m, 1 H), ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 145.8, 132.8, 125.8, 118.2, 112.8, 86.8, 59.7, 31.5, 28.5; IR (film) ν_{max} 2229, 2102, 1778, 1176, 1070, 937, 838, 729 cm^{-1}; R_f(toluene: ethyl acetate = 3:1)= 0.4; Anal. Calcd. For $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16. Found: C, 59.57; H, 4.42. $[\alpha]_D^{24}$ = + 10.8 (c= 0.5, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 85:15, 1.0 mL/min, 230 nm, t_R = 30.6 min (major) and 34.3 min (minor).



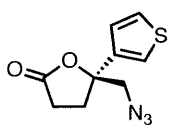
(*S*)-5-(azidomethyl)-5-(4-trifluoromethylphenyl)dihydro furan-2(3H)-one (4e) Following a slightly modified general procedure A in which (1) tetrakis(acetonitrile)copper(I) hexafluorophosphate (14.9 mg, 0.04 mmol, 0.08 equiv) and 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (11.8 mg, 0.04 mmol, 0.08 equiv) were used; (2) the combined organic layers after ethyl ether extraction was

briefly washed with Na_2CO_3 aqueous solution (0.02 M, 10 mL × 2) before concentrating *in vacuo*, the title compound was synthesized from 4-(4-trifluoromethylphenyl)pent-4-enoic acid (**2e**) (122 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: toluene: ethyl acetate = 1:0:0 to 0:1:0 to 0:12:1 to 0:8:1) to afford **4e** (65.5 mg, 46% yield, 90% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.4 Hz, 2 H), 7.53 (d, J = 8.4 Hz, 1 H), 3.68 (d, J = 13.2 Hz, 1 H), 3.57 (d, J = 13.2 Hz, 1 H), 2.84-2.70 (m, 2 H), 2.54 (m, 1 H), 2.43 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 144.7, 131.1 (q, J_{CF} = 32 Hz), 126.1 (q, J_{CF} = 4 Hz), 125.4, 123.9 (q, J_{CF} = 270 Hz), 87.1, 59.9, 31.6, 28.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8 (s); IR (film) ν_{max} 2102, 1738, 1365, 1229, 1217, 1115, 1077cm^{-1}; R_f (toluene: ethyl acetate = 6:1)= 0.2; HRMS: $[M+NH_4]^+$ Calcd. For $C_{12}H_{14}N_4F_3O_2$: 303.1063; Found: 303.1050. $[\alpha]_D^{24}$ = -11.6 (c = 0.4, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm, t_R = 19.8 min (major) and 25.6 min (minor).

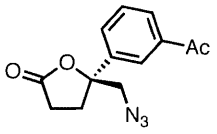


(*S*)-5-(azidomethyl)-5-(4-methoxyphenyl)dihydrofuran-2(3H)-one (4f) Following general procedure A, the title compound was synthesized from 4-(4-methoxyphenyl)pent-4-enoic acid (**2f**) (103 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: toluene: ethyl acetate = 1:0:0 to 0:1:0 to 0:12:1 to 0:7:1) to afford **4f** (79.6 mg, 65% yield, 75% ee) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J =8.8 Hz, 1 H), 6.91 (d, J =8.8 Hz, 1 H), 3.80 (s, 3 H), 3.64 (d, J = 13.2 Hz, 1 H), 3.48 (d, J = 13.2 Hz, 1 H), 2.76-2.61 (m, 2 H), 2.51 (m, 1 H), 2.40 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 159.7, 132.4, 126.1, 114.2, 87.6, 60.1, 55.4, 31.3, 28.8; IR (film) ν_{max} 2098, 1772, 1611, 1513, 1247, 1175, 1068, 934 cm^{-1}; R_f(toluene: ethyl acetate = 4:1)= 0.5; Anal. Calcd. For $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30. Found: C, 58.44; H, 5.49. $[\alpha]_D^{24}$ = +1.6 (c= 0.6, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm, t_R = 23.2 min (major) and 27.6 min (minor).

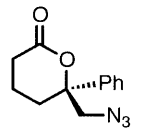
(*S*)-5-(azidomethyl)-5-(thiophen-3-yl)dihydrofuran-2(3H)-one (4g) Following a slightly modified general procedure A in which additional 2,6-di-*tert*-butylpyridine (120 mL, 0.55 mmol, 1.1 equiv,) was added via syringe after the addition of trimethylsilyl azide, the title compound was synthesized from 4-(3-thiophenyl)pent-4-enoic acid (**2g**) (91



mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: toluene: ethyl acetate = 10:0:1 to 6:1:1) to afford **4g** (76.1 mg, 68% yield, 82% ee) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* =5.2 Hz, 3.0 Hz. 1 H), 7.31 (dd, *J* =3.0 Hz, 1.2 Hz. 1 H), 7.02 (dd, *J* =5.2 Hz, 1.2 Hz. 1 H), 3.71 (d, *J* = 13.0 Hz, 1 H), 3.53 (d, *J* = 13.0 Hz, 1 H), 2.77-2.52 (m, 3 H), 2.40 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 141.7, 127.6, 124.7, 121.9, 86.4, 59.3, 31.3, 28.8; IR (film) ν_{max} 2102, 1775, 1181, 1070, 1040, 942, 847 cm^{-1}; R_f(toluene: ethyl acetate = 4:1)= 0.6; Anal. Calcd. For $C_9H_9N_3O_2S$: C, 48.42; H, 4.06. Found: C, 48.34; H, 3.97. $[\alpha]_D^{24}$ = -9.0 (c= 0.5, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm, t_R = 29.0 min (major) and 36.9 min (minor).

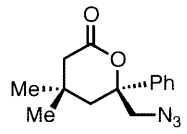


(*S*)-5-(azidomethyl)-5-(3-acetylphenyl)dihydrofuran-2(3H)-one (4h) Following a slightly modified general procedure A in which tetrakis(acetonitrile)copper(I) hexafluorophosphate (14.9 mg, 0.04 mmol, 0.08 equiv) and 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (11.8 mg, 0.04 mmol, 0.08 equiv) were used, the title compound was synthesized from 4-(3-acetylphenyl)pent-4-enoic acid (**2h**) (109 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: toluene: ethyl acetate = 1:0:0 to 0:1:0 to 0:10:1 to 0:5:1) to afford **4h** (67.7 mg, 52% yield, 90% ee) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m ,2 H), 7.62 (m, 1 H), 7.51 (m, 1 H), 3.67 (d, *J* = 13.2 Hz, 1 H), 3.57 (d, *J* = 13.2 Hz, 1 H), 2.81-2.69 (m, 2 H), 2.61 (s, 3 H), 2.56-2.42 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 175.4, 141.5, 137.7, 129.5, 129.4, 128.7, 124.4, 87.3, 60.0, 31.5, 28.7, 26.8; IR (film) ν_{max} 2101, 1773, 1682, 1365, 1217, 1069, 938 cm^{-1}; R_f(toluene: ethyl acetate = 4:1)= 0.3; Anal. Calcd. For $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05. Found: C, 60.38; H, 5.12. $[\alpha]_D^{24}$ = -12.8 (c= 0.5, $CHCl_3$). m. p. 80-81 °C. The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel IA 4.6 mm x 250 mm, hexanes:*i*-PrOH = 90:10, 1.0 mL/min, 230 nm, t_R = 20.5 min (major) and 18.7 min (minor).

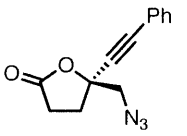


(*S*)-6-(azidomethyl)-6-phenyltetrahydro-2H-pyran-2-one (4i) Following general procedure A, the title compound was synthesized from 5-phenylhex-5-enoic acid (**2i**) (95 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: toluene: ethyl acetate = 1:0:0 to 0:1:0 to 0:12:1 to 0:8:1) to afford **4i** (69.8 mg, 60% yield, 89% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-

7.32 (m, 5 H), 3.61 (d, J = 12.8 Hz, 1 H), 3.42 (d, J = 12.8 Hz, 1 H), 2.50 (ddd, J = 18 Hz, 9.6 Hz, 7.2 Hz, 1 H), 2.45 (ddd, J = 18 Hz, 7.2 Hz, 4 Hz, 1 H), 2.31-2.22 (m, 2 H), 1.83 (m, 1 H), 1.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 140.4, 129.2, 128.5, 125.3, 86.9, 60.8, 29.3, 29.1, 16.2; IR (film) ν_{max} 2096, 1736, 1447, 1232, 1187, 1048, 934 cm^{-1}; R_f(toluene: ethyl acetate = 4:1) = 0.6; Anal. Calcd. For $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67. Found: C, 62.51; H, 5.78. $[\alpha]_D^{24}$ = +24.9 (c= 0.5, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm, t_R = 19.5 min (major) and 26.5 min (minor).

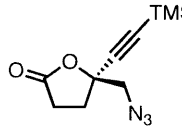


(*S*)-6-(azidomethyl)-4,4-dimethyl-6-phenyltetrahydro-2H-pyran-2-one (4j) Following general procedure A, the title compound was synthesized from 3,3-dimethyl-5-phenylhex-5-enoic acid (**2j**) (109 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: toluene : ethyl acetate = 1:0:0 to 0:1:0 to 0:20:1 to 0:15:1 to 0:10:1) to afford **4j** (83.0 mg, 64% yield, 92% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.30 (m, 5 H), 3.50 (d, J = 12.8 Hz, 1 H), 3.29 (d, J = 12.8 Hz, 1 H), 2.33-2.17 (m, 4 H), 1.09 (s, 3 H), 0.78 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 141.6, 129.0, 128.3, 125.1, 85.8, 62.0, 43.8, 41.7, 31.9, 30.7, 29.1; IR (film) ν_{max} 2970, 2097, 1739, 1447, 1365, 1217, 1060, 759, 702 cm^{-1}; R_f(toluene: ethyl acetate = 5:1) = 0.7; HRMS: $[M+Na]^+$ Calcd. For $C_{14}H_{17}N_3O_2Na$: 282.1213; Found: 282.1205. $[\alpha]_D^{24}$ = +35.9 (c= 0.8, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm, t_R = 13.0 min (major) and 15.0 min (minor).

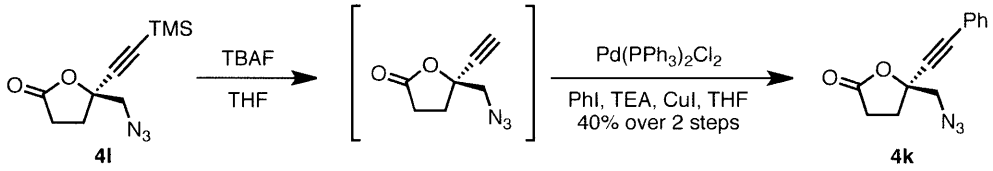


(*S*)-5-(azidomethyl)-5-(phenylethynyl)dihydrofuran-2(3H)-one (4k) Following a slightly modified general procedure A in which tetrakis(acetonitrile)copper(I) hexafluorophosphate (14.9 mg, 0.04 mmol, 0.08 equiv) and 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (11.8 mg, 0.04 mmol, 0.08 equiv) were used, the title compound was synthesized from 4-methylene-6-phenylhex-5-ynoic acid (**2k**) (100 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: toluene : ethyl acetate = 1:0:0 to 0:1:0 to 0:15:1 to 0:8:1) to afford **4k** (61.4 mg, 51% yield, 72% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2 H), 7.38-7.31 (m, 3 H), 3.77 (d, J = 13.2 Hz, 1 H), 3.61 (d, J = 13.2 Hz, 1 H), 2.83 (ddd, J = 17.6 Hz, 9.6 Hz, 9.2 Hz, 1 H), 2.71 (ddd, J = 17.6 Hz, 7.6 Hz, 6.4 Hz, 1 H), 2.53-2.49 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2,

132.0, 129.5, 128.6, 121.1, 88.1, 85.3, 80.0, 57.9, 32.2, 28.7; IR (film) ν_{max} 2990, 2099, 1738, 1365, 1228, 1217, 918, 756 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1) = 0.5; HRMS: $[M+NH_4]^+$ Calcd. For $C_{13}H_{15}N_4O_2$: 259.1190; Found: 259.1183. $[\alpha]_D^{24}$ = +35.7 (c= 1, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm, t_R = 17.0 min (major) and 19.7 min (minor).



(*S*)-5-(azidomethyl)-5-((trimethylsilyl)ethynyl)dihydrofuran-2(3H)-one (4l) Following a slightly modified general procedure A in which tetrakis(acetonitrile)copper(I) hexafluorophosphate (14.9 mg, 0.04 mmol, 0.08 equiv) and 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (11.8 mg, 0.04 mmol, 0.08 equiv) were used, the title compound was synthesized from 4-methylene-6-(trimethylsilyl)hex-5-ynoic acid (**2l**) (96 mg, 0.50 mmol). The product was purified by silica gel flash column chromatography (hexanes: toluene : ethyl acetate = 1:0:0 to 0:1:0 to 0:20:1 to 0:15:1 to 0:10:1) to afford **4l** (52.9 mg, 45% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.65 (d, *J* = 13.2 Hz, 1 H), 3.49 (d, *J* = 13.2 Hz, 1 H), 2.75 (ddd, *J* = 17.6 Hz, 9.6 Hz, 9.2 Hz, 1 H), 2.63 (ddd, *J* = 17.6 Hz, 7.2 Hz, 6.8 Hz, 1 H), 2.43-2.39 (m, 2 H), 0.18 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 101.2, 94.0, 79.4, 57.7, 32.1, 28.6, -0.4; IR (film) ν_{max} 2103, 1784, 1739, 1365, 1249, 1174, 1056, 841 cm^{-1}; R_f(toluene: ethyl acetate = 10:1) = 0.6; HRMS: $[M+NH_4]^+$ Calcd. For $C_{10}H_{19}N_4O_2Si$: 255.1272; Found: 255.1275. $[\alpha]_D^{24}$ = +28.6 (c= 1, $CHCl_3$).

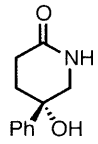


4l **4k**

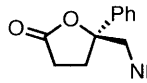
Enantiomeric excess determination of **4l** by converting to **4k**: To a solution of **4l** (15 mg, 0.06 mmol) in anhydrous THF (0.5 mL) was added tetrabutylammonium fluoride (1 M in THF, 0.12 mL) slowly at 0 °C. The yellow mixture was stirred at the same temperature for 0.5 h before diluted with saturated aqueous NH_4Cl (1 mL). The aqueous layer was separated and extracted with ethyl ether (1 mL×2). The combined organic layers was dried over Na_2SO_4, passed through a silica gel plug, and concentrated *in vacuo* to afford the crude product. Under an Ar atmosphere, a mixture of this crude product, $PdCl_2(PPh_3)_2$ (3.5 mg), iodobenzene (24 mg), and triethylamine (20 mg) in anhydrous THF (1 mL) was stirred at room temperature (25 °C) for 5 min before CuI (1.9 mg) was added. The reaction vessel was briefly evacuated and backfilled with argon. The reaction mixture was stirred at 70 °C for 2 h before diluted with ethyl ether (2

mL), saturated aqueous NH_4Cl (1 mL) and 1 M aqueous HCl (1 mL). The aqueous layer was separated and extracted with ethyl ether (1 mL × 2). The combined organic layers was concentrated *in vacuo*. The residue was purified by preparative thin-layer-chromatography to afford **4k** (6 mg, *ca.* 40% yield over 2 steps, 82% ee). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm, t_R = 17.0 min (major) and 19.7 min (minor).

Derivatization of Oxyazidation Product ***4a***

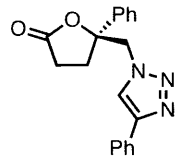


(*S*)-5-hydroxy-5-phenylpiperidin-2-one (5) A mixture of **4a** (32 mg, 0.15 mmol, 1.0 equiv, 89% ee) and 5% Pd/C (6 mg) in methanol (1 mL) was stirred at room temperature (25 °C) under H_2 atmosphere for 16 h. 4-Dimethylaminopyridine (2 mg, 0.015 mmol, 0.1 equiv) was added to the reaction mixture and the resulting mixture was stirred at room temperature for 8 h before concentrating *in vacuo*. The residue was purified by silica gel flash column chromatography (ethyl acetate: methanol = 1:0 to 5:1) to afford **5** (22 mg, 78% yield, 89% ee) as a colorless solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (m, 2 H), 7.37 (m, 2 H), 7.28 (m, 1 H), 3.60 (d, *J* =12.8 Hz, 1 H), 3.28 (dd, *J* =12.8 Hz, 2.8 Hz, 1 H), 2.67 (m, 1 H), 2.48-2.33 (m, 2 H), 2.01 (m, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.6, 146.6, 129.4, 128.5, 126.1, 70.8, 54.2, 33.5, 28.9; IR (film) ν_{max} 3225, 2917, 2384, 1633, 1494, 1233, 978, 768 cm^{-1}; R_f(methanol: ethyl acetate = 5:1)= 0.40; HRMS: $[M+H]^+$ Calcd. For $C_{11}H_{14}NO_2$: 192.1019; Found: 192.1026. $[\alpha]_D^{24}$ = -2.2 (c= 0.9, MeOH). m. p. 198-199 °C. The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel IA 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm, t_R = 67.5 min (major) and 80.1 min (minor).



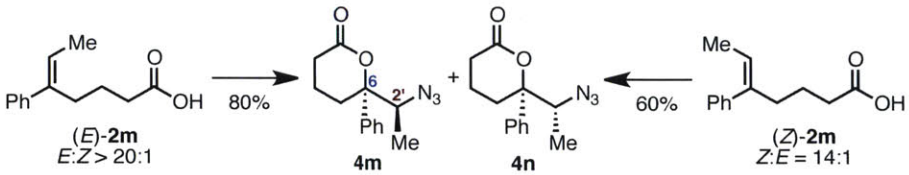
(*S*)-*tert*-butyl((5-oxo-2-phenyltetrahydrofuran-2-yl)methyl)carbamate (6) A mixture of **4a** (56 mg, 0.26 mmol, 1.0 equiv, 89% ee), di-*tert*-butyl dicarbonate (84 mg, 0.39 mmol, 1.5 equiv) and 5% Pd/C (5 mg) in THF (1.5 mL) was stirred at room temperature (25 °C) under H_2 atmosphere for 15 h. The reaction mixture was then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 10:1 to 1:1) to afford **6** (66 mg, 88% yield, 89% ee) as a colorless sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5 H), 4.91 (br, 1 H), 3.71 (dd, *J* =14.8 Hz, 7.6 Hz, 1 H), 3.42 (dd, *J* =14.8 Hz, 5.2 Hz, 1 H), 2.67-2.33 (m, 4 H), 1.39 (s, 9 H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 176.5, 156.2, 141.1, 128.8, 128.2, 124.8, 89.1, 80.0, 49.3, 31.2, 28.8, 28.3; IR (film) v_{max} 1774, 1709, 1508, 1365, 1245, 1163, 1115, 1092, 1069, 912, 730, 700 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1)= 0.2; Anal. Calcd. For $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27. Found: C, 65.84; H, 7.31. $[\alpha]_D^{24}$ = -36.1 (c= 1, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OJ-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 90:10, 1.0 mL/min, 210 nm, t_R = 8.2 min (major) and 7.3 min (minor).



(*S*)-5-phenyl-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)dihydrofuran-2(3H)-one (**7**) To a mixture of **4a** (1.0 equiv, 22 mg, 0.1 mmol), phenyl acetylene (1.1 equiv, 11 mg, 0.11 mmol) in H_2O/^{t}BuOH (1 mL/1 mL) was added $CuSO_4$•$5H_2O$ (0.4 equiv, 10 mg) and sodium ascorbate (0.8 equiv, 16 mg). The resulting mixture was stirred at room temperature for 17 h before diluted with ethyl acetate (5 mL), saturated aqueous EDTA solution (0.2 mL) and water (5 mL). The aqueous layer was extracted with ethyl acetate (5 mL×3). The combined organic layers were dried over Na_2SO_4, filtered through a short silica gel plug, and concentrated *in vacuo*. The residue was triturated with hexanes to afford **7** as a white solid (31 mg, 96% yield, 89% ee). ^{1}H NMR (400 MHz, $CDCl_3$,) δ 7.85 (s, 1 H), 7.81 (d, *J* = 7.2 Hz, 1 H), 7.45-7.32 (m, 8 H), 4.88 (d, *J* = 14.8 Hz, 1 H), 4.69 (d, *J* = 14.8 Hz, 1 H), 2.70 (ddd, *J* = 13.2, 9.6, 8.0 Hz, 1 H), 2.52 (ddd, *J* = 13.2, 10.0, 5.6 Hz, 1 H), 2.39 (ddd, *J* = 17.6, 9.6, 8.0 Hz, 1 H), 2.09 (ddd, *J* = 17.6, 10.0, 5.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 148.4, 139.7, 130.2, 129.2, 129.1, 129.0, 128.5, 126.0, 124.8, 121.4, 87.0, 58.5, 31.3, 28.1; IR (film) v_{max} 1777, 1738, 1449, 1365, 1228, 1217, 1147, 931, 764, 697 cm^{-1}; R_f(hexanes: ethyl acetate = 2:1)= 0.1; HRMS: $[M+H]^+$ Calcd. For $C_{19}H_{18}N_3O_2$: 320.1394; Found: 320.1373. $[\alpha]_D^{24}$ = -0.6 (c= 0.5, $CHCl_3$). m. p. 151-152 °C. The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel IA 4.6 mm x 250 mm, hexanes:*i*-PrOH = 85:15, 1.0 mL/min, 210 nm, t_R = 27.1 min (major) and 20.5 min (minor).

Trisubstituted Alkene Substrates as Mechanistic Probes (Scheme 3) [31]



substrate	d.r.[b]	4m ee [%][b]	4n ee [%][b]	ratio of stereoisomers 4m : *ent*-4m : 4n : *ent*-4n
(*E*)-**2m**	10 : 1	12	93	51.1 : 40.0 : 8.6 : 0.3
(*Z*)-**2m**	10 : 1	11	93	50.6 : 40.3 : 8.8 : 0.3

Reaction with (*Z*)-2m: An oven-dried 20 × 125 mm re-sealable test tube (Fisher Scientific, Cat. #1495937) equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (3.8 mg, 0.01 mmol, 0.1 equiv), 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (3.0 mg, 0.01 mmol, 0.1 equiv) and (*Z*)-**2m** (0.10 mmol, 1.0 equiv). The reaction tube was sealed with a septum screw-cap (10/90, Teflon/SIL, National Scientific) and connected to a Schlenk line. The reaction tube was then briefly evacuated and backfilled with argon (this sequence was repeated a total of two times). The septum screw-cap was removed, (diacetoxyiodo)benzene (80 mg, 0.25 mmol, 2.5 equiv, dried under high vacuum for 2 h in advance.) was added into the tube quickly and the tube was sealed again with the septum screw-cap. The reaction tube was connected to a Schlenk line. The reaction tube was then briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). The reaction tube was cooled to -78 °C. At the same temperature, without stirring, anhydrous diethyl ether (6 mL) was added to the tube via syringe followed by trimethylsilyl azide (32 μL, 0.24 mmol, 2.4 equiv). After cooled at -78 °C for 2 min, argon pressure was removed and the reaction mixture was moved to a -10 °C bath and stirred at the same temperature for 16 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution (6 mL). The aqueous layer was separated and extracted with diethyl ether (5 mL × 3). The combined organic layers was concentrated *in vacuo*. Phenanthrene (9.0 mg) was added and the crude product was analyzed by ^{1}H NMR spectroscopy. The total yield of **4m** and **4n** was 60% as determined by ^{1}H NMR spectroscopy.

A small portion of the crude product was then subjected to a rapid TLC purification to remove the non-polar components (internal standard and iodobenzene) as well as the polar carboxylic acid derivatives. The residue (R_f (toluene: ethyl acetate = 5:1) between 0.4 and 0.8) was analyzed by chiral HPLC. Chiralcel OD-H/OD-H 4.6 mm x 250 mm, pentane:EtOH = 97:3, 0.8 mL/min, 210 nm. **4m** (11% ee): t_R = 35.5 min (major) and 37.6 min (minor). **4n** (93% ee): t_R = 33.5 min (major) and 44.8 min (major). d.r.(**4m**: **4n**) = 10:1. Stereoisomer ratio calculated: (**4m** + *ent*-**4m**):(**4n** + *ent*-**4n**) = 51:49.

The rest of the crude material was purified by preparative thin-layer chromatography to afford an inseparable mixture of **4m** and **4n**. IR (film) ν_{max} 2094, 1739, 1447, 1365, 1230, 1217, 1033, 760, 702 cm^{-1}; HRMS: $[M+NH_4]^+$ Calcd. For $C_{13}H_{19}N_4O_2$: 263.1503; Found: 263.1507. $[\alpha]_D^{24}$ = +1.2 (c= 0.8, $CHCl_3$).

Major diastereomer:**(*S*)-6-((*S*)-1-azidoethyl)-6-phenyltetrahydro-2H-pyran-2-one** (**4m**) ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.31 (m, 5 H), 3.78 (q, *J* = 6.8 Hz, 1 H), 2.56 (dtd, *J* =14.4 Hz, 4.4 Hz, 0.8 Hz, 1 H), 2.46 (ddd, *J* = 18.4 Hz, 9.2 Hz, 7.6 Hz, 1 H), 2.37 (dddd, *J* =18.4 Hz, 7.2 Hz, 3.6 Hz, 0.8 Hz, 1 H), 2.06 (ddd, *J* = 14.4 Hz, 12.4 Hz, 4.4 Hz, 1 H), 1.85 (m, 1 H), 1.62 (m, 1 H), 1.11 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 138.8, 128.8, 128.5, 126.5, 88.5, 65.0, 28.3, 28.0, 16.2, 14.0.

Minor diastereomer:**(*S*)-6-((*R*)-1-azidoethyl)-6-phenyltetrahydro-2H-pyran-2-one** (**4n**) ^1H NMR (400 MHz, $CDCl_3$): δ 3.57 (q, *J* = 6.8 Hz, 1 H), 2.22 (td, *J* =13.6 Hz, 3.6 Hz, 1 H), 1.17 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 140.6, 129.1, 128.2, 125.5, 88.8, 64.1, 29.8, 29.6, 16.2, 13.0.

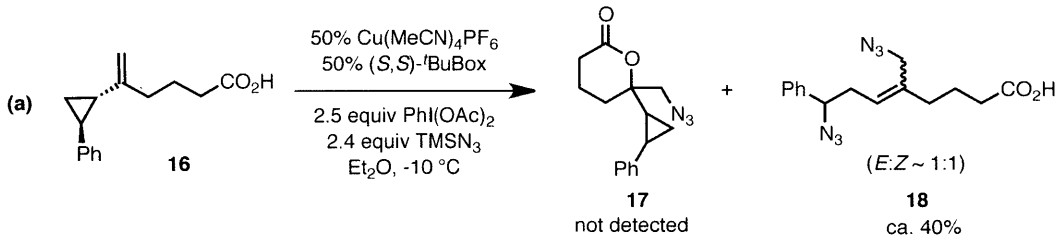
The relative stereochemistry of **4m** and **4n** were assigned based on comparison with known compounds.[27]

Reaction with (*E*)-2m: Following the same procedure for the reaction with (*E*)-**2m** described above, an over-dried 20 × 125 mm re-sealable test tube (Fisher Scientific, Cat. #1495937) equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (3.8 mg, 0.01 mmol, 0.1 equiv), 2,2'-isopropylidenebis[(4S)-4-tert-butyl-2-oxazoline] (3.0 mg, 0.01 mmol, 0.1 equiv) and (*E*)-**2m** (0.10 mmol, 1.0 equiv). The reaction tube was sealed with a septum screw-cap (10/90, Teflon/SIL, National Scientific) and connected to a

Schlenk line. The reaction tube was then briefly evacuated and backfilled with argon (this sequence was repeated a total of two times). The septum screw-cap was removed, (diacetoxyiodo)benzene (80 mg, 0.25 mmol, 2.5 equiv, dried under high vacuum for 2 h in advance.) was added into the tube quickly and the tube was sealed again with the septum screw-cap. The reaction tube was connected to a Schlenk line. The reaction tube was then briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). The reaction tube was cooled to -78 °C. At the same temperature, without stirring, anhydrous diethyl ether (6 mL) was added to the tube via syringe followed by trimethylsilyl azide (32 μL, 0.24 mmol, 2.4 equiv). After cooled at -78 °C for 2 min, argon pressure was removed and the reaction mixture was moved to a -10 °C bath and stirred at the same temperature for 16 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution (6 mL). The aqueous layer was separated and extracted with diethyl ether (5 mL × 3). The combined organic layers was concentrated *in vacuo*. Phenanthrene (9.0 mg) was added and the crude product was analyzed by ^{1}H NMR spectroscopy. The total yield of **4m** and **4n** was 80% as determined by ^{1}H NMR spectroscopy.

A small portion of the crude product was then subjected to a rapid TLC purification to remove the non-polar components (internal standard and iodobenzene) as well as the polar carboxylic acid derivatives. The residue (R_f (toluene: ethyl acetate = 5:1) between 0.4 and 0.8) was analyzed by chiral HPLC. **4m**:12% ee; **4n**: 93% ee; d.r.(**4m**: **4n**) = 10:1. Stereoisomer ratio calculated: (**4m** + *ent*-**4m**):(**4n** + *ent*-**4n**) = 51:49.

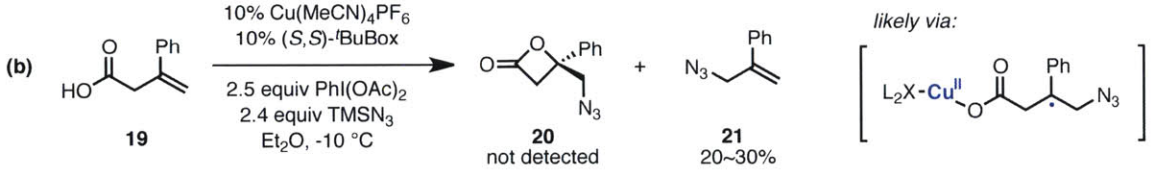
Additional Evidence Consistent with the Proposed Mechanism (footnote 16)



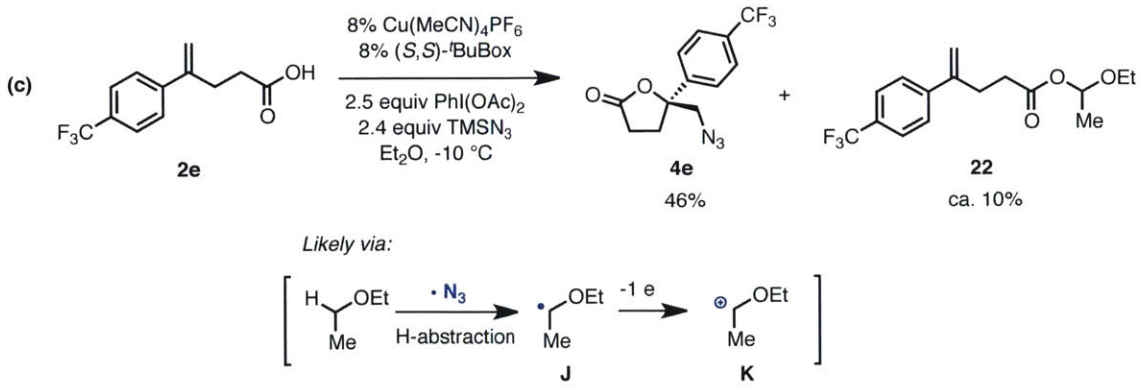
(a) Radical clock substrate **16** was treated with $PhI(OAc)_2$ and $TMSN_3$ in the presence of 0.5 equiv of the copper catalyst and the ligand using a protocol similar to the general procedure

described before. The oxyazidation product **17** was not observed. Cyclopropane ring-opening product **18** (1:1 mixture of alkene geometric isomers, chromatographically inseparable from other carboxylic acid derivatives in the crude reaction mixture) was detected by ^{1}H NMR analysis of the crude reaction mixture.

8-azido-5-(azidomethyl)-8-phenyloct-5-enoic acid (18) ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48 and 5.46 (t, J = 7.2 Hz, 1 H), 4.50 and 4.48 (t, J = 6.8 Hz, 1 H), 3.73 and 3.69 (s, 2 H), 2.64-2.50 (m, 2 H), 2.32 (m, 2 H), 2.17-2.09 (m, 2 H), 1.79-1.62 (m, 2 H); HRMS (DART, Negative): $[M-H]^-$ Calcd. for $C_{15}H_{17}N_6O_2$: 313.1418; Found: 313.1420.



(b) 3-Phenylbut-3-enoic acid (**19**) was treated with $PhI(OAc)_2$ and $TMSN_3$ in the presence of 0.1 equiv of the copper catalyst and the ligand using a protocol similar to the general procedure described before. The oxyazidation product **20** was not observed, while (3-azidoprop-1-en-2-yl)benzene (**21**)[28] was detected by ^{1}H NMR analysis of the crude reaction mixture. It is likely that **21** was formed via the copper-mediated decarboxylative elimination of the β-radical-carboxylate intermediate[29] derived from the azidyl radical addition of **19**.



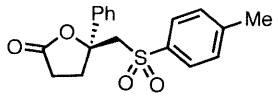
(c) In the oxyazidation reaction of an electron-deficient styrene derivative **2e**, side product **22** was identified by ^{1}H NMR analysis of the crude reaction mixture. (characteristic ^{1}H NMR signals (400 MHz, $CDCl_3$): δ 5.97 (q, J = 5.2 Hz, 1 H); chromatographically inseparable from other acetal derivatives in the crude reaction mixture) It is likely that **22** was formed via the nucleophilic trapping of a cationic intermediate **K** derived from the hydrogen-abstraction of a solvent molecule by an azidyl radical followed by one-electron oxidation.[30]

Enantioselective Oxysulfonylation:

General procedure B for optimization (Table 2): An oven-dried Fisher Scientific 13×100 mm re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (3.7 mg, 0.010 mmol, 0.10 equiv), 2,2'-isopropylidenebis[(4*S*)-4-tert-butyl-2-oxazoline] (2.9 mg, 0.010 mmol, 0.10 equiv), arylsulfonyl chloride (0.11 mmol, 1.1 equiv), base and **2a** (0.10 mmol, 1.0 equiv). The reaction tube was sealed with a septum screw-cap (Thermo Scientific ASM PHN CAP w/PTFE/SIL, cat. #03378316). The reaction tube was connected to a Schlenk line though a needle. The reaction tube was then briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). Anhydrous EtOAc (2 mL) was added to the tube via syringe and the argon pressure was removed. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (4 mL) and ethyl acetate (2 mL). The aqueous layer was separated and extracted with ethyl acetate (4 mL×3). The combined organic layers was concentrated *in vacuo*. The residue was analyzed by ^{1}H NMR spectroscopy using phenanthrene as an internal standard. The residue was purified by thin-layer chromatography to afford the oxysulfonylation product **8a**, which was analyzed by chiral HPLC.

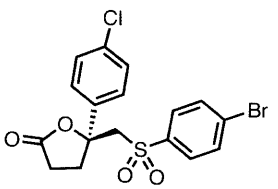
General procedure C for substrate scope (Scheme 4): An oven-dried Fisher Scientific 20×150 mm re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (18.7 mg, 0.05 mmol, 0.10 equiv), 2,2'-isopropylidenebis[(4*S*)-4-tert-butyl-2-oxazoline] (14.7 mg, 0.05 mmol, 0.10 equiv), arylsulfonyl chloride (0.55 mmol, 1.1 equiv), silver carbonate (82.8 mg, 0.60 mmol, 1.2 equiv) and **2** (0.5 mmol, 1.0 equiv). The reaction tube was sealed with a septum screw-cap (10/90, Teflon/SIL, National Scientific) and connected to a Schlenk line. The reaction tube was then briefly

evacuated and backfilled with argon (this sequence was repeated a total of three times). Anhydrous EtOAc (8 mL) was added to the tube via syringe and the argon pressure was removed. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (8 mL) and ethyl acetate (4 mL). The aqueous layer was separated and extracted with ethyl acetate (8 mL×3). The combined organic layers was concentrated *in vacuo*. The residue was then purified by silica gel flash column chromatography (Et_2O/Hexanes or EtOAc/Hexanes) to afford the oxysulfonylation product **8**.



(*S*)-5-phenyl-5-(tosylmethyl)dihydrofuran-2(3H)-one (8a) Following general procedure C, the title compound was synthesized from 4-phenylpent-4-enoic acid (**2a**) (0.50 mmol, 88 mg) and tosyl chloride (0.55 mmol, 105 mg). The product was purified by silica gel flash column chromatography (Et_2O/hexanes = 1:1 to 3:1) to afford **8a** (149.8 mg, 91% yield, 74% ee).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* =8.0 Hz, 2 H), 7.35-7.28 (m, 7 H), 3.77 (d, *J* =14.8 Hz, 1 H), 3.72 (d, *J* =14.8 Hz, 1 H), 3.35 (ddd, *J* =12.8 Hz, 10.0 Hz, 8.0 Hz, 1 H), 2.84 (ddd, *J* =17.6 Hz, 10.0 Hz, 4.8 Hz, 1 H), 2.63 (ddd, *J* =12.8 Hz, 10.0 Hz, 4.8 Hz, 1 H), 2.48 (ddd, *J* =17.6 Hz, 8.0 Hz, 10.0 Hz, 1 H), 2.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 145.0, 142.0, 137.6, 128.9, 128.0, 124.6, 4.8, 65.1, 32.6, 28.3, 21.7; IR (film) ν_{max} 1776, 1596, 1449, 1318, 1285, 1173, 1137, 1084, 1049, 841 cm^{-1}; R_f(hexanes: ethyl ether = 1:2)= 0.3; HRMS: $[M+NH_4]^+$ Calcd. For $C_{18}H_{22}NO_4S$: 348.1264; Found: 348.1248. $[\alpha]_D^{24}$ = -3.2 (c = 1.5, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel IA 4.6 mm x 250 mm, hexanes:*i*-PrOH = 90:10, 1.0 mL/min, 230 nm, t_R = 34.5 min (minor) and 36.9 min (major).

(*S*)-5-(((4-bromophenyl)sulfonyl)methyl)-5-(4-chlorophenyl)dihydrofuran-2(3*H*)-one (8b) Following general procedure C, the title compound was synthesized from 4-(4-chlorophenyl) pent-4-enoic acid (**2c**) (0.50 mmol, 105 mg) and 4-bromobenzenesulfonyl chloride (0.55 mmol, 140.5 mg). The product was purified by silica gel flash column chromatography (Et_2O/hexanes = 3:1 to 7:1 to EtOAc/hexanes = 1:1) to afford **8b** (204.8 mg, 95% yield, 78% ee).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.31 (d, *J* =8.4 Hz, 2 H), 7.23 (d, *J* =8.4 Hz, 2 H), 3.73 (m, 2 H), 3.27 (ddd, *J* =12.8 Hz, 9.6 Hz, 8.4 Hz, 1 H), 2.82 (ddd, *J* =17.6 Hz, 9.6 Hz, 4.4 Hz, 1 H), 2.61 (ddd, *J* =12.8 Hz, 9.6 Hz, 4.4 Hz, 1 H), 2.49 (ddd, *J* =17.6 Hz, 8.4 Hz, 9.6 Hz,



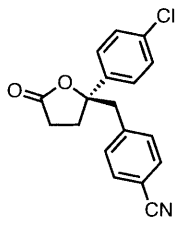
1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 139.8, 139.3, 135.0, 132.7, 129.6, 129.2, 126.3, 84.1, 65.1, 33.1, 28.1; IR (film) ν_{max} 1776, 1572, 1326, 1140, 1067, 1137, 997, 812 cm^{-1}; R_f(hexanes: ethyl acetate = 1:1)= 0.2; HRMS: $[M+NH_4]^+$ Calcd. For $C_{17}H_{18}ClBrNO_4S$: 447.9808; Found: 447.9827. $[\alpha]_D^{24}$ = +12.9 (c = 1, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel IA 4.6 mm x 250 mm, hexanes:*i*-PrOH = 85:15, 1.0 mL/min, 230 nm, t_R = 35.0 min (minor) and 68.4 min (major).

(*S*)-5-(3-acetylphenyl)-5-(((4-(trifluoromethyl)phenyl)sulfonyl)methyl)dihydrofuran-2(3*H*)-one (8c) An oven-dried Fisher Scientific 20×150 mm re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (18.7 mg, 0.05 mmol, 0.10 equiv), 2,2'-isopropylidenebis[(4*S*)-4-tert-butyl-2-oxazoline] (14.7 mg, 0.05 mmol, 0.10 equiv), silver carbonate (82.8 mg, 0.60 mmol, 1.2 equiv) and **2h** (109 mg, 0.50 mmol, 1.0 equiv). The reaction tube was sealed with a septum screw-cap (10/90, Teflon/SIL, National Scientific) and connected to a Schlenk line. The reaction tube was then briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). A solution of 4-trilfuoromethylbenzenesulfonyl chloride (134 mg, 0.55 mmol, 1.1 equiv) in anhydrous EtOAc (8 mL) was added to the tube via syringe under argon. The argon pressure the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (8 mL) and ethyl acetate (4 mL). The aqueous layer was separated and extracted with ethyl acetate (8 mL×3). The combined organic layers was concentrated *in vacuo*. The residue purified by silica gel flash column chromatography (Et_2O/hexanes = 3:1 to EtOAc/hexanes = 1:1) to afford **8c** (142.2 mg, 67% yield, 80% ee).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* =8.4 Hz, 2 H), 7.84 (m, 2 H), 7.75 (d, *J* =8.4 Hz, 2 H), 7.56 (m, 1 H), 7.45 (m, 1 H), 3.86 (d, *J* =15.2 Hz, 1 H), 3.83 (d, *J* =15.2 Hz, 1 H), 3.28 (ddd, *J* =12.8 Hz, 9.6 Hz, 8.0 Hz, 1 H), 2.85 (ddd, *J* =17.6 Hz, 9.6 Hz, 4.8 Hz, 1 H), 2.66 (ddd, *J* =12.8 Hz, 9.6 Hz, 4.8 Hz, 1 H), 2.57 (s, 3 H), 2.50 (ddd, *J* =17.6 Hz, 8.0 Hz, 9.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 174.8, 143.7, 142.1, 137.7, 135.6 (q, J_{CF} = 33 Hz), 129.5, 129.3, 128.9, 128.8, 126.5 (q, J_{CF} = 4 Hz), 124.3, 123.1 (q, J_{CF} = 272 Hz), 84.1, 64.9, 33.4, 28.0, 26.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.3 (s); IR (film) ν_{max} 1782, 1683, 1403, 1320, 1167, 1132, 1061, 914, 844 cm^{-1}; R_f(hexanes: ethyl acetate = 1:1)= 0.2; HRMS: $[M+NH_4]^+$ Calcd. For $C_{20}H_{21}F_3NO_5S$: 444.1087; Found: 444.1090. $[\alpha]_D^{24}$ = -0.8 (c = 0.9, $CHCl_3$). The enantiomeric

excess was determined by chiral HPLC analysis: Chiralcel IA 4.6 mm x 250 mm, hexanes:*i*-PrOH = 85:15, 1.0 mL/min, 230 nm, t_R = 51.6 min (minor) and 55.5 min (major).

Enantioselective oxyarylation

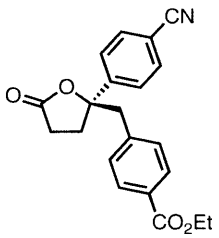
General procedure D for the enantioselective oxyarylation (Scheme 5): An oven-dried Fisher Scientific 20×150 mm re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (22.4 mg, 0.06 mmol, 0.12 equiv), 2,2-isopropylidenebis[(4*S*)-4-tert-butyl-2-oxazoline] (14.7 mg, 0.05 mmol, 0.1 equiv), aryldiazonium tetrafluoroborate (1.0 mmol, 2.0 equiv) and **2** (0.50 mmol, 1.0 equiv). The tube was then sealed with a septum screw-cap (10/90, Teflon/SIL, National Scientific) and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). Anhydrous EtOAc (8 mL) was added to the tube via syringe followed by 2,6-di-*tert*-butylpyridine (224 μL, 2.0 equiv). The argon pressure was removed and the reaction mixture was stirred at room temperature (25 °C) for 16 h. The reaction mixture was carefully diluted with saturated aqueous sodium bicarbonate solution (8 mL) and EtOAc (4 mL). The aqueous layer was separated and extracted with EtOAc (8 mL×3). The combined organic layers were concentrated *in vacuo*. The residue was then purified by silica gel flash column chromatography (Et_2O/Hexanes or EtOAc/Hexanes) to afford the oxyarylation product **9**.



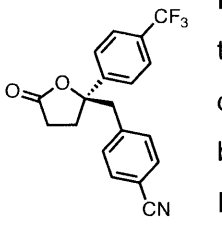
(R)-4-((2-(4-chlorophenyl)-5-oxotetrahydrofuran-2-yl)methyl)benzonitrile (9a) Following general procedure D, the title compound was synthesized from 4-(4-chlorophenyl)pent-4-enoic acid (**2c**) (105 mg, 0.50 mmol) and 4-cyanophenyldiazonium tetrafluoroborate (217 mg). The product was purified by silica gel flash column chromatography (Et_2O/hexanes = 2:1 to EtOAc/hexanes = 2:1) to afford **9a** (115.1 mg, 74% yield, 73% ee) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* =8.4 Hz, 2 H), 7.30 (d, *J* =8.8 Hz, 2 H), 7.16 (d, *J* =8.8 Hz, 2 H), 7.11 (d, *J* =8.4 Hz, 2 H), 3.26 (d, *J* =14.4 Hz, 1 H), 3.22 (d, *J* =14.4 Hz, 1 H), 2.55-2.50 (m, 2 H), 2.42-2.38 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 140.6, 140.3, 134.2, 132.1, 131.4, 128.9, 126.4, 118.7, 111.3, 87.9, 48.6, 34.3, 28.5; IR (film) ν_{max} 1742, 1434, 1366, 1229, 1217 cm^{-1}; R_f(hexanes: ethyl acetate = 1:1)= 0.3; HRMS: $[M+NH_4]^+$ Calcd. For $C_{18}H_{18}ClN_2O_2$: 329.1051; Found: 329.1071. $[\alpha]_D^{24}$ = +48.8 (c = 1.1, $CHCl_3$). The enantiomeric excess was determined by

chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 90:10, 1.0 mL/min, 230 nm, t_R = 34.5 min (major) and 39.5 min (minor).

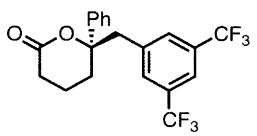
(*R*)-ethyl-4-((2-(4-cyanophenyl)-5-oxotetrahydrofuran-2-yl)methyl)benzoate (9b) Following general procedure D, the title compound was synthesized from 4-(4-cyanophenyl)pent-4-enoic acid (**2d**) (100 mg, 0.50 mmol) and 4-ethoxycarbonylphenyldiazonium tetrafluoroborate (264 mg). The product was purified by silica gel flash column chromatography (Et_2O/hexanes = 2:1 to EtOAc/hexanes = 1:1) to afford **9b** (132.0 mg, 76% yield, 71% ee) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* =8.0 Hz, 2 H), 7.64 (d, *J* =8.8 Hz, 2 H), 7.40 (d, *J* =8.8 Hz, 2 H), 7.11 (d, *J* =8.0 Hz, 2 H), 4.36 (q, *J* =7.2 Hz, 2 H), 3.27 (d, *J* =14.0 Hz, 1 H), 3.21 (d, *J* =14.0 Hz, 1 H), 2.62 (ddd, *J* =12.8 Hz, 10.0 Hz, 7.2 Hz, 1 H), 2.51-2.33 (m, 2 H), 2.26 (ddd, *J* =17.2 Hz, 9.6 Hz, 6.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 166.4, 148.1, 139.3 132.6, 130.6, 129.9, 129.7, 125.8, 118.4, 112.2, 87.9, 61.2, 48.5, 33.6, 28.5, 14.5; IR (film) ν_{max} 2228, 1774, 1738, 1717, 1365, 1277, 128, 1217, 1104, 1021 cm^{-1}; R_f(hexanes: ethyl acetate = 1:1)= 0.1; HRMS: $[M+NH_4]^+$ Calcd. For $C_{21}H_{23}N_2O_4$: 367.1652; Found: 367.1665. $[\alpha]_D^{24}$ = +11.3 (c = 1, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel AD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 85:15, 1.0 mL/min, 230 nm, t_R = 20.3 min (major) and 29.1 min (minor).



(R)-4-((5-oxo-2-(4-(trifluoromethyl)phenyl)tetrahydrofuran-2-yl)methyl)benzonitrile (9c) Following general procedure D, the title compound was synthesized from 4-(4-trifluoromethylphenyl)pent-4-enoic acid (**2e**) (122 mg, 0.50 mmol) and 4-cyanophenyldiazonium tetrafluoroborate (217 mg). The product was purified by silica gel flash column chromatography (Et_2O/hexanes = 2:1 to EtOAc/hexanes = 1:1) to afford **9c** (90.4 mg, 52% yield, 76% ee) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* =8.4 Hz, 2 H), 7.51 (d, *J* =8.4 Hz, 2 H), 7.37 (d, *J* =8.4 Hz, 2 H), 7.14 (d, *J* =8.4 Hz, 2 H), 3.30 (d, *J* =14.4 Hz, 1 H), 3.26 (d, *J* =14.4 Hz, 1 H), 2.63-2.51 (m, 2 H), 2.47-2.33 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 146.2, 140.0, 132.2, 131.4, 130.6 (q, J_{CF} = 32 Hz), 125.8 (q, J_{CF} = 3 Hz), 125.4, 123.9 (q, J_{CF} = 270 Hz), 118.7, 111.5, 87.8, 48.5, 34.2, 28.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 (s); IR (film) ν_{max} 1738, 1434, 1365, 1229, 1217, 1163 cm^{-1}; R_f(toluene: ethyl acetate = 5:1)= 0.3; HRMS: $[M+NH_4]^+$

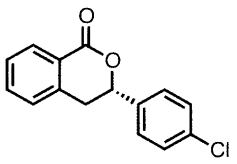


Calcd. For $C_{19}H_{18}F_3N_2O_2$: 363.1315; Found: 363.1332. $[\alpha]_D^{24}$ = +8.0 (c = 0.9, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 90:10, 1.0 mL/min, 230 nm, t_R = 30.3 min (major) and 37.6 min (minor).



(*R*)-6-(3,5-bis(trifluoromethyl)benzyl)-6-phenyltetrahydro-2*H*-pyran-2-one (9d) Following general procedure D, the title compound was synthesized from 5-phenylhex-5-enoic acid (**2i**) (95 mg, 0.50 mmol) and 3,5-bis(trifluoromethyl)phenyldiazonium tetrafluoroborate (328 mg). The product was purified by silica gel flash column chromatography (hexanes: ethyl acetate = 10:1 to 4:1) to afford **9d** (164.9 mg, 82% yield, 56% ee) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1 H), 7.36-7.30 (m, 5 H), 7.19-7.178 (m, 2 H), 3.28 (d, *J* =14.0 Hz, 1 H), 3.26 (d, *J* =14.0 Hz, 1 H), 2.47-2.33 (m, 3 H), 1.97 (ddd, *J* =14.4, 12.8, 4.8 Hz, 1 H), 1.80 (m, 1 H), 1.63 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 141.3, 137.7, 131.1 (q, J_{CF} = 33 Hz), 130.9, 129.0, 128.2, 125.3, 123.3 (q, J_{CF} = 271 Hz), 120.9 (m), 86.7, 49.9, 31.7, 29.1, 16.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9 (s); IR (film) ν_{max} 1736, 1378, 1275, 1235, 1167, 1125, 1044, 894 cm^{-1}; R_f(toluene: ethyl acetate = 5:1)= 0.6; $[M+NH_4]^+$ Calcd. For $C_{20}H_{20}F_6NO_2$: 420.1393; Found: 420.1370. $[\alpha]_D^{24}$ = +2.3 (c= 0.7, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 90:10, 1.0 mL/min, 230 nm, t_R = 7.1 min (major) and 10.6 min (minor).

(*S*)-3-(4-chlorophenyl)isochroman-1-one (12) (Scheme 6) An oven-dried Fisher Scientific 20×150 mm re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged



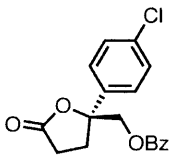
with tetrakis(acetonitrile)copper(I) hexafluorophosphate (28.0 mg, 0.075 mmol, 0.15 equiv), 2,2-isopropylidenebis[(4*S*)-4-tert-butyl-2-oxazoline] (22.1 mg, 0.075 mmol, 0.15 equiv), 2-carboxybenzenediazonium tetrafluoroborate (236 mg, 1.0 mmol, 2.0 equiv). The tube was then sealed with a Teflon septum screw-cap (10/90, Teflon/SIL, National Scientific) and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). Anhydrous EtOAc (8 mL) was added to the tube via syringe followed by 2,6-di-*tert*-butylpyridine (224 μL, 2.0 equiv) and 4-chlorostyrene (69 mg, 1.0 equiv, 0.50 mmol) via syringe. The argon pressure was removed and the reaction mixture was stirred at room temperature (25 °C) for 16 h. The reaction mixture was carefully diluted with saturated

aqueous sodium bicarbonate solution (8 mL) and EtOAc (4 mL). The aqueous layer was separated and extracted with EtOAc (8 mL×3). The combined organic layers were concentrated *in vacuo.* The residue was then purified by silica gel flash column chromatography (hexanes: ethyl acetate = 10:1 to 4:1) to afford **12** (23.9 mg, 19% yield, 46% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* =7.2 Hz, 1 H), 7.58 (td, *J* =7.2, 1.2 Hz, 1 H), 7.46-7.38 (m, 5 H), 7.29 (d, *J* =7.6 Hz, 1 H), 5.54 (dd, *J* =12.0, 3.2 Hz, 1 H), 3.30 (dd, *J* =16.4, 12.0 Hz, 1 H), 3.13 (dd, *J* =16.4, 3.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 138.7, 137.3, 134.7, 134.2, 130.7, 129.1, 128.2, 127.6, 127.5, 125.2, 79.3, 35.7; IR (film) ν_{max} 1722, 1602, 1492, 1459, 1268, 1224, 1082, 816, 741 cm^{-1}; R_f(toluene: ethyl acetate = 5:1)= 0.5; $[M+H]^+$ Calcd. For $C_{15}H_{12}ClO_2$: 259.0520; Found: 259.0538. $[\alpha]_D^{24}$ = -51.9 (c= 0.6, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel IA 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm, t_R = 23.2 min (major) and 19.3 min (minor). The absolute configuration was assigned based on optical rotation comparison with literature report (Iwao et al. *Tetrahedron*, **2005**, 61, 3289)

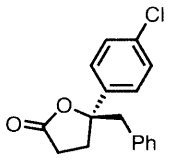
Enantioselective diacyloxylation

(*S*)-(2-(4-chlorophenyl)-5-oxotetrahydrofuran-2-yl)methyl (13) and benzoate(*R*)-5-benzyl-5-(4-chlorophenyl)dihydrofuran-2(3*H*)-one (14) (Scheme 7) An oven-dried Fisher Scientific 20×150 mm re-sealable test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (18.7 mg, 0.05 mmol, 0.10 equiv), 2,2'-isopropylidenebis[(4*S*)-4-tert-butyl-2-oxazoline] (14.7 mg, 0.05 mmol, 0.10 equiv), dibenzoyl peroxide (75%) (244 mg, 0.75 mmol, 1.5 equiv), manganese powder (55 mg, 1.0 mmol, 2.0 equiv) and **2c** (105 mg, 0.50 mmol, 1.0 equiv). The tube was then sealed with a Teflon screw-cap septum (10/90, Teflon/SIL, National Scientific) and connected to a Schlenk line. The vessel was briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). Anhydrous EtOAc (8 mL) was added to the tube via syringe and the argon pressure was removed. The reaction mixture was stirred at room temperature (25 °C) for 16 h. The reaction mixture was carefully diluted with saturated aqueous sodium bicarbonate solution (8 mL) and EtOAc (4 mL). Internal standard (phenanthrene) was added. The aqueous layer was separated and extracted with EtOAc (8 mL×3). The combined organic layers were concentrated *in vacuo.* The residue was analyzed by ^{1}H NMR spectroscopy (^{1}H NMR yield: **13**: 29%; **14**: 40%). The residue was then purified by silica gel flash column chromatography (hexanes: ethyl acetate =

10:1 to 4:1 to toluene: ethyl acetate = 4:1) to afford **13** (42.5 mg, 26% yield, 65% ee) and **14** (50.8 mg, 35% yield, 66% ee).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2 H), 7.59 (m, 1 H), 7.47-7.41 (m, 6 H), 4.64 (d, *J* =12.4 Hz, 1 H), 4.45 (d, *J* =12.4 Hz, 1 H), 2.82-2.71 (m, 2 H), 2.63-2.45 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 166.0, 138.7, 134.8, 133.73, 129.8, 129.3, 129.2, 128.8, 126.6, 86.6, 69.9, 31.5, 28.9; IR (film) ν_{max} 1779, 1720, 1264, 1111, 1093, 1012, 910 cm^{-1}; R_f(toluene: ethyl acetate = 5:1)= 0.4; $[M+H]^+$ Calcd. For $C_{18}H_{16}ClO_4$: 331.0732; Found: 331.0750. $[\alpha]_D^{24}$ = -16.4 (c= 0.4, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 90:10, 1.0 mL/min, 230 nm, t_R = 16.8 min (major) and 31.9 min (minor).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.23 (m, 7 H), 7.08 (m, 2 H), 3.22 (d, *J* =14.0 Hz, 1 H), 3.10 (d, *J* =14.0 Hz, 1 H), 2.57 (ddd, *J* =12.8, 10.4, 7.2 Hz, 1 H), 2.44-2.28 (m, 2 H), 2.11 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 142.1, 134.8, 133.8, 130.8, 128.7, 128.5, 127.4, 126.4, 88.6, 48.8, 33.2, 28.8; IR (film) ν_{max} 1772, 1492, 1163, 1003, 926, 808, 701 cm^{-1}; R_f(toluene: ethyl acetate = 5:1)= 0.6; $[M+NH_4]^+$ Calcd. For $C_{17}H_{19}ClNO_2$: 304.1099; Found: 304.1105. $[\alpha]_D^{24}$ = +4.1 (c= 1, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H 4.6 mm x 250 mm, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm, t_R = 19.5 min (major) and 18.2 min (minor).

3.5 References and Notes

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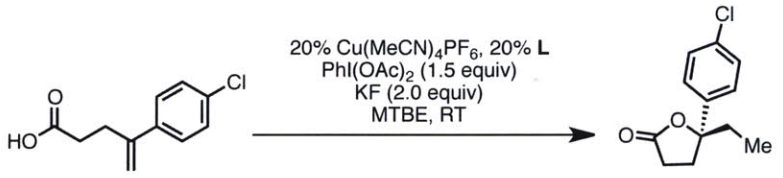

2c **15**

20% yield, 54% ee

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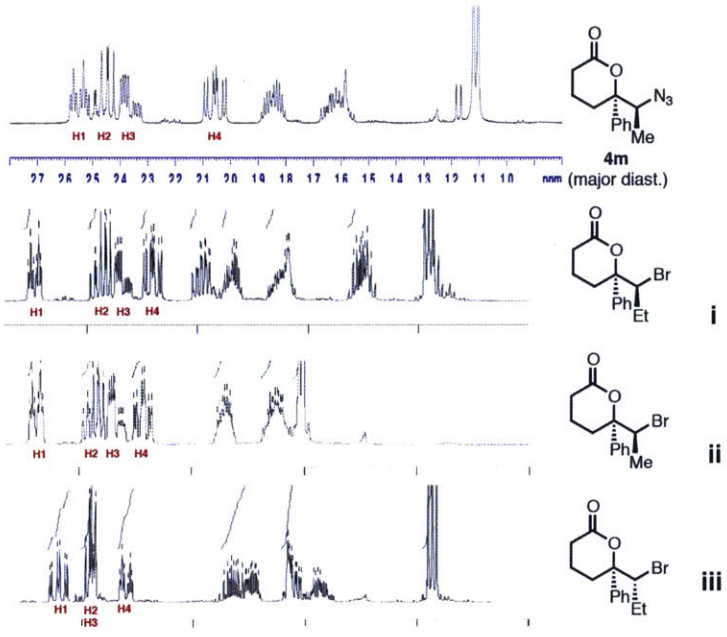

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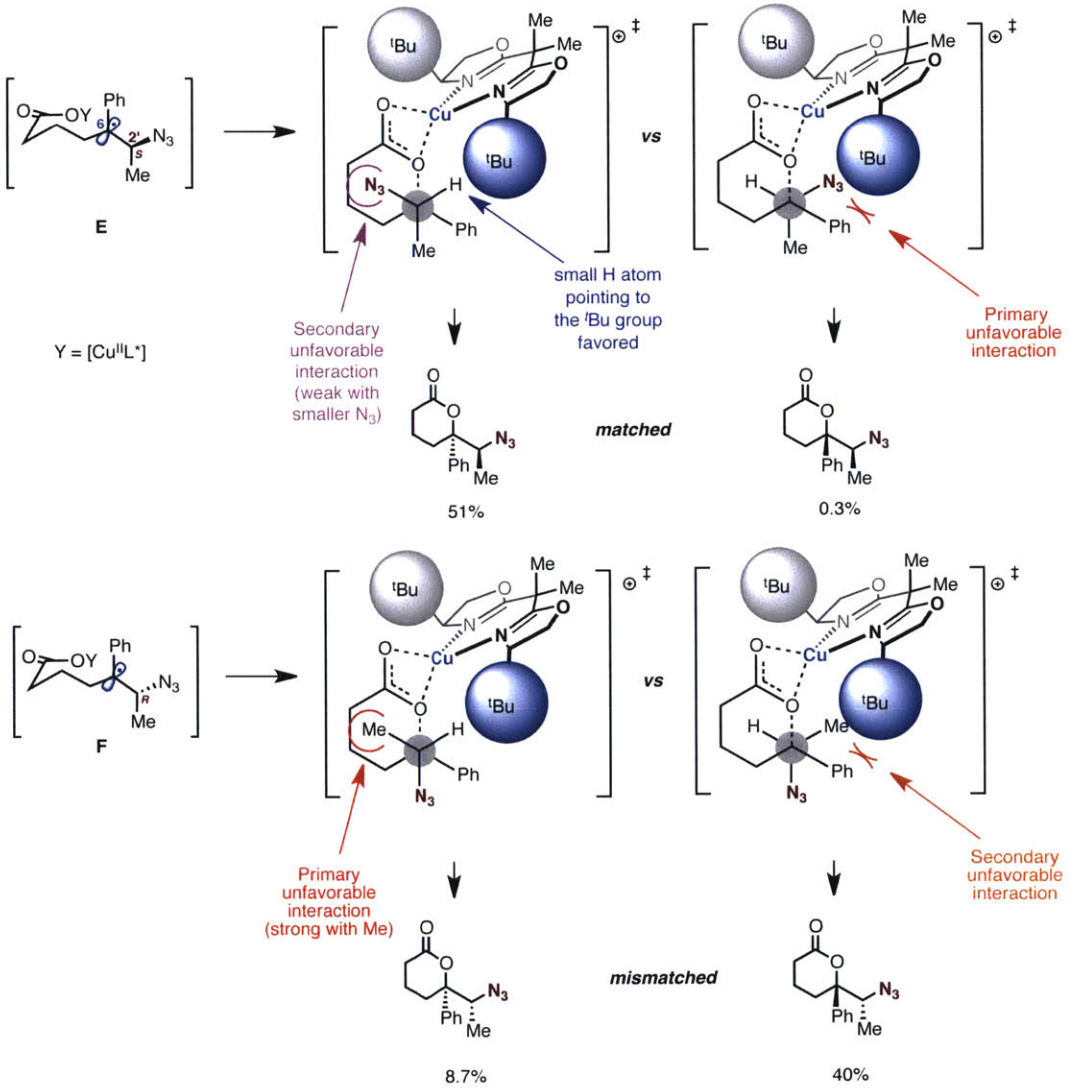
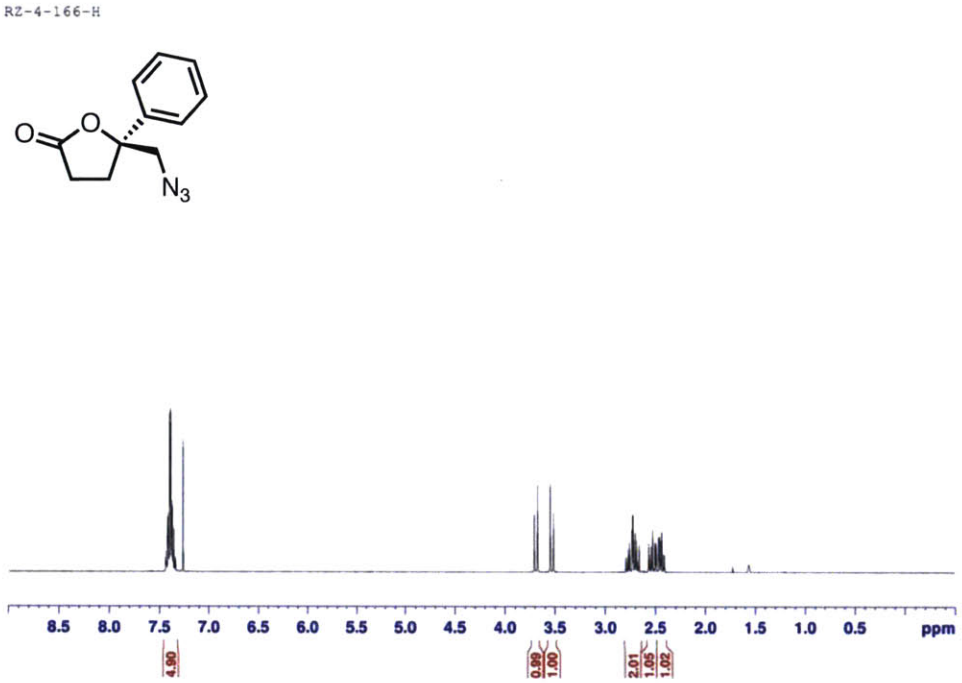
[31] A possible explanation for the stereoselectivity observed: In the top case, primary unfavorable interaction between the aryl group and the ligand's ^{t}Bu group lead to high selectivity towards (6S,2'S) product because the secondary unfavorable interaction caused by the azide group is very small. In contrast, the unfavorable interaction cause the methyl group is so strong that the interaction between the aryl group and the ^{t}Bu group is overwhelmed in the bottom case.

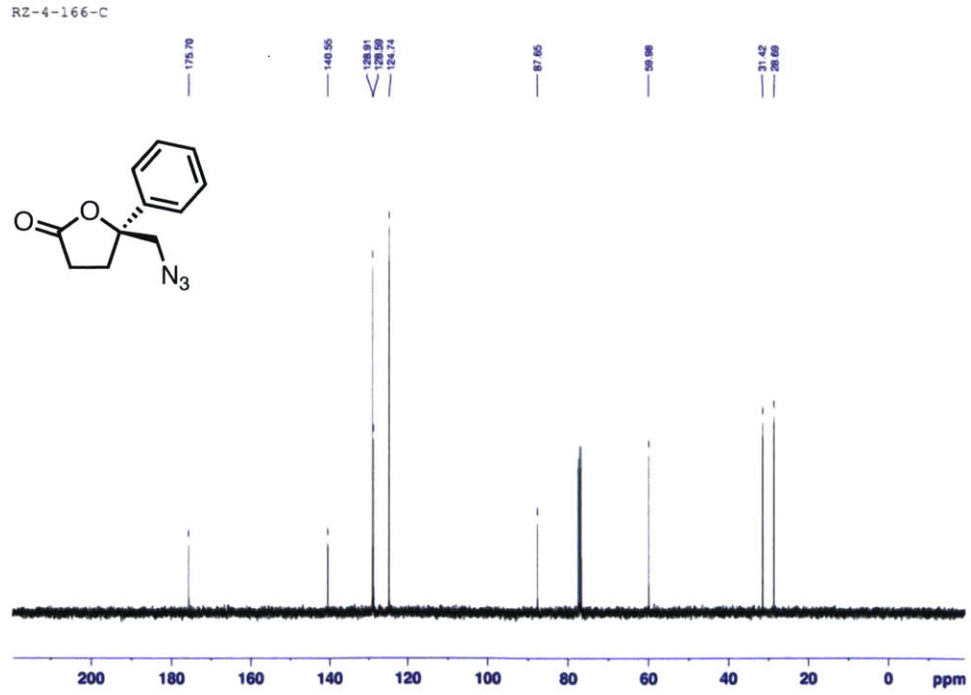


3.6 Spectra and HPLC traces

4a ^{1}H NMR (400 MHz, $CDCl_3$)

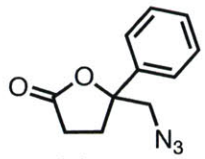


4a ^{13}C NMR (100 MHz, $CDCl_3$)



HPLC traces for 4a:

Sample Name: RZ-4-166-RAC



(±)-**4a**

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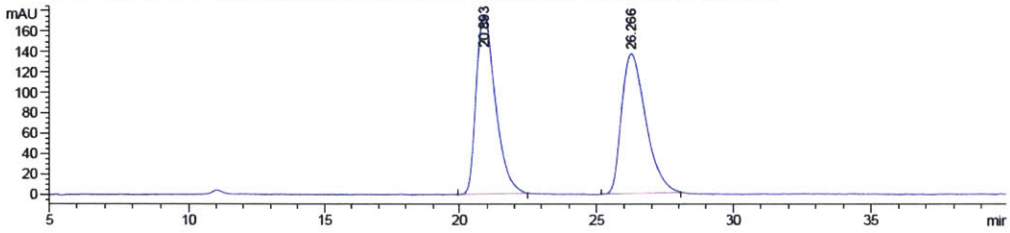
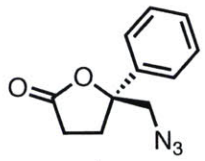


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.893	BB	0.7269	8601.23047	175.76074	50.1902
2	26.266	BB	0.7623	8536.03516	137.86684	49.8098
Totals :				1.71373e4	313.62758	

Sample Name: RZ-4-166



4a

```
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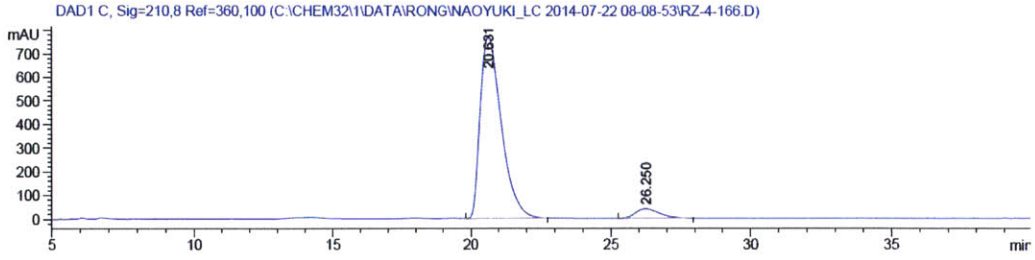

Signal 3: DAD1 C, Sig=210,8 Ref=360,100

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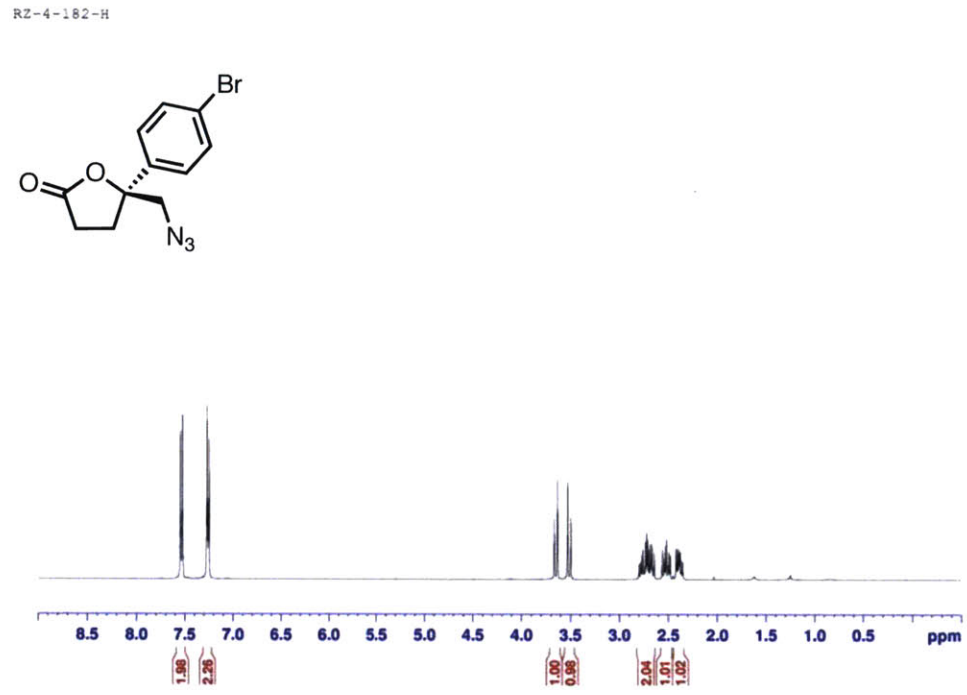
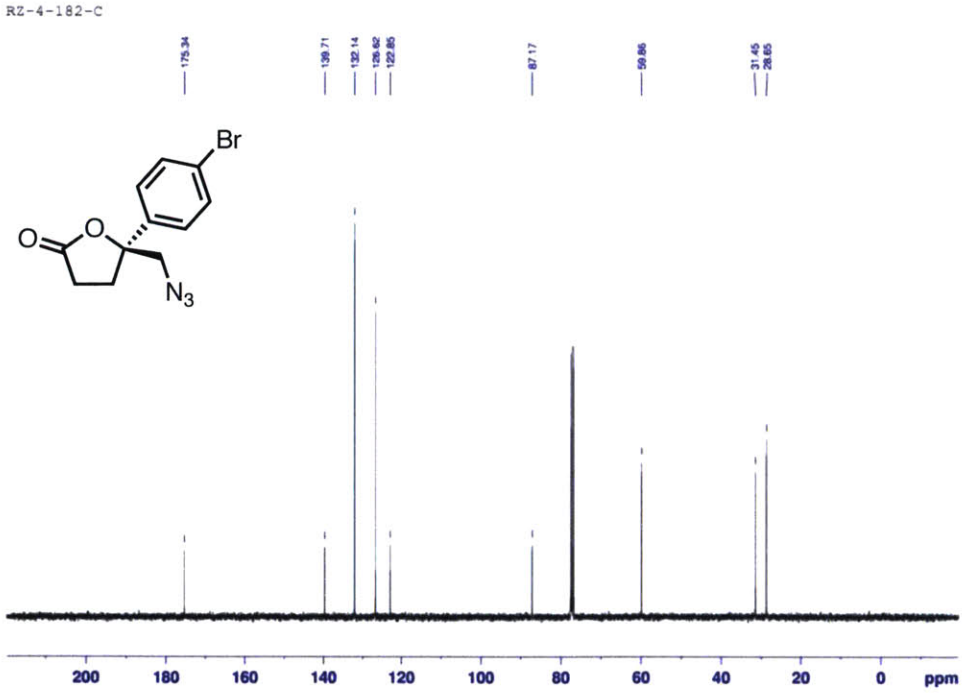
1	20.631	BV	0.7812	4.02596e4	773.55682	94.3599
2	26.250	VB	0.7156	2406.40234	40.01611	5.6401
Totals :				4.26660e4	813.57293	

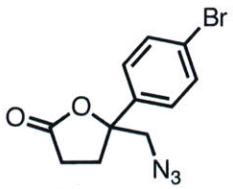
4b ^{1}H NMR (400 MHz, $CDCl_3$)



4b ^{13}C NMR (100 MHz, $CDCl_3$)



HPLC traces for 4b:



(±)-**4b**

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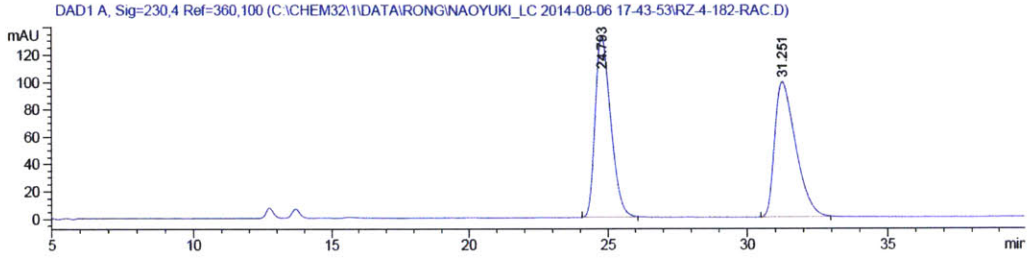

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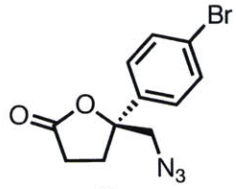
1	24.793	BB	0.6001	5160.43164	133.17227	49.9961
2	31.251	BB	0.7904	5161.24463	99.30509	50.0039
Totals :				1.03217e4	232.47736	



4b

Sample Name: RZ-4-182

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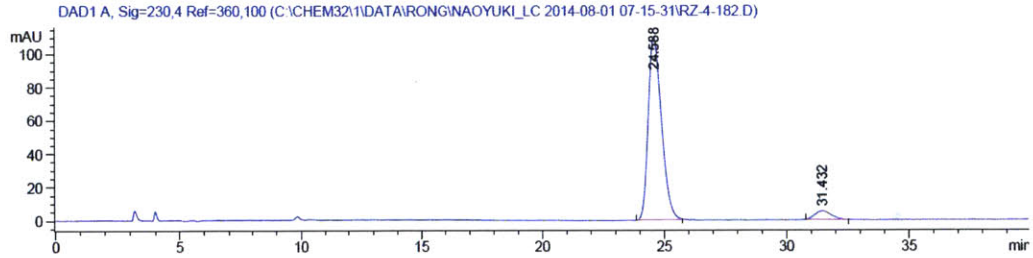
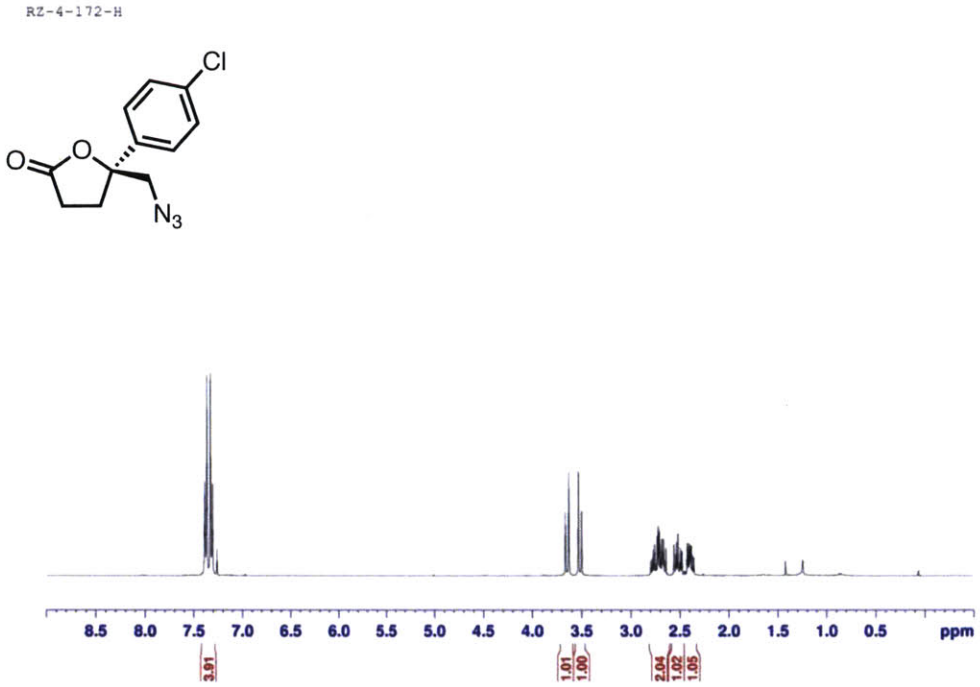


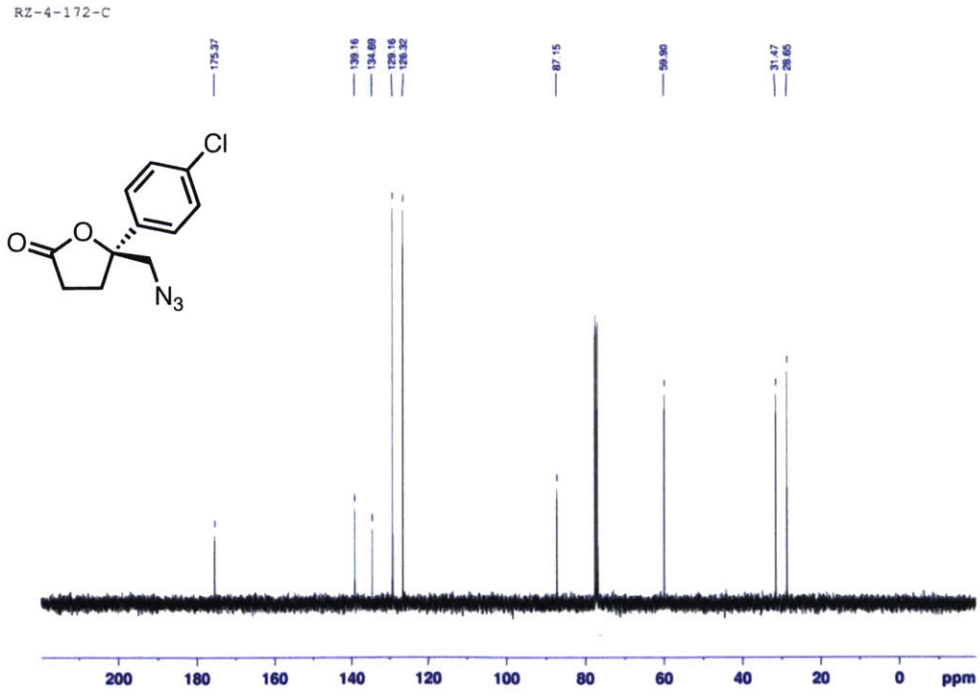
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.588	BB	0.5745	4195.15039	110.60049	94.5795
2	31.432	BB	0.5531	240.42851	5.16516	5.4205
Totals :				4435.57890	115.76566	

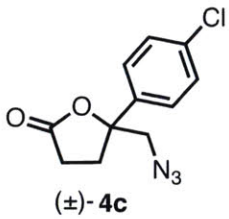
4c ^{1}H NMR (400 MHz, $CDCl_3$)



4c ^{13}C NMR (100 MHz, $CDCl_3$)



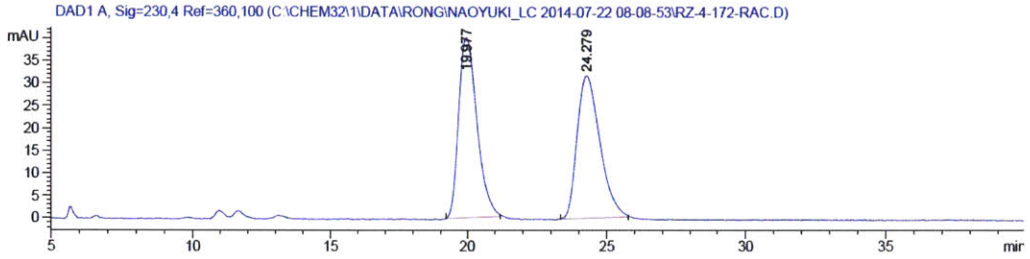
HPLC traces for 4c:



(±)-4c

Sample Name: RZ-4-172-RAC

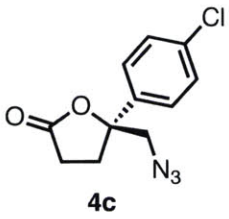
```
    ======================================================================
    Acq. Operator    : RZ                                Seq. Line :   5
    Acq. Instrument : Instrument 1                        Location : Vial 18
    Injection Date   : 7/22/2014 10:50:36 AM                  Inj :   1
                                                        Inj Volume : 1 µl
    Acq. Method      : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-07-22 08-08-53\RZ-5IPA-1ML-2013-.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

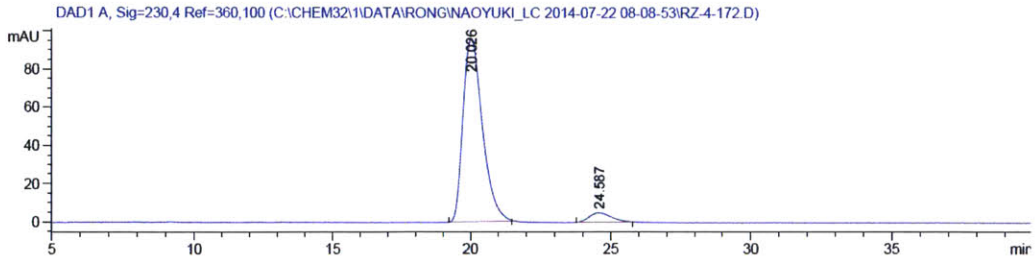
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.977	BB	0.6513	1820.84253	40.13295	50.0045
2	24.279	BB	0.7439	1820.51843	31.80194	49.9955
Totals :				3641.36096	71.93489	

Sample Name: RZ-4-172



4c

```
    ======================================================================
    Acq. Operator    : RZ                                Seq. Line :   4
    Acq. Instrument : Instrument 1                        Location : Vial 17
    Injection Date   : 7/22/2014 10:09:30 AM                  Inj :   1
                                                        Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 2 µl
    Acq. Method      : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-07-22 08-08-53\RZ-5IPA-1ML-2013-.M
```

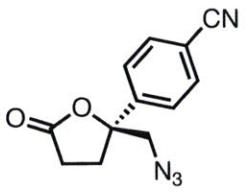


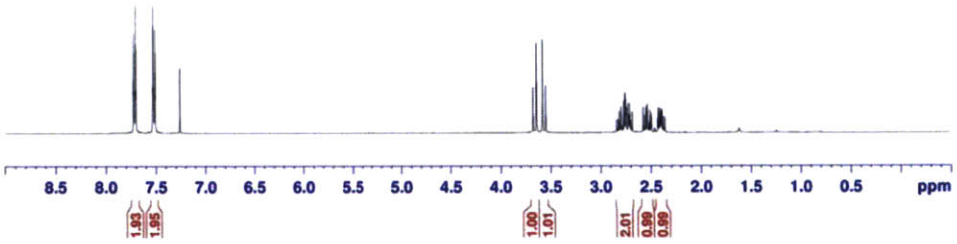
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.026	BB	0.7173	4562.40234	96.20024	94.4555
2	24.587	BB	0.6477	267.80951	4.91480	5.5445
Totals :				4830.21185	101.11505	

4d ^{1}H NMR (400 MHz, $CDCl_3$)

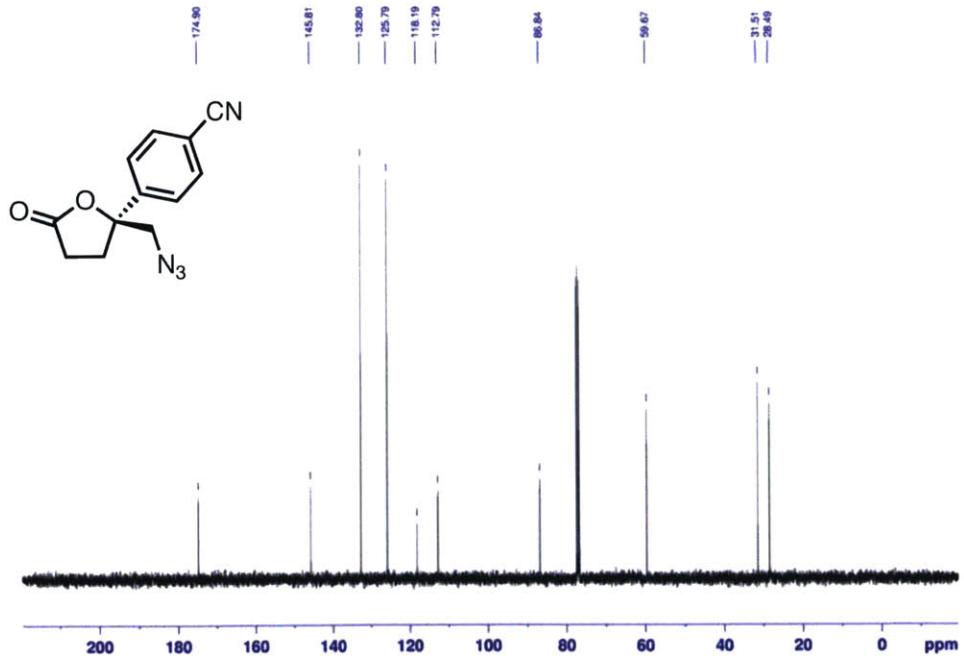
RZ-4-190-H



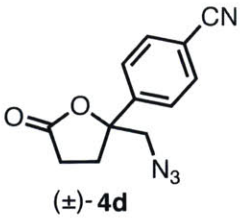


4d ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-4-190-C



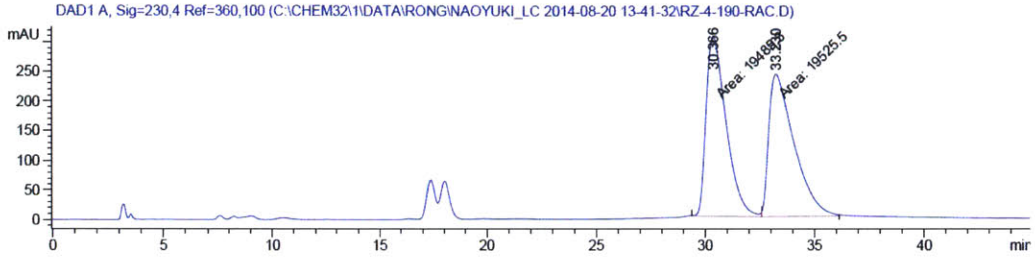
HPLC traces for 4d:



(±)-**4d**

Sample Name: RZ-4-190-RAC

```
    ======================================================================
    Acq. Operator    : RZ                                Seq. Line :   1
    Acq. Instrument : Instrument 1                        Location : Vial 17
    Injection Date   : 8/20/2014 1:43:52 PM                   Inj :   1
                                                        Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 6 µl
    Acq. Method      : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-08-20 13-41-32\RZ-15IPA-2014.M
```

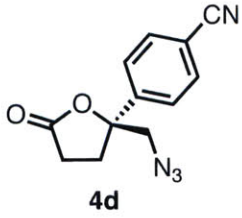



```
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  30.366 MM    1.0648 1.94853e4   304.99750  49.9484
   2  33.230 MM    1.3457 1.95255e4   241.82451  50.0516

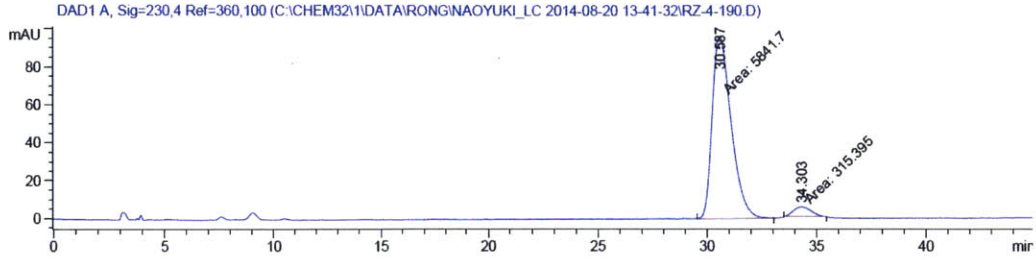
Totals :                  3.90108e4   546.82201
```

Sample Name: RZ-4-190



4d

```
    ======================================================================
    Acq. Operator    : RZ                                Seq. Line :   2
    Acq. Instrument : Instrument 1                        Location : Vial 16
    Injection Date   : 8/20/2014 2:30:02 PM                   Inj :   1
                                                        Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 6 µl
    Acq. Method      : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-08-20 13-41-32\RZ-15IPA-2014.M
```



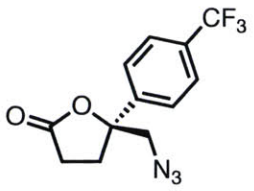

```
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  30.587 MM    1.0066 5841.70020   96.71944  94.8775
   2  34.303 MM    0.9822  315.39474    5.35182   5.1225

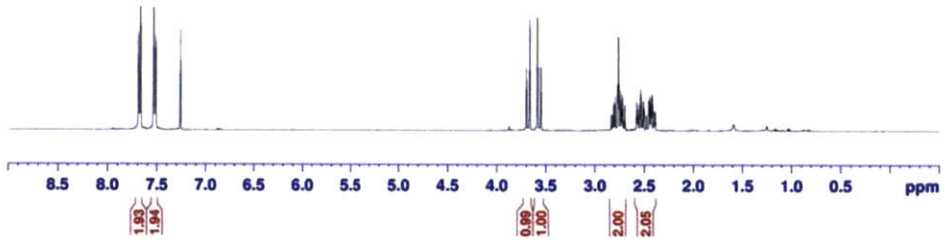
Totals :                  6157.09494  102.07127
```

4e ^{1}H NMR (400 MHz, $CDCl_3$)

RZ-4-186-H

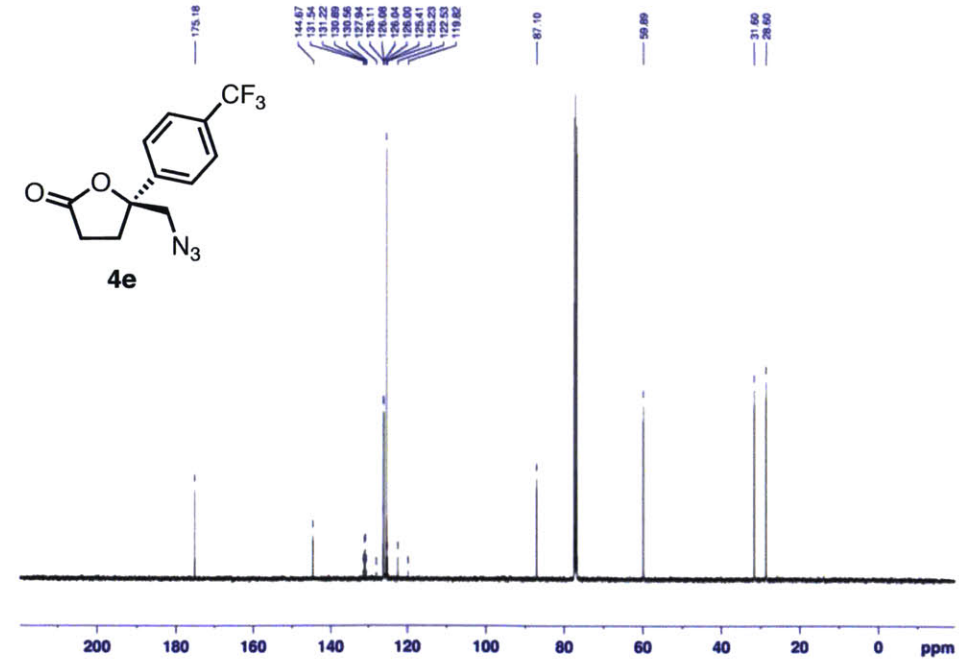


4e



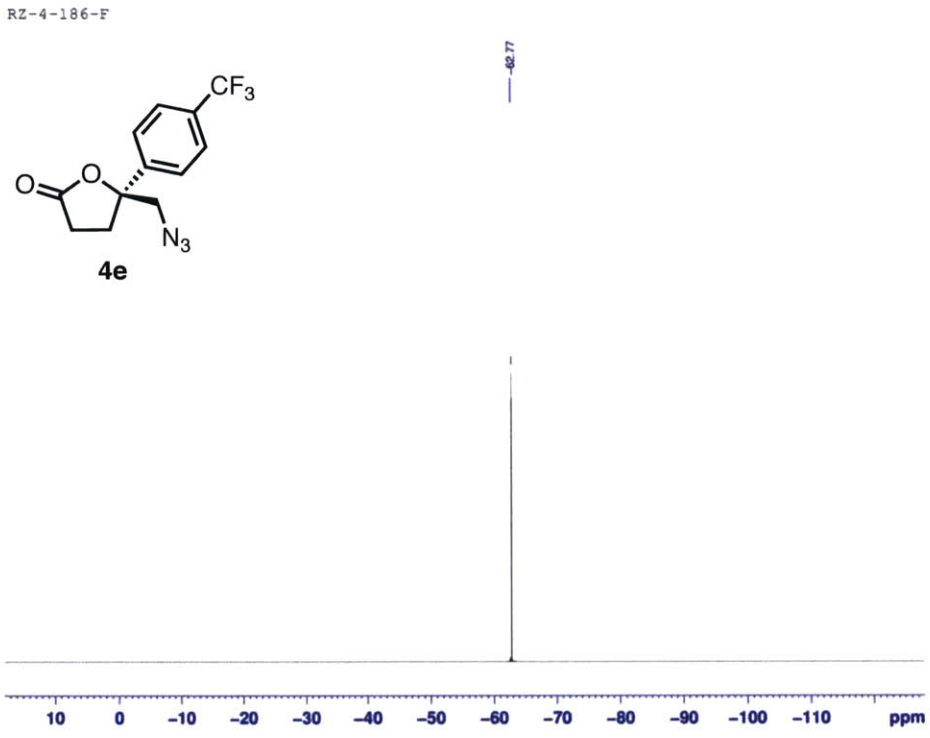
4e ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-4-186-C

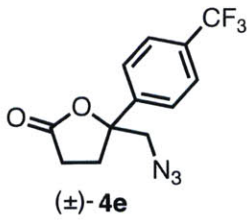


4e

4e ^{19}F NMR (376 MHz, $CDCl_3$)



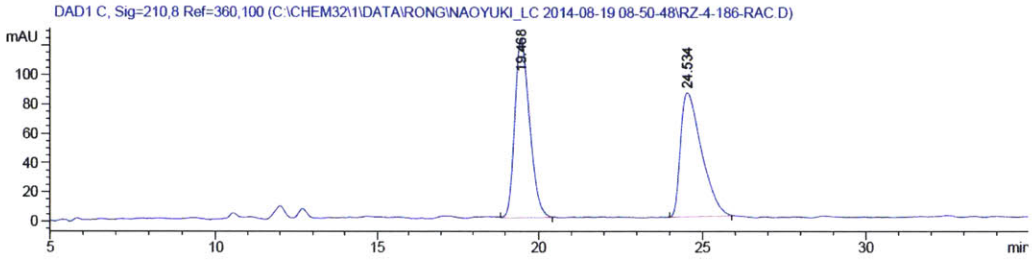
HPLC traces for 4e:



(±)-**4e**

Sample Name: RZ-4-186-RAC

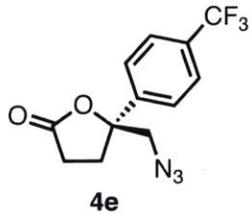
```
==================================================================
Acq. Operator    : RZ                          Seq. Line :   1
Acq. Instrument : Instrument 1                  Location : Vial 17
Injection Date  : 8/19/2014 8:53:02 AM             Inj :   1
                                               Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 3 µl
Acq. Method      : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-08-19 08-50-48\RZ-5IPA-1ML-2013-.M
```



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

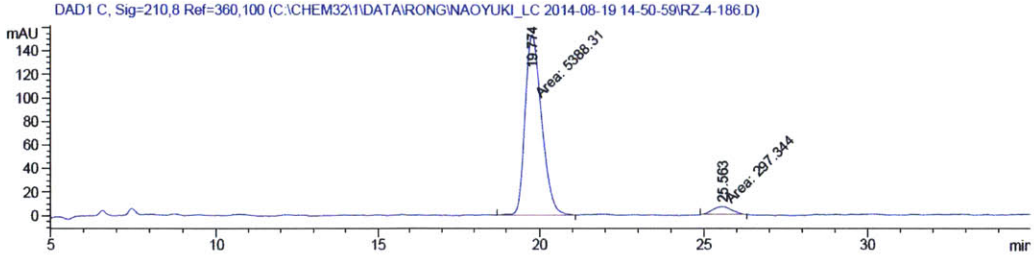
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.468	VB	0.4645	3856.93750	122.78101	50.3897
2	24.534	BB	0.6219	3797.28760	84.88390	49.6103
Totals :				7654.22510	207.66491	

Sample Name: RZ-4-186



4e

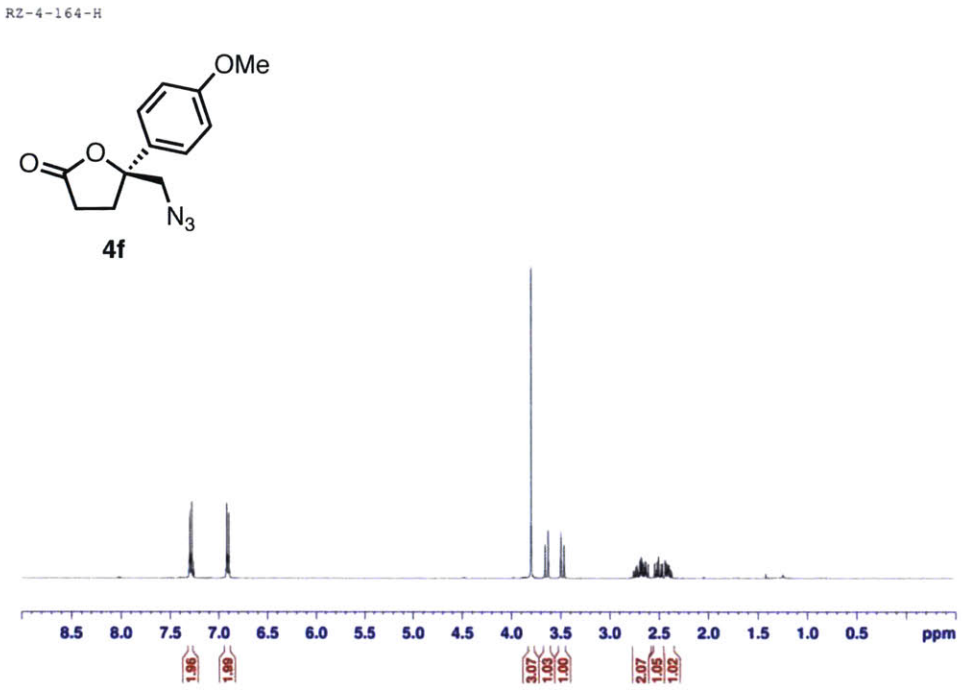
```
==================================================================
Acq. Operator    : RZ                          Seq. Line :   1
Acq. Instrument : Instrument 1                  Location : Vial 16
Injection Date  : 8/19/2014 2:53:19 PM             Inj :   1
                                               Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 12 µl
Acq. Method      : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-08-19 14-50-59\RZ-5IPA-1ML-2013-.M
```



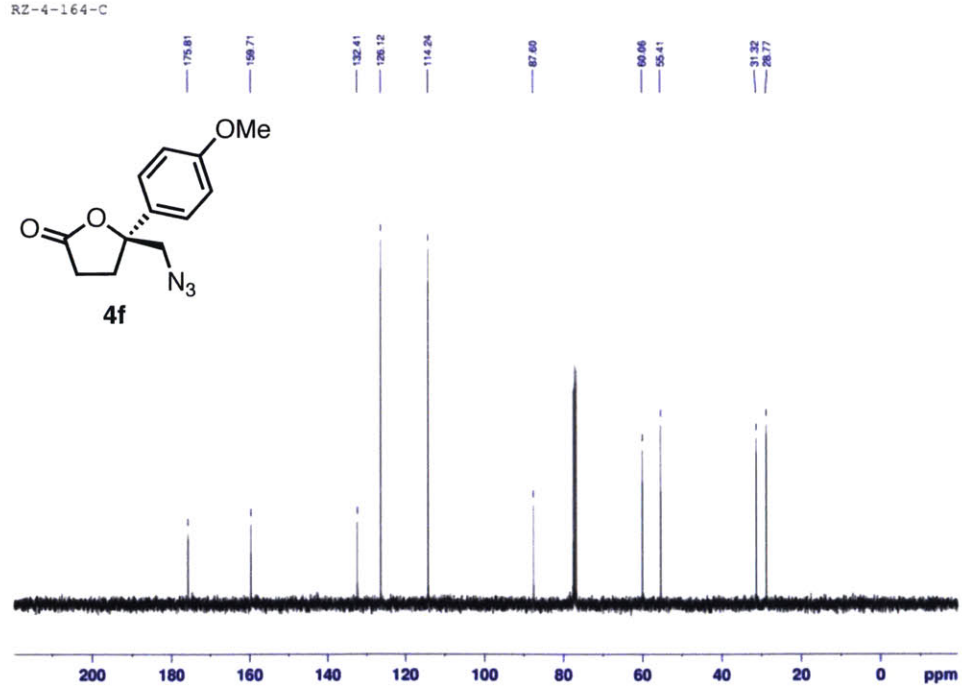
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.774	MM	0.5860	5388.30957	153.24788	94.7703
2	25.563	MM	0.7042	297.34396	7.03758	5.2297
Totals :				5685.65353	160.28546	

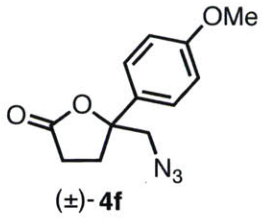
4f ^{1}H NMR (400 MHz, $CDCl_3$)



4f ^{13}C NMR (100 MHz, $CDCl_3$)



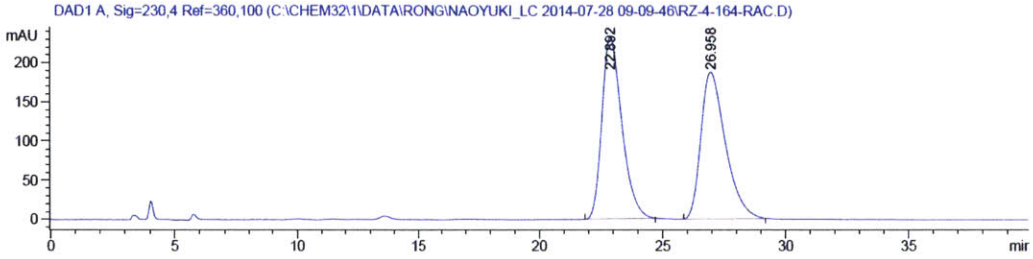
HPLC traces for 4f:



(±)-**4f**

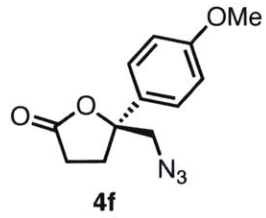
Sample Name: RZ-4-164-RAC

```
    ========================================================================
    Acq. Operator    : RZ                              Seq. Line :   2
    Acq. Instrument : Instrument 1                      Location : Vial 17
    Injection Date   : 7/28/2014 9:53:18 AM                 Inj :   1
                                                      Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 8 µl
    Acq. Method      : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-07-28 09-09-46\RZ-5IPA-1ML-2013-.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

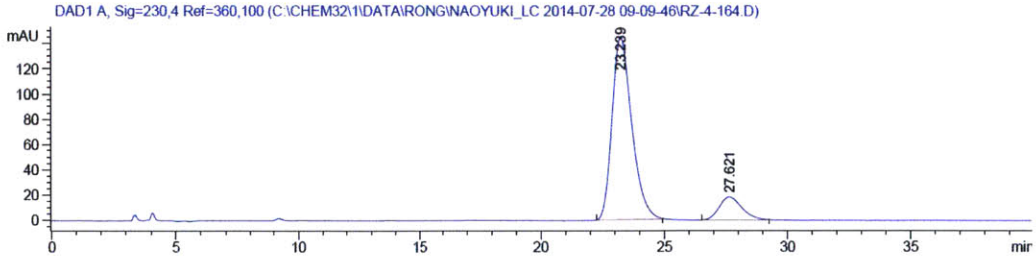
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.892	BB	0.8382	1.31085e4	233.07202	50.1893
2	26.958	BB	0.9848	1.30096e4	187.66890	49.8107
Totals :				2.61181e4	420.74092	



4f

Sample Name: RZ-4-164

```
    ========================================================================
    Acq. Operator    : RZ                              Seq. Line :   1
    Acq. Instrument : Instrument 1                      Location : Vial 16
    Injection Date   : 7/28/2014 9:12:06 AM                 Inj :   1
                                                      Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method      : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-07-28 09-09-46\RZ-5IPA-1ML-2013-.M
```

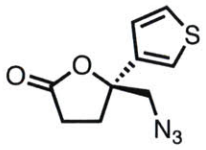


Signal 1: DAD1 A, Sig=230,4 Ref=360,100

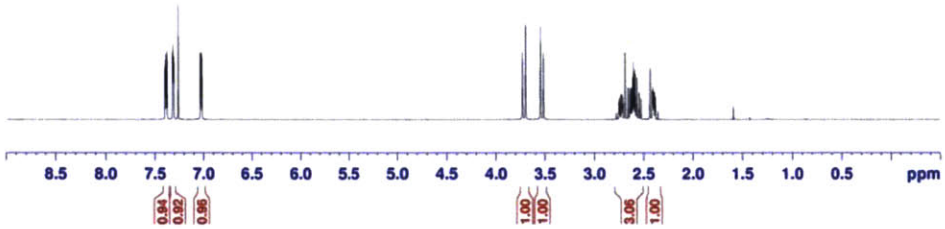
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.239	BB	0.8258	8031.23877	145.08575	87.2371
2	27.621	BB	0.7676	1174.97656	18.23970	12.7629
Totals :				9206.21533	163.32545	

4g ^{1}H NMR (400 MHz, $CDCl_3$)

RZ-4-218A-H

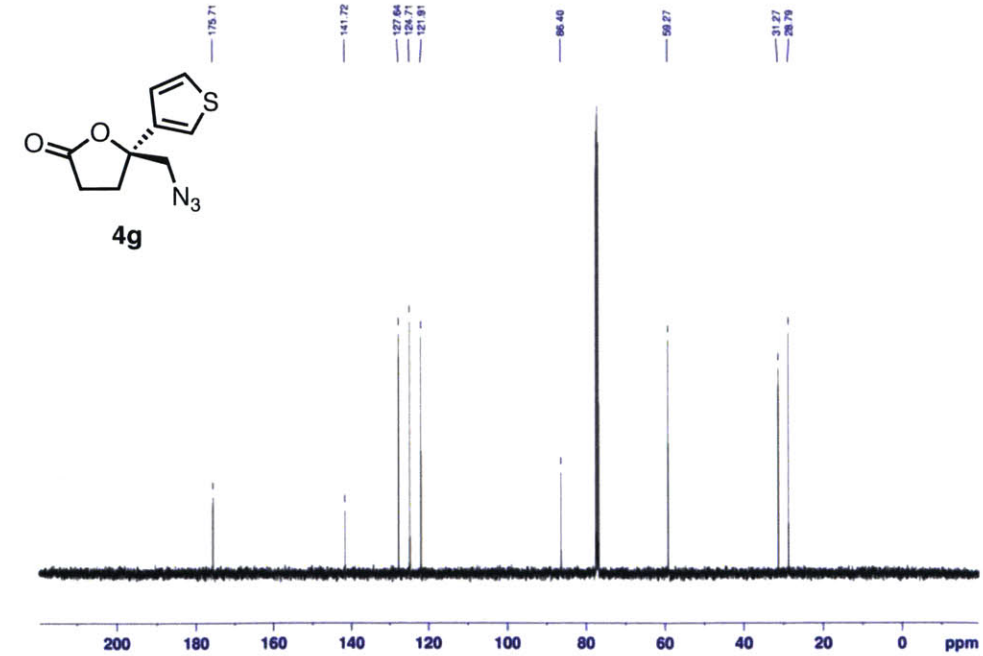


4g

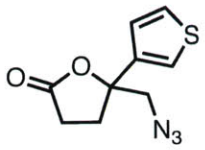


4g ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-4-218A-C



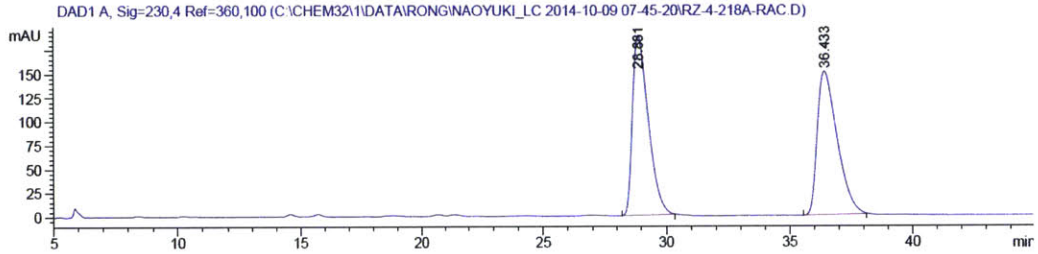
HPLC traces for 4g:



(±)-4g

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-10-09 07-45-20\RZ-4-218A-RAC.D
Sample Name: RZ-4-218A-RAC

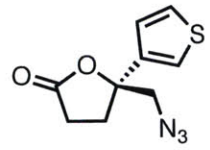
```
==================================================================
Acq. Operator   : RZ                          Seq. Line :  6
Acq. Instrument : Instrument 1                 Location : Vial 19
Injection Date  : 10/9/2014 11:09:11 AM             Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 8 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-10-09 07-45-20\RZ-5IPA-1ML-2013-.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

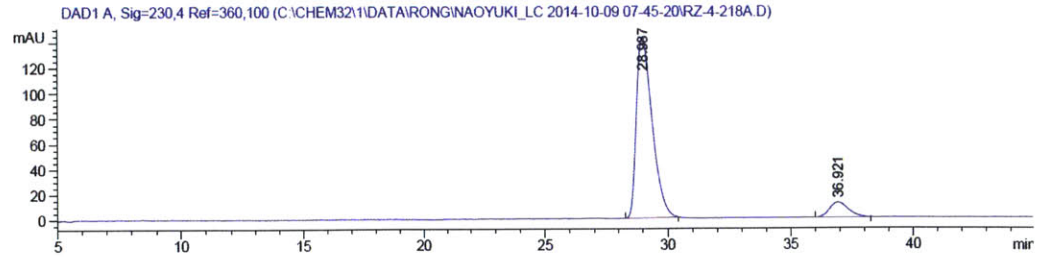
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.881	BB	0.6575	8484.71289	189.09726	50.0582
2	36.433	BB	0.7776	8464.98535	151.09933	49.9418
Totals :				1.69497e4	340.19659	

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-10-09 07-45-20\RZ-4-218A.D
Sample Name: RZ-4-218A



4g

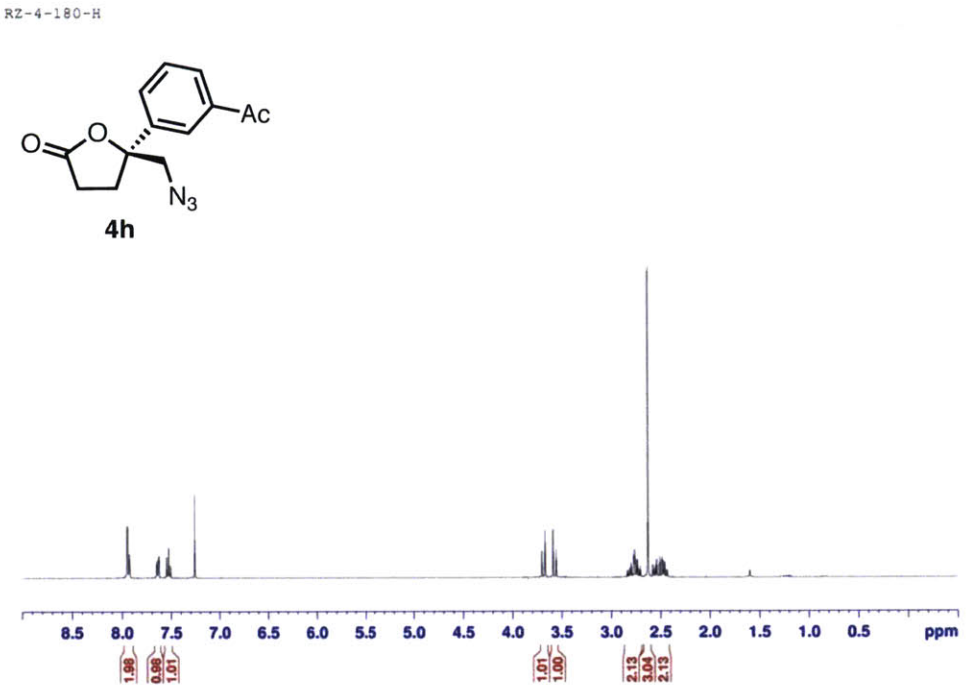
```
==================================================================
Acq. Operator   : RZ                          Seq. Line :  4
Acq. Instrument : Instrument 1                 Location : Vial 17
Injection Date  : 10/9/2014 9:36:43 AM              Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 12 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-10-09 07-45-20\RZ-5IPA-1ML-2013-.M
```



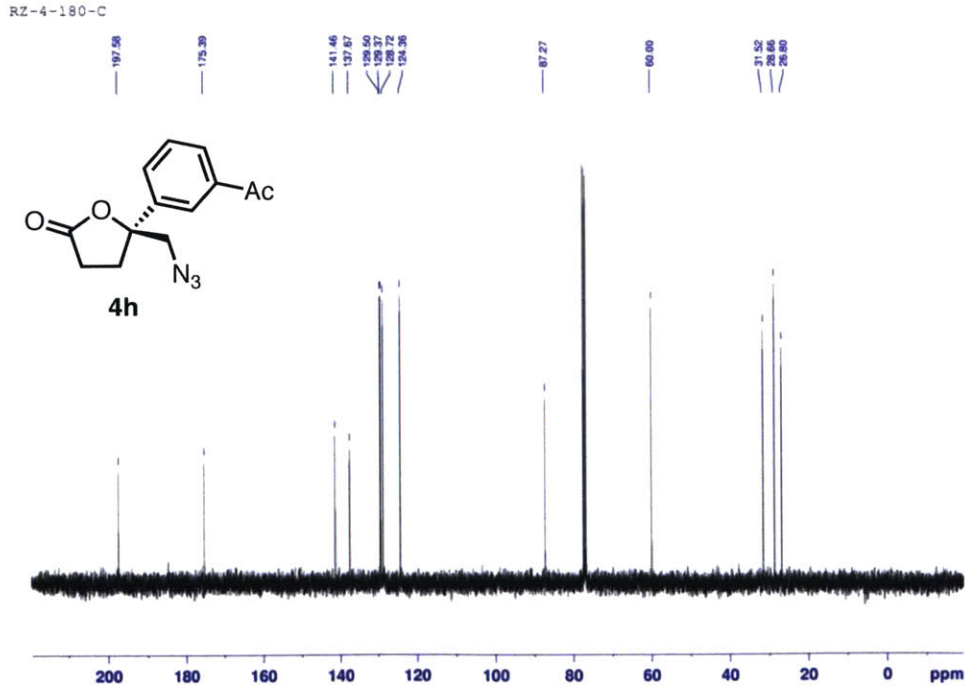
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.987	BB	0.6492	6429.18652	143.35242	91.1065
2	36.921	BB	0.6312	627.59711	11.86257	8.8935
Totals :				7056.78363	155.21498	

4h ^{1}H NMR (400 MHz, $CDCl_3$)

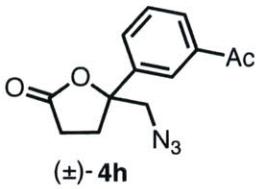


4h ^{13}C NMR (100 MHz, $CDCl_3$)



HPLC traces for 4h:

Sample Name: RZ-4-180-RAC



(±)-4h

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================================================================================
Acq. Operator   : RZ                                 Seq. Line :   1
Acq. Instrument : Instrument 1                        Location : Vial 16
Injection Date  : 9/1/2014 1:01:22 PM                     Inj :   1
                                                     Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-09-01 12-58-58\RZ-SHUTDOWN.M
```
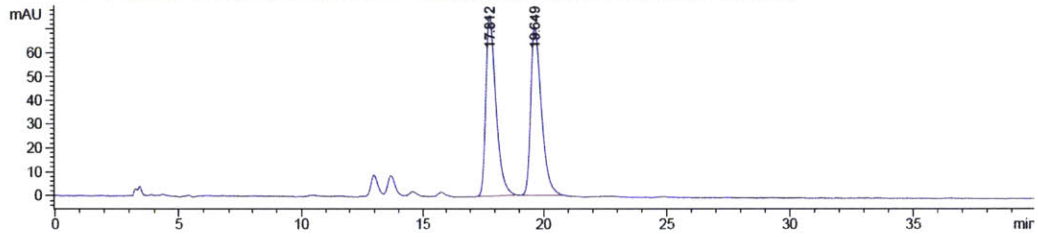
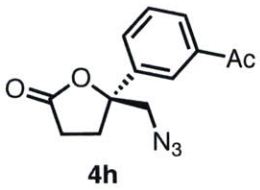

DAD1 A, Sig=230,4 Ref=360,100 (C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-09-01 12-58-58\RZ-4-180-RAC.D)



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.812	BB	0.4240	2168.58911	76.19683	50.0957
2	19.649	BB	0.4531	2160.30054	70.98513	49.9043
Totals :				4328.88965	147.18196	

Sample Name: RZ-4-180



4h

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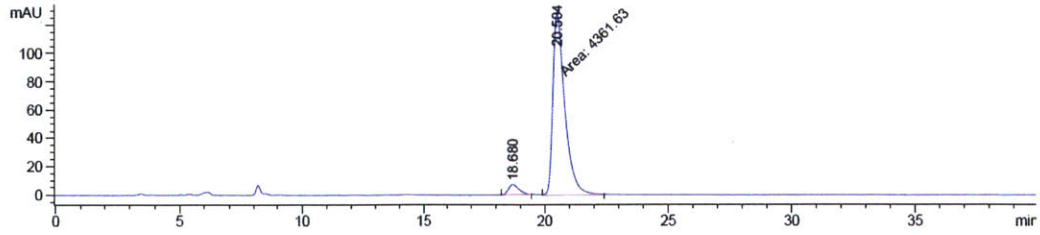
================================================================================
Acq. Operator   : RZ                                 Seq. Line :   1
Acq. Instrument : Instrument 1                        Location : Vial 16
Injection Date  : 7/29/2014 6:01:45 PM                    Inj :   1
                                                     Inj Volume : 1 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-07-29 17-59-26\RZ-SHUTDOWN.M
```

DAD1 A, Sig=230,4 Ref=360,100 (C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-07-29 17-59-26\RZ-4-180-IA.D)

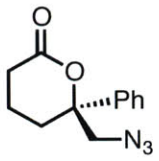


Signal 1: DAD1 A, Sig=230,4 Ref=360,100

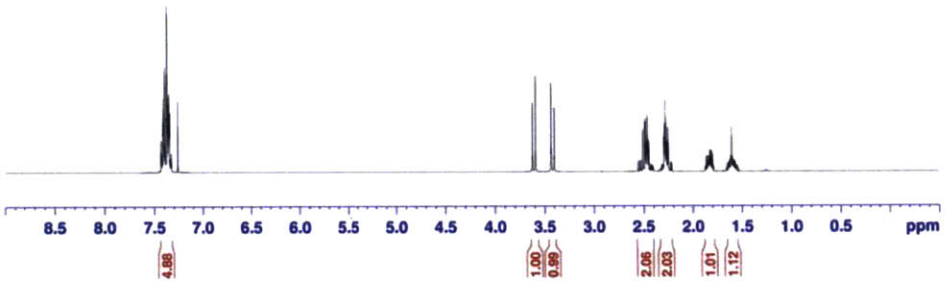
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.680	BB	0.3921	219.16219	7.26251	4.7844
2	20.504	MM	0.5649	4361.62939	128.67712	95.2156
Totals :				4580.79158	135.93964	

4i ^{1}H NMR (400 MHz, $CDCl_3$)

RZ-4-158-H

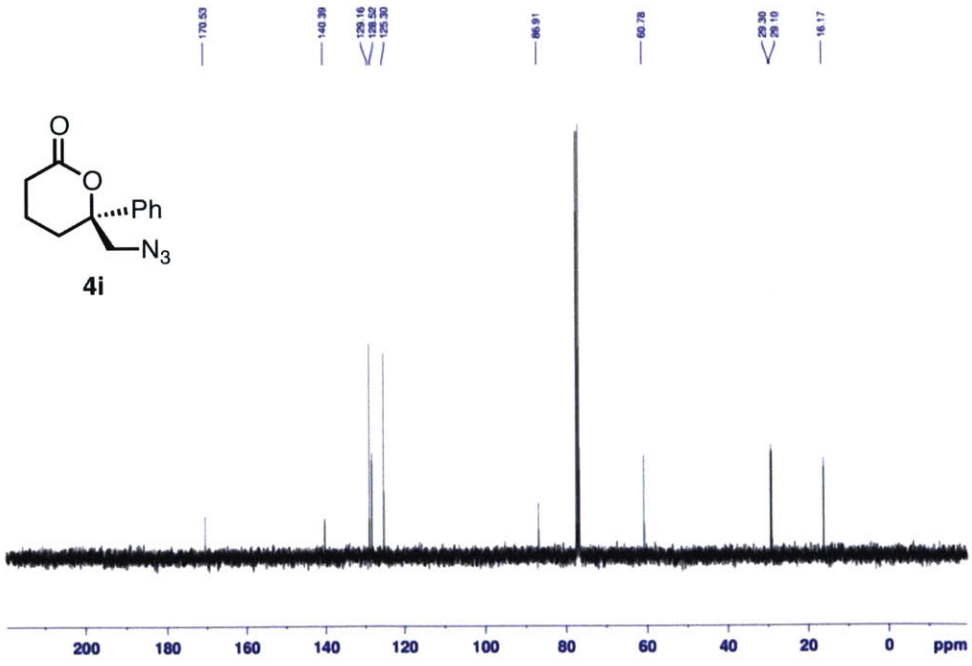


4i

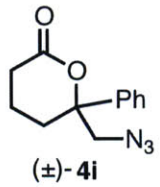


4i ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-4-158-C



HPLC traces for 4i:



(±)- **4i**

Sample Name: RZ-4-158-rac

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==================================================================
Acq. Operator   : RZ                              Seq. Line :  1
Acq. Instrument : Instrument 1                     Location : Vial 17
Injection Date  : 6/6/2014 4:34:38 PM                 Inj :  1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 3 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-06-06 16-33-29\RZ-5IPA-1ML-2013-.M
```
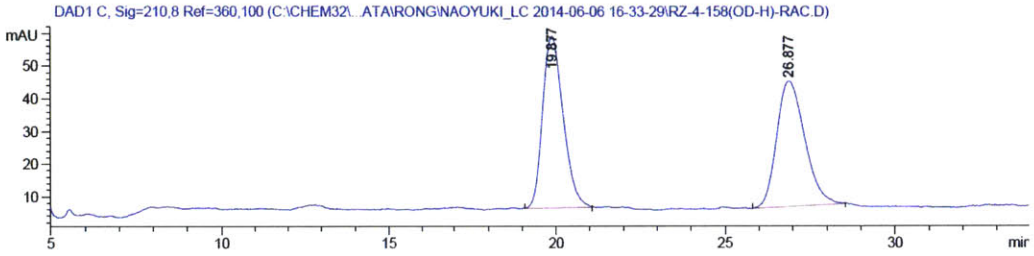
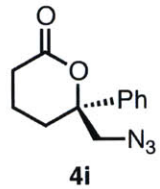



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

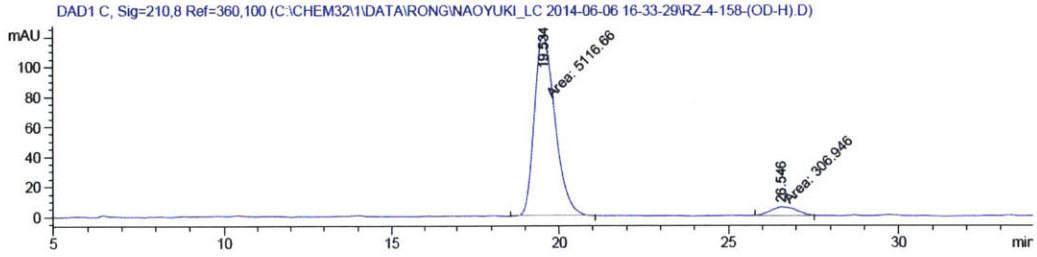
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.877	VB	0.5830	2242.23364	52.84458	50.1395
2	26.877	BB	0.6945	2229.76001	38.56628	49.8605
Totals :				4471.99365	91.41086	

Sample Name: RZ-4-158



4i

```
==================================================================
Acq. Operator   : RZ                              Seq. Line :  3
Acq. Instrument : Instrument 1                     Location : Vial 16
Injection Date  : 6/6/2014 5:45:50 PM                 Inj :  1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 0.8 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-06-06 16-33-29\RZ-5IPA-1ML-2013-.M
```

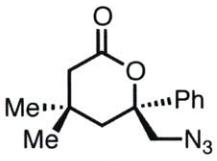


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

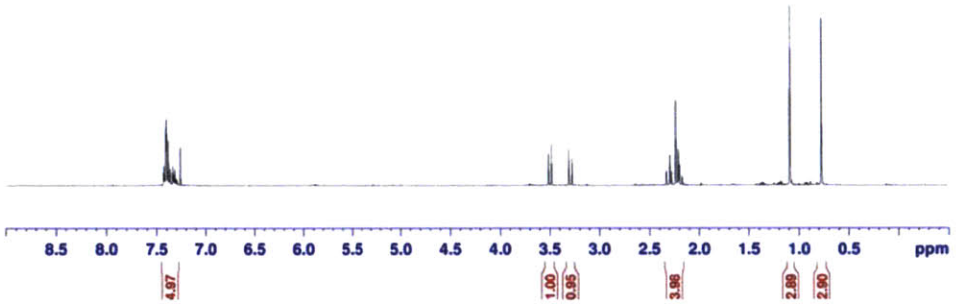
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.534	MM	0.7066	5116.65674	120.68810	94.3405
2	26.546	MM	0.8724	306.94647	5.86426	5.6595
Totals :				5423.60321	126.55235	

4j ^{1}H NMR (400 MHz, $CDCl_3$)

RZ-4-208-H

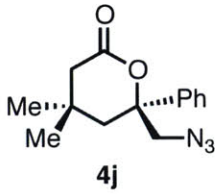


4j



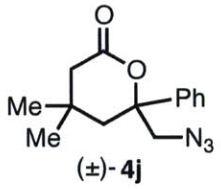
4j ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-4-208-C



4j

HPLC traces for 4j:



(±)-4j

Sample Name: RZ-4-208-RAC

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==================================================================
Acq. Operator    : RZ                          Seq. Line :   1
Acq. Instrument : Instrument 1                  Location : Vial 16
Injection Date   : 9/16/2014 3:33:43 PM            Inj :   1
                                               Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 4 µl
Acq. Method      : C:\CHEM32\1\DATA\RONG\ZY 2014-09-16 15-31-25\RZ-5IPA-1ML-2013-.M
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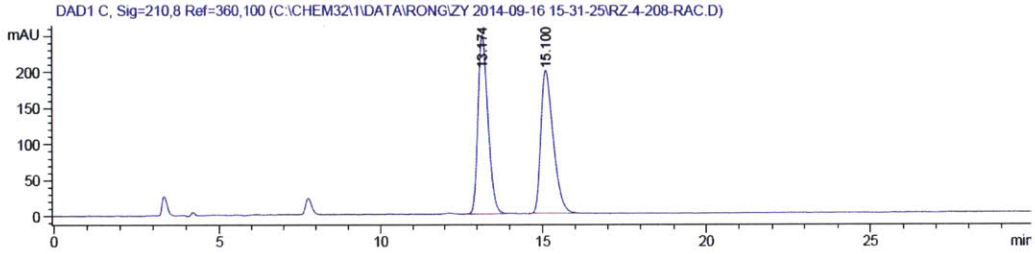
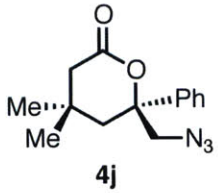


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

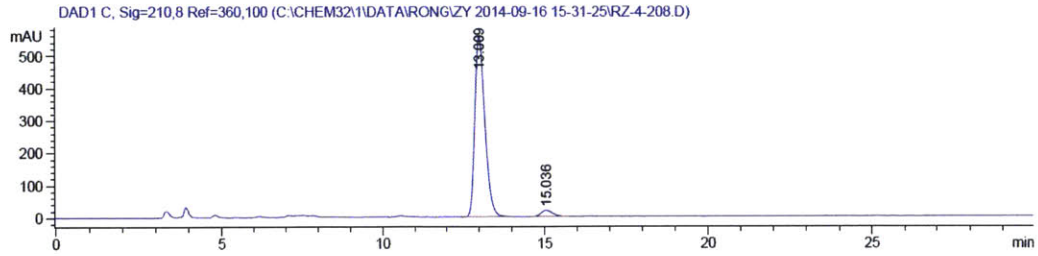
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.174	VV	0.3313	5349.82373	248.41367	50.0666
2	15.100	VV	0.4024	5335.59473	199.26160	49.9334
Totals :				1.06854e4	447.67526	

Sample Name: RZ-4-208



4j

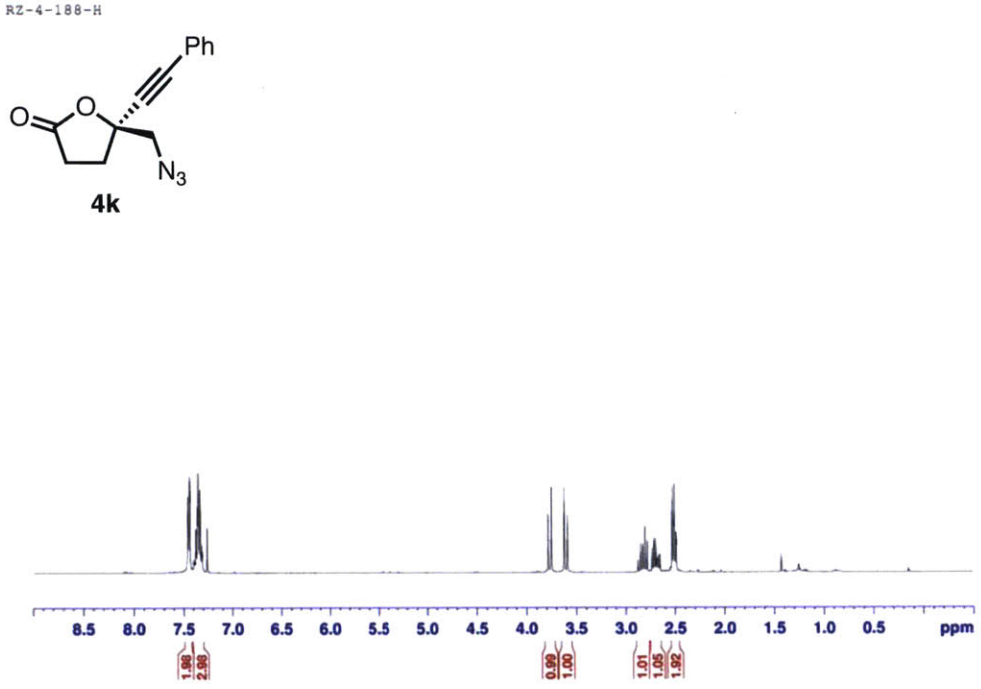
```
==================================================================
Acq. Operator    : RZ                          Seq. Line :   2
Acq. Instrument : Instrument 1                  Location : Vial 17
Injection Date   : 9/16/2014 4:05:01 PM            Inj :   1
                                               Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 3 µl
Acq. Method      : C:\CHEM32\1\DATA\RONG\ZY 2014-09-16 15-31-25\RZ-5IPA-1ML-2013-.M
```



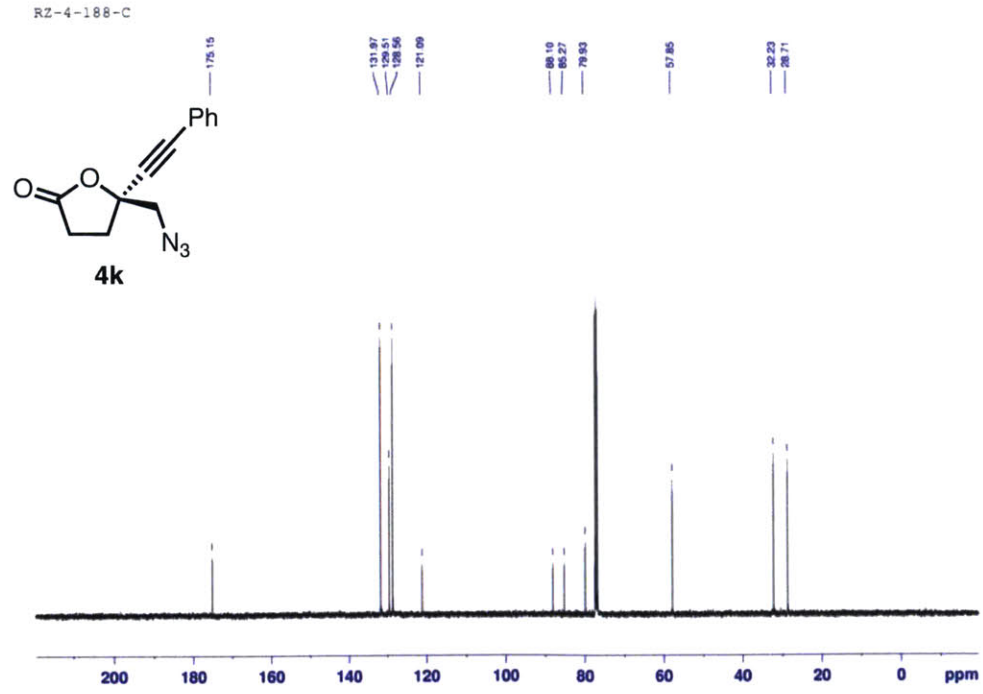
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.009	VB	0.3308	1.19998e4	558.26044	95.8692
2	15.036	BV	0.3174	517.04474	20.01099	4.1308
Totals :				1.25169e4	578.27143	

4k ^{1}H NMR (400 MHz, $CDCl_3$)

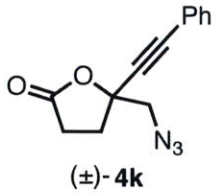


4k ^{13}C NMR (100 MHz, $CDCl_3$)



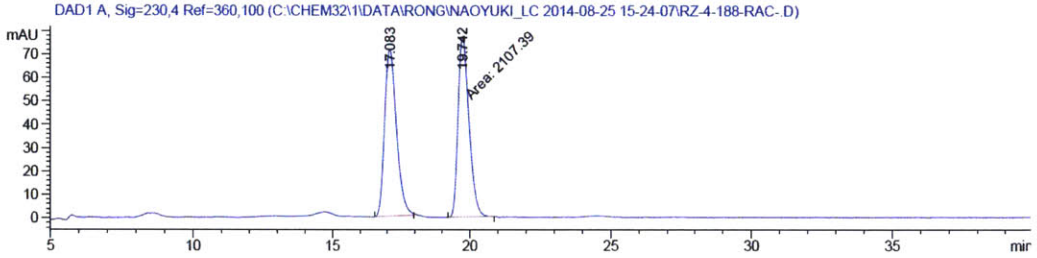
HPLC traces for 4k:

Sample Name: RZ-4-188-RAC



(±)-**4k**

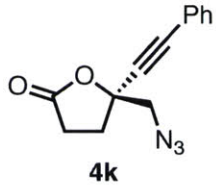
```
================================================================================
Acq. Operator   : RZ                                 Seq. Line :   2
Acq. Instrument : Instrument 1                        Location : Vial 16
Injection Date  : 8/25/2014 4:07:52 PM                    Inj :   1
                                                    Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 16 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-08-25 15-24-07\RZ-5IPA-1ML-2013-.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

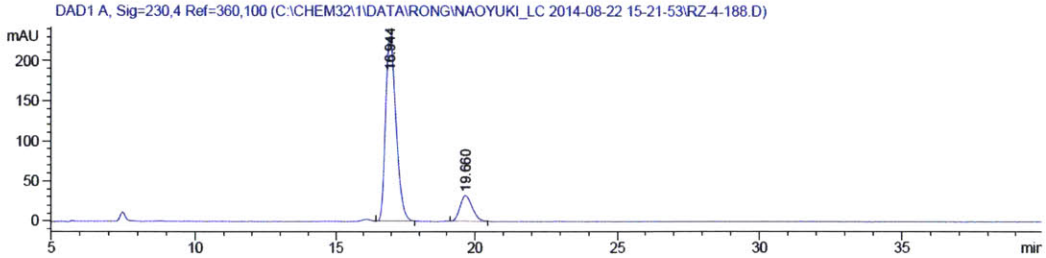
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.083	BB	0.4547	2134.21069	71.40211	50.3162
2	19.742	MM	0.4543	2107.38574	77.31142	49.6838
Totals :				4241.59644	148.71352	

Sample Name: RZ-4-188



4k

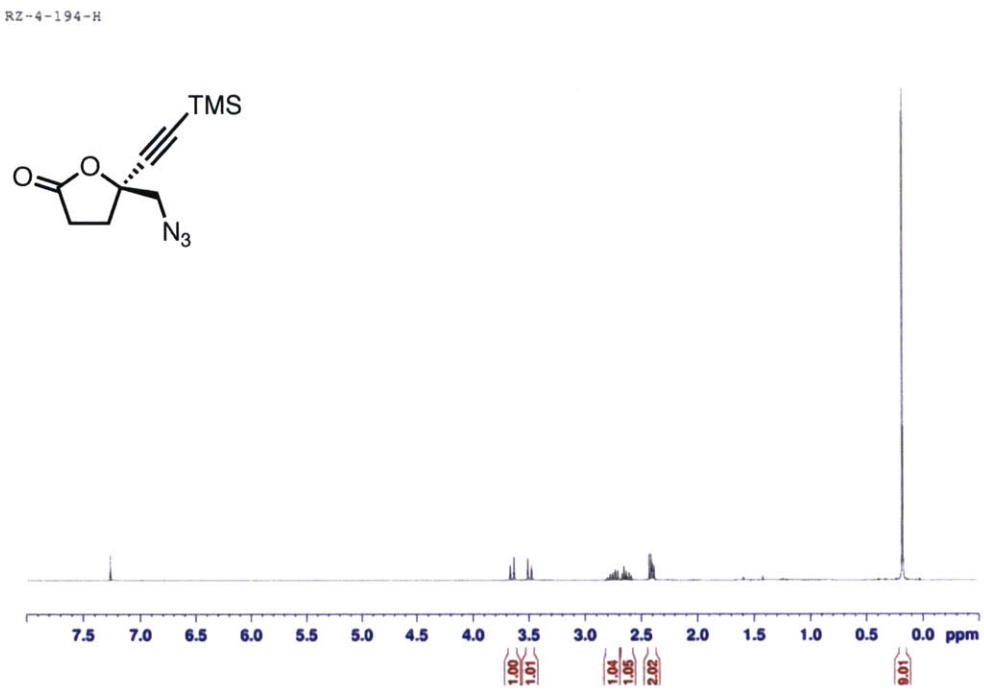
```
================================================================================
Acq. Operator   : RZ                                 Seq. Line :   1
Acq. Instrument : Instrument 1                        Location : Vial 16
Injection Date  : 8/22/2014 3:24:11 PM                    Inj :   1
                                                    Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 4 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-08-22 15-21-53\RZ-5IPA-1ML-2013-.M
```



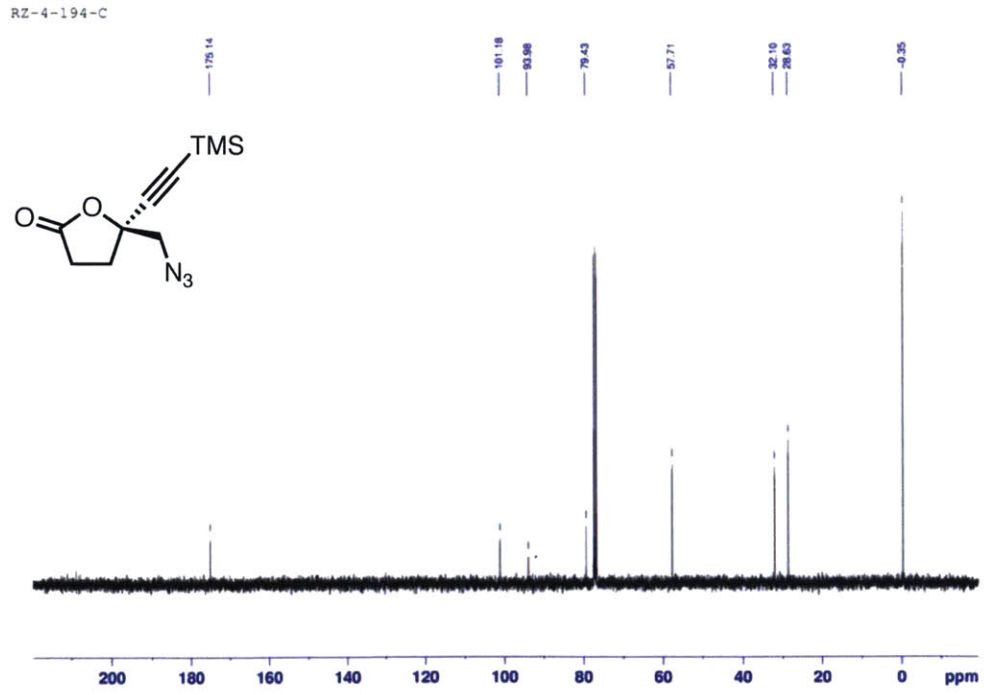
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.944	VB	0.4069	5986.67236	230.57608	85.8726
2	19.660	BB	0.4423	984.89868	32.43007	14.1274
Totals :				6971.57104	263.00615	

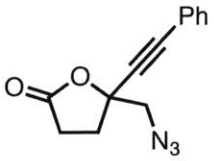
4l ^{1}H NMR (400 MHz, $CDCl_3$)



4l ^{13}C NMR (100 MHz, $CDCl_3$)



HPLC traces for compound 4k derived from 4l:



(±)-**4k**

Sample Name: RZ-4-188-RAC

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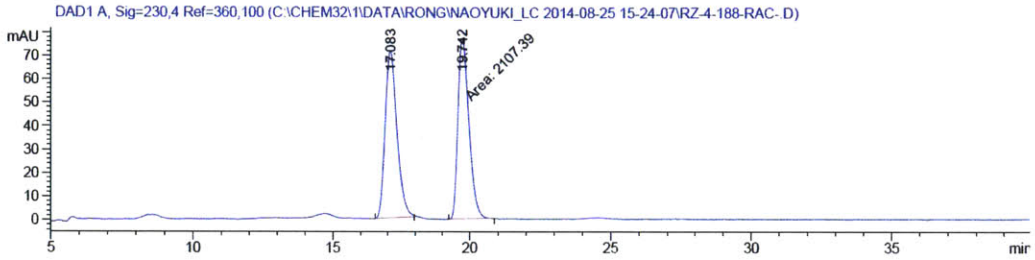
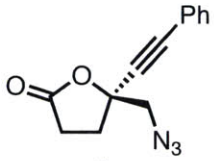
==================================================================
Acq. Operator    : RZ                          Seq. Line :   2
Acq. Instrument : Instrument 1                  Location : Vial 16
Injection Date  : 8/25/2014 4:07:52 PM             Inj :   1
                                               Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 16 µl
Acq. Method      : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-08-25 15-24-07\RZ-5IPA-1ML-2013-.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.083	BB	0.4547	2134.21069	71.40211	50.3162
2	19.742	MM	0.4543	2107.38574	77.31142	49.6838
Totals :				4241.59644	148.71352	



4k
(derived from **4l**)

Sample Name: RZ-4-195

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==================================================================
Acq. Operator    : RZ                          Seq. Line :   2
Acq. Instrument : Instrument 1                  Location : Vial 16
Injection Date  : 9/2/2014 6:38:01 PM              Inj :   1
                                               Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 4 µl
Acq. Method      : C:\CHEM32\1\DATA\RONG\ZY 2014-09-02 17-54-08\RZ-5IPA-1ML-2013-.M
```
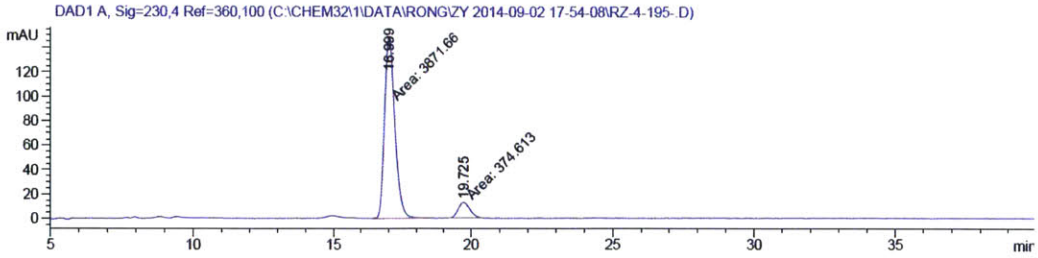
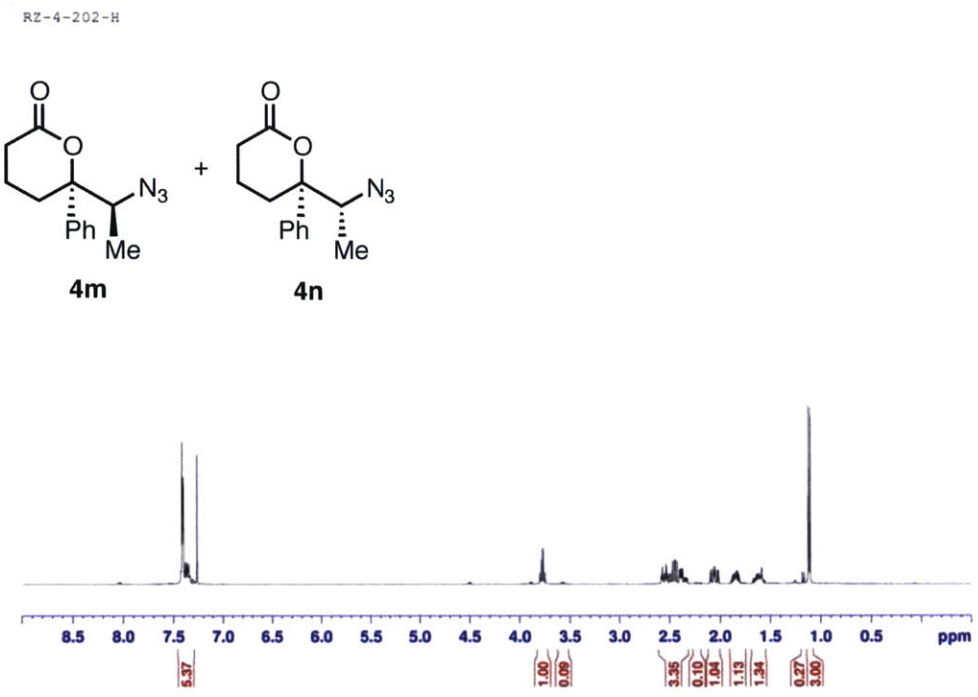



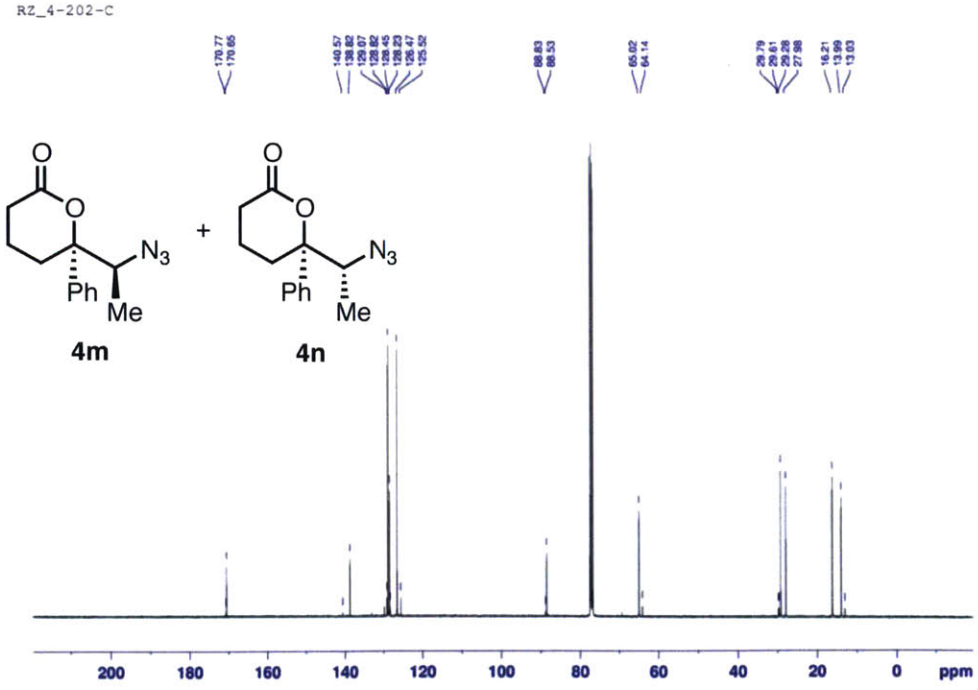
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.999	MM	0.4347	3871.66455	148.43346	91.1778
2	19.725	MM	0.4853	374.61334	12.86601	8.8222
Totals :				4246.27789	161.29947	

4m+4n ^{1}H NMR (400 MHz, $CDCl_3$)



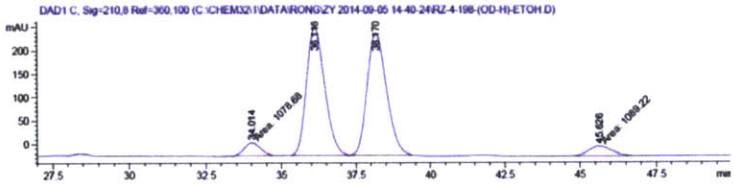
4m+4n ^{13}C NMR (100 MHz, $CDCl_3$)

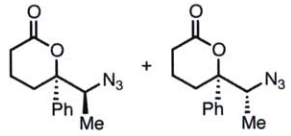


HPLC traces for 4m and 4n:

Sample Name: RZ-4-198

```
Acq. Operator   : RZ                              Seq. Line :   1
Acq. Instrument : Instrument 1                    Location : Vial 15
Injection Date  : 9/5/2014 2:42:58 PM                Inj :   1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\ZY 2014-09-05 14-40-24\RZ-3-IPA-08ML-ETOH.M
```





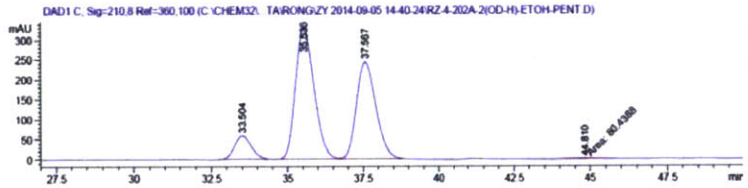
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

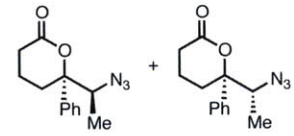
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.014	MM	0.6350	1078.68335	28.31096	4.1474
2	36.116	BB	0.6560	1.18816e4	275.04449	45.6854
3	38.170	BB	0.6922	1.19579e4	262.13486	45.9789
4	45.626	MM	0.8747	1089.22266	20.75443	4.1883
Totals :				2.60074e4	586.24474	

from (*E*)-**2m**

Sample Name: RZ-4-202A

```
Acq. Operator   : RZ                              Seq. Line :   2
Acq. Instrument : Instrument 1                    Location : Vial 16
Injection Date  : 9/5/2014 3:39:26 PM                Inj :   1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 14 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\ZY 2014-09-05 14-40-24\RZ-3-IPA-08ML-ETOH.M
```





d.r. = 10 : 1

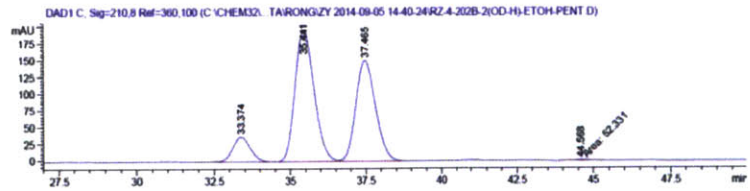
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

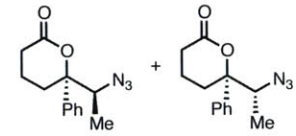
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.504	BB	0.5563	2393.19165	59.87408	8.6433
2	35.536	BV	0.6450	1.41347e4	329.12018	51.0492
3	37.567	VB	0.6900	1.10800e4	243.89116	40.0169
4	44.810	MM	1.0080	80.43877	1.32999	0.2905
Totals :				2.76884e4	634.21541	

from (*Z*)-**2m**

Sample Name: RZ-4-202B

```
Acq. Operator   : RZ                              Seq. Line :   3
Acq. Instrument : Instrument 1                    Location : Vial 17
Injection Date  : 9/5/2014 4:34:11 PM                Inj :   1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 20 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\ZY 2014-09-05 14-40-24\RZ-3-IPA-08ML-ETOH.M
```



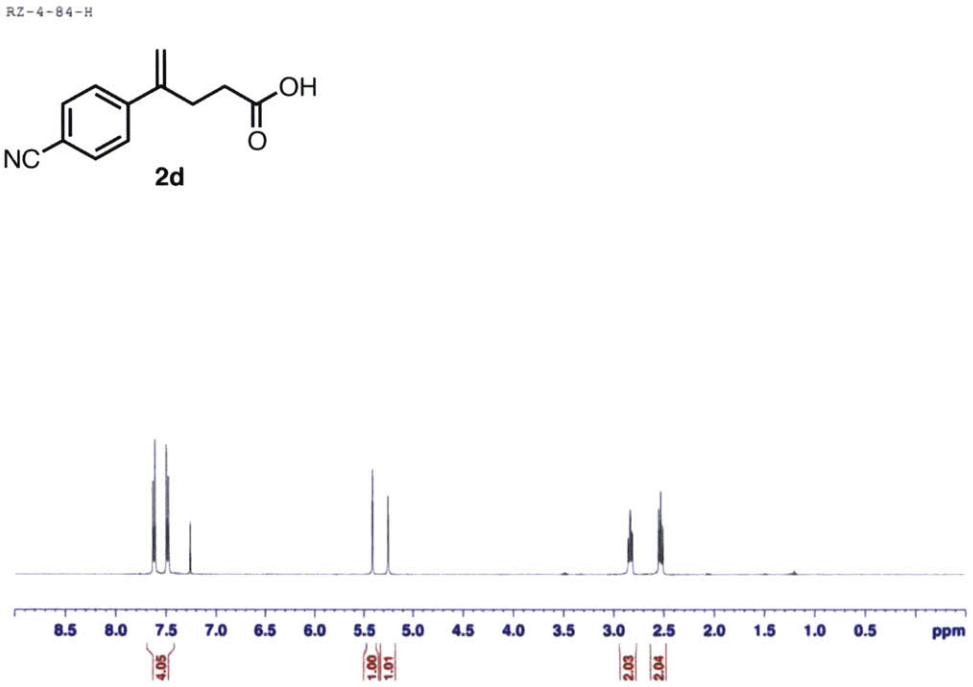


d.r. = 10 : 1

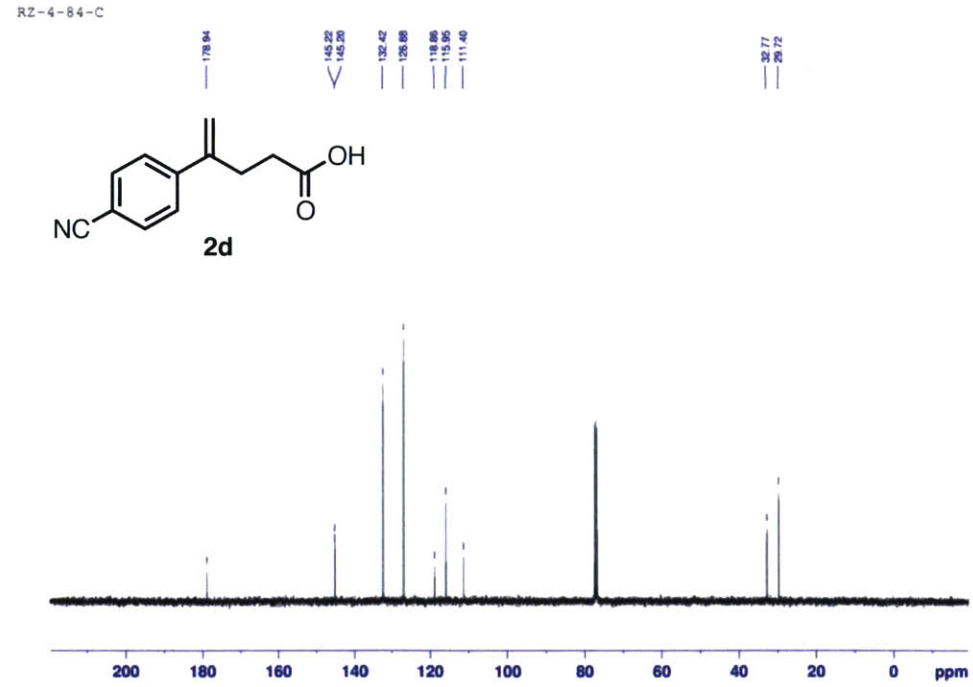
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.374	BB	0.4942	1512.04651	37.04641	8.8356
2	35.441	BB	0.6560	8655.40430	197.23421	50.5775
3	37.465	BB	0.6805	6893.37061	151.03995	40.2811
4	44.568	MM	0.6933	52.33103	1.25798	0.3058
Totals :				1.71132e4	386.57854	

2d ^{1}H NMR (400 MHz, $CDCl_3$)

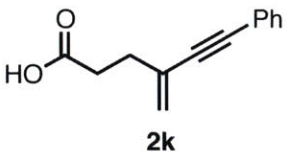


2d ^{13}C NMR (100 MHz, $CDCl_3$)

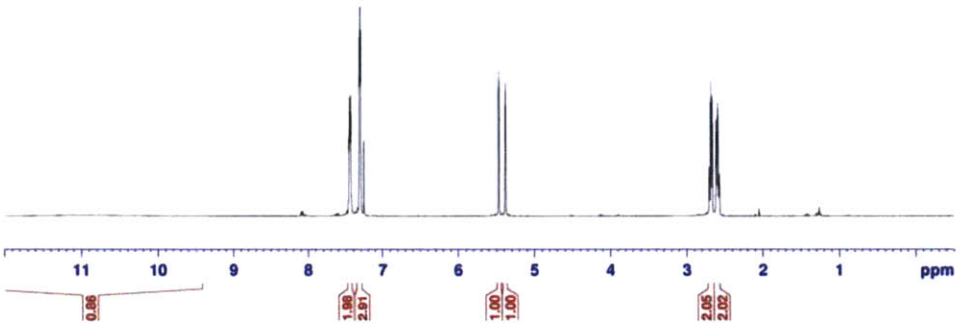


2k ^{1}H NMR (400 MHz, $CDCl_3$)

RZ-4-162r2-H

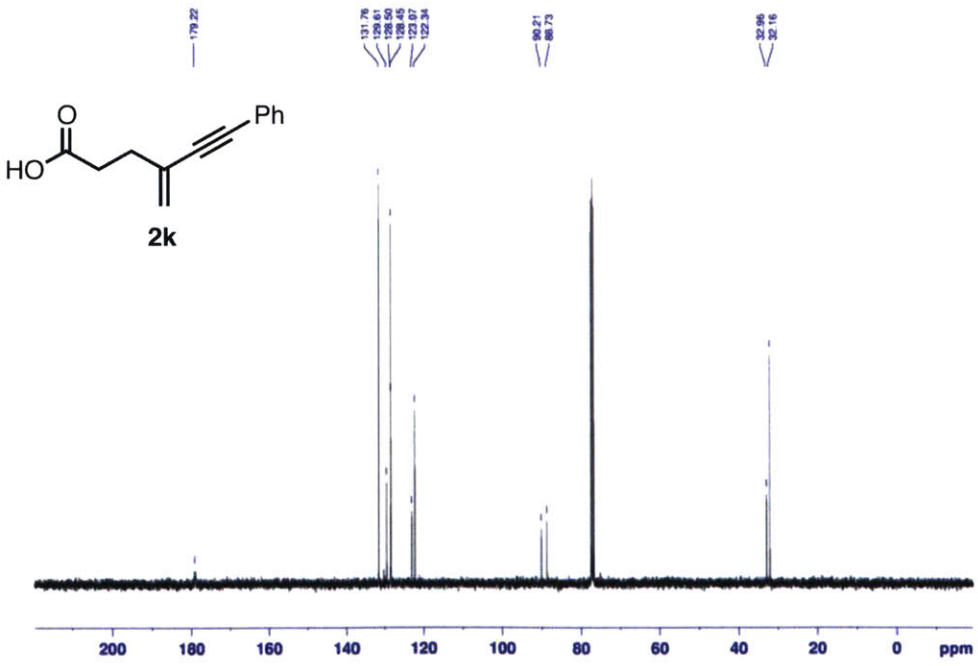


2k



2k ^{13}C NMR (100 MHz, $CDCl_3$)

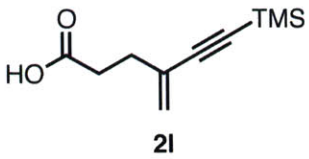
RZ-4-162r2-C



2k

2l ^{1}H NMR (400 MHz, $CDCl_3$)

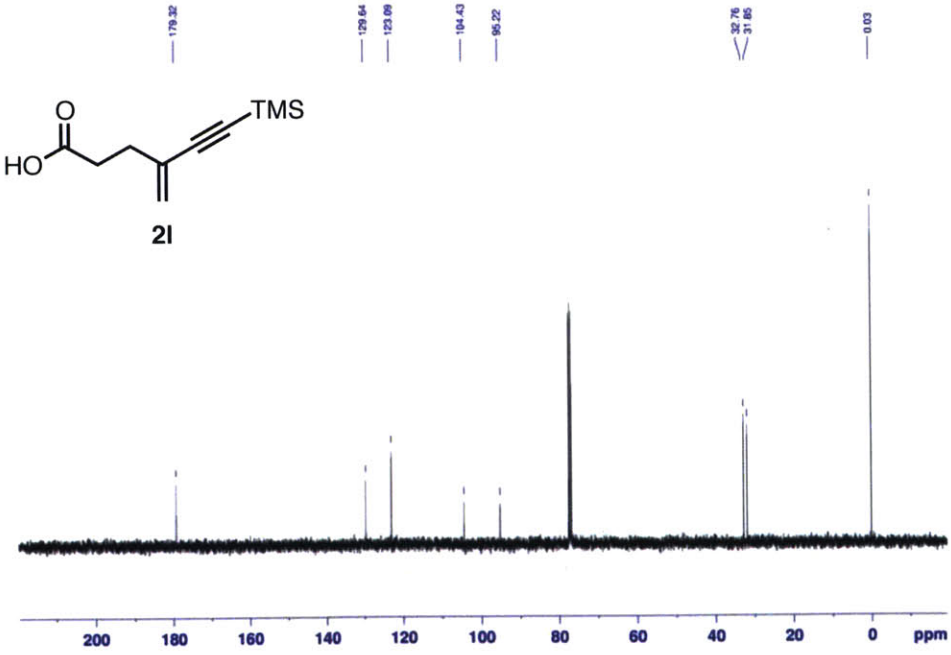
RZ-4-135-H



2l

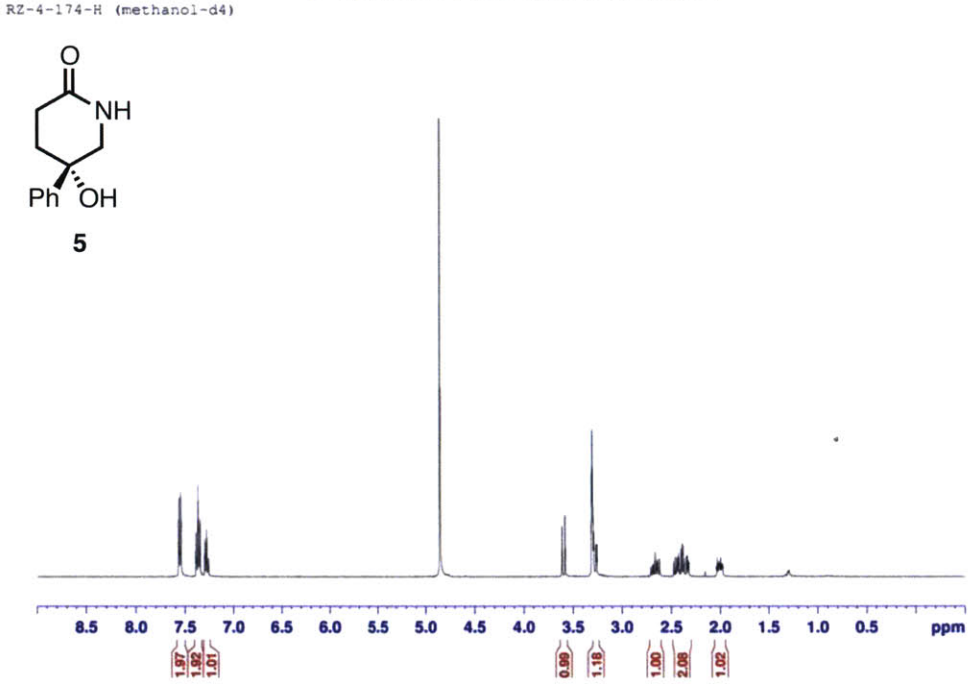
2k ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-4-135-C

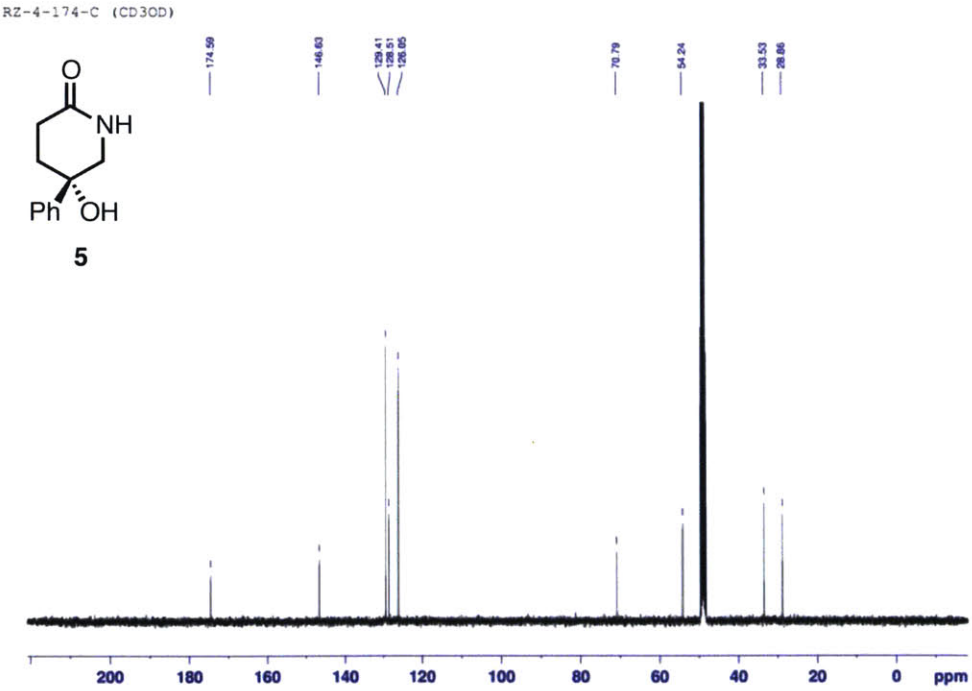


2l

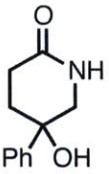
5 ^{1}H NMR (400 MHz, CD_3OD)



5 ^{13}C NMR (100 MHz, CD_3OD)



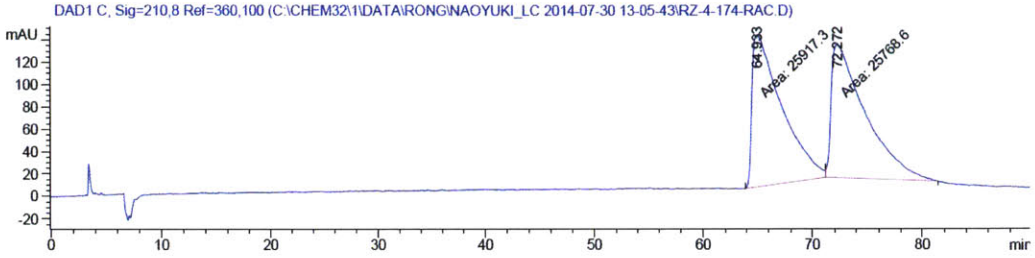
HPLC traces for 5:



(±)-5

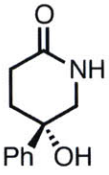
Sample Name: RZ-4-174-RAC

```
    ====================================================================
    Acq. Operator   : RZ                                Seq. Line :   1
    Acq. Instrument : Instrument 1                       Location : Vial 16
    Injection Date  : 7/30/2014 1:08:06 PM                  Inj :   1
                                                       Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 4 µl
    Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-07-30 13-05-43\RZ-5IPA-2014-70MIN.M
```



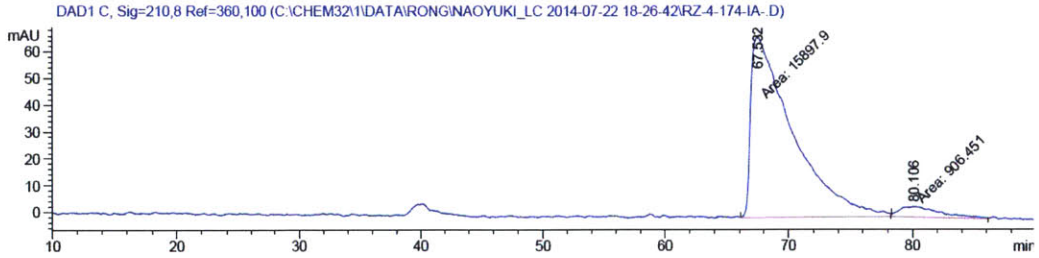

```
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  64.933 MM    3.1716 2.59173e4   136.19344  50.1438
   2  72.272 MM    3.5883 2.57686e4   119.68867  49.8562

Totals :                  5.16859e4   255.88211
```

Sample Name: RZ-4-174



5

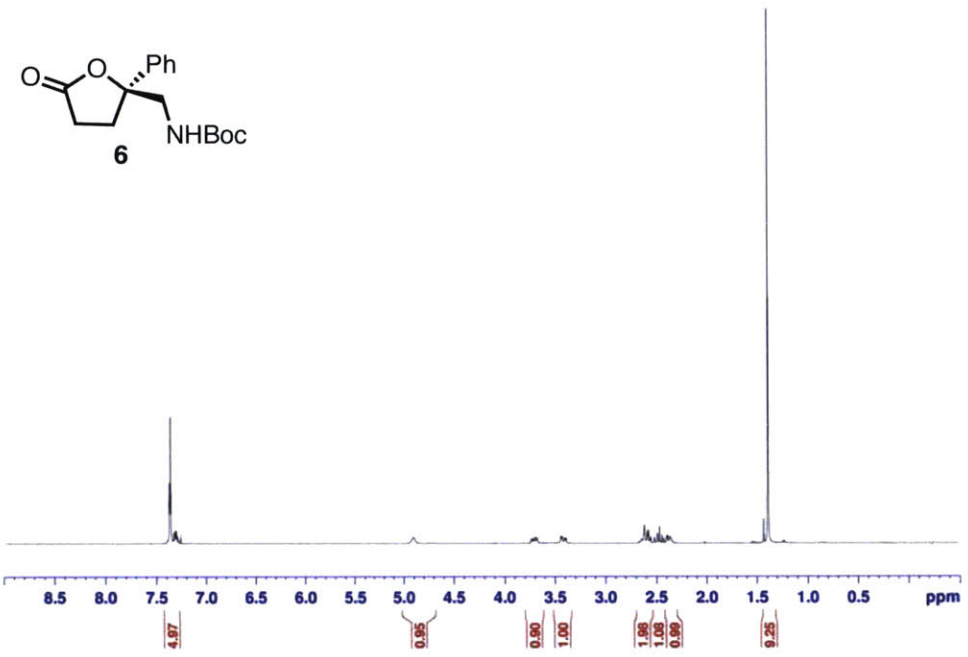
```
    ====================================================================
    Acq. Operator   : RZ                                Seq. Line :   3
    Acq. Instrument : Instrument 1                       Location : Vial 16
    Injection Date  : 7/22/2014 9:31:20 PM                  Inj :   1
                                                       Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 8 µl
    Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-07-22 18-26-42\RZ-5IPA-2014-70MIN.M
```




```
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  67.532 MM    3.8921 1.58979e4    68.07827  94.6059
   2  80.106 MM    3.7487  906.45111    4.03003   5.3941

Totals :                  1.68044e4    72.10830
```

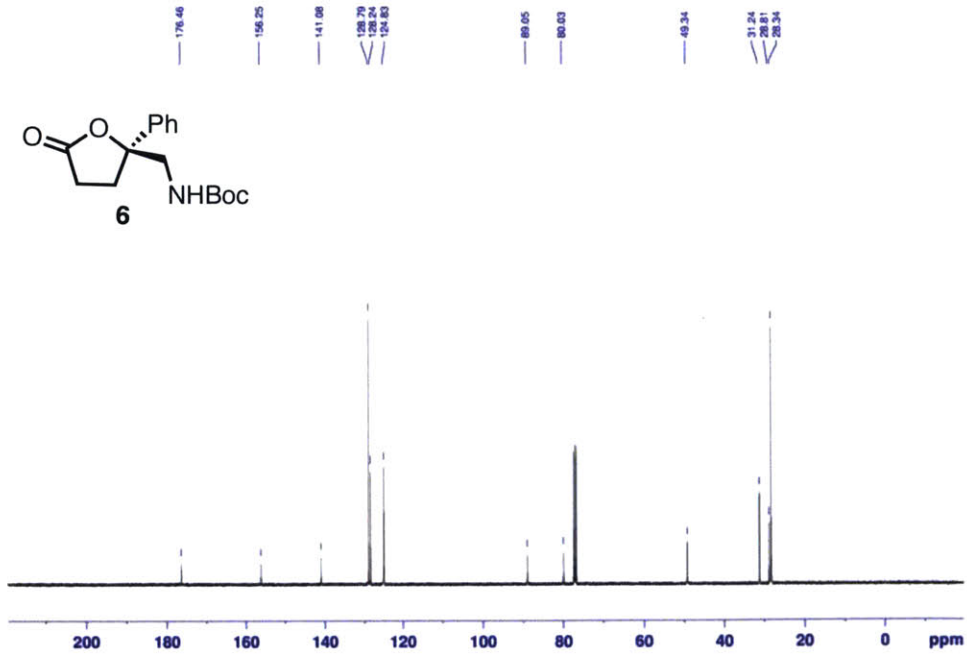
6 ^{1}H NMR (400 MHz, $CDCl_3$)

RZ-4-220-H



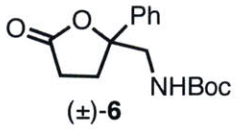
6 ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-4-220-C

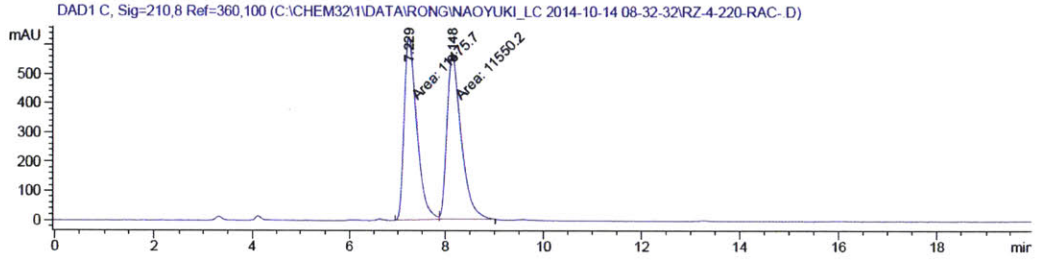


HPLC traces for 6:

```
Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-10-14 08-32-32\RZ-4-220-RAC-.D
Sample Name: RZ-4-220-RAC

    ======================================================================
    Acq. Operator    : RZ                                Seq. Line :   2
    Acq. Instrument : Instrument 1                        Location : Vial 16
    Injection Date   : 10/14/2014 8:56:28 AM                   Inj :   1
                                                        Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 3 µl
    Acq. Method      : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-10-14 08-32-32\RZ-SHUTDOWN.M
```



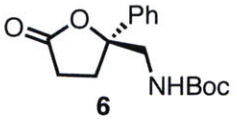
(±)-**6**



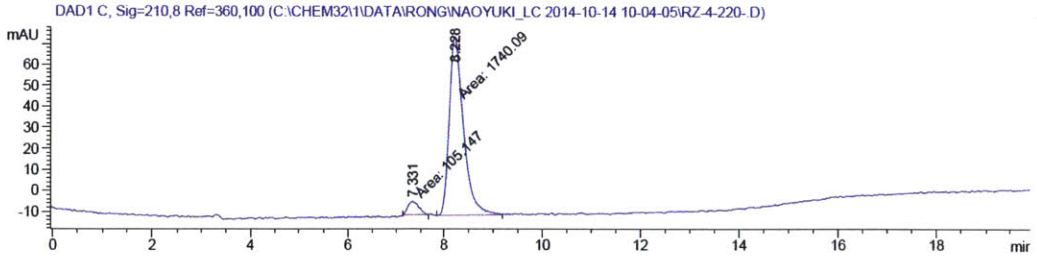

```
Signal 3: DAD1 C, Sig=210,8 Ref=360,100
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.229	MM	0.3042	1.14757e4	628.67841	49.8381
2	8.148	MM	0.3413	1.15502e4	564.09924	50.1619
Totals :				2.30259e4	1192.77765	

```
Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-10-14 10-04-05\RZ-4-220-.D
Sample Name: RZ-4-220

    ======================================================================
    Acq. Operator    : RZ                                Seq. Line :   1
    Acq. Instrument : Instrument 1                        Location : Vial 17
    Injection Date   : 10/14/2014 10:06:08 AM                  Inj :   1
                                                        Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 0.2 µl
    Acq. Method      : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-10-14 10-04-05\RZ-SHUTDOWN.M
```



6

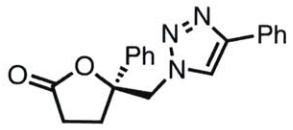



```
Signal 3: DAD1 C, Sig=210,8 Ref=360,100
```

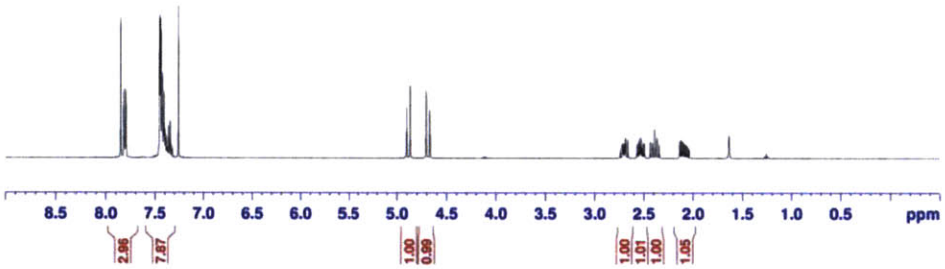
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.331	MM	0.2658	105.14742	6.59191	5.6983
2	8.228	MM	0.3391	1740.08972	85.52530	94.3017
Totals :				1845.23714	92.11721	

7 ^{1}H NMR (400 MHz, $CDCl_3$)

RZ-4-184-H

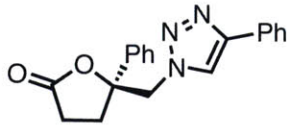


7

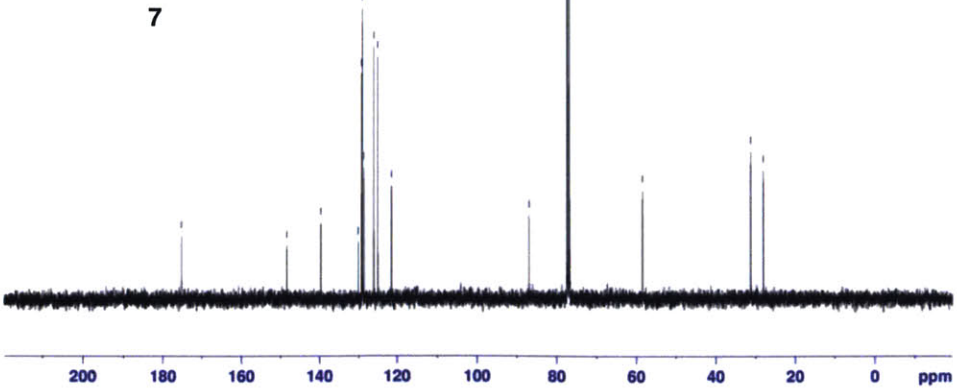


7 ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-4-184-C

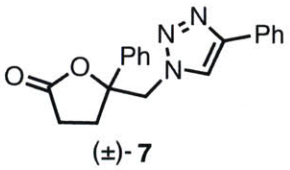


7



HPLC traces for 7:

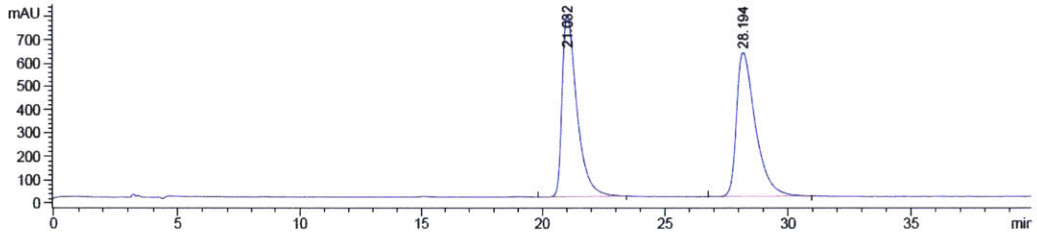
Sample Name: RZ-4-184-RAC



(±)-**7**

```
==================================================================
Acq. Operator   : RZ                          Seq. Line :  1
Acq. Instrument : Instrument 1                 Location : Vial 19
Injection Date  : 8/7/2014 9:24:47 AM              Inj :  1
                                             Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-08-07 09-22-20\RZ-15IPA-2014.M
```

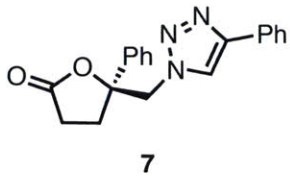
DAD1 C, Sig=210,8 Ref=360,100 (C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-08-07 09-22-20\RZ-4-184-RAC.D)



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.032	VB	0.6184	3.28333e4	781.09888	49.6663
2	28.194	VB	0.8013	3.32746e4	618.87622	50.3337
Totals :				6.61078e4	1399.97510	

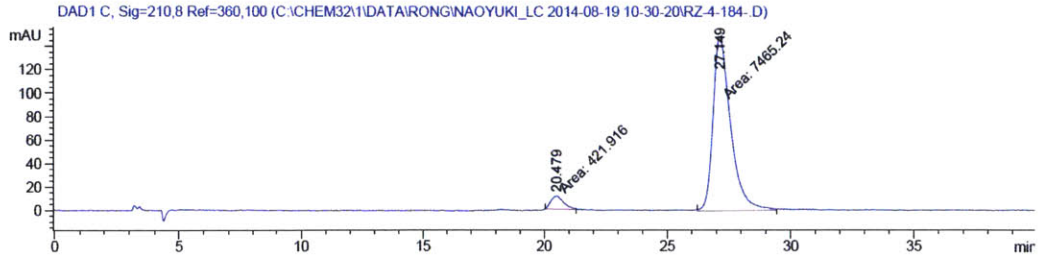
Sample Name: RZ-4-184



7

```
==================================================================
Acq. Operator   : RZ                          Seq. Line :  2
Acq. Instrument : Instrument 1                 Location : Vial 16
Injection Date  : 8/19/2014 11:13:39 AM            Inj :  1
                                             Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 2 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-08-19 10-30-20\RZ-15IPA-2014.M
```

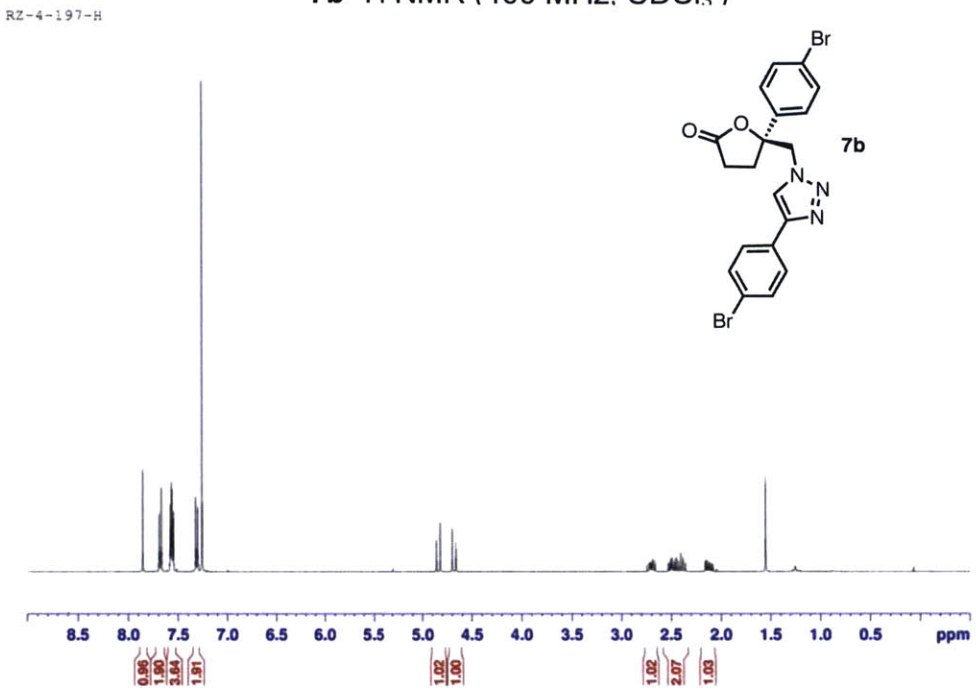
DAD1 C, Sig=210,8 Ref=360,100 (C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-08-19 10-30-20\RZ-4-184-.D)



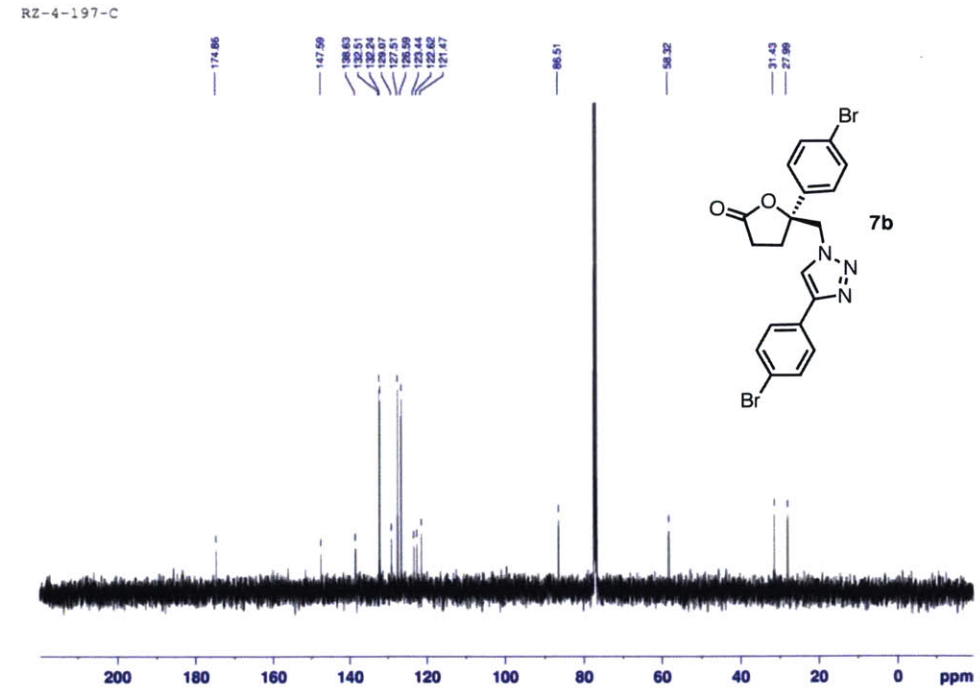
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.479	MM	0.6195	421.91553	11.35162	5.3494
2	27.149	MM	0.8317	7465.23828	149.60146	94.6506
Totals :				7887.15381	160.95307	

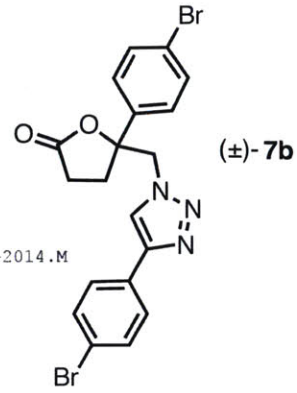
7b ^{1}H NMR (400 MHz, $CDCl_3$)



7b ^{13}C NMR (100 MHz, $CDCl_3$)



HPLC traces for 7b:



(±)-**7b**

Sample Name: RZ-4-197-RAC

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Acq. Instrument : Instrument 1                        Location : Vial 17
Injection Date  : 9/18/2014 8:27:14 AM                    Inj :   1
                                                     Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 20 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\ZY 2014-09-18 08-24-42\RZ-20IPA-2014.M
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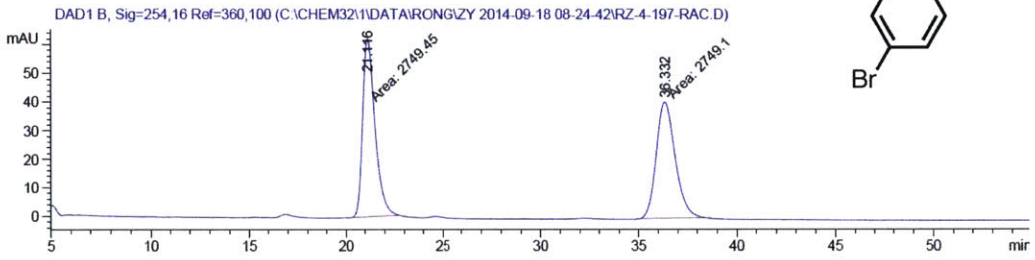
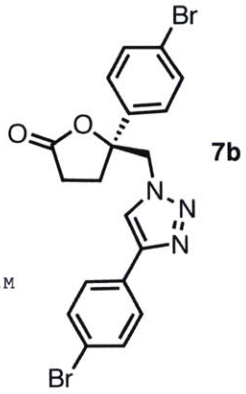


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.116	MM	0.7375	2749.44751	62.13118	50.0031
2	36.332	MM	1.1271	2749.10229	40.65299	49.9969
Totals :				5498.54980	102.78416	



7b

Sample Name: RZ-4-197

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================================================================================
Acq. Operator   : RZ                                 Seq. Line :   2
Acq. Instrument : Instrument 1                        Location : Vial 16
Injection Date  : 9/17/2014 5:41:02 PM                    Inj :   1
                                                     Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 8 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\ZY 2014-09-17 16-47-04\RZ-20IPA-2014.M
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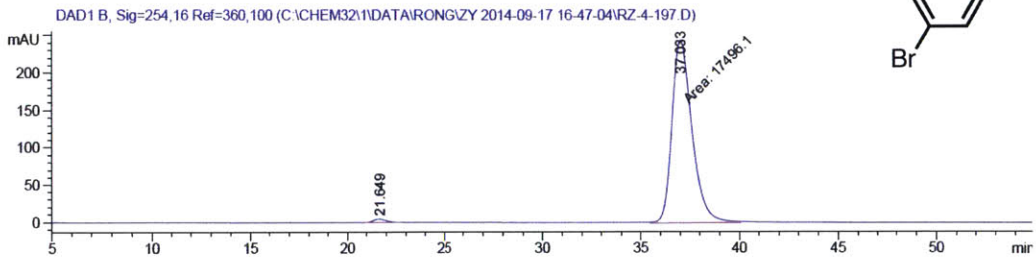
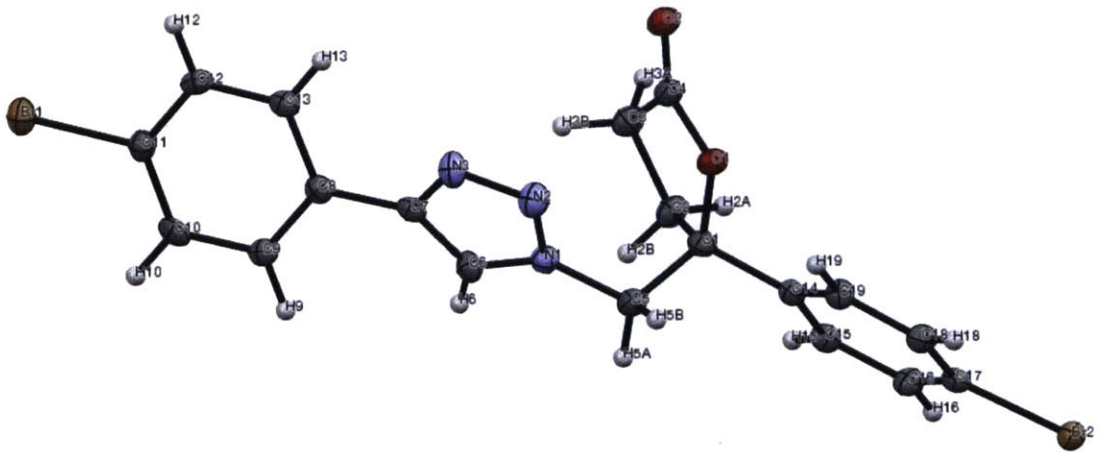


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.649	BB	0.5420	202.84988	4.48220	1.1461
2	37.033	MM	1.1893	1.74961e4	245.18356	98.8539
Totals :				1.76989e4	249.66576	



SI-Table 1. Crystal data and structure refinement for compound 7b.

Identification code	X14147	
Empirical formula	C19 H15 Br2 N3 O2	
Formula weight	477.16	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.1816(11) Å	$\alpha = 90°$.
	b = 11.0851(15) Å	$\beta = 90°$.
	c = 21.848(3) Å	$\gamma = 90°$.
Volume	1739.3(4) $Å^3$	
Z	4	
Density (calculated)	1.822 Mg/m^3	
Absorption coefficient	4.681 mm^{-1}	
F(000)	944	
Crystal size	0.110 x 0.065 x 0.015 mm^3	
Theta range for data collection	1.864 to 30.032°.	
Index ranges	-10<=h<=10, -13<=k<=14, -30<=l<=30	
Reflections collected	37176	
Independent reflections	4912 [R(int) = 0.0502]	
Completeness to theta = 25.242°	98.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.5645 and 0.4825	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4912 / 387 / 235	
Goodness-of-fit on F^2	1.028	
Final R indices [I>2sigma(I)]	R1 = 0.0326, wR2 = 0.0653	
R indices (all data)	R1 = 0.0428, wR2 = 0.0683	
Absolute structure parameter	-0.004(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.709 and -0.727 e.$Å^{-3}$	

SI-Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for compound 7b. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	6633(1)	3221(1)	6294(1)	25(1)
Br(2)	3532(1)	3581(1)	-1120(1)	21(1)
O(1)	3070(4)	5450(3)	1809(1)	19(1)
O(2)	1516(5)	6548(3)	2496(1)	26(1)
N(1)	5840(5)	4282(3)	2562(2)	19(1)
N(2)	6068(5)	5455(4)	2731(2)	23(1)
N(3)	6239(5)	5470(3)	3326(2)	21(1)
C(1)	3546(6)	4187(4)	1698(2)	18(1)
C(2)	2072(6)	3470(4)	2061(2)	22(1)
C(3)	1444(7)	4348(4)	2556(2)	22(1)
C(4)	1948(6)	5565(4)	2307(2)	19(1)
C(5)	5561(6)	3982(4)	1919(2)	19(1)
C(6)	5890(6)	3557(4)	3056(2)	20(1)
C(7)	6148(5)	4324(4)	3542(2)	17(1)
C(8)	6304(6)	4042(4)	4198(2)	18(1)
C(9)	7070(5)	2967(4)	4406(2)	19(1)
C(10)	7208(6)	2726(4)	5029(2)	20(1)
C(11)	6522(6)	3566(4)	5446(2)	19(1)
C(12)	5762(6)	4647(4)	5251(2)	20(1)
C(13)	5660(6)	4886(4)	4629(2)	19(1)
C(14)	3539(6)	4001(4)	1009(2)	17(1)
C(15)	2885(6)	2952(4)	744(2)	19(1)
C(16)	2884(6)	2812(4)	105(2)	19(1)
C(17)	3586(6)	3731(4)	-255(2)	16(1)
C(18)	4325(6)	4768(4)	0(2)	19(1)
C(19)	4289(6)	4905(4)	633(2)	18(1)

SI-Table 3. Bond lengths [Å] and angles [°] for compound 7b.

Br(1)-C(11)	1.895(4)	C(2)-C(3)	1.524(6)
Br(2)-C(17)	1.898(4)	C(2)-H(2A)	0.9900
O(1)-C(4)	1.360(5)	C(2)-H(2B)	0.9900
O(1)-C(1)	1.461(5)	C(3)-C(4)	1.498(6)
O(2)-C(4)	1.206(5)	C(3)-H(3A)	0.9900
N(1)-C(6)	1.346(6)	C(3)-H(3B)	0.9900
N(1)-N(2)	1.361(5)	C(5)-H(5A)	0.9900
N(1)-C(5)	1.457(5)	C(5)-H(5B)	0.9900
N(2)-N(3)	1.306(5)	C(6)-C(7)	1.372(6)
N(3)-C(7)	1.357(6)	C(6)-H(6)	0.9500
C(1)-C(14)	1.518(6)	C(7)-C(8)	1.471(6)
C(1)-C(5)	1.543(6)	C(8)-C(9)	1.389(6)
C(1)-C(2)	1.543(6)	C(8)-C(13)	1.406(6)

C(9)-C(10)	1.390(6)	N(1)-C(5)-H(5A)	108.9
C(9)-H(9)	0.9500	C(1)-C(5)-H(5A)	108.9
C(10)-C(11)	1.394(6)	N(1)-C(5)-H(5B)	108.9
C(10)-H(10)	0.9500	C(1)-C(5)-H(5B)	108.9
C(11)-C(12)	1.383(6)	H(5A)-C(5)-H(5B)	107.7
C(12)-C(13)	1.387(6)	N(1)-C(6)-C(7)	104.7(4)
C(12)-H(12)	0.9500	N(1)-C(6)-H(6)	127.7
C(13)-H(13)	0.9500	C(7)-C(6)-H(6)	127.7
C(14)-C(15)	1.382(6)	N(3)-C(7)-C(6)	108.6(4)
C(14)-C(19)	1.404(6)	N(3)-C(7)-C(8)	122.3(4)
C(15)-C(16)	1.404(6)	C(6)-C(7)-C(8)	129.2(4)
C(15)-H(15)	0.9500	C(9)-C(8)-C(13)	118.8(4)
C(16)-C(17)	1.381(6)	C(9)-C(8)-C(7)	122.1(4)
C(16)-H(16)	0.9500	C(13)-C(8)-C(7)	119.1(4)
C(17)-C(18)	1.383(6)	C(8)-C(9)-C(10)	120.9(4)
C(18)-C(19)	1.391(6)	C(8)-C(9)-H(9)	119.5
C(18)-H(18)	0.9500	C(10)-C(9)-H(9)	119.5
C(19)-H(19)	0.9500	C(9)-C(10)-C(11)	119.1(4)
		C(9)-C(10)-H(10)	120.4
C(4)-O(1)-C(1)	111.2(3)	C(11)-C(10)-H(10)	120.4
C(6)-N(1)-N(2)	110.5(4)	C(12)-C(11)-C(10)	121.1(4)
C(6)-N(1)-C(5)	129.8(4)	C(12)-C(11)-Br(1)	119.6(3)
N(2)-N(1)-C(5)	119.7(4)	C(10)-C(11)-Br(1)	119.3(3)
N(3)-N(2)-N(1)	107.0(4)	C(11)-C(12)-C(13)	119.3(4)
N(2)-N(3)-C(7)	109.2(4)	C(11)-C(12)-H(12)	120.4
O(1)-C(1)-C(14)	107.1(3)	C(13)-C(12)-H(12)	120.4
O(1)-C(1)-C(5)	108.0(3)	C(12)-C(13)-C(8)	120.8(4)
C(14)-C(1)-C(5)	107.1(4)	C(12)-C(13)-H(13)	119.6
O(1)-C(1)-C(2)	104.3(3)	C(8)-C(13)-H(13)	119.6
C(14)-C(1)-C(2)	115.9(4)	C(15)-C(14)-C(19)	119.0(4)
C(5)-C(1)-C(2)	114.0(3)	C(15)-C(14)-C(1)	122.1(4)
C(3)-C(2)-C(1)	103.8(4)	C(19)-C(14)-C(1)	118.9(4)
C(3)-C(2)-H(2A)	111.0	C(14)-C(15)-C(16)	120.7(4)
C(1)-C(2)-H(2A)	111.0	C(14)-C(15)-H(15)	119.6
C(3)-C(2)-H(2B)	111.0	C(16)-C(15)-H(15)	119.6
C(1)-C(2)-H(2B)	111.0	C(17)-C(16)-C(15)	118.9(4)
H(2A)-C(2)-H(2B)	109.0	C(17)-C(16)-H(16)	120.5
C(4)-C(3)-C(2)	104.2(3)	C(15)-C(16)-H(16)	120.5
C(4)-C(3)-H(3A)	110.9	C(16)-C(17)-C(18)	121.6(4)
C(2)-C(3)-H(3A)	110.9	C(16)-C(17)-Br(2)	119.6(3)
C(4)-C(3)-H(3B)	110.9	C(18)-C(17)-Br(2)	118.8(3)
C(2)-C(3)-H(3B)	110.9	C(17)-C(18)-C(19)	118.9(4)
H(3A)-C(3)-H(3B)	108.9	C(17)-C(18)-H(18)	120.5
O(2)-C(4)-O(1)	120.7(4)	C(19)-C(18)-H(18)	120.5
O(2)-C(4)-C(3)	128.8(4)	C(18)-C(19)-C(14)	120.8(4)
O(1)-C(4)-C(3)	110.5(4)	C(18)-C(19)-H(19)	119.6
N(1)-C(5)-C(1)	113.4(3)	C(14)-C(19)-H(19)	119.6

SI-Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for compound 7b. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}

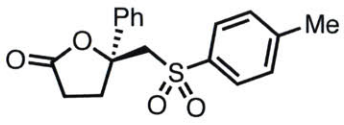
Br(1)	27(1)	30(1)	19(1)	4(1)	-2(1)	-3(1)
Br(2)	22(1)	26(1)	16(1)	-1(1)	-1(1)	3(1)
O(1)	20(2)	17(2)	18(1)	-2(1)	4(1)	0(1)
O(2)	31(2)	24(2)	22(1)	-2(1)	5(1)	4(2)
N(1)	18(2)	19(2)	19(2)	0(1)	-1(1)	0(1)
N(2)	23(2)	23(2)	24(2)	-2(2)	-3(1)	-5(1)
N(3)	22(2)	21(2)	21(2)	3(1)	-4(1)	-6(1)
C(1)	21(2)	15(2)	19(2)	0(1)	1(2)	2(2)
C(2)	25(2)	22(2)	18(2)	1(2)	4(2)	-4(2)
C(3)	22(2)	24(2)	21(2)	-1(2)	4(2)	-3(2)
C(4)	18(2)	24(2)	16(2)	-1(2)	1(2)	1(2)
C(5)	20(2)	22(2)	17(2)	-1(2)	1(2)	2(2)
C(6)	19(2)	20(2)	21(2)	0(2)	-2(2)	-1(2)
C(7)	12(2)	17(2)	21(2)	0(1)	-1(1)	1(1)
C(8)	13(2)	21(2)	19(2)	-2(1)	-1(2)	-2(2)
C(9)	15(2)	19(2)	22(2)	-5(2)	-1(1)	-1(1)
C(10)	13(2)	20(2)	27(2)	1(2)	-4(2)	1(2)
C(11)	17(2)	22(2)	17(2)	2(2)	-1(2)	-2(2)
C(12)	17(2)	20(2)	21(2)	-4(2)	4(2)	1(2)
C(13)	16(2)	19(2)	22(2)	0(2)	-1(2)	2(2)
C(14)	16(2)	16(2)	18(2)	0(1)	-1(2)	2(2)
C(15)	18(2)	17(2)	21(2)	1(2)	1(2)	-1(2)
C(16)	22(2)	15(2)	21(2)	-2(2)	0(2)	-2(2)
C(17)	14(2)	15(2)	19(2)	0(1)	1(2)	2(2)
C(18)	18(2)	18(2)	20(2)	1(2)	2(2)	-1(2)
C(19)	19(2)	16(2)	19(2)	0(2)	-1(2)	-3(2)

SI-Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for compound 7b.

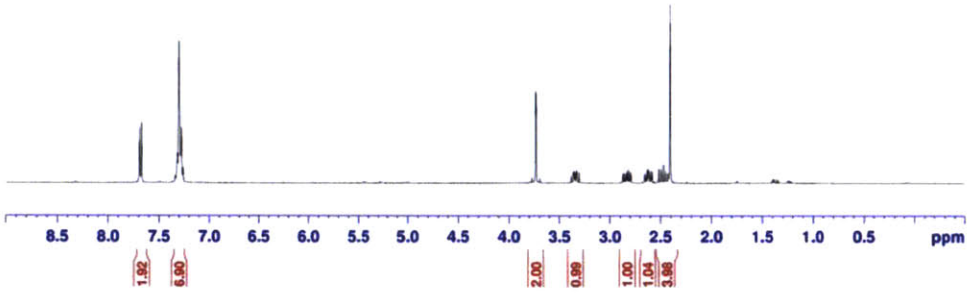
	x	y	z	U(eq)
H(2A)	1016	3236	1795	26
H(2B)	2621	2734	2243	26
H(3A)	85	4286	2626	27
H(3B)	2101	4190	2946	27
H(5A)	5895	3125	1855	23
H(5B)	6413	4479	1668	23
H(6)	5772	2704	3066	24
H(9)	7506	2389	4119	23
H(10)	7763	1998	5168	24
H(12)	5316	5218	5540	23
H(13)	5148	5629	4492	23
H(15)	2432	2319	996	22
H(16)	2407	2098	-77	23
H(18)	4848	5376	-253	23
H(19)	4779	5618	812	21

8a ^{1}H NMR (400 MHz, $CDCl_3$)

RZ-4-234-H

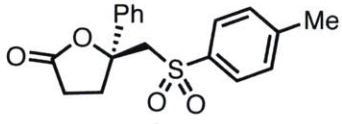


8a

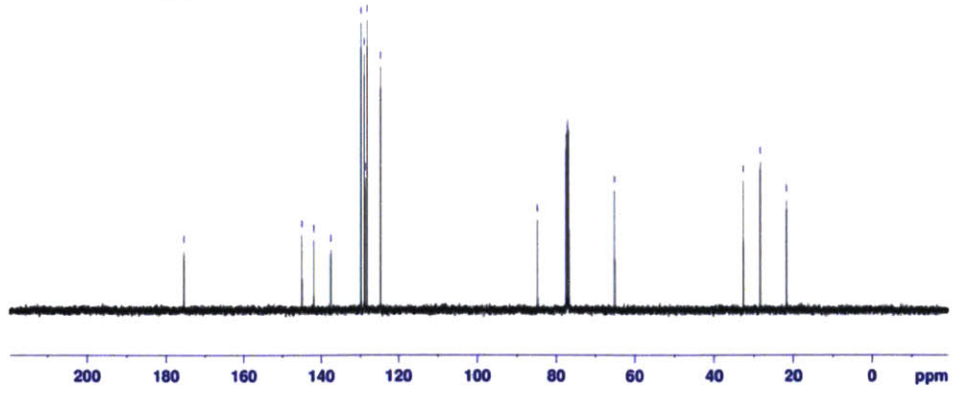


8a ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-4-234-C



8a



HPLC traces for 8a:

Data File C:\CHEM32\1\DATA\MTP1\NAOYUKI_LC 2014-12-05 10-43-13\RZ-4-234-RAC-.D
Sample Name: RZ-4-234-RAC

racemic

```
Acq. Operator   : SANDRA                          Seq. Line :  3
Acq. Instrument : Instrument 1                     Location : Vial 17
Injection Date  : 12/5/2014 12:12:25 PM                Inj :  1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 8 µl
Acq. Method     : C:\CHEM32\1\DATA\MTP1\NAOYUKI_LC 2014-12-05 10-43-13\RZ-SHUTDOWN.M
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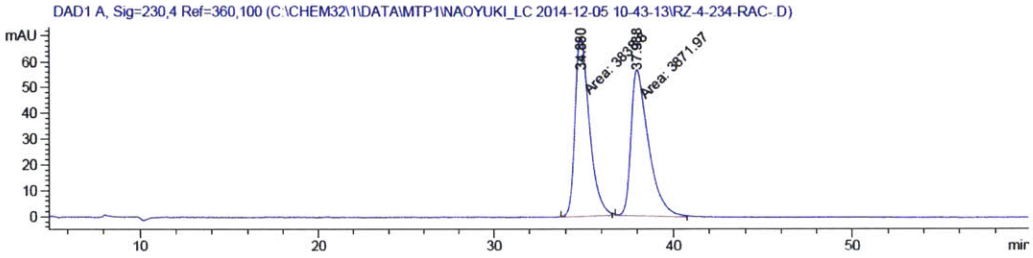
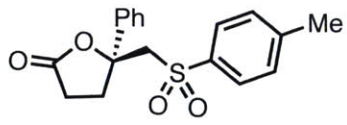


Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.880	MM	0.9182	3838.79614	69.67712	49.7849
2	37.988	MM	1.1363	3871.97144	56.78994	50.2151
Totals :				7710.76758	126.46707	



8a

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-13 14-59-43\RZ-4-234.D
Sample Name: RZ-4-234

```
Acq. Operator   : RZ                               Seq. Line :  1
Acq. Instrument : Instrument 1                     Location : Vial 16
Injection Date  : 12/13/2014 3:02:05 PM                Inj :  1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 4 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-13 14-59-43\RZ-SHUTDOWN.M
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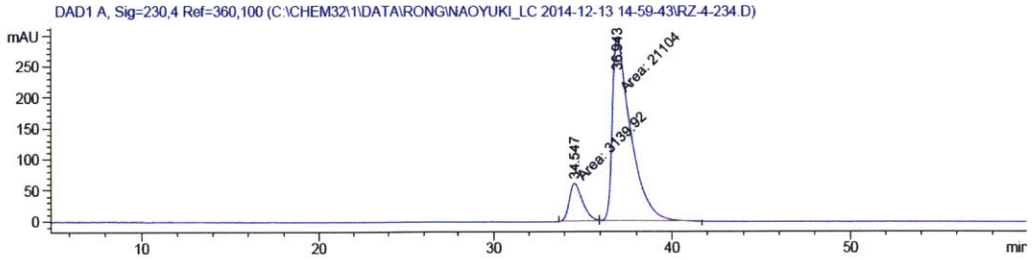
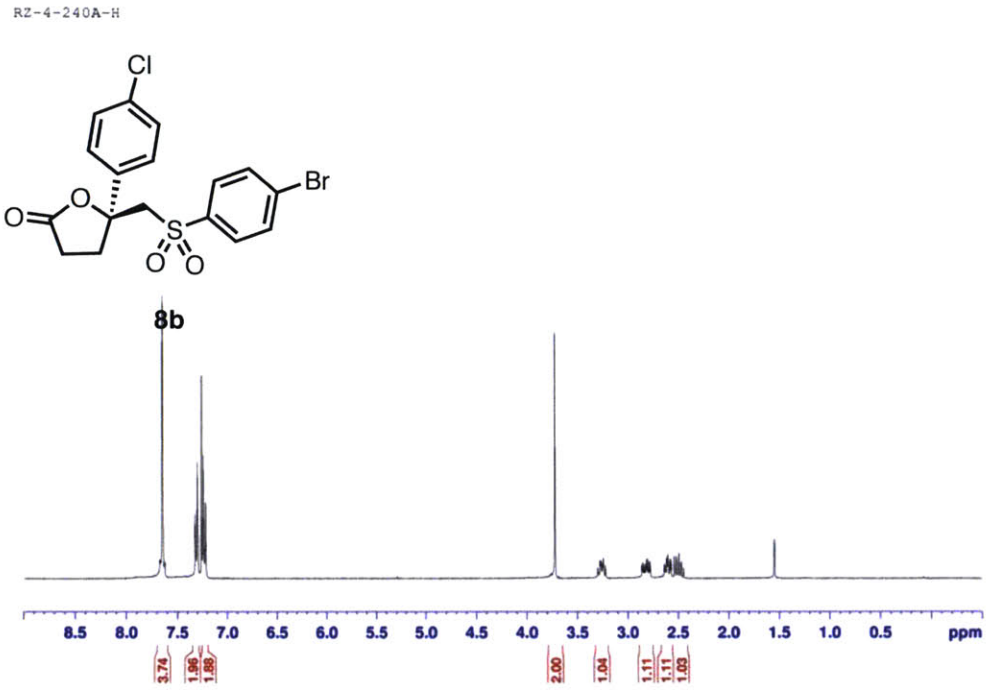


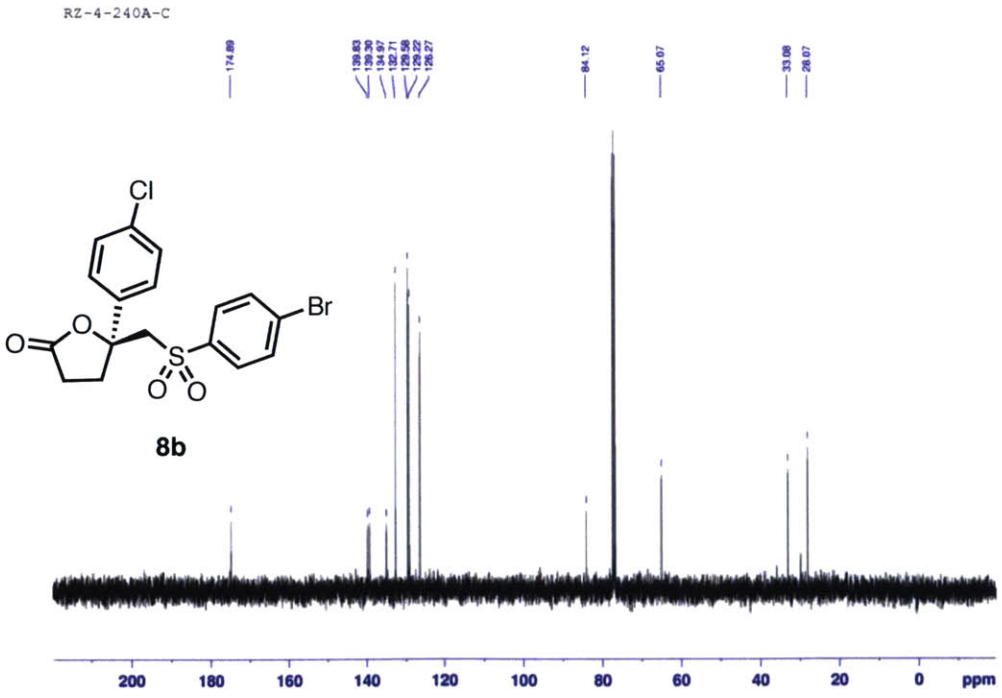
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.547	MM	0.8546	3139.91797	61.23563	12.9514
2	36.943	MM	1.1830	2.11040e4	297.32425	87.0486
Totals :				2.42439e4	358.55988	

8b ^{1}H NMR (400 MHz, $CDCl_3$)



8b ^{13}C NMR (100 MHz, $CDCl_3$)

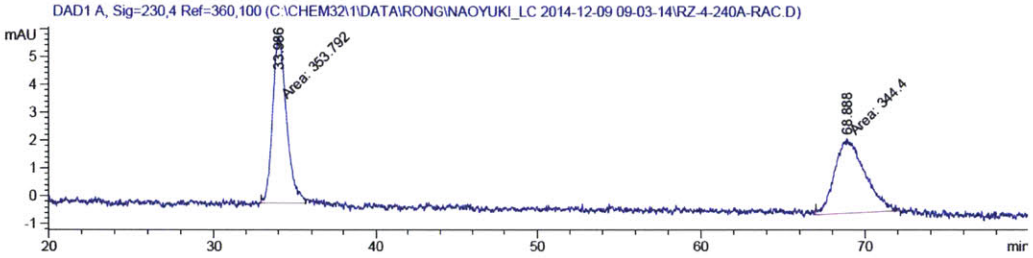


HPLC traces for 8b:

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-09 09-03-14\RZ-4-240A-RAC.D
Sample Name: RZ-4-240A-RAC

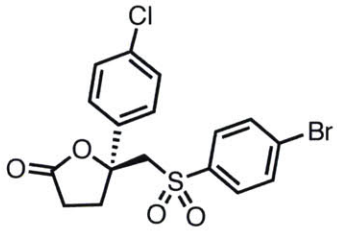
racemic

```
==================================================================
Acq. Operator   : RZ                          Seq. Line :   6
Acq. Instrument : Instrument 1                 Location : Vial 20
Injection Date  : 12/9/2014 12:57:27 PM             Inj :   1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 12 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-09 09-03-14\RZ-15IPA-2014.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

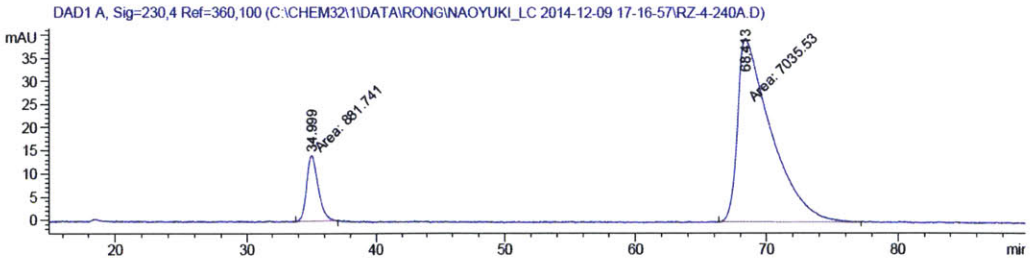
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.986	MM	0.9849	353.79236	5.98674	50.6726
2	68.888	MM	2.1221	344.40015	2.70483	49.3274
Totals :				698.19250	8.69158	



8b

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-09 17-16-57\RZ-4-240A.D
Sample Name: RZ-4-240A

```
==================================================================
Acq. Operator   : RZ                          Seq. Line :   1
Acq. Instrument : Instrument 1                 Location : Vial 28
Injection Date  : 12/9/2014 5:19:13 PM              Inj :   1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-09 17-16-57\RZ-15IPA-2014.M
```

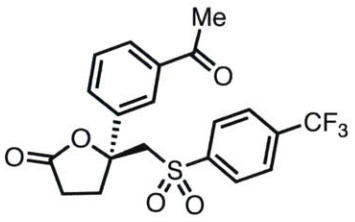


Signal 1: DAD1 A, Sig=230,4 Ref=360,100

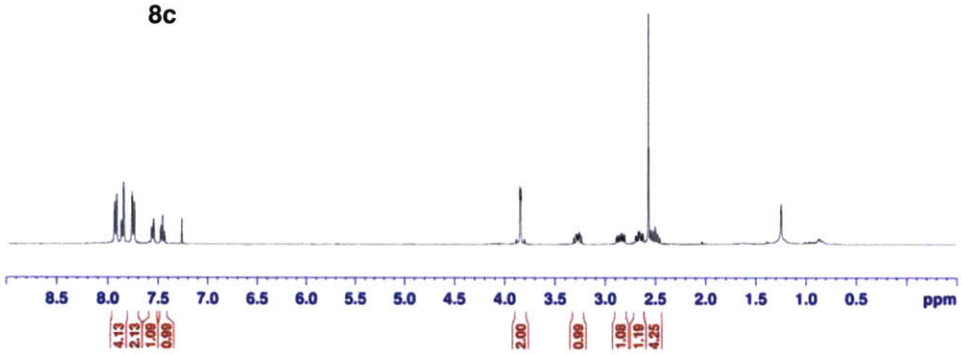
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.999	MM	1.0348	881.74060	14.20121	11.1369
2	68.413	MM	2.9414	7035.52930	39.86550	88.8631
Totals :				7917.26990	54.06671	

8c ^{1}H NMR (400 MHz, $CDCl_3$)

RZ-4-240B-H

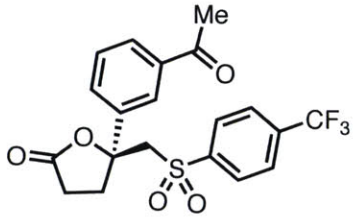


8c

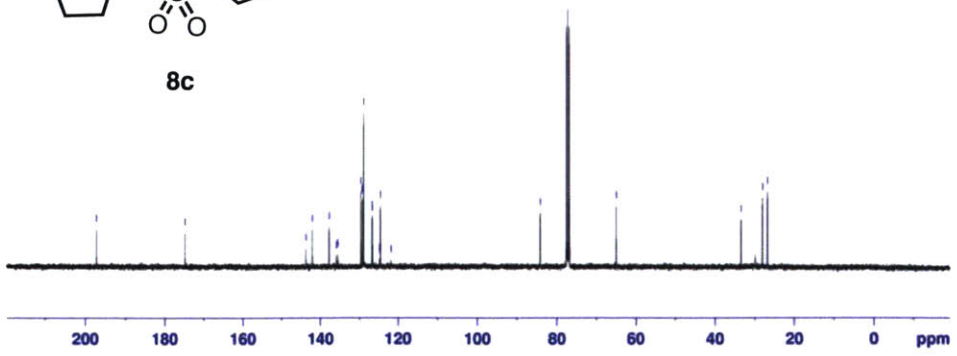


8c ^{13}C NMR (100 MHz, $CDCl_3$)

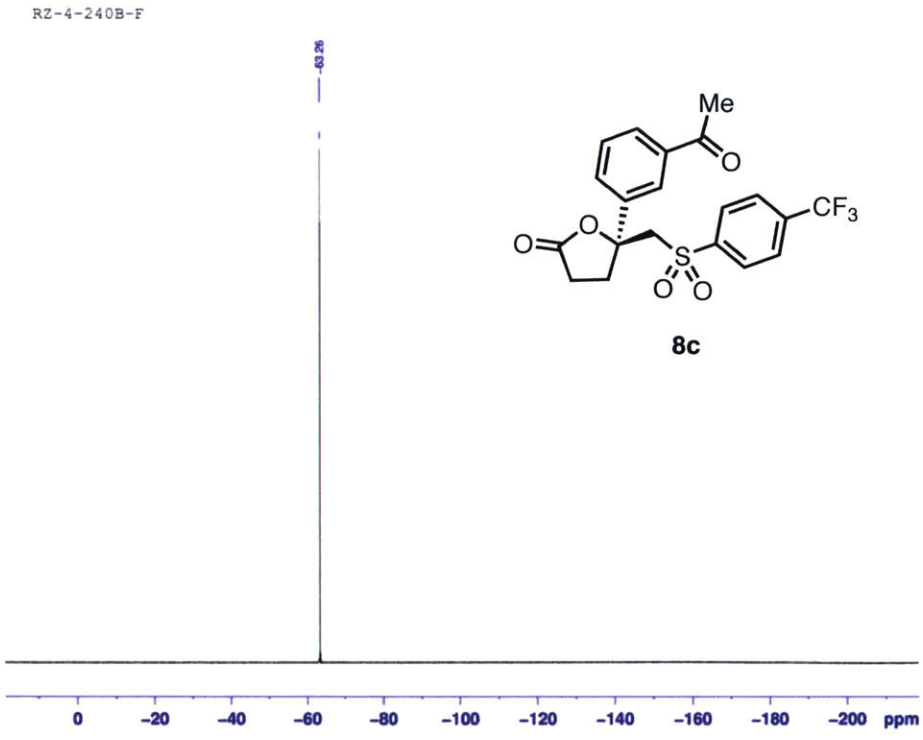
RZ-4-240B-C



8c



8c ^{19}F NMR (376 MHz, $CDCl_3$)



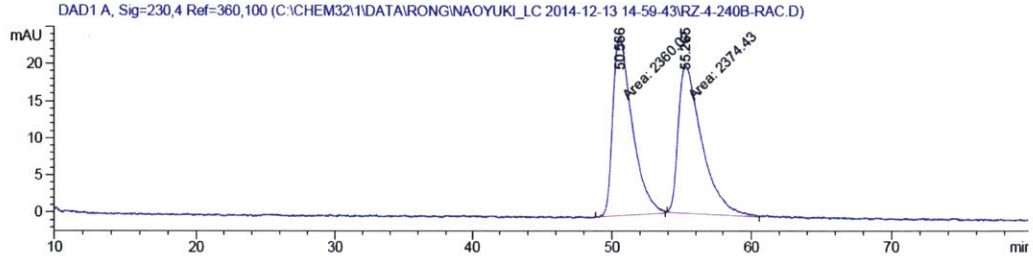
8c

HPLC traces for 8c:

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-13 14-59-43\RZ-4-240B-RAC.D
Sample Name: RZ-4-240B-RAC

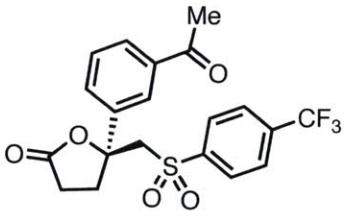
racemic

```
==================================================================
Acq. Operator   : RZ                          Seq. Line :  5
Acq. Instrument : Instrument 1                 Location : Vial 19
Injection Date  : 12/13/2014 9:06:58 PM            Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 8 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-13 14-59-43\RZ-SHUTDOWN.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

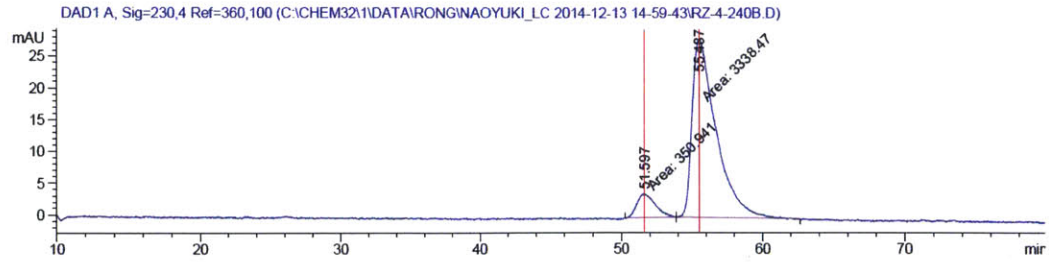
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.566	MM	1.6244	2360.01953	24.21427	49.8479
2	55.265	MM	1.9716	2374.42505	20.07225	50.1521
Totals :				4734.44458	44.28651	



8c

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-13 14-59-43\RZ-4-240B.D
Sample Name: RZ-4-240B

```
==================================================================
Acq. Operator   : RZ                          Seq. Line :  3
Acq. Instrument : Instrument 1                 Location : Vial 17
Injection Date  : 12/13/2014 6:04:25 PM            Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 4 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-13 14-59-43\RZ-SHUTDOWN.M
```

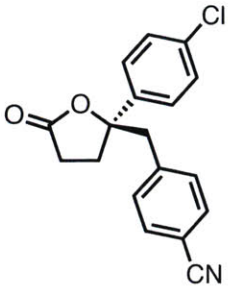


Signal 1: DAD1 A, Sig=230,4 Ref=360,100

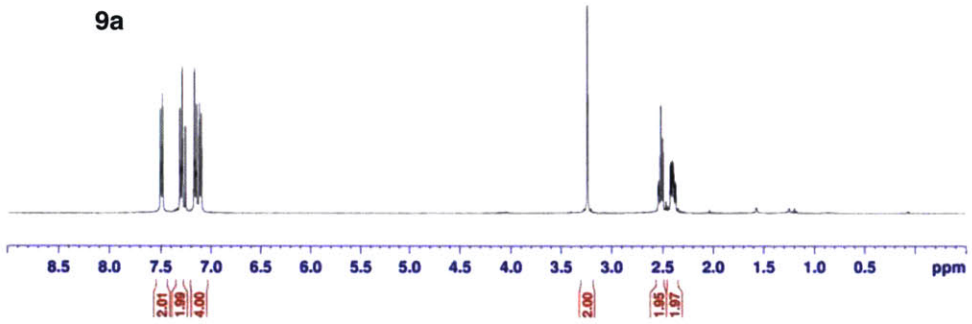
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.597	MM	1.5154	350.94086	3.85978	9.5121
2	55.487	MM	1.9667	3338.47388	28.29182	90.4879
Totals :				3689.41473	32.15160	

RZ-4-242A-H

9a ^{1}H NMR (400 MHz, $CDCl_3$)

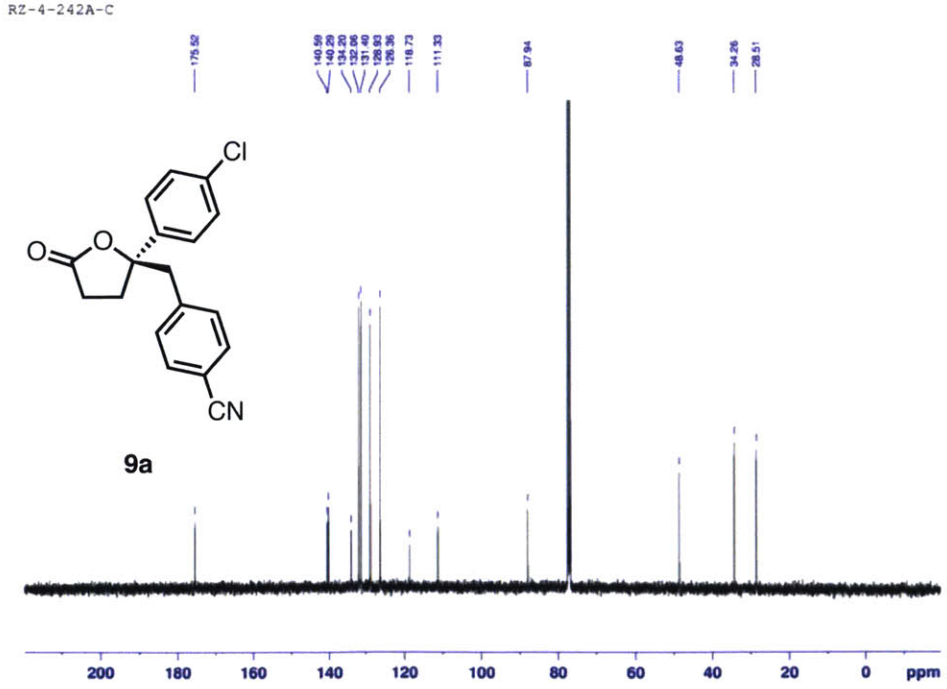


9a



9a ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-4-242A-C



HPLC traces for 9a:

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-11-24 14-06-46\RZ-4-232B-RAC.D
Sample Name: RZ-4-232B-RAC

racemic

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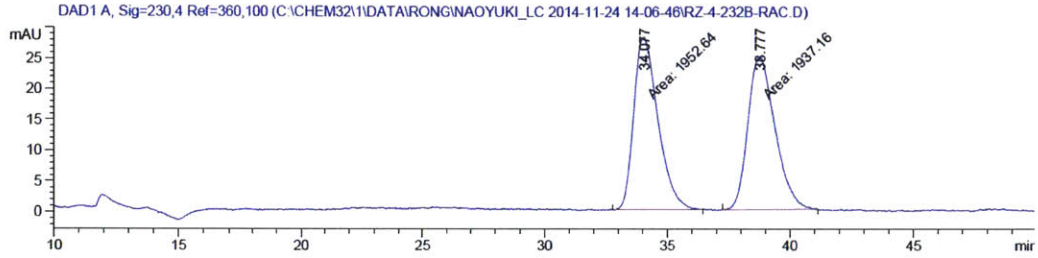
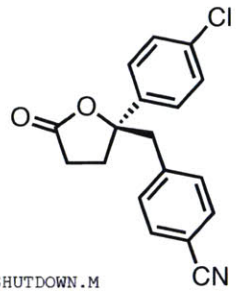
==================================================================
Acq. Operator   : RZ                          Seq. Line :  7
Acq. Instrument : Instrument 1                 Location : Vial 27
Injection Date  : 11/24/2014 6:26:06 PM             Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 8 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-11-24 14-06-46\RZ-SHUTDOWN.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.077	MM	1.1550	1952.64087	28.17696	50.1990
2	38.777	MM	1.2941	1937.16296	24.94906	49.8010

Totals : 3889.80383 53.12602



9a

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-10 12-18-53\RZ-4-242A.D
Sample Name: RZ-4-242A

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==================================================================
Acq. Operator   : RZ                          Seq. Line :  1
Acq. Instrument : Instrument 1                 Location : Vial 18
Injection Date  : 12/10/2014 12:21:12 PM            Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 8 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-10 12-18-53\RZ-SHUTDOWN.M
```
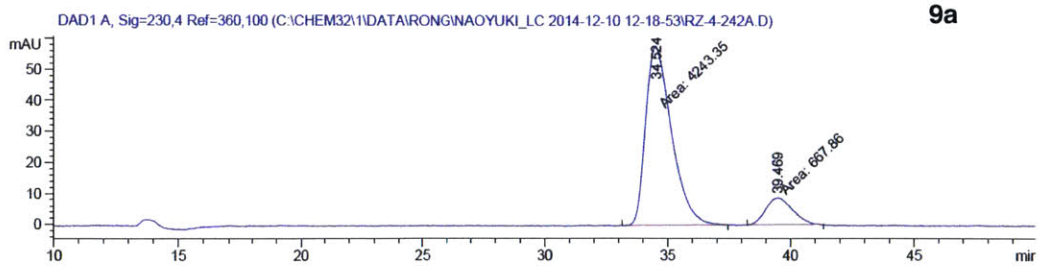
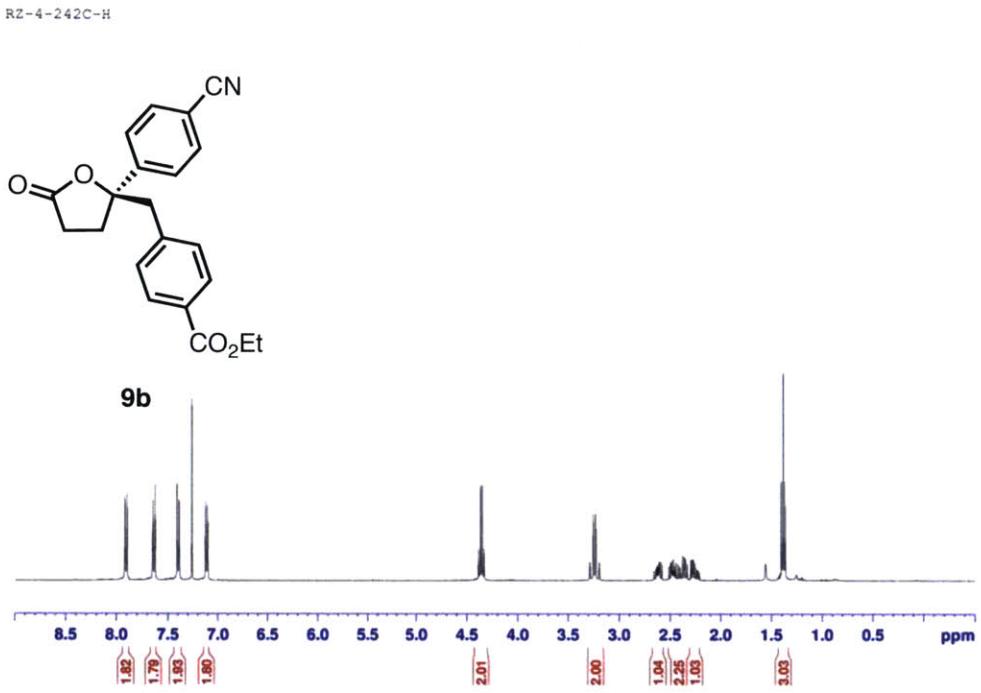



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

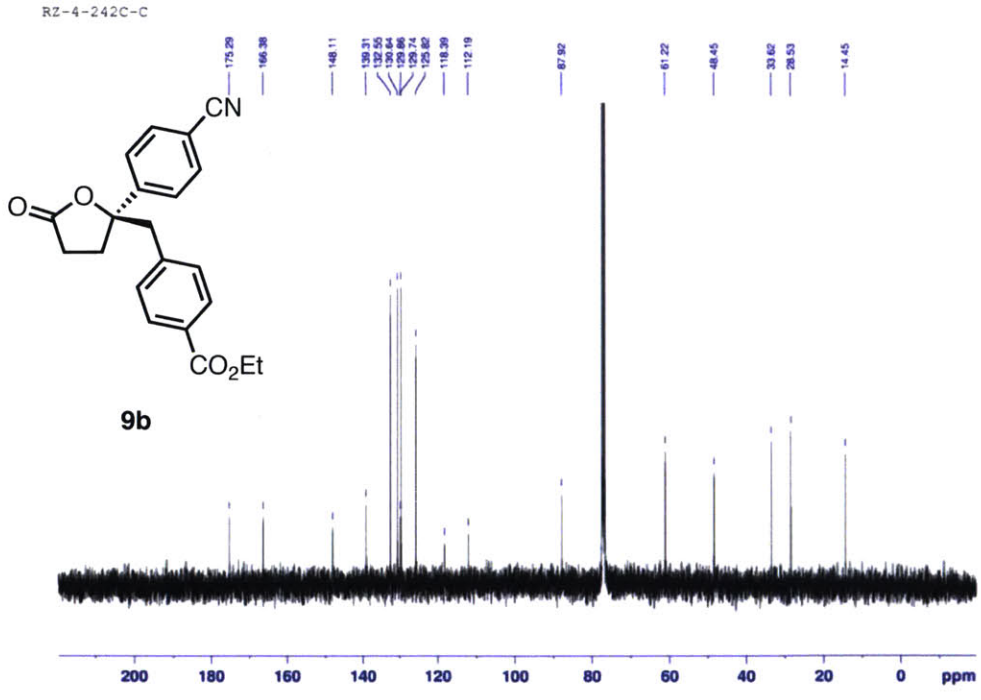
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.524	MM	1.2181	4243.34570	58.05779	86.4013
2	39.469	MM	1.2756	667.85956	8.72598	13.5987

Totals : 4911.20526 66.78376

9b ^{1}H NMR (400 MHz, $CDCl_3$)



9b ^{13}C NMR (100 MHz, $CDCl_3$)

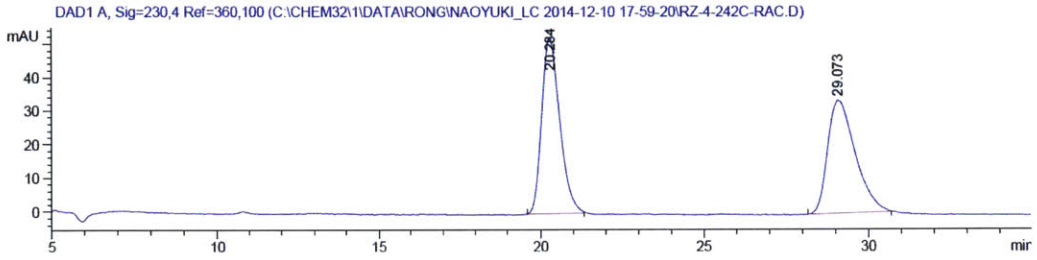


HPLC traces for 9b:

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-10 17-59-20\RZ-4-242C-RAC.D
Sample Name: RZ-4-242C-RAC

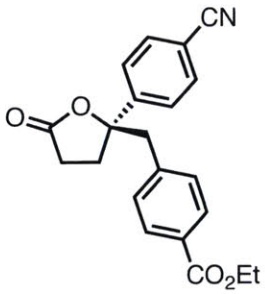
racemic

```
==================================================================
Acq. Operator   : RZ                          Seq. Line :  2
Acq. Instrument : Instrument 1                 Location : Vial 19
Injection Date  : 12/10/2014 6:53:21 PM            Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 20 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-10 17-59-20\RZ-15IPA-2014.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

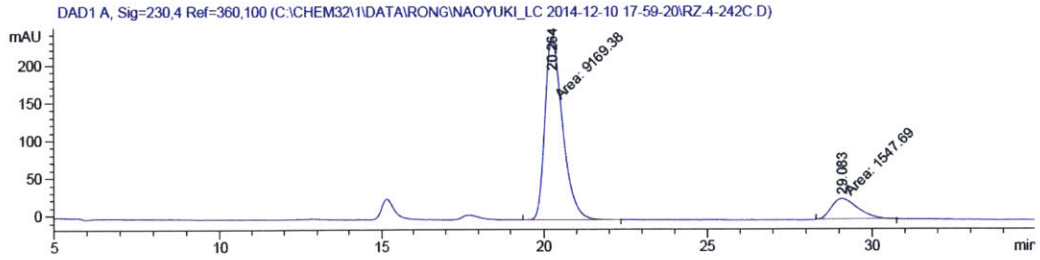
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.284	BB	0.5581	2026.92505	52.77429	50.8526
2	29.073	BB	0.6995	1958.96021	33.73444	49.1474
Totals :				3985.88525	86.50873	



9b

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-10 17-59-20\RZ-4-242C.D
Sample Name: RZ-4-242C

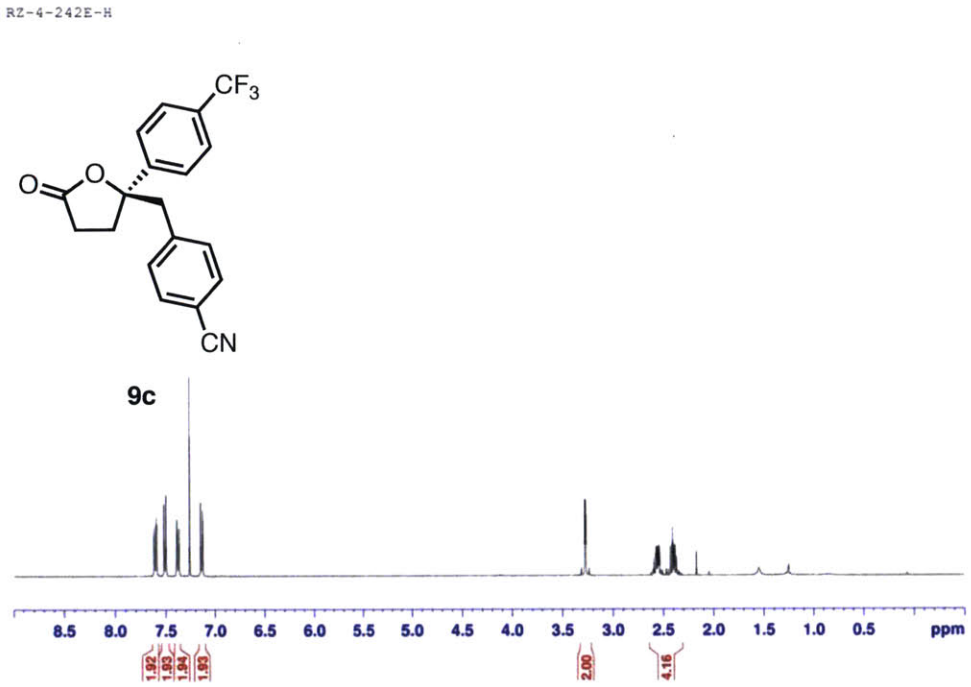
```
==================================================================
Acq. Operator   : RZ                          Seq. Line :  1
Acq. Instrument : Instrument 1                 Location : Vial 17
Injection Date  : 12/10/2014 6:01:47 PM            Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-10 17-59-20\RZ-15IPA-2014.M
```



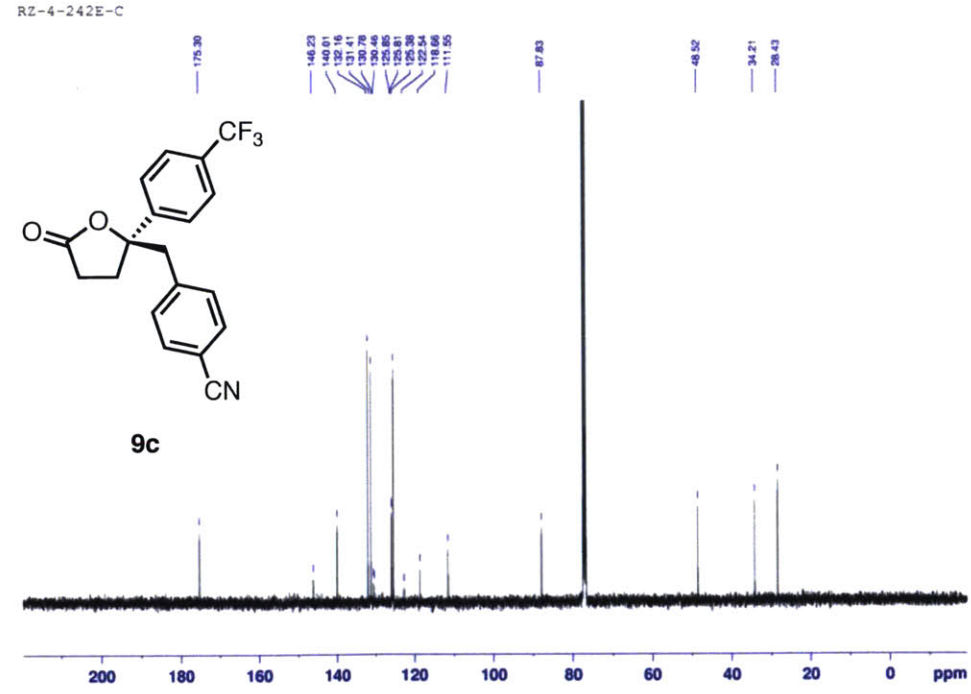
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.264	MM	0.6281	9169.38184	243.29703	85.5586
2	29.083	MM	0.9316	1547.69482	27.68975	14.4414
Totals :				1.07171e4	270.98678	

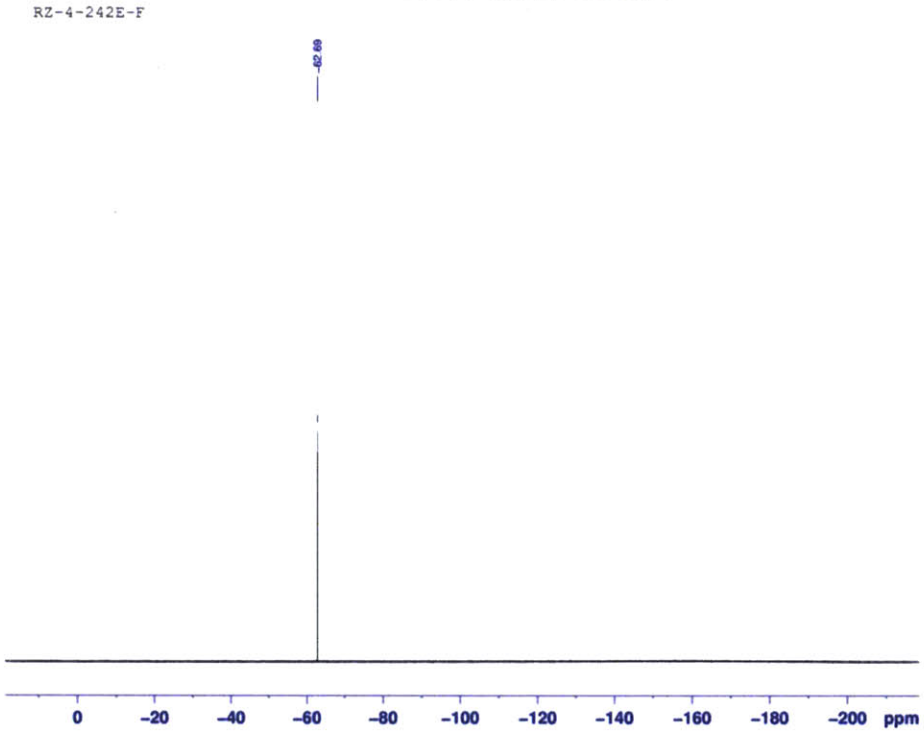
9c ^{1}H NMR (400 MHz, $CDCl_3$)



9c ^{13}C NMR (100 MHz, $CDCl_3$)



9c ^{19}F NMR (376 MHz, $CDCl_3$)

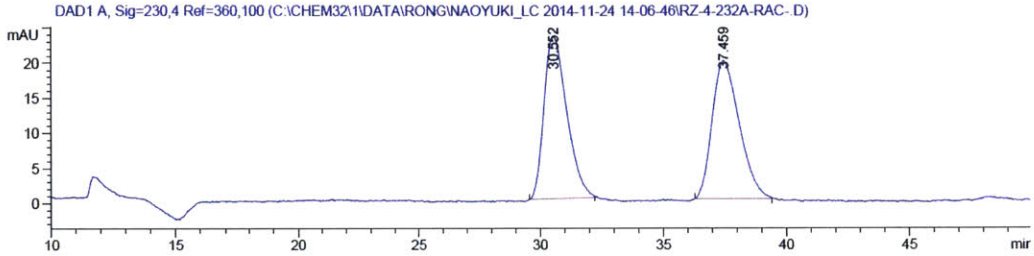


HPLC traces for 9c:

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-11-24 14-06-46\RZ-4-232A-RAC-.D
Sample Name: RZ-4-232A-RAC

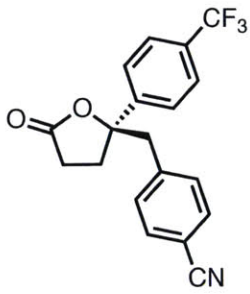
racemic

```
==================================================================
Acq. Operator   : RZ                          Seq. Line :  10
Acq. Instrument : Instrument 1                 Location : Vial 26
Injection Date  : 11/24/2014 8:59:39 PM             Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 15 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-11-24 14-06-46\RZ-SHUTDOWN.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

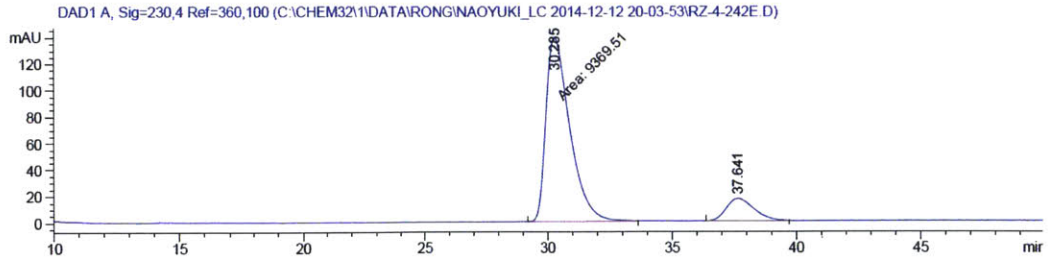
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.552	BB	0.7657	1511.29687	23.27001	49.9620
2	37.459	BB	0.9065	1513.59387	19.78445	50.0380
Totals :				3024.89075	43.05446	



9c

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-12 20-03-53\RZ-4-242E.D
Sample Name: RZ-4-242E

```
==================================================================
Acq. Operator   : RZ                          Seq. Line :  2
Acq. Instrument : Instrument 1                 Location : Vial 17
Injection Date  : 12/12/2014 9:07:15 PM             Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 3 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-12 20-03-53\RZ-SHUTDOWN.M
```

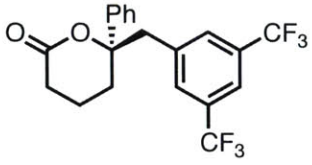


Signal 1: DAD1 A, Sig=230,4 Ref=360,100

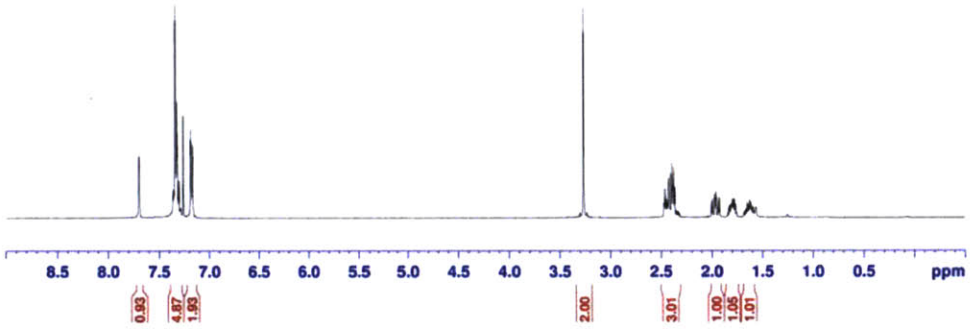
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.285	MM	1.1201	9369.51172	139.41949	87.8881
2	37.641	BB	0.9050	1291.21948	16.83233	12.1119
Totals :				1.06607e4	156.25183	

9d ^{1}H NMR (400 MHz, $CDCl_3$)

RZ-4-242B-H

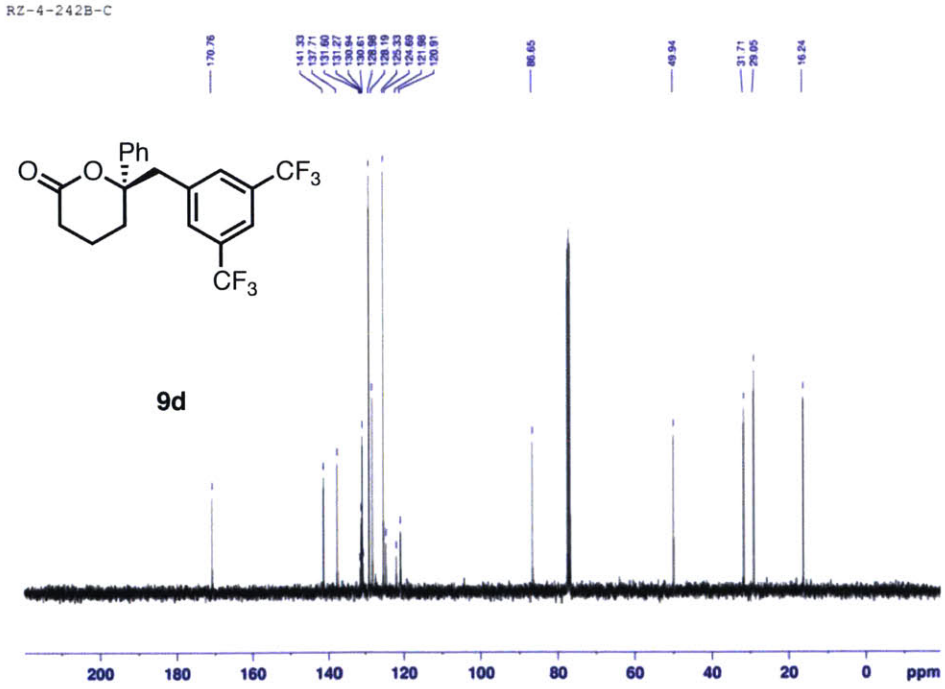


9d



9d ^{13}C NMR (100 MHz, $CDCl_3$)

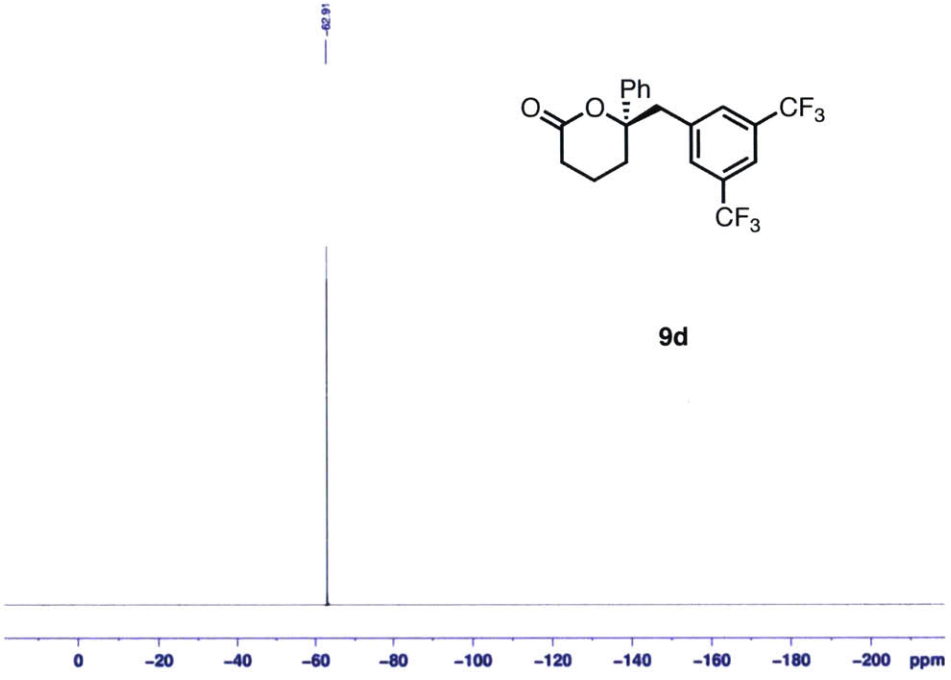
RZ-4-242B-C



9d

RZ-4-242B-F

9d ^{19}F NMR (376 MHz, $CDCl_3$)



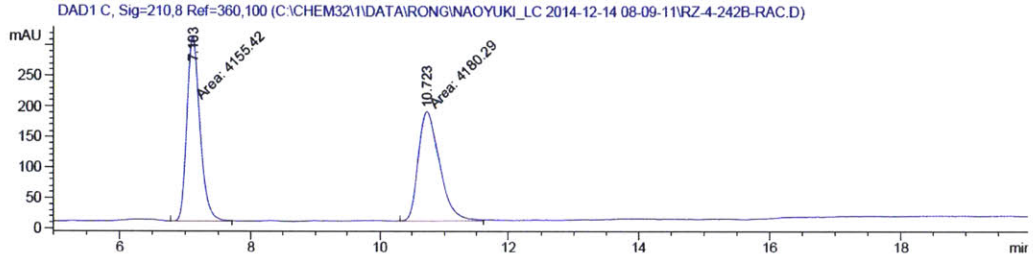
9d

HPLC traces for 9d:

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-14 08-09-11\RZ-4-242B-RAC.D
Sample Name: RZ-4-242B-RAC

```
=====================================================================
Acq. Operator   : RZ                          Seq. Line :  1
Acq. Instrument : Instrument 1                 Location : Vial 16
Injection Date  : 12/14/2014 8:11:37 AM             Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 3 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-14 08-09-11\RZ-SHUTDOWN.M
```

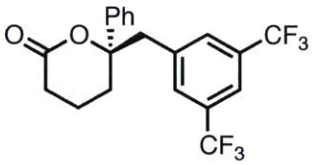
racemic



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

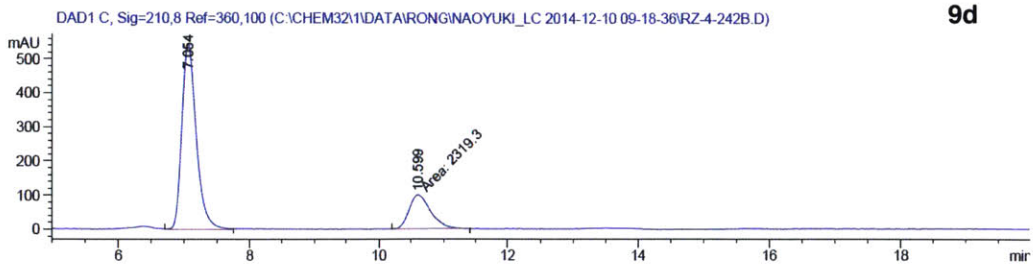
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.103	MM	0.2288	4155.41895	302.69006	49.8508
2	10.723	MM	0.3872	4180.28613	179.91805	50.1492
Totals :				8335.70508	482.60811	

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-10 09-18-36\RZ-4-242B.D
Sample Name: RZ-4-242B




```
=====================================================================
Acq. Operator   : RZ                          Seq. Line :  1
Acq. Instrument : Instrument 1                 Location : Vial 16
Injection Date  : 12/10/2014 9:20:55 AM             Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 8 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-10 09-18-36\RZ-SHUTDOWN.M
```

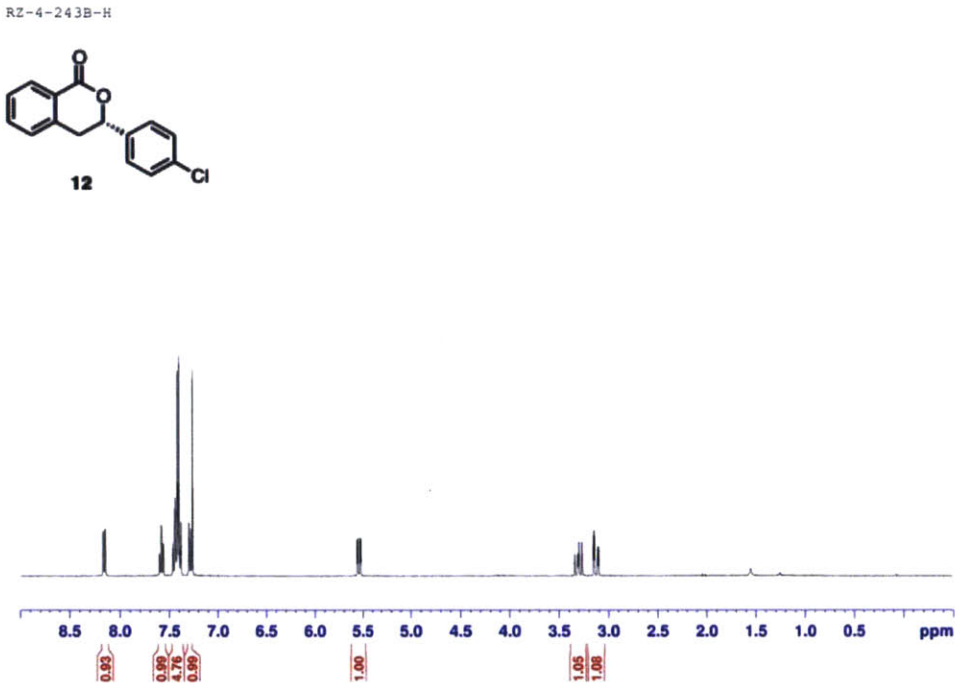
9d



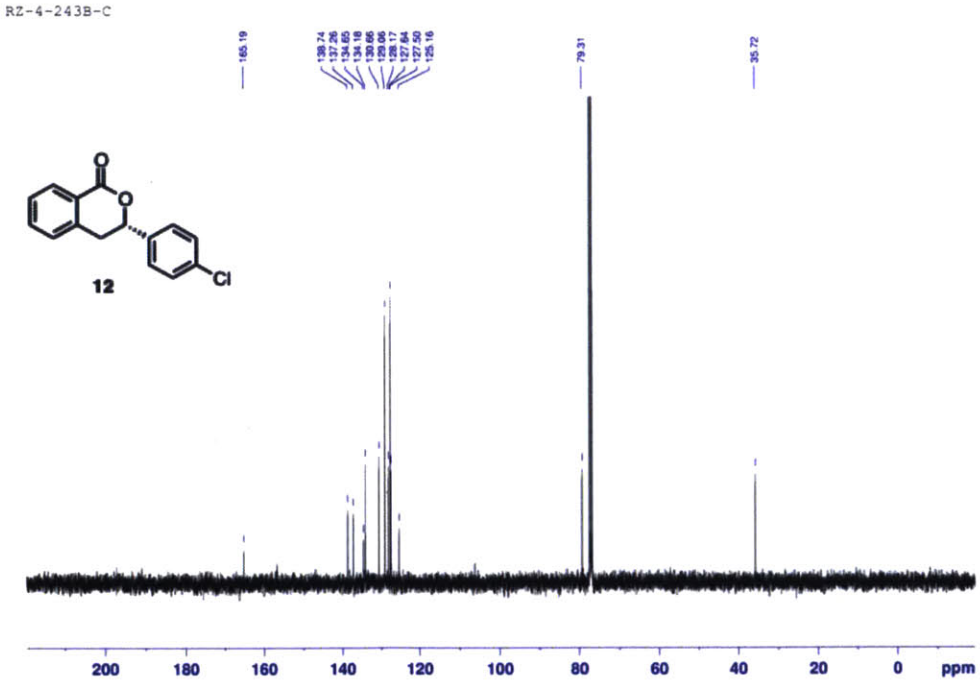
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.054	VB	0.2347	8238.34180	543.82831	78.0320
2	10.599	MM	0.3910	2319.30396	98.86506	21.9680
Totals :				1.05576e4	642.69337	

12 ^{1}H NMR (400 MHz, $CDCl_3$)



12 ^{13}C NMR (100 MHz, $CDCl_3$)

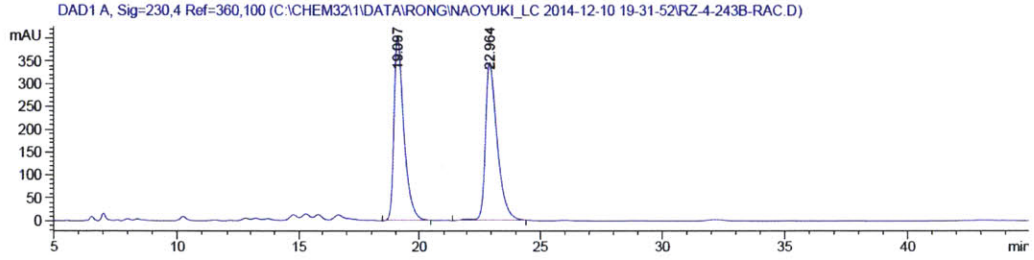


HPLC traces for 12:

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-10 19-31-52\RZ-4-243B-RAC.D
Sample Name: RZ-4-243B-RAC

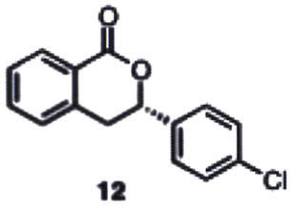
racemic

```
======================================================================
Acq. Operator   : RZ                          Seq. Line :  3
Acq. Instrument : Instrument 1                 Location : Vial 27
Injection Date  : 12/10/2014 9:16:42 PM             Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-10 19-31-52\RZ-5IPA-1ML-2013-.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

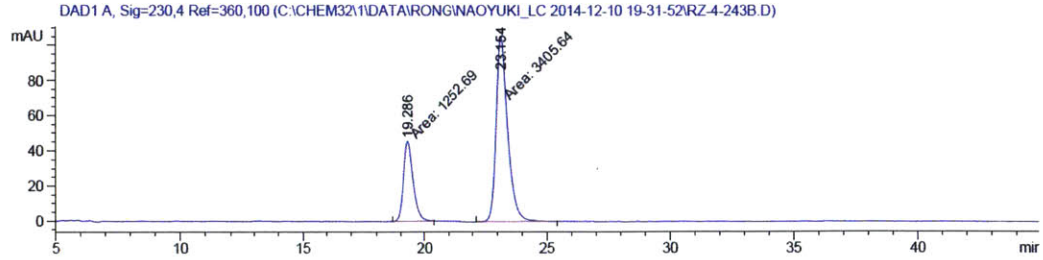
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.097	BB	0.4188	1.14534e4	403.96323	49.8268
2	22.964	BB	0.4947	1.15330e4	346.15372	50.1732
Totals :				2.29864e4	750.11694	



12

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-10 19-31-52\RZ-4-243B.D
Sample Name: RZ-4-243B

```
======================================================================
Acq. Operator   : RZ                          Seq. Line :  2
Acq. Instrument : Instrument 1                 Location : Vial 26
Injection Date  : 12/10/2014 8:25:27 PM             Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 8 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-10 19-31-52\RZ-5IPA-1ML-2013-.M
```

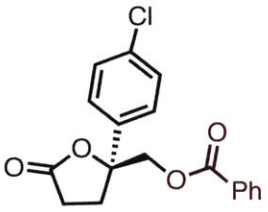


Signal 1: DAD1 A, Sig=230,4 Ref=360,100

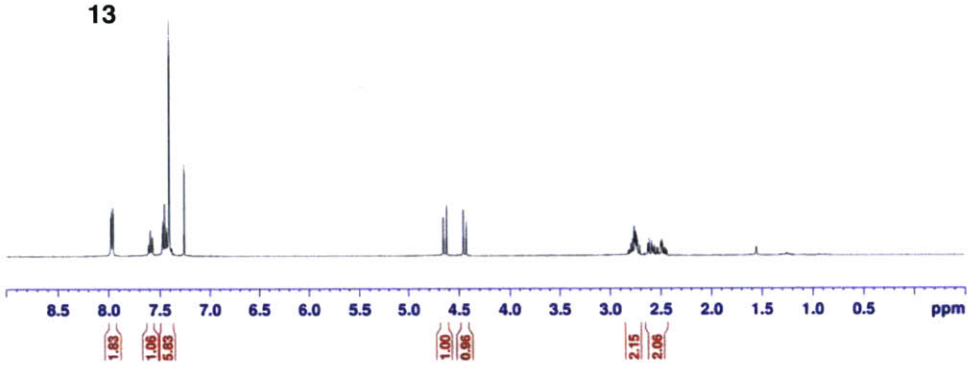
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.286	MM	0.4577	1252.69153	45.61325	26.8914
2	23.154	MM	0.5373	3405.64307	105.63242	73.1086
Totals :				4658.33459	151.24567	

13 ^{1}H NMR (400 MHz, $CDCl_3$)

RZ-4-235P1-H

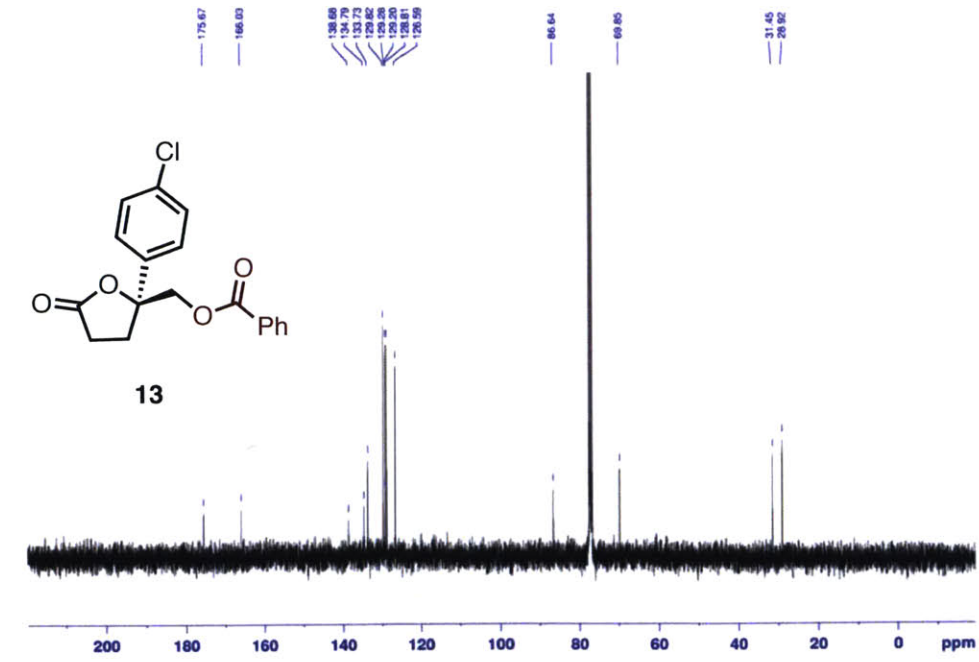


13



13 ^{13}C NMR (100 MHz, $CDCl_3$)

RZ-4-235P1-C

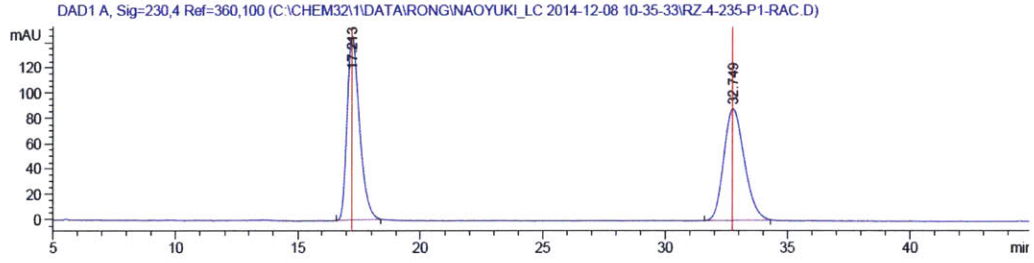


HPLC traces for 13:

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-08 10-35-33\RZ-4-235-P1-RAC.D
Sample Name: RZ-4-235-P1-RAC

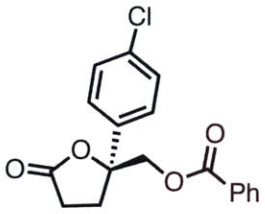
```
Acq. Operator   : RZ                                Seq. Line :  2
Acq. Instrument : Instrument 1                      Location : Vial 18
Injection Date  : 12/8/2014 11:29:03 AM                 Inj :  1
                                                Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-08 10-35-33\RZ-SHUTDOWN.M
```

racemic



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

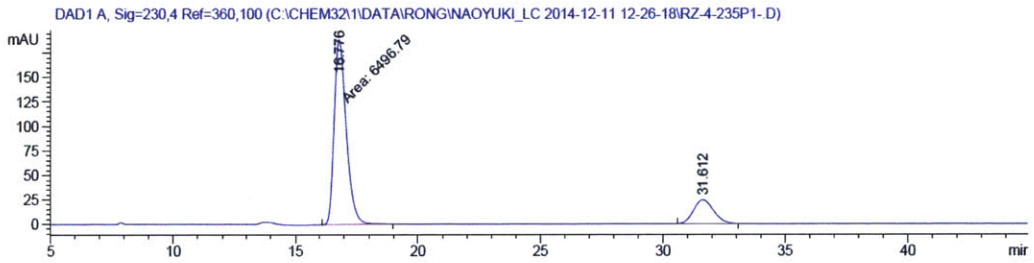
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.213	BB	0.5263	5178.36182	145.83827	49.9535
2	32.749	BB	0.8232	5187.99316	88.32819	50.0465
Totals :				1.03664e4	234.16647	



13

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-11 12-26-18\RZ-4-235P1-.D
Sample Name: RZ-4-235P1

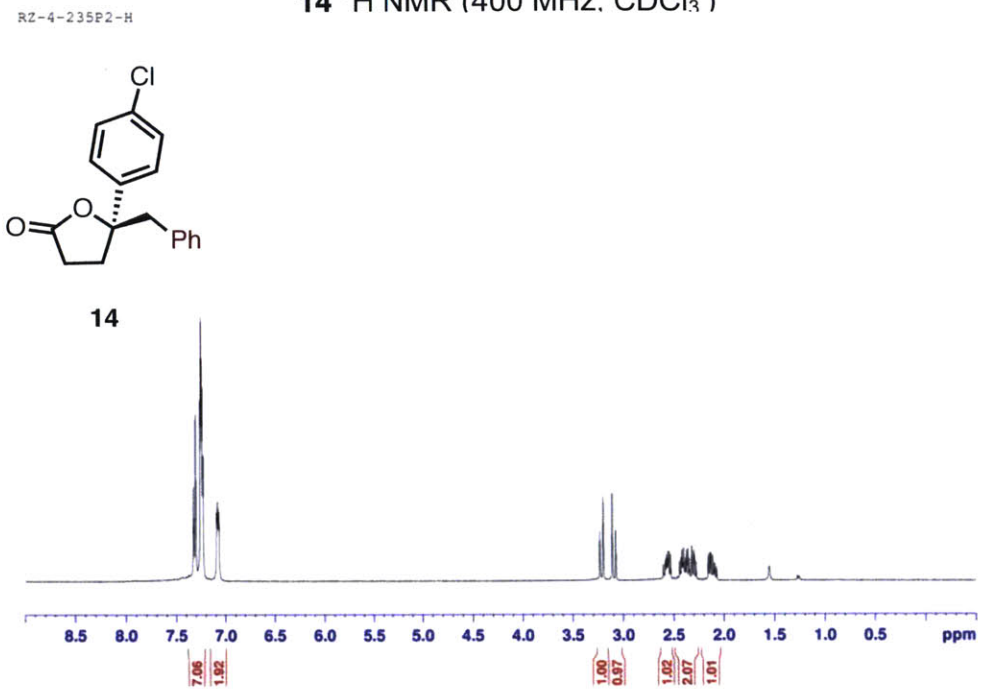
```
Acq. Operator   : RZ                                Seq. Line :  3
Acq. Instrument : Instrument 1                      Location : Vial 16
Injection Date  : 12/11/2014 2:10:58 PM                 Inj :  1
                                                Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 8 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-11 12-26-18\RZ-SHUTDOWN.M
```



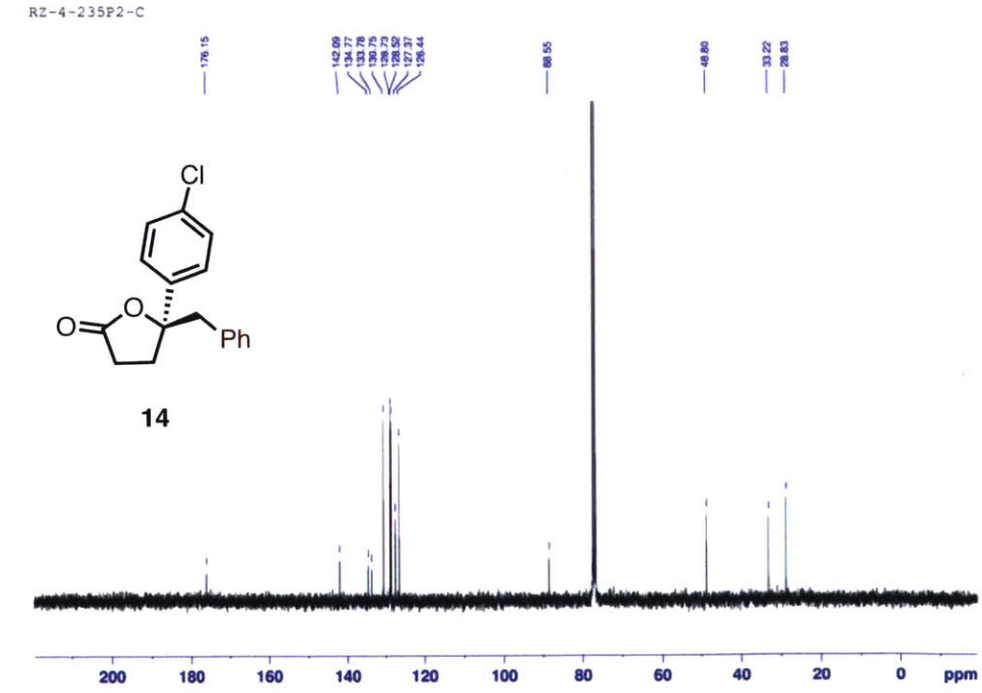
Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.776	MM	0.5730	6496.78809	188.96053	82.4137
2	31.612	BB	0.6725	1386.35205	24.48735	17.5863
Totals :				7883.14014	213.44787	

14 ^{1}H NMR (400 MHz, $CDCl_3$)



14 ^{13}C NMR (100 MHz, $CDCl_3$)

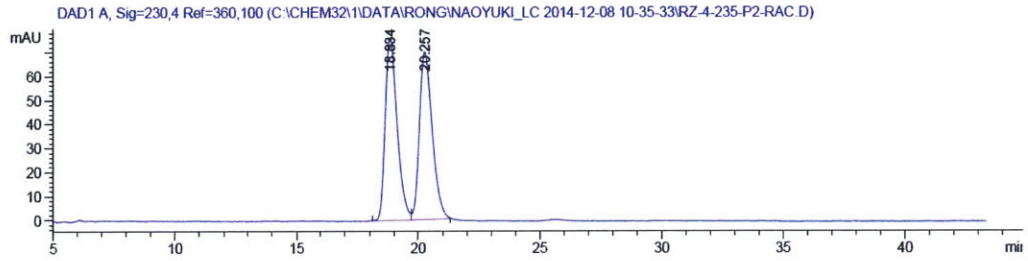


HPLC traces for 14:

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-08 10-35-33\RZ-4-235-P2-RAC.D
Sample Name: RZ-4-235-P2-RAC

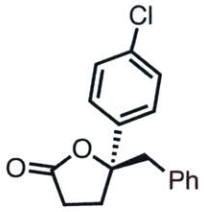
racemic

```
==================================================================
Acq. Operator   : RZ                          Seq. Line :  4
Acq. Instrument : Instrument 1                 Location : Vial 19
Injection Date  : 12/8/2014 12:33:32 PM            Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-08 10-35-33\RZ-5IPA-1ML-2013-.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

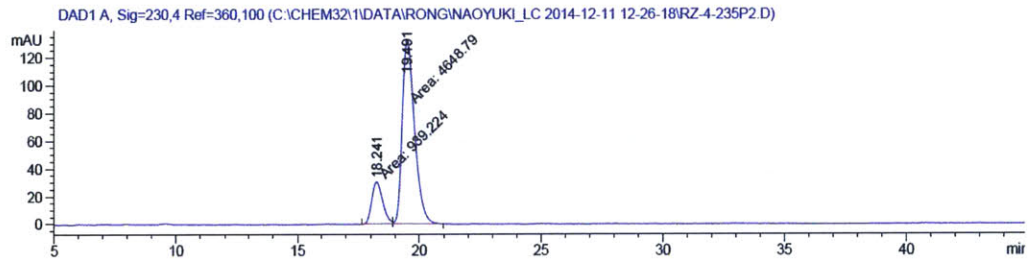
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.834	BV	0.4962	2589.89990	76.26014	50.2433
2	20.257	VB	0.5213	2564.81323	70.02714	49.7567
Totals :				5154.71313	146.28728	



14

Data File C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-11 12-26-18\RZ-4-235P2.D
Sample Name: RZ-4-235P2

```
==================================================================
Acq. Operator   : RZ                          Seq. Line :  5
Acq. Instrument : Instrument 1                 Location : Vial 17
Injection Date  : 12/11/2014 3:54:28 PM            Inj :  1
                                              Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 8 µl
Acq. Method     : C:\CHEM32\1\DATA\RONG\NAOYUKI_LC 2014-12-11 12-26-18\RZ-5IPA-1ML-2013-.M
```



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.241	MM	0.5151	939.22388	30.39110	16.8078
2	19.491	MM	0.5848	4648.78662	132.48862	83.1922
Totals :				5588.01050	162.87972	

Rong Zhu

Education

Ph.D. in Organic Chemistry 2010-2015

Massachusetts Institute of Technology

Advisor: Prof. Stephen L. Buchwald

Thesis: *Development of Copper-Catalyzed Enantioselective Alkene Difunctionalization Reactions via Radical Intermediates*

B.S. in Chemistry 2006-2010

Peking University

Advisors: Prof. Zhen Yang and Prof. Jiahua Chen

Thesis: *Development of Asymmetric Vinylogous Mukaiyama Aldol Reactions and Studies towards the Total Synthesis of Cebulactams*

Research Experience

Undergraduate Research Assistant 7/2008-8/2008

University of Michigan, Ann Arbor

Advisor: Prof. John P. Wolfe

Research Focus: *Palladium-Catalyzed Carboamination*

Honors and Awards

Wellington and Irene Loh Fund Fellowship	2013
Sumitomo Fellowship, Peking University	2009
Li Huirong Fellowship, Peking University	2008
Bao Steel Fellowship, Peking University	2007
First Prize, College Student Physics Competition, Beijing	2007
First Prize, National High School Chemistry Olympiad, China	2006

Publications

6. Zhu, R.; Buchwald, S. L.* "Enantioselective Functionalization of Radical Intermediates in Redox Catalysis: Copper-Catalyzed Asymmetric Oxytrifluoromethylation of Alkenes." *Angewandte Chemie International Edition* **2013**, *52*, 12655.
   ** Selected as Very Important Paper (VIP).*

5. Yang, S.; Xi, Y.; Zhu, R.; Wang, L.; Chen, J.*; Yang, Z.* "Asymmetric Total Syntheses of Ansamacrolactams (+)-Q-1047H-A-A and (+)-Q-1047H-R-A." *Organic Letters* **2013**, *15*, 812.

4. Zhu, R.; Buchwald, S. L.* "Copper-Catalyzed Oxytrifluoromethylation of Unactivated Alkenes."
Journal of the American Chemical Society **2012**, *134*, 12462.

3. Zhu, R.; Buchwald, S. L.* " Combined Oxypalladation/C–H Functionalization: Palladium(II)-Catalyzed Intramolecular Oxidative Oxyarylation of Hydroxyalkenes
Angewandte Chemie International Edition **2012**, *51*, 1926.

2. Wang, L.; Xi, Y.; Yang, S.; Zhu, R.; Liang, Y.; Chen, J.*; Yang, Z.*" Asymmetric Total Synthesis and Structural Elucidation of NFAT-68."
Organic Letters **2011**, *13*, 74.

1. Liang, Y.; Wang, L.; Zhu, R.; Deng, L.; Yang, Y.; Quan, J.*; Chen, J.*; Yang, Z.* " An Unprecedented Silver Salt Effect Switches the Facial Selectivity in the Vinylogous Mukaiyama Aldol Reaction."
Advanced Synthesis and Catalysis **2010**, *352*, 2387

Presentations

Boston Symposium on Organic and Bioorganic Chemistry	9/2012, Merck Research Lab, Boston
248th ACS National Meetings	8/2014, San Francisco