

COPPER-CATALYZED CONJUGATE REDUCTION

by

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Hon. B.Sc.
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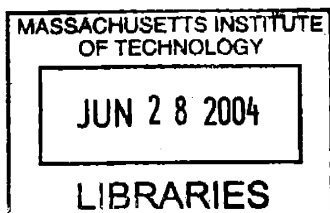
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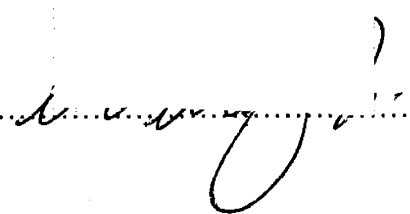


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Valdas Jurkauskas

Submitted to the Department of Chemistry May, 2004
in Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Organic Chemistry

ABSTRACT

Chapter 1.

A highly enantioselective catalyst for the asymmetric conjugate reduction of α,β -unsaturated cyclic ketones was generated upon combination of catalytic amounts of CuCl, NaO*t*-Bu, and a chiral bis-phosphine with poly(methylhydrosiloxane) (PMHS) as the stoichiometric reductant. In this process, chiral 3-alkylcyclopentanones were isolated in high enantiomeric excess ($ee \geq 92\%$) and in moderate to excellent yields (42-91%).

Chapter 2.

Kinetic resolution, with good selectivity factors (25-52), was achieved by conjugate reduction with catalytic CuCl/NaO*t*-Bu/(*S*)-*p*-tol-BINAP and stoichiometric quantities of PMHS. When stoichiometric amounts of NaO*t*-Bu and *t*-BuOH were included in the reaction mixture, rapid racemization of the starting material occurred allowing for the dynamic kinetic resolution of the cyclopentenone substrates. In this process, chiral 2,4-dialkylcyclopentanones were isolated with high stereoselectivity ($ee \geq 91\%$, $dr \geq 90:10$) and in high yield ($\geq 89\%$).

Chapter 3.

An N-heterocyclic carbene-copper chloride complex was prepared and used to catalyze the conjugate reduction of α,β -unsaturated carbonyl compounds. The combination of catalytic amounts of N-heterocyclic carbene-copper chloride complex and NaO*t*-Bu with PMHS as the stoichiometric reductant generates an active catalyst for the 1,4-reduction of tri- and tetrasubstituted α,β -unsaturated esters and cyclic enones. The active catalytic species can also be generated in situ from 1,3-bis(2,6-di-isopropylphenyl)-imidazolium chloride and CuCl₂•2H₂O in the presence of NaO*t*-Bu and PMHS.

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

PREFACE

This thesis has been adapted from articles co-written by the author. The following articles were reproduced with permission from the American Chemical Society:

“Synthesis of β -Alkyl Cyclopentanones in High Enantiomeric Excess via Copper-Catalyzed Asymmetric Conjugate Reduction” Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797.

“Dynamic Kinetic Resolution via Asymmetric Conjugate Reduction: Enantio- and Diastereoselective Synthesis of 2,4-Dialkyl Cyclopentanones” Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892.

“Conjugate Reduction of α,β -Unsaturated Carbonyl Compounds Catalyzed by a Copper Carbene Complex” Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417.

“Access to Optically Pure 4- and 5-Substituted Lactones: A Case of Chemical-Biocatalytical Cooperation” Wang, S.; Kayser, M. M.; Jurkauskas, V. *J. Org. Chem.* **2003**, *68*, 6222.

TABLE OF CONTENTS

INTRODUCTION		6
CHAPTER 1.	COPPER-CATALYZED ASYMMETRIC CONJUGATE REDUCTION OF α,β -UNSATURATED β -ALKYL CYCLIC KETONES	10
	Background and Introduction	11
	Results and Discussion	13
	Conclusions	17
	Experimental Section	18
	References	29
CHAPTER 2.	DYNAMIC KINETIC RESOLUTION via ASYMMETRIC CONJUGATE REDUCTION: ENANTIO- and DIASTEREOSELECTIVE SYNTHESIS of 2,4-DIALKYL CYCLOPENTANONES	33
	Background and Introduction	34
	Results and Discussion	35
	Conclusions	39
	Experimental Section	39
	References	62
CHAPTER 3.	CONJUGATE REDUCTION of α,β -UNSATURATED CARBONYL COMPOUNDS by a COPPER CARBENE COMPLEX	65
	Background and Introduction	66
	Results and Discussion	67
	Conclusions	74
	Experimental Section	74
	References	88

Introduction

Today's therapeutic agents, fine chemicals, agrochemicals, flavors, and fragrances are increasingly produced as enantiomerically pure compounds¹. Asymmetric catalysis has had a tremendous impact on the synthesis of chiral compounds,² particularly for the preparation of 3° carbon chiral centers which possess a hydrogen atom at the stereogenic center. Such hydrogen atom can be introduced into unsaturated prochiral precursor by hydrogenation or, in the case of α,β -unsaturated carbonyl compounds, by conjugate reduction. Notably, transition metal-catalyzed asymmetric hydrogenations using chiral bis-phosphines as ligands have found a broad range of applications in both academia and industry.³

The asymmetric conjugate reduction reaction has emerged as a complementary enantioselective method to access chiral compounds that possess a hydrogen atom at the stereogenic center.⁴ Despite the numerous transition metal based catalysts available for conjugate reduction,⁵ only a chiral semicorrin cobalt system⁶ and a chiral aldiminato cobalt complex⁷ are effective catalysts for the asymmetric conjugate reductions of α,β -unsaturated esters and amides (Figure 1).

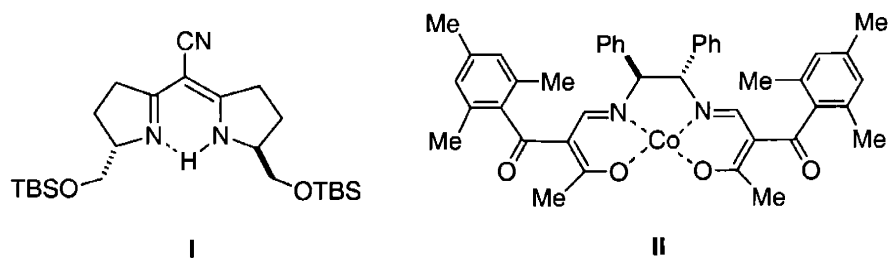


Figure 1. Chiral semicorrin ligand (I) and chiral aldiminato cobalt catalyst (II).

These systems employed borohydrides as the stoichiometric reducing agents and, hence, cannot be used for the asymmetric conjugate reduction of α,β -unsaturated ketones. Typically, the competing uncatalyzed 1,2- and 1,4-reductions of α,β -unsaturated ketones

with borohydride provide the corresponding reduction products in low enantiomeric excess and low yield.

The pioneering work of Stryker,⁸ Lipshutz,⁹ and Hiyama¹⁰ demonstrated that tri-phenylphosphine-copper hydrides preferentially effect the 1,4-reduction of α,β -unsaturated ketones. Subsequently, Buchwald and Appella showed that an in situ generated (*S*)-*p*-tol-BINAP-copper(I) hydride complex is an effective catalyst for the asymmetric conjugate reduction of α,β -unsaturated esters (Figure 2).¹¹

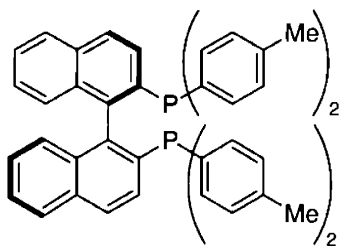


Figure 2. (*S*)-*p*-tol-BINAP.

Methods for the conjugate reduction of α,β -unsaturated esters and cyclic ketones represent the foundation of the research detailed in this thesis. In Chapter 1, a method is described for the preparation of 3-alkyl cyclic ketones in high enantiomeric excess using an in situ generated chiral bis-phosphine-copper hydride catalyst. Chapter 2 describes an extension of the copper-catalyzed asymmetric conjugate reduction to a dynamic kinetic resolution that simultaneously creates two nonadjacent chiral centers in 2,4-dialkyl cyclopentanones. Finally, Chapter 3 discusses the application of an N-heterocyclic carbene-copper chloride complex for the conjugate reduction of tri- and tetrasubstituted α,β -unsaturated esters and cyclic ketones.

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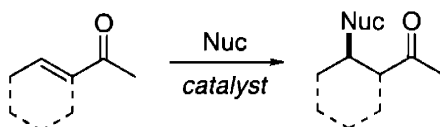
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Chapter 1.
Copper-Catalyzed Asymmetric Conjugate Reduction of
 α,β -Unsaturated β -Alkyl Cyclic Ketones

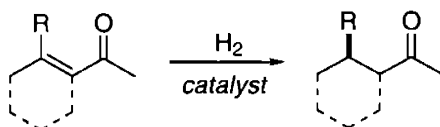
Background and Introduction

The majority of methods to access chiral β -substituted carbonyl compounds employ conjugate addition reactions.¹ Several selective systems have been developed for the asymmetric catalytic conjugate addition of alkylmetals to α,β -unsaturated ketones and esters.² In some instances, asymmetric hydrogenation can also provide access to products with stereocenters β to carbonyl groups.³ The asymmetric conjugate reductions of β -disubstituted unsaturated carbonyl compounds offer a complementary method to access β -chiral carbonyl compounds (Figure 1).

Conjugate addition:



Hydrogenation:



Conjugate reduction:

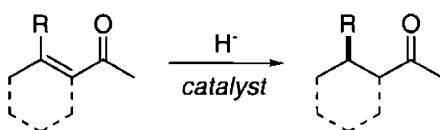


Figure 1. Methods to access compounds with stereocenters β to carbonyls.

The cobalt catalyzed asymmetric conjugate reductions of α,β -unsaturated esters and amides in the presence of stoichiometric amounts of borohydrides have been reported.⁴ Notably, the same catalyst system cannot be used for the asymmetric conjugate reductions of enones because reduction by the borohydride is rapid and nonselective, giving 1,2- and 1,4-reduction products. The pioneering work of Stryker, Lipshutz, and Hiyama demonstrated that achiral phosphine-copper hydrides, such as $[(\text{Ph}_3\text{P})\text{CuH}]_6$,

preferentially reduce enones via 1,4-reduction.⁵ We have previously reported a new chiral (bis-phosphine)-copper catalyst for the asymmetric conjugate reduction of α,β -unsaturated esters.⁶ This catalyst employs poly(methylhydrosiloxane) (PMHS) as the stoichiometric reductant. Using this method, a variety of α,β -unsaturated esters can be reduced with high levels of enantioselectivity (Figure 2).

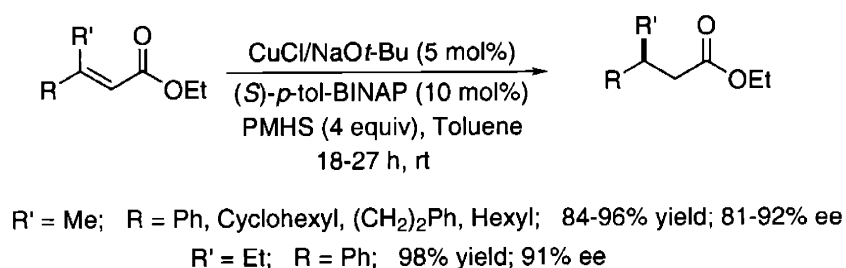
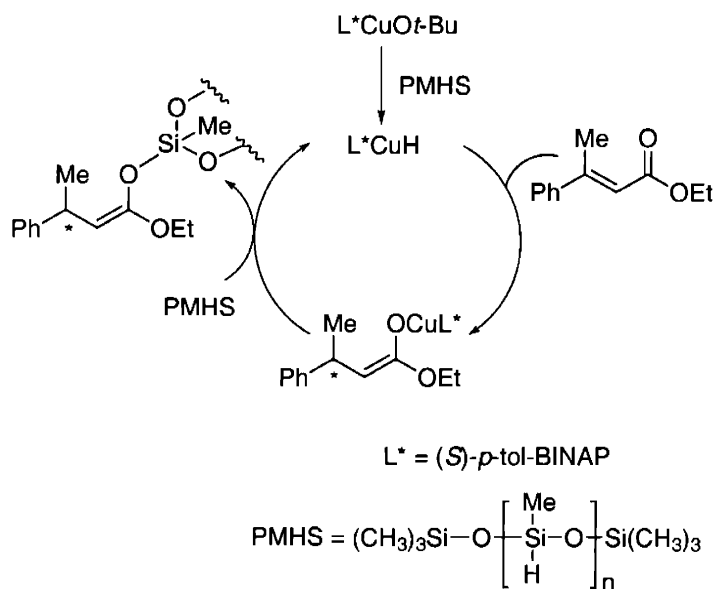


Figure 2. Copper-catalyzed asymmetric conjugate reduction α,β -unsaturated esters.

The proposed mechanism for this transformation is illustrated in Scheme 1.⁶ We postulated that mixing of CuCl, NaOt-Bu, and chiral bis-phosphine ligand results in a ((*S*)-*p*-tol-BINAP)CuOt-Bu species,⁷ which, upon addition of PMHS, undergoes σ -bond metathesis with siloxane⁸ to yield ((*S*)-*p*-tol-BINAP)CuH. The asymmetric conjugate reduction of the α,β -unsaturated ester results in a formation of copper enolate.⁹ Subsequent σ -bond metathesis with siloxane provides a silylketene acetal and regenerates the Cu-hydride catalyst.

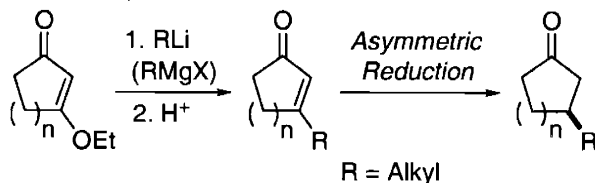


Scheme 1. Proposed mechanism for the copper-catalyzed conjugate reduction. Adapted with permission from Reference 6. Copyright 1999 American Chemical Society.

We were interested in extending this method to the preparation of the chiral β -substituted cyclic enones.

Results and Discussion

We envisioned that a procedure based on copper-catalyzed asymmetric conjugate reduction of β -substituted cyclic enones could provide a useful synthetic route to enantiomerically enriched β -substituted cyclic ketones (Scheme 2).¹⁰ Notably, the requisite β -substituted cyclic enones can be conveniently prepared via the Stork-Danheiser protocol (Scheme 2).¹¹



Scheme 2. Synthesis of chiral β -substituted cyclic ketones. Adapted with permission from Reference 10. Copyright 2000 American Chemical Society.

Efficient catalysts were generated in situ by combining a chiral bis-phosphine ((*S*)-*p*-tol-BINAP, (*S*)-BINAP or (*S*)-BIPHEMP),¹² CuCl, and NaO*t*-Bu in toluene, followed by the addition of PMHS and then the substrate. As shown in Table 1, cyclopentanones were obtained in high yields and excellent enantioselectivities. A number of cyclopentanones were prepared to test the catalyst's tolerance to functional groups and steric hindrance. Notably, substrates containing an isolated double bond (entry 5), a benzyl ether (entry 6), and an ester group (entry 7) were successfully reduced within 24 hours; in each instance, reduction products were obtained in high enantioselectivity and with the functional group intact. As anticipated, longer reaction times were required as the steric hindrance at the β -carbon atom increased. The reduction of 3-isopropylcyclopentenone (entry 8) proceeded to 90% completion after 3 days at 0 °C to afford the desired reduction product in 88% yield and 94% ee. Furthermore, cyclopentanones with substituents larger than an isopropyl group on the β -carbon did not undergo conjugate reduction under the reaction conditions. In particular, 3-*tert*-butyl cyclopentenone could not be successfully reduced. Additionally, we were unable to reduce 2,3-disubstituted cyclopentenones.

The conjugate reductions of β -substituted cyclohexenones and cycloheptenones gave the desired products in high enantiomeric excess. A pertinent study by Dr. Yasunori Moritani and Dr. Daniel H. Appella showed that for the reduction cyclohexenones (entries 9-10), the BIPHEMP-derived catalyst (Figure 3) afforded reduction products in higher enantiomeric excess than a catalyst derived from (*S*)-*p*-tol-BINAP or (*S*)-BINAP.

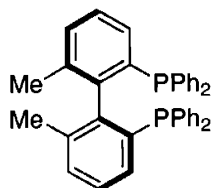


Figure 3. (*S*)-BIPHEMP.

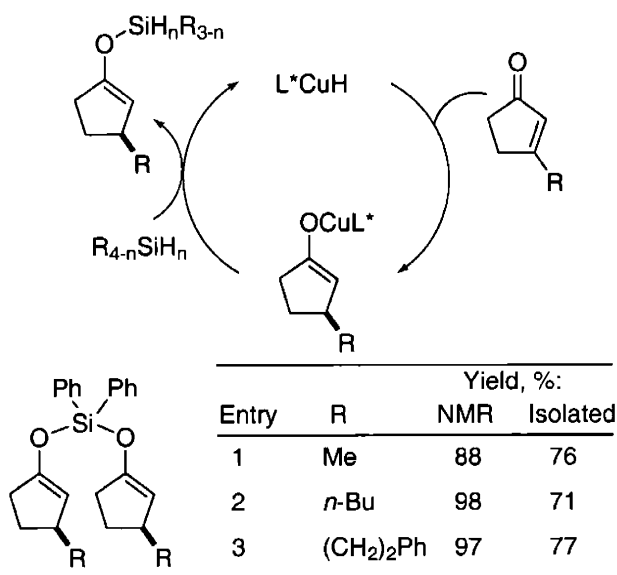
Table 1. Asymmetric conjugate reductions of β -substituted cyclic ketones with ((*S*)-*p*-tol-BINAP (5.0 Mol%), CuCl (5.0 Mol%), NaOt-Bu (5.0 Mol%), and PMHS (1.05 equiv).

Entry	Substrate	Product		Temp., °C	Yield, % ^a	ee, % ^b
1			R = Me	-78	42	94
2			<i>n</i> -Bu	0	84	98
3 ^c			CH ₂ Ph	0	78	96
4			CH ₂ CH ₂ Ph	0	86	94
5 ^c				15	87	96 ^d
6				0	91	94
7				0	86	92
8				0	88	94
9 ^c			R = Me	-78	61	92 ^e
10 ^c			<i>n</i> -Bu	0	82	87 ^e
11 ^c				0	82	96 ^d

^a Yields are the average of at least two isolated yields of >95% purity as determined by GC and ¹H NMR. ^b The average ee for at least two reactions is reported for each entry. The absolute stereochemistry of the products in entries 1, 2, 8, 9, and 10 was assigned by comparing the sign of their optical rotations to literature values. The absolute stereochemistry of all other products was assigned by analogy. ^c Reactions were performed by Dr. Yasunori Moritani and Dr. Daniel H. Appella. ^d (*S*)-BINAP was the ligand. ^e (*S*)-BIPHEMP was the ligand. Adapted with permission from Reference 10. Copyright 2000 American Chemical Society.

However, (*S*)-BINAP was the ligand of choice for the reduction of 3-phenethylcycloheptenone in which the desired product was obtained in 96% ee (entry 11). Notably, a competing 1,2-reduction of the substrate was observed in cases of 3-butylcyclohexenone (entry 10, 6% of 1,2-reduction product) and 3-phenethylcycloheptenone (entry 11, 9% of 1,2-reduction product).

Our current view is that a (bis-phosphine)CuH complex is the key intermediate in the catalytic cycle of the reduction. Conjugate reduction of cyclic enones by such complex should result in the formation of copper enolate⁹ that subsequently undergoes σ -bond metathesis with silane⁸ to form a silyl enol ether (Scheme 3).

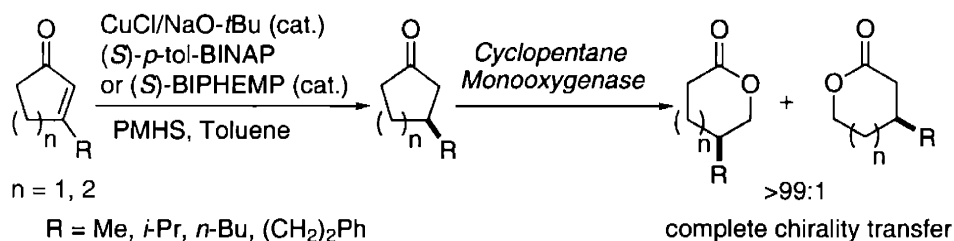


Scheme 3. Proposed catalytic cycle for the copper catalyzed asymmetric conjugate reductions of cyclic enones. Adapted with permission from Reference 10. Copyright 2000 American Chemical Society.

The evidence supporting this mechanism was obtained when silyl bis-(enol ethers) (Scheme 3, entries 1-3) were isolated as reduction products of the corresponding cyclopentenones. Since PMHS is a polymeric species, diphenylsilane was used as a stoichiometric reductant to enable us to fully characterize the silyl bis-(enol ethers) using

conventional methods (^1H and ^{13}C NMR, IR). Notably, treatment of the aforementioned silyl bis-(enol ethers) with tetra-butyl ammonium fluoride (TBAF) afforded the 3-alkylcyclopentanones with the same enantiomeric excess as the catalytic reduction with PMHS.

We then extended this method to the preparation of chiral 4- and 5-substituted lactones. As shown in Scheme 4, a combination of chemical catalysis and biocatalysis provided a convenient route to a number of these useful chiral compounds. The two-step procedure involved copper-catalyzed asymmetric conjugate reduction of β -substituted enones followed by a subsequent cell-catalyzed Baeyer-Villiger oxidation¹³ of the reduction products. A very high proximal regioselectivity and complete chirality transfer was obtained using a recombinant *E. coli* strain that overexpresses cyclopentanone monooxygenase (CPMO).¹⁴ The biocatalytic Baeyer-Villiger oxidations were developed and performed at Professor Margaret M. Kayser's laboratory.



Scheme 4. Access to chiral 4- and 5-substituted lactones via chemical-biocatalytical cooperation. Adapted with permission from Reference 14. Copyright 2003 American Chemical Society.

Conclusions

We have shown that the combination of catalytic amounts of CuCl , NaOt-Bu , and a chiral bis-phosphine with PMHS generates a highly enantioselective catalyst for the asymmetric conjugate reduction of α,β -unsaturated cyclic ketones. This catalyst reacts with cyclopentenones exclusively via 1,4-reduction. The reductions of cyclohexenones and cycloheptenones also gave 1,4-reduction products in high enantiomeric excess,

however, in some instances minor amounts (6-9 %) of the 1,2-reduction products were obtained.

This study led to the application of similar (bis-phosphine)-CuH catalytic systems to the asymmetric conjugate reductions of α,β -unsaturated lactones and lactams,¹⁵ acyclic enones,¹⁶ and β,β -disubstituted nitroalkenes.¹⁷

Experimental Section

General considerations. THF, Et₂O, and C₆D₆ were distilled under argon from sodium/benzophenone ketyl. Toluene was distilled under argon from molten sodium. CuCl (99.995%) and (*S*)- and (*R*)-*p*-tol-BINAP were purchased from Strem. NaOt-Bu, PMHS, and benzyl 4-bromobutylether were purchased from Aldrich. (*S*)-BINAP was a gift from Pfizer, (*S*)-BIPHEMP was a gift from Hoffman-LaRoche. All other reagents were available from commercial sources and were used without further purification.

All manipulations involving air-sensitive materials were conducted in a Vacuum Atmospheres drybox under an atmosphere of nitrogen. Unless stated otherwise, all reactions were conducted in flasks sealed with rubber septum or teflon screw cap under a positive pressure of argon.

Flash chromatography was performed on a E. M. Science Kieselgel 60 (230-400 mesh) silica. Yields refer to isolated compounds of greater than 95% purity as estimated by capillary GC and ¹H NMR. Yields reported in this section refer to a single experiment, while those reported in the tables are an average of two or more runs, so the numbers may differ slightly. All new chiral ketones that were prepared using copper-catalyzed asymmetric conjugate reduction were characterized by ¹H NMR, ¹³C NMR, and IR spectroscopy, in addition to elemental analysis (Atlantic Microlabs, Inc.) or high resolution mass spectrometry (HRMS).

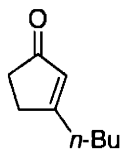
Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury 300, a Varian Unity 300, or a Varian Inova 500. The splitting patterns are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; td, triplet of doublets; q,

quartet; qd, quartet of doublets; m, multiplet. All ^1H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (0.00 ppm). All ^{13}C NMR chemical shifts (δ) are reported in ppm relative to deuteriochloroform (77.23 ppm), and all were obtained with ^1H decoupling. Infrared (IR) spectra were recorded on an ASI Applied Systems ReactIR 1000 (liquids were measured neat on a DiComp probe).

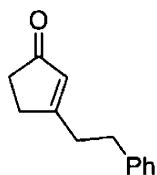
Melting points were measured on a Mel-Temp apparatus. Gas chromatography (GC) analyses were performed on a Hewlett-Packard 6890 gas chromatograph with an FID detector using a 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase. GC-mass spectrometry (GC-MS) analyses were performed on a Hewlett-Packard G1800B gas chromatograph with a electron ionization detector using the same GC column described above. Chiral GC analyses were performed on a Hewlett-Packard 5890 gas chromatograph using a Chiraldex G-TA column (20 m x 0.25 mm). Chiral HPLC analyses were performed on a Hewlett-Packard 1100 system with an HP 1100 Diode Array Detector (monitoring at 254, 225, and 210 nm) using a Chiracel OD or OJ column (25 cm x 0.46 cm).

Racemic compounds analogous to the enantiomerically enriched compounds described below were prepared by reduction of the olefin substrates under hydrogen atmosphere catalyzed by Pd/C, except for 3-(5-hexenyl)cyclopentanone and 3-benzyloxybutyl-cyclopentenone. The latter cyclic enones were reduced using 5% $[(\text{PPh}_3)\text{CuH}]_6$ and stoichiometric phenylsilane.^{5b} The HPLC or GC retention times of the racemic products were the same as those of the enantiomerically enriched products.

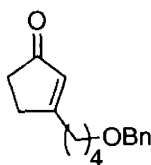
I. General Procedure for the synthesis of substrates (β -substituted- α,β -unsaturated cyclic ketones).



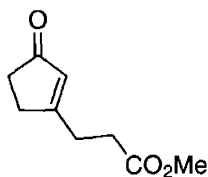
3-Butylcyclopentenone. To a cold (0 °C), stirred solution of *n*-BuLi (18.8 mL, 30.0 mmol, 1.6 M in hexane) in a Schlenk flask was added a solution 3-ethoxycyclopentenone (2.52 g, 20.0 mmol) in dry THF (40 mL) via syringe. The resulting mixture was stirred at room temperature for 12 hours. Aqueous 1 M HCl (40 mL) was slowly added, the layers were separated and the aqueous phase was extracted 3x with diethyl ether. The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes:ethyl acetate) on silica afforded the product as a colorless liquid (1.76 g, 64% yield). Spectroscopic data were consistent with previously reported data for this compound.¹⁸



3-Phenethylcyclopentenone. General Procedure for the preparation of substrates using 3-ethoxycyclopentenone (1.45 g, 11.5 mmol) and phenethylmagnesium chloride (23.0 mmol, 1 M in THF) gave, after flash chromatography (4:1 hexanes:ethyl acetate), the title compound as a white solid (2.01 g, 94% yield). Melting point: 39-40 °C. Spectroscopic data were consistent with previously reported data for this compound.¹⁹

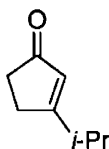


3-Benzyloxybutylcyclopentenone. Mg turnings (0.30 g, 12.4 mmol) and an iodine crystal were placed into a dry Schlenk flask, then THF (5.5 mL) was added. 1-Bromo-4-benzyloxybutane (2.75 g, 11.3 mmol) was placed into a separate dry flask, dissolved in THF (5.5 mL), then added via syringe to the Mg turnings. The resulting mixture was heated at 60 °C for 16 hours, then cooled to room temperature. The solution of Grignard reagent was then separated from the remaining Mg solid by transferring the solution via syringe to another Schlenk flask. General Procedure for the preparation of substrates using 3-ethoxycyclopentenone (0.67 mL, 5.65 mmol) gave, after 12 hours and flash chromatography (3:1, then 2:1 hexanes:ethyl acetate), the title compound as a white solid (0.66 g, 48% yield). Melting point: 46-47 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.34-7.25 (m, 5 H), 5.94 (s, 1 H), 4.50 (s, 2 H), 3.49 (t, *J* = 6.0 Hz, 2 H), 2.58-2.55 (m, 2 H), 2.41-2.38 (m, 3 H), 1.70-1.67 (m, 4 H). ¹³C NMR (75 MHz, CDCl₃): δ 210.2, 182.9, 138.6, 129.7, 128.6, 127.8, 127.7, 73.3, 70.0, 35.6, 33.6, 31.8, 29.8, 24.2. IR (neat): 2941, 2853, 1710, 1613, 1451, 1366, 1185, 1119, 1000, 842, 749 cm⁻¹.



3-(3-Oxo-cyclopent-1-enyl)-propionic acid methyl ester. This compound was synthesized according to a published procedure.²⁰ A dry round bottom flask was charged with cyclopentenone (0.55 mL, 6.54 mmol) and THF (13 mL). To this, at room temperature, tri-phenylphosphine (1.80 g, 6.86) and *tert*-butyl-dimethylsilyl triflate (1.5 mL, 6.54 mmol) were added and the resulting mixture was stirred for 1.5 hours. The clear

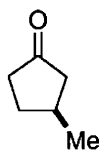
solution was then cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of *n*-BuLi in hexane (4.10 mL, 1.0 M) was added dropwise. The reaction was stirred for 10 min at $-78\text{ }^{\circ}\text{C}$, then warmed to $0\text{ }^{\circ}\text{C}$. The resulting dark purple solution was cooled to $-78\text{ }^{\circ}\text{C}$ and methylacrylate (0.62 mL, 6.86 mmol) followed by tri-methylsilyl triflate (1.24 mL, 6.86 mmol) were added. The resulting clear solution was stirred for 1 hour at $-78\text{ }^{\circ}\text{C}$, then 2 mL of isopropanol were slowly added at this temperature. The mixture was then allowed to warm to room temperature and 5 mL of water were added. The aqueous phase was separated and extracted 3x with diethyl ether. The combined organic phases were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash chromatography (3:1, then 1:1 hexanes:ethyl acetate) afforded the product as a colorless oil (1.76 g, 64% yield). Spectroscopic data were consistent with previously reported data for this compound.²¹



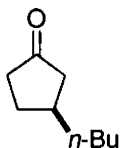
3-Isopropylcyclopentenone. Isopropylmagnesium chloride (5.0 mL, 10.0 mmol, 2 M in diethyl ether) was placed in a dry flask and cooled to a $0\text{ }^{\circ}\text{C}$. 3-Ethoxycyclopentenone (0.88 g, 7.0 mmol) was added dropwise to the solution of the Grignard reagent, and the resulting mixture was stirred at room temperature for 23 hours. At this point, 1 M HCl (15 mL) was added gradually, the aqueous phase was separated and extracted 3x with diethyl ether. The combined organic phases were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The product was purified first by Kugelrohr distillation (0.1 torr, $120\text{ }^{\circ}\text{C}$), then by flash chromatography (1:1 pentane:diethyl ether) to afford the title compound as a colorless liquid (0.17 g, 20% yield). Spectroscopic data were consistent with previously reported data for this compound.²²

II. General Procedure for the asymmetric conjugate reduction of α,β -unsaturated β -substituted cyclic ketones.

A chiral bis-phosphine ((*S*)-*p*-tol-BINAP, (*S*)-BINAP, or (*S*)-BIPHEMP) (0.05 mmol) was placed in to a flame-dried Schlenk tube and dissolved in toluene (2 mL). The Schlenk tube was moved into a nitrogen-filled drybox. In the drybox, NaOt-Bu (5.0 mg, 0.05 mmol) and CuCl (5.0 mg, 0.05 mmol) were weighed into a vial. The toluene solution of the chiral bis-phosphine was added via pipet to the vial to dissolve the solids and the resulting solution was then transferred back into the Schlenk tube. The Schlenk tube was removed from the drybox, the solution was stirred 10-20 min, and PMHS (0.063 mL, 1.05 mmol) was added to the solution under argon purge. The resulting solution turned a reddish orange color. The solution was then cooled to the specified temperature. The α,β -unsaturated ketone (1.0 mmol) was added to the reaction solution under argon purge and the resulting solution was stirred for the indicated period of time. Consumption of the α,β -unsaturated ketone was monitored by GC. When the reaction was complete, the Schlenk tube was opened and water (1 mL) was added. The resulting solution was diluted with diethyl ether, washed 1x with water, 1x with brine, and back-extracted with diethyl ether. To the combined organic extracts was added TBAF (1 mmol, 1 M in THF) and the resulting solution stirred for 3 hours. The solution was the washed 1x with water, 1x with brine, and back-extracted with diethyl ether and the organic layer was dried over MgSO₄. The solvent was then removed *in vacuo* and the product was purified by silica column chromatography.



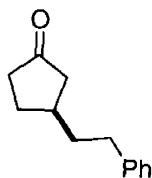
3-(*S*)-Methylcyclopentanone (Table 1, entry 1). General Procedure using (*S*)-*p*-tol-BINAP and 3-methylcyclopentanone (0.1 mL, 1.0 mmol) gave, after 24 hours at -78 °C, the title compound in 86% GC yield. Purification by flash chromatography (3:1 pentane: diethyl ether) afforded the pure product as a clear liquid (0.04 g, 44% yield). Spectroscopic data were identical with commercially available (*R*)-3-methylcyclopentanone; $[\alpha]_{\text{D}}^{25^\circ\text{C}} -156^\circ$ (*c* 0.91, CHCl_3). Commercially available (*R*)-3-methylcyclopentanone had $[\alpha]_{\text{D}}^{25^\circ\text{C}} +143^\circ$ (*c* 1.0, CHCl_3). Chiral GC analysis (Chiraldex G-TA column) indicated that the title compound was obtained in 94% ee.



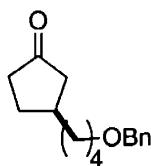
3-(*S*)-Butylcyclopentanone (Table 1, entry 2). General Procedure using (*S*)-*p*-tol-BINAP and 3-butylcyclopentanone (0.138 mL, 1.0 mmol) gave, after 12 hours at 0 °C and flash chromatography (20:1 hexanes:ethyl acetate), the title compound as a clear oil (0.126 g, 90% yield). Spectroscopic data were consistent with previously reported data for this compound.²³ $[\alpha]_{\text{D}}^{25^\circ\text{C}} -157^\circ$ (*c* 1.14, CHCl_3) (lit.²⁴ $[\alpha]_{\text{D}}^{25^\circ\text{C}} -59^\circ$ (*c* 3.30, CHCl_3) for 46% ee); $[\alpha]_{\text{D}}^{25^\circ\text{C}} -143^\circ$ (*c* 1.13, toluene) (lit.²³ $[\alpha]_{\text{D}}^{25^\circ\text{C}} -87^\circ$ (*c* 1.2, toluene) for 65% ee). In order to determine the ee, the product was converted to the corresponding 2,3-(*R,R*)-dimethylethylene ketal (see procedure below), and the GC analysis (Chiraldex G-TA) of the diastereomeric ketals indicated that the title compound was obtained in 97% ee.

General Procedure A for conversion of β -substituted ketones to diastereomeric 2,3-(*R,R*)-dimethylethylene ketals for the determination of the enantiomeric excess.²⁵

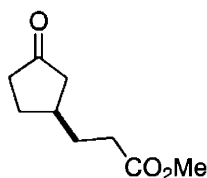
3-Butylcyclopentanone (24.0 mg, 0.17 mmol) was dissolved in toluene (1 mL), *p*-toluenesulfonic acid (1.0 mg) and 2,3-(*R,R*)-butanediol (0.03 mL, 0.344 mmol) were added and the resulting solution was heated at 120 °C for 30 min. The solution was cooled to room temperature, poured into water, diluted with diethyl ether, washed 1x with water, and washed 1x with brine. The organic layer was dried over MgSO₄, and the solvent removed *in vacuo*. The two diastereomeric ketals were separated by chiral GC (Chiraldex G-TA). This procedure was performed on both racemic ketones and optically enriched ketones that were obtained using the asymmetric conjugate reduction protocol. Crude yields of the ketal were 95% or greater.



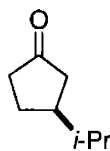
3-(*S*)-Phenethylcyclopentanone (Table 1, entry 4). General Procedure using (*S*)-*p*-tol-BINAP and 3-phenethylcyclopentanone (0.186 g, 1.0 mmol) gave, after 24 hours at 10 °C and flash chromatography (10:1 hexanes:ethyl acetate), the title compound as a clear oil (0.159 g, 84% yield). Spectroscopic data were consistent with previously reported data for this compound. Chiral HPLC analysis (Chiracel OD column) indicated that the title compound was obtained in 97% ee.²⁶



3-(S)-Benzyloxybutylcyclopentanone (Table 1, entry 6). General Procedure using (*S*)-*p*-tol-BINAP and 3-benzyloxybutylcyclopentanone (0.146 g, 0.6 mmol) gave, after 30 hours at 0 °C and flash chromatography (1:2 pentane:diethyl ether), the title compound as a clear oil (0.139 g, 94% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.37-7.23 (m, 5 H), 4.50 (s, 2 H), 3.47 (t, *J* = 6.3 Hz, 2 H), 2.43-2.04 (m, 5 H), 1.78 (ddd, *J* = 18.0, 9.6, 1.2 Hz, 1 H), 1.70-1.56 (m, 2 H), 1.56-1.34 (m, 5 H). ¹³C NMR (75 MHz, CDCl₃): δ 219.8, 138.6, 128.4, 127.7, 127.6, 73.1, 70.3, 45.4, 38.7, 37.4, 35.7, 30.0, 29.7, 24.8. IR (neat): 2934, 2860, 1741, 1455, 1405, 1363, 1158, 1100, 737, 699 cm⁻¹. HRMS *m/z* calcd for C₁₆H₂₂O₂ 246.1620, obsd 246.1615. [α]_D^{25°C} -89° (*c* 1.4, CHCl₃). Chiral HPLC analysis (Chiracel OD column) indicated that the title compound was obtained in 94% ee.



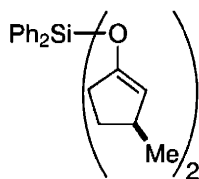
3-(S)-(3-Oxo-cyclopentyl)-propionic acid methyl ester (Table 1, entry 7). General Procedure using (*S*)-*p*-tol-BINAP and 3-(3-oxo-cyclopent-1-enyl)-propionic acid methyl ester (0.084 g, 0.5 mmol) gave, after 24 hours at 0 °C and flash chromatography (4:1, then 2:1 hexane:ethyl acetate), the title compound as a clear oil (0.075 g, 88% yield). Spectroscopic data were consistent with previously reported data for this compound.²⁷ [α]_D^{25°C} -112° (*c* 1.3, CHCl₃). Conversion of the title compound to the corresponding benzyl ester followed by chiral HPLC analysis (Chiracel OD column) indicated that the title compound was obtained in 91% ee.



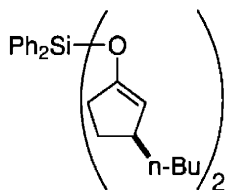
3-(S)-Isopropylcyclopentanone (Table 1, entry 8). General Procedure using (*S*)-*p*-tol-BINAP and 3-isopropylcyclopentanone (0.11 g, 0.9 mmol) gave, after 3 days at 0 °C and Kugelrohr distillation (0.4 torr, 220 °C) followed by flash chromatography (10:1pentane:diethyl ether), the title compound as a clear liquid (0.10 g, 88% yield). Spectroscopic data were consistent with previously reported data for this compound.²⁸ $[\alpha]_D^{25^\circ\text{C}}$ -200° (*c* 1.6, CHCl₃) (lit.²⁸ $[\alpha]_D^{25^\circ\text{C}}$ -110° (*c* 1.0, CHCl₃) for 60% ee). Chiral GC analysis (Chiraldex G-TA column) indicated that the title compound was obtained in 94% ee.

III. General Procedure B for the asymmetric conjugate reduction of α,β -unsaturated cyclic ketones and isolation of bis-(silylenol ethers).

The reaction was performed using the General Procedure, except that Ph₂SiH₂ was added to the reaction instead of PMHS. After stirring for the specified time at the specified temperature, the reaction was warmed to the room temperature, and the solvent was removed *in vacuo*. The Schlenk flask was moved into the inert gas-filled dry box, and 1,4-dimethoxybenzene (5.0 mg) was added to the crude mixture. Analysis by ¹H NMR (anhydrous C₆D₆) indicated the approximate yield of the bis-(silylenol ether) (yield calculated from integrations of the signal of vinylic protons of the product relative to that of the methoxy protons of the 1,4-dimethoxybenzene). The solvent was then removed *in vacuo*, and the product was purified by flash chromatography (EM Science Silica gel 60, 3 cm diameter column, 8 cm silica, 2 mL fractions, R_f 0.4 - 0.5) eluting with 50:1 pentane:diethyl ether.

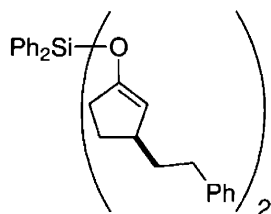


Bis-(silylenol ether) from the reduction of 3-methylcyclopentenone (Scheme 3, entry 1). General Procedure B for the reduction and isolation of bis-(silylenol ethers) using 3-methylcyclopentenone (0.10 mL, 1.01 mmol) and Ph_2SiH_2 (0.10 mL, 0.53 mmol) gave, after 4 hours at $-78\text{ }^\circ\text{C}$, an 88% NMR yield of the title compound. Purification by flash chromatography gave the title compound as a clear oil (0.148 g, 78% yield). ^1H NMR (500 MHz, C_6D_6): δ 7.87-7.84 (m, 4 H), 7.15-7.12 (m, 6 H), 4.99-4.98 (m, 2 H), 2.58-2.55 (m, 2 H), 2.44-2.36 (m, 4 H), 1.90-1.83 (m, 2 H), 1.30-1.17 (m, 2 H), 0.86 (d, $J = 6.5\text{ Hz}$, 6 H). ^{13}C NMR (125 MHz, C_6D_6): δ 153.2, 135.2, 132.4, 130.8, 128.1, 111.4, 36.5, 33.3, 30.5, 22.3. IR (neat): 3072, 2952, 2865, 1648, 1594, 1455, 1430, 1370, 1343, 1324, 1227, 1183, 1127, 1117, 1083, 1028 cm^{-1} . Anal. calcd. for $\text{C}_{24}\text{H}_{28}\text{SiO}_2$: C, 76.55; H, 7.49. Found: C, 76.60; H, 7.60.



Bis-(silylenol ether) from the reduction of 3-butylcyclopentenone (Scheme 3, entry 2). General Procedure B for the reduction and isolation of bis-(silylenol ethers) using 3-butylcyclopentenone (0.162 g, 1.17 mmol) and Ph_2SiH_2 (0.11 mL, 0.61 mmol) gave, after 4 hours at $0\text{ }^\circ\text{C}$, an 98% NMR yield of the title compound. Purification by flash chromatography gave the title compound as a clear oil (0.188 g, 70% yield). ^1H NMR (500 MHz, C_6D_6): δ 7.90-7.86 (m, 4 H), 7.15-7.13 (m, 6 H), 5.08-5.07 (m, 2 H), 2.51-2.41 (m, 6 H), 1.91-1.84 (m, 2 H), 1.34-1.07 (m, 14 H), 0.82 (t, $J = 7.0\text{ Hz}$, 6 H). ^{13}C

NMR (125 MHz, C_6D_6): δ 153.4, 135.2, 132.4, 130.9, 128.2, 109.9, 42.0, 37.1, 33.1, 29.9, 28.5, 23.2, 14.3. IR (neat): 3072, 2954, 2921, 2852, 1648, 1594, 1457, 1430, 1378, 1339, 1225, 1183, 1127, 1117, 1054, 1044 cm^{-1} . Anal. calcd. for $C_{30}H_{40}SiO_2$: C, 78.21; H, 8.75. Found: C, 78.29; H, 8.78.



Bis-(silylenol ether) from the reduction of 3-phenethylcyclopentenone (Scheme 3, entry 3). General Procedure B for the reduction and isolation of bis-(silylenol ethers) using 3-phenethylcyclopentenone (0.143 g, 0.77 mmol) and Ph_2SiH_2 (0.075 mL, 0.404 mmol) gave, after 2 hours at 0 °C, an 97% NMR yield of the title compound. Purification by flash chromatography gave the title compound as a clear oil (0.168 g, 79% yield). 1H NMR (500 MHz, C_6D_6): δ 7.89-7.86 (m, 4 H), 7.15-7.11 (m, 10 H), 7.06-7.03 (m, 2 H), 6.99-6.97 (m, 4 H), 5.07-5.06 (m, 2 H), 2.50-2.34 (m, 10 H), 1.87-1.80 (m, 2 H), 1.52-1.41 (m, 4 H), 1.32-1.26 (m, 2 H). ^{13}C NMR (125 MHz, C_6D_6): δ 153.7, 142.8, 135.2, 130.9, 128.6, 128.4, 128.2, 128.1, 125.8, 109.5, 41.5, 39.2, 34.0, 33.1, 28.3. IR (neat): 3062, 3027, 2923, 2850, 1648, 1603, 1594, 11495, 1455, 1430, 1345, 1225, 1185, 1127, 1117, 1081, 1057. 1030 cm^{-1} . Anal. calcd. for $C_{38}H_{40}SiO_2$: C, 81.97; H, 7.24. Found: C, 82.13; H, 7.30.

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Chapter 2.
Dynamic Kinetic Resolution via Asymmetric Conjugate Reduction:
Enantio- and Diastereoselective Synthesis of
2,4-Dialkyl Cyclopentanones

Background and Introduction

Kinetic resolution has been long recognized as an effective tool for the preparation of enantiomerically enriched compounds.¹ Kinetic resolution can be defined as a process in which two enantiomers of a racemate are transformed to the products at different rates, $k_R \neq k_S$, where k is the rate constant for the R and S enantiomers. If kinetic resolution is efficient, one enantiomer undergoes transformation to the product at much higher rate ($k_R \gg k_S$) than the other one (Figure 1). Thus, such consumption of one enantiomer of a racemate leads to enantiomerically enriched unreacted starting material.

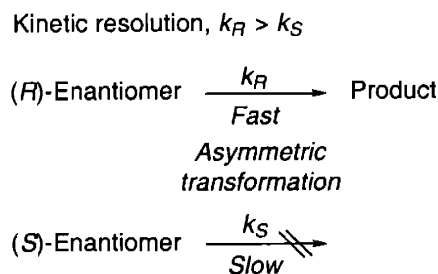


Figure 1. Kinetic resolution.

The selectivity factor, s , for kinetic resolution is proportional to the ratio between fast- and slow-reacting enantiomers of the racemic starting material (equation 1). Notably, the selectivity factor is independent of conversion.^{1a}

$$s = \frac{k(\text{fast-reacting enantiomer})}{k(\text{slow-reacting enantiomer})} \quad (1)$$

The process has the limitation of having a maximum yield of 50%. In contrast, a procedure that facilitates in situ epimerization of the less reactive enantiomer under the reaction condition would allow for a quantitative conversion of the racemic starting material into a single stereoisomer of the product (Figure 2). This process is known as dynamic kinetic resolution.²

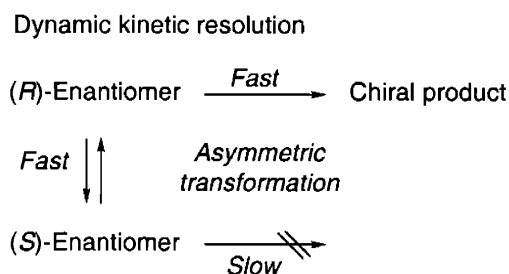
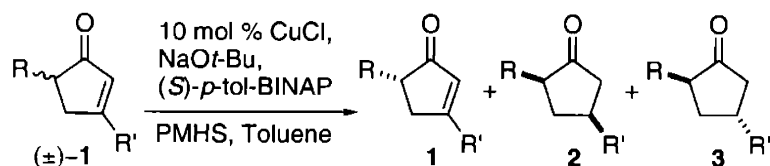


Figure 2. Dynamic kinetic resolution.

We envisioned that the racemic disubstituted α,β -unsaturated cyclic ketones ((\pm)-**1**) could undergo kinetic resolution under the copper-catalyzed asymmetric conjugate reduction conditions³ (Scheme 1). Furthermore, we thought that the in situ epimerization of the unreactive enantiomer would lead to the dynamic kinetic resolution of the substituted cyclic enones.



Scheme 1. Kinetic resolution of 3,5-dialkylcyclopentenones via asymmetric conjugate reduction.

Results and Discussion

The different rates of reaction for the enantiomers of racemic 3,5-dialkylcyclopentenones in the asymmetric copper-catalyzed conjugate reduction enabled us to perform efficient kinetic resolution of these substrates. As is shown in Table 1, high selectivity factors⁴ (*s*) were obtained under the kinetic resolution conditions regardless of the alkyl substituent at the 5-position.⁵ In cases where primary alkyl and methyl groups were at the 5-position (entries 1, 2, 5-7), the reductions were performed at low temperatures (-50 to -70 °C) in order to obtain high selectivity. Notably, high diastereomeric ratios (*dr*) were observed for all reduction products **2** under the kinetic

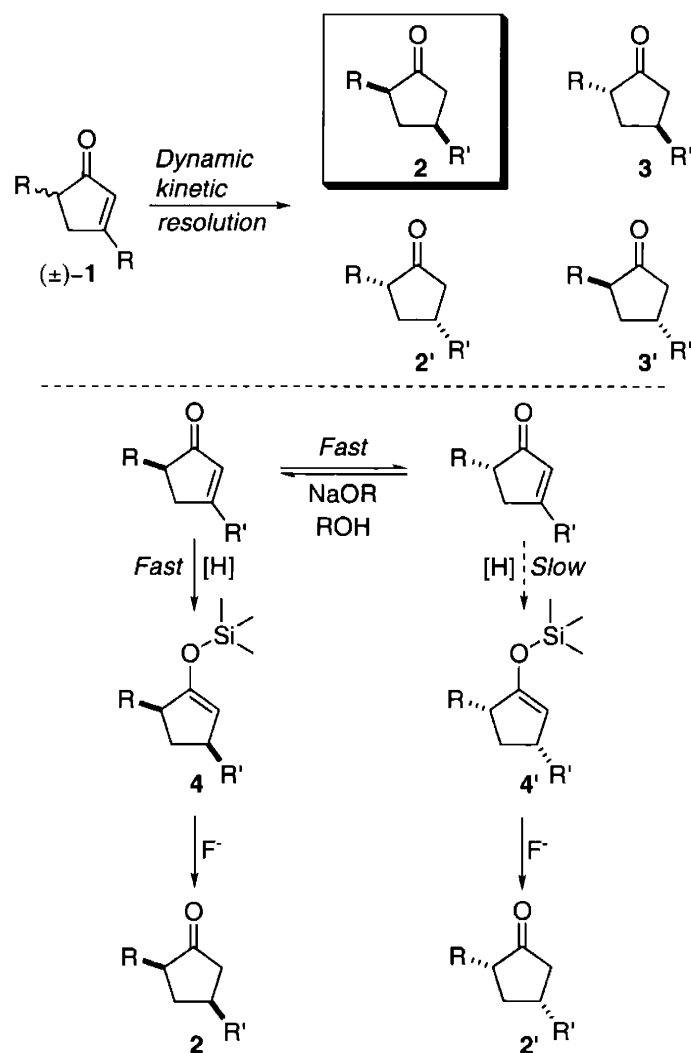
resolution conditions ($dr \geq 92:8$).⁶ It is important to note that the kinetic resolution of 3,4-dialkylcyclopentenones gave lower s values (< 10).

Table 1. Kinetic resolution of 3,5-dialkylcyclopentenones.

Entry	1	R	ee (%) ^b of 1 (conversion (%)) ^c	s^d
1 ^a		(1a) Me	94.6 (55.6) ^e	26
2		(1b) <i>n</i> -Bu	90.6 (53.2) ^e	27
3		(1c) <i>i</i> -Pr	97.4 (56.5) ^f	30
4		(1d) <i>t</i> -Bu	91.0 (50.7) ^f	52
5		(1e) CH ₂ CO ₂ <i>t</i> -Bu	95.3 (56.0) ^g	25
6		(1f)	95.6 (56.0) ^e	26
7		(1g)	71.6 (43.6) ^{e,h}	32

^a See Experimental Section of Chapter 2 for absolute stereochemistry determination of **1a**. ^b Determined by HPLC. ^c Reaction time = 4-12 h. ^d Selectivity factors (s) (averages of two or more runs). The % ee and conversion reported are for specific runs. ^e Reaction at -78 °C. ^f Reaction at 0 °C. ^g Reaction at -50 °C. ^h Reaction time = 72 h. Adapted with permission from Reference 5. Copyright 2002 American Chemical Society.

Encouraged by our kinetic resolution results, we sought to extend this method to the dynamic kinetic resolution of 3,5-dialkylcyclopentenones (Scheme 2). We previously postulated^{3b} that upon asymmetric conjugate reduction of the enone, a copper enolate⁷ intermediate is formed. Subsequent σ -bond metathesis with silane⁸ yields silyl enol ether^{3b} **4** and regenerates the Cu-hydride catalyst. We reasoned that if the reduction was performed under basic conditions (e.g., NaO*t*-Bu, LiHMDS), rapid racemization of the starting material should occur. Furthermore, since the product ketone is masked as silyl enol ether **4**, epimerization at the α -stereocenter of the desired product would be obviated.



Scheme 1. Dynamic kinetic resolution of 3,5-dialkylcyclopentenones. Adapted with permission from Reference 5. Copyright 2002 American Chemical Society.

In our initial studies, we determined that the use of amide bases in the dynamic kinetic resolution resulted in low conversions and poor enantioselectivities. Fortuitously, it was discovered that stoichiometric NaOt-Bu could effect the racemization of **1** at temperatures as low as $-50\text{ }^\circ\text{C}$ in toluene. Unfortunately, this epimerization was too slow relative to the rate of conjugate reduction under these conditions. However, addition of *t*-BuOH (5 equiv) as a kinetically labile proton source dramatically enhanced the rate of

Table 2. Dynamic kinetic resolution of 3,5-dialkylcyclopentenones.

Entry	2	R	Yield (%) ^b	<i>syn:anti</i> ^c	ee (%) ^c
1 ^a		(2a) Me	89 ^d	91:9	91
2		(2c) <i>i</i> -Pr	94 ^e	93:7	93
3		(2d) <i>t</i> -Bu	94 ^f	93.5:6.5	94
4		(2e) CH ₂ CO ₂ <i>t</i> -Bu	91 ^d	90:10	93
5		(2f)	95 ^d	91.5:8.5	93
6		(2g)	90 ^{d,g}	96.5:3.5	91

^a See Experimental Section for Chapter 2 for the determination of relative and absolute stereochemistry of **2a**. Absolute stereochemistry of all other products was assigned by analogy to **2a**. ^b Isolated yield (sum of both diastereomers; average of at least two runs of > 95% purity as determined by GC, ¹H and ¹³C NMR). ^c Determined by HPLC. Average % ee and dr for at least two runs. ^d Reaction at -50 °C. ^e Reaction at -30 °C. ^f Reaction at 0 °C. ^g 3.1 equiv of PMHS and 2.4 equiv of NaO*t*-Bu, reaction time = 48 h. Adapted with permission from Reference 5. Copyright 2002 American Chemical Society.

racemization, resulting in the production of **2** in high enantiomeric and diastereomeric excesses (Table 2).

PMHS proved to be the silane of choice; the use of more reactive silanes (e.g., Ph₂SiH₂) resulted in diminished enantioselectivities. In most cases where the α-substituent was either Me or 1° alkyl, it was necessary to perform the dynamic kinetic resolutions at higher temperatures than the corresponding kinetic resolutions, presumably in order to achieve efficient racemization of **1** (Table 2, entries 1, 4-6). In contrast, carrying out the dynamic kinetic resolution of isopropyl-substituted ketone **1c** at 0 °C (the optimum temperature for the kinetic resolution) resulted in a diminished diastereomeric ratio (85:15). We hypothesized that this was due to competitive partial decomposition of

silyl enol ether **4** and subsequent epimerization. Thus, lowering the reaction temperature to -30 °C allowed for the clean conversion of (\pm)-**1c** (94% yield, 93% ee, 93:7 dr). Greater than 95% conversion of the starting material to the desired reduction product was observed in all reactions.

Conclusions

The method described above represents an example of a dynamic kinetic resolution with simultaneous creation of two non-adjacent chiral centers. The combination of catalytic amounts of CuCl, a commercially available chiral bis-phosphine, and NaOt-Bu with PMHS generates a highly enantio- and diastereoselective complex that reacts exclusively via 1,4-reduction. The dynamic kinetic resolution conditions for this catalytic system were achieved by employing stoichiometric amounts of NaOt-Bu and *t*-BuOH.

Experimental Section

General considerations. Toluene, THF, and Et₂O were purchased from J. T. Baker in CYCLE-TAINER[®] solvent delivery kegs, which were vigorously purged with argon for 2 h. Toluene was further purified by passing through two packed columns of neutral alumina and copper (II) oxide under argon pressure. THF and Et₂O were further purified by passing through a column of neutral alumina.⁹

CuCl (99.995%) was purchased from Strem and NaOt-Bu was purchased from Aldrich and stored in a nitrogen-filled drybox. PMHS and anhydrous *t*-BuOH were purchased from Aldrich, (*S*)-*p*-tol-BINAP was purchased from Strem. All other reagents were available from commercial sources and were used without further purification, unless otherwise noted. All manipulations involving air-sensitive materials (but not the reactions) were conducted in a Vacuum Atmospheres drybox under an atmosphere of

nitrogen or argon. All reactions, unless otherwise noted, were carried out in flasks sealed with a rubber or teflon screw septum under an atmosphere of argon.

Analytical thin layer chromatography was performed using E.M. Reagents 0.25 mm silica gel 60 plates, and visualization was accomplished with potassium permanganate. Flash chromatography was performed on E.M. Science Kieselgel 60 (230-400 mesh).

Yields refer to isolated yields of compounds of greater than 95% purity as estimated by capillary GC and ^1H NMR. Yields reported in this section refer to a single experiment, while those reported in the tables are an average of two or more runs, so the numbers may differ slightly from those reported in the tables.

All new compounds were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy, in addition to elemental analysis (Atlantic Microlabs, Inc) or high resolution mass spectrometry (Finnegan MAT System 8200 spectrometer).

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian Mercury 300, a Varian Unity 300, or a Varian Inova 500. Splitting patterns are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; td, triplet of doublets; q, quartet; qd, quartet of doublets; m, multiplet. All ^1H NMR spectra are reported in units of chemical shift δ , parts per million (ppm) downfield from tetramethylsilane. All ^{13}C NMR spectra are reported in ppm relative to deuteriochloroform (77.23 ppm), and all were obtained with ^1H decoupling.

Infrared (IR) spectra were recorded on an ASI Applied Systems ReactIR 1000 (liquids and solids were measured neat on a DiComp probe). Melting points (uncorrected) were obtained on a Mel-Temp capillary melting point apparatus. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Gas chromatography (GC) analyses were performed on a Hewlett-Packard 6890 gas chromatograph with an FID detector using 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase. GS-mass spectrometry (GC-MS)

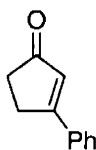
analyses were performed on a Hewlett-Packard G1800B gas chromatograph with an electron ionization detector using the same GC column described above.

Chiral HPLC analysis were performed on a Hewlett-Packard 1100 system with an HP 1100 Diode Array Detector (monitoring at 254, 225, and 210 nm) using a Chiralpak AD and Chiralcel OB, OD, OD-H, and OJ columns (25 cm x 0.46 cm). Chiral semi-preparative HPLC separation was performed on Waters 515 HPLC Pump and Waters Lambda-Max Model 481 LC Spectrophotometer using semi-preparative Chiralcel OD column (1 cm x 25 cm). Racemic compounds analogous to the enantio- and diastereomerically enriched compounds described below were prepared by reduction of the corresponding olefin substrates under hydrogen atmosphere catalyzed by Pd/C. The HPLC or GC retention times of racemic products were the same as those of the enantiomerically enriched products.

Preparation of Substrates.

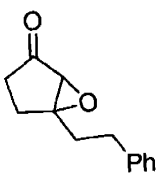
I. Procedures for the synthesis of 3-alkylcyclopentenones.¹⁰

3-Phenethylcyclopentenone and 3-isopropylcyclopentenone were prepared using procedures described in Experimental Section of Chapter 1.



3-Phenylcyclopentenone. Phenyllithium (5.60 mL, 10.1 mmol, 1.8 M in cyclohexane:Et₂O 7:3) was placed into an oven-dried Schlenk flask and cooled to 0 °C. 3-Ethoxycyclopentenone (0.64 g, 5.50 mmol) was added to a separate dry flask, dissolved in THF (8 mL), then added via syringe to the phenyllithium solution. The resulting solution was stirred at room temperature for 16 hours. At this point, the reaction was

cooled to 0 °C and 1 M HCl (20 mL) was gradually added until pH=0. The aqueous phase was separated and extracted three times with diethyl ether. The combined organic phases were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (2:1, then 1:1 hexane:Et₂O) afforded the product as white crystals (0.693 g, 87% yield). Melting point: 81 °C. Spectroscopic data were consistent with previously reported data for this compound.¹¹

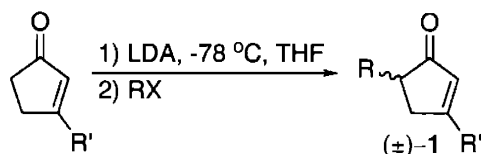


3-Phenethylcyclopentyl epoxide.¹² To a stirring solution of enone (1.01 g, 5.43 mmol) in 5.2 mL of MeOH was added dropwise a 30% solution of H₂O₂ (3.80 mL, 32.6 mmol) in H₂O, maintaining the reaction temperature between 15 and 20 °C. Then, a 6.0 N solution of NaOH (0.46 mL, 2.8 mmol) in H₂O was added dropwise to the reaction over a 30-min period, maintaining the temperature between 15 and 20 °C. The reaction was stirred for additional 3.5 hours, maintaining the temperature between 20 and 25 °C. The reaction was then diluted with diethyl ether, the organic phase was separated and the aqueous phase extracted twice with diethyl ether. The combined organic extracts were washed once with brine, and the organic layer dried over anhydrous MgSO₄. The solvent was then removed *in vacuo* and the product was purified by silica column chromatography (3.5:1 hexanes:ethyl acetate), yielding the title compound as white crystals (0.82 g, 75% yield). Melting point: 56-57 °C. ¹H NMR (500 MHz, C₆D₆) δ: 7.13-7.09 (m, 2 H), 7.05-7.02 (m, 1 H), 6.89-6.88 (m, 2 H), 2.77 (s, 1 H), 2.38-2.23 (m, 2 H), 2.01-1.93 (m, 1 H), 1.68-1.52 (m, 4 H), 1.10-1.04 (m, 1 H). ¹³C NMR (125 MHz, C₆D₆) δ: 208.8, 141.1, 128.7, 128.2, 126.4, 67.8, 60.0, 33.3, 32.3, 31.0, 25.8. IR (neat): 3027, 2935, 2869, 1739, 1602, 1492, 1455, 1401, 1370, 1291, 1191, 1030, 984, 928, 857, 799,

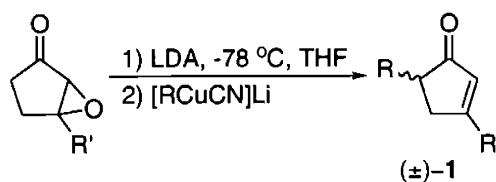
760, 706, 693. cm^{-1} . Anal. calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2$: C, 77.20; H, 6.98. Found: C, 76.99; H, 7.04.

II. General Procedures for the synthesis of 3,5-dialkylcyclopentenones.

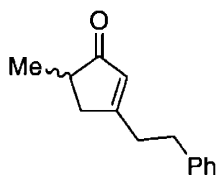
General Procedure A:



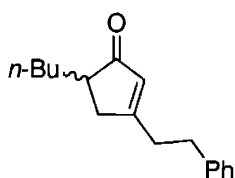
An oven-dried Schlenk flask was charged with diisopropyl amine (0.91 mL, 6.5 mmol) and THF (9 mL). The resulting solution was cooled to 0 °C and 1.6 M solution of *n*-BuLi (3.36 mL, 5.43 mmol) was added dropwise. The reaction was stirred for 30 min at 0 °C. The reaction mixture was then cooled to -78 °C and a solution of enone (4.9 mmol) in THF (10 mL) was added dropwise to the reaction and stirred for 1 hour at -78 °C. Neat alkyl halide (5.4 mmol) was added dropwise to the reaction at -78 °C. The reaction was then stirred for additional 16 hours while gradually warming to room temperature. The reaction mixture was poured onto a saturated solution of aqueous ammonium chloride. The aqueous phase was extracted three times with diethyl ether. The combined organic extracts were washed once with brine, and dried over anhydrous MgSO_4 . The solvent was then removed *in vacuo* and the product was purified by silica column chromatography.

General Procedure B:¹³

An oven-dried Schlenk flask was charged with diisopropyl amine (0.68 mL, 4.80 mmol) and with THF (5 mL). The resulting solution was cooled to $0\text{ }^\circ\text{C}$ and 1.6 M solution of *n*-BuLi (2.80 mL, 4.40 mmol) was added dropwise. The reaction was stirred for 30 min at $0\text{ }^\circ\text{C}$ then cooled to $-78\text{ }^\circ\text{C}$ and a solution of epoxide (3.70 mmol) in THF (6 mL) was added dropwise to the reaction and stirred for 1 hour at $-78\text{ }^\circ\text{C}$. An oven-dried round bottom flask was taken into a nitrogen-filled drybox where CuCN (1.32 g, 14.8 mmol) was weighed and added to the flask. The round bottom flask was capped with a septum and removed from the drybox. To this flask diethyl ether (65 mL) was added, and the resulting white suspension was cooled to $-40\text{ }^\circ\text{C}$ (acetone/dry ice). A solution of alkyllithium or alkylmagnesium chloride (14.8 mmol) was added dropwise to the suspension at $-40\text{ }^\circ\text{C}$ and the reaction mixture was warmed to $0\text{ }^\circ\text{C}$ over a 45-min period. The resulting dark brown solution/suspension was then added via cannula to the epoxy enolate at $-78\text{ }^\circ\text{C}$. The reaction was stirred for 16 hours while it was gradually allowed to warm to room temperature. The reaction mixture was then cooled to $0\text{ }^\circ\text{C}$ and saturated aqueous ammonium chloride was carefully added. The aqueous layer was extracted three times with diethyl ether. The combined organic extracts were washed once with brine and dried over anhydrous MgSO_4 . The solvent was then removed *in vacuo* and the product was purified by silica column chromatography.

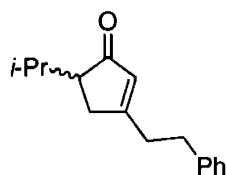


(±)-5-Methyl-3-phenethylcyclopentenone ((±)-1a). Using General Procedure A with 3-phenethylcyclopentenone (0.92 g, 4.90 mmol) and iodomethane (0.34 mL, 5.5 mmol) gave, after flash chromatography (7:1 hexanes:ethyl acetate), the title compound as a clear oil (0.79 g, 80% yield). ¹H NMR (500 MHz, CDCl₃) δ: 7.32-7.29 (m, 2 H), 7.23-7.19 (m, 3 H), 5.95 (s, 1 H), 2.92-2.89 (m, 2 H), 2.85-2.80 (m, 1 H), 2.74-2.70 (m, 2 H), 2.43-2.40 (m, 1 H), 2.20-2.16 (m, 1 H), 1.17-1.16 (d, *J* = 7.5 Hz, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ: 213.2, 180.6, 141.2, 129.3, 129.2, 128.9, 127.1, 41.4, 41.3, 35.7, 34.0, 17.2. IR (neat): 3013, 2912, 1698, 1614, 1495, 1454, 1431, 1179, 1080, 1030, 905, 856, 751, 700 cm⁻¹. HRMS (EI, *m/e*) calcd for C₁₄H₁₆O: 200.1195 (M⁺). Found: 200.1202.

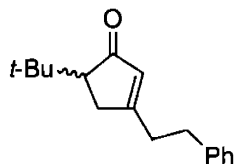


(±)-5-Butyl-3-phenethylcyclopentenone ((±)-1b). Using General Procedure B (Note: a dark brown solution resulted upon addition of 1.6 M *n*-BuLi solution in hexane (8.1 mL, 13.0 mmol) to a suspension of CuCN (1.20 g, 13.0 mmol) in Et₂O) with 3-phenethylcyclopentyl epoxide (0.66 g, 3.257 mmol) gave, after flash chromatography (10:1 hexanes:ethyl acetate), the title compound as a clear oil (0.36 g, 45% yield). ¹H NMR (500 MHz, CDCl₃) δ: 7.32-7.19 (m, 5 H), 5.96-5.94 (m, 1 H), 2.93-2.90 (m, 2 H), 2.78-2.71 (m, 3 H), 2.38-2.36 (m, 1 H), 2.29-2.24 (dd, *J* = 18.3, 1.5 Hz, 1 H), 1.82-1.78 (m, 1 H), 1.35-1.27 (m, 5 H), 0.92-0.88 (t, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ: 212.4, 180.5, 140.8, 129.4, 128.8, 128.4, 126.6, 46.5, 38.7, 35.3, 33.6, 31.4, 29.7, 22.9, 14.2. IR

(neat): 3013, 2919, 2861, 1696, 1614, 1490, 1449, 1177 cm^{-1} . Anal. calcd for $\text{C}_{17}\text{H}_{22}\text{O}$: C, 84.25; H, 9.15. Found: C, 84.35; H, 9.26.

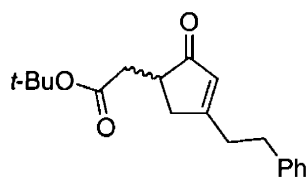


(±)-5-Isopropyl-3-phenethylcyclopentenone ((±)-1c). Using General Procedure B (Note: a dark brown suspension resulted upon addition of 2.0 M *i*-PrMgCl solution in Et_2O (7.50 mL, 15.0 mmol) to a suspension of CuCN (1.34 g, 15.0 mmol) in Et_2O) with 3-phenethylcyclopentyl epoxide (0.76 g, 3.74 mmol) gave, after flash chromatography (10:1 hexanes:ethyl acetate), the title compound as a clear oil (0.31g, 40% yield). ^1H NMR (300 MHz, CDCl_3) δ : 7.32-7.18 (m, 5 H), 5.94 (s, 1 H), 2.94-2.89 (m, 2 H), 2.76-2.71 (m, 2 H), 2.58-2.52 (m, 1 H), 2.40-2.19 (m, 3 H), 0.97-0.95 (d, $J = 6.8$ Hz, 3 H), 0.74-0.72 (d, $J = 6.8$ Hz, 3 H). ^{13}C NMR (75 MHz, CDCl_3) δ : 211.8, 180.9, 140.7, 130.3, 128.8, 128.4, 126.5, 52.2, 35.4, 34.1, 33.7, 28.9, 21.2, 17.2. IR (neat): 3064, 3027, 2958, 2929, 2871, 1692, 1617, 1497, 1465, 1455, 1370, 1235, 1181, 853, 753, 699 cm^{-1} . Anal. calcd for $\text{C}_{16}\text{H}_{20}\text{O}$: C, 84.16; H, 8.83. Found: C, 83.96; H, 8.98.



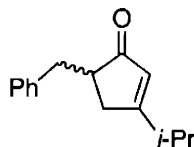
(±)-5-tert-Butyl-3-phenethylcyclopentenone ((±)-1d). Using General Procedure B (Note: a dark brown solution resulted upon addition of 1.70 M *t*-BuLi solution in pentane (8.80 mL, 14.8 mmol) to a suspension of CuCN (1.32 g, 14.8 mmol) in Et_2O) with 3-phenethylcyclopentyl epoxide (0.755 g, 3.74 mmol) gave, after flash chromatography (10:1 hexanes:ethyl acetate), the title compound as a clear oil (0.55 g, 60% yield). ^1H

NMR (500 MHz, CDCl₃) δ : 7.32-7.24 (m, 2 H) 7.22-7.20 (m, 3 H), 5.92 (s, 1 H), 2.93-2.90 (m, 2 H), 2.74-2.70 (m, 2 H), 2.64-2.58 (dd, $J = 18.6, 6.7$ Hz, 1 H), 2.42-2.38 (dd, $J = 18.6, 2.7$ Hz, 1 H), 2.20-2.18 (dd, $J = 6.7, 2.7$ Hz, 1 H), 0.98 (s, 9 H). ¹³C NMR (125 MHz, CDCl₃) δ : 211.1, 179.4, 140.8, 130.8, 128.8, 128.4, 126.6, 55.6, 35.8, 35.1, 33.5, 27.6. IR (neat): 3025, 2953, 2870, 1692, 1620, 1496, 1450, 1362, 1233, 1182, 851, 749, 697 cm⁻¹. Anal. calcd for C₁₇H₂₂O: C, 84.25; H, 9.15. Found: C, 84.22; H, 9.19.



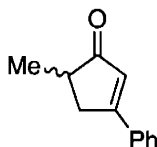
(±)-(2-Oxo-4-phenethylcyclopent-3-enyl)-acetic acid *tert*-butyl ester ((±)-1e).

Using General Procedure A with 3-phenethylcyclopentenone (0.90 g, 4.84 mmol) and *tert*-butyl bromoacetate (0.79 mL, 5.32 mmol) gave, after flash chromatography (4:1 hexanes:ethyl acetate), the title compound as white crystals (0.92 g, 64% yield). Melting point: 71 °C. ¹H NMR (500 MHz, CDCl₃) δ : 7.30-7.27 (m, 2 H), 7.21-7.17 (m, 3 H), 5.97 (s, 1 H), 2.91-2.82 (m, 3 H), 2.74-2.70 (m, 4 H), 2.37-2.28 (m, 2 H), 1.43 (s, 9 H). ¹³C NMR (125 MHz, CDCl₃) δ : 209.7, 180.2, 171.4, 140.5, 128.9, 128.7, 128.2, 126.4, 80.9, 42.7, 38.5, 36.5, 35.1, 33.3, 28.1. IR (neat): 3066, 3025, 2985, 2933, 1725, 1694, 1613, 1497, 1364, 1227, 1158, 870, 753, 700 cm⁻¹. Anal. calcd for C₁₉H₂₄O₃: C, 75.97; H, 8.06. Found: C, 76.14; H, 8.14.



(±)-5-Benzyl-3-isopropylcyclopentenone ((±)-1f). Using General Procedure A with 3-isopropylcyclopentenone (0.60 g, 4.84 mmol) and benzyl bromide (0.63 mL, 5.32

mmol) gave, after flash chromatography (7:1 hexanes:ethyl acetate), the title compound as a clear oil (0.73 g, 71% yield). ^1H NMR (300 MHz, CDCl_3) δ : 7.31-7.18 (m, 5 H), 5.92 (s, 1 H), 3.26-3.20 (dd, $J = 13.7, 3.9$ Hz, 1 H), 2.76-2.50 (m, 4 H), 2.34-2.27 (m, 1 H), 1.12-1.11 (d, $J = 1.1$ Hz, 3 H), 1.09-1.09 (d, $J = 1.1$ Hz, 3 H). ^{13}C NMR (75 MHz, CDCl_3) δ : 211.5, 187.7, 139.8, 129.1, 128.7, 127.1, 126.5, 47.7, 37.4, 35.6, 32.3, 21.0, 21.0. IR (neat): 3062, 3027, 2966, 2931, 2875, 1696, 1609, 1495, 1453, 1428, 1385, 1343, 1262, 1173, 864, 747, 700 cm^{-1} . Anal. calcd for $\text{C}_{15}\text{H}_{18}\text{O}$: C, 84.07; H, 8.47. Found: C, 83.98; H, 8.54.

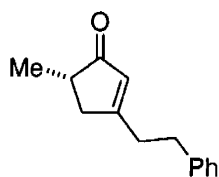


(±)-5-Methyl-3-phenylcyclopentenone ((±)-1g). Using General Procedure A with 3-phenylcyclopentenone (0.42 g, 2.66 mmol) and iodomethane (0.02 mL, 3.03 mmol) gave, after flash chromatography (4:1 pentane: Et_2O), the title compound as white crystals (0.29 g, 64% yield). Melting point: 36 °C. ^1H NMR (500 MHz, CDCl_3) δ : 7.65-7.62 (m, 2 H), 7.46-7.41 (m, 3H), 6.52 (s, 1 H), 3.30-3.24 (m, 1 H), 2.63-2.57 (m, 2 H), 1.27-1.25 (d, $J = 7.6$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ : 212.2, 172.3, 134.2, 131.5, 129.1, 127.1, 126.4, 41.0, 37.7, 16.9. IR (neat): 3062, 2964, 2929, 2871, 1690, 1602, 1573, 1495, 1447, 1372, 1343, 1331, 1272, 1177, 1075, 1030, 866, 760, 699 cm^{-1} . Anal. calcd for $\text{C}_{12}\text{H}_{12}\text{O}$: C, 83.69; H, 7.02. Found: C, 83.57; H, 6.95.

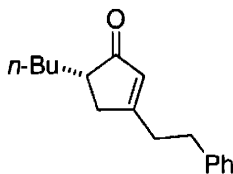
III. General Procedure for the kinetic resolution via asymmetric conjugate reduction of 3,5-dialkylcyclopentenones.

An oven-dried Schlenk flask was evacuated and backfilled with argon. (*S*)-*p*-tol-BINAP (28 mg, 0.04 mmol, 10 mol %) was placed in the Schlenk flask and dissolved in

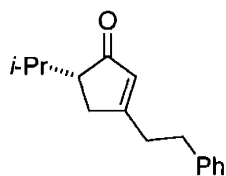
toluene (0.7 mL). The Schlenk flask was then sealed and moved into a nitrogen-filled drybox. In the drybox, NaOt-Bu (4.2 mg, 0.04 mmol, 10 mol %) and CuCl (4.2 mg, 0.04 mmol, 10 mol %) were weighed into a vial. The toluene solution of (*S*)-*p*-tol-BINAP was added via pipet to the vial to dissolve the solids and the resulting solution was then transferred back into the Schlenk flask. The Schlenk flask was sealed and removed from the drybox, the solution was stirred for 10-20 min, and PMHS (0.03 mL, 0.45 mmol) was added to the solution under argon purge and stirred for 10 min at room temperature. The resulting reddish orange solution was then cooled to the specified temperature. A solution of 3,5-dialkylcyclopentenone (0.41 mmol) and mesitylene (0.06 mL, 0.41 mmol), as an internal standard, in 0.7 mL of toluene was added (on the walls of the Schlenk flask) to the reaction solution. The reaction was stirred for the indicated period of time. The consumption of 3,5-dialkylcyclopentenone was monitored by GC. An aliquot was taken after the indicated period time and quenched by addition to 1 mL of water. The sample was then diluted with 1 mL Et₂O and the organic phase was separated. The catalyst-free sample was then analyzed by GC to determine the percent conversion. The Schlenk flask was opened to the air and water (1 mL) was added. The resulting solution was diluted with diethyl ether and washed once with brine. The brine layer was back extracted with diethyl ether. To the combined organic extracts was added TBAF (0.43 mL, 1.0 M in THF) and the resulting solution was stirred for 1 hour. The solution was then washed once with brine. The brine layer was back extracted with diethyl ether, and the organic layers were combined and dried over anhydrous MgSO₄. The solvent was then removed *in vacuo* and the enantiomerically enriched starting material was then purified by silica column chromatography and analyzed by chiral HPLC to determine the selectivity factor (*s*).⁴



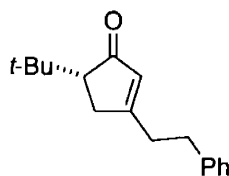
5-(S)-Methyl-3-phenethylcyclopentenone (1a). Using the General Procedure for the kinetic resolution with (\pm)-5-methyl-3-phenethylcyclopentenone (0.065 g, 0.325 mmol) gave, after 10 hours at $-78\text{ }^{\circ}\text{C}$, 55.6% conversion (GC). Flash chromatography (15:1, then 7:1 hexanes:ethyl acetate) afforded the title compound as a clear oil (0.027 g, 42% yield). Spectroscopic data were identical to the racemic compound reported earlier. Chiral HPLC analysis (Chiralcel OD column, 3.0% isopropanol in hexane, 0.7 mL/min, $t_r(1a) = 24.77\text{ min}$, $t_r(1a') = 26.32\text{ min}$) indicated that the title compound was obtained in 94.6% ee. $[\alpha]_D^{25} -9^{\circ}$ ($c\ 0.7$, CHCl_3). This ee value corresponds to a selectivity factor of 25.5.



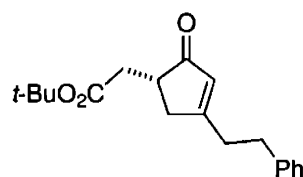
5-(S)-Butyl-3-phenethylcyclopentenone (1b). Using the General Procedure for the kinetic resolution with (\pm)-5-butyl-3-phenethylcyclopentenone (0.053 g, 0.22 mmol) gave, after 10 hours at $-78\text{ }^{\circ}\text{C}$, 53.2% conversion (GC). Flash chromatography (15:1, then 7:1 hexanes:ethyl acetate) afforded the title compound as a clear oil (0.024 g, 45% yield). Spectroscopic data were identical to the racemic compound reported earlier. Chiral HPLC analysis (Chiralcel OD column, 2.0% isopropanol in hexane, 0.7 mL/min, $t_r(1b) = 25.88\text{ min}$, $t_r(1b') = 27.96\text{ min}$) indicated that the title compound was obtained in 90.6% ee. $[\alpha]_D^{25} -60^{\circ}$ ($c\ 1.4$, CHCl_3). This ee value corresponds to a selectivity factor of 27.3.



5-(*R*)-Isopropyl-3-phenethylcyclopentenone (1c). Using the General Procedure for the kinetic resolution with (\pm)-5-isopropyl-3-phenethylcyclopentenone (0.093 g, 0.41 mmol) gave, after 4 hours at 0 °C, 56.5% conversion (GC). Flash chromatography (15:1, then 7:1 hexanes:ethyl acetate) afforded the title compound as a clear oil (0.023 g, 41% yield). Spectroscopic data were identical to the racemic compound reported earlier. Chiral HPLC analysis (Chiralcel OD column, 2.0% isopropanol in hexane, 0.7 mL/min, $t_r(1c) = 23.19$ min, $t_r(1c') = 24.99$ min) indicated that the title compound was obtained in 97.4% ee. $[\alpha]_D^{25} -68^\circ$ (c 1.3, CHCl_3). This ee value corresponds to a selectivity factor of 29.4.

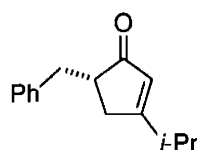


5-(*R*)-*tert*-Butyl-3-phenethylcyclopentenone (1d). Using the General Procedure for the kinetic resolution with (\pm)-5-*tert*-butyl-3-phenethylcyclopentenone (0.325 g, 1.34 mmol) gave, after 12 hours at 0 °C, 50.7% conversion (GC). Flash chromatography (20:1, then 10:1 hexanes:ethyl acetate) afforded the title compound as a clear oil (0.157 g, 48% yield). Spectroscopic data were identical to the racemic compound reported above. Chiral HPLC analysis (Chiralcel OD column, 1.8% isopropanol in hexane, 0.7 mL/min, $t_r(1d) = 23.01$ min, $t_r(1d') = 24.52$ min) indicated that the title compound was obtained in 91.0% ee. $[\alpha]_D^{25} +42^\circ$ (c 1.3, CHCl_3). This ee value corresponds to a selectivity factor of 51.7.

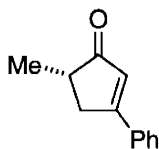


1-(*R*)-(2-Oxo-4-phenethyl-cyclopent-3-enyl)-acetic acid *tert*-butyl ester (1e).

Using the General Procedure for the kinetic resolution with (\pm)-(2-oxo-4-phenethyl-cyclopent-3-enyl)-acetic acid *tert*-butyl ester (0.076 g, 0.25 mmol) gave, after 4 hours at -50 °C, 56.0 % conversion (GC). Flash chromatography (10:1, then 4:1 hexanes:ethyl acetate) afforded the title compound as white crystals (0.036 g, 40% yield). Melting point: 71 °C. Spectroscopic data were identical to the racemic compound reported earlier. Chiral HPLC analysis (Chiralcel OD column, 10.0% isopropanol in hexane, 0.7 mL/min, $t_r(1e) = 18.49$ min, $t_r(1e') = 23.55$ min) indicated that the title compound was obtained in 95.3% ee. $[\alpha]_D^{25} +22^\circ$ (c 3.6, CHCl_3). This ee value corresponds to a selectivity factor of 25.5.



5-(*R*)-Benzyl-3-isopropylcyclopentenone (1f). Using the General Procedure for the kinetic resolution with (\pm)-5-benzyl-3-isopropylcyclopentenone (0.131 g, 0.61 mmol) gave, after 12 hours at -78 °C, 56.0% conversion (GC). Flash chromatography (10:1 hexanes:ethyl acetate) afforded the title compound as a clear oil (0.054 g, 41% yield). Spectroscopic data were identical to the racemic compound reported earlier. Chiral HPLC analysis (Chiralpak AD column, 1.0% isopropanol in hexane, 0.7 mL/min, $t_r(1f) = 20.10$ min, $t_r(1f') = 22.10$ min) indicated that the title compound was obtained in 95.6% ee. $[\alpha]_D^{25} +111^\circ$ (c 3.4, CHCl_3). This ee value corresponds to a selectivity factor of 26.3.

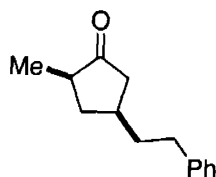


5-(*S*)-Methyl-3-phenylcyclopentenone (1g). Using the General Procedure for the kinetic resolution with (\pm)-5-methyl-3-phenylcyclopentenone (0.067 g, 0.39 mmol) gave, after 72 hours at $-78\text{ }^{\circ}\text{C}$, 45.0% conversion (GC). Flash chromatography (10:1, then 4:1 pentane:Et₂O) afforded the title compound as white crystals (0.034 g, 50% yield). Melting point: $36\text{ }^{\circ}\text{C}$. Spectroscopic data were identical to the racemic compound reported earlier. Chiral HPLC analysis (Chiralcel OB column, 10.0% isopropanol in hexane, 0.7 mL/min, $t_r(1g) = 13.55\text{ min}$, $t_r(1g') = 16.20\text{ min}$) indicated that the title compound was obtained in 71.6% ee. $[\alpha]_D^{25} -108^{\circ}$ ($c\ 1.6$, CHCl₃). This ee value corresponds to a selectivity factor of 32.0.

IV. General Procedure for the dynamic kinetic resolution via asymmetric conjugate reduction of 3,5-dialkylcyclopentenones.

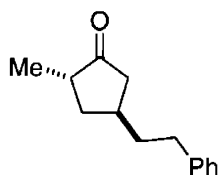
An oven-dried Schlenk flask was evacuated and backfilled with argon. (*S*)-*p*-tol-BINAP (22 mg, 0.03 mmol, 10 mol %) was placed in the Schlenk flask and dissolved in toluene (0.4 mL). The Schlenk flask was then sealed and moved into a nitrogen-filled drybox. In the drybox, NaO*t*-Bu (30 mg, 0.31 mmol) and CuCl (3.2 mg, 0.03 mmol, 10 mol %) were weighed into a vial. The toluene solution of (*S*)-*p*-tol-BINAP was added via pipet to the vial and the resulting suspension was then transferred back into the Schlenk flask. The Schlenk flask was sealed and removed from the drybox, the suspension was stirred for 10-20 min. PMHS (0.024 mL, 0.403 mmol) was then added to the suspension under argon purge and stirred for 10 min at room temperature. The resulting reddish orange solution was then cooled to the specified temperature. The solution of 3,5-dialkylcyclopentenone (0.310 mmol), *t*-BuOH (0.148 mL, 1.55 mmol) and mesitylene

(0.043 mL, 0.31 mmol), as an internal standard, in 0.4 mL of toluene was added (down the wall of the Schlenk flask to allow for cooling of the solution) to the reaction solution. After the reaction was stirred for 21 hours, additional amounts of NaOt-Bu (21 mg, 0.217 mmol) and PMHS (0.017 mL, 0.279 mmol) in 0.7 mL of toluene were added. The reaction was stirred for an additional 5 hours unless otherwise noted. The consumption of 3,5-dialkylcyclopentenone was monitored by GC. The Schlenk flask was opened to the air and water (1 mL) was added. The resulting solution was diluted with diethyl ether, washed once with brine. The brine layer was extracted with diethyl ether. To the combined organic extracts was added TBAF (0.738 mL, 1.0 M in THF) and the resulting solution was stirred for 1 hour. The solution was then washed once with brine. The brine layer was extracted with diethyl ether, and the organic layer was dried over anhydrous MgSO₄. The solvent was then removed *in vacuo* and the product was purified by silica column chromatography.

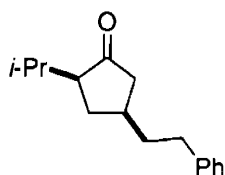


2-(R)-Methyl-4-(S)-phenethylcyclopentanone (2a). Using the General Procedure for the dynamic kinetic resolution with (\pm)-5-methyl-3-phenethylcyclopentenone (0.062 g, 0.310 mmol) gave, after 26 hours at 0 °C, 99% conversion (GC). Flash chromatography (20:1 hexane:ethyl acetate) afforded the title compound as a colorless oil (0.057 g, 91% yield). ¹H NMR (500 MHz, CDCl₃) δ : 7.32-7.29 (m, 2 H), 7.22-7.19 (m, 3 H), 2.70-2.67 (m, 2 H), 2.54-2.48 (dd, J = 18.6, 7.6 Hz, 1 H), 2.40-2.38 (m, 1 H), 2.19-2.09 (m, 2 H), 1.83-1.75 (m, 3 H), 1.19-1.12 (m, 1 H), 1.11-1.10 (d, J = 7.0 Hz, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ : 221.0, 142.2, 128.7, 128.5, 126.2, 45.5, 44.8, 39.0, 37.9, 34.5, 34.4, 14.2. IR (neat): 3025, 2919, 2861, 1737, 1596,

1496, 1455, 1396, 1151, 1032, 908, 744, 697 cm^{-1} . HRMS (EI, m/e) calcd for $\text{C}_{14}\text{H}_{18}\text{O}$: 202.1352 (M^+). Found: 202.1349. $[\alpha]_{\text{D}}^{25}$ -56° (c 1.6, CHCl_3). Chiral HPLC analysis (Chiralcel OD-H column, 1.5% isopropanol in hexane, 0.7 mL/min, $t_{\text{r}}(2\text{a}') = 18.71$ min, $t_{\text{r}}(3\text{a}') = 19.89$ min, $t_{\text{r}}(2\text{a}) = 24.35$ min, $t_{\text{r}}(3\text{a}) = 25.55$ min) indicated that the title compound was obtained in 92% ee and 90.5:9.5 *syn:anti* diastereomeric ratio.

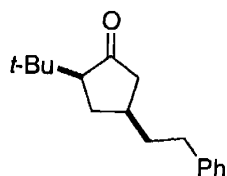


2-(S)-Methyl-4-(S)-phenethylcyclopentanone (3a). The title compound was obtained (5 mg) using the semi-preparative HPLC (Chiralcel OD, 1.0% isopropanol in hexanes, 2 mL/min) for the purpose of NOE difference experiment to determine relative stereochemistry. ^1H NMR (500 MHz, C_6D_6) δ : 7.35-7.31 (m, 2 H), 7.15-7.10 (m, 1 H), 6.97-6.94 (m, 2 H), 2.24-2.10 (m, 2 H), 2.05-1.96 (m, 1 H), 1.92-1.83 (m, 1 H), 1.71-1.62 (m, 1 H), 1.55-1.53 (m, 1 H), 1.36-1.18 (m, 4 H), 0.90-86 (d, $J = 7.0$ Hz, 3 H). ^{13}C NMR (125 MHz, C_6D_6) δ : 218.4, 142.2, 128.6, 128.5, 126.1, 43.9, 41.3, 37.4, 36.8, 34.3, 32.9, 15.5. IR (neat): 3062, 3027, 2929, 2871, 2858, 1739, 1603, 1497, 1455, 1405, 1372, 1181, 1164, 1142, 1063, 1030, 747, 699 cm^{-1} . HRMS (EI, m/e) calcd for $\text{C}_{14}\text{H}_{18}\text{O}$: 202.1352 (M^+). Found: 202.1354.



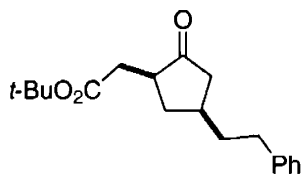
2-(R)-Isopropyl-4-(S)-phenethylcyclopentanone (2c). Using the General Procedure for the dynamic kinetic resolution with (\pm)-5-isopropyl-3-phenethylcyclopentanone (0.071 g, 0.311 mmol) gave, after 26 hours at -30°C , 98%

conversion (GC). Flash chromatography (15:1 hexane:ethyl acetate) afforded the title compound as a colorless oil (0.067 g, 93% yield). ^1H NMR (500 MHz, CDCl_3) δ : 7.32-7.28 (m, 2 H), 7.22-7.18 (m, 3 H), 2.71-2.65 (m, 2 H), 2.51-2.46 (m, 1 H), 2.21-2.00 (m, 4 H), 1.82-1.69 (m, 3 H), 1.35-1.28 (m, 1 H), 0.99-0.98 (d, $J = 6.7$ Hz, 3 H), 0.83-0.81 (d, $J = 6.7$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ : 220.7, 142.7, 129.1, 129.0, 128.9, 57.0, 46.9, 38.4, 34.9, 34.8, 31.9, 27.8, 21.8, 19.0. IR (neat): 3064, 3027, 2958, 2927, 2871, 1735, 1603, 1497, 1455, 1405, 1368, 1156, 749, 699 cm^{-1} . HRMS (EI, m/e) calcd for $\text{C}_{16}\text{H}_{22}\text{O}$: 230.1665 (M^+). Found: 230.1676. $[\alpha]_{\text{D}}^{25} -115^\circ$ (c 1.4, CHCl_3). Chiral HPLC analysis (Chiralcel OD-H column, 1.0% isopropanol in hexane, 0.7 mL/min, $t_{\text{r}}(\mathbf{3c}')$ = 14.82 min, $t_{\text{r}}(\mathbf{2c}')$ = 17.49 min, $t_{\text{r}}(\mathbf{2c})$ = 20.34 min, $t_{\text{r}}(\mathbf{3c})$ = 25.33 min) indicated that the title compound was obtained in 94% ee and 93:7 *syn:anti* diastereomeric ratio.

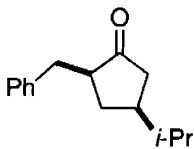


2-(*R*)-tert-Butyl-4-(*S*)-phenethylcyclopentanone (2d). Using the General Procedure for the dynamic kinetic resolution with (\pm)-5-*tert*-butyl-3-phenethylcyclopentenone (0.075 g, 0.310 mmol) gave, after 26 hours at 0 $^\circ\text{C}$, 100% conversion (GC). Flash chromatography (20:1 hexane:ethyl acetate) afforded the title compound as a colorless oil (0.074 g, 98% yield). ^1H NMR (500 MHz, CDCl_3) δ : 7.32-7.22 (m, 2 H), 7.22-7.17 (m, 3 H), 2.70-2.64 (m, 2 H), 2.47-2.41 (m, 1 H), 2.29-2.20 (m, 1 H), 2.04-1.91 (m, 2 H), 1.81-1.71 (m, 3 H), 1.40-1.31 (m, 1 H), 0.99 (s, 9 H). ^{13}C NMR (125 MHz, CDCl_3) δ : 219.6, 142.2, 128.6, 128.5, 126.1, 59.4, 47.5, 38.0, 34.4, 33.7, 33.4, 32.7, 28.0. IR (neat): 3064, 3027, 2954, 2867, 1733, 1603, 1497, 1455, 1405, 1393, 1364, 1246, 1152, 745, 699 cm^{-1} . Anal. calcd for $\text{C}_{17}\text{H}_{24}\text{O}$: C, 83.55; H, 9.90. Found: C, 83.14; H, 9.97. $[\alpha]_{\text{D}}^{25} -113^\circ$ (c 1.1, CHCl_3). Chiral HPLC analysis (Chiralcel OD-H column,

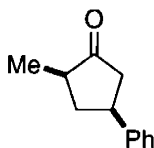
1.5% isopropanol in hexane, 0.7 mL/min, $t_r(3d') = 11.33$ min, $t_r(2d') = 14.78$ min, $t_r(2d) = 15.85$ min, $t_r(3d) = 16.66$ min) indicated that the title compound was obtained in 94% ee and 92:8 *syn:anti* diastereomeric ratio.



1-(S)-(2-Oxo-4-(S)-phenethyl-cyclopent-3-enyl)-acetic acid *tert*-butyl ester (2e). Using the General Procedure for the dynamic kinetic resolution with (\pm)-(2-oxo-4-phenethyl-cyclopent-3-enyl)-acetic acid *tert*-butyl ester (0.093 g, 0.310 mmol) gave, after 26 hours at -50 °C, 97% conversion (GC). Flash chromatography (10:1 hexane:ethyl acetate) afforded the title compound as a colorless oil (0.081 g, 87% yield). ^1H NMR (500 MHz, C_6D_6) δ : 7.16-7.13 (m, 2 H), 7.08-7.05 (m, 1 H), 7.00-6.92 (m, 2 H), 2.64-2.60 (dd, $J = 16.8, 4.3$ Hz, 1 H), 2.30-2.25 (m, 3 H), 2.13-2.05 (m, 2 H), 1.95-1.90 (m, 1 H), 1.49-1.45 (m, 2 H), 1.34 (s, 9 H), 1.32-1.28 (m, 2 H), 0.95-0.88 (m, 1 H). ^{13}C NMR (125 MHz, C_6D_6) δ : 215.7, 171.1, 142.2, 128.5, 127.7, 126.0, 80.0, 46.6, 44.0, 37.6, 35.8, 35.2, 34.2, 34.1, 28.0. IR (neat): 3062, 3027, 2977, 2927, 2858, 1727, 1603, 1497, 1455, 1393, 1366, 1316, 1248, 1152, 1123, 1079, 849, 749, 700 cm^{-1} . HRMS (EI, m/e) calcd for $\text{C}_{19}\text{H}_{26}\text{O}_3$: 302.1876 (M^+). Found: 302.1881. $[\alpha]_{\text{D}}^{25} -84^\circ$ (c 1.1, CHCl_3). Chiral HPLC analysis (Chiralcel OJ column, 3.0% isopropanol in hexane, 0.7 mL/min, $t_r(\mathbf{2f}) = 9.12$ min, $t_r(\mathbf{2f}') = 9.75$ min, $t_r(\mathbf{3f}') = 11.40$ min, $t_r(\mathbf{3f}) = 13.62$ min) indicated that the title compound was obtained in 92% ee and 90:10 *syn:anti* diastereomeric ratio.



2-(R)-Benzyl-4-(S)-isopropylcyclopentanone (2f). Using the General Procedure for the dynamic kinetic resolution with (\pm)-5-benzyl-3-isopropylcyclopentenone (0.066 g, 0.308 mmol) gave, after 26 hours at $-50\text{ }^{\circ}\text{C}$, 96% conversion (GC). Flash chromatography (20:1 hexane:ethyl acetate) afforded the title compound as a colorless oil (0.063 g, 95% yield). ^1H NMR (500 MHz, CDCl_3) δ : 7.31-7.27 (m, 2 H), 7.23-7.17 (m, 3 H), (dd, $J = 13.7, 4.0$ Hz, 1 H), 2.57-2.39 (m, 3 H), 2.22-2.16 (m, 1 H), 1.85-1.66 (m, 2 H), 1.47-1.40 (m, 1 H), 1.21-1.13 (m, 1 H), 0.91-0.89 (d, 6 H). ^{13}C NMR (75 MHz, CDCl_3) δ : 219.7, 140.4, 129.1, 128.7, 126.4, 52.9, 44.0, 42.4, 35.9, 34.7, 33.9, 21.5, 20.7. IR (neat): 3062, 3027, 2960, 2927, 2871, 1739, 1603, 1495, 1453, 1403, 1385, 1368, 1158, 1075, 1030, 920, 737, 699 cm^{-1} . Anal. calcd for $\text{C}_{15}\text{H}_{20}\text{O}$: C, 83.29; H, 9.32. Found: C, 83.48; H, 9.37. $[\alpha]_{\text{D}}^{25} -198^{\circ}$ (c 1.1, CHCl_3). Chiral HPLC analysis (Chiralcel OJ column, 1.5% isopropanol in hexane, 0.7 mL/min, $t_{\text{r}}(\mathbf{2e}') = 19.49$ min, $t_{\text{r}}(\mathbf{3e}') = 22.42$ min, $t_{\text{r}}(\mathbf{3e}) = 24.80$ min, $t_{\text{r}}(\mathbf{2e}) = 31.06$ min) indicated that the title compound was obtained in 93% ee and 91.5:8.5 *syn:anti* diastereomeric ratio.



2-(R)-Methyl-4-(S)-phenylcyclopentanone (2g). Using the General Procedure for the dynamic kinetic resolution with (\pm)-5-methyl-3-phenylcyclopentenone (0.061 g, 0.355 mmol) (except that additional amounts of NaOt-Bu (23 mg, 0.264 mmol) and PMHS (0.019 mL, 0.320 mmol) in 0.7 mL of toluene were added after 21 and 36 hours, respectively) gave, after 48 hours at $-50\text{ }^{\circ}\text{C}$, 98% conversion (GC). Flash chromatography (10:1 pentane: Et_2O) afforded the title compound as a colorless oil (0.054 g, 87% yield).

^1H NMR (500 MHz, CDCl_3) δ : 7.37-7.34 (m, 2 H), 7.28-7.24 (m, 3 H), 3.39-3.31 (m, 1 H), 2.81-2.75 (m, 1 H), 2.64-2.59 (m, 1 H), 2.40-2.28 (m, 2 H), 1.68-1.61 (m, 1 H), 1.20-1.19 (d, $J = 7.0$ Hz, 3 H). ^{13}C NMR (75 MHz, CDCl_3) δ : 219.9, 143.3, 128.9, 127.0, 126.9, 45.9, 45.6, 40.3, 40.2, 14.1. IR (neat): 3062, 3029, 2964, 2931, 2873, 1737, 1603, 1495, 1455, 1407, 1366, 1328, 1268, 1239, 1146, 1069, 1028, 901, 760, 699 cm^{-1} . HRMS (EI, m/e) calcd for $\text{C}_{12}\text{H}_{14}\text{O}$: 174.1039 (M^+). Found: 174.1042. $[\alpha]_{\text{D}}^{25} -65^\circ$ (c 1.3, CHCl_3). Chiral HPLC analysis (Chiralcel OD column, 1.0% isopropanol in hexane, 0.7 mL/min, $t_{\text{r}}(\mathbf{3g}') = 19.50$ min, $t_{\text{r}}(\mathbf{3g}) = 20.61$ min, $t_{\text{r}}(\mathbf{2g}) = 22.50$ min, $t_{\text{r}}(\mathbf{2g}') = 24.62$ min) indicated that the title compound was obtained in 90% ee and 97:3 *syn:anti* diastereomeric ratio.

V. Determination of the relative and absolute stereochemistry.

The relative stereochemistry of **2a** was determined by nuclear Overhauser effect (NOE) ^1H NMR (500 MHz) experiment. 4.0% NOE enhancement of the proton at C-4 was observed when a proton at C-2 was irradiated. This indicated *syn* relationship between the alkyl substituents (Figure 3). Similar NOE enhancement of proton at C-2 was observed when the proton at C-4 was irradiated. When a similar ^1H NMR experiment was conducted with **3a**, no NOE enhancement of the proton at C-4 upon irradiation of the proton at C-2 was observed, indicating an *anti* relationship between the alkyl substituents.

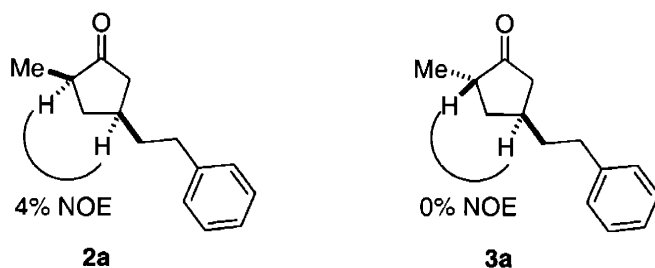
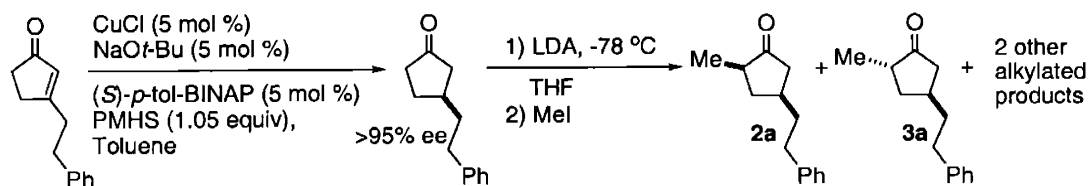


Figure 3. Relative stereochemistry determination by NOE. Adapted with permission from Reference 5. Copyright 2002 American Chemical Society.

The absolute stereochemistry was established by synthesizing the known compound, (*S*)-3-phenethylcyclopentanone, in high enantiomeric excess.^{3b} Subsequent alkylation yielded a mixture of diastereomeric 2-methyl-4-phenethylcyclopentanones **2a** and **3a** of known absolute configuration (Scheme 3).



Scheme 3. Synthesis of diastereomeric 2,4-dialkylcyclopentanones **2a** and **3a**. Adapted with permission from Reference 5. Copyright 2002 American Chemical Society.

After comparing HPLC retention times for compounds **2a** and **3a** prepared according to the scheme in Table 2 with the products of the dynamic kinetic resolution of (\pm)-**1a** using (*S*)-*p*-tol-BINAP, it was determined that compound 2(*R*),4(*S*)-**2a** is the major enantiomer of the major diastereomer in this reaction. Thus, the slow-reacting enantiomer under the kinetic resolution conditions using (*S*)-*p*-tol-BINAP as ligand can be assigned as 5-(*S*)-methyl-3-phenethylcyclopentanone (5-(*S*)-**1a**), and the fast-reacting enantiomer is 5-(*R*)-**1a**. The absolute stereochemistries of **1b-1g**, **2c-2g** and **3c-3g** were assigned by analogy.

Table 3. Methods used to assay chiral 3,5-dialkylcyclopentenones. Adapted with permission from Reference 5. Copyright 2002 American Chemical Society.

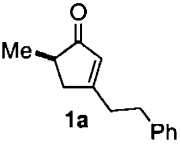
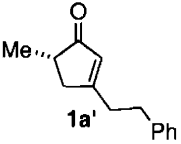
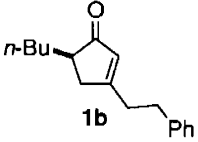
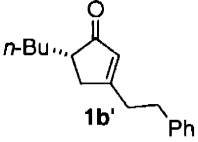
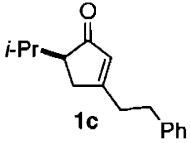
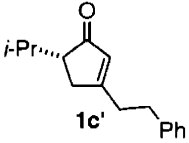
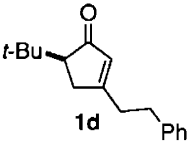
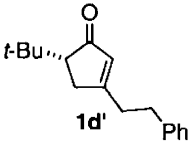
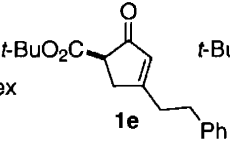
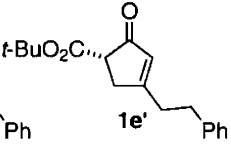
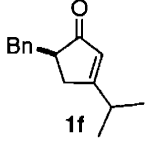
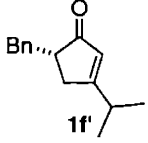
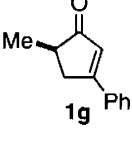
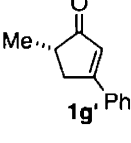
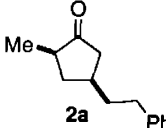
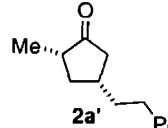
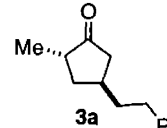
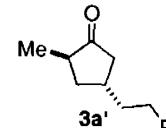
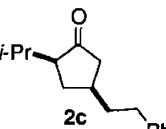
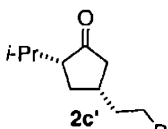
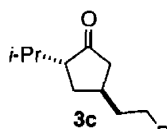
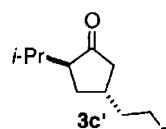
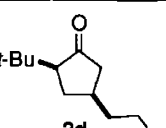
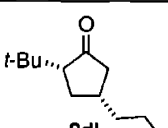
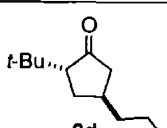
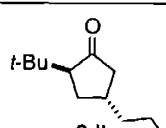
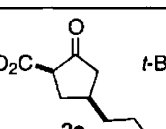
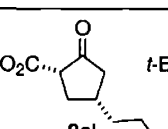
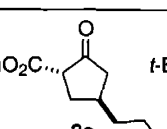
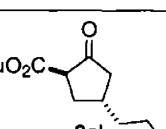
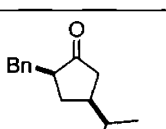
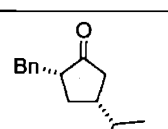
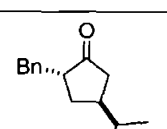
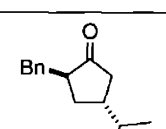
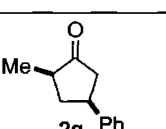
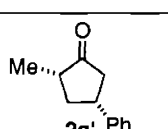
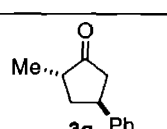
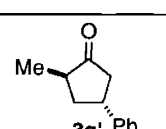
HPLC column	Substrate	
OD 3.0% IPA in Hex 0.7 ml/min	 1a	 1a'
Retention times (min)	24.77	26.32
OD 2.0% IPA in Hex 0.7 ml/min	 1b	 1b'
Retention times (min)	25.88	27.96
OD 2.0% IPA in Hex 0.7 ml/min	 1c	 1c'
Retention times (min)	23.19	24.99
OD 1.8% IPA in Hex 0.7 ml/min	 1d	 1d'
Retention times (min)	23.01	24.52
OD 10.0% IPA in Hex 0.7 ml/min	 1e	 1e'
Retention times (min)	18.49	23.55
AD 1.0% IPA in Hex 0.7 ml/min	 1f	 1f'
Retention times (min)	20.10	22.10
OB 10.0% IPA in Hex 0.7 ml/min	 1g	 1g'
Retention times (min)	13.55	16.20

Table 4. Methods used to assay chiral 2,4-dialkylcyclopentanones. Adapted with permission from Reference 5. Copyright 2002 American Chemical Society.

HPLC column	Substrate			
OD-H 1.5% IPA in Hex 0.7 ml/min				
Retention times (min)	24.35	18.71	25.55	19.89
OD-H 1.0% IPA in Hex 0.7 ml/min				
Retention times (min)	20.34	17.49	25.33	14.82
OD-H 1.5% IPA in Hex 0.7 ml/min				
Retention times (min)	15.85	14.78	16.66	11.33
OJ 3.0% IPA in Hex 0.7 ml/min				
Retention times (min)	31.06	19.49	24.80	22.42
OJ 0.7% EtOH in Hex 0.7 ml/min				
Retention times (min)	9.12	9.75	13.62	11.40
OD 1.0% IPA in Hex 0.7 ml/min				
Retention times (min)	22.50	24.62	20.61	19.50

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4. Selectivity factor, $s = k_r/k_s = \ln[(1 - C)(1 - ee)]/[(1 - C)(1 + ee)]$, where ee is the percent enantiomeric excess of **1** and C is the conversion. For each substrate, comparable selectivity factors (s) were observed at low (24-30 %) and at high (43-61%) conversions.
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Chapter 3.
Conjugate Reduction of α,β -Unsaturated Carbonyl Compounds
Catalyzed by a Copper Carbene Complex

Background and Introduction

N-Heterocyclic carbene metal complexes have been known since the 1960s,¹ but they received little attention until Arduengo and co-workers isolated and characterized a nucleophilic N-heterocyclic carbene in 1991.² In the past decade, N-heterocyclic carbenes have emerged as a valuable new class of ligands for homogeneous catalysis.³

N-Heterocyclic carbenes have a singlet (σ^2) electronic ground state. Frenking and coworkers argued that the stabilization of such carbene center arises primarily from π -donation by the lone pairs of the nitrogen atoms into the formally empty p_π orbital of the carbenic C atom (Figure 1).⁴ The evidence of electron delocalization in imidazol-2-ylidenes and display of aromatic character was supported by other studies.⁵

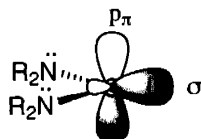


Figure 1. Representation of nonbonding σ and empty p_π orbitals of the carbenic C atom.

Being strong σ -donors but very poor π -acceptors,⁶ NHC's exhibit bonding similar to that of bulky phosphines.⁷ However, in contrast to phosphines, the carbene ligands do not readily undergo dissociation from the metal center, even at elevated temperatures, and form metal complexes that have remarkable stability to heat, oxygen, and moisture.⁸

The use of imidazol-2-ylidines was found to be practical in a broad scope of transition metal-catalyzed transformations. Figure 2 shows some imidazolium salts (**I-V**), which are employed as stable and easily handled precursors to the corresponding N-heterocyclic carbenes, which have found multiple applications in transition metal catalysis. In particular, **I** with a metal effects Suzuki⁹ and Sonogashira¹⁰ reactions, amide α -arylation,¹¹ hydrogenation,¹² and hydroformylation,¹³ while **II** effects olefin metathesis¹⁴ and Sonogashira¹⁰ cross-coupling reactions; **III** is successfully employed in

aryl amination,¹⁵ **IV** is used in Heck¹⁶ and Kumada¹⁷ cross-coupling reactions, and **V** is used in Stille¹⁸ cross-coupling reactions.

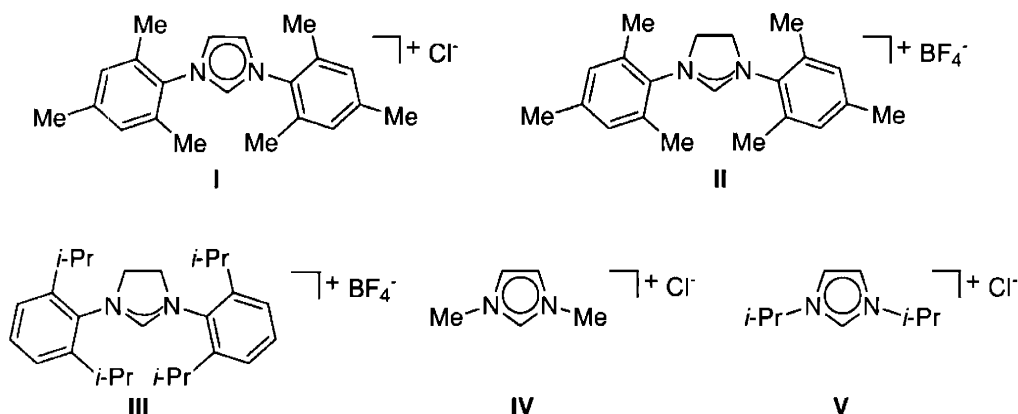


Figure 2. Imidazolium salts as precursors to N-heterocyclic carbenes.

Arduengo reported the first N-heterocyclic carbene-copper complex derived from imidazolium salt and copper triflate.^{19,20} Similar copper complexes were later shown to catalyze the conjugate addition of diethylzinc to enones. Modest to excellent enantioselectivities were obtained using chiral versions of carbene ligands for these transformations.²¹

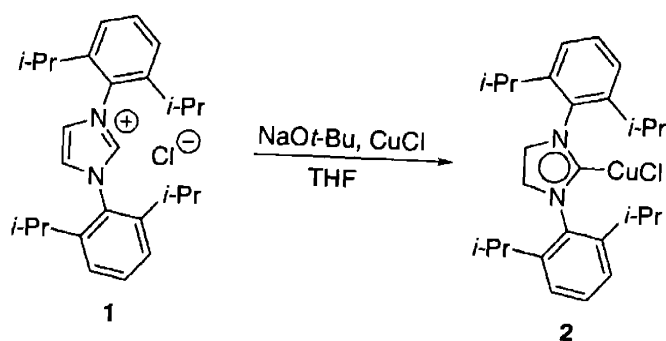
We were interested in employing N-heterocyclic carbenes as ligands for the copper-catalyzed conjugate reduction of α,β -unsaturated carbonyl compounds.

Results and Discussion

We have described the asymmetric conjugate reductions of α,β -unsaturated esters and cyclic ketones catalyzed by a chelating phosphine in combination with CuCl.²² In the course of studying the reaction chemistry between transition metal complexes and carbon dioxide, Professor Joseph P. Sadighi prepared complex **2**. With a preparative route to **2**

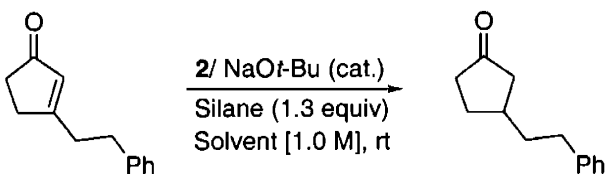
now available, we felt it natural to investigate the use of **2** in copper-catalyzed conjugate reductions of α,β -unsaturated carbonyl compounds.²³

We chose 1,3-bis(2,6-di-isopropylphenyl)-imidazolium chloride (**1**)²⁴ for the preparation of the copper adduct. The air- and moisture-stable N-heterocyclic carbene-copper(I) complex **2** was readily prepared by deprotonation of **1** with NaOt-Bu in the presence of CuCl (Scheme 1).



Scheme 1. Preparation of N-heterocyclic carbene-copper (I) complex. Adapted with permission from Reference 25. Copyright 2003 American Chemical Society.

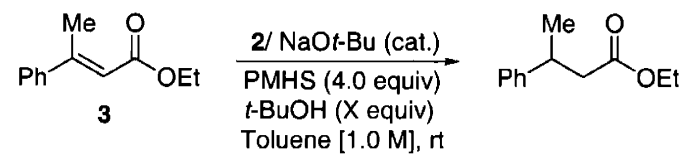
The initial study of conjugate reductions using **2** and NaOt-Bu in the presence of poly(methylhydrosiloxane) (PMHS) as stoichiometric reductant showed that **2** is an effective catalyst even when used at high substrate:catalyst ratio (Tables 1 and 2). Notably, the reaction is not limited to the use of PMHS; no change in reaction time or yield was observed with diphenylsilane as the stoichiometric reducing agent (Table 1, entries 1 and 2). Similarly, conjugate reductions catalyzed by **2** can be performed in either toluene or tetrahydrofuran with comparable efficiency (Table 1, entries 1 and 3). It is noteworthy that a cyclic enone can undergo conjugate reduction with as little as 0.05 mol % of **2**, although a longer reaction time is required (Table 1, entry 5).²⁵

Table 1. Catalytic conjugate reduction of a cyclic enone.


Entry	Silane	Solvent	2 , mol%	Time, h	Yield, ^a %
1	PMHS	Toluene	0.1	1	88
2	Ph ₂ SiH ₂	Toluene	0.1	1	87
3	PMHS	THF	0.1	1	86
4	Ph ₂ SiH ₂	THF	0.1	1	88
5	PMHS	Toluene	0.05	6	86

^a Isolated yield. All reactions reached full conversion as determined by GC. Adapted with permission from Reference 25. Copyright 2003 American Chemical Society.

We also investigated the use of **2** for the conjugate reduction of α,β -unsaturated esters. However, using 1 mol % of **2**, the reduction of ethyl *trans*- β -methylcinnamate (**3**) remained incomplete even after 20 hours.

Table 2. Catalytic conjugate reduction of an α,β -unsaturated ester.


Entry	<i>t</i> -BuOH, equiv	2 , mol%	Time, h	Conver., ^a %	Yield, %
1	-	1.0	20	65	-
2	3	0.1	20	80	-
3	4	0.1	20	100	89
4	4	0.3	1	100	91

^a Conversions were determined by GC. Adapted with permission from Reference 25. Copyright 2003 American Chemical Society.

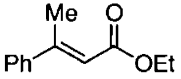
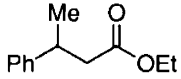
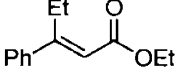
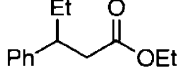
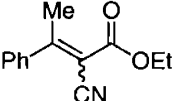
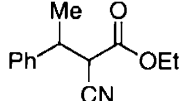
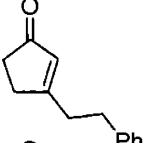
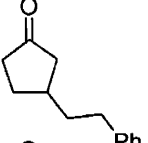
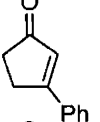
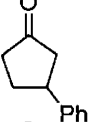
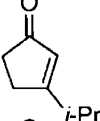
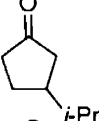
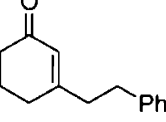
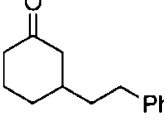
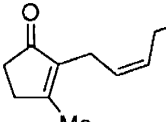
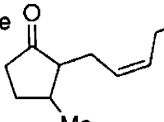
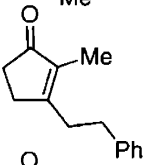
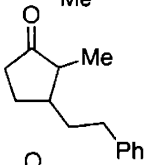
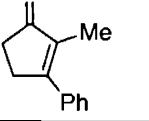
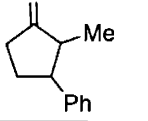
We previously found that the presence of an alcohol in the conjugate reduction of unsaturated esters, lactones, and lactams leads to an increased rate of reduction.^{22f} Here, too, a rate enhancement for the conjugate reduction of α,β -unsaturated esters was

observed in the presence of a bulky alcohol (Table 2, entries 1 and 2).²⁶ Thus, in the presence of *t*-BuOH (4 equiv), the conjugate reduction of **3** can be accomplished in 1 hour with only 0.3 mol % of **2** (Table 2, entry 4).

Encouraged by these results, we investigated the scope of conjugate reductions catalyzed by **2**. Several α,β -unsaturated carbonyl compounds were tested to determine the catalyst's tolerance to steric hindrance at the β -carbon, number of substituents at the double bond, and different functional groups (Table 3). As shown in Table 3, 0.1 mol % of **2** was sufficient to catalyze 1,4-reductions of trisubstituted cyclic enones, regardless of the size of the substituent at the β -carbon (entries 4-7). It is important to note that similar reductions catalyzed by (bis-phosphine)CuH complex require much larger amounts of catalyst and longer reaction times.^{23b}

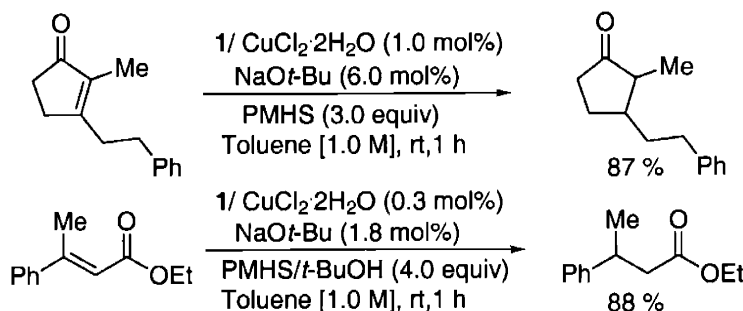
The conjugate reduction of a tetrasubstituted double bond represents a great challenge. Gratifyingly, using **2**, the efficient 1,4-reduction of tetrasubstituted double bonds can be accomplished (Table 3, entries 3, 8-10). Furthermore, substrates containing a cyano group (entry 3) or an isolated double bond (entry 8) were chemoselectively reduced; in each instance, the reduction product was obtained with the functional group intact.

Table 3. N-Heterocyclic carbene copper complex (**2**)-catalyzed conjugate reductions of α,β -unsaturated carbonyl compounds.

Entry	Starting material	Product	2 , mol %	Time, h	Yield, ^a %
1 ^b			0.3	1	91
2 ^b			0.3	1	97
3 ^c			2	4	93 ^d
4 ^e			0.1	1	88
5 ^e			0.1	3	95
6 ^e			0.1	1	81
7 ^e			0.1	1	93
8 ^f			1	1	85 ^g
9 ^f			1	1	90 ^h
10 ^f			3	3	94 ⁱ

^a Full conversions as determined by GC. Isolated yield of > 95 % purity as determined by GC and ¹H NMR. ^b 4 equiv of PMHS and 4 equiv of *t*-BuOH were used. ^c 12 equiv of PMHS and 12 equiv of *t*-BuOH were used. ^d 1.5:1 dr as determined by ¹H NMR. ^e 1.6 equiv of PMHS were used. ^f 3 equiv of PMHS were used. ^g 4:1 dr as determined by GC. ^h 4:1 dr as determined by GC. ⁱ 5:1 dr as determined by GC. Adapted with permission from Reference 25. Copyright 2003 American Chemical Society.

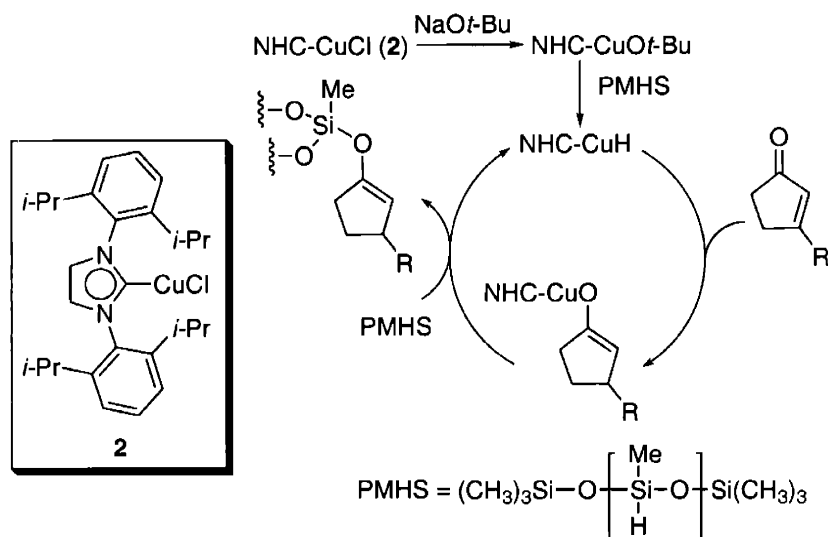
It is also possible to generate the N-heterocyclic carbene-copper catalyst in situ²⁷ by mixing imidazolium salt **1**, air- and moisture-stable $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, and NaOt-Bu in toluene followed by the addition of PMHS. When used in conjugate reduction reactions, the in situ-generated catalyst exhibited identical efficiency to that found for **2** (Scheme 2).



Scheme 2. In situ generation of N-heterocyclic carbene-copper catalyst. Adapted with permission from Reference 25. Copyright 2003 American Chemical Society.

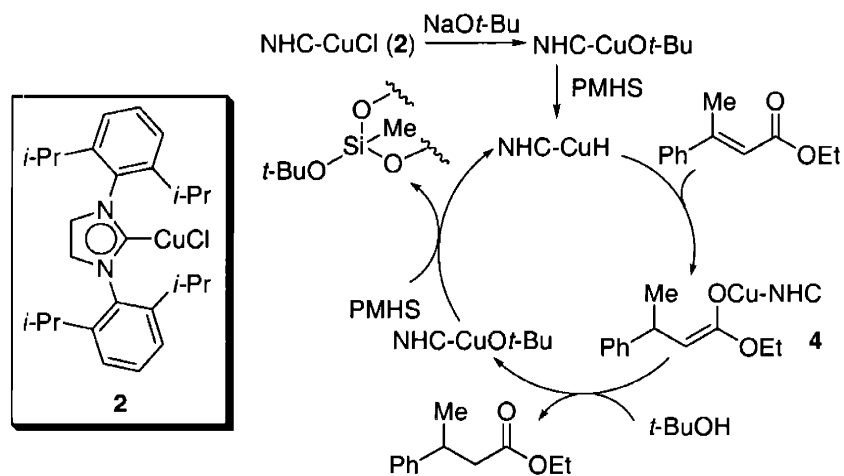
It is important to note that conjugate reduction catalyst can also be generated in situ by mixing 1,3-bis(2,6-di-*isopropylphenyl*)-4,5-dihydro-imidazolium tetrafluoroborate,²⁴ $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, and KOt-Bu in THF/toluene in the presence of PMHS, although much higher amounts of catalyst (2-5 mol %) were needed to effectively reduce trisubstituted α,β -unsaturated carbonyl compounds.

We propose that an N-heterocyclic carbene copper hydride (NHC-CuH) is the active catalyst in the catalytic cycle of the reaction.²² We postulate that upon combining **2** and NaOt-Bu , formation of N-heterocyclic carbene-CuOt-Bu occurs.²⁸ Presumably, addition of PMHS results in a σ -bond metathesis between N-heterocyclic carbene-CuOt-Bu and siloxane,²⁹ generating N-heterocyclic carbene-CuH (Scheme 3). Conjugate reduction then takes place, resulting in the formation of a copper enolate intermediate that in turn undergoes σ -bond metathesis with PMHS to produce a silyl enol ether in the case of a cyclic enone.³⁰



Scheme 3. Proposed catalytic cycle for the conjugate reduction of cyclic enone. Adapted with permission from Reference 25. Copyright 2003 American Chemical Society.

Since addition of *t*-BuOH results in a rate enhancement for the reductions of α,β -unsaturated esters, this suggests that the intermediate copper ketene acetal **4** undergoes rapid protonation by *t*-BuOH to afford the saturated ester, regenerating N-heterocyclic carbene-CuOt-Bu. The latter then undergoes σ -bond metathesis with PMHS to regenerate the active N-heterocyclic carbene-CuH catalyst (Scheme 4).³¹



Scheme 4. Proposed catalytic cycle for the conjugate reduction of α,β -unsaturated ester. Adapted with permission from Reference 25. Copyright 2003 American Chemical Society.

Conclusions

The method we report here represents the most active catalytic system to date for the conjugate reductions of α,β -unsaturated carbonyl compounds. While displaying great reactivity, a high level of functional group tolerance is also observed. The combination of catalytic amounts of **2** and NaOt-Bu, with PMHS or a silane as stoichiometric reductant, generates an N-heterocyclic carbene-CuH species that efficiently catalyzes 1,4-reductions of tri- and tetrasubstituted α,β -unsaturated esters and cyclic enones. Additionally, the N-heterocyclic carbene-CuH catalyst can be generated in situ from commercially available 1,3-bis(2,6-di-*isopropylphenyl*) imidazolium salt **1**, CuCl₂•2H₂O, NaOt-Bu, and PMHS.

Experimental Section

General considerations. Toluene, THF, and diethyl ether were purchased from J. T. Baker in CYCLE-TAINER[®] solvent delivery kegs which were vigorously purged with argon for 2 hours. Toluene was further purified by passing through two packed columns of neutral alumina and copper (II) oxide under argon pressure. THF was further purified by passing through a column of neutral alumina.³²

CuCl (99.995%) was purchased from Strem and NaOt-Bu was purchased from Aldrich and stored in a nitrogen-filled drybox. PMHS and anhydrous *t*-BuOH were purchased from Aldrich; CuCl₂•2H₂O (99+%), (*S*)-*p*-tol-BINAP, 1,3-bis(2,6-di-*i*-propylphenyl) imidazolium chloride, and diphenyl silane were purchased from Strem. All other reagents were available from commercial sources and were used without further purification, unless otherwise noted. All manipulations involving air-sensitive materials (except the reactions) were conducted in a Vacuum Atmospheres drybox under an atmosphere of nitrogen. All reactions, unless otherwise noted, were carried out in flasks sealed with a rubber or teflon screw septum under an atmosphere of argon.

Analytical thin layer chromatography was performed using E.M. Reagents 0.25 mm silica gel 60 plates, and visualization was accomplished with potassium

permanganate. Flash chromatography was performed on E.M. Science Kieselgel 60 (230-400 mesh).

Yields refer to isolated yields of compounds of greater than 95% purity as estimated by capillary GC and ^1H NMR. Yields reported in this section refer to a single experiment, while those reported in the tables are an average of two or more runs, so the numbers may differ slightly.

All new compounds were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy in addition to elemental analysis (Atlantic Microlabs) and/or high resolution mass spectra (Finnegan MAT System 8200 spectrometer).

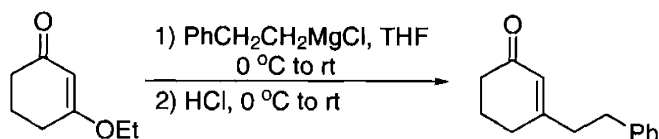
Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian Mercury 300, a Varian Unity 300, or a Varian Inova 500. Splitting patterns are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; td, triplet of doublets; q, quartet; qd, quartet of doublets; m, multiplet. All ^1H NMR spectra are reported in chemical shift (δ) units, parts per million (ppm) downfield from tetramethylsilane. All ^{13}C NMR spectra are reported in ppm relative to deuteriochloroform (77.23 ppm), and all were obtained with ^1H decoupling.

Infrared (IR) spectra were recorded on an ASI Applied Systems ReactIR 1000 (liquids and solids were measured neat on a DiComp probe). Melting points (uncorrected) were obtained on a Mel-Temp capillary melting point apparatus.

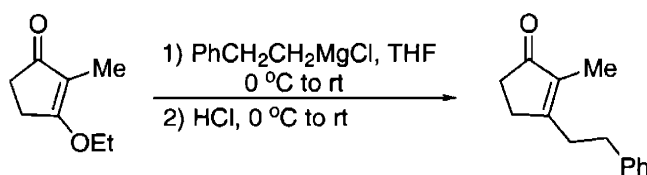
Gas chromatography (GC) analyses were performed on a Hewlett-Packard 6890 gas chromatograph with an FID detector using 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase. GS-mass spectrometry (GC-MS) analyses were performed on a Hewlett-Packard G1800B gas chromatograph with an electron ionization detector using the same GC column described above.

I. Synthesis of α,β -unsaturated carbonyl compounds.

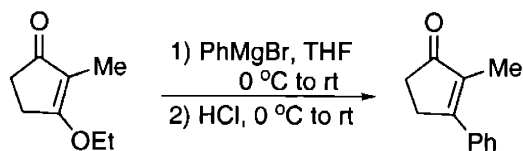
Ethyl *trans*- β -methylcinnamate, ethyl 2-cyano-3-phenyl-2-butenolate, and 2-(2-*cis*-pentenyl)-3-methyl-cyclopentenone (*cis*-jasnone) were purchased from Aldrich. 3-Phenethylcyclopentenone, 3-isopropylcyclopentenone, and 3-phenylcyclopentenone were prepared using procedures described in Experimental Sections of Chapters 1 and 2.



3-Phenethylcyclohexenone. Phenethylmagnesium chloride (64.0 mL, 64.0 mmol, 1.0 M in THF) was placed into an oven-dried Schlenk flask and cooled to 0 °C. 3-Ethoxycyclohexenone (4.50 mL, 32.0 mmol) was added to a separate dry flask, dissolved in THF (50 mL), then added via syringe to the phenethylmagnesium chloride solution.³³ The resulting solution was stirred at room temperature for 16 hours. At this point, the reaction was cooled to 0 °C and 1 M HCl (40 mL) was gradually added until pH=0 (as determined by ColorpHfast indicator strips). The aqueous phase was separated and extracted 3x with diethyl ether. The combined organic phases were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexane:ethyl acetate) afforded the product as a colorless oil (6.34 g, 99% yield). ¹H NMR (500 MHz, CDCl₃): δ 7.30-7.18, (5 H, m), 5.90 (1 H, s), 2.85-2.82 (2 H, m), 2.55-2.54 (2 H, m), 2.38-2.37 (2 H, m), 2.35-2.31 (2 H, m), 2.01-1.98 (2 H, m). ¹³C NMR (125 MHz, CDCl₃): δ 200.1, 165.6, 140.9, 128.7, 128.4, 126.5, 126.2, 39.9, 37.5, 33.6, 30.1, 22.9. IR (neat): 3062, 3027, 2921, 2858, 1702, 1675, 1615, 1495, 1455, 1436, 1409, 1339, 1287, 1231, 1183, 841, 753, 700 cm⁻¹. HRMS (EI, *m/e*) calcd for C₁₄H₁₆O: 200.1195 (M⁺). Found: 200.1194.

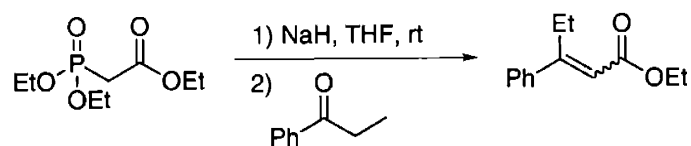


2-Methyl-3-phenethylcyclopentenone. Phenethylmagnesium chloride (10.0 mL, 10.0 mmol, 1.0 M in THF) was placed into an oven-dried Schlenk flask and cooled to 0 °C. 2-Methyl-3-ethoxycyclopentenone (0.7 g, 5.0 mmol) was added to a separate dry flask, dissolved in THF (2.0 mL), then added via syringe to the phenethylmagnesium chloride solution. The resulting solution was stirred at room temperature for 12 hours. At this point, the reaction was cooled to 0 °C and 1 M HCl (10 mL) was gradually added until pH=0 (as determined by ColorpHfast indicator strips). The aqueous phase was separated and extracted three times with diethyl ether. The combined organic phases were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (7:1 hexane:ethyl acetate) afforded the product as a colorless oil (0.68 g, 68% yield). ¹H NMR (500 MHz, CDCl₃): δ 7.31-7.27 (2 H, m), 7.23-7.17 (3 H, m), 2.87-2.83 (2 H, m), 2.75-2.72 (2 H, m), 2.50-2.48 (2 H, m), 2.37-2.36 (2 H, m), 1.50 (3 H, s). ¹³C NMR (125 MHz, CDCl₃): δ 210.4, 172.6, 141.0, 137.1, 128.8, 128.5, 126.6, 34.4, 33.6, 33.3, 29.7, 8.1. IR (neat): 3062, 3027, 2921, 2860, 1694, 1644, 1603, 1495, 1453, 1441, 1383, 1320, 1301, 1204, 1052, 751, 700 cm⁻¹. HRMS (EI, *m/e*) calcd for C₁₄H₁₆O: 200.1195 (M⁺). Found: 200.119.



2-Methyl-3-phenylcyclopentenone. Phenylmagnesium bromide (13.4 mL, 13.4 mmol, 1.0 M in THF) was placed into an oven-dried Schlenk flask and cooled to 0 °C. 2-Methyl-3-ethoxycyclopentenone (0.94 g, 6.68 mmol) was added to a separate dry flask,

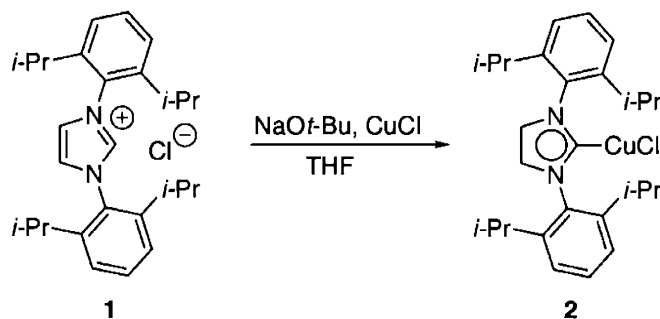
dissolved in THF (2.0 mL), then added via syringe to the phenylmagnesium bromide solution. The resulting solution was stirred at room temperature for 12 hours. At this point, the reaction was cooled to 0 °C and 1 M HCl (10 mL) was gradually added until pH=0 (as determined by ColorpHfast indicator strips). The aqueous phase was separated and extracted three times with diethyl ether. The combined organic phases were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (7:1 hexane:ethyl acetate) afforded the product as a colorless oil (0.70 g, 61% yield). Spectroscopic data were consistent with previously reported data for this compound.³⁴



Ethyl 3-phenylpent-2-enoate. Triethylphosphonoacetate (4.5 g, 20.0 mmol) was added to an oven-dried round bottom flask and dissolved in THF (10 mL). NaH was weighed out in a nitrogen-filled dry-box, and added in one portion to the above solution (evolution of gas was observed). The resulting solution was stirred for 30 min at room temperature. Propiophenone (2.7 g, 20.0 mmol) was added to a separate oven-dried round bottom flask and dissolved in THF (10 mL). The solution of propiophenone was then added via cannula to the reaction and the resulting solution was stirred at room temperature for 20 hours. The THF was removed *in vacuo*, and diethyl ether (50 mL) and aqueous NaHCO₃ (50 mL) were added. The aqueous phase was separated and extracted (3 x 150 mL) with diethyl ether. The combined organic phases were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. Purification by column chromatography (20:1 hexanes:diethyl ether) afforded the (*E*)-isomer (2.03 g, 50% yield) (*R*_f = 0.29) as a

colorless oil and the (*Z*)-isomer (1.75 g, 43% yield) ($R_f = 0.13$) as a colorless oil. Spectroscopic data were consistent with previously reported data for this compound.^{22a}

II. Synthesis of N-heterocyclic carbene copper (I) chloride complex (2).

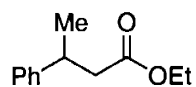


1,3-Bis(2,6-di-*i*-propylphenyl)imidazolium copper (I) chloride (2). An oven-dried Schlenk flask was charged with 1,3-bis(2,6-di-*i*-propylphenyl) imidazolium chloride (1) (0.45 g, 1.06 mmol). Fresh CuCl (0.105 g, 1.06 mmol), NaOt-Bu (0.102 g, 1.06 mmol), and THF (5.3 mL) were added to this Schlenk flask. The resulting suspension was stirred at room temperature for 4 hours, then filtered over celite and concentrated *in vacuo*. The title compound was obtained as a gray powder (0.387 g, 75% yield). Melting point: >300 °C. ¹H NMR (500 MHz, Acetone-*d*₆): δ 7.26 (s, 2 H), 7.57-7.54 (dd, *J* = 15.5, 8.0 Hz, 2 H), 7.43-7.41 (d, *J* = 8.0 Hz, 4 H), 2.70-2.65 (m, 4 H), 1.32-1.31 (d, *J* = 7.0 Hz, 12 H), 1.27-1.25 (d, *J* = 6.5 Hz, 12 H). ¹³C NMR (125 MHz, Acetone-*d*₆): δ 180.2, 146.0, 135.1, 130.6, 124.2, 24.4, 23.3. IR (neat): 2968, 2927, 2871, 1680, 1647, 1470, 1457, 809, 764, 743 cm⁻¹. Elemental analysis: Calcd: C 66.51%, H 7.44%. Found: C 66.34, H 7.44%. HRMS (EI, *m/e*) calcd for C₁₄H₁₆O: 389.2951 (-CuCl M⁺). Found: 389.2962.

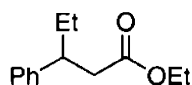
III. Conjugate reductions of α,β -unsaturated esters using 2.

General Procedure A: conjugate reductions of trisubstituted α,β -unsaturated esters.

An oven-dried flask was charged with N-heterocyclic carbene copper chloride complex (2) (8.0 mg, 0.02 mmol, 0.3 mol %), fresh NaO*t*-Bu (2.0 mg, 0.02 mmol, 0.3 mol %), and toluene (1.0 mL). The mixture was stirred at room temperature for 10 min, then PMHS (0.33 mL, 5.5 mmol) was added and the resulting yellow/orange solution was stirred at room temperature for 5 min. Additional amounts of toluene (2.0 mL) followed by PMHS (0.99 mL, 16.4 mmol) were added to the solution of catalyst. A solution of trisubstituted α,β -unsaturated ester (5.5 mmol, 1.0 equiv) and *t*-BuOH (1.26 mL, 21.9 mmol) in toluene (2.5 mL) was then added via cannula to the solution of catalyst and PMHS (evolution of gas was observed). The reaction was stirred at room temperature for 1 hour, then water (5 mL) was added and the biphasic mixture was stirred for 5 min. Full conversion was confirmed by gas chromatography (GC). Ethyl acetate (50 mL) and water (10 mL) were added and resulting phases separated. The aqueous phase was extracted with ethyl acetate (3x 150 mL) and the combined organic extracts were washed with brine, dried over anhydrous MgSO₄, and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel.

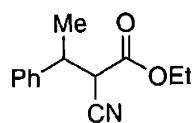


Ethyl 3-phenylbutyrate (Table 3, entry 1). Following General Procedure A, ethyl *trans*- β -methylcinnamate (1.00 mL, 5.48 mmol) was converted in 1 hour to the title compound. Purification by flash chromatography (30:1 hexanes:ethyl acetate) afforded the pure product as a clear oil (0.947 g, 90 % yield). Spectroscopic data were consistent with previously reported data for this compound.^{22a}



Ethyl 3-phenylpentanoate (Table 3, entry 2). Following General Procedure A, ethyl (*E*)-3-phenylpent-2-enoate (1.12 g, 5.48 mmol) was converted to the title compound in 1 hour. Purification by flash chromatography (20:1 hexanes:ethyl acetate) afforded the pure product as a clear oil (1.08 g, 96 % yield). Spectroscopic data were consistent with previously reported data for this compound.^{22a,35}

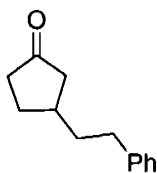
General Procedure B: conjugate reduction of tetrasubstituted α,β -unsaturated ester. An oven-dried flask under was charged with **2** (8.0 mg, 0.02 mmol, 3.0 mol %), fresh NaO*t*-Bu (2.0 mg, 0.02 mmol, 3.0 mol %), and toluene (0.5 mL). The mixture was stirred at room temperature for 10 min, then PMHS (0.395 mL, 6.58 mmol, 12.0 equiv) was added and the resulting yellow/orange solution was stirred at room temperature for 5 min. A neat tetrasubstituted α,β -unsaturated ester (0.55 mmol, 1.0 equiv) was added to the solution of catalyst in one portion at room temperature and stirred for 1 min. Then neat *t*-BuOH (0.63 mL, 6.58 mmol, 12.0 equiv) was added (evolution of gas was observed). The reaction was stirred at room temperature for 3 hours, then water (1 mL) was added and the biphasic mixture was stirred for 5 min. Full conversion was confirmed by GC. Ethyl acetate (10 mL) and water (5 mL) were added and the resulting phases separated. The aqueous phase was extracted with ethyl acetate (3x 50 mL) and the combined organic extracts were washed with brine, dried over anhydrous MgSO₄, and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel.



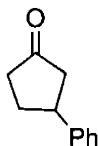
Ethyl 2-cyano-3-phenylbutyrate (Table 3, entry 3). Following General Procedure B, ethyl (*E/Z*)-2-cyano-3-phenylbutyrate (0.108 mL, 0.548 mmol) was converted in 3 hours to the title compound (with 1.5:1 diastereomeric ratio as determined by ¹H NMR). Purification by flash chromatography (hexanes:ethyl acetate 20:1) afforded the pure product as a clear oil (0.11 g, 93 % yield for the mixture of diastereomers). Spectroscopic data were consistent with previously reported data for this compound.³⁶

IV. Conjugate reductions of α,β -unsaturated cyclic enones using 2.

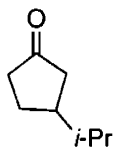
General Procedure C: conjugate reductions of trisubstituted α,β -unsaturated cyclic enones. An oven-dried flask under argon was charged with 2 (3.0 mg, 6.5×10^{-3} mmol, 0.1 mol %), fresh NaOt-Bu (1.0 mg, 6.5×10^{-3} mmol, 0.1 mol %), and toluene (1.0 mL). The mixture was stirred at room temperature for 10 min, then PMHS (0.23 mL, 3.9 mmol) was added and the resulting yellow/orange solution was stirred at room temperature for 5 min. Additional amounts of toluene (5.5 mL) followed by PMHS (0.38 mL, 6.4 mmol, 1.0 equiv) were added to the solution of catalyst. A neat trisubstituted α,β -unsaturated cyclic enone (6.45 mmol) was added to this solution in one portion and the reaction was stirred at room temperature for the indicated period of time. Water (5 mL) was added and the biphasic mixture was stirred for 5 min. Full conversion was confirmed by gas chromatography (GC). Ethyl acetate (50 mL) and water (10 mL) were added and the resulting phases separated. The aqueous phase was extracted with ethyl acetate (3x 150 mL) and the combined organic extracts were washed with brine, dried over anhydrous MgSO₄, and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel.



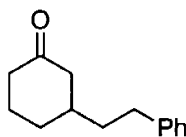
3-Phenethylcyclopentanone (Table 3, entry 4). Following General Procedure C, 3-phenethylcyclopentenone (1.20 g, 6.5 mmol) was converted to the title compound in 1 hour. Purification by flash chromatography (hexanes:ethyl acetate 10:1) afforded the pure product as a clear oil (1.08 g, 89 % yield). Spectroscopic data were consistent with previously reported data for this compound.³⁷



3-Phenylcyclopentanone (Table 3, entry 5). Following General Procedure C, 3-phenylcyclopentenone (1.02 g, 6.5 mmol) was converted to the title compound in 3 hours. Purification by flash chromatography (hexanes:ethyl acetate 10:1) afforded the pure product as a clear oil (0.98 g, 95 % yield). Spectroscopic data were consistent with previously reported data for this compound.^{37,38}

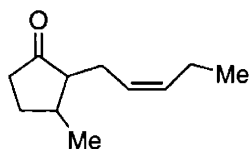


3-Isopropylcyclopentanone (Table 3, entry 6). Following General Procedure C, 3-isopropylcyclopentenone (0.80 g, 6.5 mmol) was converted to the title compound in 1 hour. Purification by flash chromatography (pentane:diethyl ether 10:1) afforded the pure product as a clear liquid (0.65 g, 80 % yield). Spectroscopic data were consistent with previously reported data for this compound.³⁹

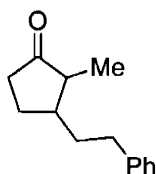


3-Phenethylcyclohexanone (Table 3, entry 7). Following General Procedure C, 3-phenethylcyclohexenone (1.29 g, 6.5 mmol) was converted to the title compound in 1 hour. Purification by flash chromatography (hexanes:ethyl acetate 10:1) afforded the pure product as a clear liquid (1.21 g, 93 % yield). Spectroscopic data were consistent with previously reported data for this compound.³⁷

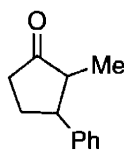
General Procedure D: conjugate reductions of tetrasubstituted α,β -unsaturated cyclic enones. An oven-dried flask under argon was charged with **2** (1.0-3.0 mol %, as indicated later), fresh NaOt-Bu (1.0-3.0 mol %, as indicated later), and toluene (0.5 mL). The mixture was stirred at room temperature for 10 min, then PMHS (0.18 mL, 3.0 mmol) was added and the resulting yellow/orange solution was stirred at room temperature for 5 min. A neat tetrasubstituted α,β -unsaturated cyclic enone (1.0 mmol, 1.0 equiv) was added to this solution in one portion and the reaction was stirred at room temperature for the indicated period of time. Water (1 mL) was added and the biphasic mixture was stirred for 5 min. Full conversion was confirmed by GC. Ethyl acetate (20 mL) and water (10 mL) were added and the resulting phases separated. The aqueous phase was extracted with ethyl acetate (3x 100 mL) and the combined organic extracts were washed with brine, dried over anhydrous MgSO₄, and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel.



3-Methyl-2-(2-*cis*-pentenyl)cyclopentanone (Table 3, entry 8). Following General Procedure D, using 1.0 mol % of **2** and NaOt-Bu, *cis*-jasmone (0.175 mL, 1.00 mmol) was converted to the title compound in 1 hour. GC indicated full conversion and 4:1 diastereomeric ratio. Purification by flash chromatography (pentane:diethyl ether 15:1) afforded the pure product as a clear liquid (0.141 g, 85 % yield for the mixture of diastereomers 4:1). Spectroscopic data were consistent with previously reported data for this compound.⁴⁰

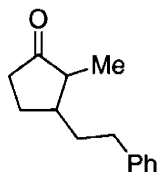


2-Methyl-3-phenethylcyclopentanone (Table 3, entry 9). Following General Procedure D, using 1.0 mol % of **2** and NaOt-Bu, 2-methyl-3-phenethylcyclopentanone (0.20 g, 1.00 mmol) was converted to the title compound in 1 hour. GC indicated full conversion and 4:1 diastereomeric ratio. Purification by flash chromatography (hexanes:ethyl acetate 20:1) afforded the pure product as a clear oil (0.182 g, 90 % yield for the mixture of diastereomers 4:1). Spectroscopic data were consistent with previously reported data for this compound.^{22c}



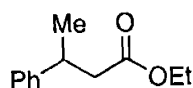
2-Methyl-3-phenylcyclopentanone (Table 3, entry 10). Following General Procedure D, using 3.0 mol % of **2** and NaOt-Bu, 2-methyl-3-phenylcyclopentanone (0.172 g, 1.00 mmol) was converted to the title compound in 3 hours. GC indicated full conversion and 5:1 diastereomeric ratio. Purification by flash chromatography (pentane:diethyl ether 10:1) afforded the pure product as a clear oil (0.164 g, 94 % yield for the mixture of diastereomers 5:1). Spectroscopic data were consistent with previously reported data for this compound.³⁶

V. Conjugate reductions with in situ generated copper carbene catalyst.



2-Methyl-3-phenethylcyclopentanone (Scheme 2). An oven-dried flask was charged with 1,3-bis(2,6-di-*i*-propylphenyl) imidazolium chloride (**1**) (5.0 mg, 0.012 mmol, 1.0 mol %), CuCl₂•2H₂O (2.0 mg, 0.012 mmol, 1.0 mol %), NaOt-Bu (7.0 mg, 0.072 mmol, 6.0 mol %), and toluene (1.2 mL). The mixture was stirred at room temperature for 30 min, then PMHS (0.22 mL, 3.60 mmol) was added and the resulting solution was stirred at room temperature for 15 min. Neat 2-methyl-3-phenethylcyclopentanone (0.24 g, 1.2 mmol) was added to this solution in one portion and the reaction was stirred at room temperature for 1 hour. Water (1 mL) was added and the biphasic mixture was stirred for 5 min. GC indicated full conversion and 2:1 diastereomeric ratio for the product. Ethyl acetate (20 mL) and water (10 mL) were added

and the resulting phases separated. The aqueous phase was extracted with ethyl acetate (3x 100 mL) and the combined organic extracts were washed with brine, dried over anhydrous MgSO_4 , and concentrated *in vacuo*. Purification by flash chromatography (hexanes:ethyl acetate 20:1) afforded the pure product as a clear oil (0.21 g, 87 % yield for the mixture of diastereomers 2:1). Spectroscopic data were consistent with previously reported data for this compound.^{22c}



Ethyl 3-phenylbutyrate (Scheme 2). An oven-dried flask was charged with **1** (5.0 mg, 0.01 mmol, 0.03 mol %), $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (2.0 mg, 0.01 mmol, 0.3 mol %), NaOt-Bu (7.0 mg, 0.07 mmol, 1.8 mol %), and toluene (1.0 mL). The mixture was stirred at room temperature for 30 min, then PMHS (0.23 mL, 3.8 mmol) was added and the resulting solution was stirred at room temperature for 15 min. Additional amounts of toluene (2.8 mL) followed by PMHS (0.69 mL, 12.0 mmol) were added to the solution of catalyst. Neat ethyl *trans*- β -methylcinnamate (0.70 mL, 3.8 mmol) was then added in one portion and the reaction was stirred for 1 min. Neat *t*-BuOH (1.47 mL, 15.3 mmol) was then added to the reaction at room temperature (evolution of gas was observed). The reaction was stirred at room temperature for 1 hour, then water (5 mL) was added and the biphasic mixture was stirred for 5 min. Full conversion was confirmed by GC. Ethyl acetate (50 mL) and water (10 mL) were added and the resulting phases separated. The aqueous phase was extracted with ethyl acetate (3x 150 mL) and the combined organic extracts were washed with brine, dried over anhydrous MgSO_4 , and concentrated *in vacuo*. Purification by flash chromatography (30:1 hexanes:ethyl acetate) afforded the pure product as a clear oil (0.648 g, 88 % yield). Spectroscopic data were consistent with previously reported data for this compound.³⁴

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