Development and optimization of photoredox-mediated methine epimerization

by

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ABSTRACT

Reactions that edit the stereochemistry of individual atoms are enabling tools in synthetic chemistry. The Wendlandt lab has developed a sequential H-atom abstraction and donation strategy to synthesize rare sugars from biomass platform molecules such as D-glucose. Efforts to apply this strategy to the epimerization of steroids gave poor results and demonstrated limited selectivity, but insights gained from this work were used to develop a hypothesis for epimerization. We proposed that H-atom abstraction and donation occur to release diaxial strain and form the most conformationally stable isomer. This hypothesis guided the development of an epimerization method for methine stereocenters. This work describes the optimization and development of methine epimerization of isomenthyl acetate. The epimerization of tertiary alkyl stereocenters is also applied to access an otherwise synthetically challenging stereochemical outcome from a Diels-Alder reaction sequence. Data from primary literature and mechanistic experiments are used to provide a proposed mechanism through which this epimerization proceeds.

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I. Introduction

Radical-mediated epimerization reactions

Relative and absolute stereochemical configurations of a molecule are critical to defining and differentiating the properties of chemical compounds, and methods that can selectively edit a single stereocenter can potentially provide a synthetic platform that delivers access to stereochemical outcomes inaccessible via bond-forming reaction steps along a synthetic route. The potential diversity of stereochemical outcomes obtained from employing epimerization reactions renders the development of selective and efficient epimerization methods an enabling objective for organic chemists.[1]

Traditional epimerization schemes rely on functional group handles for chemical manipulation. Commonly employed strategies include Mitsunobu reactions or oxidation-reduction sequences, which find utility in the epimerization of alcohols or functional groups that may be readily converted to alcohols, such as amines or halides.[2–4] The epimerization of stereocenters containing aliphatic or aromatic groups is generally limited to thermodynamic resolutions of base-labile stereocenters.[5]

Research conducted in the Wendlandt lab leverages energy input from light to generate high-energy intermediates that promote H-atom abstraction. The resultant stereoablated carbon-centered radical readily abstracts hydrogen from an H-atom donor to provide epimerization. This strategy has been applied to the synthesis of rare sugar isomers from biomass-derived platform molecules such as D-glucose, demonstrating how the framework of stereochemical editing can be leveraged for the construction of synthetically challenging or otherwise inaccessible stereochemical outcomes.[6] We hoped to expand the scope of this transformation outside the context of carbohydrate synthesis; to this end, I will briefly introduce my research efforts translating a photocatalytic epimerization platform from sugar substrates to steroids and other cyclohexanols. The initial insights gained from this work were applied to develop the epimerization of tertiary, unactived methine stereocenters. Then, I will discuss a synthetic application of our reaction, where we leverage epimerization to access a stereochemical outcome that bond-constructing reactions fail

to establish. Finally, I will synthesize data collected in our lab and reported in the literature to provide mechanistic insight towards understanding the potential limitations of this chemistry. The research disclosed herein represents an incremental step towards establishing epimerization as a platform for stereochemical editing.

Expansion of epimerization platform to steroids and cyclohexanols

In preliminary work conducted by Dr. Yong Wang and Ellie Plachinski, previously-developed conditions were applied to the epimerization of steroids. Steroids were chosen as a class of natural products of interest because of the dense stereochemical features contained within their tetracyclic scaffolds. Current industry-scale steroid chemistry relies on steroidal feedstock from biomass, and synthesis of steroidal active pharmaceutical ingredients (APIs) typically leverages stereochemical information intrinsic to the steroidal nucleus the API is derived from.[7–10] However, inversion of the stereochemistry of C3-hydroxyl groups in steroids is a chemically valuable transformation in providing access to *epi*-steroids as potential drug targets. In addition to traditional schemes for alcohol inversion such as Mitsunobu or stoichiometric oxidation-reduction schemes,[11] catalytic methods to epimerize secondary alcohols on steroids proceeding via sequential β-hydride elimination and hydride donation elementary steps have been developed using ruthenium complexes.[12,13] Catalytic epimerizations of secondary alcohols on steroids proceeding via one-electron processes (i.e. sequential H-atom abstraction and donation) have not been disclosed, and we hoped to investigate the feasibility of this prospect using chemistry developed in our lab.

Initial work identified the epimerization of cholesterol to 3-*epi*-cholesterol as a platform suitable for optimization. Under our proposed model for epimerization via radical intermediates, H-atom abstraction by quinuclidinium radical cation occurs from the C3 stereocenter, generating a 2º alcohol radical stabilized through induction. Then, H-atom donation from adamantane thiol proceeds via an equatorial delivery in order to obtain the inverted alcohol. Product formation of up to 44% was detected by crude NMR analysis, however, up to 38% of additional material was consumed and unaccounted for, indicating the need for further screening and optimization. Despite extensive screening, attempts to reproduce this result were

unsuccessful, and I was unable to obtain 3-*epi*-cholesterol in greater than 11% yield. We then pivoted our goal towards investigating whether this low yield was due to poor reactivity between the catalysts and the substrate or poor selectivity of H-atom abstraction or donation. Authentic 3-*epi*-cholesterol was prepared following literature procedures from cholesterol via Dess-Martin oxidation followed by L-Selectride reduction,[14,15] and a series of mechanistic studies were conducted (Figure 1.1). The epimerization of cholesterol only afforded 6% 3-*epi*-cholesterol and subjecting 3-*epi*-cholesterol to the same reaction conditions produced cholesterol in 10% yield. Additionally, under *d*-incorporation conditions, epimerization of either isomer results in comparably low-yielding product formation, with *d*-incorporation into the axial C-H of cholesterol observed in both cases. Importantly, no *d*-incorporation was observed into the equatorial C-H of 3-epi-cholesterol. The poor yields of epimerization in either direction suggest that overall reaction of the starting material with the catalyst system is poor, and *d*-incorporation into only one isomer regardless of which starting isomer is subjected to the reaction conditions suggests that axial H-atom donation is favored in this reaction system.

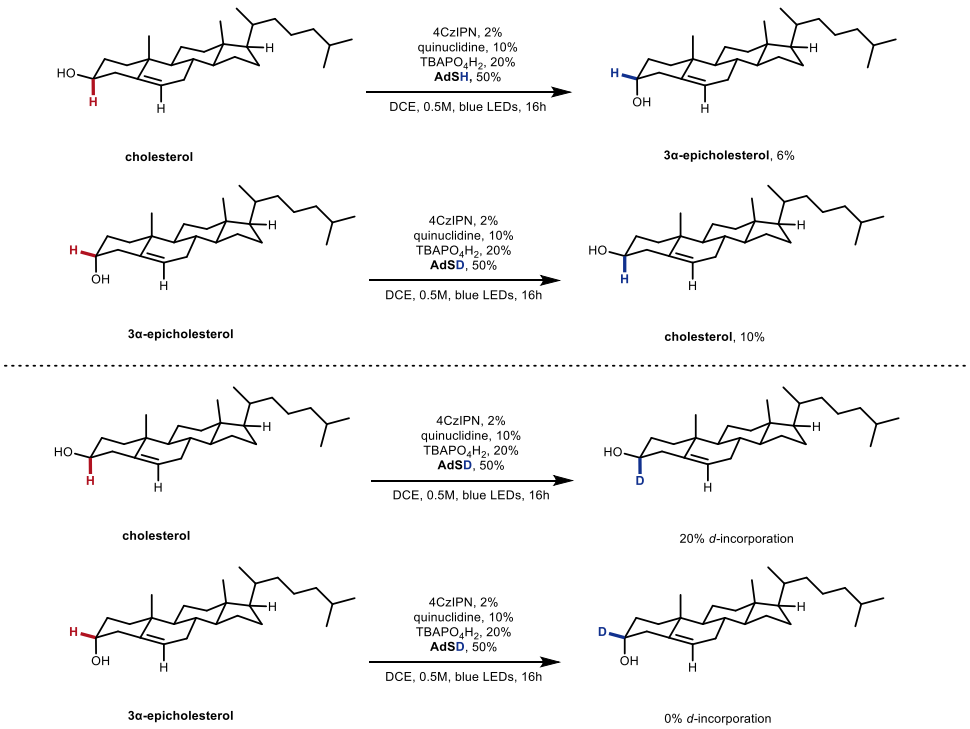


Figure 1.1 Epimerization of steroids proceeds with both poor conversion and poor selectivity.

Insight gained from studying conversion versus selectivity in the cholesterol system led to the genesis of a hypothesis for whether axial H-atom donation is generally preferred in the epimerization of cyclohexanols as a broader class of substrates, resulting in epimerization that favors the thermodynamically more stable isomer. Parallel progress towards the epimerization of cyclohexane diols was made by Dr. Yu-An Zhang, so I chose to explore my hypothesis using the epimerization of neomenthol to menthol as a platform for optimization due to the conformational stability afforded by the equatorial *i*Pr group. Conditions for alcohol epimerization using $(Ir[dF(Me)ppy]_2(dtbbpy))PF_6$ (IrF), quinuclidine, and triphenylsilane thiol afforded low but promising yields of the epimerization of neomenthol to menthol, and trace amounts of the epimerization of menthol to neomenthol also occurred. Following optimization of catalyst loadings, the epimerization of neomenthol to menthol was obtained in 86% yield (Figure 1.2). Comparing epimerization yield in either direction with quantitation of *d*-incorporation revealed that under these conditions, reaction conversion is high but selectivity is still poor. The lack of catalyst control over H-atom donation selectivity poses a limitation for the utility of this method, but preliminary results corroborated the hypothesis for an epimerization reaction that overall favors the more stable isomer.

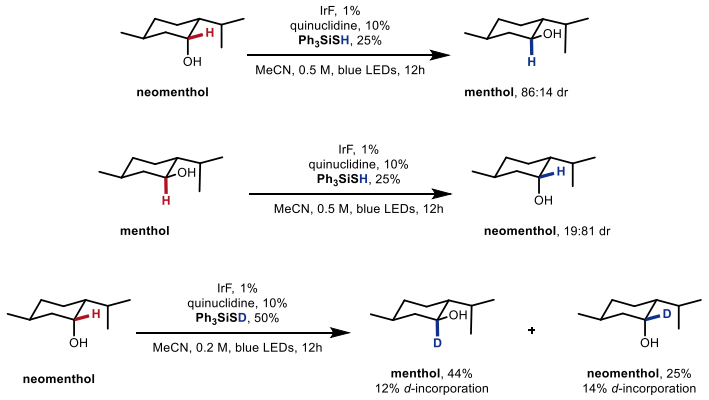


Figure 1.2 Epimerization of neomenthol and menthol proceeds with high conversion and poor H-atom donation selectivity.

II. Methine epimerization

Inspiration and optimization

Recognizing the limitations of a thermodynamic epimerization of secondary alcohol stereocenters, which can also be accessed via Mitsunobu or oxidation-reduction schemes, I sought to test whether the hypothesis for H-atom donation to afford more stable isomers could be leveraged towards the epimerization of tertiary alkyl stereocenters instead. Reactions that are used to form tertiary alkyl centers often also provide a distribution of diastereomers that is dependent on the factors governing the bond-forming reaction,[16] and an epimerization reaction that can access and edit tertiary alkyl stereocenters independent of the bond-forming reaction is widely enabling in instances where a different stereochemical outcome is desired. Previous work published by Chen reports an epimerization method using superstoichiometric amounts of a benziodoxole precursor forms an azide radical H-atom abstractor that is compatible with tertiary alkyl stereocenters.[17] Product distributions typically favor more stable thermodynamic isomers, and the proposed mechanism for epimerization proceeds via a thermodynamic equilibration between an H-atom abstractor and the tertiary methine stereocenter. However, undesired reactivity such as azidation and epimerization at multiple sites is also observed.

Under conditions using IrF, quinuclidine, and triphenylsilane thiol, the epimerization of isomenthol to menthol was observed in 27% yield. Formation of neomenthol was also observed, indicative of poor selectivity in H-atom abstraction for this particular substrate, albeit in a low yield. Acetate protection of the secondary alcohol mitigated this selectivity issue. Several photocatalysts afforded epimerization with triphenylsilane thiol as an H-atom shuttle, but reactivity was best with tetrabutylammonium decatungstate (TBADT) as an H-atom abstractor and diaryl disulfide as an H-atom donor (Figure 2.2 A, entry 5). The addition of water improved reaction yields (Figure 2.3, entry 5), and this is hypothesized to stabilize the highly polar reactive state of the photocatalyst in solution. Strongly electron-donating substituents on aryl thiols or diaryl disulfides gave moderately diminished epimerization yield, consistent with predicted reactivity based on BDE (Figure 2.2 B). Other variation of aryl substituents on the disulfide catalyst resulted

in little or no effect on the observed distribution of isomers. However, use of alkyl disulfides, alkyl thiols, or silane thiols were ineffective in comparison. In the presence of oxygen, alkyl radicals generated from H-atom abstraction by TBADT react to form oxygenated products.[18,19] Injecting 50 uL of air via gas-tight syringe and addition of reaction components under air rather than nitrogen resulted in only slightly diminished yields (Figure 2.3, entries 6 and 7), but no oxygenated byproducts were observed.

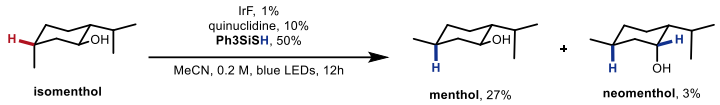


Figure 2.1 Initial observation of isomenthol epimerization.

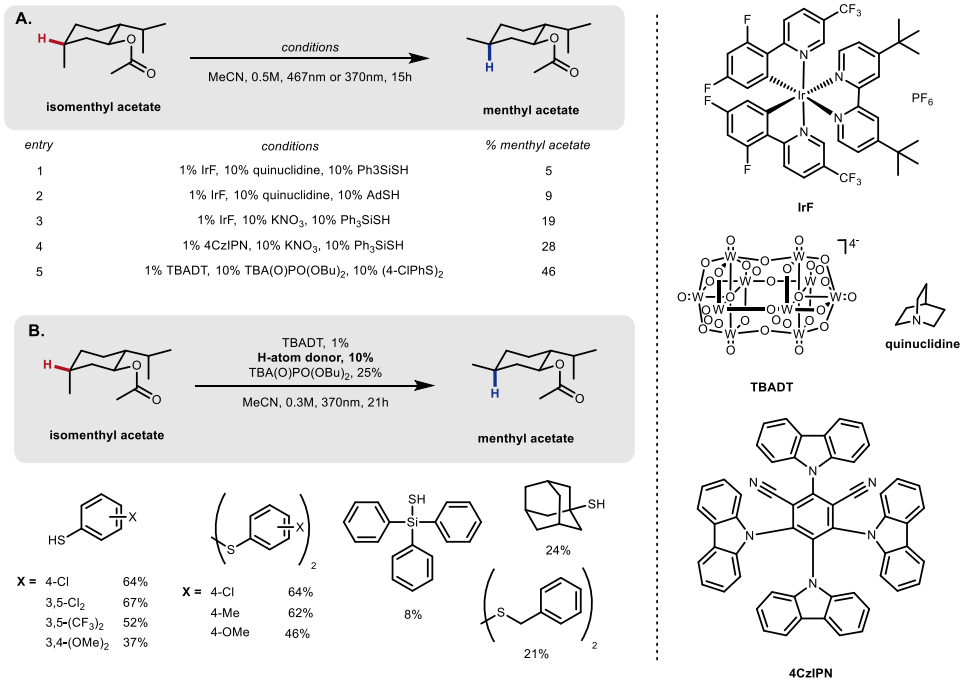
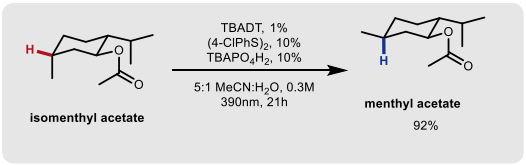


Figure 2.2 A. Compatible systems for epimerization of isomenthyl acetate. B. Effect of H-atom donor on reaction yield.



entry	*conditions*	*% menthyl acetate*
1	no light	0
2	no TBADT	0
3	no disulfide	10
4	no base	72
5	no water	64
6	+ 50μL air	85
7	set up under air	75

Figure 2.3 Optimized conditions and reaction tolerance.

Epimerization of Diels-Alder adduct

With optimized conditions in hand, we sought to apply our epimerization conditions to provide access to synthetically challenging stereochemical outcomes. The Diels-Alder cycloaddition of (E,E)-2,4-hexadiene and maleimide yields the *endo* adduct in excellent yield and diastereoselectivity. Following hydrogenation, subjecting **1** to epimerization conditions provides *exo* isomer **2** in 94% yield. The structures of both isomers were unambiguously confirmed via NOE experiments. Mechanistic studies probing the site of epimerization revealed deuterium incorporation at nearly every C-H bond (Figure 2.4), so the specific site of epimerization remains unclear. The overall isomerization of the kinetically-favored *endo* **1** to the thermodynamically-favored *exo* **2** is conistent with a predicted outcome based on conformational analysis. Attempts at an authentic preparation of the thermodynamically-favored adduct **2** from the cycloaddition of maleimide with freshly prepared (Z,Z)-2,4-hexadiene[20] failed: only kinetically-favored adduct was observed. Although this example represents a specific case that lacks broad applicability to synthetic methods at large, the demonstrated access to diverse stereochemical outcomes adds value to the epimerization method, and further efforts to develop this idea into a more general platform are underway in the Wendlandt lab.

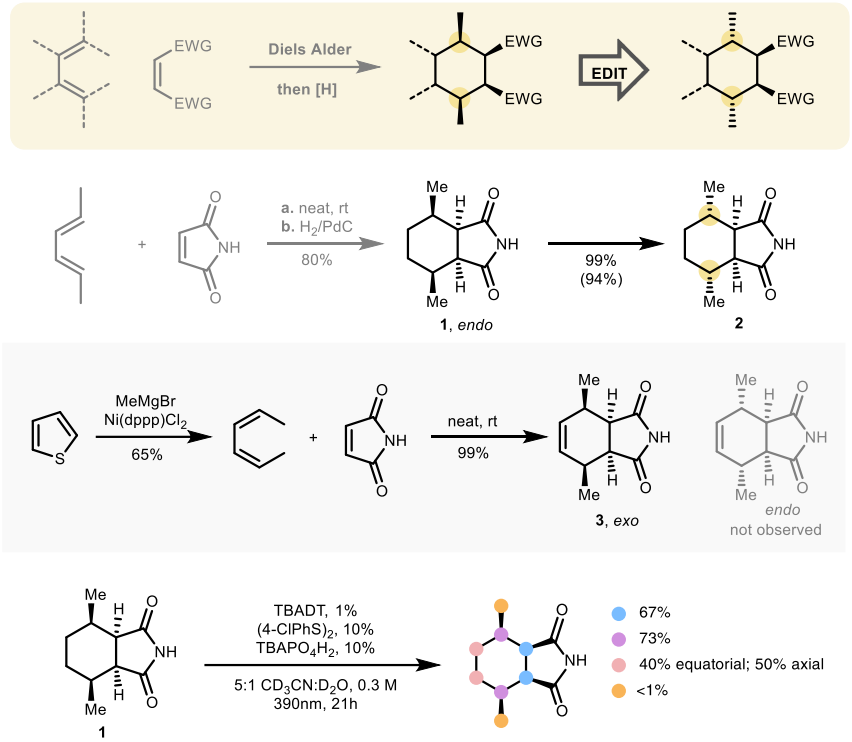


Figure 2.4 Stereochemical editing of Diels-Alder cycloaddition.

Mechanistic insights

While the reactivity and photophysical properties of TBADT have been documented in the literature, unlike other photocatalysts such as IrF or 4CzIPN, polyoxometalate anions and the subsequently generated excited states and reduced states do not fluoresce. Instead, quenching kinetics are obtained by monitoring the transient absorbance kinetics corresponding to the decay of the decatungstate reactive state (**wO**) absorbance on nanosecond time scales.[21–23] The **wO** reactive state can quench via either single-electron transfer or H-atom transfer, and it is likely that direct H-atom transfer between **wO** and the substrate is responsible for the generation of the alkyl radical intermediate.[24,25] Formation of a thiyl radical can occur via oxidation of thiolate by **wO**, and while reports of thiyl radical-mediated H-atom abstraction have been published by Roberts,[26–29] Dilman[30] and others,[31–34] H-atom abstraction occurring between p-chlorophenylthiyl radical and substrate in the presence of **wO** is unlikely. Kinetic absorption spectrophotometry performed by Miyashita use laser flash photolysis to generate free thiyl radical and measure its decay.[35] Their studies show that when p-chlorophenylthiyl radical is generated in cyclohexane,

its decays following second order kinetics, consistent with thiyl-thiyl recombination to form disulfide and not consistent with thiyl-mediated H-atom abstraction from cyclohexane. However, when p-chlorophenylthiyl radical is generated in cumene, pseudo-first order decay is observed, indicating that dimerization is suppressed in favor of H-atom abstraction from the benzylic position. The observed rate of reaction between thiyl radical and cumene is about 20 times slower than the rate of H-atom abstraction between t-butoxyl radical and cumene. In comparison, the rate of H-atom abstraction from cyclohexane by **wO** is roughly 40 times faster than the rate of H-atom abstraction from cyclohexane by *t*-butoxyl radical.[21,36] While these data do not provide a perfect interpretation of H-atom abstraction rates in our epimerization reactions, even in the presence of a thiyl radical, H-atom abstraction mediated by **wO** is likely responsible for the generation of the alkyl radical intermediate. Cross coupling and functionalization reactions proceeding via alkyl radicals generated by TBADT catalysis published by MacMillan,[37,38] Noel,[19,39] and others[24,40] also contribute to the consensus that **wO** is responsible for the H-atom abstraction elementary step.

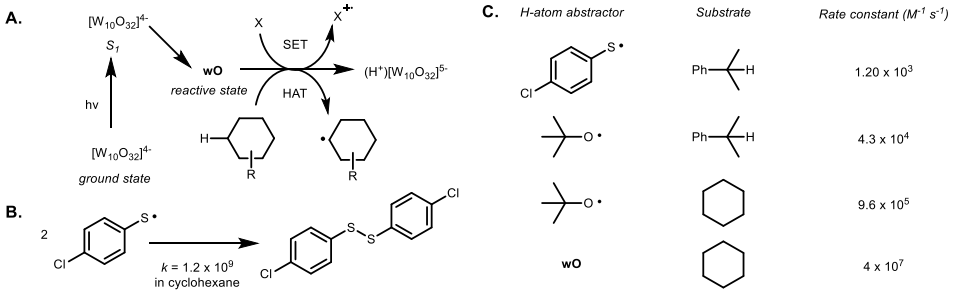


Figure 2.5 A. Decatungstate anion excitation and reactive state quenching pathways, adapted from Ravelli and Fagnoni.[24] B. Second-order decay of thiyl radical in cyclohexane. C. Comparison of rates of H-atom abstraction.[21,35,36]

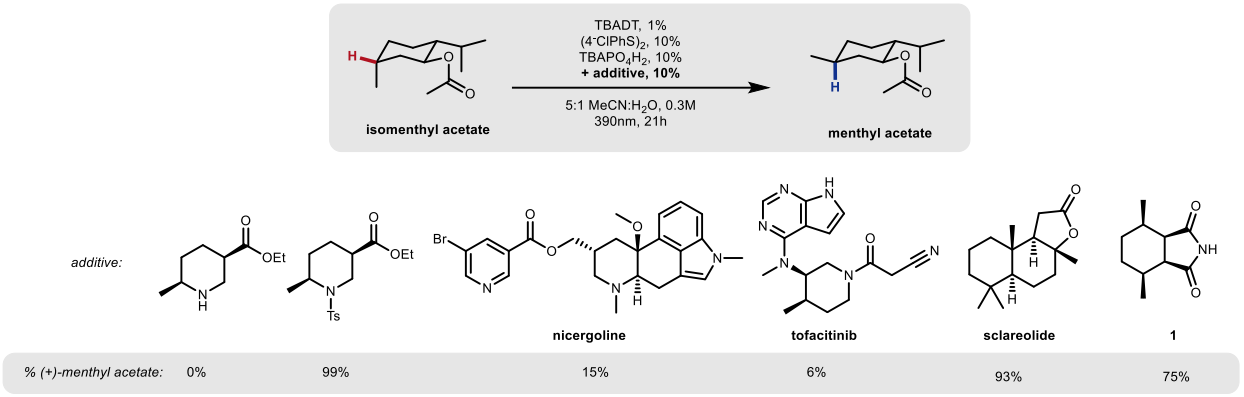
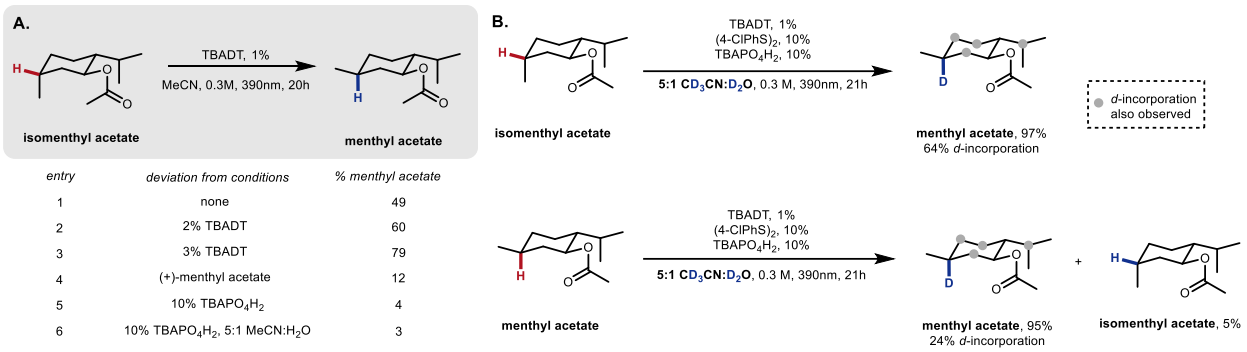


Figure 2.6 Effect of additives on epimerization yield.

Similarly, since **wO** can be quenched through either H-atom or single electron transfer (SET) pathways, we sought to understand whether this reactivity feature would limit the compatibility of this reaction system with organic functional groups. Introduction of 10 mol% of piperidine into the epimerization of isomenthyl acetate results in slightly diminished mass balance and formation of the isomerized product is not observed. Epimerization suppression was also observed when tertiary amine-bearing drug molecules nicergoline and tofacitinib were introduced as additives as well. However, protection of the secondary amine with an electron withdrawing tosylate group significantly hinders single electron oxidation such that quenching via SET no longer competes with the H-atom abstraction pathway, as reflected in a 99% epimerization yield when 10 mol% of the tosylated piperidine is introduced as an additive. Likewise, when substrates that are reported to quench **wO** via H-atom transfer are introduced to the reaction mixture as additives, the yield of menthyl acetate epimer obtained is similarly unaffected. These results suggest that in the presence of an electron rich amine, the **wO** reactive state is consumed via SET at rates that compete with rates of hydrogen atom transfer, and these data are consistent with transient absorbance spectroscopy kinetics studies detailing reaction rates of **wO** quench with alkyl and aryl amines.[21,41]



entry	*deviation from conditions*	*% menthyl acetate*
1	none	49
2	2% TBADT	60
3	3% TBADT	79
4	(+)-menthyl acetate	12
5	10% $TBAPO_4H_2$	4
6	10% $TBAPO_4H_2$, 5:1 MeCN:H_2O	3

Figure 2.7 A. Epimerization with TBADT only. B. Deuterium incorporation of isomenthyl acetate and menthyl acetate epimerization reactions.

Initial reports conducted by Hill studied TBADT in MeCN as a catalyst for the generation of alkyl radical intermediates, and the epimerization of cis-decalone to its trans isomer was observed without addition of any other reagents or catalysts.[42] Epimerization via intermolecular alkyl radical H-atom abstraction from solvent or a second substrate molecule is highly unlikely or extremely inefficient – previous studies report photooxygenation of alkyl substrates via TBADT-mediated generation of alkyl radicals in <0.2 quantum yields.[21,22,41] Thus, the protonated reduced state is purportedly responsible for back H-atom transfer to decalyl radical, ultimately resulting in epimerization. Treatment of isomenthyl acetate to conditions including only substrate, TBADT, and solvent yields 49% of the product isomer (Figure 2.7 A, entry 1). In agreement with a mechanism that proceeds via back H-atom transfer from the protonated reduced state of the photocatalyst, no *d*-incorporation is observed when *d*-MeCN is used as solvent. Product yield increases with increasing TBADT concentration, which is in line with a bimolecular reaction rate for initial alkyl radical generation via **wO** quench and in agreement with previous kinetic data collected from transient absorbance spectroscopy.[21] Importantly, the addition of base and the addition of water results in significantly diminished epimerization yields, and product is observed in only 4% and 3% yield, respectively (Figure 2.7 A, entries 5 and 6). These data suggest that proton transfer between phosphate base or water and the protonated reduced form of the photocatalyst occurs faster than back H-atom donation from the protonated reduced photocatalyst to the alkyl radical to form the resultant epimer.

In the fully constituted catalytic system, we propose that H-atom donation to the alkyl radical occurs via cleavage of the thiol S-H bond. To probe the regioselectivity of H-atom abstraction and the stereoselectivity of H-atom donation, isomenthyl acetate was treated to *d*-incorporation conditions. As previously observed, no *d*-incorporation occurred when *d*-MeCN was used in place of MeCN; however, introduction of D_2O results in *d*-incorporation, suggesting that deuteron transfer to thiolate delivers deuterium to the product isomer. Under *d*-incorporation conditions, the epimerization of isomenthyl acetate proceeds with 97% yield and 64% *d*-incorporation into the axial position at the site of epimerization is observed. Deuterium is also incorporated at nearly every methylene and methyl group as well, but importantly, no *d*-incorporation is observed at the carbons adjacent to the iPr or OAc substituents. These results suggest the indiscriminate nature of H-atom abstraction by TBADT, and a similar lack of regioselectivity has been reported by Hill,[42–44] MacMillan,[37,45] and others[46] as well. When menthyl acetate is subjected to the reaction conditions, *d*-incorporation is also observed across nearly all other methylene and methyl C-H bonds, and this is consistent with regiochemically unselective H-atom abstraction by TBADT (Figure 2.7 B). Additionally, 5% epimerization to produce isomenthyl acetate is observed, with 24% *d*-incorporation into the axial C-H of menthyl acetate. One possible hypothesis to explain the differing degrees to which *d*-incorporation is observed is that strain release-driven H-atom abstraction to planarize an axial methyl group (i.e. release 1,3-diaxial strain) occurs at a faster rate compared to H-atom abstraction that planarizes an already equatorial methyl group.[47] In this mechanistic scenario, the overall epimerization outcome is governed by a substrate-controlled kinetic equilibrium of relative rates of H-atom abstraction. The extent to which this hypothesis may be applied generally or only on a case-by-case basis remains to be explored.

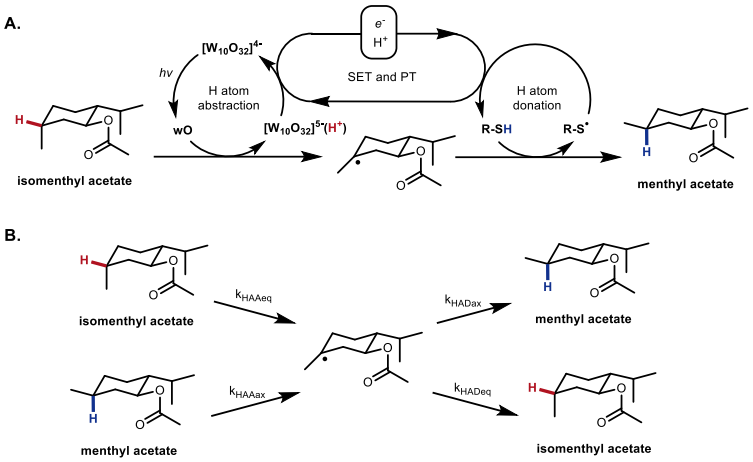


Figure 2.8 A. Proposed mechanism. B. Proposed model for selectivity.

In line with the data and interpretations presented here, a mechanism for epimerization that proceeds via stepwise H-atom abstraction by **wO** and H-atom donation by thiol is proposed. Future work investigating this system would ideally ascertain whether epimerization yield observed in the presence of only substrate, solvent, and TBADT is a result of slow conversion or poor selectivity in order to better understand the role of thiol and base.

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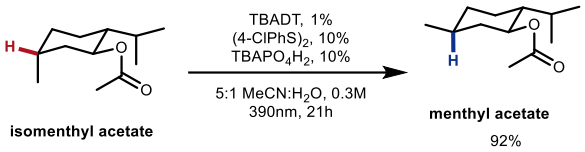
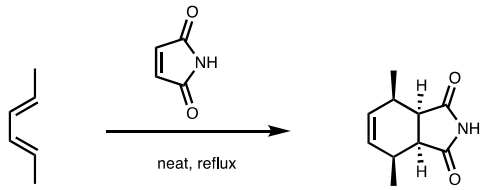
Experimental

Representative procedure for methine epimerization:

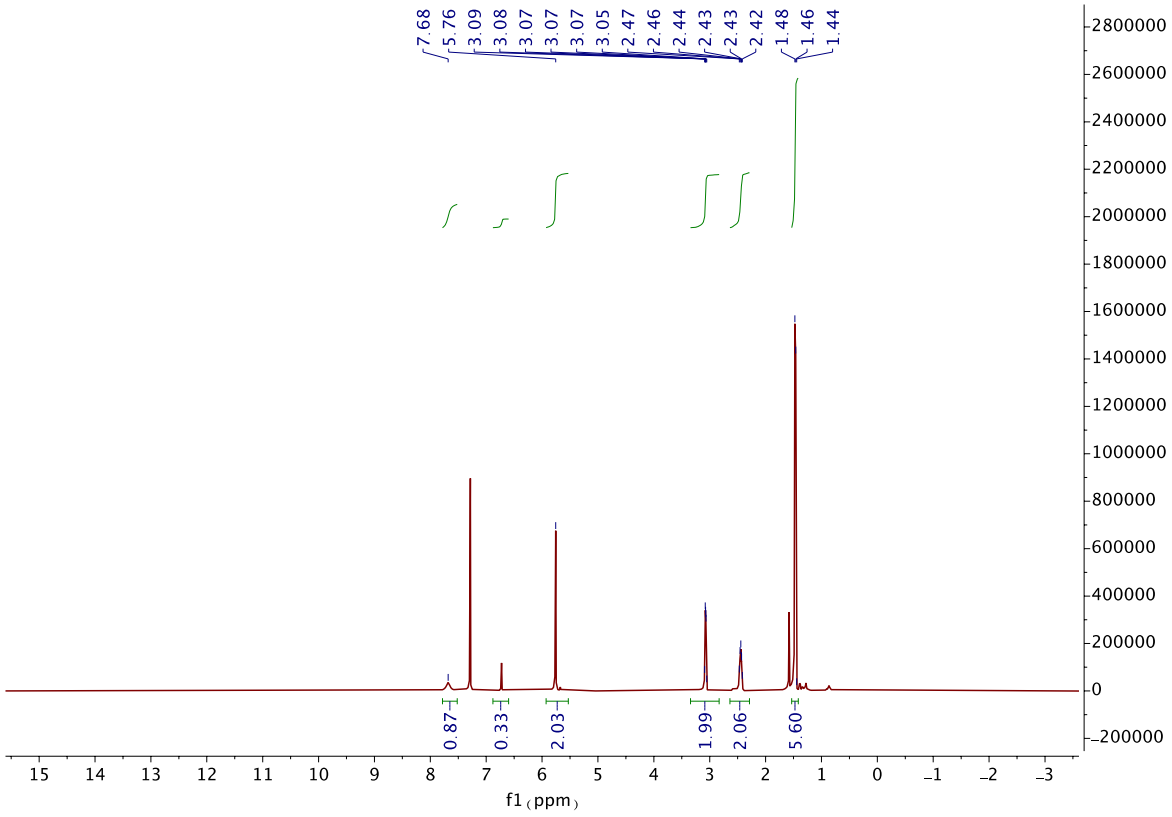


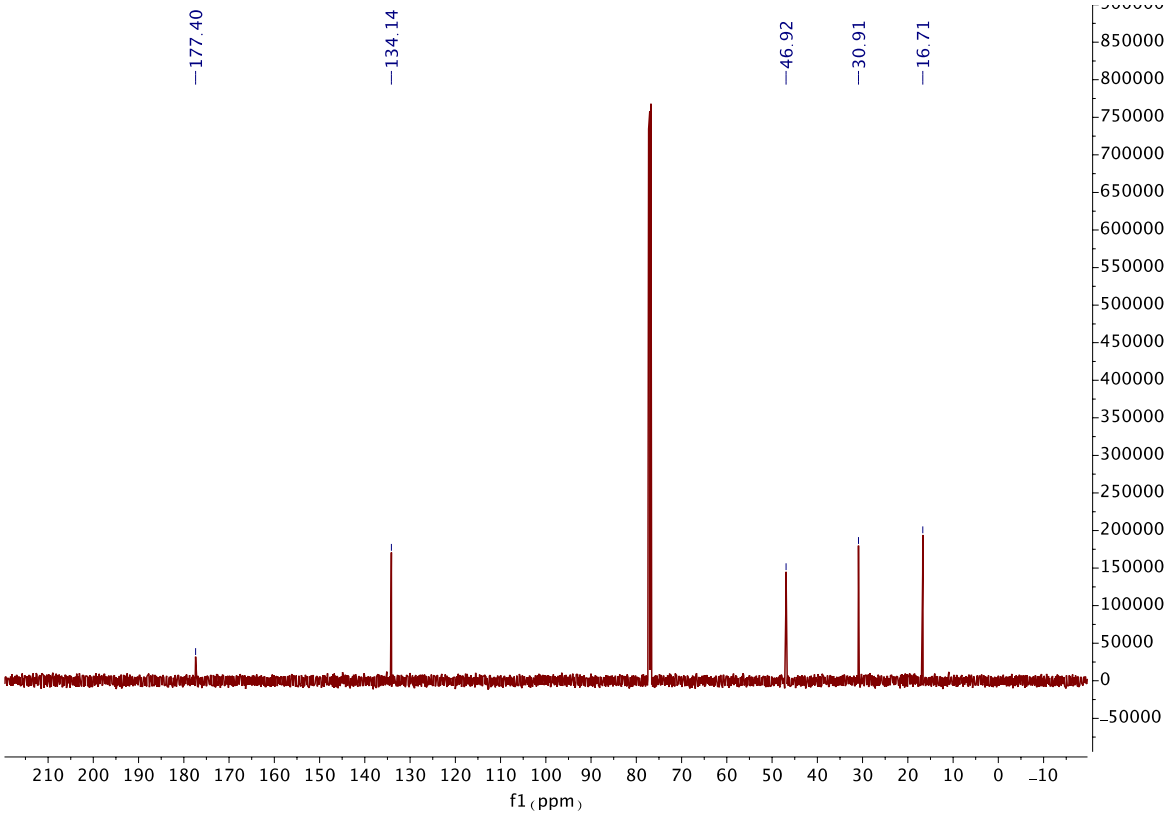
To an oven-dried 1-dram vial equipped with a stir bar was added tetrabutylammonium decatungstate (3.3 mg, 1 mol%), 4-chlorodiphenyl disulfide (2.8 mg, 10 mol%), tetrabutylammonium phosphate (3.5 mg, 10 mol%), and isomenthyl acetate (19.8 mg, 0.1 mmol). The reaction vessel was evacuated and refilled with nitrogen three times during transfer to a nitrogen atmosphere box, where dried and degassed MeCN was added. The reaction was sealed with a cap equipped with a PTFE/silicone septa and removed from the nitrogen atmosphere box and water was added via Hamilton syringe. After 21h, the reaction was removed from irradiation and solvent was removed. Reaction yield was determined by NMR with the addition of 0.1 mmol nitrobenzene as a standard.

Synthesis of (3a*R*,4*R*,7*S*,7a*S*)-4,7-dimethyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione:



Following a modified literature procedure,[48] to a 2-dram vial fitted with a stir bar was added maleimide (194 mg, 2.0 mmol, 1.0 equiv) and 2,4-hexadiene (0.46 mL, 4.0 mmol, 2.0 equiv). The reaction was stirred neat and heated to reflux for 24 hours. The mixture was concentrated and washed with hexanes to yield the cycloaddition product as a white powder (330 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (s, 1H), 3.07 (dd, *J* = 4.6, 2.2 Hz, 1H), 2.45 (q, *J* = 6.9 Hz, 1H), 1.47 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.40, 134.14, 46.92, 30.91, 16.71. IR (neat, cm^{-1}): 3179 (br), 3086 (w), 2930 (w), 2892 (w), 1703 (s), 1334 (m), 1927 (m), 1092 (m), 1055 (m), 980 (m), 802 (m). HRMS (DART) ([M+H]$^{+}$) Calcd. for C10H13NO2: 179.0946, found 179.0947.




177.40
134.14
46.92
30.91
16.71
850000
800000
750000
700000
650000
600000
550000
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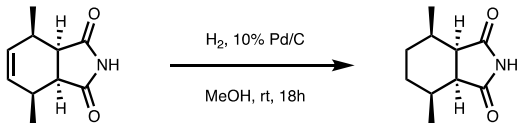
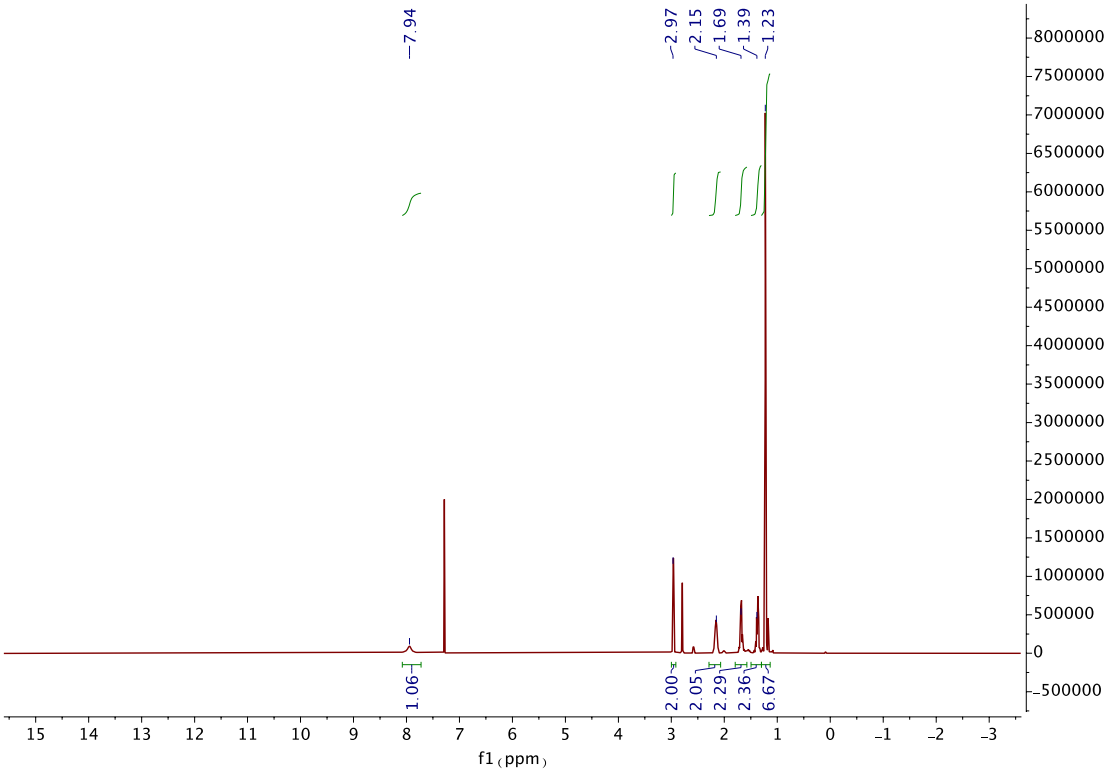
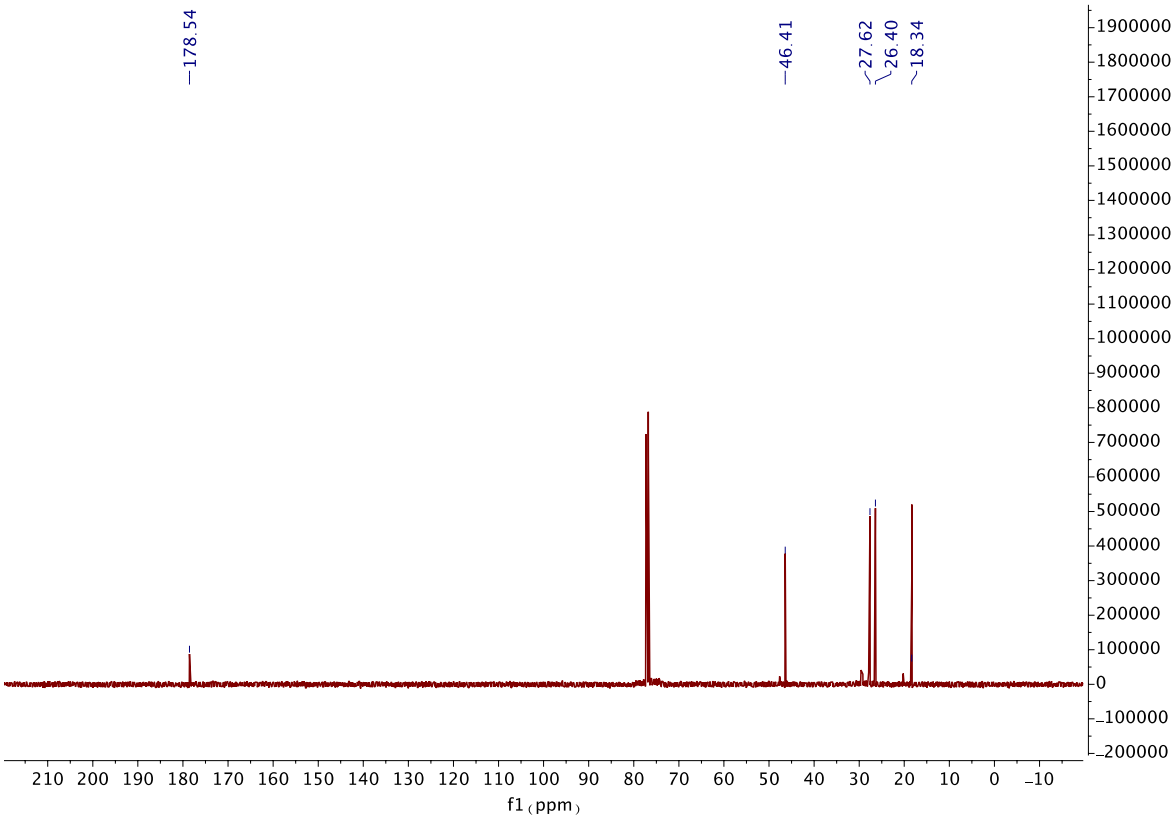
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
−50000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

Synthesis of (3a*R*,4*R*,7*S*,7a*S*)-4,7-dimethylhexahydro-1*H*-isoindole-1,3(2*H*)-dione (**1**):



To a 50mL round bottom fitted with a stir bar was added the alkene (330 mg, 1.84 mmol) in methanol. The vessel was sparged with inert gas before adding Pd/C (10% by weight, 18 mg). The flask then sparged with H_2 from a balloon before stirring under H_2 overnight for 18 hours at room temperature. The reaction mixture was filtered through a Celite pad and washed with methanol, and concentrated to give the product as a white powder (291 mg, 87% yield, 98:2 dr). Stereochemical assignment was made based on 0% enhancement of methyl shifts following selective irradiation of α-carbonyl protons. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 2.98 (m, 2H), 2.14 (m, 2H), 1.69 (m, 2H), 1.37 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.54, 46.41, 27.62, 26.40, 18.34. IR (neat, cm^{-1}): 3235 (br), 2937 (w), 2873 (w), 1699 (s), 1364 (m), 1334 (m), 1230 (m), 1193 (m), 1148 (m), 1036 (m), 749 (s). HRMS (DART) ([M+H]$^+$) Calcd. for C10N15NO2: 181.1103, found 181.1107.

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100000
0
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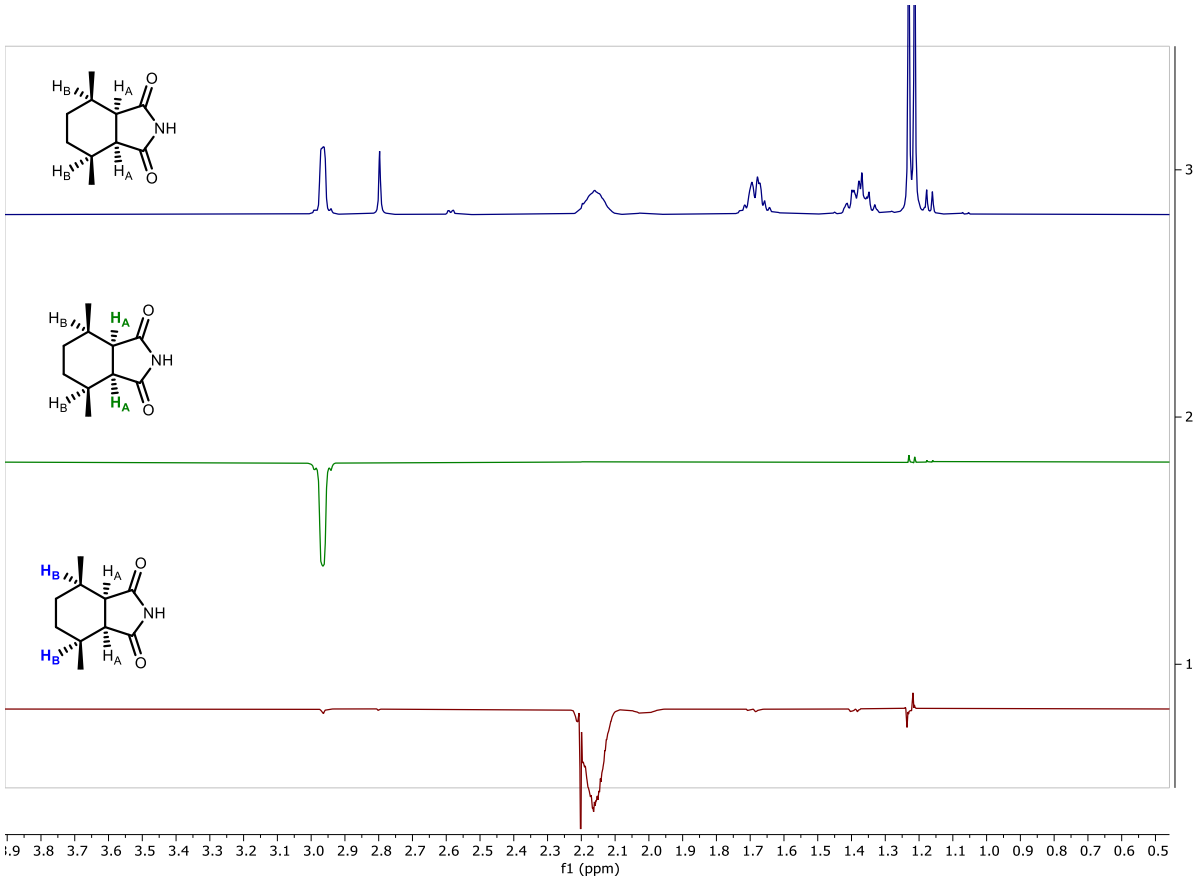
−200000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


HB
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NH
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HA
O
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HA
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NH
HB
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2
HB
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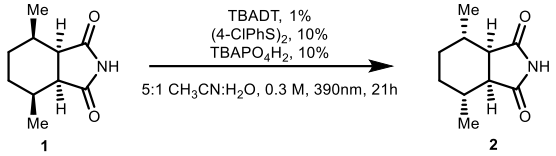
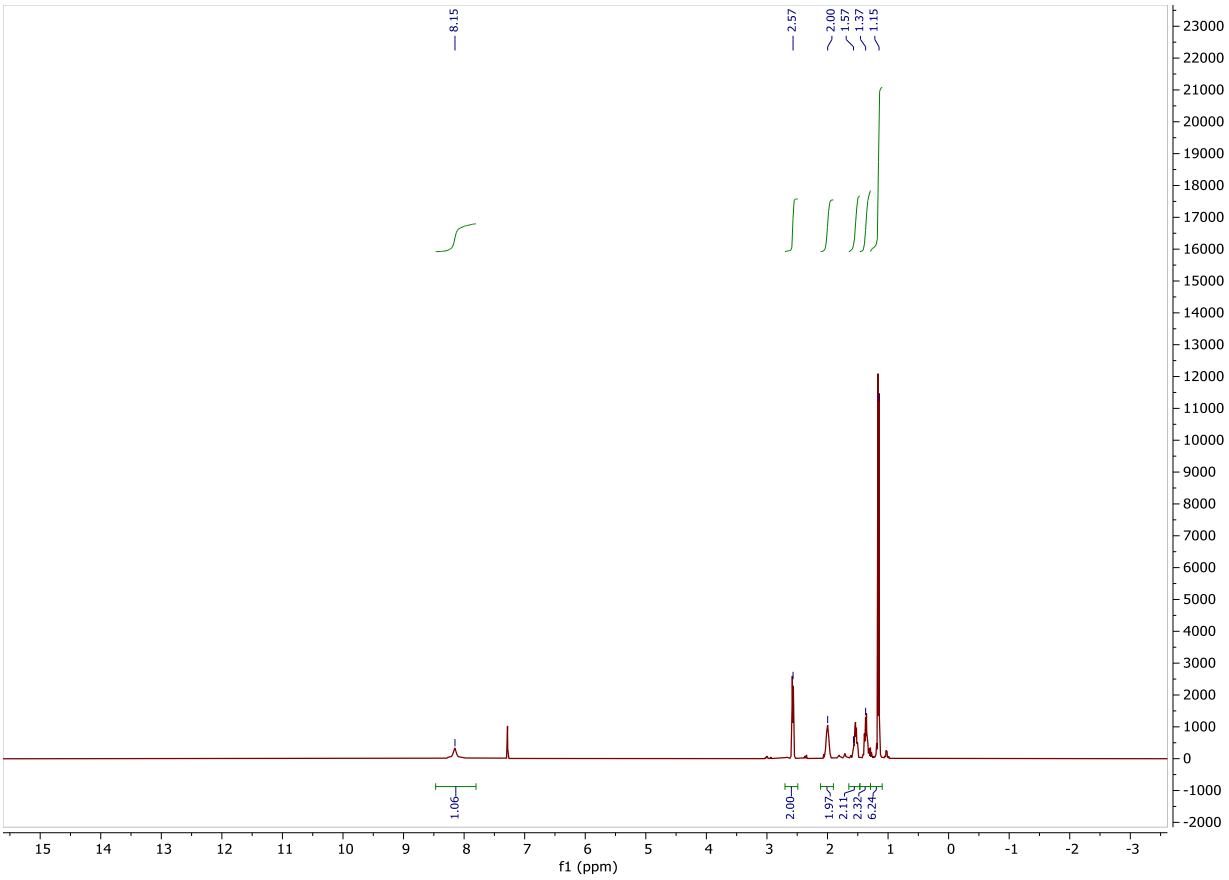
HA
O
1
3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5
f1 (ppm)

Synthesis of (3aR,4S,7R,7aS)-4,7-dimethylhexahydro-1H-isoindole-1,3(2H)-dione (**2**):



The epimerization of **1** was set up following the representative procedure described above. Analysis of the reaction mixture following 21h of irradiation showed a 99% yield, and the crude mixture was purified via column chromatography (1:1 H:EA, Rf = 0.5). Stereochemical assignment was made based on 53% enhancement of methyl shifts following selective irradiation of α-carbonyl protons. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 2.98 (m, 2H), 2.14 (m, 2H), 1.69 (m, 2H), 1.37 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.54, 46.41, 27.62, 26.40, 18.34. IR (neat, cm^{-1}): 3228 (br), 2967 (s), 2929 (m), 1700 (s), 1357 (m), 1197 (m), 1144 (m), 812 (m). HRMS (DART) ($[M+H]^+$) Calcd. for C15H23O10: 181.1103, found 181.1109.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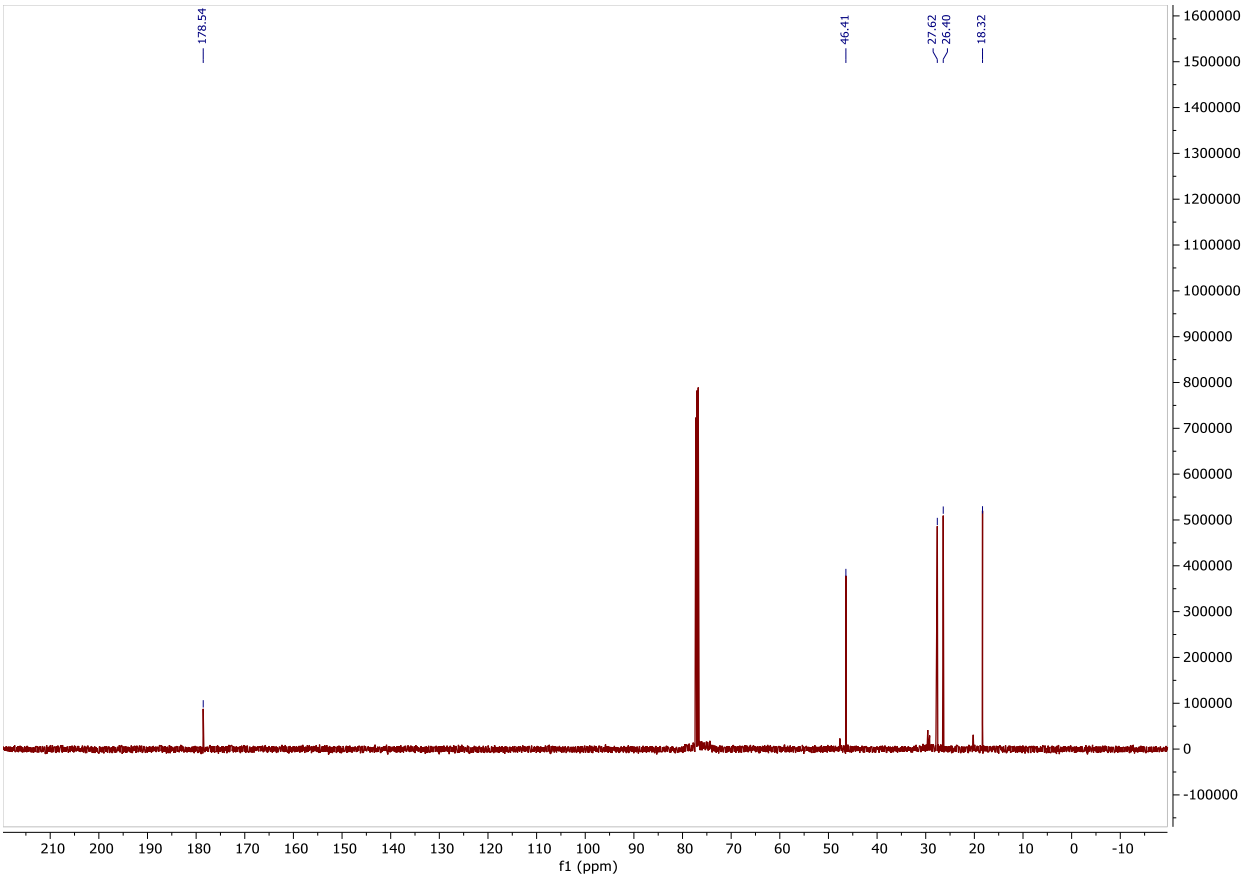
2.00
1.57
1.37
1.15
1.06
2.00
1.97
2.11
2.32
6.24
f1 (ppm)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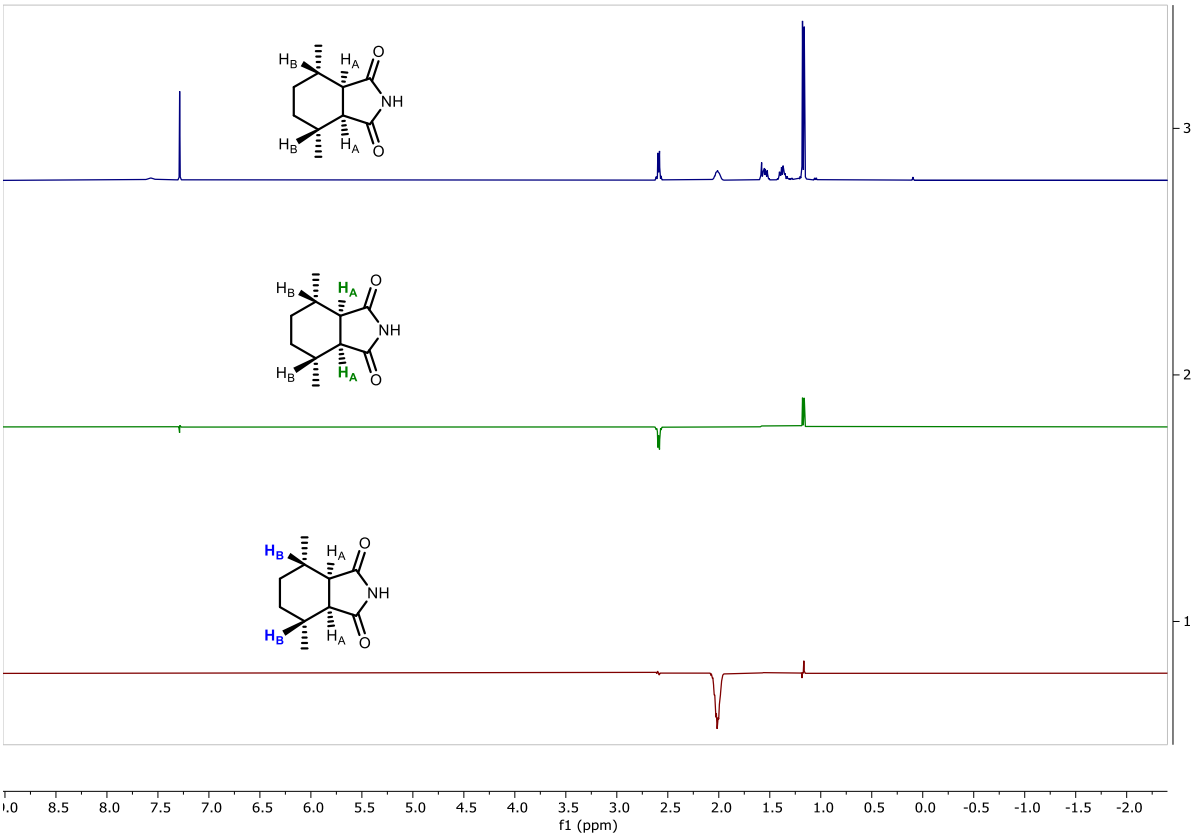
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


HB
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HA
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2
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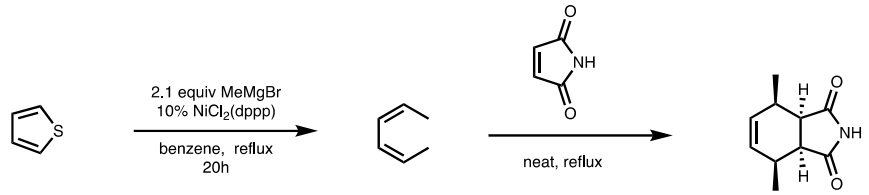
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
f1 (ppm)

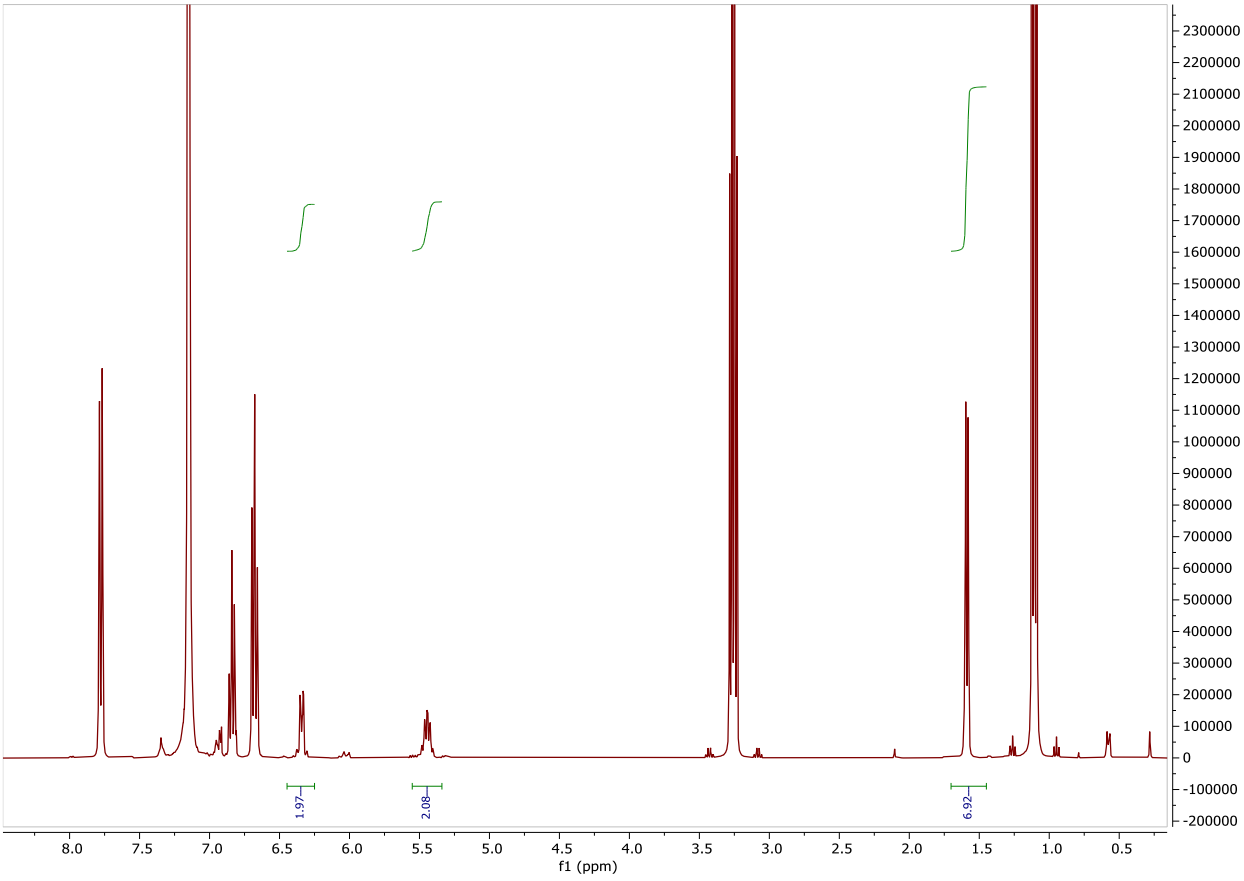
Synthesis of (3a*R*,4*R*,7*S*,7a*S*)-4,7-dimethyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione from (Z,Z)-diene:



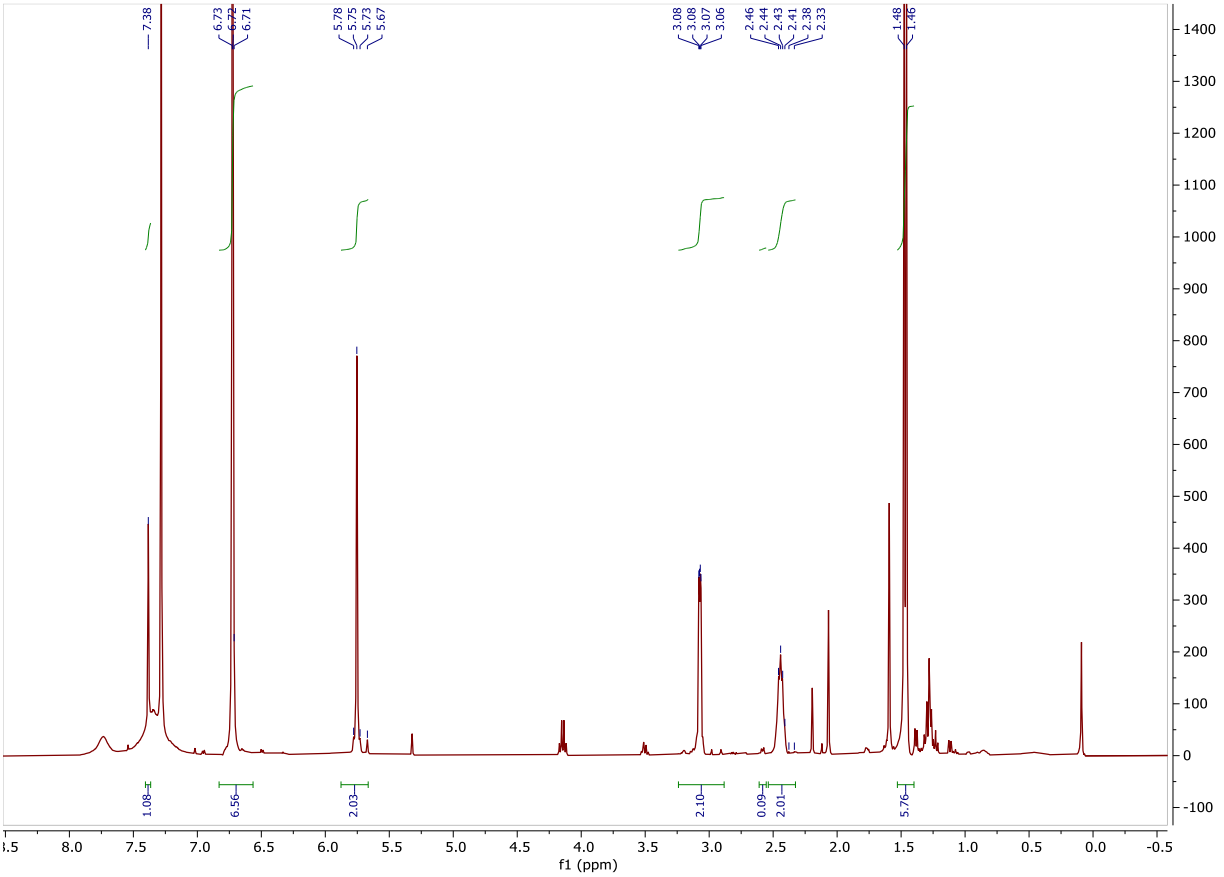
To a two-neck round bottom flask fitted with a reflux condenser and stir bar was added thiophene (84 mg, 1.0 mmol, 1.0 equiv) and nickel catalyst (53 mg, 0.1 equiv) in benzene. The vessel was sparged with inert gas and methyl Grignard (2.5 mL, 2.5M in Et_2O, 2.1 equiv) was added at room temperature. The flask was heated to reflux and left to stir at reflux for 20 hours. The reaction progress was monitored by NMR and the product was isolated as a 0.125M solution in Et_2O via vac transfer. The solution was used directly in the following reaction. ^{1}H NMR (400 MHz, Et_2O and C_6H_6) δ 6.51 (d, *J* = 6.7 Hz, 2H), 5.69 (m, 2H), 1.87 (d, *J* = 6.7 Hz, 6H).

To a 2-dram vial fitted with a stir bar was added maleimide (49 mg, 0.5 mmol) and diene in solution. The reaction was heated to reflux and stirred overnight for 24 hours. The mixture was concentrated and washed with hexanes to yield the cycloaddition product as a white powder (89 mg, 99% yield).

Spectrum of (Z,Z)-hexadiene isolated via vac transfer in Et_2O. A 250µL aliquot was used to prepare this NMR sample. Nitrobenzene was added to the NMR sample as a standard to quantify the amount of (Z,Z)-diene isolated.



Crude spectrum of DA reaction with maleimide. Solution of hexadiene in Et2O was added directly to the reaction.



Authentic (3a*R*,4*R*,7*S*,7a*S*)-4,7-dimethyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (top) stacked with crude product obtained in reaction of maleimide with (Z,Z)-hexadiene.