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Construction of Stereogenic α,α-Disubstituted Cycloalkanones via 1° Amine Thiourea Dual Catalysis: Experimental Scope and Computational Analyses

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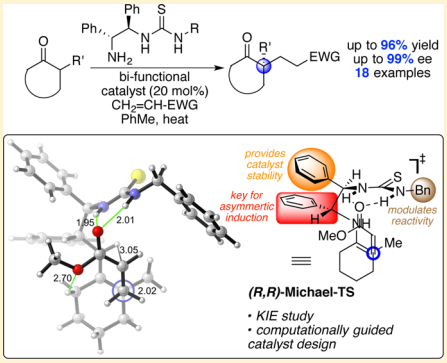
Supporting Information

ABSTRACT: The mechanistic exploration and an expanded experimental discussion of the organocatalyzed, asymmetric Pfau–d'Angelo reaction by exploiting a bifunctional 1° amine thiourea catalyst system is disclosed. Notable breadth in substrate scope has been demonstrated on both the cyclic ketone moiety and the α,β-unsaturated electrophile. Exploration into the matched and mismatched selectivity of this process with a ketone containing pre-existing stereocenters has been demonstrated. Computational analyses of the reaction mechanism are reported. In concert with kinetic isotope effect (KIE) experiments, these computational results provide a detailed understanding of the likely mechanism, including the aspects of the organocatalyst scaffold that are critical for stereoselectivity.



INTRODUCTION

Efficient methods for accessing stereogenic, all-carbon quaternary centers continues to be an important area of research due to their prevalence in natural products and biologically relevant targets.[1] This functionality is widely regarded as among the most difficult to introduce in a stereoselective fashion. Within the category of all-carbon quaternary stereocenters, stereogenic α,α-disubstituted cycloalkanones are an important subarea that has attracted the focus of numerous laboratories. Considerable attention has been focused on transition metal-mediated solutions to this challenge, primarily using variants of the Tsuji–Trost π-allyl couplings.[2,3] Palladium-mediated alkylations to form all-carbon quaternary centers have also proven successful since Tsuji's pioneering work.[2] Hayashi,[4] Ito,[5] Trost,[3] and Dai[6] have all made seminal contributions in the area, focusing primarily on structures bearing two electron-withdrawing groups (Scheme 1, eq 1) or decalone systems (Scheme 1, eq 2). Stoltz and co-workers have developed elegant methods for expanding this strategy to systems derived from 2-alkyl-substituted cycloalkanones (Scheme 1, eq 4).[7] Stoltz's "Focus Review" nicely summarizes much of the work in the area.[8] Complementary to the Trost–Tsuji allylation, Pfau and d'Angelo pioneered a nontransition metal-mediated method for this transformation (Scheme 2).[9] The Pfau–d'Angelo reaction offers unique advantages depending on the specific functionality needed in the resultant product. This method involves the condensation of α-methyl benzylamine with an α-substituted cycloalkanone. This condensed species exists primarily as imine **16**; however, a small amount of reactive enamine **17** is also formed, which rapidly reacts with a Michael acceptor to ultimately provide the desired product. It is important to recognize that, although 2° amines (e.g., pyrrolidine) typically prefer to react via the less substituted enamine **21** to avoid unfavorable pseudo-*syn*-pentane interactions, less sterically encumbered 1° amines typically react via the more substituted enamine **17**. Although this protocol had only been reported in a stoichiometric sense, we were intrigued by the potential of this technology in catalytic processes. Our laboratory has made a concerted effort to develop asymmetric methods for accessing these types of structural motifs, particularly for α,α-cycloalkanones[10] and γ,γ-disubstituted cycloalkenones.[11] These efforts led us to develop the first organocatalytic method[10] for accessing α,α-disubstituted cycloalkanones through the use of a primary amine/thiourea dual-catalyzed Pfau–d'Angelo reaction. Herein, we provide an expanded discussion of the experimental development and scope of this transformation as well as a detailed analysis of the reaction mechanism through experiments and computations. Discussion of the experimental results will focus on previously unreported work with a summary of previously reported results[10] to enable a full understanding of the chemistry.

RESULTS AND DISCUSSION

On the basis of Pfau and d'Angelo's pioneering work, we hypothesized that their concept could be rendered catalytic as illustrated in Scheme 3. The key to any such catalysis would be the control of multiple equilibriums. We proposed that a bifunctional catalyst system would be needed to exert control and effect turnover. We hypothesized that an effective catalyst

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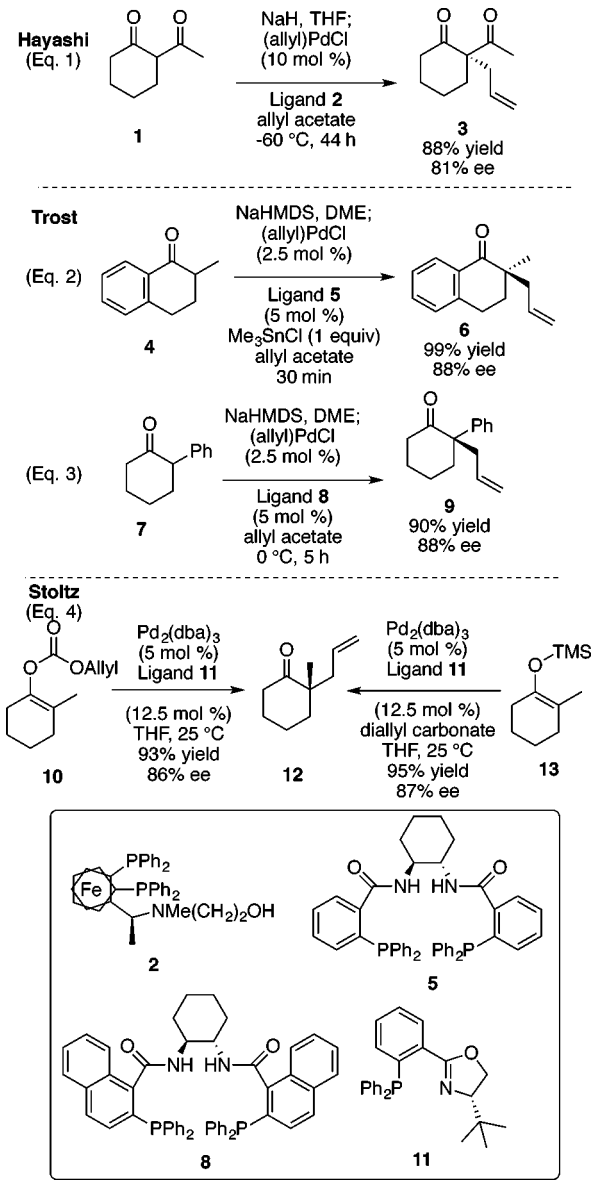
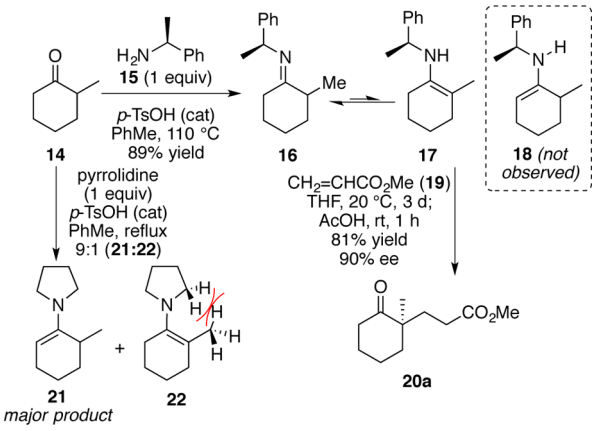
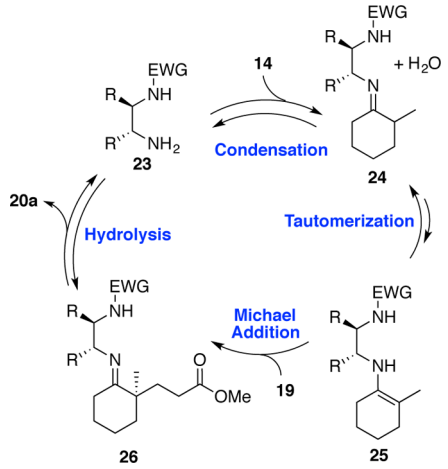
Scheme 1. Palladium-Catalyzed Asymmetric Allylation of Cyclic Ketones



Scheme 2. Pfau–d'Angelo Asymmetric Michael Addition to 2-Methyl Cyclohexanone



Scheme 3. Proposed Mechanism of the Catalytic, Asymmetric Pfau–d'Angelo Reaction



could contain (a) a 1° amine functionality for facilitation of the Michael addition through enamine catalysis as well as a (b) Brønsted acid motif to help preorganize the nucleophile and mediate enamine/imine formation and hydrolysis. We expected rapid condensation of the bifunctional catalyst with the ketone to form imine intermediate **24**. On the basis of Pfau and d'Angelo's pioneering work and with the added functionality of the now appended Brønsted acid, we were optimistic that an equilibrium could be established between imine **24** and required enamine **25**. The Brønsted acid moiety (depicted as NH-EWG) would facilitate the Michael addition through hydrogen bonding stabilization of the developing anion to yield adduct **26**. This process could occur via a discrete enolate from the conjugate addition or via direct protonation of that enolate by the Brønsted acid in a more concerted process. Finally, hydrolysis of the imine Michael product would regenerate catalyst **23** and release final product **20a**.

Our development and optimization of a catalytic Pfau–d'Angelo reaction is shown in Table 1. Aspects of this work have been previously disclosed in our communication, and comments will focus on previously unreported information.[10] After initially exploring substoichiometric quantities of α-methylbenzylamine with and without a Brønsted acid additive (entries 1–2), we transitioned to exploring a variety of bifunctional organocatalysts that contained both required functionalities in the same molecule. A wide range of Brønsted acid functional groups were conceivable (e.g., thiourea, sulfonamide, phosphoric acid). We initially screened the *p*-dodecylphenylsulfonamide derived from valine. This previously unknown sulfonamide catalyst **29** was inspired by our laboratory's efforts with proline sulfonamides, which have proven useful in a range of transformations.[12] Unfortunately, this catalyst did not prove effective for this transformation (entry 3). We subsequently gravitated to thioureas **30**–**33**, as we hypothesized that the bidentate binding mode may result in distinct advantages. Fortunately, these thiourea/1° amine catalysts are readily available from their corresponding diamines and the requisite isothiocyanates.[13] Ultimately, we discovered that benzyl substituent **33** provided the optimum level of chemical yield while retaining high stereoselectivity (entry 7).

We next explored the scope of the electrophiles that would be tolerated using this catalyst system (Table 2). As we have shown previously,[10] successful coupling of acyrlates, α,β-

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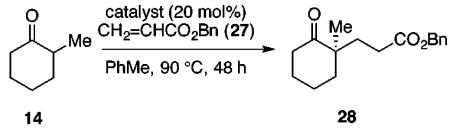
Table 1. Development and Optimization of the Catalytic, Asymmetric Pfau–d'Angelo Reaction



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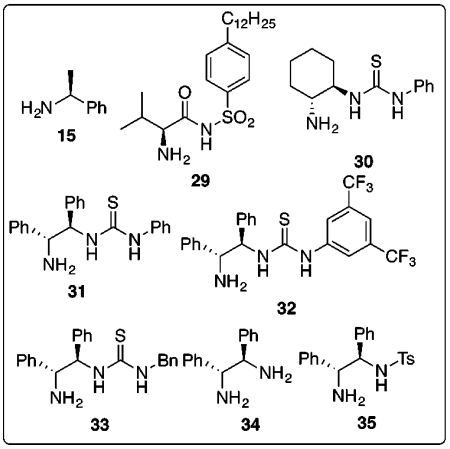
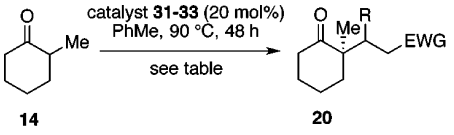


entry	catalyst	% yield	% ee[a]
1	**15**	10	90
2	**15**, *p*-TsOH (1 mol %)	0	n/a
3[b]	**29**	7	n/d
4	**30**	18	67
5	**31**	49	98
6	**32**	80	98
7	**33**	**95**	**98**
8	**34**	5	n/d
9	**35**	17	98

[a]Determined by chiral HPLC analysis. [b]The reaction time for this experiment was 46 h.

Table 2. Variation of the Electrophile in the Catalytic, Asymmetric Pfau–d'Angelo Reaction



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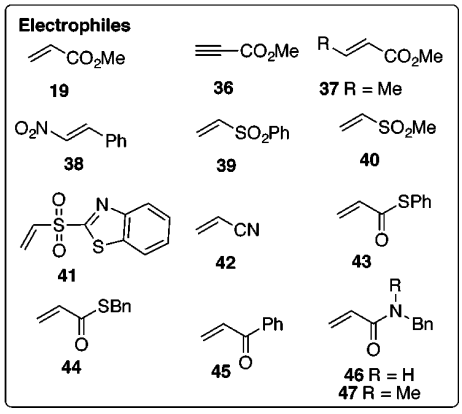

entry	electrophile	catalyst	% yield	% ee[a]
a	**19**	**33**	91	98
b	**36**	**31**	0	n/a
c	**37**	**32**	0	n/a
d	**38**	**32**	0	n/a
e	**39**	**31**	94	98
f	**40**	**31**	50	>95%[b]
g	**41**	**32**	0	n/a
h	**42**	**33**	75	85
i	**43**	**32**	0	n/a
j	**44**	**32**	0	n/a
l	**45**	**32**	0	n/a
m[c]	**46**	**32**	0	n/a
n	**47**	**32**	0	n/a

[a]Determined by chiral HPLC analysis. [b]Determined by ^{1}H NMR using europium tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorate]. [c]Catalyst **31** was similarly ineffective.

unsaturated sulfones (**39**–**40**), and acrylonitrile (**42**) provided generally good chemical yields and reasonable enantioselectivities. Interestingly, the use of an alkyne electrophile did not provide any observable product (entry b). Similarly, the use of an electrophile containing β-substitution proved ineffective (entries c and d). Finally, thioesters, ketones, and amides were all unreactive substrates for this Michael reaction (entries i–n).

After exploring the electrophile scope with the parent 2-methylcyclohexanone substrate scaffold, we fully explored the nature of the nucleophilic component (Schemes 4 and 5). We have previously shown our catalyst system to be effective with ethyl moieties (Scheme 4, eq 1).[10] Herein, we demonstrate that a propyl moiety appears to be tolerated at a similar level to the ethyl with the parent catalyst (54% yield, 95% ee, Scheme 4, eq 2). Further variation of substitution at that position was problematic, as both 2-phenyl and 2-chloro did not provide any of the desired product (Scheme 4, eqs 3 and 4). The failure of these reactions is somewhat surprising, as the increased acidities (reduced pK_a) of the α-proton could help stabilize the reactive enamine intermediate. We also explored the matched/mismatched capabilities of this system using dihydrocarvone (**56**). Previously, we showcased the matched case (Scheme 4, eq 5).[10] We were pleased to see that the use of the enantiomeric catalyst *ent*-**32** gave the opposite diastereomer in reasonable levels of selectivity (7.5:1 dr) and yield (70%) (Scheme 4, eq 6). We screened the impact of a fused aromatic ring on the cyclohexanone scaffold (Scheme 4, eq 7). Despite the increased pK_a of the α-proton in this case, no desired product was observed. We attribute the failures of compounds **7** and **4** to undergo this process to the increased steric (allylic strain) demands placed on the system, further reducing/inhibiting the formation of the tetrasubstituted enamine required for C–C bond formation. We also extensively explored variations of the core 6-membered ring scaffold of the nucleophile (e.g., 5- and 7-membered variants, heterocycles), which proved to be generally quite effective (Scheme 5).[10]

We also briefly explored the derivatization of one of the Michael products to show its utility (Scheme 6). Treatment of methyl sulfone product **20f** with potassium *t*-butoxide gave 6,6-bicyclic system **74** in good yield. The stereochemistry of the 3° alcohol was not rigorously verified. Subsequent dehydration using thionyl chloride and pyridine gave β,γ-unsaturated alkene **75** in excellent yield.

Analyses of Mechanism, Origins of Stereocontrol, and Substitution Effects on Selectivity. We were intrigued by the origin of stereoselectivity in this process as well as the controlling elements in the catalytic cycle. We therefore conducted a theoretical study to complement experiments. A manual, exhaustive conformational search of the intermediate

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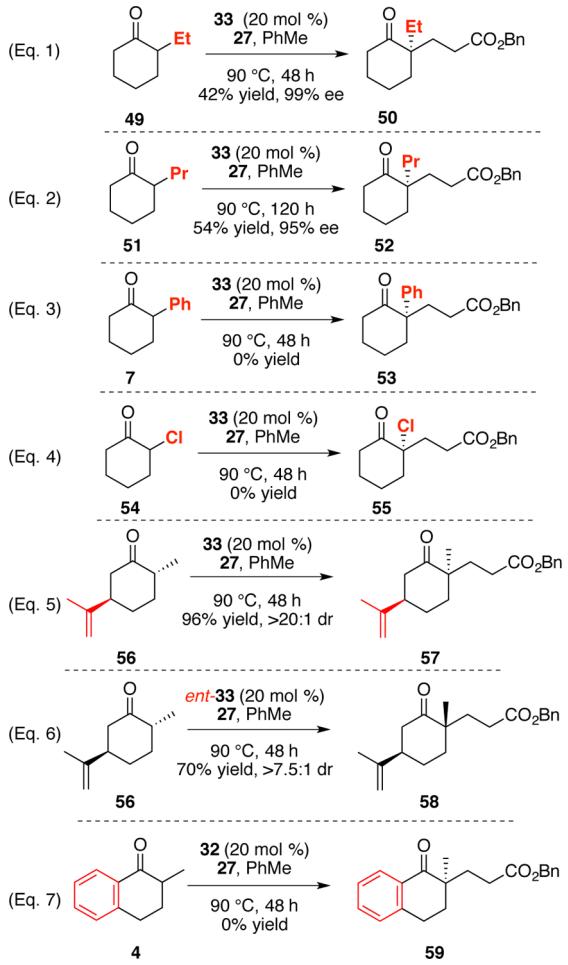
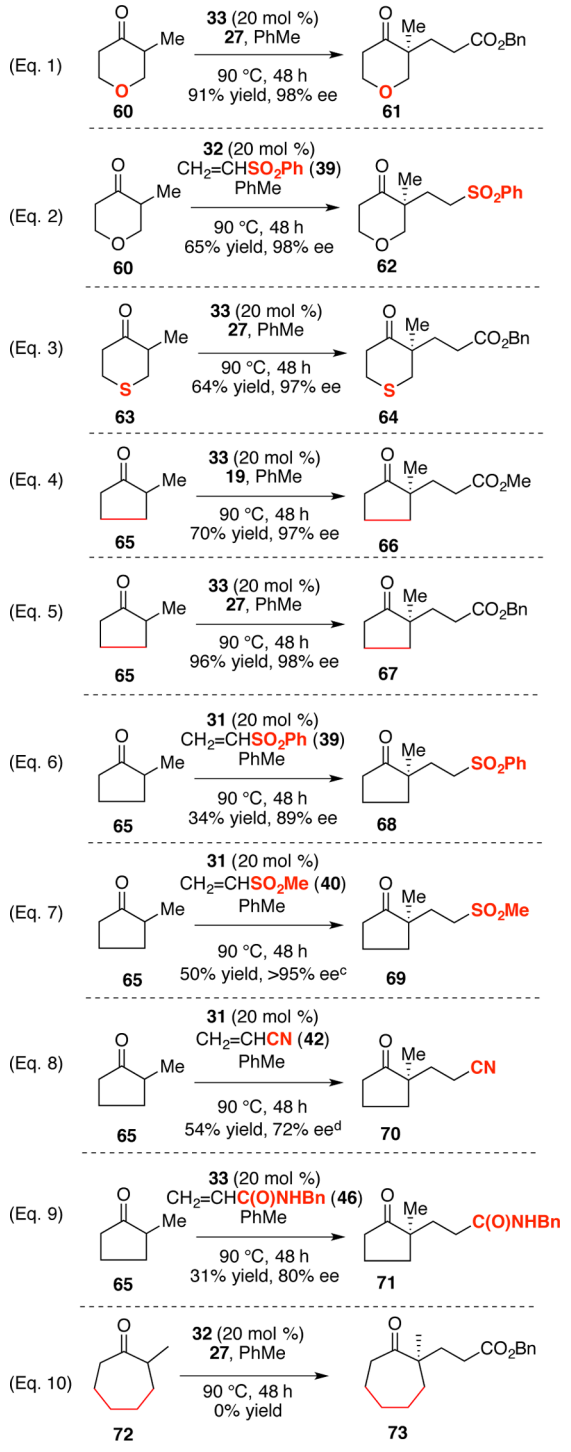
Scheme 4. Exploration of Cyclohexanone-Derived Nucleophiles in the Catalytic, Asymmetric Pfau−d'Angelo Reaction[a]



[a]Enantiomeric excess determined by chiral HPLC analysis. Diastereomeric excess determined by ^{1}H NMR.

Scheme 5. Variation of Cycloalkanones in the Catalytic, Asymmetric Pfau−d'Angelo Reaction[a,b]



[a]Enantiomeric excess determined by chiral HPLC analysis. [b]Diastereomeric excess determined by ^{1}H NMR. [c]Enantiomeric excess determined by ^{1}H NMR using europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]. [d]Enantiomeric excess determined by chiral GC analysis.

and transition state (TS) structures along the reaction coordinate were performed to ensure that all relevant structures were located. Quantum mechanical computations were performed at the SCS-MP2[14]/Def2[15]-∞[16]//B3LYP[17]/6-31G-(d)[18]/SMD[19](toluene) level of theory.[20] The reaction coordinate is shown in Figure 1. Condensation of ketone **14** with catalyst **33** leads to imine **76**. In agreement with experiments, theory predicts that catalyst imine **76** lies in equilibrium (~85% formation) with ketone **14**. The tautomerization to enamine **77** leads to the rate- and stereodetermining Michael addition (**TS-78**) of the acrylate. Interestingly, the concerted C−C bond formation and proton transfer TS structure could not be located; all efforts to locate this structure led to stepwise transition structures. Transient iminium **79** is rapidly deprotonated by the enolate, leading to product imine **81**. Finally, hydrolysis of the product imine releases product **20a** and catalyst **33**.

We set out to establish the likely rate-determining step (RDS) for this process (Scheme 7) by corroborating experimental kinetic isotope effect (KIE) experiments. The use of deuterium labeling on the electrophilic olefin **19-D$_3$** would allow us to determine whether the reaction is concerted or stepwise C−C bond formation and proton transfer and identify the rate-determining step based on comparisons with computations. The computed 2° KIE (k_H/k_D = 0.84) matched the experimental value (0.86 and 0.82, Scheme 7), consistent with the computed mechanism and suggesting that the Michael C−C bond formation is the rate-determining step.

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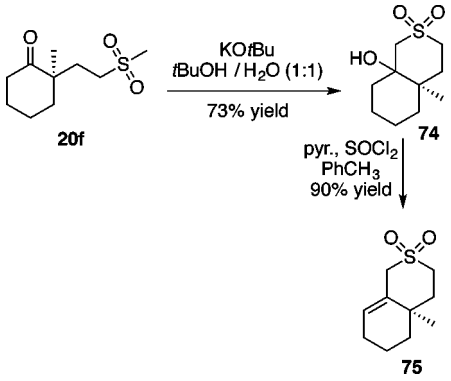
J. Org. Chem. 2016, 81, 3629−3637

Scheme 6. Derivatization of Michael Product



The major TS for the rate and stereodetermining Michael step, (***R,R***)**-TS-78** (Figure 1, bottom), exemplifies the signature thiourea hydrogen bonding motifs. The electrophile adopts an s-*trans* conformation; this electrostatically stabilizes the TS by placing the enolate on maximum facial contact with the forming iminium. This *endo* orientation of the electrophile affords a stabilizing C−H_{ax}···O interaction[21] (shown as a green line). The minor (***S,S***)**-TS-78** is higher in energy by 5.1 kcal/mol (selectivity of 99.8% ee). Theory overpredicts the observed experimental selectivity of 3.3 kcal/mol (98% ee).[22] The (*S,S*)-TS shows a similar s-*anti* electrophile orientation that allows the electrostatic stabilization of the forming enolate/iminium. The phenyl groups orient antiperiplanar to each other, which requires the electrophile to orient *exo* to accommodate the forward-projecting α-phenyl moiety. Although this orientation affords a stabilizing C−H···O interaction with the β-phenyl, an unavoidable destabilizing short H···H contact is incurred with the α-phenyl in the process.

We sought to understand the bifunctionality of the catalyst more deeply. Taking the benzylamine as an achiral representation of **15**, we computed the C−C bond forming TSs with and without the free thiourea (Figure 2). Surprisingly, the enthalpic stabilization afforded by the thiourea is negligible (TS-I vs TS-II, $\Delta\Delta G^{\ddagger}$ = 0.1 kcal mol^{-1}) with any stabilizing effects apparently being offset by the entropic penalty of intermolecularity. We next computed the desdiphenyl version of bifunctiuonal catalyst **82** (TS-III) to test the role of intramolecularity. Only when bound through the ansa chain can the thiourea exert any appreciable amount ($\Delta\Delta G^{\ddagger}$ = 3.7 kcal

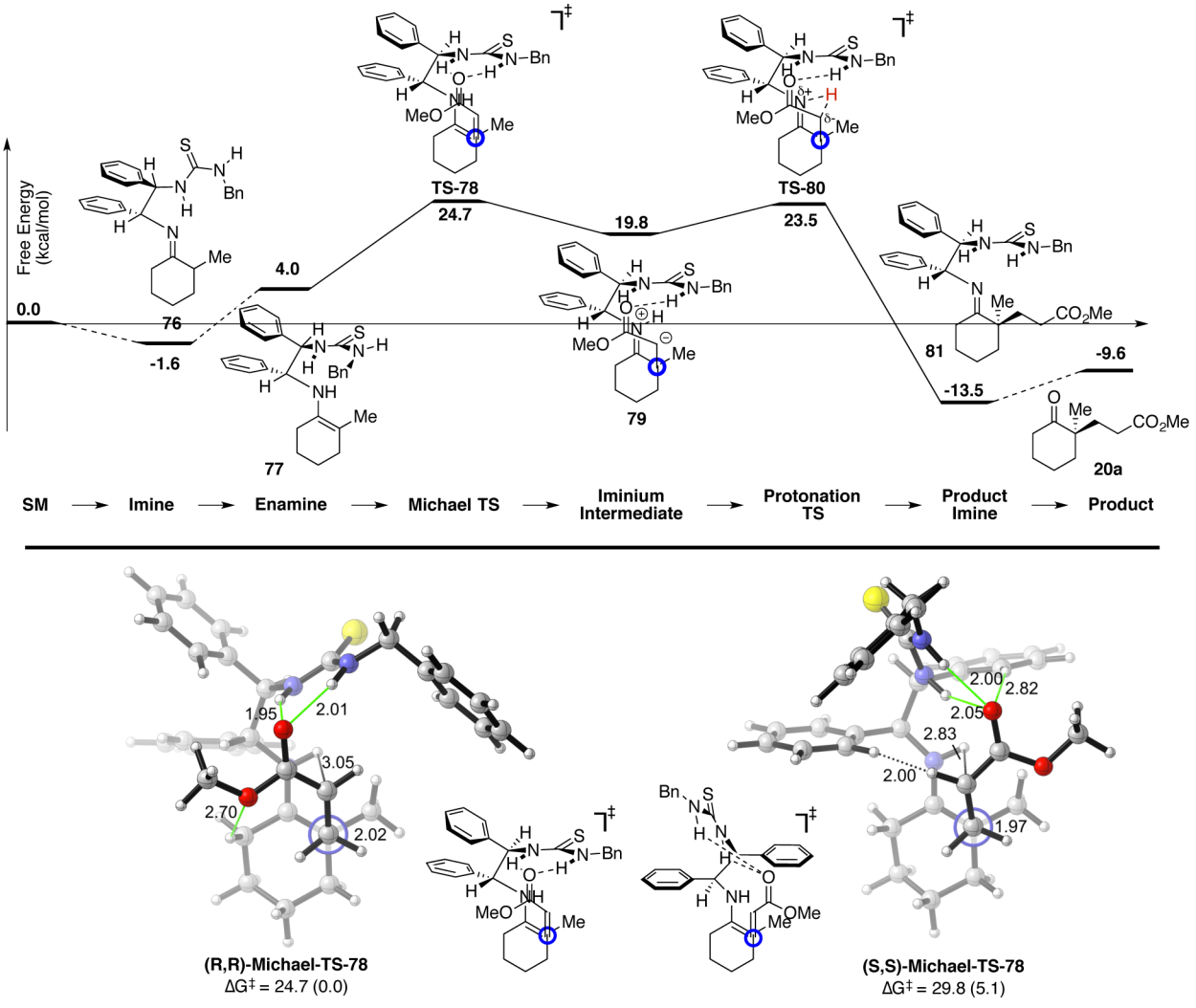


Figure 1. Reaction profile for the present reaction (top) and the major (left) and minor (right) transition states for the Michael step, **TS-78** (bottom). Energies are reported from the product imine in kcal/mol with the relative energies in parentheses. Dotted lines indicate repulsive interactions, and green lines indicate stabilizing interactions.

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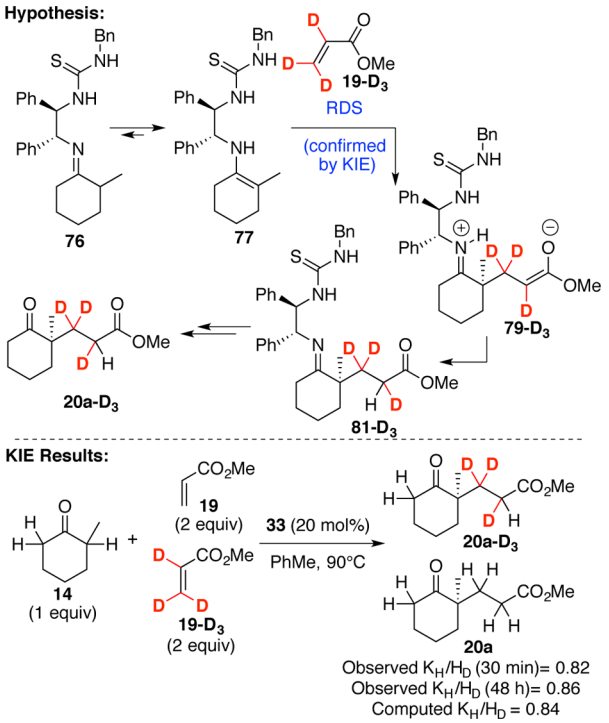
Scheme 7. Mechanistic Justification and Experimental Results of Kinetic Isotope Experiments in the Catalytic, Asymmetric Pfau–d'Angelo Reaction



mol^{-1}) of hydrogen bonding stabilization on the electrophile (cf. catalyst **82** (TS-II) vs benzylamine alone (TS-III)). Furthermore, the addition of stereodirecting groups onto **33** largely does not affect the TS barrier leading to the major product.

We next investigated the origins of selectivity by systematically substituting phenyls along the ansa bridge (Figure 3 and Table 3). *α*-Phenyl-substituted catalyst **83** is predicted to give 6.3 kcal/mol selectivity as a result of repulsion at the short H···H distance (2.02 Å) between the *α*-phenyl and the electrophile. *β*-Phenyl-substituted catalyst **84** is predicted to give lower selectivity (~3.3 kcal/mol). The repulsive H···H contact is replaced by a favorable C–H···O interaction with the *β*-phenyl. The heightened selectivity of **83** compared to catalyst **33** is thus a result of the absence of the *β*-phenyl, which would otherwise provide a mismatched stabilization of the minor TS evident with catalyst **84**. These results collectively indicate that the stereoselectivity is derived from the *α*-substituent. Furthermore, increased selectivities may be obtained through deletion of the *β*-substituent.

To test the computational hypothesis, we synthesized the most promising second-generation catalyst **83** that retains the *α*-phenyl (Table 3). We were disappointed to find that catalyst **83** was less selective (entry 2) at only 80% ee (1.6 kcal/mol) compared to 98% ee with **33** (entry 4). We extended the *α*-keto substituent in 2-ethylcyclohexanone to drive up selectivity, but this too led to lower enantioselectivity (83% ee; Scheme 8, eq 2) than with the parent catalyst (99% ee; Scheme 4, eq 1). This less hindered catalyst was also unable to catalyze transformations with alternate electrophiles **36** and **37** (Scheme 8, eqs 3 and 4). An exhaustive conformational search of the minor Michael TS involving catalyst **83** revealed a new lowest energy minor transition state; however, the computed selectivity still remained relatively high at $\Delta\Delta G^{\ddagger}$ = 5.6 kcal/mol (99.2% ee).

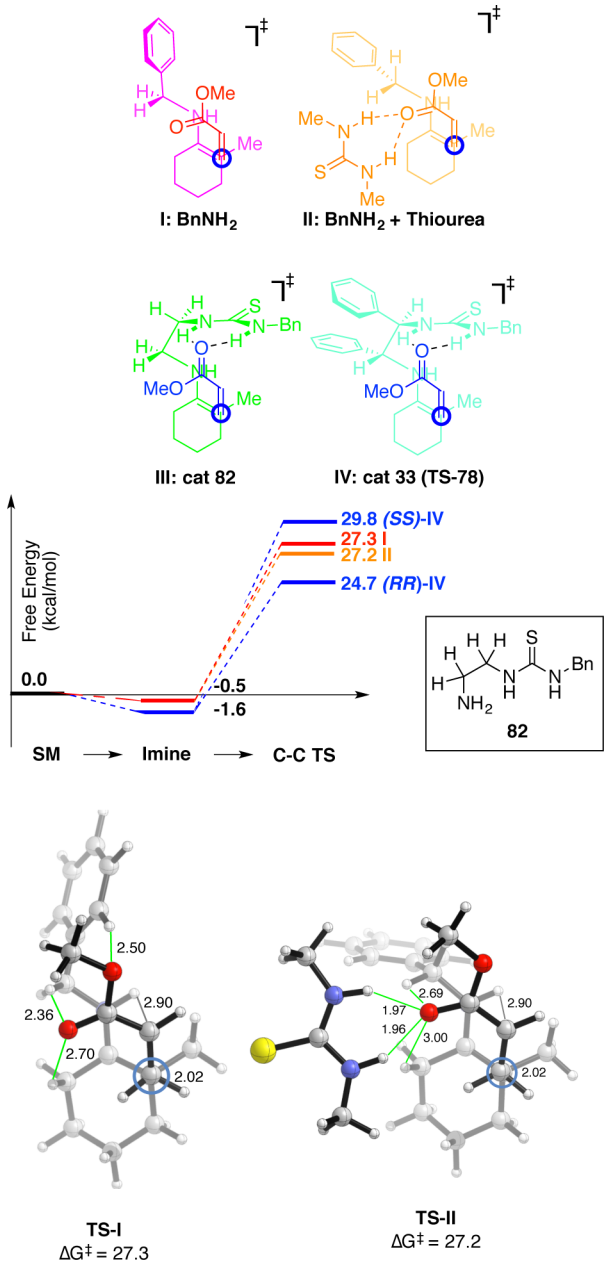


Figure 2. Comparison of Michael C–C transition states with amines **33** and benzylamine (top). Benzylamine-catalyzed enamines with and without thiourea hydrogen bonding shows that thiourea does not sufficiently activate the electrophile (bottom).

Considering the exhaustiveness of the conformational search and accuracies of the computational method,[23] we speculated that the selectivity trend discrepancies between experiments and computations might arise from alternate pathways, e.g., such as through catalyst decomposition products. Calculations (Figure 2) suggest that benzylamine can competitively catalyze this reaction, with a barrier lying between the major and minor TSs of catalyst **33**. Interestingly, concurrent experiments showed that when the experimental ee was measured after only 3 h (compared to the normal 48 h), a slight improvement in stereoselectivity was observed at 86% ee. On the basis of these combined results, we hypothesize that selectivity erosion is occurring through racemic catalysis by a catalyst decomposition product, such as benzylamine. Indeed, we observed

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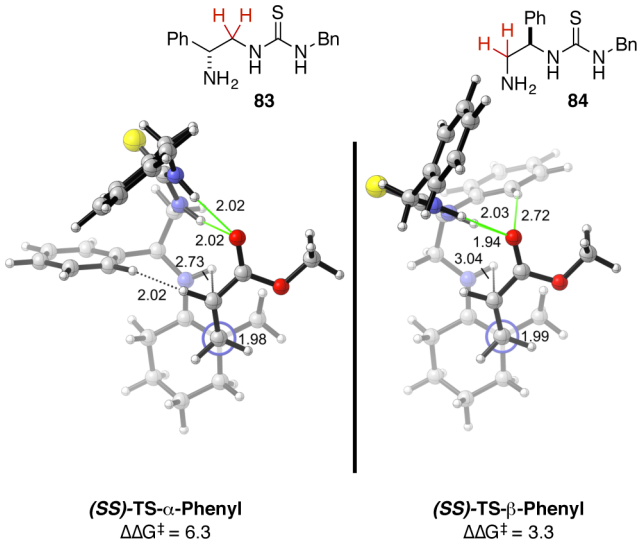
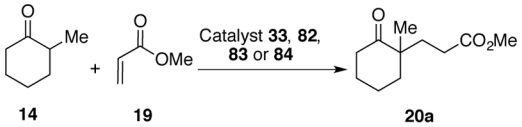
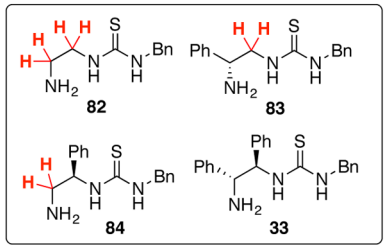


Figure 3. Minor transition structures for the α-phenyl catalyst (**83**) and β-phenyl catalyst (**84**). Selectivities are with respect to the major transition structures of each (not shown) and are in kcal/mol. Dotted lines indicate repulsive interactions, whereas green lines indicate stabilizing interactions.

Table 3. Computed Selectivities for Catalysts 33 and 82−84 in the Catalytic, Asymmetric Pfau−d'Angelo Reaction[a]



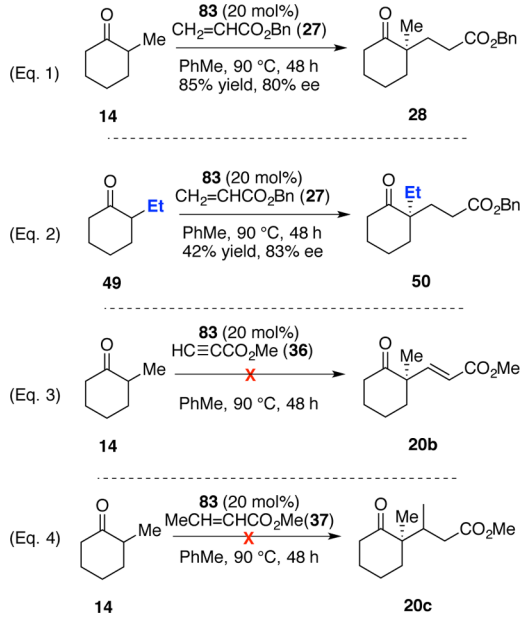


		catalyst %, ee			
		computed		experiments	
entry	cat.	(kcal/mol)	(% ee)	(kcal/mol)	(% ee)
1	**82**	N/A	N/A	N/A	N/A
2	**83**	6.0	>99.99	1.3	80[a]
3	**84**	3.0	98.7		
4	**33**	5.1	>99.99	2.7	98

[a]The experimental data was collected on the benzyl acrylate.

nonisolable, volatile decomposition products of catalyst **83** in the reaction mixture by NMR. We attribute these results to the fact that catalyst **83** was less stable than catalyst **33**; noticeable amounts of decomposition to the presumed thiourea and free amine were observed under the reaction conditions. Decomposition could have complicated the asymmetric induction in the process, as benzylamine is known to serve as an active, noncatalytic additive to accelerate this reaction. Given the lack of chirality of benzyl amine, any reaction meditated by it would be inherently racemic and lead to erosion of the overall enantioselectivity of the process.

Scheme 8. Exploration of the Reactivity of des-Phenyl Catalyst 83[a]



[a]Enantiomeric excess determined by chiral HPLC analysis.

CONCLUSIONS

In conclusion, a highly efficient organocatalytic system for the enantioselective synthesis of α,α-disubstituted cycloalkanones has been discovered. The logistical ease of the reaction process, the high yield and stereoselectivity, as well as the ready availability of the organocatalyst should make this transformation highly attractive for use in chemical synthesis. Furthermore, the wide scope of this transformation and the potential for derivatization of the α,α-disubstituted cycloalkanones will enable synthetic chemists to access these challenging scaffolds. The demonstrated synergy between experiment and computation led to an extensive understanding of the mechanistic underpinnings of this reaction and the development of second-generation catalysts. Computational analysis led to the discovery that the selectivity in this organocatalyzed Michael addition likely originates from the α-phenyl moiety on the catalyst. A superficial analysis of purely the experimental results would have mistakenly led to the conclusion that both stereocenters are essential for selectivity. Prodded by computations, careful analysis of the initial period of the reaction with des-phenyl catalyst **83** showed that enantioselectivity appeared to erode as a function of time due to catalyst decomposition and subsequent background reaction. Consequently, we have concluded that the α-phenyl moiety is critical for stereoselectivity and the β-phenyl moiety is needed for improved catalyst stability. Further computationally guided reaction development in this area will likely focus on expanding the reaction scope to include β-electrophiles. Currently, that transformation is only feasible using stoichiometric levels of α-methyl benzyl amine under forcing conditions.[9e]

EXPERIMENTAL SECTION

General. Infrared spectra were recorded neat unless otherwise indicated and are reported in cm^{-1}. ^1H NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded in deuterated solvents and are reported in

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J. Org. Chem. 2016, 81, 3629−3637

ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. Chiral HPLC was performed with chiral columns (chirapak AD, OD, AS-H, AY-H columns; Daicel Chemical Ind., Ltd.). HRMS data was acquired on a TOF-MS instrument with an EI or ES source.

Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230−400 mesh silica gel.

Air and/or moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon in glassware dried in an oven at 120 °C or by flame and then cooled under argon. Dry toluene was obtained via a solvent purification system. All other solvents and commercially available reagents were either purified via literature procedures or used without further purification.

General Procedure for Thiourea-Catalyzed Michael Addition. To a solution of catalysts **31**−**33**[24] (0.10 mmol, 20 mol %) in toluene (0.50 mL) were added the corresponding ketone (0.50 mmol, 1.0 equiv) and Michael acceptor (1.00 mmol, 2.0 equiv) at room temperature, and the resulting mixture was stirred at 90 °C. After 48 h, the solvent was removed in vacuo, and the crude was purified by chromatography over silica gel, eluting with 10−60% EtOAc/hexanes to give the corresponding Michael product.

*(R)-Benzyl 3-(2-Oxo-1-propylcyclohexyl)propanoate (**52**).* This reaction was run with catalyst **33** (colorless oil, 82 mg, 54%, 95% ee); $[\alpha]_D^{20}$ −14.6 (*c* 1.0, $CHCl_3$); IR (neat) 2957, 2872, 1739, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.35 (m, 5H), 5.12 (s, 2H), 2.44−2.31 (m, 3H), 2.24−2.16 (m, 1H), 2.01−1.84 (m, 3H), 1.79−1.60 (m, 6H), 1.45−1.41 (m, 1H), 1.39−1.22 (m, 1H), 1.10−1.01 (m, 1H), 0.91 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.7, 173.6, 136.0, 128.5, 128.2 (2C), 66.2, 50.9, 39.0, 36.9, 36.2, 29.5, 29.0, 27.0, 20.7, 16.5, 14.7; HRMS (ES+) calcd for $C_{19}H_{26}O_3Na$ (M + Na) 325.1780, found 325.1793; HPLC, Daicel Chiralpak IF; hexanes/*i*-PrOH, 99.8:0.2, 0.2 mL min^{-1}, 254 nm; t_R (major) = 115.0 min, t_R (minor) = 105.8 min.

*Benzyl 3-((1S,4R)-1-Methyl-2-oxo-4-(prop-1-en-2-yl)cyclohexyl)-propanoate (**58**).* This reaction was run with catalyst *ent*-**33** (colorless oil, 110 mg, 70%, >7.5:1 dr); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.32 (m, 5H), 5.18 (s, 2H), 4.79 (s, 1H), 4.73(s, 1H), 2.52−2.50 (m, 1H), 2.48−2.33 (m, 4H), 1.89−1.60 (m, 6H), 1.77 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 173.7, 147.3, 136.0, 128.5, 128.2, 128.1, 110.0, 66.2, 46.9, 45.7, 43.2, 36.5, 32.7, 29.4, 25.9, 22.9, 20.7.

*(4aR,8aS)-8a-Hydroxy-4a-methyloctahydro-1H-isothiochromene 2,2-Dioxide (**74**).* To a solution of K^{t}OBu (7 mg, 0.06 mmol, 0.3 equiv) in ^{t}BuOH/THF (1:1, 2 mL) at −78 °C was added a solution of sulfone **20f** (44 mg, 0.20 mmol, 1.0 equiv) in THF (0.5 mL), and the resulting mixture was stirred for 2 h and then warmed to room temperature. After 24 h at room temperature, water (1 mL) was added and then extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20−50% EtOAc/hexanes to obtain **74** (white solid, 32 mg, 73%); IR (neat) 3500, 2931, 2866, 1298, 1265, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (bs, 1H), 3.70−3.63 (m, 1H), 3.30−3.15 (m, 1H), 3.09−3.00 (m, 1H), 2.85−2.72 (m, 1H), 2.50−2.40 (m, 1H), 1.92−1.32 (m, 9H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.3, 54.4, 47.0, 37.2, 35.4, 34.0, 33.0, 22.7, 21.4, 20.4; HRMS (EI+) calcd for $C_{10}H_{18}O_3S$ (M+) 218.0977, found 218.0980.

*(R)-4a-Methyl-3,4,4a,5,6,7-hexahydro-1H-isothiochromene 2,2-Dioxide (**75**).* To a solution of sulfone alcohol **74** (20 mg, 0.09 mmol, 1.0 equiv) in toluene (2.4 mL) at −78 °C were added pyridine (73 mg, 0.92 mmol, 10.0 equiv) and $SOCl_2$ (65 mg, 0.55 mmol, 6.0 equiv), and the solution was then warmed to room temperature. After 1 h at room temperature, it was quenched with sat. aq $NaHCO_3$ solution and extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20−50% EtOAc/hexanes to obtain **75** (white solid, 18 mg, 90%); $[\alpha]_D$ +0.2 (*c* 1.0, $CHCl_3$); mp 123−125 °C; IR (neat) 2968, 2852, 1303, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (bs, 1H), 3.91 (dd, *J* = 14.4, 2.0 Hz, 1H), 3.48 (dd, *J* = 14.4, 2.0 Hz, 1H), 3.28 (ddd, *J* = 14, 14, 4 Hz, 1H), 3.11−3.06 (m, 1H), 2.19−2.11 (m, 2H), 1.89 (ddd, *J* = 12, 8, 4 Hz, 1H), 1.77−1.63 (m, 5H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2, 131.0, 57.7, 48.3, 38.1, 36.8, 33.5, 25.6, 23.3, 18.5; HRMS (EI+) calcd for $C_{10}H_{16}O_2S$ (M+) 200.0871, found 200.0867.

*(R)-1-(2-Amino-2-phenylethyl)-3-benzylthiourea (**83**).* To a solution of (*R*)-1-phenylethane-1,2-diamine (190 mg, 1.40 mmol, 1.0 equiv) in CH_2Cl_2 (14 mL) at 0 °C was added (isothiocyanatomethyl)-benzene (208 mg, 1.40 mmol, 1.0 equiv) dropwise over 30 min. After 6 h at room temperature, it was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20−50% CH_2Cl_2/MeOH to obtain **83** (white form, 190 mg, 48%); IR (neat) 3263, 3064, 3033, 2923, 1551, 1498, 1456, 1284 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.24 (m, 10H), 6.82 (bs, 1H), 4.61 (bs, 2H), 4.11 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.77 (bs, 1H), 3.49−3.42 (m, 1H), 1.85 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.5, 142.8, 137.3, 128.8, 128.7, 127.7 (2C), 126.9, 126.0, 55.2, 52.1, 48.3; HRMS (ES+) calcd for $C_{16}H_{19}N_3S$ (MH+) 286.1378, found 286.1377.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00280.

Complete computational data, including molecular geometries and energies (PDF)

Copies of ^1H and ^{13}C NMR spectra for all new compounds along with chiral HPLC/GC traces for all new asymmetric reactions (PDF)

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Notes

The authors declare no competing financial interest.

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