

Primary Amine, Thiourea-Based Dual Catalysis Motif for Synthesis of Stereogenic, All-Carbon Quaternary Center-Containing Cycloalkanones

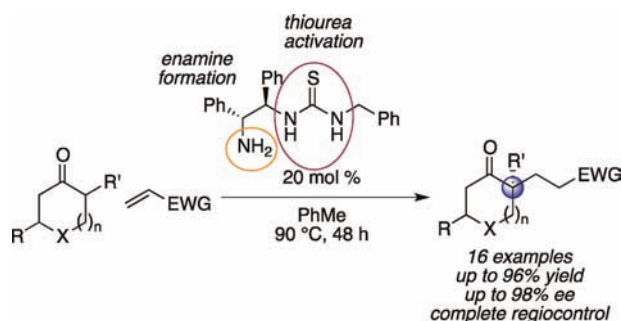
Jun Yong Kang and Rich G. Carter*

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331, United States

rich.carter@oregonstate.edu

Received May 8, 2012

ABSTRACT



The enantioselective synthesis of α,α -disubstituted cycloalkanones has been developed using a primary amine, thiourea-based dual catalysis pathway. A range of electrophiles and ring sizes are tolerated under the reaction conditions. A possible catalytic cycle is presented to explain the reactivity.

Stereogenic, α,α -disubstituted cycloalkanones have attracted the attention of numerous researchers due to their use as versatile building blocks in pharmaceuticals and natural product synthesis.¹ Despite this utility, primarily stoichiometric auxiliary and transition-metal-catalyzed approaches have been reported in the literature. Pfau and d'Angelo reported one of the earliest methods (Scheme 1).² Their traceless auxiliary protocol employed stoichiometric (+)- α -methylbenzylamine to generate and isolate a chiral imine/enamine intermediate, which was then reacted with Michael acceptors such as methyl vinyl ketone and methyl acrylate to generate quaternary centers with good levels of enantiomeric excess (Scheme 1).²

Key to this transformation is the observation that the imine derived from the primary amine slowly tautomerizes selectively to the more substituted enamine. In contrast, attempted direct formation of the desired enamine geometry using pyrrolidine (**7**) preferentially gives the unwanted enamine **8** (9:1 rr).³ While palladium-based catalytic, asymmetric methods for allylation of cycloalkanones have been developed,^{4–10} we are unaware of an organocatalytic method for facilitating the Michael addition of α -alkyl-substituted cycloalkanones with acrylates.¹¹ In this Communication, we describe the development of a

(3) Gurowitz, W. D.; Joseph, M. A. *J. Org. Chem.* **1967**, *32*, 3289–3292.

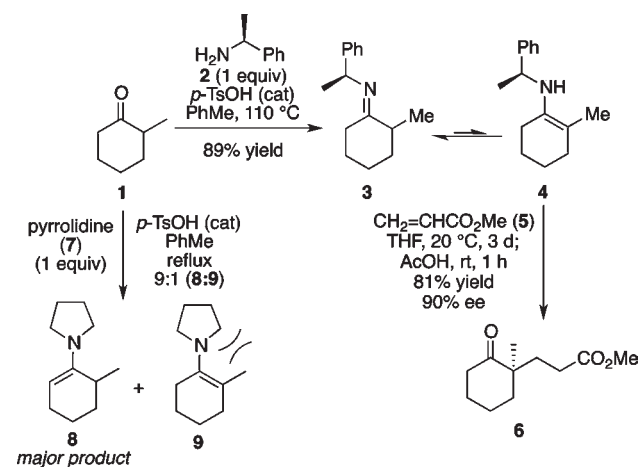
(4) (a) Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144–152. (b) Tsuji, J. *Pure Appl. Chem.* **1982**, *54*, 197–206. (c) Tsuji, J. *Pure Appl. Chem.* **1986**, *58*, 869–878. (d) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140–145. (e) Tsuji, J. *Pure Appl. Chem.* **1989**, *61*, 1673–1680. (f) Tsuji, J. *Pure Appl. Chem.* **1999**, *71*, 1539–1547.

(5) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113–120.

(6) (a) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586–2592. (b) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309–3310. (c) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236–3237. (d) Kuwano, R.; Uchida, K.; Ito, Y. *Org. Lett.* **2003**, *5*, 2177–2179.

primary amine, thiourea bifunctional catalyst system¹² to facilitate this key transformation.

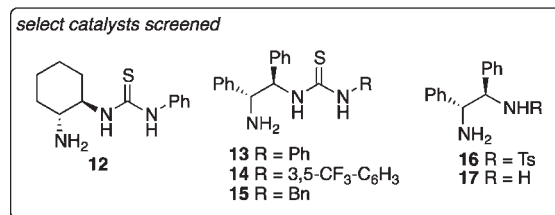
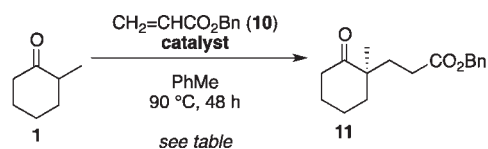
Scheme 1. Precedent for Enamine-Mediated Michael Additions of α -Substituted Cycloalkanones



The development of an organocatalyzed method for the synthesis of α,α -disubstituted cyclohexanone **11** is shown in Table 1. In order to facilitate a catalytic version of enamine-mediated, α,α -disubstituted cycloalkanone synthesis, we first attempted to simply use substoichiometric amounts of primary amine **2** (entry 1). Not surprisingly,

this reaction proceeded in low yield. Interestingly, addition of Brønsted acid additives such as *p*-TsOH completely suppressed the reaction (entry 2). We next screened a series of bifunctional thiourea/primary amine catalysts **12**–**15**.¹³ While cyclohexyl-based catalyst **12** performed poorly in this transformation (entry 3), use of an acyclic diamine backbone (e.g., catalyst **13**) provided dramatic increases in both chemical yield (49%) and enantioselectivity (98%) (entry 4). Further increases in chemical yield were achieved using the benzyl thiourea derivative **15**, now providing the optimum level of chemical yield (95%) with continued high enantioselectivity (98% ee) (entry 6). The absolute configuration was established by comparison with the optical rotation with literature values.^{2a} Use of alternate solvents (xylenes, 1,4-dioxane, MeCN, DMF) or lower temperatures (e.g., 60 °C) provided inferior chemical yields. The thiourea motif appeared important to catalytic turnover, as use of a sulfonamide derivative **16** or the parent diamine **17** led to a significant reduction in chemical yield.

Table 1. Optimization of Organocatalyzed Michael Addition to 2-Methylcyclohexanone



entry	conditions	% yield	% ee ^a
1	2 (20 mol %)	10	90
2	2 (20 mol %), <i>p</i> -TsOH (1 mol %)	0	n/a
3	12 (20 mol %)	18	67
4	13 (20 mol %)	49	98
5	14 (20 mol %)	80	98
6	15 (20 mol %)	95	98
7	15 (10 mol %)	76	98
8	16 (20 mol %)	17	98
9	17 (20 mol %)	5	n/d

^a Determined by chiral HPLC analysis.

With these catalytic reaction conditions established, we studied the scope of the reaction of nucleophiles with

(7) (a) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879–7880. (b) Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed.* **1997**, *36*, 2635–2637. (c) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759–6760. (d) M., B.; Schroeder, G. M.; Kristensen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3492–3495. (e) Trost, B. M.; Schroeder, G. M. *Chem.—Eur. J.* **2005**, *11*, 174–184.

(8) (a) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1933–1934. (b) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* **2001**, *3*, 149–151. (c) Yan, X.-X.; Liang, C.-G.; Zhang, Y.; Hong, W.; Cao, B.-X.; Dai, L.-X.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6544–6546.

(9) (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) Enquist, J. A.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231. (c) Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 194–211. (d) Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2010**, 192–196.

(10) Mohr, J. T.; Stoltz, B. M. *Chem.—Asian J.* **2007**, *2*, 1476–1491. (11) Examples have been reported using indanones which lowers the pK_a of the α -hydrogens of the ketone: Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710–4711.

(12) (a) Yalalov, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366–6370. (b) Zheng, X.-J.; Liu, S.-P.; Lao, J.-H.; Du, G.-J.; Yan, M.; Chan, A. C. *Tetrahedron: Asymmetry* **2009**, *20*, 1451–1458. (c) Lao, J.-H.; Zhang, X.-J.; Wang, J.-J.; Li, X.-M.; Yan, M.; Luo, H.-B. *Tetrahedron: Asymmetry* **2009**, *20*, 2818–2822. (d) He, T.; Gu, Q.; Wu, X.-Y. *Tetrahedron* **2010**, *66*, 3195–3198. (e) Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286–9288. (f) Chen, J.-R.; Zou, Y.-Q.; Fu, L.; Ren, F.; Tan, F.; Xiao, W.-J. *Tetrahedron* **2010**, *66*, 5367–5372. (g) Xue, F.; Liu, L.; Zhang, S.; Duan, W.; Wang, W. *Chem.—Eur. J.* **2010**, *16*, 7979–7982. (h) Yu, F.; Jin, Z.; Huang, H.; Ye, T.; Liang, X.; Ye, J. *Org. Biomol. Chem.* **2010**, *8*, 4767–4774. (i) Yang, J.; Li, W.; Jin, Z.; Liang, X.; Ye, J. *Org. Lett.* **2010**, *12*, 5218–5221. (j) Bia, J.-F.; Peng, L.; Wang, L.-L.; Wang, L.-X.; Xu, X.-Y. *Tetrahedron* **2010**, *66*, 8928–8932. (k) Basak, A. K.; Shimada, N.; Bow, W. F.; Vicic, D. A.; Tius, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 8266–8267. (l) Miura, T.; Nishida, S.; Masuda, A.; Tada, N.; Itoh, A. *Tetrahedron Lett.* **2011**, *52*, 4158–4160. (m) Ma, Z.-W.; Liu, Y.-X.; Zhang, W.-J.; Tao, Y.; Zhu, Y.; Tao, J.-C.; Tang, M.-S. *Eur. J. Org. Chem.* **2011**, *2011*, 6747–6754. (n) Ma, Z.-W.; Liu, Y.-X.; Li, P.-L.; Ren, H.; Zhu, Y.; Tao, J.-C. *Tetrahedron: Asymmetry* **2011**, *22*, 1740–1748.

(13) (a) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965. (b) Touchard, F.; Fache, F.; Lemaire, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3319–3326. (c) He, T.; Qian, J.-Y.; Song, H.-L.; Wu, X.-Y. *Synlett* **2009**, 3195–3197. (d) Han, B.; Liu, Q.-P.; Li, R.; Tian, X.; Xiong, X.-F.; Deng, J.-G.; Chen, Y.-C. *Chem.—Eur. J.* **2008**, *14*, 8094–8097. (e) Yu, F.; Jin, Z.; Huang, H.; Ye, T.; Liang, X.; Ye, J. *Org. Biomol. Chem.* **2010**, *8*, 4767–4774. (f) Isobe, T.; Fukuda, K.; Tokunaga, T.; Seki, H.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7774–7778.

Michael acceptor **10** (Table 2). Five- and six-membered cycloalkanones underwent clean reaction to provide the desired products in excellent yields and enantioselectivities after 48 h at 90 °C (42–96% yields, 97–98% ee). Larger ring sizes appeared to be problematic; 2-methylcycloheptanone provided none of the desired product. Steric effects were important in transforming nucleophiles to the desired products. For instance, 2-ethyl cyclohexanone **18c** (entry 3) provided a lower yield than the parent 2-methyl cyclohexanone **11** (42% and 95% yields respectively). The heterocyclic nucleophiles provided good to excellent chemical yields (91 and 64% yield, entries 4 and 5).¹⁴ Dihydrocarvone (**18f**) has been exploited previously in modestly diastereoselective Michael additions (e.g., methyl acrylate, *t*-BuOK, *t*-BuOH, 0 °C, 76% yield, 6:1 dr).¹⁵ We were pleased to observe excellent levels of diastereoselectivity and chemical yield (96% yield, >95% de) using our catalyst system (entry 6).¹⁶ In all cases shown in Table 2, none of the potential 2,6-substituted regioisomeric cycloalkanones were observed.

Table 2. Exploration of Substrate Scope (Nucleophile)



entry	x	n	R', R''	% yield	% ee ^a
1	CH ₂	0	Me, H	96 (19a)	99
2	CH ₂	2	Me, H	0 (19b)	n/a
3	CH ₂	1	Et, H	42 (19c)	99
4	O	1	Me, H	91 (19d)	98
5	S	1	Me, H	64 (19e)	97
6	CH ₂	1	Me, 2-propenyl	96 (19f)	>95 ^b

^a Determined by chiral HPLC analysis. ^b Determined diastereomeric excess by ¹H NMR.

We next explored the scope of electrophiles in this organocatalyzed process (Table 3). We were pleased to observe that other acrylates^{2a} were tolerated in the transformation (entries 1–2). Vinyl sulfones proved effective under the reaction conditions (entries 3–7). It should be noted that the phenyl-substituted thiourea catalyst **13** generally gave improved chemical yields with both phenyl vinyl sulfone (**20b**)¹⁷ and methyl vinyl sulfone (**20c**). We attribute this difference in reactivity to the more ionic nature of the phenyl-substituted thiourea N–H bonds, which better coordinates with the sulfone moiety. Acrylonitrile (**20d**) also proved to be effective in this transformation;

(14) (a) Smith, A. B., III; Empfield, J. R.; Vaccaro, H. A. *Tetrahedron Lett.* **1989**, *30*, 7325–7328. (b) Spears, G. W.; Caufield, C. E.; Still, W. C. *J. Org. Chem.* **1987**, *52*, 1226–1231.

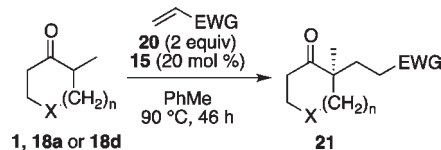
(15) Shono, T.; Kise, N.; Fujimoto, T.; Tominaga, N.; Morita, H. *J. Org. Chem.* **1992**, *57*, 7175–7187.

(16) Faraldos, J. A.; Kariuki, B.; Allemann, R. K. *J. Org. Chem.* **2010**, *75*, 1119–1125.

(17) Hickmott, P. W.; Rae, B. *Tetrahedron Lett.* **1985**, *26*, 2577–2580.

however, the enantioselectivities for these substrates were reduced (entries 8–9).^{2b,18} One rationale may be found in the sp-hybridized nature of the nitrile moiety, reducing the efficiency of preorganization with the catalyst. Finally, the amide derivative **20e** was a viable electrophile using 2-methylcyclopentanone (**18a**) providing product **21j**; however, no Michael addition product was observed in the analogous six-membered ring series.

Table 3. Exploration of Substrate Scope (Electrophile)



entry	n	X	EWG	% yield	% ee ^a
1	0	CH ₂	CO ₂ Me (20a)	70 (21a)	99
2	1	CH ₂	CO ₂ Me (20a)	91 (21b)	98
3 ^b	0	CH ₂	SO ₂ Ph (20b)	34 (21c)	89
4 ^b	1	CH ₂	SO ₂ Ph (20b)	65 (21d)	94
5 ^c	1	O	SO ₂ Ph (20b)	65 (21e)	98
6 ^b	0	CH ₂	SO ₂ Me (20c)	50 (21f)	>95 ^d
7 ^b	1	CH ₂	SO ₂ Me (20c)	50 (21g)	>95 ^d
8 ^b	0	CH ₂	CN (20d)	54 (21h)	72 ^e
9	1	CH ₂	CN (20d)	75 (21i)	85
10	0	CH ₂	C(O)NHBn (20e)	31 (21j)	80
11	1	CH ₂	C(O)NHBn (20e)	0 (21k)	n/a

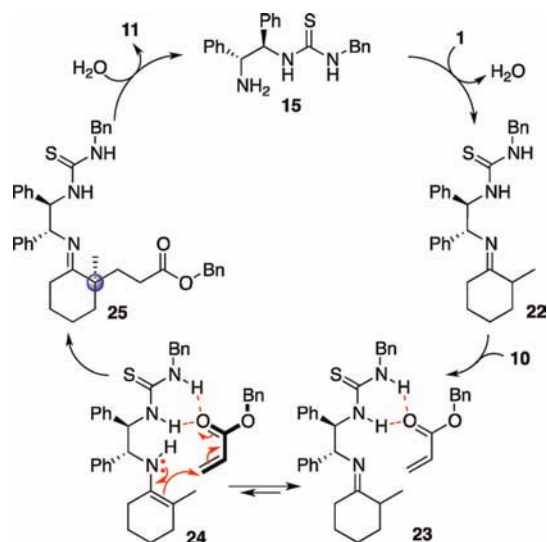
^a Determined by chiral HPLC analysis. ^b Catalyst **13** (20 mol %) proved to be the optimum catalyst for this transformation. ^c Catalyst **14** (20 mol %) proved to be the optimum catalyst for this transformation. ^d Determined by ¹H NMR using europium tris[3-(heptafluoropropyl)-hydroxymethylene-(+)-camphorate]. ^e Determined by chiral GC analysis.

A possible catalytic cycle is illustrated in Scheme 2. Imine formation using the primary amine **15** and ketone **1** would generate the imine **22**. Next, complexation of the thiourea **22** with the electrophile **10** could generate intermediate **23**. The imine/enamine equilibrium likely favors the imine **23**; however, only reactive intermediate enamine **24** is capable of undergoing hydrogen-bond assisted Michael addition and protonation to form the key carbon–carbon bond. Hydrolysis of the sterically congested imine **25** is likely facilitated by the pendant thiourea motif to regenerate catalyst **15** and release product **11**.

In summary, we have developed an organocatalyzed, asymmetric protocol for the construction of α,α -disubstituted cycloalkanones containing all-carbon, quaternary stereocenters in high levels of chemical yield and enantioselectivity. This process proceeds on both five- and six-membered cycloalkanones as well as heterocyclic ketones. A range of electrophiles are tolerated under the process. The disclosed technology efficiently addresses the complete regioselective control of the catalytic, enantioselective Michael addition using unsymmetrically functionalized

(18) Kuehne, M. E.; King, J. C. *J. Org. Chem.* **1973**, *38*, 304–311.

Scheme 2. Simplified Catalytic Cycle for Michael Addition



ketones (e.g., **1**) with an α,β -unsaturated electrophile. While two regiomer ic enamines could potentially be generated under the reaction conditions, a preferential reaction through the sterically more congested enamine is achieved under the thiourea/primary amine bifunctional catalyst

system. This work represents one of the first general one-step catalytic, asymmetric methods to facilitate stereoselective, all-carbon quaternary center bond-forming reactions (e.g., Michael additions) using simple, unsymmetrical ketones (e.g., 2-alkylcycloalkanones) as starting materials. The products derived from this transformation should serve as useful building blocks in organic synthesis. Further application of this technology will be reported in due course.

Acknowledgment. Financial support was provided by the National Science Foundation (NSF) (CHE-0848704) and Oregon State University. We thank Professor Max Deinzer and Dr. Jeff Morr  (OSU) for mass spectra data. The authors are grateful to Professor Hua Yang (Central South University) for his early, related work in this area and to Professor Paul Ha-Yeon Cheong (OSU), Mr. Ryne Johnston (OSU), and Dr. Roger Hanselmann (Rib-X Pharmaceuticals) for their helpful discussions

Supporting Information Available. Complete experimental procedures and copies of ^1H and ^{13}C spectra for all new compounds are provided. Copies of chiral HPLC/GC traces for asymmetric reactions are also included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.