

Enantioselective Organocatalytic Michael Addition of Malonates to α,β -Unsaturated Ketones

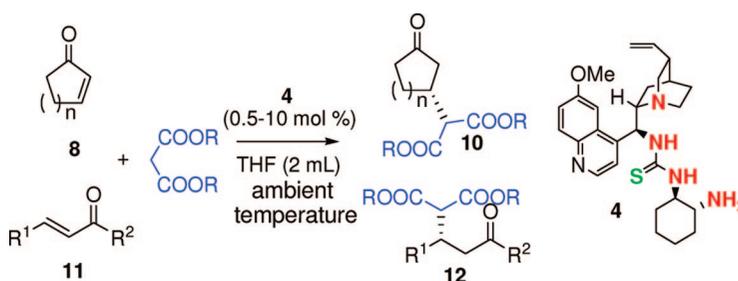
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ABSTRACT



A novel type of primary amine thiourea organocatalysts derived from 1,2-diaminocyclohexane and 9-amino (9-deoxy) cinchona alkaloid was developed into asymmetric Michael addition of malonates to enones. A series of cyclic and acyclic enones could react very well with different malonates in the presence of 4 with 0.5–10 mol % catalyst loading affording chiral Michael adducts with excellent yields and ee values.

As one of the most powerful and typical carbon–carbon bond-forming reactions, the asymmetric Michael reaction enables access to a variety of optically active adducts affording synthetically useful building blocks in organic synthesis.¹ Due to two electron-withdrawing esters leading to enolate formation under mild conditions, malonates most notably have been used as easily accessible nucleophilic donors in the Michael addition.

Many types of catalysts such as proline salts,² chiral metal complexes,³ chiral ionic liquids,⁴ phase-transfer catalysts,⁵

and organocatalysts⁶ have been developed for the Michael addition of malonates to enones. However, substrate dependence still remains an important issue. Therefore, develop-

(2) (a) Yamaguchi, M.; Shiraishi, T.; Hiram, M. *Angew. Chem., Int. Ed.* **1993**, *32*, 1176. (b) Yamaguchi, M.; Shiraishi, T.; Hiram, M. *J. Org. Chem.* **1996**, *61*, 3520.

(3) For some selected references in this area, see: (a) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. (b) End, N.; Macko, L.; Zehnder, M.; Pfaltz, A. *Chem.–Eur. J.* **1998**, *4*, 818. (c) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506. (d) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (e) Agostinho, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2430.

(4) (a) Toma, S.; Gotov, B.; Kmentová, I.; Solcániová, E. *Green Chem.* **2000**, *2*, 149. (b) Wang, Z.; Wang, Q.; Zhang, Y.; Bao, W. *Tetrahedron Lett.* **2005**, *46*, 4657. (c) Mečiarová, M.; Toma, *Chem.–Eur. J.* **2007**, *13*, 1268.

(5) (a) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299. (b) Dere, R. T.; Pal, R. R.; Patil, P. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2003**, *44*, 5351. (c) Ooi, T.; Ohara, D.; Fukumoto, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 3195.

[†] Chinese Academy of Science.

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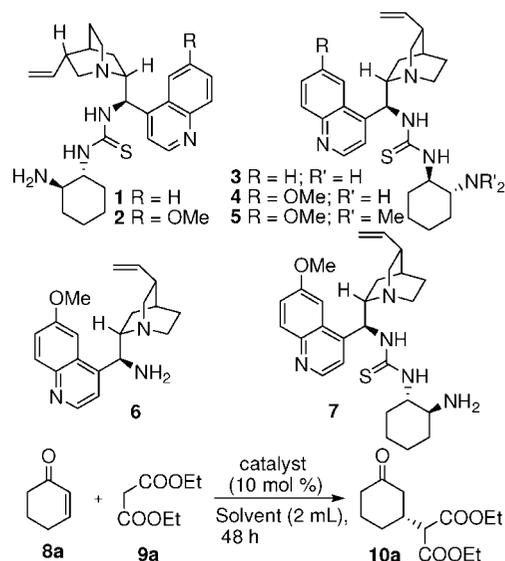
(1) For several selected published books on asymmetric organocatalysis, see: (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2004. (c) Dalko, P. I. *Enantioselective Organo-catalysis*; Wiley-VCH: Weinheim, Germany, 2007.

ment of an efficient catalyst with a broad range of enone substrates is a goal of considerable importance.

The potential of modified cinchona alkaloids⁷ and (thio)urea derivatives⁸ as efficient and enantioselective organocatalysts for asymmetric synthesis has been demonstrated. As a result, a new type of organocatalyst derived from modified cinchona alkaloids and (thio)urea was under consideration, which is expected to exhibit synergistic cooperation and effect organic reactions with excellent efficiency and stereoselectivities. Recently, we have reported a new type of primary amine thiourea consisting of 1,2-diaminocyclohexane and 9-amino cinchona alkaloid derivatives, which catalyzed Michael addition of nitroalkanes to α,β -unsaturated ketones with high enantioselectivity and efficiency.⁹ We wondered whether this approach could be extended to Michael addition of malonate to enones. Fully aware of the potential benefits but also of the many difficulties we would likely encounter, we decided to pursue this challenge.

At the outset of the investigation, we focused our attention on the primary amine thiourea catalytic Michael addition of diethyl malonate (**9a**) to cyclohex-2-enone (**8a**), and the results are shown in Table 1. After the screening of catalysts, it was confirmed by results that the reaction could be

Table 1. Catalyst and Reaction Condition Screen for the Reaction between **8a** and **9a**^a



entry	catalyst	solvent	convn (%) ^b	ee (%) ^b
1	1	toluene	59	82
2	2	toluene	73	82
3	3	toluene	78	84
4	4	toluene	88	92
5	5	toluene	9	10
6	6	toluene	13	-83
7	7	toluene	43	-79
8 ^c	4	neat	89	84
9	4	DMSO	25	50
10	4	MeOH	34	48
11	4	hexane	98	76
12	4	CH ₂ Cl ₂	72	94
13	4	CHCl ₃	72	94
14	4	DMF	74	80
15	4	Et ₂ O	82	88
16	4	EtOAc	88	91
17	4	MeCN	88	88
18	4	1,4-dioxane	80	92
19	4	THF	91	95
20 ^d	4	THF	96	97
21 ^e	4	THF	>99	94
22 ^f	4	THF	95	96
23 ^g	4	THF	>99	96
24 ^h	4	THF	60	93

^a Reaction conditions: A mixture of **5a** (1.0 mmol), **6a** (3.0 mmol), and the catalyst (10 mol %) in the solvent (2.0 mL) was stirred at ambient temperature for the time given. ^b Conversion and enantiomeric excess were determined by chiral GC. ^c For 12 h. ^d At 40 °C for 12 h. ^e At 70 °C for 8 h. ^f With 2 mol % catalyst loading at 40 °C for 36 h. ^g With 1 mol % catalyst loading at 40 °C for 72 h. ^h **8a** (4.0 mmol) reacted with **9a** (12.0 mmol) at 40 °C for 48 h with 0.5 mol % catalyst loading.

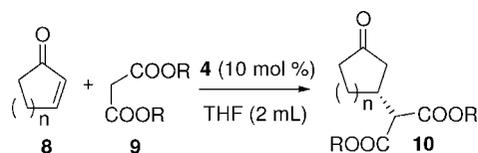
catalyzed by the primary amine thiourea (Table 1, entries 1–4). Especially, up to 88% of conversion and 92% ee were obtained in toluene after 48 h with **4** prepared from (1*R*,2*R*)-1,2-diaminocyclohexane and 9-amino (9-deoxy) epiquinine (Table 1, entry 4). However, poor results were obtained when catalyst **5** was employed, in which the primary amine was substituted with two methyl groups (Table 1, entry 5).

(6) (a) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661. (b) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652. (c) Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem. Commun.* **2006**, 66. (d) Wascholowski, V.; Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem.–Eur. J.* **2008**, *14*, 6155. (e) Jiang, Z.; Ye, W.; Yang, Y.; Tan, C.-H. *Adv. Synth. Catal.* **2008**, *350*, 2345.

(7) For several reviews on modified cinchona alkaloids, see: (a) Eames, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 885. (b) Chen, Y.; Mcdaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965. (c) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; Mcdaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (d) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496. For selected examples catalyzed by modified cinchona alkaloids, see: (e) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542. (f) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195. (g) Mcdaid, P.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 338. (h) Tiseni, P. S.; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 5325. (i) Poisson, T.; Dalla, V.; Marsais, F.; Dupas, G.; Oudeyer, S.; Levacher, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7090. (j) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157. (k) Furukawa, T.; Shibata, N.; Mizuta, S.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8051. (l) Elsner, P.; Bernardi, L.; Salla, G. D.; Overgaard, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 4897. (m) Bandini, M.; Sinisi, R.; Umami-Ronchi, A. *Chem. Commun.* **2008**, 4360.

(8) For some reviews on (thio)urea derivatives, see: (a) Connon, S. J. *Chem.–Eur. J.* **2006**, *12*, 5418. (b) Connon, S. J. *Chem. Commun.* **2008**, 2499. (c) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785. (d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. For selected examples catalysed by (thio)urea derivatives, see: (e) Curran, D. P.; Kuo, H. L. *J. Org. Chem.* **1994**, *59*, 3259. (f) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (g) Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett.* **2003**, 1919. (h) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (i) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589. (j) Okino, T.; Hoashi, Y.; Furukawa, T.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (k) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032. (l) McCooney, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (m) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (n) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (o) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293. (p) Wang, Y.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156. (q) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (r) Gao, P.; Wang, C.; Wu, Y.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2008**, 4563. (s) Peng, F.; Shao, Z.; Fan, B.; Song, H.; Li, G.; Zhang, H. *J. Org. Chem.* **2008**, *73*, 5202.

(9) Li, P.; Wang, Y.; Liang, X.; Ye, J. *Chem. Commun.* **2008**, 3302.

Table 2. 4-Catalyzed Michael Addition Reactions between **8** and **9**^a

entry	n	R	time (h)	adduct	yield (%) ^b	ee (%) ^c
1	2 (8a)	Et (9a)	60	10aa	88	96
2	2 (8a)	Me (9b)	60	10ab	83	96
3	2 (8a)	<i>i</i> -Pr (9c)	72	10ac	80	95
4 ^d	2 (8a)	Et (9a)	12	10aa	95	96
5 ^d	2 (8a)	Me (9b)	18	10ab	91	93
6 ^d	2 (8a)	<i>i</i> -Pr (9c)	18	10ac	95	96
7 ^d	3 (8b)	Et (9a)	72	10ba	83	93
8 ^d	1 (8c)	Et (9a)	72	10ca	64	63
9 ^d	2 ^e (8d)	Et (9a)	72	10da	77	91

^a Reaction conditions: A mixture of **8** (1.0 mmol), **9** (3.0 mmol), and the catalyst **4** (10 mol %) in THF (2.0 mL) was stirred at ambient temperature for the time given. ^b Isolated yield. ^c Enantiomeric excess was determined by chiral HPLC or GC. ^d Reaction temperature was 40 °C. ^e The enone used was 4,4-dimethylcyclohex-2-enone.

Recently, 9-amino (9-deoxy) epicinchona alkaloids have been successfully used as chiral catalysts in the asymmetric reactions, which exhibited high efficiency and enantioselectivity.¹⁰ However, the conjugate addition of malonate to enone catalyzed by 9-amino (9-deoxy) epiquinine afforded poor conversion (Table 1, entry 6). Therefore, it could be concluded that both the primary amine and thiourea played an important role in the process. If (1*R*,2*R*)-1,2-diaminocyclohexane was replaced with (1*S*,2*S*)-1,2-diaminocyclohexane, instead of catalyst **4** with catalyst **7**, the configuration of adduct was reversed, which indicated that the stereochemistry was controlled by the 1,2-diaminocyclohexane motif (Table 1, entry 7). This could explain the fact that low enantioselectivity was obtained when the primary amine was blocked.

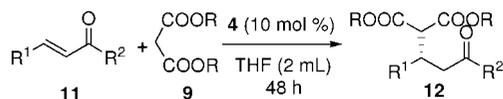
Having identified the best catalyst (catalyst **4**) for the conjugate addition, optimizing reaction conditions were under investigation. It was found that the reaction media had an impact on the process (Table 1, entries 8–19). Without solvent, the adduct was formed quickly with an 84% ee value (Table 1, entry 8). Except in DMSO (Table 1, entry 9, 25% conversion and 50% ee) and MeOH (Table 1, entry 10, 34% conversion and 48% ee), the reactions were carried out smoothly and afforded the 1,4-adduct with good enantioselectivities and conversions in the rest of the media probed in Table 1, and the best results were obtained with THF

(Table 1, entry 19, 95% ee and 91% conversion). For most catalytic systems, higher conversion could be achieved at elevated reaction temperature within a shorter time but generally accompanied by decreased enantioselectivity. It should be noted that up to 97% ee and 96% of conversion were obtained at 40 °C (Table 1, entry 20). When the reaction temperature was elevated to 70 °C, **8a** was almost completely converted to adduct just after 8 h (Table 1, entry 21). A lower catalyst loading also afforded excellent conversions and enantioselectivities. When a catalyst loading of 2.0 mol % was employed, up to 96% ee and 95% of conversion were obtained after 36 h (Table 1, entry 22). Even with a catalyst loading of 1.0 mol %, more than 99% of conversion and 96% ee could still be obtained after three days (Table 1, entry 23). When catalyst loading was decreased to 0.5 mol %, the 1,4-adduct was formed in 60% of conversion with 93% ee in 48 h (Table 1, entry 24). These encouraging results indicated that this methodology might be a very efficient tool for construction of chiral building blocks from asymmetric Michael addition in total syntheses of bioactive natural products.¹¹

Under the optimized conditions, the primary amino thiourea **4**-catalyzed Michael additions with a variety of cyclic enones **8a–d** and malonates **9a–c** were tested, and the results are presented in Table 2. It is known that the ester group has a large effect on the asymmetric induction of the reaction. To our great delight, all malonates reacted smoothly with **8a** to generate adducts with high yields and excellent enantioselectivities (Table 2, entries 1–3). Moreover, excellent yields were obtained accompanied by similar ee values within shorter time when the reactions were carried out at 40 °C (Table 2, entries 4–6). The reaction of **8b** was relatively slow, but 83% yield and 95% ee were still obtained after a longer time (Table 2, entry 7). The only exception

(10) For selected recent publications on 9-amino (9-deoxy) epicinchona alkaloid, see: (a) Xie, J.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.; Chen, Y. *Org. Lett.* **2007**, *9*, 413. (b) Xie, J.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.; Wu, Y.; Zhu, J.; Deng, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 389. (c) Zheng, B.; Liu, Q.; Guo, C.; Wang, X.; He, L. *Org. Biomol. Chem.* **2007**, *5*, 2913. (d) Chen, W.; Du, W.; Duan, Y.; Wu, Y.; Yang, S.; Chen, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667. (e) McCooney, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599. (f) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaiolli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (g) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422. (h) Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134. (i) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070.

(11) Ohshima, T. *Chem. Pharm. Bull.* **2004**, *52*, 1031.

Table 3. 4-Catalyzed Michael Addition Reactions between **11** and **9**^a

entry	R ¹	R ²	R	adduct	yield (%) ^b	ee (%) ^c
1	Ph (11a)	Me	9a	12aa	92	96
2	Ph (11a)	Me	9b	12ab	92	94
3	Ph (11a)	Me	9c	12ac	90	96
4	4-ClPh (11b)	Me	9a	12ba	95	93
5	2-BrPh (11c)	Me	9a	12ca	94	94
6	4-BrPh (11d)	Me	9a	12da	94	94
7	2-NO ₂ Ph (11e)	Me	9a	12ea	97	94
8	4-NO ₂ Ph (11f)	Me	9a	12fa	90	93
9	2-MePh (11g)	Me	9a	12ga	92	93
10 ^d	3-MePh (11h)	Me	9a	12ha	86	94
11 ^d	4-MePh (11i)	Me	9a	12ia	91	94
12 ^d	2-MeOPh (11j)	Me	9a	12ja	71	97
13	2-NO ₂ Ph (11e)	Me	9b	12eb	93	93
14 ^d	2-thienyl (11k)	Me	9a	12ka	83	90
15	<i>n</i> -Pr (11l)	Me	9a	12la	91	96
16	<i>n</i> -Bu (11m)	Me	9a	12ma	90	97
17 ^e	Ph (11n)	Et	9a	12na	80	83

^a Reaction conditions: A mixture of **11** (1.0 mmol), **9** (3.0 mmol), and the catalyst **4** (10 mol %) in THF (2.0 mL) was stirred at ambient temperature for the time given. ^b Isolated yield. ^c Determined by chiral HPLC. ^d Reaction time was 72 h. ^e Reaction temperature was 40 °C.

was **8c**, which gave 64% yield and 63% ee (Table 2, entry 8). It is noteworthy that the sterically more hindered enone **8d** was also successfully used in this Michael reaction, and 91% ee value and 77% yield were obtained (Table 2, entry 9).

On the basis of these satisfying results, the acyclic α,β -unsaturated ketone substrates were surveyed, and the results are displayed in Table 3.

Catalyzed by primary amino thiourea **4**, the Michael additions of malonates to the acyclic enones were quite successful. The Michael adducts, **12aa** and **12ab**, were formed in excellent yields and enantioselectivities (Table 3, entries 1 and 2). Even though from sterically more hindered **9c**, excellent yield and asymmetric induction were also obtained (Table 3, entry 3). It should be noted that electron-withdrawing (Table 3, entries 4–8) and electron-donating substituents (Table 3, entries 9–12) can be introduced into the aromatic ring, with a little effect on the yield or

enantioselectivity. All of the substituted aromatic enones afforded the Michael adducts with more than 90% ee values in good to excellent yields, and the effect of ester group on yield and enantioselectivity was also insignificant. The 1,4-adduct was formed from dimethyl malonate with 93% of asymmetric induction and 93% yield (Table 3, entry 13). The heteroaromatic enone was also found to react with malonate successfully, which generated adduct with 83% yield and 90% ee (Table 3, entry 14). The alkyl-substituted enones were found to react also very well, and the Michael adducts were formed in excellent yields and ee values (Table 3, entries 15 and 16). Besides the methyl ketone, ethyl ketones were also investigated. The use of 1-phenylpent-1-en-3-one afforded 80% yield and 83% ee value (Table 3, entry 17). Even at refluxing temperature, the reaction was slow when sterically more hindered 4-methyl-1-phenylpent-1-en-3-one was used (40% yield after 48 h, not given in Table 3).

The absolute configuration of **4**-catalytic Michael adducts diethyl 2-(3-oxocyclohexyl)malonate was *R*, which was determined by comparison of optical rotations according to the literature.^{6d}

In summary, we have developed a new organocatalytic method for asymmetric Michael addition of malonate to α,β -unsaturated ketone with high efficiency and excellent enantioselectivity employing a type of primary amine thiourea derived from the cinchona alkaloid and 1,2-diaminocyclohexane. It is noteworthy that, in contrast to previous reports, this reaction system exhibits excellent catalysis in asymmetric Michael addition of malonates to acyclic enone and has a broad substrate scope. Further investigations to clarify the exact catalytic mechanism, as well as the capacity of this methodology, are currently under investigation in our laboratory, and results from these studies will be presented in the future.

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Supporting Information Available: Experimental procedures and characterizations, copies of CSP-GC or CSP-HPLC analysis, and ¹H NMR and ¹³C NMR spectra of adducts. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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