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Diastereo- and Enantioselective Conjugate Addition of 3-Substituted Oxindoles to Nitroolefins Catalyzed by a Chiral $Ni(OAc)_2$-Diamine Complex under Mild Conditions

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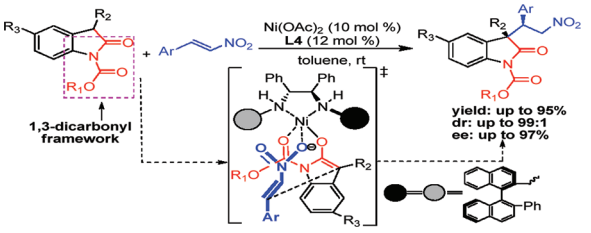
ABSTRACT



A simple catalyst system assembled from an enantiomerically pure diamine ligand and $Ni(OAc)_2$ efficiently generates chiral metal enolates derived from 3-substituted oxindoles bearing an *N*-1 carbonyl group. The enolates smoothly undergo diastereo- and enantioselective conjugate addition to a wide range of nitroolefins under mild reaction conditions, furnishing 3,3-disubstituted oxindole products bearing two vicinal quaternary/tertiary stereocenters in 74−95% yields and 60:40 to 99:1 dr, 71−97% ee.

3-Tetrasubstituted oxindoles have attracted significant attention of some synthetic and medicinal chemistry communities because of the prevalence of them in a wide variety of structurally complex and biologically active compounds.[1] In particular, 3,3′-disubstituted oxindoles with β-amino functionality are a key structural feature of several classes of pharmaceuticals and natural products and are extremely versatile building blocks that can undergo synthetically useful transformations.[1,2] The development of efficient synthetic methods for the asymmetric stereocontrolled construction of 3,3′-disubstituted oxindoles bearing β-amino functionality would be especially desirable.[3,4] Therefore, in view of the high nucleophilicity

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(1) For selected reviews, see: (a) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2001**, *18*, 66. (b) Da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J. *Braz. Chem. Soc.* **2001**, *12*, 273. (c) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (d) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (e) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (f) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.

(2) For selected review, see: Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003 and references therein.

(3) For selected examples, see: (a) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (b) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303. (c) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548. (d) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8666. (e) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590. (f) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261.

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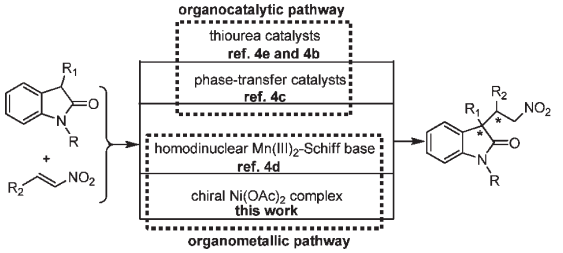
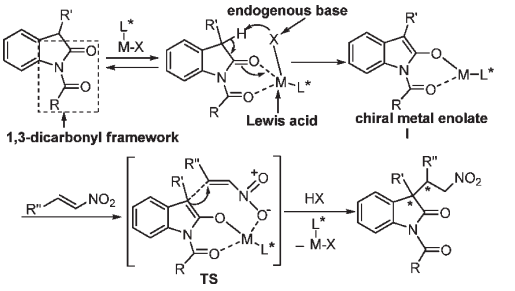
Scheme 1



of the oxindole 3-position[5] and the high potential to rapidly increase molecular complexity as well as the rich chemistry of the nitro group,[6] the catalytic asymmetric conjugate addition of 3-substituted oxindoles to nitroolefins represents one of the most powerful and straightforward approaches toward optically active 3,3′-disubstituted oxindoles with β-amino functionality and has understandably attracted great synthetic interest.[4] However, to the best of our knowledge, so far, there are only three reports concerning this conjugate addition reaction with organocatalysts described by Barbars,[4e] Luo,[4b] and Maruoka,[4c] respectively (Scheme 1), and only one approach via an organometallic pathway was realized by Shibasaki and coworkers with a homodinuclear Mn(III)$_2$−Schiff base complex as catalyst (Scheme 1).[4d] Even so, other new and more general and efficient catalyst systems for this conjugate addition reaction are still needed. Herein is presented our recent effort in the development of Ni(OAc)$_2$−diamine-catalyzed asymmetric conjugate addition of 3-substituted oxindoles to nitroolefins, giving a series of Michael adducts in up to 95% yield with up to 95% ee and 99:1 dr.

In addition, our recent endeavor to construct novel 3-tetrasubstituted oxindole-containing compounds and utilize the nucleophilicity of the oxindole 3-position in asymmetric synthesis led us to further focus on the asymmetric conjugate addition of 3-substituted oxindoles to nitroolefins with metallic catalysts.[7] Importantly, we envisioned that the specified 3-substituted oxindoles, incorporating an carbonyl group at *N*-1 position, were prone to coordination with a variety of chiral Lewis acids via their 1,3-dicarbonyl framework

Scheme 2. Strategy for Metal-Catalyzed Asymmetric Conjugate Addition of 3-Substituted Oxindoles to Nitroolefins



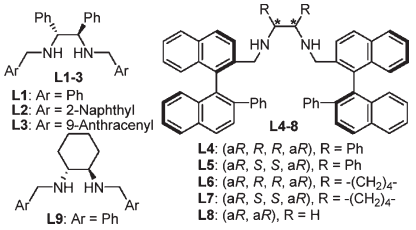


Figure 1. Chiral diamine ligands evaluated in this study.

(Scheme 2), and then the activation by metal complexes with an endogenous basic counteranion might deliver a chiral metal enolate (I) with a specific geometry. Afterward, the chiral metal enolate (I) assembly with Michael acceptor nitroolefins via **TS** would promote the reaction in a stereoselective manner for giving the desired chiral adducts (Scheme 2). Notably, the accomplishment of this research will represent another successful approach for the conjugate addition reaction of 3-substituted oxindoles to nitroolefins via organometallic pathway after Shibasaki's report.[4d]

Initially, diamine ligand[8] **L1** (Figure 1) was selected to coordinate with various metal salts for promoting the conjugate addition reaction of oxindole **1a** with nitroolefin **2a** (Table 1). Delightfully, it was found that the desired product **3a** was obtained with Cu(acac)$_2$−**L1** complex as catalyst in 66% yield in 10 h but with only 3% ee (Table 1, entry 1). However, some other complexes based on ligand **L1** with various salts, such as Zn(OTf)$_2$, Cu(OTf))$_2$, $CrCl_2$, $NiCl_2$, Ni(OAc)$_2\cdot 4H_2O$, and Ni(OAc)$_2$, showed good inductive potential for this reaction (Table 1, entries 2−7). By comparison, the cheap and air-stable Ni(OAc)$_2$ was especially attractive because product **3a** could be smoothly obtained in 86% yield with 96:4 dr and 85% ee (Table 1, entry 7).

(5) For a recent review relating to the application of oxindoles as nucleophiles, see: Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381 and references therein.

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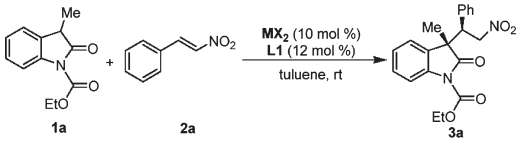
(7) For reports pertinent to the asymmetric catalysis from our research group, see: (a) Liao, Y.-H.; Zhang, H.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron: Asymmetry* **2009**, *20*, 2397. (b) Liao, Y.-H.; Chen, W.-B.; Wu, Z.-J.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2010**, *352*, 827. (c) Chen, W.-B.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2010**, *66*, 1441. (d) Liao, Y.-H.; Liu, X.-L.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 2896. (e) Chen, W.-B.; Wu, Z.-J.; Pei, Q.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 3132. (f) Liu, X.-L.; Liao, Y.-H.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2010**, *75*, 4872. (g) Chen, W.-B.; Wu, Z.-J.; Hu, J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2011**, *13*, 2472. (h) Liu, X.-L.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2011**, *76*, 4008. (i) Sun, H.-W.; Liao, Y.-H.; Wu, Z.-J.; Wang, H.-Y.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2011**, *67*, 3991. (j) Liao, Y.-H.; Liu, X.-L.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2011**, *353*, 1720.

(8) For selected examples with chiral diamine ligands for asymmetric induction, see: (a) Nakamura, A.; Lectard, S.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4036. (b) Berthiol, F.; Matsubara, R.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 7803. (c) Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 7993. (d) Matsubara, R.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3814. (e) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3257. (f) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1679. (g) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583.

Table 1. Seeking Optimal Metal Salts[a]



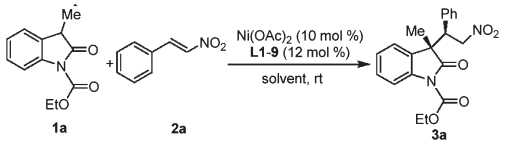
entry	MX_2	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	$Cu(acac)_2$	10	66	89/11	−3
2	$Zn(OTf)_2$	10	72	92/8	53
3	$Cu(OTf))_2$	17	38	95/5	81
4	$CrCl_2$	16	64	92/8	66
5	$NiCl_2$	16	86	95/5	83
6	$Ni(OAc)_2 \cdot 4H_2O$	10	93	96/4	76
7	$Ni(OAc)_2$	10	86	96/4	85

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.15 mmol), **2a** (0.225 mmol), MX_2 (0.015 mmol), and **L1** (0.018 mmol) in toluene (0.5 mL) under N_2 atmosphere at room temperature for the indicated time. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Determined by chiral HPLC.

With this promising lead in hand, we next sought to further optimize reaction conditions. A series of chiral diamine ligands **L1**−**9** (Figure 1) were designed, synthesized, and further evaluated in the model reaction (Table 2). To our delight, high yields and stereoselectivities were obtained with chiral 1,2-diphenylethane-1,2-diamine-derived ligands **L1**−**3**, respectively (Table 2, entries 1−3). In addition, the use of the ligand **L4**,[9] synthesized first by us for strengthening the asymmetric inductive potential, resulted in better reactivity, diastereoselectivity, and enantioselectivity (Table 2, entry 4).[9] We further synthesized the similar ligands **L5**−**7** and employed them into the same reaction. It was found that these ligands were not superior to **L4** and led to a longer reaction time and decreased diastereo- and enantioselectivity, as well as inducted an opposite configuration (Table 2, entries 5−7 vs entry 4). Furthermore, when ligands **L8** and **L9** were examined, the enantioselectivities were significantly decreased (Table 2, entries 8 and 9). These studies indicated that the appropriate match between the chiral diamine moiety and the axial chiral binaphthalene moiety in the ligands **L4** was crucial for the enantioselectivity. Afterward, the effect of solvent, reaction temperature, catalyst loading, and reactant concentration for this transformation was further investigated with **L4** as the optimal catalyst (Table 2, entries 10−18). Various solvents were well tolerated, but toluene was identified as the most favorable solvent (Table 2, entry 4 vs 10−13). It is noteworthy that a racemic product was obtained in DMF as solvent (Table 2, entry 11), and then the suitable reaction temperature and catalyst loading were determined as at room temperature and with 10 mol % $Ni(OAc)_2$−**L4** complex (Table 2, entry 4 vs 14−17). Finally, the transformation was carried out at lower concentration, giving rise to an significantly increased ee value (Table 2, entry 18).

(9) For the detailed information about the synthesis of **L4**−**8**, see the Supporting Information.

Table 2. Optimization of the Reaction Conditions[a]

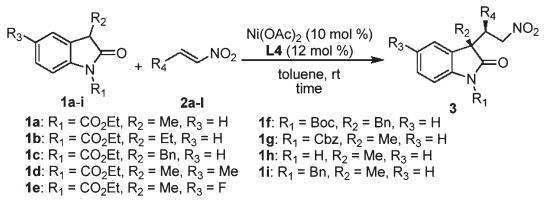


entry	ligand	solvent	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	**L1**	toluene	10	86	96/4	85
2	**L2**	toluene	11	88	89/11	82
3	**L3**	toluene	11	93	90/10	76
4	**L4**	toluene	5	93	99/1	89
5	**L5**	toluene	6	98	89/11	−81
6	**L6**	toluene	9	91	90/10	−16
7	**L7**	toluene	9	87	79/21	−33
8	**L8**	toluene	9	91	84/16	−10
9	**L9**	toluene	5	96	94/6	39
10	**L4**	CH_2Cl_2	5	91	94/6	87
11	**L4**	DMF	5	93	63/37	0
12	**L4**	THF	5	89	84/16	7
13	**L4**	CH_3CN	5	96	85/15	32
14	**L4**	toluene	10	91	81/19	54[e]
15	**L4**	toluene	5	92	99/1	77[f]
16	**L4**	toluene	9	87	95/5	79[g]
17	**L4**	toluene	4	93	99/1	89[h]
18	**L4**	toluene	20	91	99/1	95[i]

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.15 mmol), **2a** (0.225 mmol), $Ni(OAc)_2$ (0.015 mmol), and ligand (0.018 mmol) in toluene (0.5 mL) under N_2 atmosphere at room temperature for the indicated time. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Determined by chiral HPLC. [e] Run at 0 °C. [f] Run at 40 °C. [g] With 5 mol % Ni complex as catalyst. [h] With 20 mol % Ni complex as catalyst. [i] 3.0 mL of toluene was used, c = 0.05 M based on substrate **1a**.

With the optimized reaction conditions in hand, the substrate scope of this reaction was explored by the reaction of 3-substituted oxindoles with various substituted nitroolefins. As shown in Table 3, the nitroolefins with both electron-withdrawing and electron-donating aromatic substituents at the β-position reacted smoothly with oxindole **1a** to give the desired adducts in good to high enantioselectivities (71−95% ee) and good to excellent diastereoselectivities (75:25 to 99:1 dr) (Table 3, entries 2−9). Additionally, the process was also applicable to heteroaromatic nitroolefins, and the corresponding product was obtained in highly stereoselectivity (up to 99:1 dr and 97% ee) under the mild reaction conditions (Table 3, entries 10−11). On the other hand, consistently high diastereoselectivities (90:10 to 99:1 dr) and enantioselectivities (76% to 90% ee) were observed for oxindoles with different substituents at the C3 and C5 positions (Table 3, entries 12−15). Moreover, similar satisfied results were also achieved, respectively, with *N*-Boc-oxindole **1f** and *N*-Cbz-oxindole **1g** as Michael donor addition to **2a** under the same reaction conditions (Table 3, entries 16−17). Unfortunately, we found that oxindole **1a**, which readily reacted with various aromatic nitroolefins, was not able to react with aliphatic nitroolefins **2l** under the standard reaction conditions (Table 3, entry 18). After that, we also found that no reaction proceeded with *N*-H- or

Table 3. Scope of the Reaction[a]



entry	1	R_4	time (h)	3/yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	Ph (**2a**)	20	**3aa**/91	99/1	95
2	**1a**	4-Br-C_6H_4 (**2b**)	18	**3ab**/94	99/1	95
3	**1a**	4-Cl-C_6H_4 (**2c**)	18	**3ac**/93	99/1	93
4	**1a**	4-NO_2-C_6H_4 (**2d**)	18	**3ad**/95	90/10	88
5	**1a**	4-MeO-C_6H_4 (**2e**)	36	**3ae**/74	99/1	89
6	**1a**	4-Me-C_6H_4 (**2f**)	36	**3af**/76	99/1	85
7	**1a**	4-F-C_6H_4 (**2g**)	16	**3ag**/91	99/1	95
8	**1a**	2- Br-C_6H_4 (**2h**)	16	**3ah**/91	90/10	95
9	**1a**	2-MeO-C_6H_4 (**2i**)	36	**3ai**/74	75/25	71
10	**1a**	2-furyl (**2j**)	20	**3aj**/90	90/10	83
11	**1a**	4-thienyl (**2k**)	20	**3ak**/91	99/1	97
12	**1b**	Ph (**2a**)	48	**3ba**/81	90/10	85
13	**1c**	Ph (**2a**)	48	**3ca**/79	90/10	76
14	**1d**	Ph (**2a**)	24	**3da**/95	99/1	90
15	**1e**	Ph (**2a**)	24	**3ea**/94	90/10	80
16	**1f**	Ph (**2a**)	12	**3fa**/74	60/40	nd[e]
17	**1g**	Ph (**2a**)	11	**3ga**/83	99/1	nd[e]
18	**1a**	*c*-hexyl (**2l**)	24	**3al**/nr[f]		
19	**1h**	Ph (**2a**)	24	**3ha**/nr[f]		
20	**1i**	Ph (**2a**)	24	**3ia**/nr[f]		

[a] Unless otherwise noted, the reactions were carried out with **1** (0.15 mmol), **2** (0.225 mmol), $Ni(OAc)_2$ (0.015 mmol), and **L4** (0.018 mmol) in toluene (3.0 mL) under N_2 atmosphere at room temperature for the indicated time. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC. [e] Not determined because the method for chiral HPLC analysis was not yet established. [f] nr = no reaction.

N-Bn-oxindole (Table 3, entries 19 and 20). Thus, these substrates scope studies reveal that the carbonyl protecting group in the *N*-1 position is essential for the formation of 1,3-dicarbonyl framework of oxindoles and that the 1,3-dicarbonyl scaffold facilitates the coordination of oxindoles with the $Ni(OAc)_2$−diamine complex and further formation of the metal enolate, thus promoting the occurrence of conjugate addition reaction (Scheme 2).

The absolute and relative stereochemistry of **3aa** was determined by transforming the *N*-ethoxycarbonyl group of **3aa** into the *N*-Boc group and then comparing the chiral HPLC analysis with the literature report.[10] The absolute configuration of the two vicinal quaternary/tertiary stereocenters was finally assigned as *S* for C3 and *R* for the remaining stereocenter.[10] Those of other adducts were assumed to have similar configurations as **3aa**. Moreover, on the basis of the results as studied above and the relevant research reported by Evans et al.,[8g] the observed stereochemistry can be explained rationally by the proposed transition-state models shown in Figure 2. One can assume

(10) For more details about the determination of the configuration of the products, see the Supporting Information.

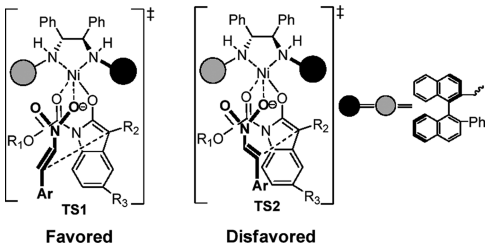


Figure 2. Proposed transition-state models for the conjugate addition.

that in the transition state the nitronate anion is stabilized by interaction at the open apical positon on the nickel. In the disfavored transition state, the aromatic group of the nitroolefins faces steric interactions with the bulky binaphthalene moiety of chiral ligand **L4**; thus, the activated metal enolate attacks the Michael acceptor from the *Re* face (Figure 2, **TS2**). On the other hand, in the favored transition state, the bulky binaphthalene moiety of chiral ligand **L4** is oriented away form the aromatic group of the nitroolefins, and the transition state **TS1** is more favorably formed than **TS2**. Consequently, the activated metal enolate approaches the Michael acceptor from its *Si* face accounting for the absolute configuration of the final products (Figure 2, **TS1**). Additionally, the $\pi-\pi$ stacking interaction between the phenyl ring of 3-substituted oxindoles and the aromatic groups on the nitroolefins probably has an important effect on the reactivity of addition reaction since no reaction was observed when aliphatic nitroolefin substrate was used (Table 3, entry 18).

In conclusion, a simple catalyst system assembled from an enantiomerically pure diamine ligand and $Ni(OAc)_2$ efficiently generates chiral metal enolates derived from 3-substituted oxindoles bearing an *N*-1 carbonyl group. The enolates smoothly undergo diastereo- and enantioselective conjugate addition to a wide range of nitroolefins under mild reaction conditions, furnishing the corresponding 3,3-disubstituted oxindole products bearing two vicinal quaternary/tertiary stereocenters in 74−95% yields and 60:40 to 99:1 dr, 71−97% ee. It is worth noting that incorporating a carbonyl group on *N*-1 for the formation of the 1,3-dicarbonyl framework of oxindoles is crucial to the formation of chiral metal enolate and then promoting the conjugate addition reaction in a stereoselective manner. Studies to explore the addition of similar chiral metal enolates to alternative electrophiles and to apply these enolization conditions to alternative nucleophilic components are underway and will be reported in due course.

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Supporting Information Available. Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.