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Construction of Contiguous Tetrasubstituted Chiral Carbon Stereocenters via Direct Catalytic Asymmetric Aldol Reaction of α-Isothiocyanato Esters with Ketones

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The direct catalytic asymmetric aldol reaction is a powerful and atom-economical method for synthesizing chiral β-hydroxy carbonyl compounds. Many metal and organocatalysts for reactions of aldehyde electrophiles have been developed in the past decade.[1] The use of ketone electrophiles in direct aldol reactions for the construction of a tetrasubstituted carbon stereocenters,[2] however, is limited to either activated ketones (e.g., α-keto esters, α-keto phosphonates, and isatins) or intramolecular reactions with organocatalysts.[3] Although catalytic enantioselective intermolecular aldol reactions with simple ketones have been achieved using either preformed silyl enolates[4] or in situ-generated enolates with stoichiometric reducing reagents (reductive aldol reactions),[5] a direct catalytic asymmetric intermolecular aldol reaction with simple ketones under proton-transfer conditions has not been established.[6] Furthermore, catalytic asymmetric construction of two contiguous tetrasubstituted chiral carbon stereocenters in C−C bond-forming reactions is rare,[7] possibly because of severe steric hindrance. Herein, we report our efforts to address these issues. Mg Schiff base catalysts **1** (Figure 1) promoted a direct asymmetric aldol reaction of α-substituted α-isothiocyanato esters **2** with simple ketones, producing protected α-amino-β-hydroxy esters with contiguous tetrasubstituted chiral carbon stereocenters in up to 98% ee and 98:2 dr.

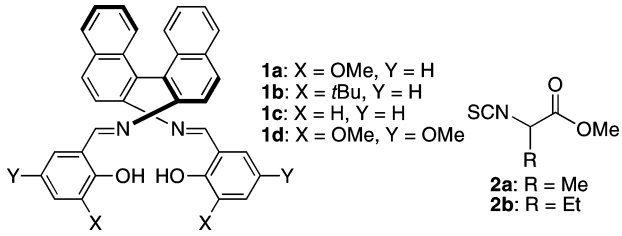


Figure 1. Structures of Schiff bases **1a**−**d** and α-substituted α-isothiocyanato esters **2**.

The direct catalytic intermolecular aldol reaction of ketone electrophiles is difficult because of the small equilibrium constants for ketone electrophiles compared with those of aldehyde electrophiles (a vs b in Scheme 1).[8] Aldol adducts of ketone electrophiles are unstable under basic reaction conditions.[8c] To overcome the inherent instability of the aldol adducts formed using ketones, we assumed that irreversibly trapping the unstable tertiary aldols might be key to kinetically producing more stable adducts. We selected α-isothiocyanato esters **2** as nucleophiles to produce protected α-amino-β-hydroxy esters (Scheme 1c).[9,10] For the challenging catalytic asymmetric construction of two contiguous tetrasubstituted chiral carbon stereocenters, we optimized the reaction conditions using α-substituted α-isothiocyanato ester **2a** and ketone **3a** (Table 1). Screening chiral ligands and metal sources gave promising results for Schiff base **1a** derived from vanillin and binaphthyldiamine. A 1:1 Bu_2Mg/**1a** complex[11] effectively promoted the reaction in THF at room temperature, giving product **4aa** in >95% yield, 93:7 dr, and 95% ee (entry 1). Ligands **1b** with a *tert*-butyl substituent and **1c** without a substituent gave much less satisfactory enantioselectivities (0−10% ee; entries 2−3). Other metal sources, such as Et_2Zn, $Sr(O\text{-}iPr)_2$, $Ba(O\text{-}iPr)_2$, and $La(O\text{-}iPr)_3$, also resulted in poor selectivity or reactivity (entries 4−7). The diastereoselectivity improved to 97:3 in toluene while a high yield and enantioselectivity were maintained (97% isolated yield and 97% ee; entry 8).

Scheme 1. Strategy To Obtain Aldol-Type Adducts from Ketone Electrophiles

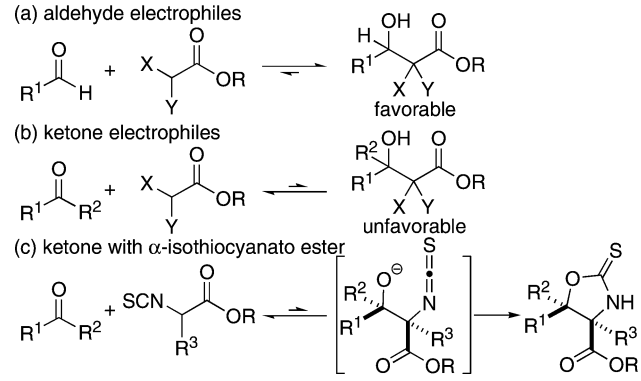
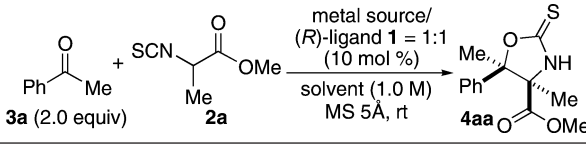


Table 1. Optimization Studies and Control Experiments



entry	metal source	ligand	solvent	time (h)	% yield[a]	dr[a]	% ee of **4aa**
1	Bu_2Mg	**1a**	THF	43	>95	93:7	95
2	Bu_2Mg	**1b**	THF	43	13	52:48	0
3	Bu_2Mg	**1c**	THF	43	>95	68:32	10[c]
4	Et_2Zn	**1a**	THF	43	0	−	−
5	$Sr(O\text{-}iPr)_2$	**1a**	THF	43	93	30:70	13
6	$Ba(O\text{-}iPr)_2$	**1a**	THF	43	>95	38:62	21[c]
7	$La(O\text{-}iPr)_3$	**1a**	THF	43	90	75:25	14[c]
8	Bu_2Mg	**1a**	toluene	36	97[b]	97:3	97

[a] Determined by ^1H NMR analysis of the crude mixture. [b] Isolated yield. [c] *ent*-**4aa** was obtained as the major product.

The substrate scope of the reaction is summarized in Table 2.[12] The Bu_2Mg/Schiff base **1a** complex promoted the addition of α-isothiocyanato ester **2a** to aryl and heteroaryl methyl ketones (entries 1−10). The reaction proceeded even with 2.5 mol % catalyst loading and on an 8.0 mmol scale (1.16 g of **2a**) while maintaining a high yield, dr, and enantioselectivity (entry 2). A longer reaction time (69 h), however, was required because of the modest catalyst turnover frequency. Various acetophenone derivatives with either an electron-donating or electron-withdrawing substituent at the para or meta

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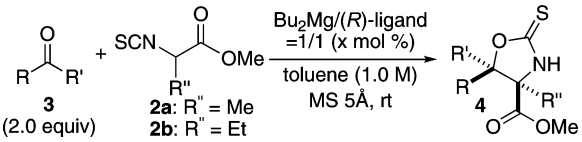
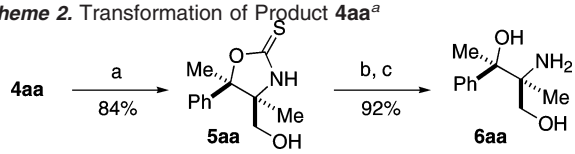
Table 2. Direct Catalytic Asymmetric Aldol Reactions of α-Substituted α-Isothiocyanato Esters **2** with Ketones **3a**−**m**[a]



entry	3 R	3 R'	2		ligand (x mol %)	time (h)	4	% yield[b]	dr[c]	% ee
1	Ph	Me	**3a**	**2a**	**1a** (10)	36	**4aa**	97	97:3	97
2[d]	Ph	Me	**3a**	**2a**	**1a** (2.5)	69	**4aa**	95	96:4	97
3	4-Cl-C_6H_4	Me	**3b**	**2a**	**1a** (10)	36	**4ba**	89	97:3	98
4	3-Cl-C_6H_4	Me	**3c**	**2a**	**1a** (10)	48	**4ca**	99	96:4	98
5	4-Me-C_6H_4	Me	**3d**	**2a**	**1a** (10)	48	**4da**	92	95:5	95
6	3-Me-C_6H_4	Me	**3e**	**2a**	**1a** (10)	48	**4ea**	91	95:5	95
7	4-MeO-C_6H_4	Me	**3f**	**2a**	**1a** (10)	48	**4fa**	68	85:15	89
8	2-furyl	Me	**3g**	**2a**	**1a** (10)	48	**4ga**	87	86:14	97
9	3-thienyl	Me	**3h**	**2a**	**1a** (10)	48	**4ha**	93	98:2	98
10	4-pyridyl	Me	**3i**	**2a**	**1a** (10)	48	**4ia**	71	91:9	95
11	$-(CH_2)_4-$		**3j**	**2a**	**1a** (20)	48	**4ja**	75	—	94
12	$PhCH_2CH_2$	Me	**3k**	**2a**	**1d** (20)	48	**4ka**	81	74:26	97
13	cyclopropyl	Me	**3l**	**2a**	**1d** (20)	48	**4la**	79	81:19	93
14	Ph	Me	**3m**	**2a**	**1d** (20)	48	**4ma**	96	78:22	96
15	Ph	Me	**3a**	**2b**	**1a** (10)	48	**4ab**	94	91:9	82
16	4-Cl-C_6H_4	Me	**3b**	**2b**	**1a** (10)	48	**4bb**	76	95:5	95
17	3-thienyl	Me	**3h**	**2b**	**1a** (10)	48	**4hb**	84	96:4	95

[a] Reaction was performed using 0.20 mmol of **2**, 2.0 equiv of **3**, and 5 Å molecular sieves (40 mg) in toluene (1.0 M), unless otherwise noted. [b] Isolated yield based on the amount of **2** used. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Reaction was performed using 8.0 mmol of **2a**, 2.0 equiv of **3a**, and 5 Å molecular sieves (800 mg) in toluene (2.0 M).

Scheme 2. Transformation of Product **4aa**[a]



[a] Reagents and conditions: (a) $LiAlH_4$, −78 °C to rt, 1 h, 84% yield; (b) Boc_2O, cat. DMAP, CH_2Cl_2, rt, 40 min, then H_2O_2, HCO_2H, rt, 24 h; (c) LiOH(aq), 1,4-dioxane/H_2O, reflux, 24 h, 92% yield (from **5aa**).

position of the aromatic ring gave products in good yield and dr with high enantioselectivity (95−98% ee; entries 3−6). **3f** with a 4-MeO substituent, however, resulted in somewhat lower stereoselectivity and yield (89% ee; entry 7). Heteroaryl ketones **3g**−**i** were also applicable, giving products in 95−98% ee (entries 8−10). Ketones **3j**−**m** showed lower reactivity than aryl methyl ketones, and 20 mol % catalyst was required to obtain the products in good yield (entries 11−14). Cyclic ketone **3j** gave **4ja** in 75% yield and 94% ee (entry 11). For alkyl methyl ketone **3k**, the Bu_2Mg/**1a** catalyst resulted in poor yield (<30%). Modification of the ligand was effective in improving the yield, and the Bu_2Mg/**1d** complex gave **4ka** in 81% yield and 97% ee (entry 12).[13] Bu_2Mg/**1d** was also applicable to ketone **3l** and alkenyl ketone **3m**, giving products in 93 and 96% ee, respectively (entries 13 and 14). The reaction with α-ethyl isothiocyanato ester **2b** proceeded smoothly to afford products in good yields and diastereoselectivities (76−94%, 92:8−96:4 dr), but the enantioselectivity somewhat decreased to 82−95% ee (entries 15−17). The transformation of oxazolidinethione **4aa** into amino alcohol **6aa** was performed (Scheme 2). After reduction of **4aa** into **5aa**, the oxazolidinethione moiety was converted into an oxazolidinone using a reported procedure.[9a] Treatment with LiOH gave unprotected **6aa** in 92% yield (two steps from **5aa**).

In summary, we have developed a direct catalytic asymmetric aldol reaction of α-substituted α-isothiocyanato esters with aryl, heteroaryl, alkyl, and alkenyl methyl ketones and a cyclic ketone. Mg Schiff base complexes catalyzed the direct aldol reaction/cyclization sequence at room temperature, giving protected α-amino-β-hydroxy esters with *contiguous tetrasubstituted chiral carbon stereocenters* in 99 to 68% yield, 98:2 to 74:26 dr, and 98 to 82% ee. Further studies to improve the reaction rate through catalyst modification, including the use of bimetallic Schiff base catalysts, are ongoing.[14]

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

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(12) The absolute and relative configurations of **4aa** were determined by single-crystal X-ray analysis. Those of others were tentatively assigned by analogy.
(13) Because ligand **1d** with additional MeO substituents showed better reactivity than **1a** for ketone **3k**, we assume that the nucleophilicity of the Mg enolates generated from the Bu_2Mg/**1** catalysts would be important in promoting the reaction. Mechanistic studies will be reported in due course as a full article.
(14) For the utility of a bimetallic system with Schiff bases derived from vanillin, see: Mihara, H.; Xu, Y.; Shepherd, N. E.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 8384 and references therein.

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