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Tetrahedron Letters 47 (2006) 3985–3989
Tetrahedron Letters

Direct catalytic asymmetric Mannich-type reactions of isomerizable aliphatic imines: chemoselective enolate formation from a hydroxyketone by a Zn-catalyst

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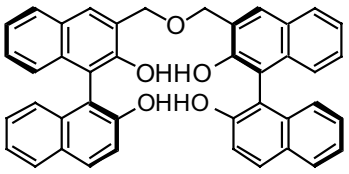
Received 6 March 2006; revised 5 April 2006; accepted 7 April 2006
Available online 2 May 2006

Abstract—A direct catalytic asymmetric Mannich-type reaction of isomerizable aliphatic imines is described. A Et_2Zn/(*S*,*S*)-linked-BINOL complex was suitable for chemoselective enolate formation from a hydroxyketone in the presence of isomerizable aliphatic *N*-diphenylphosphinoyl imines. The reaction proceeds smoothly and β-alkyl-β-amino-α-hydroxyketones were obtained in good yield and high enantioselectivity (up to 99% ee), albeit in modest to low diastereoselectivity.

Chiral β-amino alcohols are important building blocks, found in natural products, pharmaceuticals, chiral auxiliaries, and chiral ligands.[1] Tremendous effort has, therefore, been devoted to the synthesis of chiral β-amino alcohols.[2] Among the methods available, catalytic asymmetric Mannich-type reactions[3] of α-oxy donors effectively provide chiral β-amino alcohols with a concomitant carbon–carbon bond-forming reaction. Various methods are developed utilizing α-oxy donors in the Mannich-type reaction.[4] Recently, direct catalytic asymmetric Mannich-type reactions,[5] in which unmodified α-oxy donors rather than preformed latent enolates such as a ketene silyl acetal are utilized, have been intensively studied. High diastereoselectivities and enantioselectivities have been realized using organo-catalysts[6,7] and metal complexes,[8,9] including our metal/linked-BINOL (**1**, Fig. 1) complexes.[9–12] Most of the examples reported to date are, however, limited to non-enolizable aryl imines. The use of isomerizable aliphatic imines is rare. Notable achievements were reported by Barbas and co-workers using proline as a catalyst.[6f] With both a branched aliphatic imine and an α-benzyloxy imine, good yields (70–74%) and high ees (91–93%) were realized using hydroxyacetone as a donor (2 examples). A linear unbranched imine, however, still resulted in modest chemical yield (46%). Enders and co-workers realized high yield and excellent ee using branched aliphatic imines and an α-benzyloxy imine, when 2,2-dimethyl-1,3-dioxan-5-one was used as a donor.[6f]



(*S*,*S*)-linked-BINOL **1**

Figure 1. Structure of linked-BINOL **1**.

In the metal-catalyzed direct Mannich-type reaction, the chiral metal-catalyst functions as a Brønsted base to deprotonate the α-proton of a ketone donor, generating a metal enolate in situ. When using isomerizable imines, a chemoselectivity issue arises. Deprotonation of the α-proton of α-oxy donor is required for the desired reaction. However, the Brønsted basic catalyst could also effect α-deprotonation of the aliphatic imine, leading to undesired enamine or enamide formation. Quite recently, the report of a successful metal-catalyzed direct catalytic asymmetric Mannich-type reaction of isomerizable aliphatic imines by Trost and co-workers prompted us to report our preliminary results on this matter.[13,14] In this manuscript, we describe a Et_2Zn/linked-BINOL

Keywords: Asymmetric catalysis; Mannich; β-amino alcohol; Zinc; Linked-BINOL.
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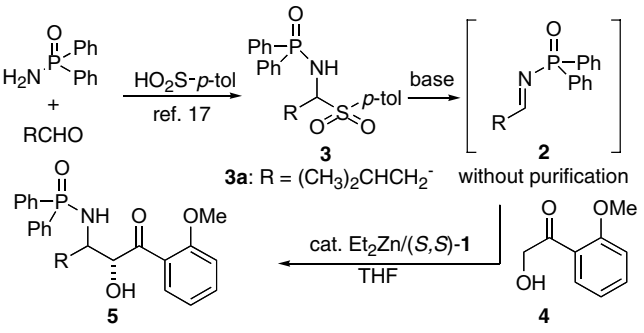
doi:10.1016/j.tetlet.2006.04.016

1 complex[15] catalyzed chemoselective enolate formation from a hydroxyketone in the presence of isomerizable imines,[16] including non-branched linear aliphatic imines. Mannich-type reactions proceeded in high enantioselectivity (up to 99%) and good yield (up to 92% yield), albeit in modest diastereoselectivity.

Because we previously reported the direct Mannich-type reaction of non-enolizable *N*-diphenylphosphinoyl imines (*N*-Dpp imine) and hydroxyketones,[9] we initiated our study using aliphatic *N*-Dpp imines **2**. Aliphatic imines were synthesized by the method reported by Charette and co-workers with a slight modification.[17] α-Amino sulfones **3** were synthesized from *p*-toluenesulfinic acid, aldehydes, and diphenylphosphinamide (Scheme 1). Although the precedent reports utilize **3** to generate aliphatic imines in situ in the presence of excess base and chiral catalyst,[16,17] that strategy was not applicable to our system. With 1.1 equiv of Et_2Zn and 5 mol % of linked-BINOL **1**, both yield and ee were unsatisfactory (Table 1, entry 1). Therefore, conditions for isolating aliphatic *N*-Dpp imine **2a** were examined. Because aliphatic *N*-Dpp imines are relatively unstable, isolated imine **2a** was used for the Mannich reaction without purification (Scheme 1, Table 1, entries 2–6). *N*-Dpp imine **2a** was readily generated by treatment of **3a** with K_2CO_3 and Na_2SO_4 in CH_3CN at room temperature; however, the Mannich reaction gave only modest yield probably due to impure imine **2a** (entry 2). The use of polymer-supported amine[18] also failed in the present system (entry 3). Conditions reported for aliphatic *N*-Ts-imine synthesis[19] were suitable for *N*-Dpp imines; an aq $NaHCO_3/CH_2Cl_2$ biphasic system gave pure imine **2a**[20] and showed the best results in the Mannich reaction (entry 4, 82% yield). Isolated yield of Mannich adduct **5a** improved slightly at 0 °C (entry 5: 89%, *syn*/*anti* = 76/24). Isolated yield decreased when the amount of Et_2Zn increased, probably because excess Et_2Zn caused undesired imine isomerization (entry 6).



Scheme 1. General scheme for preparation of enolizable aliphatic *N*-Dpp imines **2** and application to Mannich-type reaction.

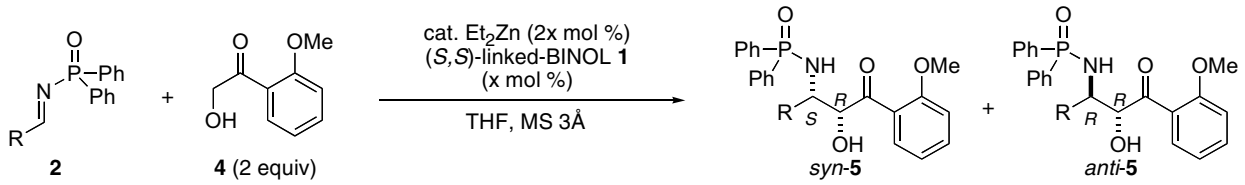
The optimized reaction conditions were applicable to several aliphatic imines as summarized in Table 2.[21] With imine **2a**, reaction proceeded smoothly with reduced catalyst loading (2 mol %, entry 2), affording the product in 92% yield, *syn*/*anti* = 82/18, and 98% ee (*syn*). It is noteworthy that the Mannich reaction proceeded even using linear unbranched imines **2b** and **2c** (entries 3 and 4), which are especially prone to isomerization to enamides under basic conditions. With imine **2c**, the reaction was performed at −30 °C to avoid undesired imine isomerization. The results in Table 2 suggested that the Et_2Zn/linked-BINOL **1** complex was effective for chemoselective enolate formation from hydroxyketone **4**. Our previous mechanistic studies in direct aldol reactions suggested that the active species of the reaction would consist of Zn, linked-BINOL **1**, and hydroxyketone **4**.[15a] We assume that high chemoselectivity was realized because of the high affinity of hydroxyketone **4** toward Zn complex. On the other hand, in contrast to our previous report using non-enolizable *N*-Dpp imines,[9a] diastereoselectivity for the present aliphatic *N*-Dpp imines was low to modest, although enantioselectivity was high in all entries. Diastereoselectivity was strongly dependent on the imine substituent (*syn*/*anti* = 82/18–35/65).[22] The similar absolute config-

Table 1. Optimization of reaction conditions

Entry	Et_2Zn (mol %)	Imine synthesis[a]	Temp (°C)	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee (*syn*/*anti*)
1	110	A	−20	12	15	61/39	12/67
2	10	B	−20	16	63[d]	71/29	92/99
3	10	C	−20	21	Trace[d]	—	—
4	10	D	−20	19	82	70/30	96/99
5	10	D	0	19	89	76/24	96/97
6	20	D	0	19	76	88/12	98/94

[a] Imine preparation conditions: A: in situ generation from **3a**, THF/CH_2Cl_2; B: **3a**, K_2CO_3, Na_2SO_4, CH_3CN; C: **3a**, polymer-supported piperidine, CH_2Cl_2; D: **3a**, aq $NaHCO_3$, CH_2Cl_2. See, Ref. 20.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis of crude mixtures.
[d] Imine was not pure.

Table 2. Direct catalytic asymmetric Mannich-type reactions of various aliphatic imines **2a–f**



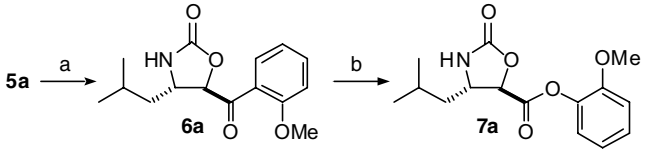
Entry	Imine (R)	Product	(*S*,*S*)-**1** (*x*mol %)	Temp (°C)	Time (h)	Yield[a] (%)	dr[b] (*syn*/*anti*)	ee[c] (*syn*/*anti*)
1	**2a**	**5a**	5	0	18	89	76/24	96/97
2	**2a**	**5a**	2	0	24	92	82/18	98/97
3	**2b**	**5b**	5	0	19	85	56/44	95/98
4	**2c**	**5c**	5	−30	13	79	65/35	>99/99
5	**2d**	**5d**	5	0	19	89	52/48	97/94
6	**2e**	**5e**	5	0	18	77	55/45	90/99
7	**2f**	**5f**	5	0	15	88	35/65	96/99

[a] Isolated yield.
[b] Determined by ^{1}H NMR analysis of crude mixture.
[c] Determined by chiral HPLC analysis.

urations of the major enantiomers of *syn*-**5** (2*R*,3*S*) and *anti*-**5** (2*R*,3*R*) suggest that enantioface selection of Zn-enolate generated in situ from ketone **4** and the Et_2Zn/linked-BINOL **1** complex is good. Low diastereoselectivity is, therefore, ascribed to the low facial selectivity of imines **2**. Further trials to improve the diastereoselectivity are ongoing.

The usefulness of Mannich adducts **5** is enhanced by the presence of a 2-methoxyphenyl group—a placeholder for further conversion. As shown in Scheme 2, Baeyer–Villiger oxidation[23] of carbamate **6a** proceeded smoothly with the aid of the electron donating methoxy group, affording β-alkyl-β-amino-α-hydroxy ester **7a** in 60% yield.

In summary, we succeeded in chemoselective enolate formation from hydroxyketone **4** in the presence of isomerizable aliphatic *N*-Dpp imines **2**. The Et_2Zn/linked-BINOL **1** complex (2–5 mol %) effectively promoted the Mannich-type reaction, affording β-alkyl-β-amino-α-hydroxy ketones in high enantioselectivity (90–>99% ee) and good yield (77–92%), albeit in modest to low diastereoselectivity (88/12–35/65).



Scheme 2. Transformation of Mannich adduct **5a**. Reagents and conditions: (a) (i) concd aq HCl/dioxane, rt, 3 h; (ii) triphosgene, pyridine, −78 to −40 °C, 0.5 h, 69% (two steps); (b) *m*CPBA, Na_2HPO_4, 4,4′-thiobis(6-*tert*-butyl-*m*-cresol), $Cl(CH_2)_2Cl$, 60 °C, 13 h, 60%.

Acknowledgements

This work was supported by Grant-in-Aid for Specially Promoted Research and Grant-in-Aid for Encouragements for Young Scientists (B) (for S.M.) from JSPS and MEXT.

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21. *Representative procedure for Mannich-type reaction* (Table 2): A test tube with 40 mg of MS 3 Å was flame-dried and heated at 160 °C for 3 h under reduced pressure. After cooling down to room temperature, (*S*,*S*)-linked BINOL **1** (0.01 mmol) in THF (0.2 mL) was added and the mixture was cooled to the indicated reaction temperature (0 or −30 °C). To the mixture was added successively Et_2Zn (20 μL, 0.02 mmol, 1.0 M in hexanes), hydroxylketone **4** (0.4 mmol) in THF (0.45 mL), and then imine (0.2 mmol) in THF (0.5 mL). The reaction mixture was stirred for the indicated time in Table 2, and quenched with satd aq NH_4Cl. The mixture was extracted with ethyl acetate (×2). Combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation, the residue was purified by flash silica gel column chromatography to afford Mannich adduct.
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