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A Direct Catalytic Asymmetric Mannich-type Reaction via a Dinuclear Zinc Catalyst:

Synthesis of Either *anti*- or *syn- α* -Hydroxy- β -Amino Ketones

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The Mannich reaction is one of the most widely utilized chemical transformations for the construction of β -amino carbonyl compounds and 1,2-amino alcohol derivatives, valuable synthetic intermediates for the synthesis of drugs and biologically active compounds.¹ Only recently, several groups have reported a direct catalytic asymmetric Mannich reaction without resorting to preactivation of the pronucleophile using organocatalysts and metal catalysts,^{2,3} including our own dinuclear zinc complex **2**.^{3b} Most of the examples reported to date are limited to reaction of unmodified ketone or hydroxyketone donors with imine acceptors. In addition, the cleavage of the *N*-protective group also requires harsh oxidizing conditions. Shibasaki, recently, reported pioneering work on the Et₂Zn/(*S,S*)-linked-BINOL catalysis using an easily removable *N*-protective diphenylphosphinoyl (Dpp) imine and Boc-imine, which selectively provided either *anti*- and *syn- β* -amino alcohols, respectively.^{3c-d} The successful donors are 2'- and 4' - methoxy substituted hydroxyacetophenones and so far the successful imine acceptors have been limited to those derived from non-enolizable aldehydes, most notably aryl. In this paper, we report the application of our dinuclear zinc catalyst to the complementary direct catalytic asymmetric Mannich-type reaction of α -hydroxyketones using α -enolizable Dpp-imines⁴ and Boc-imines,⁵ which we have found to be stable at 0° at least for several days, to generate either *anti*- or *syn- β* -amino alcohols, respectively (Scheme 1).

We first examined the reaction of Dpp-imine **4a** with hydroxy ketone **3a** (Table 1) using dinuclear zinc catalyst **2a**,⁶ which was prepared from chiral ligand **1a** and 2 equiv of Et₂Zn in THF (Scheme 2). Initially subjection of the catalyst **2a** (3.5 mol%) to a mixture of **3a** (1.4 equiv) and Dpp-imine **4a** in the presence of 4ÅMS in THF afforded the desired amino alcohol **5a** in reasonable yield but with poor dr (entries 1 and 2). Changing the sequence of addition by subjection of **3a** and then **4a** in THF to the suspension of the catalyst **2a** and 4ÅMS in THF and lowering the reaction temperature to -25 °C (entry 3) led to a significant increase in *anti* selectivity. Increasing the catalyst loading to 5 mol%, and the amount of ketone to 2.0 equiv, and stirring the reaction at -30 °C (entry 4) gave a high yield of **5a** with high dr and ee. Increasing the size of the chiral ligand by switching from **1a** (Ar = Ph) to **1b** (Ar = 4-biphenyl) gave comparable yield and ee but with slightly increased dr (entry 5). On the other hand, using ligand **1c** decreased both yield and dr (entry 6). By lowering the catalyst loading to 3.5 and 2.5 mol % (entries 7 and 8), the desired product **5a** was also obtained in high yield and selectivity. With 2.5 mol% **2a**, however, a longer reaction time (36 h) was necessary (entry 8).

The optimized reaction conditions (Table 1, entry 7) was applicable to various aliphatic Dpp-imine **5**, and the results are summarized in Table 2. Increasing the size of the α -substituents of

the Dpp-imines increases the dr and ee. Reacting **3a** with imine **4d-f** (entries 4-6) derived from primary aldehydes (bearing both linear and β -branched aliphatic chains) also afforded the *anti*-amino alcohols **5d-f**, respectively, in good yields and excellent ee with high diastereoselectivity (dr >4:1).

In an analogous manner, Mannich-type reaction with other hydroxyketone donors was then investigated to extend the scope of the reaction (Table 2, entries 7 to 13). The use of hetero-aromatic hydroxyketone was found to be applicable in our Mannich-type reaction. With 2-hydroxyacetylfuran **3b** and imine **4a**, an increase in both yield and stereoselectivity of the resultant amino alcohol **5g** was observed with a higher catalyst load (entries 7 and 8). Surprisingly, hydroxyketone **3c** (entries 9 and 10), the best ketone donor in Shibasaki's results, **3c-d** saw a dramatic drop in both dr and ee. The hydroxyketones **3d** and **3e** (entries 11 to 15) were studied in order to gain insight on the origin of the observed selectivity. With ketone **3d** and **4c** using 3.5 mol% catalyst loading, dr was modest (entry 11). Increasing catalyst loading to 5 mol%, dr was significantly improved (entry 12). The use of hydroxyketone **3e** and imine **4c** in the presence of 5 mol% **2a** also provided the Mannich adduct **5j** in high ee (95%) with good *anti* selectivity (entry 14). Furthermore, the enantiomeric product was smoothly obtained in comparable yield and dr with completely reverse enantioselectivity when (*R,R*)-**2a** was used (entry 15). It is clear from our results that the methoxy substituent in the ortho-position plays a significant role in the loss of the yield and selectivity.

Another class of imine investigated was Boc-imine **6** (Table 3). Surprisingly the *syn*- β -amino alcohol **7a** was selectively obtained in a ratio of 5 (*syn*, 94% ee) to 1 (*anti*) on treatment of imine **6a** with **3a** in the presence of 5 mol% catalyst **2a** and 4 Å MS in THF (entry 1). In this reaction, the undesired product **8a** derived from alkoxide attack on the imine was isolated as a minor product (6%). The reaction of **3a** with acyclic imine **6b** also afforded the *syn*-**7b** in good yield and excellent ee. To the best of our knowledge, this is the first example of a direct catalytic asymmetric Mannich-type reaction using a Bocimine derived from an α -enolizable aldehyde.

The relative and absolute stereochemistry were established by converting the amino alcohols into their corresponding 1,3-oxa-zolidin-2-one through NOE studies,⁷ and *O*-methyl mandelic amides, respectively.⁸ It is noteworthy that our dinuclear zinc catalyst **2** provides the Mannich adduct, *anti*-**5** and *syn*-**7**, together with aldol adduct⁶ with the same absolute configuration at the α -position. On the other hand, the stereoselectivity at the β -position of the amino alcohol derivatives is differentiated. The observed stereoselectivities (see Scheme 1) can be understood by assuming the following mechanism. With the more bulky Dpp-imine, *anti* selectivity dominates to avoid the steric repulsion between the Dpp-group and the Zn-enolate.^{3d} Conversely, to avoid the steric repulsion between a substituent (R group) of the less sterically demanding Boc-imine and zinc-enolate, the *syn*-amino alcohol **7** was observed in this case.

In summary, we have demonstrated the application of our dinuclear zinc catalyst for the synthesis of either *syn*- or *anti*-amino alcohols. Typically, with aliphatic Dpp-imines, the desired amino alcohols were obtained with *anti*-selectivity (yield up to 86, dr up to 6:1, ee up to >99%). On the other hand, *syn* selectivity was obtained in the reaction with Boc-imines. Detailed mechanistic studies of the present reaction, and further application of our catalyst with others hydroxyketone donors, and aliphatic Boc-imines are ongoing.

Supplementary Material

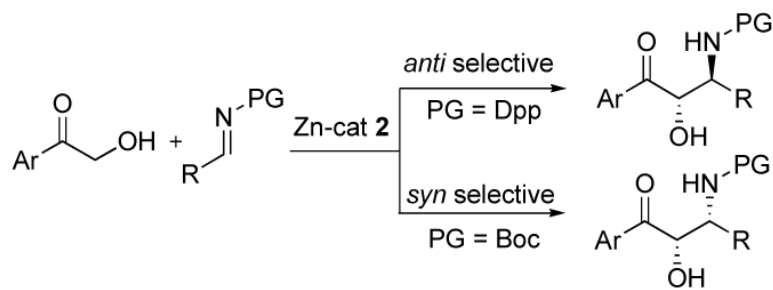
Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

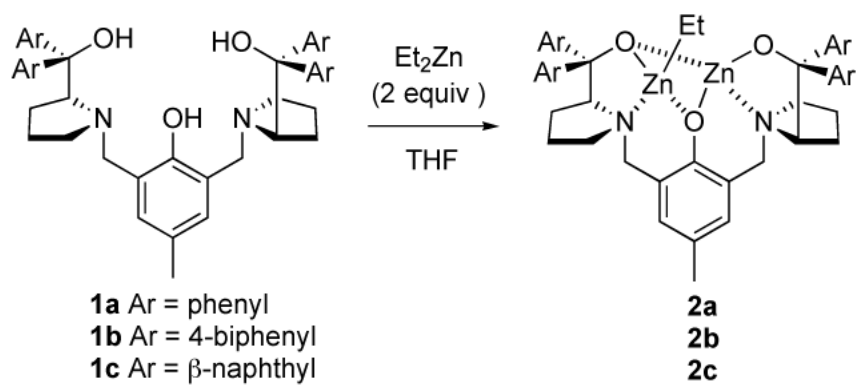
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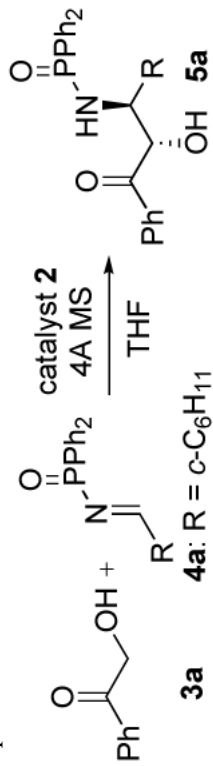


Scheme 1.
Anti- and *Syn*- β -Amino Alcohol Synthesis



Scheme 2.
Generation of Dinuclear Zinc Catalyst

Table 1

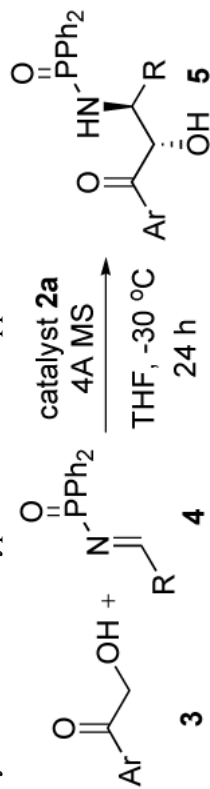
Optimization Studies^a

entry	3a (equiv)	4a (equiv)	cat. 2 (mol%)	temp (°C)	time (h)	yield (%) ^b	dr (anti:syn) ^c	ee (%) (anti) ^d
1 ^e	1.4	1	2a (3.5)	23	17	62	1:1	ND
2 ^e	1.4	1	2a (3.5)	-5	17	66	1:1	(-)-67
3	1.4	1	2a (3.5)	-25	14	62	5:1	(-)-96
4	2	1	2a (5.0)	-30	36	86	5:1	(-)-94
5	2	1	2b ^f (5.0)	-30	36	80	6:1	(+)-96
6	2	1	2c (5.0)	-30	36	75	4:1	ND
7	2	1	2a (3.5)	-30	24	86	5:1	(-)-94
8	2	1	2a (2.5)	-30	36	90	5:1	(-)-92

ND = not determined.

^aTo mixture of catalyst **2**, ketone **3a** and 4Å MS in THF was added imine **4a** in THF at the temperature shown in the Table.^bIsolated yield.^cDetermined by the ¹H NMR of the crude mixture.^dDetermined utilizing chiral HPLC.^eTo suspension of **3a**, imine **4a**, and 4Å MS in THF was added the catalyst **2** in THF.^f(*R,R*)-catalyst **2b** was used.

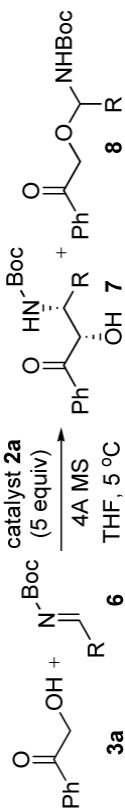
Table 2

Asymmetric Mannich-type Reaction with Dpp-Imine^a

entry	Ar	R	product	yield (%) ^b	dr (anti:syn) ^c	ee (%) (anti) ^d
1	Ph	3a <i>cyclo</i> -hexyl	4a	86	5:1	94
2	Ph	3a <i>cyclo</i> -propyl	4b	79	5:1	83
3	Ph	3a <i>i</i> -propyl	4c	83	6:1	>99
4	Ph	3a <i>i</i> -butyl	4d	80	5:1	96
5	Ph	3a PhCH ₂ CH ₂	4e	76	4:1	96
6	Ph	3a <i>n</i> -hexyl	4f	71	4:1	96
7	2-furyl	3b <i>cyclo</i> -hexyl	4a	73	3:1	83
8 ^e		3b <i>cyclo</i> -hexyl	4a	85	4:1	90
9	2-MeOC ₆ H ₄	3c <i>cyclo</i> -hexyl	4a	65	2:1	56
10 ^e		3c	4a	70	1:1	57
11	1-naphthyl	3d <i>i</i> -propyl	4c	71	3:1	87
12 ^e		3d	4c	74	4:1	88
13	2-naphthyl	3e <i>i</i> -propyl	4c	69	3:1	(-)-86
14 ^e		3e	4c	77	4:1	(-)-95
15 ^f		3e	4c	74	4:1	(+)-95

^a All reactions were performed using 3.5 mol% **2a** and 2 equiv of **3** in THF at 0.3 M unless noted otherwise.^b Isolated yield.^c Determined by the ¹H NMR of the crude mixture.^d Determined utilizing chiral HPLC.^e 5 mol% catalyst **2a**.^f 5 mol% (*R,R*)-catalyst **2a**.

Table 3

Asymmetric Mannich-type Reaction with Boc-Imine^a

entry	R	product	time(h)	yield (%) ^b	dr ^c (<i>anti:syn</i>)	ee ^d (%) (<i>anti:syn</i>)	8(h) (%) ^b
1	cyclo-hexyl	7a	14	77	1:5	ND,94	6
2	<i>i</i> -propyl	7b	19	70	1:3	95,90	5

ND = not determined.

^a All reactions were performed using 5 mol% **2a** and 2 equiv of **3a** in THF at 0.3 M unless noted otherwise.^b Isolated yield.^c Determined by the ¹H NMR of the crude mixture.^d Determined utilizing chiral HPLC.