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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**.[3 b] 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 Et_2Zn/(*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-imines[4] 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 Et_2Zn 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 4Å MS 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 **1 c** 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

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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' 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 4Å 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 adduct[6] 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.

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(4). Dpp-imine was prepared by treatment of *N*-(diphenylphosphinoyl)-*α*-(*p*-toluenesulfonyl) alkylamine 9 with sat. aq. $NaHCO_3$ in CH_2Cl_2: see Supporting Information for details. For preparation of 9, see:Côté A, Boezio AA, Charette AB. Proc. Natl. Acad. Sci. U.S.A 2004;101:5405. [PubMed: 15064400]

(5). Boc-imine was prepared by treatment of *N*-(*N*-*tert*-butyloxy-carbonyl)-*α*-(phenylsulfonyl) alkylamine 10 with 1.5 M aq. K_2CO_3 in CH_2Cl_2: see Supporting Information for details. For preparation of 10, see:Pearson WH, Lindbeck AC, Kampf JW. J. Am. Chem. Soc 1993;115:2622.

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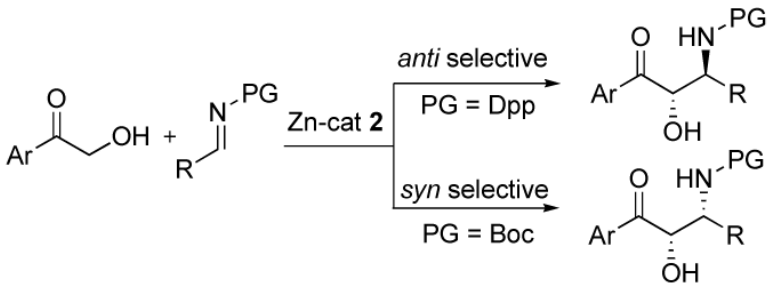
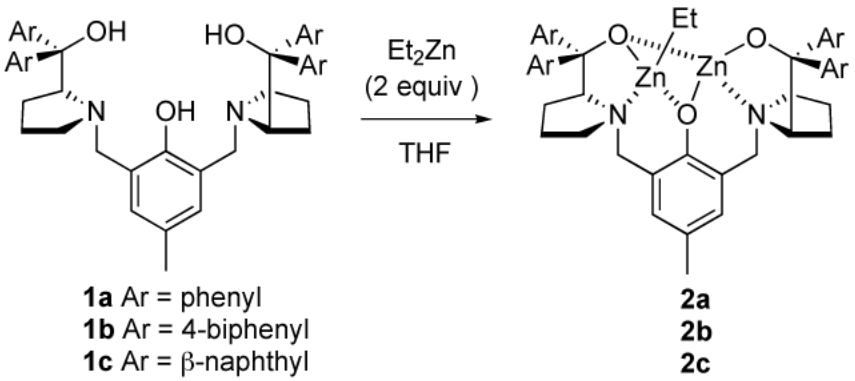


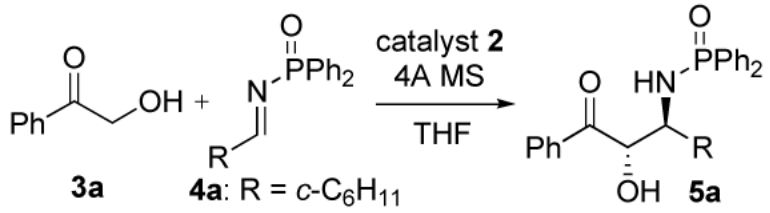
Scheme 1.
Anti- and *Syn*-*β*-Amino Alcohol Synthesis



Scheme 2.
Generation of Dinuclear Zinc Catalyst

Table 1

Optimization Studies[a]



3a **4a**: R = *c*-C_6H_{11} **5a**

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.

[a] To mixture of catalyst **2**, ketone **3a** and 4Å MS in THF was added imine **4a** in THF at the temperature shown in the Table.

[b] Isolated yield.

[c] Determined by the ^{1}H NMR of the crude mixture.

[d] Determined utilizing chiral HPLC.

[e] To suspension of **3a**, imine **4a**, and 4Å MS in THF was added the catalyst 2 in THF.

[f] (*R,R*)-catalyst **2b** was used.

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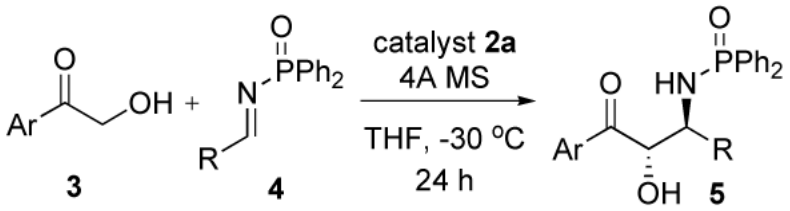
Table 2

Aymmetric Mannich-type Reaction with Dpp-Imine[a]



entry	Ar	R		product	yield (%)[b]	dr (anti:syn)[c]	ee (%) (anti)[d]
1	Ph	**3a** *cyclo*-hexyl	**4a**	**5a**	86	5:1	94
2	Ph	**3a** *cyclo*-propyl	**4b**	**5b**	79	5:1	83
3	Ph	**3a** *i*-propyl	**4c**	**5c**	83	6:1	>99
4	Ph	**3a** *i*-butyl	**4d**	**5d**	80	5:1	96
5	Ph	**3a** $PhCH_2CH_2$	**4e**	**5e**	76	4:1	96
6	Ph	**3a** *n*-hexyl	**4f**	**5f**	71	4:1	96
7	2-furyl	**3b** *cyclo*-hexyl	**4a**	**5g**	73	3:1	83
8[e]		**3b**	**4a**	**5g**	85	4:1	90
9	2-$MeOC_6H_4$	**3c** *cyclo*-hexyl	**4a**	**5h**	65	2:1	56
10[e]		**3c**	**4a**	**5h**	70	1:1	57
11	1-naphthyl	**3d** *i*-propyl	**4c**	**5i**	71	3:1	87
12[e]		**3d**	**4c**	**5i**	74	4:1	88
13	2-naphthyl	**3e** *i*-propyl	**4c**	**5j**	69	3:1	(-)-86
14[e]		**3e**	**4c**	**5j**	77	4:1	(-)-95
15[f]		**3e**	**4c**	**5j**	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 ^{1}H NMR of the crude mixture.

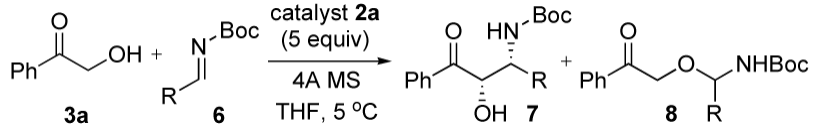
[d] Determined utilizing chiral HPLC.

[e] 5 mol% catalyst **2a**.

[f] 5 mol% (*R*,*R*)-catalyst **2a**.

Table 3

Aymmetric Mannich-type Reaction with Boc-Imine[a]



3a 6 7 8

entry	R	product	time(h)	yield (%)[b]	dr[c] (*anti:syn*)	ee[d] (%) (*anti,syn*)	8(h) (%)[b]
1	*cyclo*-hexyl	**6a** **7a**	14	77	1:5	ND,94	6
2	*i*-propyl	**6b** **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 ^{1}H NMR of the crude mixture.

[d] Determined utilizing chiral HPLC.