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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 Et_2Zn/(*S*,*S*)-linked-BINOL catalysis using an easily removable *N*-protective diphenylphosphinoyl (Dpp) imine and Boc-imine, which selectively provided either *anti*- or *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 nonenolizable 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 °C 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 hydroxyketone **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 4 Å MS in THF afforded the desired amino alcohol **5a** in reasonable yield but with poor diastereomeric ratios (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 4 Å 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 (enantiomeric excesses). 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 % of **2a**, however, a longer reaction time (36 h) was necessary (entry 8).

The optimized reaction conditions (Table 1, entry 7) were 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 7−13). The use of heteroaromatic 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 11−15) were studied

Scheme 1. *anti*- and *syn*-*β*-Amino Alcohol Synthesis

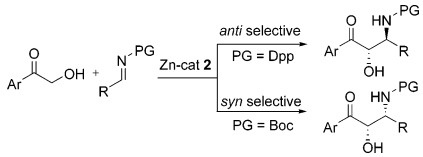
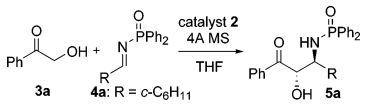


Table 1. Optimization Studies[a]



entry	**3a** (equiv)	**4a** (equiv)	cat. **2** (mol %)	temp (°C)	time (h)	yield[b] (%)	dr[c] (*anti*:*syn*)	ee[d] (%) (*anti*)
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

[a] To a mixture of catalyst **2**, ketone **3a**, and 4 Å 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 4 Å MS in THF was added the catalyst **2** in THF. [f] (*R*,*R*)-Catalyst **2b** was used. ND = not determined.

Scheme 2. Generation of Dinuclear Zinc Catalyst

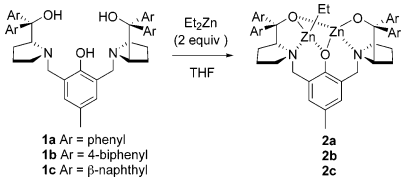


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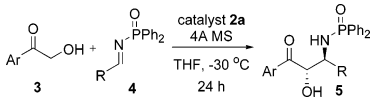
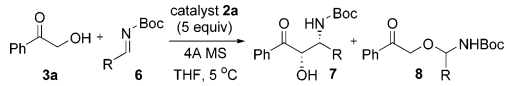
Table 2. Asymmetric Mannich-type Reaction with Dpp-Imine[a]



entry	Ar		R		product	yield[b] (%)	dr[c] (*anti*:*syn*)	ee[d] (%) (*anti*)
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 % of **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] With 5 mol % catalyst **2a**. [f] With 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] (*anti*:*syn*)	ee[d] (%) (*anti*:*syn*)	**8**[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

[a] All reactions were performed using 5 mol % of **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. ND = not determined.

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 reversed 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 % of 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 Boc-imine derived from an α-enolizable aldehyde.

The relative and absolute stereochemistry were established by converting the amino alcohols into their corresponding 1,3-oxazolidin-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 adducts, *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 other hydroxyketone donors and aliphatic Boc-imines are ongoing.

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

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