

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/7270534>

A Direct Catalytic Asymmetric Mannich-type Reaction via a Dinuclear Zinc Catalyst: Synthesis of Either anti - or s yn - α -Hydroxy- β -Amino Ketones

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · APRIL 2006

Impact Factor: 12.11 · DOI: 10.1021/ja057498v · Source: PubMed

CITATIONS

138

READS

24

3 AUTHORS, INCLUDING:



Jaray Jaratjaroonphong

Burapha University

14 PUBLICATIONS 216 CITATIONS

SEE PROFILE

Published in final edited form as:

J Am Chem Soc. 2006 March 8; 128(9): 2778–2779. doi:10.1021/ja057498v.

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

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

Barry M. Trost^a, Jaray Jaratjaroonphong^{a,b}, and Vichai Reutrakul^b

^aDepartment of Chemistry, Stanford University, Stanford, California 94305-5080 ^bDepartment of Chemistry, Faculty of Science, Mahidol University, Rama VI Road, Bangkok 10400, Thailand

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-hydroxyacetyl furan **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

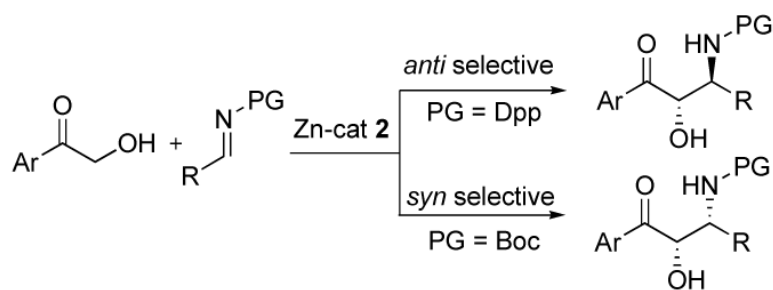
Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

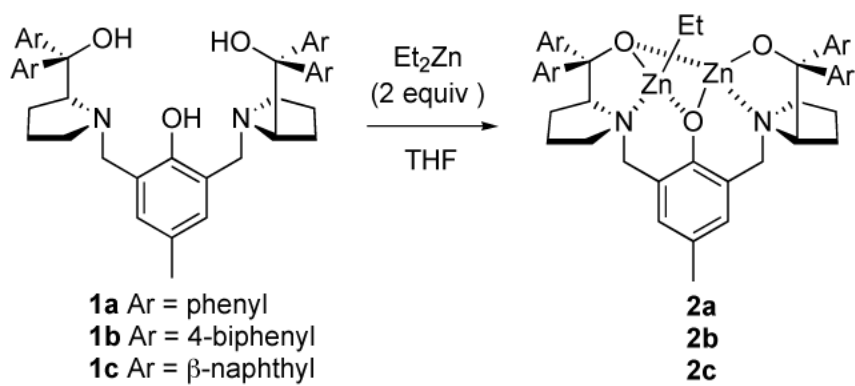
We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences (GM-13598) for their generous support. The awards of the Royal Golden Jubilee Ph.D. Scholarship to JJ and a Senior Research Scholar to VR by the Thailand Research Fund are also gratefully acknowledged. We also thank the Higher Education Development project: PERCH for financial support. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California-San Francisco supported by the NIH Division of Research Resources.

References

- (1). Reviews:(a)DenmarkSENicaiseOJ-CJacobsenENPfaltzAYamamotoHComprehensive Asymmetric Catalysis1999923961SpringerHeidelberg(b)KleinmannEFTrostBMComprehensive Organic Synthesis19912Pergamon PressNew YorkChapter 4.1 (c) Arend M, Westermann B, Risch N. Angew. Chem. Int. Ed 1998;37:1044. (d) Kobayashi S, Ishitani H. Chem. Rev 1999;99:1069. [PubMed: 11749440]
- (2). A review of the direct Mannich reaction:Córdova A. Acc. Chem. Res 2004;37:102. [PubMed: 14967057]
- (3). Selected examples for metal catalysts, see:(a) Juhl K, Gathergood N, Jørgensen KA. Angew. Chem. Int. Ed 2001;40:2995. (b) Trost BM, Terrell LR. J. Am. Chem. Soc 2003;125:338. [PubMed: 12517138] (c) Matsunaga S, Kumagai N, Harada S, Shibasaki M. J. Am. Chem. Soc 2003;125:4712. [PubMed: 12696881] (d) Matsunaga S, Yoshida T, Morimoto H, Kumagai N, Shibasaki M. J. Am. Chem. Soc 2004;126:8777. [PubMed: 15250731] (e) Harada S, Handa S, Matsunaga S, Shibasaki M. Angew. Chem. Int. Ed 2005;44:4365. For organocatalysts, see: (f) List B. J. Am. Chem. Soc 2000;122:9336. (g) List B, Pojarliev P, Biller WT, Martin HJ. J. Am. Chem. Soc 2002;124:827. [PubMed: 11817958] (h) Córdova A, Notz W, Zhong G, Betancort JM, Barbas CF III. J. Am. Chem. Soc 2002;124:1842. [PubMed: 11866583]
- (4). Dpp-imine was prepared by treatment of *N*-(diphenylphosphinoyl)- α -(*p*-toluenesulfonyl) alkylamine 9 with sat. aq. NaHCO₃ in CH₂Cl₂: 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*-butoxy-carbonyl)- α -(phenylsulfonyl) alkylamine 10 with 1.5 M aq. K₂CO₃ in CH₂Cl₂: see Supporting Information for details. For preparation of 10, see:Pearson WH, Lindbeck AC, Kampf JW. J. Am. Chem. Soc 1993;115:2622.
- (6). Leading reference:Trost BM, Ito H. J. Am. Chem. Soc 2000;122:12003.
- (7). In support of our assignment, the relative stereochemistry of oxazolidinones can also be determined by examination of the *J*₄₋₅ coupling constants:Murakami M, Ito H, Ito Y. J. Org. Chem 1993;58:6766.
- (8). Trost BM, Bunt RC, Rulley SR. J. Org. Chem 1994;59:4202.



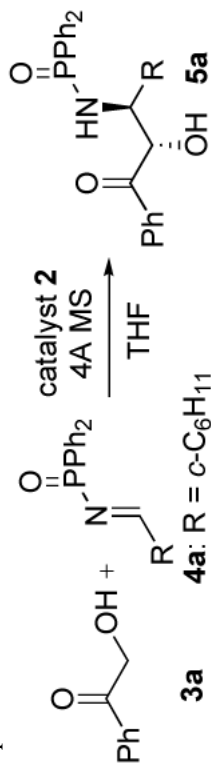
Scheme 1.
Anti- and *Syn*- β -Amino Alcohol Synthesis



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.

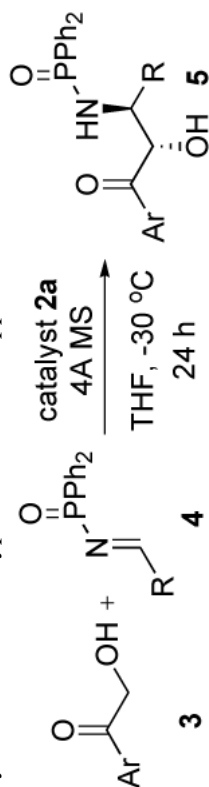
^dDetermined utilizing chiral HPLC.

^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	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.

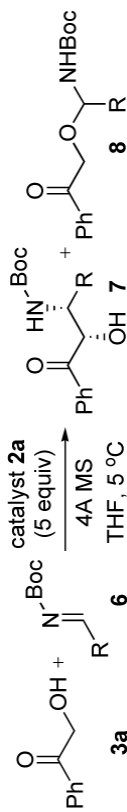
^d Determined utilizing chiral HPLC.

^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.