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ARTICLE TYPE

P-Chirogenic organocatalysts: Application to the aza-Morita-Baylis-Hillman (aza-MBH) reactions of ketimines

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The P-chirogenic organocatalysts were found to promote the enantioselective aza-Morita-Baylis-Hillman reaction of ketimines derived from acyclic α-keto esters. In the P-chirogenic organocatalyzed aza-MBH reactions, α,α-disubstituted α-amino acid derivatives were obtained in high yields with high enantioselectivities (up to 97% ee).

Chiral α,α-disubstituted unnatural amino acids are important building blocks for biologically important compounds and natural products.[1] The catalytic enantioselective addition of carbon nucleophiles to ketimines[2] is an efficient and straightforward method to construct chiral unnatural amino acids. However ketimines are considerably less reactive than aldimines, and enantioface differentiation of ketimines is more difficult because of the smaller steric and electronic differences between the two substituents on prochiral carbons. Therefore, construction of tetrasubstituted carbon stereogenic centers is still a subject of intensive research in asymmetric organic chemistry.[2,3]

The aza-Morita–Baylis–Hillman (aza–MBH) reaction is known to be a useful and atom-economical C–C bond–forming reaction of electron-deficient alkenes with imines catalyzed by Lewis bases (LBs). The aza-MBH adducts are highly functionalized β-amino acid derivatives and are valuable building blocks in medicinal chemistry.[4] However, a number of attractive systems have been developed for the aza-MBH reaction,[5] a few reports on reaction of ketimines have been published. In 2001 Burger reported that the mixed reagent 1,4-diazabicyclo[2.2.2]octane (DABCO) (100 mol%) and CaH_2 (70 mol%) promoted the reaction of acrylates with *N*-benzoyl or *N*-*tert*-butoxycarbonyl ketimines derived from hexafluoroacetone to afford β,β-bis(trifluoromethyl) β-amino acids in up to 65% yield.[6] In 2012, Ye reported achiral LB-catalyzed cycloaddition reactions of allenoates with cyclic ketimines for the synthesis of trisubstituted *N*-heterocycles.[7] As first enantioselective aza-MBH studies of ketimines, in 2013, Shi and Li group and Chen group indipendantly reported aza-MBH reaction of ketimine promoted by acid-base organocatalysts such as β-ICD.[8] Effective and enantioselective construction of tetrasubstituted carbon stereogenic centers *via* the aza-MBH reaction of ketimines has been a challenge in asymmetric synthetic chemistry. Herein we report the enantioselective aza-MBH reaction of ketimines, alkyl 2-aryl-2-(tosylimino)acetates **4** producing multifunctional α,α-disubstituted unnatural amino acid derivatives **5**. The newly developed P-chirogenic organocatalysts **1** or **2** promote the reaction of enones **3** with ketimines **4** to give the corresponding α,α-disubstituted amino acid derivatives **5** in high yields with moderate to high enantioselectivities (Figure 1).

As the first step in the development of the aza-MBH reaction of ketimines, the reaction of methyl vinyl ketone (**3a**) with ethyl 2-phenyl-2-(tosylimino)acetate (**4a**) was attempted using 10 mol% of achiral LB catalysts. Among the catalysts we examined, PPh_3 was found to promote the reaction efficiently to give the aza-MBH adduct **5a** in 74% yield. The reaction in *tert*-butyl methyl ether (TBME) gave good result to afford **5a** in 96% yield.[9]

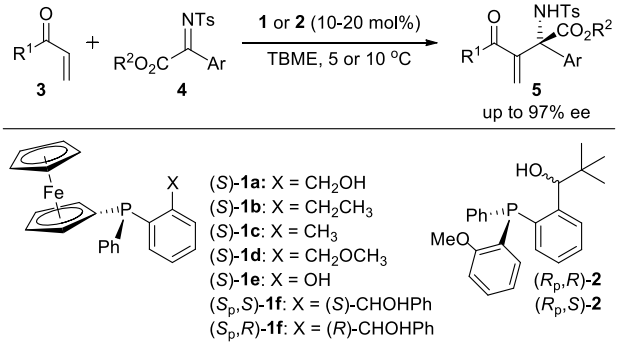
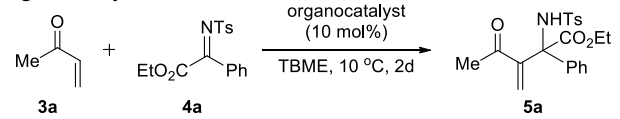


Figure 1. P-Chirogenic organocatalyzed aza-MBH reaction of enones **3** with ketimines **4**.

Next, various chiral catalysts were tested as shown in Table 1. (*S*)-(+)-NMDPP, (*R*)-(*S*)-PPFA, (*S*)-BINAP, (*R*)-MOP, β-ICD and chiral catalysts (*S*) or (*R*)-**6**–**9**, some of which are known to mediate the enantioselective MBH-type processes,[5,10] showed no activity (entries 1–5). A mixed reagent of (*S*)-BINOL (10 mol%) with PPh_3 (10 mol%) and chiral organocatalysts (*R*)-**10** possessing highly nucleophilic phosphine led to racemic products (entries 6 and 7). The acid–base organocatalyst (*S*)-**11**[10e] promoted the reaction to give **5a** in 25% yield with 38% ee (entry 8), along with ethyl 2-oxo-2-phenylacetate generated from the hydrolysis of **4a**.[11] During this screening process, P-chirogenic[12,13] organocatalysts were found to promote the aza-MBH reaction of ketimine **4a** to give adduct **5a** without the decomposition of **4a** (entries 9–12). The synthesis of P-chirogenic *o*-(hydroxyalkyl)phenyl phosphine boranes such as (*S*)-**1a** or (S_p,*S*)-**1f**, were achieved by hydroxyalkylation of their corresponding *o*-bromophenylphosphines (free or borane complex).[13d] Thus, the ferrocenyl P-chirogenic organocatalysts (*S*)-**1a** promoted the reaction in 87% yield with 96% ee[9] (entry 9), whereas (*S*)-**1c** with a methyl and (*S*)-**1d** with a methoxymethyl as *ortho*-substituents exhibited low asymmetric inductions (entries 11 and 12). No catalytic activity was observed when using P-chirogenic acid-base organocatalyst (*S*)-**1e** bearing an

ortho-hydroxy substituent (entry 13). Since the organocatalyst (*S*)-**1b** having an ethyl substituent afforded **5a** with high enantioselectivity (entry 10), the steric effect of the hydroxymethyl group or the ethyl substitutent on the catalysts **1a** and **1b** would be important to promote the reaction with high enantiocontrol. Catalyst activity of **1a** exhibited higher than that of **1b** because the hydroxy group in **1a** could work as a proton-shuttle in a proton-transfer rate determining step.[5]

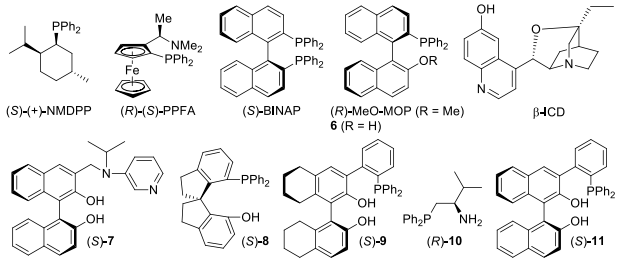
Table 1. Enantioselective aza-MBH reaction of **3a** with **4a** using organocatalysts[a]



3a **4a** **5a**

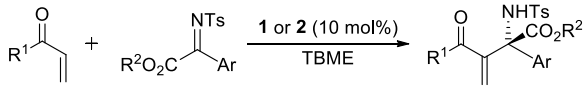
entry	chiral organocatalyst	yield (%)	ee (%)[b]
1	(*S*)-(+)-NMDPP	trace	-
2	(*R*)-(*S*)-PPFA	trace	-
3	(*S*)-BINAP	trace	-
4	(*R*)-MeO-MOP	trace	-
5	β-ICD, (*S*) or (*R*)-**6**-**9**	trace	-
6[c]	PPh_3 + (*S*)-BINOL	13	0
7	(*R*)-**10**	29	0
8	(*S*)-**11**	25	38
9	(*S*)-**1a**	87	96
10	(*S*)-**1b**	36	89
11	(*S*)-**1c**	42	15
12	(*S*)-**1d**	52	17
13	(*S*)-**1e**	trace	-

[a]Conditions: **3a** (0.12 mmol), **4a** (0.040 mmol), catalyst (10 mol%) in TBME (0.2 mL). [b]Determined by HPLC (Daicel Chiralpak IC). [c]PPh_3 (10 mol%) and (*S*)-BINOL (10 mol%) were used.



With the optimized conditions, we focused on the substrate scope (Table 2). In the P-chirogenic organocatalyzed aza-MBH reaction of ketimines, moderate to high enantioselectivities were obtained irrespective of the electronic nature of the substituent on the aromatic ring of **4**. In the reactions of ketimines **4j**–**m**, diastereomeric catalysts (S_p,*S*)-**1e** or (S_p,*R*)-**1e** and (R_p,*R*)-**2** or (R_p,*S*)-**2** were utilized (entries 15–22). The reactions using catalysts (S_p,*R*)-**1e** and (R_p,*S*)-**2** exhibited enantioselectivites lower than those using (S_p,*S*)-**1e** and (R_p,*R*)-**2**.[14,15] In terms of enantioselectivities, the P-chirogenic organocatalyst **1a** afforded the best outcome (97% ee) for substrate **4e** (entry 5). The compounds 2-thiophenyl ketimine **4i** and 2-naphthyl ketimine **4j** were also found to be suitable substrates (entries 9 and 15). The reaction of ethyl vinyl ketone (**3b**) with **4a** afforded the adduct **5j** with high enantioselectivity (entry 10).[16] However, the introduction of substituent in *ortho* position of the aromatic ring of **4** led to no reaction, probably because of steric hindrance (entries 23 and 24). Examining the substituent R^2 on *N*-tosylketimine **4**, the catalyst **1a** gave adducts **5** in good yields with high enantioselectivities, except for benzyl ester **4f** (entries 1, 5 and 6). The absolute configuration of **5** was assigned by comparison with an optical rotation of **5o** reported in the literature (Scheme 1).[8]

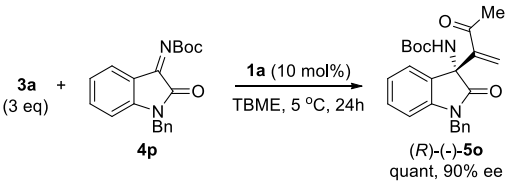
Table 2. Scope of enantioselective aza-MBH reaction of **3a** with **4**[a]



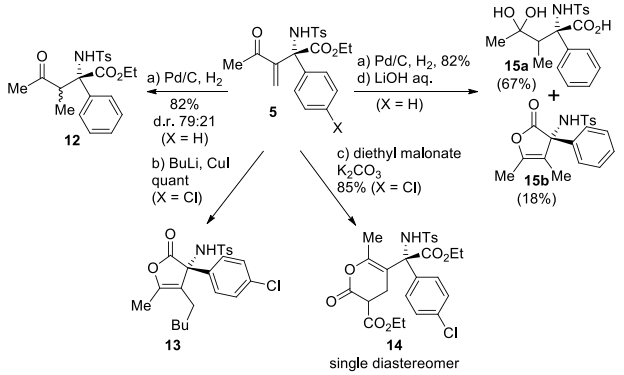
3 **4** **5**

entry	R^1	Ar, R^2	**1** or **2**	°C/ day	yield (%)	ee (%)[b]
1	**3a**, Me	**4a**, Ph, Et	**1a**	10/2	**5a**, 87	96
2	**3a**	**4b**, 4-Me-C_6H_4,Et	**1a**	5/4	**5b**, 81	89
3	**3a**	**4c**, 4-MeO-C_6H_4, Et	**1a**	10/2	**5c**, 79	80
4	**3a**	**4d**, 4-Cl-C_6H_4, Et	**1a**	5/2	**5d**, 59	86
5	**3a**	**4e**, Ph, CH_2CF_3	**1a**	5/3	**5e**, 89	97
6	**3a**	**4f**, Ph, Bn	**1a**	5/7	**5f**, 98	41
7	**3a**	**4g**, 3,4-(OCH_2O)-C_6H_3	**1a**	10/2	**5g**, 86	96
8	**3a**	**4h**, 4-Br-C_6H_4, Et	**1a**[c]	5/10	**5h**, 91	96
9	**3a**	**4i**, 2-thiophenyl, Et	**1a**	5/3	**5i**, 81	76
10	**3b**, Et	**4a**	**1a**	5/4	**5j**, 83	85
11	**3a**	**4a**	**1b**	10/5	**5a**, 70	89
12	**3a**	**4b**	**1b**	5/9	**5b**, 87	96
13	**3a**	**4c**	**1b**	10/4	**5c**, 92	94
14	**3a**	**4d**	**1b**	5/4	**5d**, 95	88
15	**3a**	**4j**, 2-naphthyl, Et	(S_p,*S*)-**1e**	5/3	**5k**, 93	94
16	**3a**	**4j**	(S_p,*R*)-**1e**	5/9	**5k**, 55	52
17	**3a**	**4k**, 3-Me-C_6H_4, Et	(R_p,*R*)-**2**[c]	5/10	**5l**, 70	64
18	**3a**	**4k**	(R_p,*S*)-**2**[c]	5/9	**5l**, 63	54
19	**3a**	**4l**, PhCH=CH_2, Et	(R_p,*R*)-**2**[c]	5/9	**5m**, 67	72
20	**3a**	**4l**	(R_p,*S*)-**2**[c]	5/8	**5m**, 96	53
21	**3a**	**4m**, Ph, Me	(R_p,*R*)-**2**	5/3.5	**5n**, 90	93
22	**3a**	**4m**	(R_p,*S*)-**2**	5/2.5	**5n**, 98	56
23	**3a**	**4n**, 2-Me-C_6H_4, Et	**1** or **2**	5/10	nr	-
24	**3a**	**4o**, 2-Br-C_6H_4, Et	**1** or **2**	5/10	nr	-

[a]Conditions: **3a** (0.12 mmol), **4** (0.040 mmol), catalyst (10 mol%) in TBME (0.2 mL). [b]Determined by HPLC (Daicel Chiralpak IC for **5a**; Daicel Chiralpak AS for **5b** and **5i**; Daicel Chiralpak IB for **5c**; Daicel Chiralpak IA for **5d**; Daicel Chiralcel OD-H for **5g**; Daicel Chiralpak AS-H for **5e**, **f**, **5h,** and **5j**–**n**). [c]20 mol% of catalyst was used. nr = no reaction.



Scheme 1. Enantioselective aza-MBH reaction of **3a** with **4p**.



Conditions: a) Pd/C, MeOH, H_2 (1 atm), RT, 2 h, 82% (d.r. 79:21, determined by ^{1}H-NMR); b) BuLi (2.2 equiv.), CuI (2.2 equiv.), THF, −78°C, overnight, 85%; c) diethyl malonate (1.2 equiv.), K_2CO_3 (2.5 equiv.), DMSO, RT, 2.5 h, 85% (d.r. >99:1, determined by HPLC); d) LiOH (1.5 equiv) in H_2O/THF (1:1), RT, 10 h, **15a** + **15b** = 67% + 18%. d.r. = diastereomeric ratio.

Scheme 2. Transformations of α,α-disubstituted amino acid derivatives (*R*)-**5**.

To demonstrate the synthetic utility of the highly functionalized aza-MBH product **5**, a variety of transformations were performed (Scheme 2). The α-methyl ketone **12** was obtained in good yield by 1,4-conjugate reduction of **5a** using Pd/C under H_2 without over reduction. Furthermore, the Michael addition of BuLi with CuI or diethyl malonate with K_2CO_3 to **5d** produced the cyclic product **13** or **14** via sequential 1,4-addition/lactonization with over 85% yields, respectively. Finally, **5a** could be hydrolysed to the amino acid **15a** by exposure to aqueous LiOH/THF, accompanied by a five-membered ring product **15b**.

In summary, we have developed the first highly enantioselective P-chirogenic organocatalyzed C-C bond-forming reaction to produce the tetrasubstituted carbon stereogenic centers. The product obtained was transformed reliably into a variety of α,α-disubstituted α-amino acid derivatives. Further investigation of the reaction mechanism and the reaction scope and application of the protocol to the enantioselective synthesis of biologically active compounds is currently underway. This work was supported by the Japan Science and Technology Corporation and the Ministry of Education, Culture, Sports, Science and Technology, Japan. This research was also supported by the CNRS (Centre National de la Recherche Scientifique), the "Ministère de l'Education National et de la Recherche", and the Agence Nationale de la Recherche for funding (ANR BLAN *MetChirPhos*). We acknowledge the technical staff of the Comprehensive Analysis Center of ISIR, Osaka Univ. (Japan).

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and analytical data. See DOI: 10.1039/b000000x/

1 For reviews on bioactive α,α-disubstituted amino acid derivatives, see: (*a*) J. Kobayashi and H. Morita, In *Alkaloids* Ed. G. A. Cordell, Academic Press, New York, 2003, **60**, pp. 165. (*b*) I. Moldvai, E. Temesvari-Major, M. Incze, G. Döernyei, E. Szentirmay and C. Szantay, *Helv. Chim. Acta* 2005, **88**, 1344. (*c*) T. Reynolds, *Phytochemistry* 2005, **66**, 1399.

2 For recent reviews and reports on catalytic enantioselective addition of carbon nucleophiles to ketimines, see: (*a*) M. Shibasaki and M. Kanai, *Chem. Rev*. 2008, **108**, 2853. (*b*) S. Kobayashi, Y. Mori, J. S. Fossey and M. M. Salter, *Chem. Rev*. 2011, **111**, 2626. (*c*) D. Wang, J. Liang, J. Feng, K. Wang, Q. Sun, L. Zhao, D. Li, W. Yan and R. Wang, *Adv. Synth. Catal.* 2013, **355**, 548. (*d*) L. Yin, Y. Otsuka, H. Takada, S. Mouri, R. Yazaki, N. Kumagai and M. Shibasaki, *Org. Lett.* 2013, **15**, 698. (*e*) L.-H. Sun, Z.-Q. Liang, W.-Q. Jia and S. Ye, *Angew. Chem. Int Ed*. 2013, **52**, 5803. (*f*) Y.-L. Liu and J. Zhou, *Chem. Commun*. 2013, **49**, 4421. (*g*) M. Hayashi, M. Sano, Y. Funahashi and S. Nakamura, *Angew. Chem. Int Ed*. 2013, **52**, 5557. (*h*) L. Yin, H. Takada, N. Kumagai and M. Shibasaki, *Angew. Chem. Int Ed*. DOI: 10.1002/anie.201303119.

3 J. Clayden, M. Donnard, J. Lefranc and D. J. Tetlow, *Chem. Commun.* 2011, **47**, 4624.

4 For recent reviews on applications of MBH adducts to bioactive molecules, see: (*a*) V. Declerck, J. Martinez and F. Lamaty, *Chem. Rev*. 2009, **109**, 1. (*b*) D. Basavaiah, B. S. Reddy and S. Badsara, *Chem. Rev.* 2010, **110**, 5447. (*c*) C. G. Lima–Junior and M. L. A. A. Vasconcellos, *Bioorg. Med. Chem*. 2012, **20**, 3954.

5 For recent reviews on enantioselective MBH reaction, see: (*a*) G. Masson, C. Housseman and J. Zhu, *Angew. Chem. Int. Ed*. 2007, **46**, 4614. (*b*) Y. Wei and M. Shi, *Acc. Chem. Res*. 2010, **43**, 1005. (*c*) S.-X. Wang, V. Han, F. Zhong, Y. Wang and Y. Lu, *Synlett* 2011, 2766.

6 N. N. Sergeeva, A. S. Golubev and K. Burger, *Synthesis* 2001, 281.

7 (*a*) X.-Y. Chen, R.-C. Lin and S. Ye, *Chem. Commun*. 2012, **48**, 1317. (*b*) X.-Y. Chen and S. Ye, *Eur. J. Org. Chem*. 2012, 5723.

8 (*a*) F.-L. Hu, Y. Wei, M. Shi, S. Pindi and G. Li, *Org. Biomol. Chem.* 2013, **11**, 1921. (*b*) Y. Yao, J.-L. Li, Q.-Q. Zhou, L. Dong and Y.-C. Chen, *Chem. Eur. J.* DOI: 10.1002/chem.201301558.

9 See, ESI, Table S1 and S2.

10 (*a*) Y. Iwabuchi, M. Nakatani, N. Yokoyama and S. Hatakeyama, *J. Am. Chem. Soc.* 1999, **121**, 10219. (*b*) M. Shi and Y.-M. Xu, *Angew. Chem. Int. Ed.* 2002, **41**, 4507. (*c*) M. Shi and L.-H. Chen, *Chem. Commun*. 2003, 1310. (*d*) K. Matsui, S. Takizawa and H. Sasai, *J. Am. Chem. Soc*. 2005, **127**, 3680. (*e*) K. Matsui, S. Takizawa and H. Sasai, *Synlett* 2006, 761. (*f*) K. Matsui, K. Tanaka, A. Horii, S. Takizawa and H. Sasai, *Tetrahedron: Asymmetry* 2006, **17**, 578. (*g*) N. Abermil, G. Masson and J. Zhu, *J. Am. Chem. Soc*. 2008, **130**, 12596. (*h*) X. Wang, Y.-F. Chen, L.-F. Niu and P.-F. Xu, *Org. Lett*. 2009, **11**, 3310. (*i*) S. Takizawa, N. Inoue, S. Hirata and H. Sasai, *Angew. Chem. Int. Ed*. 2010, **49**, 9725. (*j*) S. Takizawa, N. Inoue and H. Sasai, *Tetrahedron Lett.* 2011, **52**, 377. (*k*) S. Takizawa, K. Kiriyama, K. Ieki and H. Sasai, *Chem. Commun.* 2011, **47**, 9227. (*l*) S. Takizawa, T. M.-N. Nguyen, A. Grossmann, D. Enders and H. Sasai, *Angew. Chem. Int. Ed*. 2012, **51**, 5423. (*m*) S. Takizawa, T. M.-N. Nguyen, A. Grossmann, M. Suzuki, D. Enders and H. Sasai, *Tetrahedron* 2013, **69**, 1202. (*n*) S. Kitagaki, Y. Ohta, R. Takahashi, M. Komizu and C. Mukai, *Tetrahedron Lett*. 2013, **54**, 384.

11 To suppress the decomposition of the moisture–sensitive ketimine, molecular sieve (MS) 4A was added to the reaction media. Although the addition of MS 4A improved enantioselectivity (80% ee), the desired product **5a** was obtained in only 17% yield.

12 For the use of P-chirogenic organophosphorus compounds in asymmetric organocatalyzed reactions, see: (*a*) K. Iseki, Y. Kuroki, M. Takahashi and Y. Kobayashi, *Tetrahedron Lett.* 1996, **29**, 5149. (*b*) O. Chiodi, F. Fotiadu, M. Sylvestre and G. Buono, *Tetrahedron Lett.* 1996, **37**, 39. (*c*) S. E. Denmark and J. Fu, *Chem. Rev.* 2003, **103**, 2763. (*d*) E. Vedejs and O. Daugulis, *J. Am. Chem. Soc.* 2003, **125**, 4166. (*e*) M. Sampath and T.-P. Loh, *Chem. Sci.* 2010, **1**, 739. (*f*) E. Rémond, J. Bayardon, S. Takizawa, Y. Rousselin, H. Sasai and Jugé, S. *Org. Lett*. 2013, **15**, 1870.

13 For recent references on functional P-chirogenic phosphines, see: (*a*) T. Imamoto, *J. Synth. Org. Chem. Jpn.* 2007, **66**, 18. (*b*) T. Imamoto, K. Tamura, T. Ogura, Y. Ikematsu, D. Mayama and M. Sugiya, *Tetrahedron Asymmetry* 2010, **21**, 1522. (*c*) M. Stephan, B. Modec and B. Mohar, *Tetrahedron Lett.* 2011, **52**, 1086. (*d*) J. Bayardon, H. Laureano, V. Diemer, M. Dutartre, U. Das, Y. Rousselin, J.-C. Henry, F. Colobert, F. R. Leroux and S. Jugé, *J. Org. Chem*. 2012, **77**, 5759. (*e*) J. Bayardon and S. Jugé, *P-Chiral Ligands* in *Phosphorus (III) Ligands in Homogeneous Catalysis: Design and Synthesis* Eds. P. C. J. Kamer and P. W. N. M. van Leeuwen, Wiley : Chichester, U.K. 2012 pp 355.

14 In the reactions of ketimines **4j**, **k** and **4m** with catalyst **1a** or **1b**, the lower enantioselectivities (**5k**: 84 % ee with **1a**, 79% ee with **1b**; **5l**: 50 % ee with **1a**, 45% ee with **1b**; **5n**: 83 % ee with **1a**, 75% ee with **1b**) were obtained than that of using catalyst (S_p,*R*)-**1e** or (R_p,*S*)-**2**.

15 The reaction of **3a** and **4l** mediated by the P-chirogenic catalysts **1** gave the known tetrahydropyridines *via* aza-Rauhut-Currier process, see: (*a*) Z. Shi, P. Yu, T.-P. Loh and G. Zhong, *Angew. Chem. Int. Ed.* 2012, **51**, 7825. (*b*) Z. Jin, R. Yang, Y. Du, B. Tiwari, R. Ganguly and Y. R. Chi, *Org. Lett.* 2012, **14**, 3226.

16 When the use of 2-naphthyl acrylate (**3c**) for a coupling of **4a**, the corresponding adduct **5p** was obtained in 75% yield with 53% ee.