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Synthesis of β-Amino Acid Derivatives via Copper-Catalyzed Asymmetric 1,4-Reduction of β-(Acylamino)acrylates

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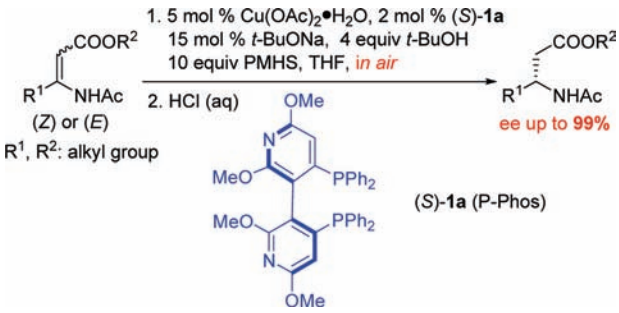

A new set of reaction conditions has been established to facilitate the copper-catalyzed enantioselective 1,4-reduction of β-(acylamino)acrylates toward a selection of β-alkyl-β-amino acid derivatives in high yields and with uniformly high ee values (up to 99%) irrespective of the use of (*E*)- or (*Z*)-substrates.

Chiral β-amino acids constitute crucial structural elements of β-peptides, β-lactam antibiotics, and many other biologically active compounds.[1] Catalytic asymmetric hydrogenation of β-(acylamino)acrylates as one of the most facile methods toward optically enriched β-amino acid derivatives has been intensively studied (Scheme 1).[1b,2] Good to excellent enantioselectivities (up to >99% ee) have been realized by using a variety of chiral Ru,[2,3] Rh,[2,4] or Ir[5] catalysts. In addition of the need for using precious metal catalysts, a problem often encountered in previously studied hydrogenation methods arises from the different catalytic behaviors attributed to (*Z*)- and (*E*)-isomeric substrates. Generally (*E*)-isomers led to higher ee values than the

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(1) (a) von Nussbaum, F.; Spiteller, P. In *Highlights in Bioorganic Chemistry: Methods and Application*; Schmuck, C., Wennemers, H., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 63−89. (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Soloshnok, V., Eds.; John Wiley & Sons Inc: Hoboken, NJ, 2005.

(2) For some recent representative reviews, see: (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035. (b) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290–4299. (c) Bruneau, C.; Renaud, J.-L.; Jerphagnon, T. *Coord. Chem. Rev.* **2008**, *252*, 532–544. (d) Weiner, B.; Szymański, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2010**, *39*, 1656–1691 and references cited therein.

(3) Examples include the following: (a) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543–554. (b) Wu, J.; Chen, X.; Guo, R.; Yeung, C.-H.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 2490–2493. (c) Qiu, L.; Wu, J.; Chan, S.; Au-Yeung, T. T.-L.; Ji, J.-X.; Guo, R.; Pai, C.-C.; Zhou, Z.; Li, X.; Fan, Q.-H.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5815–5820. (d) Qiu, L.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.; Yu, W.-Y.; Li, Y.-M.; Guo, R.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955–5965.

(4) Examples include the following: (a) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907–6910. (b) Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett.* **2001**, *3*, 1701–1704. (c) You, J.; Drexler, H.-J.; Zhang, S.; Fischer, C.; Heller, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 913–916. (d) Dubrovina, N. V.; Tararov, V. I.; Monsees, A.; Spannenberg, A.; Kostas, I. D.; Börner, A. *Tetrahedron: Asymmetry* **2005**, *16*, 3640–3649. (e) Reetz, M. T.; Li, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 2959–2962.

(5) Enthaler, S.; Erre, G.; Junge, K.; Schröder, K.; Addis, D.; Michalik, D.; Hapke, M.; Redkin, D.; Beller, M. *Eur. J. Org. Chem.* **2008**, 3352–3355.

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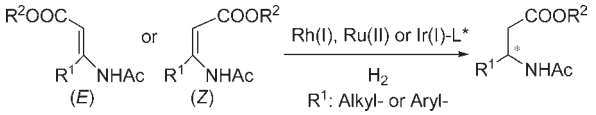
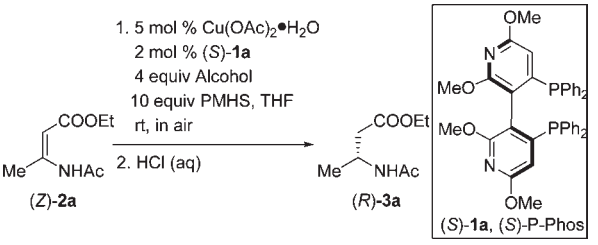
Scheme 1. Rh-, Ru-, or Ir-Catalyzed Asymmetric Hydrogenation of β-Substituted β-(Acylamino)acrylates



corresponding (*Z*)-substrates, which are the major isomers formed in most current synthetic protocols.[3a,4a] Although some Rh[6] and Ru[7]catalysts can hydrogenate (*Z*)-substrates with competitively high degrees of enantioinduction as those for (*E*)-isomers, the development of practical and cost-effective catalytic systems that can perform well for both isomers, especially for (*Z*)-isomers, is still highly desirable.

In the past decade, copper-mediated asymmetric 1,4-hydrosilylation of various α,β-unsaturated Michael acceptors has gained considerable attention[8,9] owing to the economic benefits of using nonprecious metal, the mild reaction conditions, and the technical simplicity, whereas the application of chiral copper catalysts in the 1,4-reduction of β-dehydroamino acid derivatives is relatively unexplored. Noteworthy is the elegant report in 2004 by Buchwald et al.[10] on the copper-BINAP[11] catalyst system, which allowed for the asymmetric conjugate hydrosilylation of various β-amino-substituted α,β-unsaturated esters to β-azaheterocyclic acid derivatives of excellent enantiopurities. Later on, Zheng and co-workers successfully applied this system in the synthesis of various γ-amino butyric acid derivatives.[12] Herein, we describe the first example of copper-catalyzed enantioselective 1,4-hydrosilylation of a selection of β-(acylamino)-acrylates under air atmosphere in high yields and with uniformly good to excellent ee values (up to 99%) irrespective of the use of (*E*)- or (*Z*)-substrates.

Table 1. Effect of Additives on the Copper-Catalyzed Asymmetric 1,4-Reduction of (*Z*)-**2a** in Air[a]



entry	alcohol	base [mol %]	*t* (h)	yield (%)[b]	ee (%)[c]
1			15	27	79
2	*t*-BuOH		15	99	79
3[d]	*t*-BuOH		72	55	80
4[d]	*t*-BuOH	*t*-BuONa [15]	72	97[e]	91
5	*t*-BuOH	*t*-BuONa [15]	1	97	84
6	*t*-BuOH	*t*-BuONa [5]	1	29	81
7	*t*-BuOH	*t*-BuONa [10]	1	45	83
8		*t*-BuONa [15]	15	87	81
9	*i*-PrOH	*t*-BuONa [15]	1	84	85
10	EtOH	*t*-BuONa [15]	1	88	85
11	MeOH	*t*-BuONa [15]	1	40	80
12	*t*-BuOH	*t*-BuOK [15]	1	13	72
13	*t*-BuOH	MeONa [15]	1	86	80
14[f]	*t*-BuOH	*t*-BuONa [15]	1	60	84

[a] Reaction conditions: 0.15−1 mmol of substrate, substrate concentration = 0.2−0.5 M in THF. [b] Determined by NMR and GC analysis. [c] The ee values were determined by chiral GC analysis. The absolute configuration was determined by comparing the retention times with known data (see the Supporting Information). [d] Reaction temperature = −20 °C. [e] The isolated yield was 93%. [f] N_2 atmosphere.

We commenced our studies by examining the ability of chiral dipyridylphosphine ligand P-Phos (Table1, **1a**),[13] which was previously demonstrated to be highly efficient in the Cu(II)-catalyzed asymmetric hydrosilylation of a diverse assortment of prochiral ketones,[14] to promote the conjugate reduction of the model substrate (*Z*)-**2a**. In the presence of 5 mol % of $Cu(OAc)_2 \cdot H_2O$, 2 mol % of (*S*)-**1a**, and 10 equiv of PMHS (polymethylhydrosiloxane), the reaction proceeded in THF at room temperature to only 27% yield (GC and NMR) after 15 h to furnished (*R*)-**3a** in 79% ee (entry 1). Similar to previous findings,[8c,9d,9e,10,15]

(6) Examples include the following: (a) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159–4161. (b) Lee, S.-G.; Zhang, Y. J. *Org. Lett.* **2002**, *4*, 2429–2431. (c) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552–14553. (d) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509–3511. (e) Wu, H.-P.; Hoge, G. *Org. Lett.* **2004**, *6*, 3645–3647. (f) Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G. *Org. Lett.* **2004**, *6*, 1733–1735. (g) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2005**, *7*, 419–422. (h) Tang, W.; Capacci, A. G.; White, A.; Ma, S.; Rodriguez, S.; Qu, B.; Savoie, J.; Patel, N. D.; Wei, X.; Haddad, N.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 1104–1107. (i) Zhang, X.; Huang, K.; Hou, G.; Cao, B.; Zhang, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 6421–6424.

(7) Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952–4953.

(8) For some recent reviews, see: (a) Riant, O.; Mostefai, N.; Courmarcel, J. *Synthesis* **2004**, 2943–2958. (b) Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 498–504. (c) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2927. (d) Lipshutz, B. H. *Synlett* **2009**, 509–524 and references cited therein.

(9) Examples include the following: (a) Moritani, Y.; Apella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797–6798. (b) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789–4792. (c) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473–9474. (d) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253–11258. (e) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352–8353. (f) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793–4795. (g) Czekelius, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4575–4577. (h) Lee, D.; Kim, D.; Yun, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2785–2787. (i) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3329–3332.

(10) Rainka, M. P.; Aye, Y.; Buchwald, S. L. *Proc. Natl. Acad. Sci. U. S.A.* **2004**, *101*, 5821–5823.

(11) BINAP = 2,2′-bis(diphenyllphosphino)-1,1′-binaphthyl: (a) Noyori, R.; Takaya, H. *Acc .Chem. Res.* **1990**, *23*, 345–350. (b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022.

(12) Deng, J.; Hu, X.-P.; Huang, J.-D.; Yu, S.-B.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2008**, *73*, 6022–6024.

(13) (a) Wu, J.; Chan, A. S. C. *Acc. Chem. Res.* **2006**, *39*, 711–720. (b) Pai, C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C.; Wong, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 11513–11514.

(14) (a) Wu, J.; Ji, J.-X.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 3570–3575. (b) Zhang, X.-C.; Wu, Y.; Yu, F.; Wu, F.-F.; Wu, J.; Chan, A. S. C. *Chem.—Eur. J.* **2009**, *15*, 5888–5891.

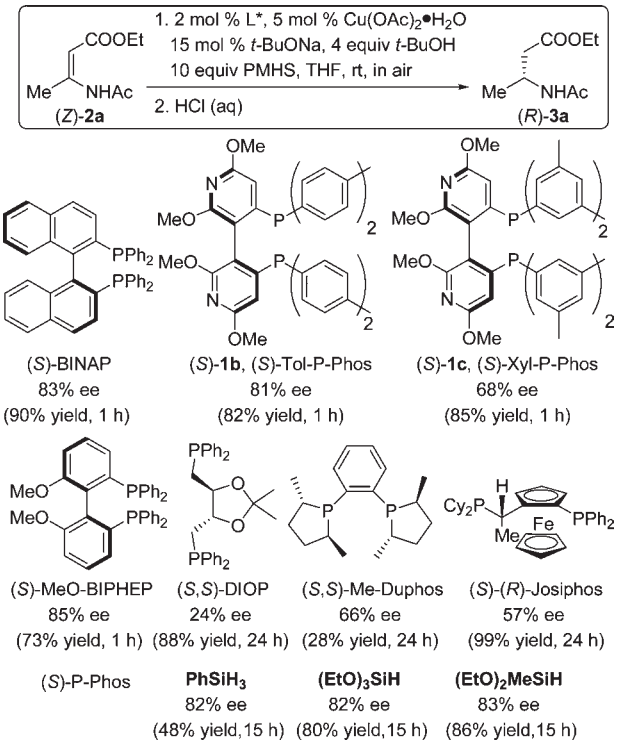
(15) (a) Yun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640–5644. (b) Hays, D. S.; Fu, G. C. *Tetrahedron* **1999**, *55*, 8815–8832.

the reaction was accelerated by alcohol additives (4 equiv of *t*-BuOH) although ee remained unchanged (entry 2 vs entry 1). The lower temperature (−20 °C) did not render a higher ee but resulted in the decrease of reaction rates (entry 3 vs entry 2). To our delight, further introduction of certain amounts of *t*-BuONa facilitated enhancements in both yield (97%) and ee (91%, entry 4 vs entry 3). Moreover, quantitative yield was achieved within just 1 h at room temperature with 84% ee (entry 5 vs entries 2 and 4). Nonetheless, less than 50% yields were obtained in the presence of 5 or 10 mol % of *t*-BuONa (entries 6 and 7 vs entry 5). Additionally, if only adding *t*-BuONa in the absence of alcohol, 87% yield was obtained after 15 h (entry 8 vs entries 2 and 5). A series of alcohols of various sizes (entries 9−11) and different bases (entries 12 and 13) were tested. Sterically hindered *t*-BuOH and *t*-BuONa appeared to be the preferred choice of additives in terms of both activities and enantioselectivities. At this stage, what is the role of the base for the increased rate and enantioselectivity remains elusive. It appeared that in the initial step of the catalytic cycle, a chiral Cu(II) alkoxide (*t*-BuO)$_2$CuL* or (*t*-BuO)CuL*(OAc) [**A**, L* = (*S*)-P-Phos] likely formed upon combining of (*S*)-P-Phos with Cu(OAc)$_2\cdot$H$_2$O and *t*-BuONa. Complex **A** may be capable of undergoing σ-bond metathesis with PMHS more rapidly than Cu(OAc)$_2$ to generate an active copper hydride species (*t*-BuO)CuHL* (**B**), which is conjectured to be the key intermediate responsible for discriminating between the enantiotopic faces of the alkene substrate. Thus, both the electronic and steric properties of the alkoxide ion of **B** should have an influence on the enantioinduction of the chiral copper hydride.[8c,9d,15a] Besides, when the reaction was conducted under inert atmosphere, the reaction rate was lower than that obtainable in air (entry 14 vs entry 5).[10,14,16]

Furthermore, as illustrated in Scheme 2, the reaction outcomes also largely relied on the selection of both ligands and silanes. Among the chiral diphosphines screened, only (*S*)-BINAP gave comparative results with those of P-Phos at room temperature (Scheme 2 vs Table 1, entry 5). Nevertheless, lowering the reaction temperature to −20 °C did not lead to a higher ee in the case of the use of (*S*)-BINAP (90% yield and 84% ee). Additionally, the electronic and steric attributes of the ligands have pronounced influences on the reaction. P-Phos showed better catalytic properties than bulky Tol-P-Phos (**1b**) and Xyl-P-Phos (**1c**).[17] As for silanes, PhSiH$_3$, (EtO)$_3$SiH, or (EtO)$_2$MeSiH exhibited inferior reactivity to the inexpensive and innocuous PMHS although the ee values were almost the same.

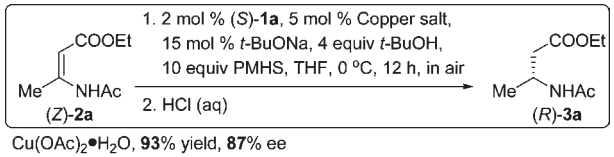
Next, the effects of various copper precursors and solvents on the reaction were investigated under a given

Scheme 2. Effects of Ligand and Silane on the Copper-Catalyzed Asymmetric 1,4-Reduction of (*Z*)-**2a** in Air



set of conditions. As the findings in Scheme 3 indicated, the extent of yields varied considerably as a function of the counterions of copper. Although promising results were achieved as well by applying CuCl, Cu(acac)$_2$, Cu(CH$_3$COCHCOCF$_3$)$_2$, or Cu(TC), Cu(OAc)$_2\cdot$H$_2$O is the most preferable choice because of its ease of handling and substantially lower cost. Besides, the reaction was also strongly solvent-dependent and THF was much more conducive than other solvents, such as CHCl$_3$, CH$_3$CN, dioxane, and toluene.

Scheme 3. Effect of Copper Salts on the Asymmetric 1,4-Reduction of (*Z*)-**2a** in Air



Cu(OAc)$_2\bullet$H$_2$O, **93**% yield, **87**% ee

CuCl, Cu(acac)$_2$, Cu(CH$_3$COCHCOCF$_3$)$_2$, Cu(TC) **90**–**93**% yield, **85**–**87**% ee

CuF$_2$, 57% yield, 87% ee, CuCl$_2\bullet$2H$_2$O, 71% yield, 87% ee

CuI, CuCl$_2$, CuBr$_2$ < 30% yield (rt, 24 h)

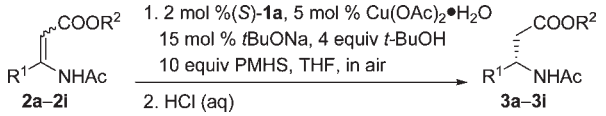
Cu(OTf)$_2$, Cu(OCH$_3$)$_2$, Cu(OCOCF$_3$)$_2\bullet$xH$_2$O, CuCN < 30% yield

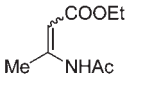
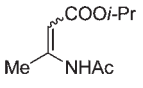
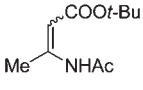
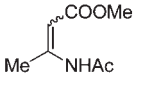
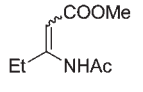
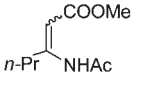
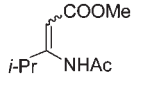
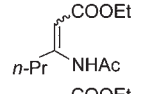
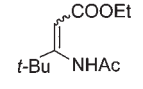
Having established the preferred conditions, we set out to evaluate the applicable scope of the Cu-catalyzed protocol. As indicated in Table 2, the present catalytic system worked efficiently for both (*Z*)- and (*E*)-substrates to

(16) (a) Sirol, S.; Courmarcel, J.; Mostefai, N.; Riant, O. *Org. Lett.* **2001**, *3*, 4111–4113. (b) Mostefaï, N.; Sirol, S.; Courmarcel, J.; Riant, O. *Synthesis* **2007**, 1265–1271.

(17) (a) Wu, J.; Chen, H.; Zhou, Z.-Y.; Yeung, C.-H.; Chan, A. S. C. *Synlett* **2001**, 1050–1054. (b) Wu, J.; Chen, H.; Kwok, W.-H.; Lam, K.-H.; Zhou, Z.-Y.; Yeung, C.-H.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 1539–1543. (c) Wu, J.; Pai, C.-C.; Kwok, W. H..; Guo, R. W.; Au-Yeung, T. T. L.; Yeung, C.-H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 987–992.

Table 2. Cu(II)-Catalyzed Asymmetric 1,4-Reduction of β-Substituted β-(Acylamino)acrylates **2** in Air[a]



entry	substrate	isomer	temp (°C)	t (h)	yield (%)[b]	ee (%)
1		(*E*)-**2a**	rt	15	95	84
2		(*E*)-**2a**	–20	72	96	90
3		(*E*/*Z*)-**2a**[c]	rt	2	95	85
4		(*Z*)-**2b**	rt	24	78	74
5		(*Z*)-**2b**	40	48	95	75
6		(*E*)-**2b**	rt	24	60	72
7		(*E*)-**2b**	40	48	58	71
8		(*Z*)-**2c**	40	48	86	64
9		(*E*)-**2c**	40	48	62	62
10		(*Z*)-**2d**	–20	72	>99	95
11		(*E*)-**2d**	–20	72	89	95
12		(*Z*)-**2e**	–20	72	>99	94
13		(*E*)-**2e**	–20	72	98	93
14[d]		(*Z*)-**2f**	–20	72	99	94 (–)
15		(*E*)-**2f**	rt	27	98	92 (+)
16[d]		(*E*)-**2f**	–20	72	81	94 (–)
17[d]		(*Z*)-**2g**	–20	72	**>99**[e]	**99**
18[d]		(*E*)-**2g**	–20	72	**94**	**98**
19		(*Z*)-**2h**	rt	24	95	81
20		(*E*)-**2h**	rt	40	93	81
21		(*E*)-**2i**	rt	40	<1	–

[a] Reaction conditions: 0.15−0.3 mmol of substrate, substrate concentration = 0.2 M in THF. [b] Determined by NMR and GC analysis. [c] E/Z = 1:1. [d] 2 mol % of (*R*)-**1a** was used. [e] The isolated yield was 95%.

afford the reduction products bearing the same configuration and similar enantiopurities. An E/Z mixture of **2a** was also reduced to afford the product (*R*)-**3a** quantitatively within 2 h in 85% ee (entry 3 vs entry 1 in Table 2 and Table 1, entry 5). The reaction rates for (*E*)-isomers in most cases were slower than those of related (*Z*)-isomers under otherwise identical conditions (for example, entry 7 vs entry 5, entry 9 vs entry 8). Noteworthy was the observation that when the ethyl ester of **2a** was changed to bulky isopropyl (**2b**) or *tert*-butyl ester (**2c**), the reaction efficiency and enantioselectivity suffered noticeably (entries 6 and 9 vs entry 1). With respect to **2d** with methyl ester, up to 95% ee and reasonably high yield were obtained as expected (entries 10 and 11). Thus, a variety of methyl ester substrates with different β-alkyl substituents (**2e**−**g**) were reduced completely with consistently high ee values for both isomeric substrates (92−99%, entries 12−18). Surprisingly, varying the β-alkyl substituents of ethyl ester substrate (**2a**) distinctly influenced the reaction outcomes (entries 20 and 21 vs entry 1, entry 19 vs Table 1, entry 5). In the case of **2i** (R^1 = *t*-Bu) almost no reduction took place (entry 21).

In conclusion, in the presence of certain amounts of *t*-BuONa and *t*-BuOH as additives, the combination of $Cu(OAc)_2 \cdot H_2O$, enantiomeric P-Phos, and hydride donor PMHS generated in situ an efficient catalyst system in normal atmosphere for the asymmetric conjugate reduction of a spectrum of β-(acylamino)acrylates with uniformly high ee values (up to 99%) for both (*Z*)- and (*E*)-isomeric substrates. Particularly, in most cases, (*Z*)-isomers were reduced at faster rates than those of (*E*)-isomers. The present catalyst system features high air-stability, good to excellent enantioselectivity, cost efficiency, and mild conditions and thus offers a good opportunity for the practical preparation of β-amino acids derivatives. Studies aimed at expanding the scope of the present catalyst system and clarifying the reaction mechanism are underway in our laboratory.

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