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Dynamic Kinetic Resolution in the Asymmetric Synthesis of β-Amino Acids by Organocatalytic Reduction of Enamines with Trichlorosilane

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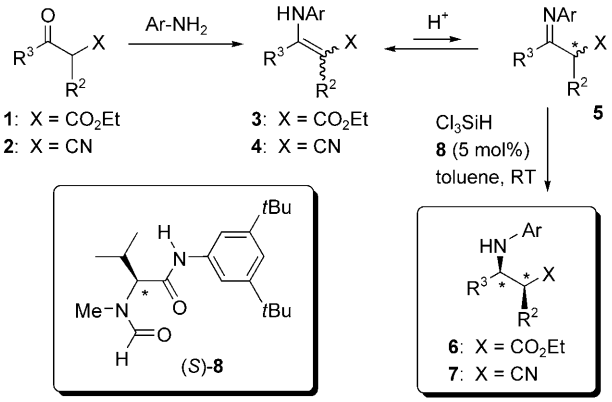
In recent years, interest in β-amino acids has continued to grow, being driven by their successful application in peptidomimetics and as valuable building blocks.[1] Therefore, development of new enantioselective approaches to β-amino acids and their derivatives remains in the focus of the fine chemicals industry, in spite of the existence of numerous methodologies.[2,3] Readily available β-ketoesters **1** or related β-ketonitriles **2** can serve as convenient precursors of β-amino acids, into which they can be converted, for example, by asymmetric reduction of the corresponding enamines **3** and **4** (Scheme 1). Catalytic hydrogenation, a preferred methodology in industry, generally requires the presence of an *N*-acyl steering group to attain high enantioselectivity[4] and works best when pure enamine isomers are used.[4b] Recently, improved catalytic systems were reported to attain high selectivity with (*E*/*Z*) mixtures[2d,4b,5] and the methodology was further extended to unsubstituted enamines (**3**, Ar = H)[6] and their *N*-aryl derivatives.[7] On the other hand, the sensitivity of asymmetric hydrogenation to the steric bulk of the substituents surrounding the enamine moiety makes the synthesis of certain β^3- and $\beta^{2,3}$-amino acids a significant challenge.[8] Herein, we present a new methodology based on the organocatalytic asymmetric hydrosilylation of enamines that allows a direct access to a range of β^3- and $\beta^{2,3}$-amino acid derivatives for some of which other methods proved less satisfactory.



Scheme 1. Enantioselective synthesis of β-amino acids and nitriles; for R^2 and R^3 see Table 1.

We have recently developed an efficient procedure for the asymmetric reduction of prochiral *N*-arylketimines with trichlorosilane (≤95% *ee*), catalyzed by Lewis-basic formamides, such as Sigamide (**8**).[9–11] The method was then extended to the reduction of α-chloro imines and successfully applied to an enantioselective synthesis of *N*-arylaziridines.[12] To further expand the scope, we have now turned to the synthesis of β-amino acids. Treatment of the β-ketoester/nitrile **1a**/**2a** (R^2 = H, R^3 = Ph; Scheme 1) with *p*-anisidine produced enamines **3a**/**4a**, which themselves cannot be reduced by Cl_3SiH.[13] On the other hand, a slow equilibration of the *E*- and *Z*-isomers of enamines **4**, observed by NMR spectroscopy, is likely to proceed through the imine form (**5**), the reduction of which with Cl_3SiH can be envisaged. Because the enamine–imine equilibration is facilitated by Brønsted acids, traces of HCl in commercial Cl_3SiH may have a beneficial effect on the reaction. Indeed, under standard reduction conditions (enamine (1 equiv), Cl_3SiH (2 equiv), and **8** (5 mol%) in toluene at RT),[9,12] enamine **3a** afforded the amino ester (*S*)-**6a** in 78% yield and 92% enantiomeric excess (*ee*); however, the reaction suffered from poor reproducibility, giving a wide distribution of

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yields and enantioselectivities, presumably due to varied concentrations of H^+. It proved difficult to control the acid content, even with freshly distilled Cl_3SiH. To "buffer" the reaction medium, a number of acid additives were examined, of which AcOH emerged as the most promising choice. However, AcOH in fact catalyzed the competing nonselective reduction, which lowered the overall enantioselectivity. In the optimized protocol, the use of one equivalent of AcOH provided a healthy compromise between reactivity and selectivity. Thus, enamine **3a** was now reduced to afford the amino ester (*S*)-**6a** in high yield and 89% *ee*, from which an enantiopure product was obtained by a single crystallization (Table 1, entry 1).

Table 1. Synthesis of β^3-amino acid derivatives (*S*)-**6** and (*S*)-**7** by reduction of enamines **3** (X = CO_2Et, R^2 = H, Ar = PMP) and **4** (X = CN, R^2 = H, Ar = PMP) with Cl_3SiH catalyzed by Sigamide (*S*)-**8**.[a]

Entry	Enamine **3**, **4**	R^3	Yield [%]	**6** or **7** [% *ee*][b]
1	**3a**	Ph	98	89 (99.8[c])
2	**3b**	4-$MeOC_6H_4$	80	88
3	**3c**	4-FC_6H_4	95	90
4	**3d**	4-$CF_3C_6H_4$	94	88
5	**3e**	3-$MeOC_6H_4$	95	88
6	**3f**	3-ClC_6H_4	91	86
7	**3g**	2-Naphth	86	88
8	**3h**	2-MeC_6H_4	84[d]	79
9	**3i**	2-ClC_6H_4	77[d]	79
10	**3j**	2-Thiophenyl	63	70
11	**3k**	*i*Pr	83	59
12	**4a**	Ph	75	87
13	**4s**[e]	Ph	97	87 (99.9[c])

[a] The reduction was carried out on a 0.2 mmol scale with Cl_3SiH (2.0 equiv) and acetic acid (1.0 equiv) at RT (18 °C) for 48 h by using catalyst **8** (5 mol%), unless stated otherwise. [b] Determined by chiral HPLC using Chiralpak IB column. [c] After a single crystallization. [d] Catalyst loading of 10 mol% was used. [e] Ar = Ph.

Reduction of the aromatic substrates **3b–g** was equally successful (Table 1, entries 2-7), whereas the sterically more hindered *ortho*-substituted derivatives **3h**,**i** and the thiophenyl analogue **3j** exhibited lower reactivity, which led to the erosion in *ee* (Table 1, entries 8–10). With the aliphatic enamine **3k**, selectivity dropped to a moderate level (Table 1, entry 11). Nitriles **4a**,**s** mirrored the reactivity of the esters (Table 1, entries 12 and 13); the amino nitrile (*S*)-**7s** was obtained as a pure enantiomer after a single crystallization (Table 1, entry 13). The absolute configuration in both amino esters **6** and amino nitriles **7** was found to be *S* by chemical correlation (see the Supporting Information).

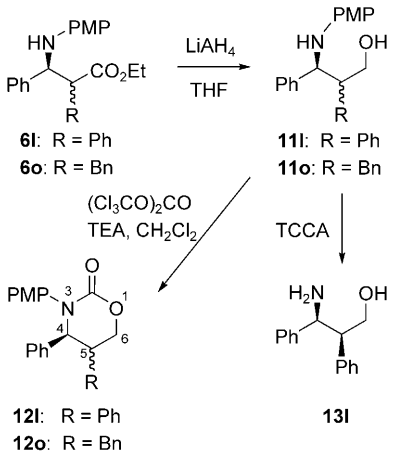
As a more challenging target, we then focused on the synthesis of $\beta^{2,3}$-amino acids. In this case, fast enamine–imine equilibration is crucial because imines **5** are chiral but racemic, so that dynamic kinetic resolution (DKR) is required to operate here[14] (along with the enantioselective reduction) to provide diastereo- and enantiocontrol. Whereas some α-alkyl β-amino acids can be accessed, for example, by the asymmetric Mannich reaction,[3a–c,e] no suitable methodology is currently available for their α-aryl analogues. Therefore, we examined reduction of α-substituted esters **3l–r** and nitriles **4l–n** with emphasis on α-aryl derivatives (Table 2). α-Aryl β-amino esters **6l–n** were obtained as single diastereoisomers in good yields and respectable enantioselectivities (Table 2, entries 1–3); single recrystallization significantly improved the enantiopurity of **6l** (96% *ee*, entry 1). Reduction of α-alkyl derivatives **3p–r** followed the same pattern (Table 2, entries 5–7) and only the α-benzyl analogue **3o** turned out to be less diastereoselective (*syn*/*anti* 1:2.6; Table 2, entry 4). High diastereoselectivity and good enantioselectivity was also observed for the reduction of nitriles **4l–n** (Table 2, entries 8–10), though at lower reaction rates.

Table 2. Synthesis of $\beta^{2,3}$-amino acid derivatives (*S*)-**6** and (*S*)-**7** by reduction of enamines **3** (X = CO_2Et, Ar = PMP) and **4** (X = CN, Ar = PMP) with Cl_3SiH catalyzed by Sigamide (*S*)-**8**.[a]

Entry	Enamine **3**, **4**	R^3	R^2	Yield [%]	*Syn*/*anti*[b]	**6** or **7** [% *ee*][c] *syn*; *anti*
1	**3l**	Ph	Ph	84	> 99:1	76 (96[d])
2	**3m**	Ph	4-$MeOC_6H_4$	80	> 99:1	77
3	**3n**	Ph	4-FC_6H_4	77	> 99:1	73[e]
4	**3o**	Ph	Bn	87	27:73	86; 76
5	**3p**	Ph	Me	85	98:2	77[e]
6	**3q**	Ph	Et	86	95:5	82[e]
7	**3r**	Ph	*n*Bu	84	95:5	76[e]
8	**4l**	Ph	Ph	46	> 99:1	83
9	**4m**	Ph	4-$MeOC_6H_4$	43	> 99:1	83
10	**4n**	Ph	4-FC_6H_4	26	> 99:1	79

[a] The enamine reduction was carried out on a 0.2 mmol scale with Cl_3SiH (2.0 equiv) and acetic acid (1.0 equiv) at RT (18 °C) for 48 h by using catalyst **8** (10 mol%). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude products. [c] Determined by chiral HPLC using Chiralpak IB or Whelk-O columns. [d] After a single crystallization. [e] Enantiomers did not give baseline separation by chiral HPLC.

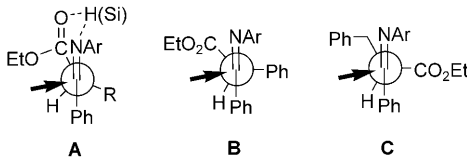
The configuration of the major diastereoisomer of **6l** was established as follows: reduction of (+)-**6l** with $LiAlH_4$, followed by cyclization of the resulting amino alcohol **11l** with triphosgene, afforded the cyclic carbamate (+)-**12l** (Scheme 2), the ^{1}H NMR spectrum of which clearly showed signals for 4-H, 5-H, and 6-H that were unequivocally assigned by the ^{13}C, DEPT edited-^{13}C, HSQC, and COSY NMR spectroscopy experiments. Because the coupling pattern of these protons was consistent with the *cis* configuration, compound **6l** must be *syn*-configured. Then, the amino alcohol **11l**, obtained from (+)-**6l** (see above), was deprotected with trichloroisocyanuric acid (TCCA)[15] and the product was found to be identical to the known (2*S*,3*S*)-(−)-3-amino-2,3-diphenyl-1-propanol (**13l**).[16] Hence, the configuration of **6l** can be inferred as (2*S*,3*S*)-(+)-**6l**. The same relative and absolute configuration was also confirmed for the α-alkyl derivatives **6p–r** by their reduction with $LiAlH_4$ into the known amino alcohols **11p–r**.[17] These results show that the catalytic reduction of the imine intermediate **5**, produced from the α-phenyl (**3l**) and α-alkyl enamines **3p–r**, proceeds from the same enantiotopic face as with those



Scheme 2. Determination of the relative and absolute configuration of amino ester **6l** and the relative configuration of amino ester **6o**.

formed from the α-unsubstituted enamines **3a** and **4a**. Analogous experiments, carried out with the α-benzyl derivative (**6o**), that is, reduction and cyclization (**6o**→**11o**→**12o**), revealed the *anti*-configuration for the major diastereoisomer.

The observed DKR in the reduction of (±)-**5l**,**p–r** is consistent with the model, in which the ester carbonyl and the imine group are held together either by hydrogen bonding (in the protonated form) or by chelation to silicon (**A**, Scheme 3). In the case of α-aryl derivatives **5l–n**, featuring



Scheme 3. Preferred directions of the nucleophilic attack at the C=N bond.

high diastereoselectivity, both the chelation and the Felkin–Anh model, in which Ph assumes a perpendicular orientation to the C=N bond (**B**, Scheme 3), predict the formation of the same *syn* diastereoisomer. Predominant formation of the *anti* isomer in the case of **3o** (in ≈3:1 ratio) is consistent with conformation **C** (Scheme 3) of the imine intermediate (±)-**5** in the catalytic reduction, which suggests a small relative difference in the conformational energies of the transition state.[18]

In summary, we have developed a new, expedient protocol for the enantioselective synthesis of β^3- and $\beta^{2,3}$-amino acid derivatives **6** and **7** from the enamine precursors **3/4**. The method relies on fast equilibration between the enamine and imine forms (**3/4**⇄**5**). Reduction of the equilibrated mixture with Cl_3SiH, catalyzed by the L-valine-derived formamide **8** (5 mol%), afforded the corresponding amino esters (*S*)-**6a–k** and amino nitriles (*S*)-**7a**,**s** in excellent yields and with high enantioselectivity (≤90% *ee*). Efficient DKR, operating in the case of the α-aryl and α-alkyl derivatives, provided a set of highly diastereoisomerically enriched $\beta^{2,3}$-amino acid derivatives **6l–n**, **6p–r**, and **7l–n** (*syn/anti* ≥95:5) with good enantioselectivity (76-86% *ee*).

Experimental Section

General procedure[7] for the synthesis of enamines 3a–j and 3l–r: A solution of ketoester **1** (5 mmol), *p*-anisidine (677 mg, 5.5 mmol), and *p*-toluenesulfonic acid monohydrate (95 mg, 0.5 mmol) in dry ethanol (5 mL) was heated at reflux for 24–48 h under argon, then cooled and evaporated. Solid residues were directly purified by crystallization. Oily residues were dissolved in CH_2Cl_2 (20 mL) and washed with water (10 mL), the organic phase was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography on silica gel.

Enamine 3k: A mixture of ketoester **1k** (791 mg, 5 mmol), *p*-anisidine (677 mg, 5.5 mmol), and acetic acid (29 μL) was placed in an ultrasound bath for 3 h, then acetic acid was evaporated in vacuo. The residue was purified by column chromatography on silica gel with a petroleum ether/ethyl acetate mixture (95:5, R_f = 0.36). Yields and spectral data are given in the Supporting Information.

General procedure[19] for the synthesis of enamines 4a, 4l–n, 4s: A solution of ketonitrile **2** (5 mmol) and *p*-anisidine (800 mg, 6.5 mmol) or aniline (605 mg, 6.5 mmol) in glacial acetic acid (2.9 mL) was stirred at 80 °C for 6 h under argon. The mixture was then cooled to room temperature and the precipitated solid was filtered off, washed with glacial acetic acid, vacuum dried, and used without further purification (**4n**, **4s**) or after additional recrystallization (**4a**). In the cases in which no solid precipitated (**4l**, **4m**), the reaction mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (3×25 mL). The organic phase was washed with 0.5 M HCl (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography on silica gel (**4l**) or by recrystallization (**4m**). Yields and spectral data are given in Supporting Information.

General procedure for the asymmetric reduction of enamines 3 and 4 with trichlorosilane: A solution of enamine **3** or **4** (0.2 mmol) in dry toluene (2 mL) was precooled to 0 °C and a 0.1 M solution of catalyst **8** in dry toluene (100 μL, 5 mol%) was added, followed by glacial acetic acid (11.5 μL, 1.0 equiv) and freshly distilled trichlorosilane (40 μL, 0.4 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 48 h, after which time a saturated aqueous solution of $NaHCO_3$ (5 mL) was added to quench the reaction. The mixture was diluted with brine (10 mL), extracted with EtOAc (2×20 mL) and the combined organic fractions were dried over $MgSO_4$. Concentration in vacuo, followed by flash chromatography on silica gel, afforded products **6** and **7**, respectively.

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Keywords: amino acids · asymmetric synthesis · imines · organocatalysis · reduction

[1] For an overview, see: D. L. Steer, R. A. Lew, P. Perlmutter, A. I. Smith, M.-I. Aguilar, *Curr. Med. Chem.* **2002**, *9*, 811–822.
[2] For overviews, see: a) D. C. Cole, *Tetrahedron* **1994**, *50*, 9517–9582; b) G. Cardillo, C. Tomasini, *Chem. Soc. Rev.* **1999**, *118*–128; c) M.

Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991–8035; d) H.-J. Drexler, J. You, S. Zhang, C. Fischer, W. Baumann, A. Spannenberg, D. Heller, *Org. Process Res. Dev.* **2003**, *7*, 355–361; e) J.-A. Ma, *Angew. Chem.* **2003**, *115*, 4426–4435; *Angew. Chem. Int. Ed.* **2003**, *42*, 4290–4299; f) N. Sewald, *Angew. Chem.* **2003**, *115*, 5972–5973; *Angew. Chem. Int. Ed.* **2003**, *42*, 5794–5795; g) L. Gerald, D. Seebach, *Biopolymers* **2004**, *76*, 206–243; h) D. Seebach, T. Kimmerlin, R. Sebesta, M. A. Campo, A. K. Beck, *Tetrahedron* **2004**, *60*, 7455–7506; i) E. Juaristi, V. A. Soloshonok, *Enantioselective Synthesis of β-Amino Acids*, Wiley, Hoboken, **2005**.

[3] For the most recent examples of catalytic enantioselective protocols for Mannich reaction, see, for example: a) M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2007**, *129*, 6756–6764; b) J. W. Yang, M. Stadler, B. List, *Angew. Chem.* **2007**, *119*, 615–617; *Angew. Chem. Int. Ed.* **2007**, *46*, 609–611; c) J. Vesely, R. Rios, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 421–425; d) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049; e) F. Tanaka, C. F. Barbas, *J. Am. Chem. Soc.* **2007**, *129*, 195–213; for the Reformatsky reaction, see: f) P. G. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 2075–2079; g) P. G. Cozzi, E. Rivalta, *Angew. Chem.* **2005**, *117*, 3666–3669; *Angew. Chem. Int. Ed.* **2005**, *44*, 3600–3603.

[4] a) J. Halpern, *Science* **1982**, *217*, 401; for an overview on asymmetric hydrogenation of functionalized alkenes, see: b) J. M. Brown, *Comprehensive Asymmetric Catalysis, Vol. 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 199–246.

[5] a) S. Lee, Y. J. Zhang, *Org. Lett.* **2002**, *4*, 2429–2431; b) W. Tang, X. Zhang, *Org. Lett.* **2002**, *4*, 4159–4161.

[6] Y. Hsiao, N. R. Rivera, T. Rosner, S. W. Krska, E. Njolito, F. Wang, Y. Sun, J. D. Armstrong, E. J. J. Grabowski, R. D. Tillyer, F. Spindler, C. Malan, *J. Am. Chem. Soc.* **2004**, *126*, 9918–9919.

[7] Q. Dai, W. Yang, X. Zhang, *Org. Lett.* **2005**, *7*, 5343–5345.

[8] a) W. Tang, S. Wu, X. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 9570–9571; b) J. Elaridi, A. Thaqi, A. Prosser, W. R. Jackson, A. J. Robinson, *Tetrahedron: Asymmetry* **2005**, *16*, 1309–1319.

[9] a) A. V. Malkov, A. Mariani, K. N. MacDougall, P. Kočovský, *Org. Lett.* **2004**, *6*, 2253–2256; b) A. V. Malkov, S. Stončius, K. N. MacDougall, A. Mariani, G. D. McGeoch, P. Kočovský, *Tetrahedron* **2006**, *62*, 264–284; c) A. V. Malkov, M. Figlus, S. Stončius, P. Kočovský, *J. Org. Chem.* **2007**, *72*, 1315–1325.

[10] For chiral pyridyloxazolines as catalysts in the reduction of both imines and ketones, see: A. V. Malkov, A. J. P. Stewart-Liddon, P. Ramírez-López, L. Bendová, D. Haigh, P. Kočovský, *Angew. Chem.* **2006**, *118*, 1460–1463; *Angew. Chem. Int. Ed.* **2006**, *45*, 1432–1435.

[11] For the asymmetric reduction of imines with trichlorosilane, see also: a) F. Iwasaki, O. Omonura, K. Mishima, T. Kanematsu, T. Maki, Y. Matsumura, *Tetrahedron Lett.* **2001**, *42*, 2525–2527; b) O. Onomura, Y. Kouchi, F. Iwasaki, Y. Matsumura, *Tetrahedron Lett.* **2006**, *47*, 3751–3754; c) Z. Wang, X. Ye, S. Wei, P. Wu, A. Zhang, J. Sun, *Org. Lett.* **2006**, *8*, 999–1001; d) Z. Wang, M. Cheng, P. Wu, S. Wei, J. Sun, *Org. Lett.* **2006**, *8*, 3045–3048.

[12] A. V. Malkov, S. Stončius, P. Kočovský, *Angew. Chem.* **2007**, *119*, 3796–3798; *Angew. Chem. Int. Ed.* **2007**, *46*, 3722–3724.

[13] For a single example of asymmetric reduction of an enamine with low selectivity, see ref. [11b].

[14] For leading reviews on DKR, see: a) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–55; b) R. S. Ward, *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490; c) F. F. Huerta, A. B. E. Minidis, J.-E. Bäckvall, *Chem. Soc., Rev.* **2001**, *30*, 321–331; d) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291–8327; e) O. Pàmies, J.-E. Bäckvall, *Chem. Rev.* **2003**, *103*, 3247–3262; for a recent example of asymmetric reductive amination by DKR, see: f) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074–13075.

[15] For the method, see: J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, P. L. Alsters, F. L. van Delft, F. P. J. T. Rutjes, *Tetrahedron Lett.* **2006**, *47*, 8109–8113.

[16] N. Berova, B. J. Kurtev, *Tetrahedron* **1969**, *25*, 2301–2311.

[17] a) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805–3808; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677–3680; b) Y. Hayashi, T. Urushima, W. Tsuboi, M. Shoji, *Nat. Protocols* **2007**, *2*, 113–118.

[18] Note that enantioselectivity in the reduction of (±)-**5** catalyzed by **8** relies predominantly on the enantiofacial discrimination of the imine group, while diastereoselectivity is controlled by kinetic preference towards the α-stereogenic center. Kinetic resolution alone (see ref. [14f]) in this case does not provide high enantioselectivity because enamine **4** (R^2 = Ph, R^3 = H, X = CN, Ar = PMP) under the standard conditions produced the corresponding β^2-amino nitrile **7** in 30% *ee*.

[19] V. V. R. Rao, C. Wentrup, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1232–1235.

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