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A practical, solvent free, one-pot synthesis of C_2-symmetrical secondary amines

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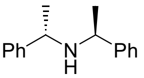
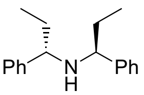
Abstract—A novel one-pot reductive amination of ketones using the combination $Ti(O^iPr)_4/H_2/Pd–C$ is reported. This practical procedure does not require any solvent, and affords C_2-symmetrical secondary amines in high yields and excellent diastereoselectivities.

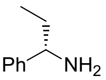
In 1980 Whitesell and Felman described the first use of the C_2-symmetrical amine **1** in the enantioselective deprotonation of cyclohexene oxide.[1] This chiral auxiliary had a tremendous influence on the later design of chiral amines. There are numerous applications of **1** as a chiral base,[2] as a nucleophile, as a ligand or as a structural part of a ligand.[3] The preparation of **1** is straightforward, and corresponds to the general approach toward the synthesis of secondary amines.[4] In connection with our program on chiral ligands for copper-catalyzed asymmetric transformations, we needed a simple and efficient way to prepare amine **2**, the ethyl homologue of **1**.



1



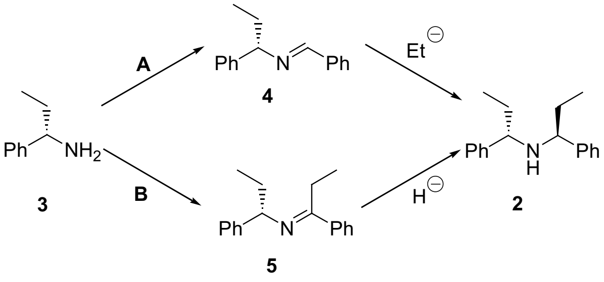
2



3

Starting from commercially available **3**, two synthetic pathways were possible (Scheme 1).

Path A needed the preparation of chiral imine **4**, starting from benzaldehyde. This was an easy and fast reaction, but the subsequent nucleophilic addition proceeded with poor diastereoselectivity. This result was not surprising: indeed, Yamada et al. showed that a bulky chiral auxiliary such as the α-naphthylethyl group was necessary to induce high diastereoselectivity in this type of asymmetric reaction.[5]



Scheme 1.

The unsatisfactory results obtained using path A prompted us to investigate the alternative reductive alkylation of amine **3**. Path B has already been explored by Yoshida and Harada for the preparation of amine **2**,[6] following the two-step procedure developed before for amine **1**.[4] Good stereoselectivities have been obtained by this procedure, but the synthesis of imine **5** starting from propiophenone required harsh conditions: the use of a catalytic amount of *p*-toluenesulfonic acid at reflux with a Dean–Stark trap to remove water, for several days.

Keywords: Reductive amination; C_2-symmetry; Chiral amines; Titanium isopropoxide.

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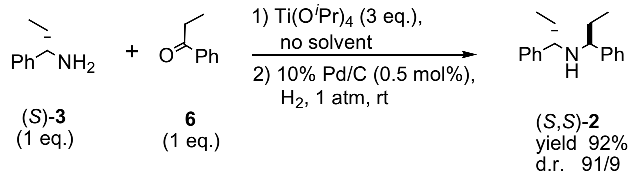


Scheme 2. Diastereoselective synthesis of (*S*,*S*)-**2** using the combination Ti(O^{i}Pr)$_4$/H$_2$/Pd–C.

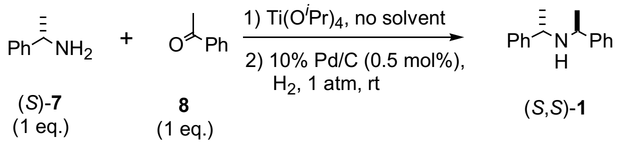
Recently, a high yielding, single-step reductive amination of carbonyl compounds has been reported, using polymethylhydrosiloxane (PMHS) as reductant and titanium(IV) isopropoxide (Ti(O^{i}Pr)$_4$) as activator.[7] This latter reagent was already known as a mild and efficient Lewis acid catalyst for imine (or a titanium complex intermediate) formation,[8] but it has also been identified as a good activator for PMHS.

Thus, in preliminary reactions, the synthesis of **2** was carried out following this one-step procedure, but the results were not satisfactory. Other reducing reagents were then tested and we were pleased to find that (*S*,*S*)-**2** could be obtained from amine (*S*)-**3** and propiophenone **6** with a high level of stereoselectivity (91:9 dr) using the combination Ti(O^{i}Pr)$_4$/H$_2$/Pd–C [Ti(OEt)$_4$ works equally well] (Scheme 2). It should be pointed out that this reaction was performed without additional solvent.

Optimization studies were carried out in order to determine the effect of the amount of Ti(O^{i}Pr)$_4$, and the results are outlined in Table 1. Having stated that Ti(O^{i}Pr)$_4$ is absolutely necessary for the reaction to occur (entry 1), it was noticed that the diastereoisomeric ratio was not dramatically influenced by the amount of Ti(O^{i}Pr)$_4$ employed (entries 2–7). However, a problem of solidification of the reaction mixture arose as the quantity decreased, since Ti(O^{i}Pr)$_4$ may play the role of solvent.

To overcome this solidification problem encountered in substoichiometric reactions, we decided to add a solvent, studying first its effect on the diastereoselectivity.

Table 1. Effect of the amount of Ti(O^{i}Pr)$_4$ on the diastereoselectivity of formation of amine **1**

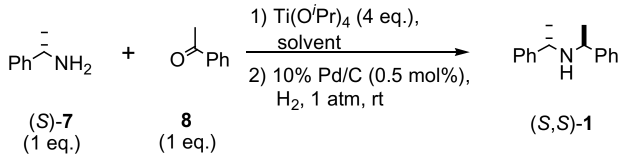


Entry	Ti(O^{i}Pr)$_4$ (equiv)	Conversion[a] (%)	Dr[b] (*S*,*S*)/(*S*,*R*)
1	0	0	—
2	6	>99	85:15
3	4	>99	88:12
4	3	>99	89:11
5	2	>99	83:17
6	1	>99	84:16
7	0.5	>99	85:15

[a] Determined by GC/MS analysis.

[b] Determined by GC/MS analysis and ^{1}H NMR spectroscopy.

Table 2. Effect of the solvent on the diastereoselectivity of formation of amine **1**



Entry	Solvent[a]	Conversion[b] (%)	Dr[c] (*S*,*S*)/(*S*,*R*)
1	EtOH	>99	91:9
2	Toluene	>99	71:29
3	AcOEt	>99	85:15
4	THF	>99	85:15

[a] [**7**] = 4 M.

[b] Determined by GC/MS analysis.

[c] Determined by GC/MS analysis and ^{1}H NMR spectroscopy.

According to the experiments shown in Table 2, a polar and protic solvent such as ethanol was required to maintain the diastereoisomeric ratio at its highest level (entry 1 vs entries 2–4). However, from a practical point of view, addition of ethanol to the reaction medium made the process very sluggish, which renders any large-scale synthesis impractical by this method. A good compromise was the use of ethyl acetate, which is the extraction solvent and which does not significantly decrease the stereoselectivity (entry 3).

As a consequence of these preliminary studies, the synthesis of several chiral C_2-symmetrical secondary amines was undertaken (Table 3).[9,10] Good yields and good diastereoisomeric ratios were obtained, probing the efficiency of this one-pot reductive amination. It should be noted that the preparation of (1*S*,1′*S*)-bis[1-(2-naphthyl)ethyl]amine **11** was performed in the presence of ethyl acetate as the corresponding substrates formed an insoluble intermediate.

These amines could be purified by recrystallization of their hydrobromide or hydrochloride salts in ethyl acetate/methanol [85/15 to 75/25 (v/v)] to afford diastereomerically pure C_2-symmetrical secondary amines. Thus, amines (*S*,*S*)-**2** (99.5:0.5 dr) and (*S*,*S*)-**11** (99.5:0.5 dr) were obtained, respectively, in 51% and 63% yields.

In conclusion, a high yielding, simple and diastereoselective synthesis of various C_2-symmetrical secondary amines was developed via one-pot reductive amination using the combination Ti(O^{i}Pr)$_4$/H$_2$/Pd–C. This procedure is not only economical, but also environment-friendly since it does not require any solvent.[11]

Acknowledgements

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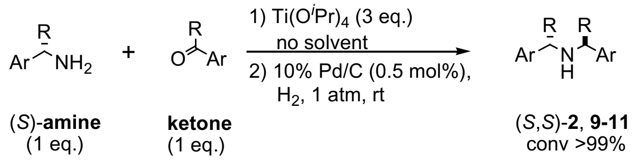
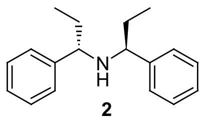
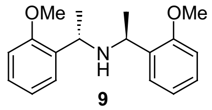
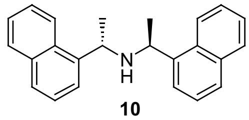
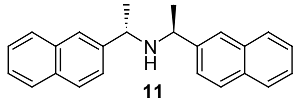
Table 3. Diastereoselective synthesis of some C_2-symmetrical secondary amines **2**, **9**–**11**



Entry	Ar	R	Solvent[a]	Product[10]	Yield (%)	Dr[b]
1	Ph	Et	—	 **2**	92	91:9
2	*o*-MeOC$_6$H$_4$	Me	—	 **9**	88	87:13
3	1-Naphthyl	Me	—	 **10**	90	94:6
4	2-Naphthyl	Me	EtOAc	 **11**	90	85:15

[a] [(*S*)-Amine] = 4 M.
[b] Determined by GC/MS analysis and ^{1}H NMR spectroscopy.

References and notes

1. Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755.
2. (a) O'Brien, P. *Tetrahedron* **2002**, *58*(23), Symposium-in-Print, Recent Developments in Chiral Lithium Amide Base Chemistry, pp 4567–4733; (b) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439; (c) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 95.
3. (a) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262; (b) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375.
4. Overberger, C. G.; Marullo, N. P.; Hiskey, R. G. *J. Am. Chem. Soc.* **1961**, *83*, 1374.
5. Yamada, H.; Kawate, T.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **1999**, *64*, 8821.
6. Yoshida, T.; Harada, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3706.
7. Chandrasekhar, S.; Reddy, C. R.; Ahmed, M. *Synlett* **2000**, 1655.
8. Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552.
9. Synthesis of (1*S*,1′*S*)-bis(1-phenylpropyl)amine [(*S*,*S*)-**2**]. Typical procedure (Table 3, entry 1). A mixture of propiophenone (14.9 g, 0.11 mol), (*S*)-α-phenylpropylamine (15.1 g, 0.11 mol) and titanium(IV) isopropoxide (100 mL, 0.33 mol) was stirred at room temperature for 20 min. The mixture was then hydrogenated at 1 atm with 10% palladium-on-charcoal (500 mg, 0.5 mol%) under vigorous stirring at room temperature. The reaction course was monitored by GC/MS. At complete conversion, the reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide (150 mL). After stirring for 10 min, the solution was extracted five times with ethyl acetate. The combined organic layers were filtered over Celite, dried over Na$_2$SO$_4$, and finally evaporated under reduced pressure.
10. Compound **2**: colorless oil; $[\alpha]^{20}_{D}$ +159° (*c* 13.5, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.75 (6H, t, $J = 7.4$ Hz), 1.55–1.68 (5H, m), 3.21 (2H, t, $J = 7.0$ Hz), 7.18–7.37 (10H, m) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 10.9, 31.5, 61.4, 126.7, 127.4, 128.2, 144.6 ppm. Compound **11**: colorless oil; $[\alpha]^{20}_{D}$ −335° (*c* 16.5, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.44 (6H, d, $J = 6.7$ Hz), 1.83 (1H, br s), 3.77 (2H, q, $J = 6.7$ Hz), 7.49–7.55 (6H, m), 7.65 (2H, br s), 7.85–7.93 (6H, m) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 24.8, 55.2, 124.7, 125.4, 125.9, 127.6, 127.7, 128.2, 132.7, 133.4, 143.0 ppm; Amines **10** and **11** were characterized by comparison of their spectral data with those reported. For amine **10**, see: Saudan, L. Ph.D. Dissertation 3013, University of Geneva, Geneva, 1998. For amine **11**, see: Yamada, H.; Kawate, T.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **1999**, *64*, 8821.
11. Ti(OR)$_4$ is considered as nontoxic waste.