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Evolution of Titanium(IV) Alkoxides and Raney Nickel for Asymmetric Reductive Amination of Prochiral Aliphatic Ketones

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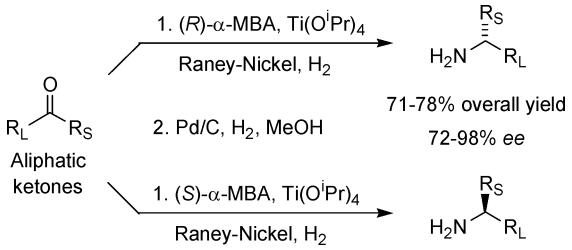
ABSTRACT



A new method for the one-pot asymmetric reductive amination of prochiral aliphatic ketones has been developed. The previously unexplored reagent combination of Ti(O^{i}Pr)$_4$/Raney Ni/H$_2$ in the presence of (*R*)- or (*S*)-α-methylbenzylamine provides good to excellent yield (76–90%) and diastereomeric excess (72–98%). The second step, hydrogenolysis, provides the corresponding primary amine in high yield (88–93%) and with uncompromised enantiomeric excess.

For over 30 years chemists have exhaustively explored the synthesis of α-chiral aliphatic amines, but methods detailing expedient synthesis and high enantiomeric excess are rare.[1−5] For racemic amine synthesis reductive amination is the most direct and efficient strategy, yet this method has been difficult to develop at the next level of complexity, namely, asymmetric synthesis.[6,7]

(1) For recent advances in diastereoselective and enantioselective enamine hydrogenation, see: (a) Ikemoto, N.; Tellers, D. M.; Dreher, S. D.; Liu, J.; Huang, A.; Rivera, N. R.; Njolito, E.; Hsiao, Y.; McWilliams, J. C.; Williams, J. M.; Armstrong, J. D.; Sun, Y.; Mathre, D. J.; Grabowski, E. J. J.; Tillyer, R. D. *J. Am. Chem. Soc.* **2004**, *126*, 3048. (b) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918.

(2) For recent advances in enantioselective alkylmetal addition to aliphatic aldimines, see: (a) Akullian, L. C.; Porter, J. R.; Traverse, J. F.; Snapper, M. L.; Hoveyda, A. H. *Adv. Synth. Catal.* **2005**, *347*, 417. (b) Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5405.

(3) For recent advances in enantioselective transfer hydrogenation of prochiral aliphatic ketimine derivatives, see: Blacker, J.; Martin J. Scale-up Studies in Asymmetric Transfer Hydrogenation. In *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches, and Solutions*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004, pp 201−216.

(4) For recent advances in diastereoselective addition of alkylmetals to chiral imines, see: (a) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39. (b) Boezio, A. A.; Solberghe, G.; Lauzon, C.; Charette, A. B. *J. Org. Chem.* **2003**, *68*, 3241. (c) Yamada, H.; Kawate, T.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **1999**, *64*, 8821.

(5) For advances in the diastereoselective reduction of chiral *N*-α-methylbenzyl ketimine derivatives, see: (a) Storace, L.; Anzalone, L.; Confalone, P. N.; Davis, W. P.; Fortunak, J. M.; Giangiordano, M.; Haley, J. J., Jr.; Kamholz, K.; Li, H.-Y.; Ma, P.; Nugent, W. A.; Parsons, R. L., Jr.; Sheeran, P. J.; Silverman, C. E.; Waltermire, R. E.; Wood, C. C. *Org. Process Res. Dev.* **2002**, *6*, 54. (b) Juaristi, E.; León-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441. (c) Bisel, P.; Breitling, E.; Frahm, A. W. *Eur. J. Org. Chem.* **1998**, 729. (d) Lauktien, G.; Volk, F.-J.; Frahm, A. W. *Tetrahedron: Asymmetry* **1997**, *8*, 3457. (e) Speckenbach, B.; Bisel, P.; Frahm, A. W. *Synthesis* **1997**, 1325. (f) Moss, N.; Gauthier, J.; Ferland, J.-M. *Synlett* **1995**, 142. (g) Marx, E.; El Bouz, M.; Célérier, J. P.; Lhommet, G. *Tetrahedron Lett.* **1992**, *33*, 4307.

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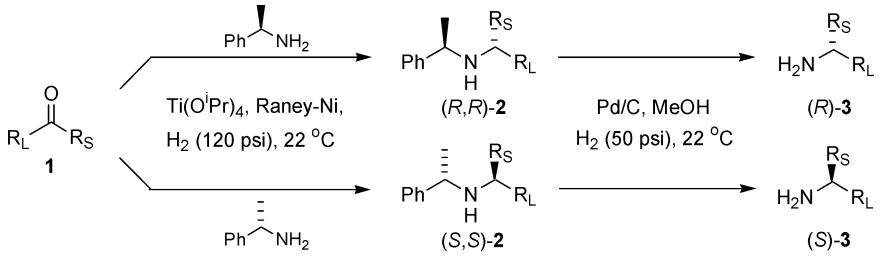
Scheme 1. Two-Step Procedure for Producing Enantioenriched Aliphatic Primary Amines

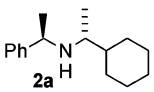
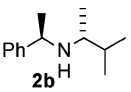
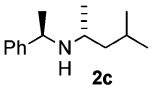
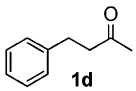
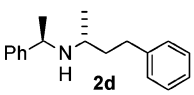
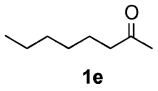
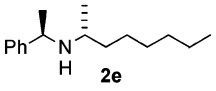


The use of titanium(IV) alkoxides for racemic reductive amination was pioneered by Reetz[8a] and Mattson[8b] using hydride reagents, and the method has more recently been exploited by Bhattacharyya.[9] In 1998, one of us realized that atom-efficient hydrogen, with Pt/C or Pd/C, could replace the previously used hydride reagents and simultaneously produced a reagent system capable of nonepimerizing diastereoselective reductive amination.[10] Recently, Alexakis et al. reported a similar reagent system for the asymmetric reductive amination of several prochiral aromatic−aliphatic ketones.[6a] In general, these systems provide poor de's for prochiral aliphatic ketones.

Herein we report the first use of an inexpensive chiral ammonia equivalent, (*R*)- or (*S*)-α-methylbenzylamine (MBA), with the previously unexplored reagent combination of Ti(O^{i}Pr)$_4$/Raney Ni/H_2 for the one-pot conversion of prochiral aliphatic ketones **1** into α-chiral amines **2** with good to excellent diastereoselectivity (Scheme 1 and Table 1). The chiral auxiliary is readily cleaved from amines **2** in high yield (90%), providing the enantioenriched α-chiral primary amines **3**. Presently, no enantioselective method, regardless of strategy (e.g., enantioselective alkylmetal addition to in situ formed aldimines),[2] is stepwise as short from aliphatic ketones or aldehydes and allows the high overall yield we observe for our enantioenriched aliphatic primary amines **3**.

For our screening studies, a structurally diverse group of prochiral aliphatic ketones (**1a**−**e**, Table 1) was chosen and used as the limiting reagent (2.5−5.0 mmol scale). Concerning the choice of our chiral ammonia equivalent, (*R*)- or (*S*)-α-MBA is commercially available in kilogram quantities, is inexpensive, and has been routinely used by the pharmaceutical industry for decades.[11] It was therefore a natural starting point for our studies, and we found it convenient to use 1.05−1.10 equiv of (*R*)-α-MBA. Ti(O^{i}Pr)$_4$ is inexpensive,[12] and we found it to be superior to other commercially available titanium(IV) alkoxides. For our screening studies 1.25 equiv was employed; for optimized procedures 1.0−1.1 equiv is usually sufficient. Attempts to perform these reactions in the absence of Ti(O^{i}Pr)$_4$ resulted in slow formation of essentially equal quantities of amine **2** and the corresponding alcohol from ketone reduction.

Table 1. Asymmetric Reductive Amination of 2-Alkanones with Ti(O^{i}Pr)$_4$/Raney Ni/H_2 and (*R*)-α-MBA[a]

2-alkanone **1**	secondary amine **2**	yield (%)[b]	*de* (%)[c]
 **1a**	 **2a**	90	98
 **1b**	 **2b**	78	98
 **1c**	 **2c**	79[d]	93
 **1d**	 **2d**	89	80
 **1e**	 **2e**	90[e]	72

[a] Ketone (5.0 mmol), Ti(O^{i}Pr)$_4$ (1.25 equiv), (*R*)-α-methylbenzylamine (1.05 or 1.10 equiv), Raney Ni, H_2 (120 psi), 22 °C, solvent 0.50 M (see Supporting Information). [b] Isolated yield of both diastereomers after chromatography. [c] de determined by GC analysis of crude product **2**. [d] 60 psi H_2 used. [e] 5.0 g scale yield.

In general the de of secondary amines **2** was solvent-independent for a diverse set of privileged solvents (THF, MTBE, DME, hexane, toluene, CH_2Cl_2, 1,2-dichloroethane,

(6) For recent advances in asymmetric reductive amination of prochiral ketones, see: (a) Alexakis, A.; Gille, S.; Prian, F.; Rosset, S.; Ditrich, K. *Tetrahedron Lett*. **2004**, *45*, 1449. (b) Borg, G.; Cogan, D. A.; Ellman, J. A. *Tetrahedron Lett.* **1999**, *40*, 6709.

(7) For recent advances in enantioselective reductive amination of α-ketoacids, see: (a) Tararov, V. I.; Börner, A. *Synlett* **2005**, 203. (b) Kadyrov, R.; Riermeier, T. H.; Dingerdissen, U.; Tararov, V. I.; Börner, A. *J. Org. Chem.* **2003**, *68*, 4067.

(8) (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Reetz, M. T., Ed.; Springer-Verlag: Berlin, 1986; p 107. (b) Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552.

(9) (a) Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463. (b) Chandrasekhar, S.; Reddy, R. C.; Ahmed, M. *Synlett* **2000**, 1655.

(10) Process for the preparation of (*S*,*S*)-*cis*-2-benzhydryl-3-benzylaminoquinuclidine. Nugent, T. C.; Seemayer, R.; Pfizer Products, Inc. and DSM Pharmaceuticals, Inc. Patent WO2004035575, 2004.

(11) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788.

(12) Lower grade Ti(O^{i}Pr)$_4$ (Sigma-Aldrich, TYZOR 97%, 2.0 L (neat) = $93.00) can be used instead of the highly purified reagent Ti(O^{i}Pr)$_4$ (99.999%).

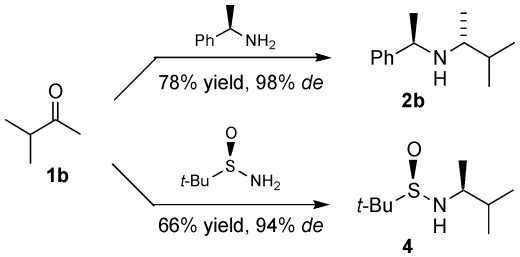
EtOAc, and EtOH), but reaction rates varied and the optimal choice depends on the ketone examined. Regarding the hydrogen pressure, 120 psi (8.3 bar) allowed short reaction times (6−11 h) to be achieved. Greater hydrogen pressures were not examined, and in general lower hydrogen pressures (60 psi) resulted in longer reaction times.

High diastereoselectivity (93−98% de) is achieved when a moderately bulky alkyl group resides on an 2-alkanone, e.g., cyclohexyl (**1a**), isopropyl (**1b**), or isobutyl (**1c**); see the corresponding amine products **2** (Table 1). Interestingly, even when a nondirecting straight chain alkyl group is present, e.g., as in 2-octanone (**1e**), the diastereoselectivity, while moderate (72% de, d.r. = 86:14), is high for the substrate under consideration. For all ketones examined, the (*R*,*R*)-**2** amine is the major diastereomer formed when (*R*)-α-MBA is employed. This was confirmed by comparison of the spectroscopic data obtained for the analytically pure major diastereomer[13] with that reported in the literature.[14]

The use of (*R*)- or (*S*)-α-MBA has previously been explored for the synthesis of α-chiral aliphatic amines.[5] The previous approaches have relied on first forming the corresponding *N*-α-methylbenzyl ketimine, isolating that chiral imine, and finally reducing it by a variety of methods. Of the few studies available for direct comparison, our system is far superior to the above two-step strategy. For example, when the (*R*)-α-methylbenzyl imine of ketone **1b** is reduced with $Zn(BH_4)_2$ in THF at 0 °C, a 48% overall yield of amine **2b** (from **1b**) is achieved in 66% de.[14b,15] Another study using $NaBH_4$ at −78 °C allowed a 78% overall yield of **2b** with 84% de.[5f] Our one-step method allows room-temperature synthesis of **2b** in 78% yield and 98% de.

Another relevant comparison can be made with the only other reported aliphatic asymmetric reductive amination study. Using the chiral ammonia equivalent (*S*)- or (*R*)-*tert*-butanesulfinamide, Ellman and co-workers have converted ketone **1b** to the chiral sulfinamide **4** in 66% yield and 94% de (Scheme 2).[6b] Similarly, he converted ketone **1c** to a chiral

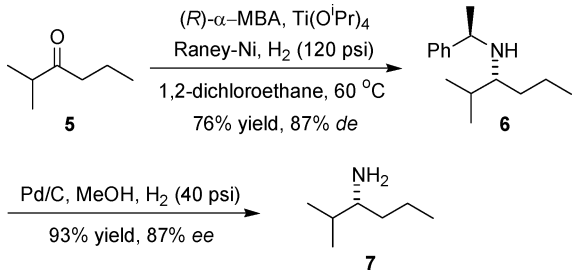
Scheme 2. Asymmetric Reductive Amination; Comparative Methods



sulfinamide product (74% yield, 84% de). Our de is higher in both instances (**1b**, 98% vs 94%; **1c**, 93% vs 84%). Additionally, the lower yield efficiency, much higher cost of the chiral ammonia equivalent (*S*)- or (*R*)-*tert*-butanesulfinamide, and low temperature (−48 °C) requirements of the Ellman method make our new method an attractive alternative.[6b,16] An additional reaction step allows **2b** or **4** to be converted to the corresponding enantioenriched primary amine **3a** (Scheme 1).

While the above ketones provided encouraging results (Table 1), all of the studied substrates were 2-alkanones. To investigate the scope of our new method further, we next examined the asymmetric reductive amination of 2-methyl-3-hexanone (**5**) (Scheme 3). This ketone is sterically con-

Scheme 3. Examination of a Sterically Hindered Ketone



gested, and under our standard reaction conditions no reaction occurred. When the reaction temperature was raised to 60 °C and the amount of $Ti(O^iPr)_4$ was increased to 2.0 equiv, only 6 area % (GC) of ketone (**5**) remained after 24 h and the amine product (**6**) was obtained in 87% de.

All previously discussed reactions were performed on a 2.5−5.0 mmol scale with Raney Ni loadings of 70−100 wt %. We then examined these reactions on a larger scale (30−40 mmol), with the expectation that lower Raney Ni catalyst loadings would be possible. Thus, for 5.00 g of 2-octanone (**1e**) the Raney Ni loading was reduced from 100 to 20 wt %. Additionally we used 97.0% (instead of 99.999%) grade $Ti(O^iPr)_4$.[12] The de remained consistent, but the reaction time lengthened from 6 to 17 h. Gratifyingly, an isolated yield of 90% was observed on scale-up. Note that no column chromatography is required. Simple acid−base extraction techniques followed by HCl salt formation are sufficient to obtain the diastereomeric product mixture in qualitative purity.

Ketone **5** proved to be more challenging on scale-up (30 mmol) than our small scale (2.5 mmol) screening reactions implied. To completely consume ketone **5** in the presence of 1.05 equiv of (*R*)-α-MBA, an 80 wt % loading of Raney

(13) In all instances the major amine diastereomer, (*R*,*R*)-**2**, could be isolated in analytically pure form using flash chromatography.

(14) For ketone **1a**, see: (a) Alvaro, G.; Savoia, D.; Valentinetti, M. R. *Tetrahedron* **1996**, *52*, 12571. For ketone **1b**, see: ref 5f and (b) Cimarelli, C.; Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 2555. For ketone **1c**, see: ref 6b and (c) Andres, C.; Nieto, J.; Pedrosa, R.; Villamanan, N. *J. Org. Chem.* **1996**, *61*, 4130. For ketone **1d**, see: refs 4c and 14b. For ketone **1e**, see: (d) Singaram, B.; Fuller, J. C.; Belisle, C. M.; Goralski, C. T. *Tetrahedron Lett.* **1994**, *35*, 5389.

(15) Reference 14b does not provide the yield for the imine step. Based on ref 5f it is assumed to be 85%.

(16) Ellman has extensively developed the use of (*R*)-(+)-*tert*-butanesulfinamide (2-methyl-2-propanesulfinamide) for the elegant synthesis of α-secondary (via sulfinyl aldimines) and α-tertiary (via sulfinyl ketimines) aliphatic chiral amines in high overall yield and ee in three synthetic steps from aldehydes and ketones, respectively; see: ref 4a and (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (b) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883.

Ni had to be employed in addition to increased $Ti(O^iPr)_4$ (3.0 equiv, 97% grade). The yield increased, 65% to 76%, and the de (87%) remained unchanged. In general it can be stated that on scale-up, we observed increased yields and consistent de but longer reaction times.

While high loadings of Raney Ni are not desirable, they are not uncommon and we found that greater loadings of Raney Ni have been used for large-scale pharmaceutical production.[17] For example, the key chiral building block of the Boehringer Ingelheim prostate drug Flomax is a prochiral aliphatic ketone that is reductively aminated with (*R*)-α-MBA. Depending on the conditions employed, turnover numbers (defined as millimole of ketone per gram of Raney Ni) of 6.7 and 8.0 are calculated.[17b] Economically, this is tolerable because Raney Ni and heterogeneous catalysts in general are low in cost compared to homogeneous catalysts, easy to handle, simple to remove, and regenerated after use by the pharmaceutical industry.[1a,18] For the two ketones that we scaled up, 2-methyl-3-hexanone (**5**) and 2-octanone (**1e**), the respective turnover numbers are 11 and 39.

Finally, knowing that (*R*)-α-MBA and simple aliphatic amines have known racemization pathways,[17g,19] we cleaved the chiral auxiliary from secondary amine **2d** and isolated the primary amine **3d** (88% yield) with the same ee (80% ee, chiral GC analysis of trifluoroacetamide derivative, see Supporting Information) as the previously observed de for amine **2d**. More interesting to us was the cleavage of the chiral auxiliary from secondary amine **6**, which was formed under the harsher reaction conditions of 60 °C. Gratifyingly, the corresponding primary amine **7** (93% yield) exhibited the same ee as the de (87%) installed during the reductive amination step for ketone **5** (Scheme 3).

In summary, we have developed a two-step method capable of producing enantioenriched aliphatic amines from prochiral aliphatic ketones in high overall yield. The previously unexplored reagent combination of $Ti(O^iPr)_4$/Raney Ni/H_2 for asymmetric reductive amination has made this breakthrough possible. Finally, access to either enantiomeric form of aliphatic primary amines is possible, all required reagents are inexpensive, and the reactions are amenable to scale up.

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

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(17) A brief examination of the Raney Ni literature revealed that catalyst loadings vary widely for both imine reduction and reductive amination protocols. The following turnover numbers (defined as millimole of starting substrate per gram of Raney Ni) were calculated: 4.9, 6.7 and 8, 20, 25, 29, 75, 80; see the respective references. It should be noted that the very good turnover numbers, 75 and 80, required a large excess of amine or ketone, and at room temperature 5 d were required for full reaction, while at 80 °C fast reactions occurred. (a) Huffmann, M. A.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 831. (b) Process for producing optically active benzene-sulfonamide derivatives. Okado, M.; Oshida, K. Y.; Takanobu, K.; Yamanouchi Pharmaceutical Co, Ltd., Japan. Patent IE63344, 1995. (c) Bringmann, G.; Geisler, J.-P. *Synthesis* **1989**, 608. (d) See ref 5c. (e) See ref 5a. (f) Clifton, J. E.; Collins, I.; Hallett, P.; Hartley, D.; Lunts, L. H. C.; Wicks, P. D. *J. Med. Chem.* **1982**, *25*, 670. (g) Hirayama, Y.; Ikunaka, M.; Matsumoto, J. *Org. Process Res. Dev.* **2005**, *9*, 30.

(18) (a) Kukula, P.; Prins, R. *Top. Catal.* **2003**, *25*, 29. (b) Török, B.; Prakash, G. K. S. *Adv. Synth. Catal.* **2003**, *345*, 165.

(19) Murahashi, S.-I.; Noriaki, Y.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002.