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A Direct and Versatile Access to α,α-Disubstituted 2-Pyrrolidinylmethanols by SmI_2-Mediated Reductive Coupling

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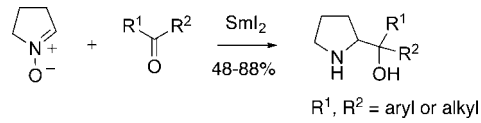
ABSTRACT



Various α,α-disubstituted 2-pyrrolidinylmethanols are efficiently prepared in a single step from ketones using a SmI_2-mediated cross-coupling with 1-pyrroline *N*-oxide. The *N*-hydroxy-α,α-diphenylprolinol is also easily prepared and resolved.

Enantiopure proline-derived molecules are widely used as the source of chirality in enantioselective catalysis.[1] Among them, α,α-diphenyl-2-pyrrolidinylmethanol (DPP, Figure 1)

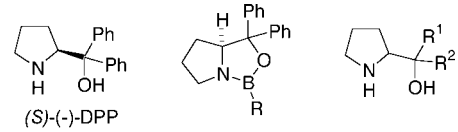


Figure 1. DPP and α,α-disubstituted 2-pyrrolidinylmethanols.

was initially introduced for the preparation of oxazaborolidines, as catalysts for CBS enantioselective reduction of ketones.[2] More recently, α,α-disubstituted 2-pyrrolidinylmethanols and their derivatives have found new and promising applications as organocatalysts for different asymmetric transformations.[1,3]

In general, these compounds have been prepared from naturally occurring l-proline, using double Grignard additions.[4] However, this pathway is limited to structures where $R^1 = R^2$ (Figure 1).

Alternatively, DPP has been prepared by asymmetric deprotonation of *N*-Boc-pyrrolidine, followed by addition onto benzophenone.[5] A general method that would allow the synthesis of both symmetrically ($R^1 = R^2$) and nonsym-

(1) (a) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (c) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.

(2) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(3) (a) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 545. (b) Trost, B. M.; Müller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438. (c) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082. (d) Chu, Q.; Yu, M. S.; Curran, D. P. *Org. Lett.* **2008**, *10*, 749. (e) Balskus, E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736. (f) Aleman, J.; Cabrera, S.; Maerten, E.; Overgaard, J.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5520. (g) Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 12686. (h) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

(4) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751.

(5) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231. For other examples of synthesis of α,α-disubstituted 2-pyrrolidinylmethanols from reaction of 2-lithiopyrrolidines with symmetrical ketones or aldehydes, see also: (a) Reitz, D. B.; Beak, P.; Tse, A. *J. Org. Chem.* **1981**, *46*, 4316. (b) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763. (c) Bertini Gross, K. M.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315. (d) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Patel, J. J.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2006**, *128*, 10943.

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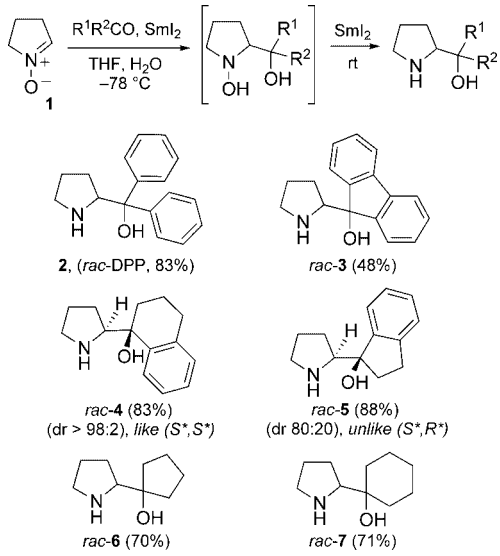
metrically ($R^1 \neq R^2$) α,α-disubstituted 2-pyrrolidinylmethanols would be valuable.

Since its introduction by Kagan, SmI_2 has become one of the most popular and versatile reagents for single-electron tranfers.[6] A few years ago, we reported the chemoselective cross-coupling of nitrones with carbonyl compounds in the presence of SmI_2. This reaction produces vicinal *N*-hydroxyamino alcohols in excellent yields.[7] We thus thought that the coupling of nitrone **1** with various ketones under these reductive conditions would give access to novel α,α-diphenyl-2-pyrrolidinylmethanols (Scheme 1).

Scheme 1. Synthesis of α,α-Disubstituted 2-Pyrrolidinylmethanols **2**−**7** by Reductive Coupling of Nitrone **1** with Various Ketones



A requisite to this synthesis was an efficient preparation of the 1-pyrroline *N*-oxide (**1**) by oxidation of pyrrolidine. This was best achieved using the UHP−MTO system.[8] Nitrone **1** was found to be quite unstable, but it could be stored for several days as a 0.5 M solution in THF at 5 °C under an inert atmosphere.

When a mixture of nitrone **1** and an aromatic ketone (benzophenone, fluorenone, tetralone, or indanone) in THF was treated at −78 °C with 2.2 equiv of SmI_2, the intermediate vicinal *N*-hydroxyamino alcohol was obtained within 15 min (Scheme 1).

At this stage, addition of excess SmI_2 and degassed water allowed in situ reduction of the hydroxylamine.[9] After 1 h at room temperature, workup provided directly β-amino alcohols **2**,[10] **3**, **4**,[11] and **5** in moderate to good yields (Scheme 1).[12] When aliphatic ketones (cyclopentanone and cyclohexanone) were used, the addition of 10 equiv of water during the coupling step was necessary for obtaining products **6**[13] and **7**[13] in good yields.

Thus, this reaction provides a direct access to various racemic α,α-disubstituted 2-pyrrolidinylmethanols in two steps from pyrrolidine and aromatic or aliphatic ketones. Convenient methods for the resolution of **2** using enantiopure *O*-acetylmandelic acid[10] or 1,1′-bi-2-naphthol and boric acid[14] have been previously described.

This synthetic pathway obviously allows easy access to original structures: compounds **3** and **5** have been prepared here for the first time.

Particularly noteworthy is the high degree of diastereoselectivity obtained in the reaction of tetralone (product **4**: a single isomer was detected by ^{1}H and ^{13}C NMR) and indanone (product **5**: dr 80/20). This prompted us to determine the relative configurations of **4** and **5** (major isomer) by X-ray crystallographic analysis of their iodhydrates[15] (Figure 2).

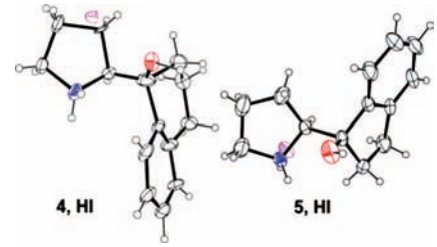


Figure 2. ORTEP drawings of **4**,HI and **5**,HI.

We were surprised to find that although product **4** exhibits a *like* (*S**,*S**)[16] configuration, the major diastereoisomer of **5** was *unlike*. This result is difficult to rationalize at this stage;

(6) Kagan, H.; Namy, J. L.; Girard, P. *Tetrahedron Suppl.* **1981**, *37*, 175. For reviews, see: (a) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (b) Kagan, H. *Tetrahedron* **2003**, *59*, 10351. (c) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (d) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

(7) Masson, G.; Py, S.; Vallee, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1772.

(8) (a) Goti, A.; Cardona, F.; Soldaini, G. *Org. Synth.* **2005**, *81*, 204. (b) Goti, A.; Nannelli, L. *Tetrahedron Lett.* **1996**, *37*, 6025. (c) Murray, R. W.; Iyanar, K.; Chen, J.; Wearing, J. T. *J. Org. Chem.* **1996**, *61*, 8099.

(9) Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991**, *32*, 1699.

(10) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

(11) Seebach, D.; Wykypiel, W. *Synthesis* **1979**, *6*, 423.

(12) General Procedure for the Synthesis of α,α-Disubstituted 2-Pyrrolidinylmethanols **2**−**7**. Method A (for aromatic ketones): To a stirred and carefully deoxygenated solution of the nitrone **1** (60 mg, 0.7 mmol) and aromatic ketone (0.5 mmol) in dry THF was added a 0.1 M solution of SmI_2 (11.0 mL, 1.1 mmol) at −78 °C under argon. After 15 min, degassed water (36 μL, 2.0 mmol) and SmI_2 (14.0 mL, 1.4 mmol) were added, and the reaction mixture was allowed to reach room temperature. After 1 h, a saturated solution of $Na_2S_2O_3$ (5 mL) and 1 M NaOH solution (15 mL) were added, and the mixture was extracted with EtOAc (20 mL). Usual workup yielded racemic products **2**−**5**. Method B (for aliphatic ketones): Same procedure as for method A, but degassed water (90 μL, 5.0 mmol) was added at the beginning of the reaction (products **6** and **7**).

(13) Reiners, I.; Wilken, J.; Martens, J. *Tetrahedron: Asymmetry* **1995**, *6*, 3063.

(14) Periasamy, M.; Kumar, N. S.; Sivakumar, S.; Rao, V. D.; Ramanathan, C. R.; Venkatraman, L. *J. Org. Chem.* **2001**, *66*, 3828, and references therein.

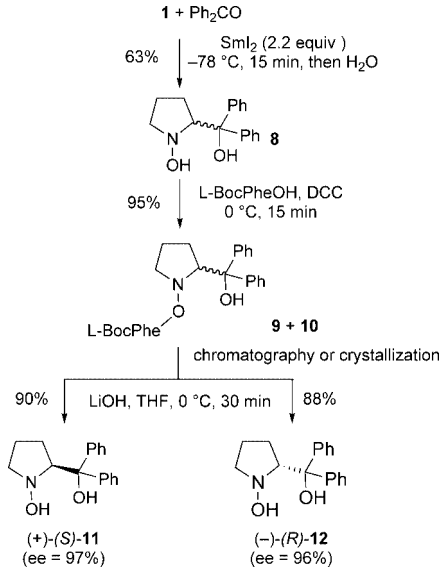
(15) Those were easily obtained by neutral (instead of basic) hydrolysis of the SmI_2 reaction mixture; see the Supporting Information.

(16) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed.* **1982**, *21*, 654.

similar inversion of stereoselectivities in SmI_2-mediated reactions have been previously observed by other groups.[17]

Although the in situ reduction of the hydroxylamine intermediate was expeditious, SmI_2-mediated cross-coupling of nitrones and carbonyl compounds is also an excellent pathway to the *N*-hydroxypyrrolidinylcarbinols. To illustrate this point, we undertook the synthesis and resolution of *N*-hydroxy-α,α-diphenyl-2-pyrrolidinylmethanol **8** (Scheme 2).

Scheme 2. Synthesis and Resolution of Optically Pure (*S*)- and (*R*)-*N*-Hydroxy-α,α-diphenyl-2-pyrrolidinylmethanol



When a mixture of nitrone **1** and benzophenone in THF was treated at −78 °C with 2.2 equiv of SmI_2 and then quenched at this temperature, the expected racemic **8** was isolated in 63% yield. We took advantage of the reactivity of the hydroxylamine group to use it as a handle for an original resolution of the racemate. The relatively unhindered hydroxylamine group was easily *O*-acylated with (*S*)-*N*-Boc-l-phenylalanine in high yield (Scheme 2). The resulting diastereomers **9** and **10** could be separated by either chromatography or crystallization. At this stage, the relative configuration of **10** was determined by X-ray analysis,[18] and its absolute configuration was deduced to be (*S*,*R*). The saponification of **9** and **10** was also easy, leading, respectively, to (+)-(*S*)-**11** (90% yield, 97% ee) and (−)-(*R*)-**12** (88% yield, 96% ee).[19]

For confirmation, a sample of (+)-(*S*)-**11** was reduced by SmI_2, yielding a levorotatory product identical to authentic (−)-(*S*)-DPP.

In conclusion, the SmI_2-mediated cross-coupling of 1-pyrroline *N*-oxide and diaryl, monoaryl, or dialkyl ketones provides a very short and versatile route to α,α-disubstituted 2-pyrrolidinylmethanols. When prochiral ketones are used, high diastereoselectivities can be attained. Thus, unsual chiral prolinol derivatives are now readily accessible, which should find interesting applications as rigid organocatalysts or, more generally, in enantioselective catalysis.

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Supporting Information Available: Detailed experimental procedures and complete characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) See for examples: (a) Aspinall, H. C.; Greeves, N.; Valla, C. *Org. Lett.* **2005**, *7*, 1919. (b) Chiara, J. L.; Garcia, A. *Synlett* **2005**, 2607.

(18) See the Supporting Information.

(19) Determined by chiral HPLC on a Daicel Chiralpak AD-RH column, acetonitrile/water; see the Supporting Information.