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Amination of Grignard Reagents with Retention of Configuration†

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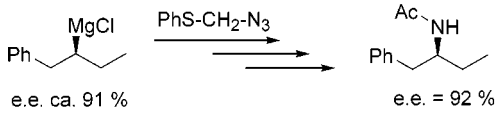
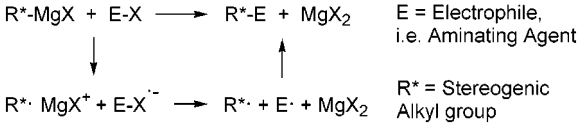
ABSTRACT



The stereochemistry of electrophilic amination has been probed using the chiral Grignard reagent 5, in which the magnesium-bearing carbon atom is the sole stereogenic center. Amination with azidomethyl phenyl sulfide 1 and with *O*-sulfonyloxime 2 were found to proceed with full retention of configuration.

The formation of carbon−nitrogen bonds by electrophilic amination of carbanions[1] is slowly gaining importance in stereoselective synthesis.[2] Stereodifferentiation is usually reached by stereogenic centers in the carbanionic moiety. The stereochemistry of the amination step itself has, however, not been addressed. We saw an opportunity to do this after we succeeded in generating a chiral secondary Grignard reagent (Scheme 1), in which the magnesium-bearing carbon atom is the sole stereogenic center.[3] Since amination of a carbanion is formally an oxidation reaction, the mechanism of amination and, hence, its stereochemical course is not a priori clear. Amination could proceed for one by a polar addition route, which should be characterized by retention of configuration at the stereogenic center. Amination could also proceed in a stepwise manner, initiated by a SET-process followed by bond formation within a radical pair, a process likely to result in racemic products.[3,4]

Scheme 1



We therefore set out to study the stereochemistry of electrophilic amination reactions in order to gain mechanistic information, important for application in stereoselective synthesis. We were limited, though, in the choice of the aminating reagents we could test by the configurational lability of our chiral Grignard reagent **5**. It racemizes with a half-life of ca. 5 h at −10 °C in the reaction cocktail it is generated in.[3] Valid stereochemical results would therefore have to rely on aminating reagents which react with Grignard reagents at temperatures below −50 °C. This condition is met by azidomethyl phenyl sulfide (**1**), an aminating reagent introduced by B. M. Trost,[5] the *O*-sulfonyloxime **2** described by Narasaka,[6] and the azodicarboxylates **3**,[7] all aminating

† Dedicated to Professor David A. Evans on the occasion of his 60th birthday.

(1) (a) *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000. (b) Dembech, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281−1286. (c) Greck, C.; Genèt, J. P. *Synlett* **1997**, 741−748. (d) Krohn, K. Electrophilic Aminations. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H. J., Braun, M., Krohn, K., Reissig, H. U., Eds.; VCH: Weinheim, 1991; pp 45−53. (e) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947−1980.

(2) Boche, G. Electrophilic Amination. In *Houben-Weyl, Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E 21 e; pp 5133−5157.

(3) Hoffmann, R. W.; Hölzer, B.; Knopff, O.; Harms, K. *Angew. Chem.* **2000**, *112*, 3206−3207; *Angew. Chem., Int. Ed.* **2000**, *39*, 3072−3074.

(4) Hoffmann, R. W.; Hölzer, B. *Chem. Commun.* **2001**, 491−492.

(5) Trost, B. M.; Pearson, W. H. *J. Am. Chem. Soc.* **1983**, *105*, 1054−1056.

(6) Tsutsui, H.; Ichikawa, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1869−1878.

(7) Carpino. L. A.; Terry, P. H.; Crowley, P. J. *J. Org. Chem.* **1961**, *26*, 4336−4340.

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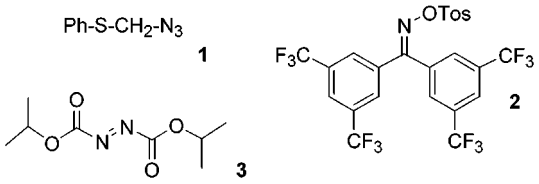
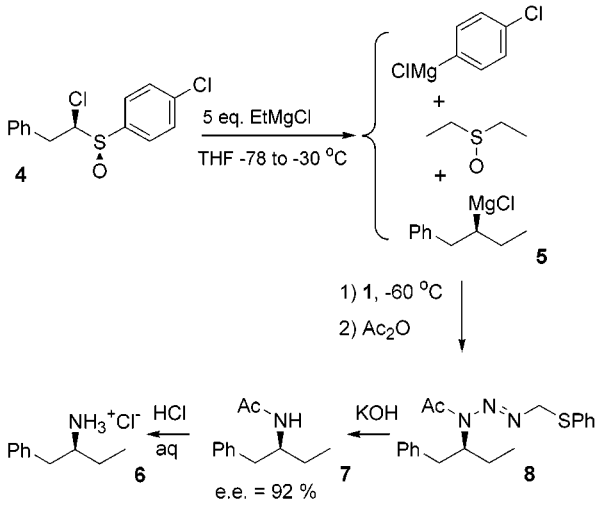
Scheme 2



agents with an sp^2-hybridized nitrogen atom as reaction center (Scheme 2). The Grignard reagent **5** was generated by reaction of the enantiomerically pure α-chlorosulfoxide **4** with 5 equiv of ethylmagnesium chloride at −78 to −30 °C (Scheme 3). The mixture was cooled to −78 °C, and the

Scheme 3



reagent **1** was added. The mixture was allowed to reach −60 °C and was subsequently quenched with acetic anhydride.

The crude acetyltriazene **8** obtained was cleaved with KOH to give the acetamide **7** in 82% overall yield. Its enantiomeric purity was established as 92% by HPLC analysis on a chiral column. When the reaction sequence was repeated using 10 equiv of ethylmagnesium chloride,[8] the ee of **7** could be raised to 95%, indicating that the enantiomeric excess of **7** likely reflects the enantiomeric excess of the Grignard reagent **5**.

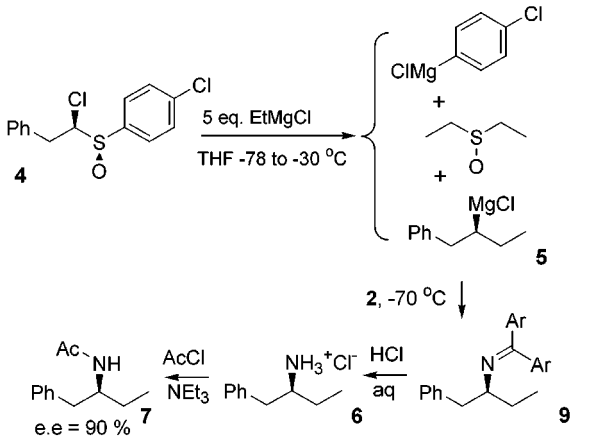
Treatment of the amide **7** with aqueous hydrochloric acid converted it to ammonium salt **6**. Its positive rotation, $[\alpha]^{23}_{D} = +30.0$ ($c = 1.00$, H_2O), corresponds to that reported for the (*S*)-enantiomer.[9] These results establish that the amination of the secondary Grignard reagent **5** by **1** occurred with (practically complete) retention of configuration at carbon.[10] A polar reaction pathway is the simplest explanation for these findings.

(8) A high concentration of ethylmagnesium chloride speeds up the substitution at the α-chloroalkylmagnesium intermediate, which undergoes a competing racemization at −50 °C.[3]

(9) Paulsen-Sörman, U. B.; Jönsson, K.-H.; Lindeke, B. G. A. *J. Med. Chem.* **1984**, *27*, 342−346.

Next we turned to amination with the *O*-sulfonyloxime **2**. Amination of Grignard reagents with **2** have been reported to give higher yields in weakly coordinating solvents, such as diethyl ether or toluene, than in THF. We therefore generated **5** by reaction of **4** with 5 equiv of ethylmagnesium chloride in 2:1 Et_2O/toluene at −78 to −30 °C. (Scheme 4).

Scheme 4



Treatment with the *O*-sulfonyloxime **2** was carried out for 10 d at −70 °C. The resulting imine **9** was cleaved by aqueous hydrochloric acid to give **6** which was acetylated to **7** in order to determine the enantiomeric purity. HPLC analysis showed that the (*S*)-isomer of **7** was obtained in 90% ee.

Amination of **5** by **2** is very slow at −70 °C. This is reflected in a low conversion and corresponding low overall yield (25%). Raising the temperature to −50 °C led after 10 d to 33% of **7** of 85% ee. The lower enantiomeric purity reflects competing racemization of the Grignard reagent **5**. Nevertheless, our results likewise suggest that the amination of **5** by **2** is also a polar process that occurs with retention of configuration.

Last, we tested the reaction of **5** with diisopropyl azodicarboxylate **3**. Previously, an exploratory experiment with racemic **5** (generated from racemic **4** in THF) showed that the reaction with **3** did not lead to the expected amination product **10**. Rather, the reaction deviated to furnish **11** (82%) and an equivalent amount of **12**, compounds identified by their NMR data (Scheme 5).[11,12]

The alkene **11** is formally a product of an atom transfer reaction between **5** and **3**,[13] similar to a diimide reduction. Evidence has been given that such products do not arise via a concerted process, cf. **13**, but rather via a SET sequence,[13] favored by the high oxidation potential of **3** (−0.63V vs Ag/

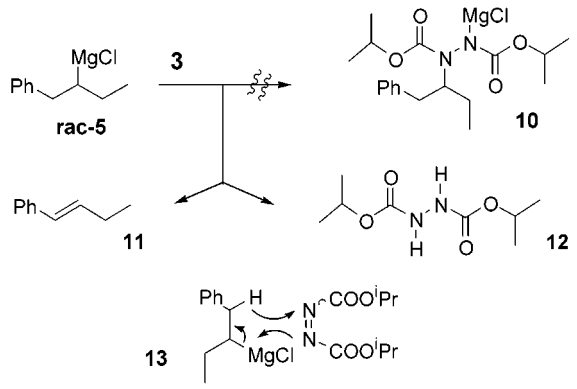
(10) A referee drew our attention to the Ph.D. Thesis of William H. Pearson, University of Wisconsin, 1982. This thesis contains data which document that the amination of norbornyl-MgBr and of a cyclopropyl-MgBr by **1** proceed with retention of configuration.

(11) Bessmertnykh, A. G.; Blinov, K. A.; Grishin, Y. K.; Donskaya, N. A.; Tveritinova, E. V.; Yur'eva, N. M.; Beletskaya, I. P. *J. Org. Chem.* **1997**, *62*, 2, 6069−6076.

(12) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967−2971.

(13) Holm, J.; Crossland, J. *Acta Chem. Scand. B* **1979**, *33*, 421−428.

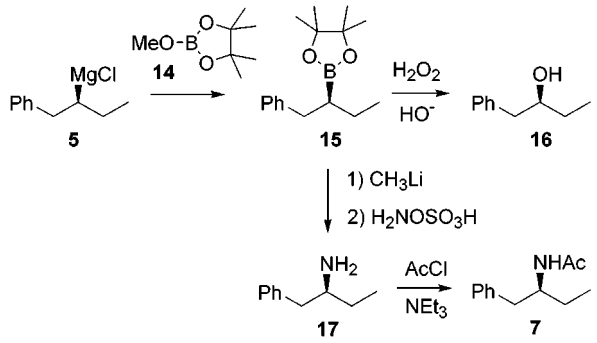
Scheme 5



AgCl in CH_3CN,[14] which is 1.2 V more positive than that of benzophenone[15]).

Amination of organomagnesium compounds can also be attained in an indirect manner, by first transmetalating to boron followed by subsequent conversion of the carbon−boron bond into a carbon−nitrogen bond. We examined this case as well for the Grignard reagent **5** (Scheme 6). Reaction

Scheme 6



of the Grignard with the mixed borate ester **14**[16] to give boronate **15** was followed by an oxidative workup, to check the stereochemistry of the borylation reaction. This led to 90% of the alcohol **16**, which was obtained as the (*S*)-enantiomer of 89% ee (by HPLC).[3] Therefore, transmetalation of **5** to **15** occurred—not unexpectedly—with full retention of configuration. This finding can be used to complete the indirect amination of **5** to **17**: As alkylboronates do not react well with hydroxylamine-*O*-sulfonic acid, we followed the procedure of H. C. Brown[17] and treated **15** first with 1 equiv of CH_3Li before adding hydroxylamine-*O*-sulfonic acid. This furnished the amine **17**, which was acetylated to the familiar amide **7**. Again the (*S*)-enantiomer was obtained with an ee of 90%. The overall yield from the sulfoxide **4** to the amide **7** amounted to 69%.[18]

The understanding of the mechanisms of reactions of organometallic compounds is key to their proper application in stereoselective synthesis. With this study we have gained information about the electrophilic amination of Grignard reagents by the azide **1** or the *O*-sulfonyloxime **2**. The

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(15) Magdesieva, T. V.; Kukhareva, I. I.; Shaposhnikova, E. N.; Artamkina, G. A.; Beletskaya, I. P.; Butin, K. P. *J. Organomet. Chem.* **1996**, *526*, 51−58.

(16) Finch, A.; Gardner, P. J.; Pearn, E. J. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1314−1324.

(17) Brown, H. C.; Kim, K.-W.; Cole, T. E.; Singaram, B. *J. Am. Chem. Soc.* **1986**, *108*, 6761−6764.

(18) **Experimental details: (*N*)-(1-Phenyl-2-butyl)acetamide (7). (1) Amination with 1:** Ethylmagnesium chloride (1.78 M in THF, 0.56 mL, 1.00 mmol) was added dropwise at −78 °C into a precooled solution of the sulfoxide **4**[19] (99% de, 99% ee, 60 mg, 0.20 mmol) in THF (0.30 mL). The solution was allowed to reach −30 °C over 1.5 h. Azidomethyl phenyl sulfide (**1**) (377 μL 4.00 mmol) was added, and the yellow-greenish mixture was stirred for 1 h at −78 °C. The temperature was allowed to reach −60 °C, and acetic anhydride (566 μL 6.00 mmol) was added. After being stirred for 1 h at −30 °C, a saturated aqueous NH_4Cl solution (5 mL) and ether (5 mL) were added. The phases were separated, and the aqueous phase was extracted with ether (2 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was taken up in DMSO (1.0 mL). Potassium hydroxide (315 mg, 5.60 mmol) was added at 0 °C, resulting in a vigorous evolution of gas. After being stirred for 3 h at room temperature, a saturated aqueous NH_4Cl solution (5 mL) and ether (5 mL) were added. The phases were separated, and the aqueous phase was extracted with ether (2 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography over silica gel with dichloromethane followed by dichloromethane/methanol = 97:3 furnished **7** (31 mg, 82%) as a colorless solid of mp 70 °C: $[\alpha]^{23}_D = -1.2$ ($c = 5.0$, methanol). The total fraction obtained was taken up in heptane/2-propanol 97:3, analyzing for an ee of 92% by HPLC. **(2) Amination with 2:** A solution of the sulfoxide **4**[19] (99% de, 99% ee, 60 mg, 0.20 mmol) in anhydrous toluene (0.30 mL) was added dropwise to a precooled (−78 °C) solution of ethylmagnesium chloride (1.81 M in diethyl ether, 0.55 mL, 1.00 mmol). The mixture was allowed to reach −30 °C over 1.5 h. A solution of **2**[6] (1.50 g, 2.40 mmol) in toluene (3 mL) was added. After being stirred for 10 d at −70 °C, an aqueous pH 9 buffer solution (5 mL) was added and the mixture was allowed to reach room temperature. The phases were separated, and the aqueous phase was extracted with ether (2 × 5 mL). The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (5 mL), dried (Na_2SO_4), and concentrated. The residue was taken up in acetone (8 mL) and water (2 mL). Aqueous hydrochloric acid (1 M, 1.60 mL) was added, and the mixture was stirred for 30 min at room temperature. The mixture was cooled to 0 °C, triethylamine (440 μL, 3.20 mmol) and then acetyl chloride (114 μL, 1.60 mmol) were added dropwise, and the solution was stirred for 30 min at room temperature. Water (5 mL) and ether (5 mL) were added. The phases were separated, and the aqueous phase was extracted with ether (2 × 5 mL). The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (2 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated. Flash chromatography as before furnished **7** (9.6 mg, 25%) as a colorless solid of mp 68 °C. HPLC analyses as above indicated an enantiomeric excess of 90%. **(3) Indirect amination via 15:** A solution of the Grignard reagent **5** was prepared as described under (1). The mixed borate **14**[16] (126 mg, 0.89 mmol) was added at −78 °C, and the solution was allowed to reach rt over 2.5 h. Water (4 mL) was added, the phases were separated, and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was taken up in anhydrous ether (1.6 mL) and cooled to −78 °C. A solution of methyllithium in ether (2.28 M, 0.42 mL, 0.96 mmol) was added, and after 3 h of stirring acetyl chloride (68 μL, 0.96 mmol). After reaching rt, the mixture was concentrated. Pentane (1 mL) was added and the mixture was filtered. The solid was washed with pentane (2 × 1 mL), and the combined filtrates were concentrated. The residue was taken up in THF (1.0 mL), hydroxylamine-*O*-sulfonic acid (181 mg, 1.60 mmol) was added, and the suspension was stirred for 20 h. The suspension was partitioned between water (5 mL) and ether (5 mL), and the phases were separated. Triethylamine (0.33 mL, 2.4 mmol) was added at 0 °C to the aqueous phase. After reaching rt, acetyl chloride (114 μL, 1.60 mmol) was added and the solution was stirred for 30 min at rt. The mixture was partitioned between water (5 mL) and ether (5 mL), the phases were separated, and the aqueous phase was extracted with ether (2 × 5 mL). The combined organic phases were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. Chromatography as under (1) furnished **7** (26 mg, 69%) of 90% ee.

(19) Hoffmann, R. W.; Nell, P. G. *Angew. Chem.* **1999**, *111*, 354−355; *Angew. Chem., Int. Ed.* **1999**, *38*, 338−340. Hoffmann, R. W.; Nell, P. G.; Leo, R.; Harms, K. *Chem. Eur. J.* **2000**, *6*, 3359−3365.

stereochemistry of these reactions is best accounted for by a polar (addition) process and not via an SET reaction cascade.

Acknowledgment. We thank Prof. Narasaka (Tokyo) for kindly carrying out exploratory experiments to demonstrate that amination of Grignard reagents by **2** can also be carried out in the absence of copper catalysts at temperatures below −35 °C. We are grateful to the Deutsche Forschungsgemeinschaft (SFB 260) and the Graduierten-Kolleg "Metallorganische Chemie" for generous support of this study.

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