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New and easy route to primary cyclopropylamines from nitriles

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Starting from readily available substrates, we have developed a new synthesis of primary cyclopropylamines. The reaction involves a cooperative Ti(II)- and Lewis acid-mediated coupling of alkanenitriles with Grignard reagents.

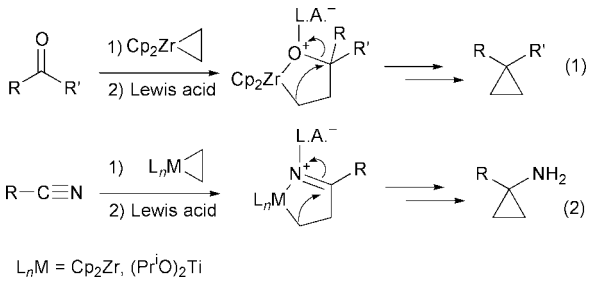
Cyclopropylamines are not only versatile synthetic intermediates,[1] but also a variety of biologically active molecules contain a cyclopropylamine moiety.[2] Yet, a few synthetic methods that allow preparation of these important compounds[1,3] often require multi-step reactions. Among the available methods, the recent de Meijere adaptation[4] of the Kulinkovich hydroxycyclopropanation[5] presents a useful synthesis of *N*,*N*-dialkylcyclopropylamines from *N*,*N*-dialkylcarboxamides and Grignard reagents in the presence of $Ti(OPr^i)_4$ or $MeTi(OPr^i)_3$. Here we disclose that primary cyclopropylamines may be easily obtained in one step by a Ti(II)-mediated coupling of Grignard reagents with alkanenitriles.

The idea of transforming nitriles to cyclopropylamines directly was initially based on our recent approach to cyclopropanes from carbonyl compounds *via* Cp_2Zr chemistry.[6] This reaction involves a deoxygenative contraction of an intermediate oxazirconacycle into a carbocycle under Lewis acid activation conditions [Scheme 1, eqn. (1)]. We envisioned that, in an analogous way, nitriles might be converted to cyclopropylamines following eqn. (2).

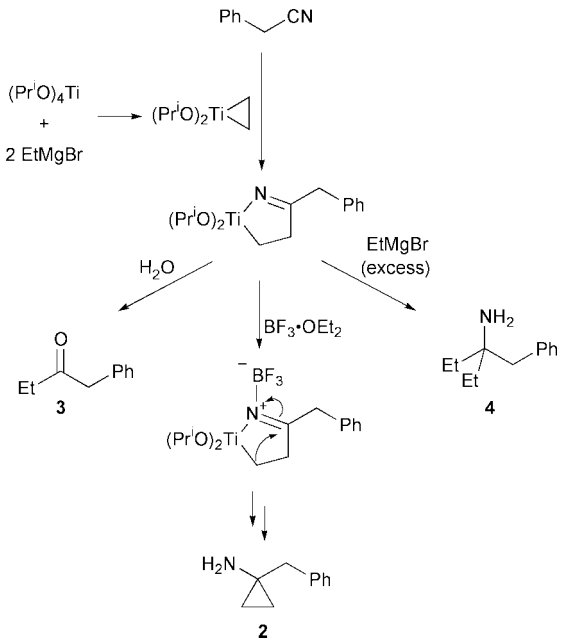
However, attempts to perform the reaction by using Cp_2Zr(ethylene) invariably led to complex reaction mixtures. Therefore, we investigated the feasibility of the reaction using the *in situ* formed (ethylene)$Ti(OPr^i)_2$[4,5] instead of (ethylene)zirconocene. We noticed that cyclopropylamines were formed by combining the use of this reagent with the subsequent addition of a Lewis acid, $BF_3{\cdot}OEt_2$ or $TiCl_4$. After optimizing the reaction conditions, synthetically useful yields were obtained. In a representative procedure, to a solution of benzyl cyanide (1 eq.) and $Ti(OPr^i)_4$ (1.1 eq.) in Et_2O was slowly added at rt EtMgBr (2 eq., 1 M solution in ether). After stirring for 1 h, $BF_3{\cdot}OEt_2$ (2 eq.) was added, and the reaction mixture further stirred for 0.5 h at rt. Finally, basic workup (10% NaOH aq) followed by extraction with ether and flash chromatography purification afforded (1-benzyl)cyclopropylamine (**2**) in 70% yield.

The following additional observations gave an insight into the reaction: (i) $BF_3{\cdot}OEt_2$ and $TiCl_4$ gave rise to similar results. (ii) The yields of **2** in the reactions employing $BF_3{\cdot}OEt_2$ were similar in THF and in Et_2O. (iii) Cyclopropylamine **2** was also formed in the absence of the additional Lewis acid, however, in this case, the yields were markedly lower in Et_2O (31%) and negligible in THF (7%); in these reactions benzyl ethyl ketone (**3**) was the major product formed (60% yield in Et_2O and 70% yield in THF). (iv) When using more than 2 eq. of EtMgBr the yield of **2** decreased significantly to detriment of the tertiary carbinamine **4**, which was obtained solely in 67% yield with 4 eq. of EtMgBr. (v) Lowering the quantity of $Ti(OPr^i)_4$ below 1 eq. decreased the yield of **2** to the detriment of **3** and **4**.

The competing reactions to afford compounds **2**, **3** and **4** are summarized in Scheme 2. In accordance with our initial hypothesis, and by analogy with the cyclopropanation of carbonyl compounds,[6] the Lewis acid plays a crucial role for the ring contraction leading to cyclopropane **2**. The reaction differs to that of the Kulinkovich and de Meijere reactions, in which the ring contraction occurs in the absence of an additional Lewis acid, spontaneously from the intermediate oxatitanacycle. In our reaction, in the absence of $BF_3{\cdot}OEt_2$ the intermediate azatitanacycle (cyclic titanium iminate) remains unchanged to furnish the ketone **3** on hydrolysis. The minor formation of **2** in this case can be explained by assuming that weak acid species always present in solution (Mg, Ti) operate, to a significantly lower degree, however, in the more coordinating THF (7% yield of **2**) than in the less coordinating Et_2O (31% yield of **2**). In contrast, when a strong Lewis acid is used, the cyclopropanation step proceeds efficiently (70% yield) in both solvents. The competing formation of **4** also deserves some comments. It is known that simple nitriles do not undergo double alkylation by alkyl Grignard reagents.[7] In contrast, the attack of a second equivalent of EtMgBr on the C atom of the titanium iminate (Scheme 2) would be an efficient process. This reaction possibly opens a simple, general way to tertiary carbinamines.



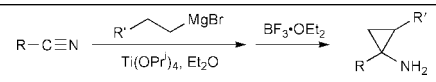
Scheme 1

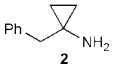
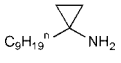
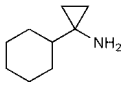
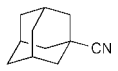
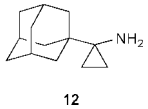
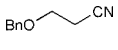
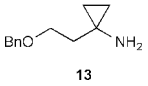
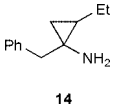
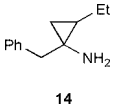
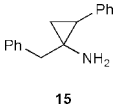
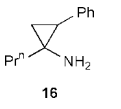


Scheme 2

 DOI: 10.1039/b105293b

Table 1 Reaction of nitriles with Grignard reagents promoted by $Ti(OPr^i)_4$ and $BF_3{\cdot}OEt_2$



Entry	Nitrile	R′-$(CH_2)_2$-MgBr	Product	Yield[a] (%)
1	 **1**	Et-MgBr	 **2**	70
2	 **5**	Et-MgBr	 **10**	70
3	 **6**	Et-MgBr	 **11**	52
4	 **7**	Et-MgBr	 **12**	53
5	 **8**	Et-MgBr	 **13**	54
6	 **1**	Bu^n-MgBr	 **14**	57 (64:36)[b]
7	 **1**	Bu^s-MgBr	 **14**	54 (55:45)[b]
8	 **1**	Ph$(CH_2)_2$-MgBr	 **15**	51 (68:32)[b]
9	 **9**	Ph$(CH_2)_2$-MgBr	 **16**	54 (68:32)[b]

[a] Yields of isolated products. [b] Mixture of diastereomers.

Furthermore, since an excess of EtMgBr strongly favours the dialkylation over the cyclopropanation reaction, the nucleophilic attack of a Grignard reagent on titanium seems not to be determining the ring contraction.[8]

To further explore the scope of the cyclopropanation reaction we tested other nitriles and Grignard reagents under the optimized reaction conditions. As shown in Table 1, the reaction employing EtMgBr proceeded smoothly from different alkanenitriles to afford the corresponding cyclopropylamines in moderate to good yields (entries 1–5). Both acyclic and cyclic nitriles were used. Particularly, the reaction took place starting from the sterically crowded adamantane-1-carbonitrile (**7**) (entry 4), and the nitrile **8** having the benzyloxy group (entry 5). Benzonitrile and acrylonitrile did not afford the corresponding cyclopropylamines under the conditions used here. The reactions employing other Grignard reagents, namely Bu^{n}MgBr, Bu^{s}MgBr and $PhCH_2CH_2MgBr$, could also be accomplished leading to 1,2-disubstituted cyclopropylamines **14**, **15** and **16** (entries 6–9). Interestingly, starting from the isomeric Grignard reagents Bu^{n}MgBr and Bu^{s}MgBr, the same compound **14** was formed solely (entries 6 and 7). A unique reaction pathway through (but-1-ene)$Ti(OPr^i)_2$ accounts for the totally regioselective formation of **14**. In all cases, a moderate diastereoselectivity of about 2:1 was observed.[9] The very easy separation by flash chromatography of diastereomeric primary cyclopropylamines (**14**, **15** and **16**) is noteworthy,[9] and should be synthetically useful.

In summary, we have presented a new method for the preparation of primary cyclopropylamines. The described reaction involves a cooperative Ti(II) and Lewis acid-mediated coupling of nitriles with Grignard reagents. Simplicity of the procedure, cheap reagents as well as readily available starting materials, and particularly different alkanenitriles, are the major advantages of this method. Studies aimed at further exploring the reaction are currently underway.

Notes and references

1 E. Vilsmaier, *The Chemistry of the Cyclopropyl Group*, ed. Z. Rappoport, Wiley, New York, 1987, ch.. 22, p. 1341.

2 For examples, see: K. Grohe, H. Zieler and K. Metzger, *Eur. Pat.* 0078362, 1983; E. S. C. Wu, T. E. Cole, T. A. Davidson, J. C. Blosser, A. R. Borrelli, C. R. Kinsolving, T. E. Milgate and R. B. Parker, *J. Med. Chem.*, 1987, **30**, 788; H. Homma, Y. Watanabe, T. Abiru, T. Murayama, Y. Nomura and A. Matsuda, *J. Med. Chem.*, 1992, **35**, 2881; M. C. Pirrung, J. Cao and J. Chen, *J. Org. Chem.*, 1995, **60**, 5790.

3 Houben-Weyl, *Methoden der Organischen Chemie*, ed. M. Regitz, Thieme, Stuttgart, 1989, 4th edn., vol. E 19b.

4 The oxatitanacyclopentane intermediate is involved in both Kulinkovich and de Meijere reactions. However, whereas the OR group of an ester further migrates to the strongly oxophilic titanium, the NR_2 group of an amide remains attached to the carbon, see: V. Chaplinski and A. de Meijere, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 413; V. Chaplinski, H. Winsel, M. Kordes and A. de Meijere, *Synlett*, 1997, 111; J. Lee and J. K. Cha, *J. Org. Chem.*, 1997, **62**, 1584.

5 O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevski and T. S. Prityts kaya, *Zh. Org. Khim.*, 1989, **25**, 2244; Recent review: O. G. Kulinkovich and A. de Meijere, *Chem. Rev.*, 2000, **100**, 2789.

6 P. Bertus, V. Gandon and J. Szymoniak, *Chem. Commun.*, 2000, 171; V. Gandon, P. Bertus and J. Szymoniak, *Eur. J. Org. Chem.*, 2000, **22**, 3713.

7 The $Ti(OPr^i)_4$-promoted double nucleophilic addition of Grignard reagents to CN triple bond of protected cyanohydrins (chelating nitriles) has recently been reported, see: A. B. Charette, A. Gagnon, M. Janes and C. Mellon, *Tetrahedron Lett.*, 1998, **39**, 5147.

8 In contrast to the Kulinkovich reaction, for which the intermediacy of a titanium ate complex has recently been postulated, see: O. G. Kulinkovich, *Pure Appl. Chem.*, 2000, **72**, 1715.

9 Selected data for **2** and **14**: **2**: ^{1}H-NMR (250 MHz; $CDCl_3$) δ 0.6–0.7 (m, 4 H), 2.72 (s, 2 H), 3.77 (s, 2 H), 7.20–7.35 (m, 5 H); ^{13}C-NMR (63 MHz; $CDCl_3$) δ 9.1, 35.4, 39.7, 127.5, 128.8, 129.8, 134.8; IR ν (cm^{-1}) 3361, 1605, 1495, 1453; MS (70 eV) *m*/*z* 147 ($M^{+\cdot}$, 44), 132 (28), 92 (71), 91 (90), 56 (100); Analysis calculated for $C_{10}H_{13}N{\cdot}HCl$: C, 65.39; H, 7.68; N, 7.63; found C, 65.34; H, 7.61; N, 7.58%. **14**: minor isomer: R_f (ether–methanol 95:5) 0.34; ^{1}H-NMR (250 MHz; $CDCl_3$) δ 0.31 (dd, J = 5.7, 4.7 Hz, 1 H), 0.75 (dd, J = 9.4, 4.7 Hz, 1 H), 0.86–0.99 (m, 1 H), 1.05 (t, J = 7.3 Hz, 3 H), 1.20–1.38 (m, 1 H), 1.56 (br s, 2 H), 1.54–1.72 (m, 1 H), 2.72 (d, J = 14.4 Hz, 1 H), 2.87 (d, J = 14.4 Hz, 1 H),7.20–7.38 (m, 5 H); ^{13}C-NMR (63 MHz; $CDCl_3$) δ 14.2, 20.2, 23.3, 28.1, 38.1, 41.4, 126.2, 128.3, 129.3, 139.5; IR ν (cm^{-1}) 3356, 1601, 1495, 1453; MS (70 eV) *m*/*z* 175 ($M^{+\cdot}$, 11), 160 (22), 146 (76), 92 (71), 91 (100). **14**: major isomer: R_f (ether–methanol 95:5) 0.70; ^{1}H-NMR (250 MHz; $CDCl_3$) δ 0.23 (t, J = 4.9 Hz, 1 H), 0.72 (dd, J = 8.9, 4.4 Hz, 1 H), 0.77–0.88 (m, 1 H), 0.95 (t, J = 7.4 Hz, 3 H), 1.30 (br s, 2 H), 1.40–1.55 (m, 2 H), 2.62 (d, J = 14.0 Hz, 1 H), 2.78 (d, J = 14.0 Hz, 1 H), 7.22–7.38 (m, 5 H); ^{13}C-NMR (63 MHz; $CDCl_3$) δ 14.3, 19.0, 21.6, 26.7, 38.4, 47.9, 126.2, 128.2, 129.2, 139.5; IR ν (cm^{-1}) 3372, 1604, 1495, 1454; MS (70 eV) *m*/*z* 175 ($M^{+\cdot}$, 10), 160 (19), 146 (68), 92 (68), 91 (100); Analysis calculated for $C_{12}H_{17}N{\cdot}HCl$: C, 68.07; H, 8.57; N, 6.62%; found C, 67.83; H, 8.54; N, 6.38%.