Iminopinacol coupling with lithium: electron-transfer mediators

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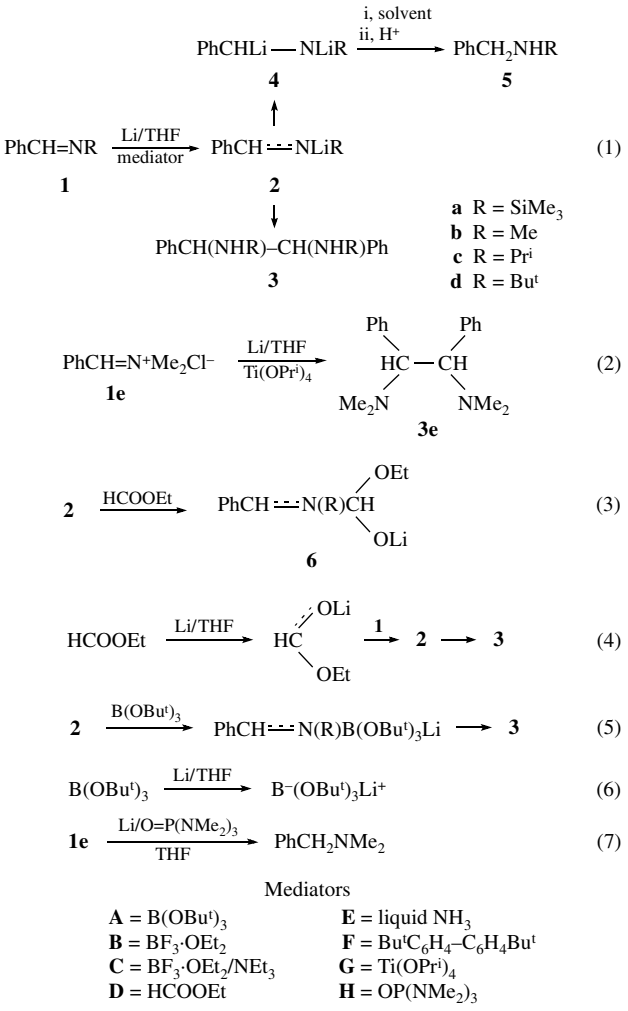
10.1070/MC2002v012n06ABEH001617

The addition of *tert*-butyl borate or ethyl formate to *N*-alkylbenzalimines directs the reaction pathway from the Birch reduction to the pinacol-type coupling with lithium in THF; an analogous reaction with a dimethylimmonium salt requires a trace titanium catalyst as the electron-transfer mediator.

The reductive coupling of aliphatic and aromatic imines is of current interest, motivated by a promising perspective in directing the stereochemistry of reaction. This interest is justified by unique properties of vicinal diamines as bases and chiral ligands.[1] The relevant publications considered a great variety of reducing metals (Mg, Zn, Cr, Ti, Ni, Nb, Sm and Yb) and metal combinations.[2–9] Considering the mechanistic aspects of the reductive coupling, we were intrigued by the conspicuous absence of lithium which, to the best of our knowledge, was mentioned only once as a metal of no value for the iminopinacol coupling.[10]

The aim of this study was to comprehend the observed specific nature of lithium as a coupling metal, the effects of additives and the nitrogen substitution. The results are presented in Table 1.†



Scheme 1

† *General procedure for iminopinacol coupling with lithium*. All reactions (except for runs 10 and 11, where a polypropylene stirrer was used) were run in argon with a stainless steel overhead stirrer, lithium was added as small chips cut from 0.2 mm foil. Ethyl formate was distilled over lithium and stored under argon.

1,2-Diphenylethylene-1,2-diamine. One-pot procedure: to a mixture of 0.1 mol Li and 0.1 mol (21 ml) of HMDS in 60 ml of THF was added 0.05 mol (6.5 ml) of isopropenylbenzene at 25–32 °C. After dissolution of the metal (~1 h), benzaldehyde (0.1 mol, 10.14 ml) was added. By cooling, the temperature was kept below 25 °C. When the exothermic formation of *N*-trimethylsilyl Schiff base **1a** was completed, the second portion of lithium (0.1 mol) was added, and the reaction mixture was kept at ~5 °C (at higher temperatures, the decomposition of THF with ethylene evolution became noticeable). After 1 h, the dissolution of the metal was almost complete, and the reaction was treated with 40 ml of conc. HCl in 30 ml of water after 2 h at room temperature. The crystalline solid was filtered off and washed with THF. The yield of chlorides is 13.1 g (*meso*/*rac*, 30:70). This mixture, after aqueous NaOH–THF treatment gave 9.4 g (88.7%) of a crystalline mixture of isomers, the crystallization of which from hexane–THF gave 6.8 g of racemic diamine (64%), mp 72 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.65 (br.s, 4H), 3.9 (s, 2H), 7.1–7.3 (m, 10H). A diagnostic signal of the *meso*-isomer is 3.8 (s).

Coupling of N-alkyl Schiff bases in the presence of the mediator. A mixture of **1b** (0.025 mol), ethyl formate (0.03 mol), 25 ml THF and Li (0.04 mol) was stirred with cooling (9–10 °C). In about 3 min, the Li chips became shiny and the solution became yellow. After 2 h cooling was terminated, and the temperature was kept ambient for 1 h. Then, the reaction mixture was treated with 15 ml of 6 N NaOH and, after pressure filtration over silica, rotary evaporated. The mixture of isomers (yield, 3.0 g) was separated by crystallization from hexane.[1] Solid isomer (*meso*), ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.05 (s, 6H), 3.62 (s, 2H), 7.15–7.3 (m, 10H). Liquid isomer (*rac*), ^{1}H NMR, δ: 2.12 (s, 6H), 3.45 (s, 2H), 7.0–7.15 (m, 10H). The reactions with mediators **A**, **B** and **C** were performed in a similar way using ammonia for the decomposition.

Coupling of immonium salt **1e** *(polypropylene stirrer)*. Salt **1e** was prepared from aminal according to a published procedure;[9] the mixture of benzaldehyde, liquid dimethylamine and calcium chloride was kept in a pressure vessel for 12 h at room temperature. The mixture of **1e** (0.52 mol), 50 ml of THF and Li (0.6 mol) was stirred for 5 min and 0.14 ml of titanium isopropylate was added. The temperature was kept at 33–35 °C. After additional stirring for 2 h, the mixture was treated with 4 ml of water and then 5 ml of 12 N NaOH. The evaporation of the organic fraction gave 5.2 g of a 1:1 mixture of racemic and *meso* diamines **3e**. By crystallization from hexane, the less soluble *meso*-isomer was isolated. ^{1}H NMR ($CDCl_3$) δ: 2.0 (s, 12H), 4.17 (s, 2H), 7.25-7.45 (m, 10H). Racemic **3e** was obtained by crystallization of **3e** phthalate. ^{1}H NMR, δ: 2.24 (s, 4H), 4.22 (s, 2H), 7.15–6.85 (m, 10H).

Table 1 The iminopinacol coupling of benzalimines with lithium: the yields of vicinal diamines in relation to the nitrogen substitution and the type of electron-transfer mediators.

Entry	Imine	Mediator	*meso* + *rac*, yield (%)	*meso*/*rac*	Reduction (%)
1[a]	**1a**	**A**	**2b**, 91	4:5	6
2[a]	**1b**	**B**	**2b**, 80	1:1	10
3[a]	**1b**	**C**	**2b**, 85	4:6	5
4	**1b**	**D**	**2b**, 90	1:1	5
5	**1b**	**E**	**2b**, *ca.* 5	1:1	95
6	**1b**	**F**			80
7	**1c**	**D**	**2c**, 70	1:2	15
8	**1d**	**D**			97
9	**1a**	none	**2a**, 81	3:7	10
10[b]	**1e**	**G**	**2e**, 90	1:1	5
11	**1e**	**H**		—	95

[a]After the hydrolysis of borates. [b]One-pot procedure based on benzaldehyde.

A. Aleexakis *et al.*[10] ascribed the role of an additive (TMSCl) to the stabilization of radical anion **2** by N-silylation. Our results are in accord with this assumption (entry 9).

Really, the sterically hindered additive *tert*-butyl borate, which cannot form strong N–B bonds, is a very effective promoter of the iminopinacol coupling with lithium (entry 1). From practical considerations, the most convenient mediator is ethyl formate. The efficiency of this reagent is not associated with the formylation of intermediate **2** (Scheme 1) since no formyl derivatives were detected after a mild workup of the reaction mixture. A reasonable explanation of the observed effects of mediators **A** and **D** may consist in the interaction with radical anions **2** according to equations (3) and (5). Intermediates **6** and **7** thus formed differ from radical anion **2** by a substantial decrease of charge density on the nitrogen and, as a result, by polarization of the C–N bond. The net result of these interactions is the blocking of the pathway from **2** to **4** and hence to Birch reduction product **5**. Another type of mediators are the boron trifluoride–diethyl ether complex alone or in combination with triethylamine (entries 2 and 3). These reagents obviously complex with the starting imines and thus stabilise intermediate radical anion **2**. The difference between mediators **B** and **C** consists in a decrease in the reduction product yield with mediator **C** (*cf.* entry 2 and 3). Data in Table 1 (entries 5, 6 and 11 with dissolved lithium) suggest that the reaction of iminopinacol coupling with lithium is basically a surface reaction similar to a Barbier-type variant of the Grignard addition. Obviously, the ratio between *meso* and racemic isomers also reflects the intimate mode of the transition state location on the metal surface resulting in a persistent ratio of isomers close to 1:1 regardless of substitutions. In terms of the surface reaction, the role of mediators may be connected with the formation of an intermediate layer of radical ions similar to that of the transition state in the acyloin coupling of esters [equations (4) and (6)]. The conception of the surface reaction was confirmed by the coupling of imminium salt **1e** (entry 10). Salt **1e** is insoluble in THF, and no reaction occurs when a suspension of the salt is stirred with Li chips (no physical contacts between reagents). However, attempts to use 'dissolved metal' (entry 11) produced only the reduction product. These observations lead to the hypothesis that the surface mode of coupling is also operative here. Really, the addition of a catalytic quantity of the titanium reagent (entry 10) starts exothermal reaction, and the coupling is the main process. Presumably, this catalytic reaction proceeds on the clusters of zero valent titanium (black suspension) acting as the mediators of electron-transfer from lithium to the Schiff base. The role of steric factors (substitution on nitrogen) may be appreciated from entries 7 and 8: there is an increase in the yield of the reduction product for isopropyl, and only the reduction of Schiff's base occurs with *tert*-butyl.

References

1 F. Fache, E. Schults, M. L. Tommasino and M. Lemario, *Chem. Rev.*, 2000, **100**, 2159.
2 F. Machrouhi, and J.-L. Namy, *Tetrahedron Lett.*, 1999, **40**, 1315.
3 J. Li, S. Wang, J. Hu and W. Chen, *Tetrahedron Lett.*, 1999, **40**, 1961.
4 B. K. Banik, O. Zegorcka, I. Banik, L. Hackfeld and F. F. Becker, *Tetrahedron Lett.*, 1999, **40**, 6731.
5 T. Hirao, B. Hatano, Y. Imamoto and A. Ogawa, *J. Org. Chem.*, 1999, **64**, 7665.
6 M. Shimizu and Y. Niwa, *Tetrahedron Lett.*, 2001, **42**, 2829.
7 R. Yanada, M. Okaniva, A. Kkaieda, T. Ibuka and Y. Takemoto, *J. Org. Chem.*, 2000, **66**, 1283.
8 S. Denmark, X. S. Nishigaichi, D. M. Coe, K.-T. Wong and S. B. D. Winter, *J. Org. Chem.*, 1999, **64**, 1958.
9 D. Betschart, B. Schmidt and D. Seebacch, *Helv. Chim. Acta*, 1988, **71**, 1999.
10 A. Aleexakis, I. Aujard and P. Mangeny, *Synlett*, 1998, 893.

Received: 19th June 2002; Com. 02/1943