

Hydroamination of cinnamyl alcohol using lithium amides

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Abstract—Hydroamination of cinnamyl alcohol is possible by reaction with lithium amides derived from primary or cyclic secondary amines.

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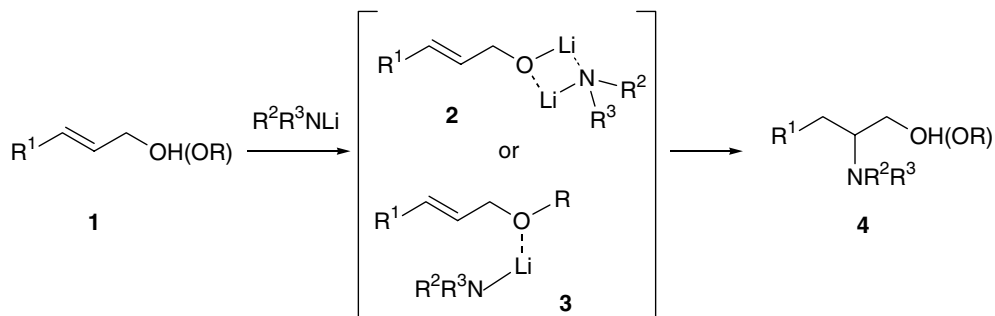
The hydroamination of alkenes is an area of current topical interest due to the importance of amines and the attraction of synthesising them without the intervention of carbonyl compounds or alkyl halides. Recently, hydroamination methods that rely on transition metals, rare earth metals, or group IV metal halides, as catalysts, have shown substantial promise.^{1,2}

Despite this progress, most examples of hydroamination involve limited ‘activated’ substrates, such as vinyl arenes or dienes, or involve intramolecular cyclisation of unsaturated amines, or their derivatives. This is true even of the most venerable approach to hydroamination, which involves base-catalysis, using metals, alkyl metals or metal amides.^{3,4} Expanding the scope of this type of process to more highly substituted or

functionalised derivatives would be useful, especially in intermolecular mode.

As part of a synthetic project we required addition of nitrogen to an allylic alcohol system and this prompted us to explore the hydroamination chemistry of cinnamyl alcohol, using lithium amides, which is the subject of this Letter.

The hydroamination of alkenes via aminolithiation has been examined with rather limited types of substrate in intermolecular mode, and the reaction often requires rather harsh conditions (e.g., high temperatures).^{3,5} We wondered if the incorporation of a proximal ether or hydroxyl function would facilitate the aminolithiation of an allylic alcohol or derivative, as outlined in [Scheme 1](#).



Scheme 1. Addition of a lithium amide to a cinnamyl alcohol or ether.

Keywords: Aminoalcohol; Hydroamination; Lithium amide; Cinnamyl alcohol.

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Table 1. Addition of primary amines to cinnamyl alcohol

$$\text{R}^1\text{-CH=CH-CH}_2\text{-OH} + \text{R}^2\text{NH}_2 \xrightarrow[\text{reflux 1-4 h}]{n\text{BuLi (2 equiv), THF, -78 }^\circ\text{C}} \text{R}^1\text{-CH}_2\text{-CH(NHR}^2\text{)-CH}_2\text{-OH}$$

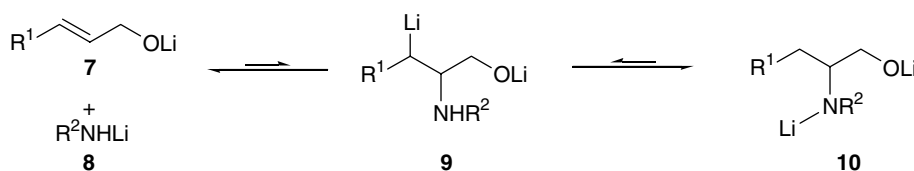
Entry	R ¹	Amine	Product	Yield (%)
1	Ph	PhCH ₂ NH ₂	6a	51
2	Ph	MeNH ₂	6b	40
3	Ph	BuNH ₂	6c	55
4	Ph	MeO(CH ₂) ₂ NH ₂	6d	50
5	Ph	Ph(CH ₂) ₂ NH ₂	6e	57
6	Ph	<i>o</i> -MeO-PhCH ₂ NH ₂	6f	37
7	<i>m</i> -MeO-Ph	PhCH ₂ NH ₂	6g	45

In the case of an allylic alcohol the use of excess base might result in the formation of a mixed aggregate **2**, whereas the use of an allylic ether would enable co-ordination of the base as shown by **3**. In either case, by rendering the process pseudo-intramolecular we hoped to facilitate the reaction, which is known to be problematic due to the unfavourable interaction between the nitrogen lone pair and the π -system of the alkene.

In initial studies we established that at *room temperature* we could achieve addition of a lithiated primary amine to the lithium alkoxide of cinnamyl alcohol (R¹ = Ph) to give products of type **4** in moderate yields, but other

try **7**) also participated. However, we also identified problematic reaction partners, such as hindered amines (e.g., ^tBuNH₂) and functionalised amines (e.g., allylamine) which gave none of the desired products. Likewise, we obtained no aminoalcohol product starting with *para*-methoxy-cinnamyl alcohol, or from either of the corresponding *ortho*- or *para*-nitro-substituted cinnamyl alcohols.

In seeking to extend the scope of the chemistry to *secondary* amines, we considered the reaction intermediates for *primary* amines in terms of two likely equilibria (Scheme 2).

**Scheme 2.** Possible equilibria in addition reactions of primary amines as lithium amides.

types of allylic alcohol (e.g., R¹ = H, Me, etc.) did not react. Under these conditions, which employed equimolar amounts of amine and alkene, the corresponding cinnamyl ether (R¹ = Ph, R = Me) gave only small amounts of the unwanted side product, dihydrocinnamaldehyde.⁶ This result seems to suggest that reaction via a mixed aggregate **2** is more facile than via the co-ordinated base **3**. Under these conditions, we also saw no reaction with secondary amines.

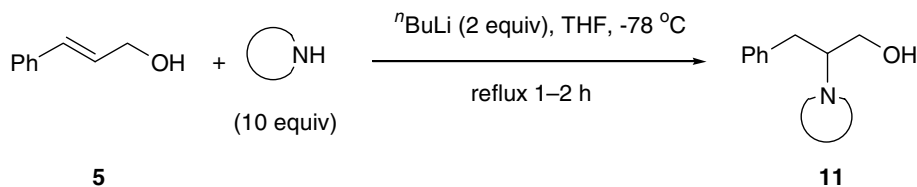
Therefore, we focused on the combination of equimolar amounts of cinnamyl alcohol with primary amines by use of ⁿBuLi (2 equiv) in THF. The reactions proved sluggish at room temperature and best results were achieved if the components were mixed at low temperature and then allowed to warm to room temperature before heating to reflux for 1–4 h (Table 1).⁷

As revealed by the results in Table 1, a number of amines gave the desired products in moderate to good chemical yields and one modified cinnamyl alcohol (en-

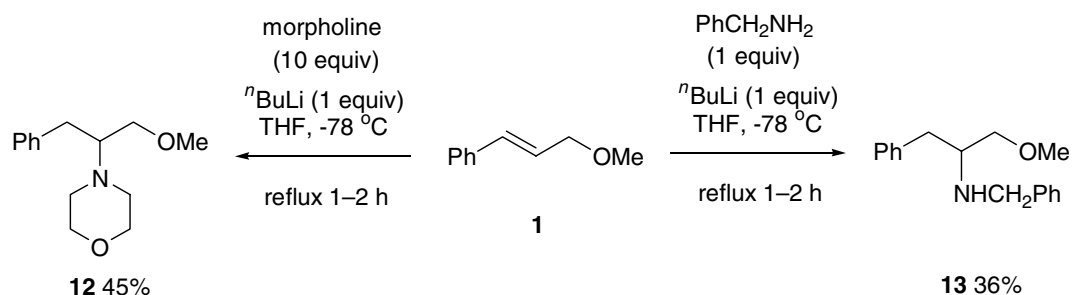
It is reasonable to assume that the initial addition process is unfavourable, the equilibrium favouring starting materials. However, the putative intermediate organolithium **9** can undergo a favourable proton transfer process to give the more stable amido-alkoxide **10**, thus shifting the equilibrium in the desired sense.

In the case of secondary amines, the intermediate corresponding to **9** has a fully alkylated nitrogen and so there is no (relatively) acidic proton in the system to pull the equilibrium to the right hand side. We reasoned that including such a proton source, in the form of excess amine, should facilitate the reaction for secondary amines, and were pleased to find that this proved to be the case, at least for cyclic amines (Table 2).^{8,9}

The yields of these products appear better than those in Table 1, although we have not reviewed the reactions with primary amines using a large excess of amine. The sensitivity of the reaction to steric effects was again evident in that acyclic secondary amines, such as

Table 2. Addition of cyclic secondary amines to cinnamyl alcohol

Entry	Amine	Product	Yield (%)
1	Pyrrolidine	11a	53
2	Piperidine	11b	69
3	Morpholine	11c	56
4	<i>N</i> -Me piperazine	11d	65

**Scheme 3.** Addition of lithium amides to cinnamyl ether.

Et_2NH or BnNHMe , did not give any of the desired product.

Finally, we found that, under our modified conditions, which typically involved heating at reflux for ca. 2 h, the methyl ether of cinnamyl alcohol **1** ($\text{R}^1 = \text{Ph}$, $\text{R} = \text{Me}$) also gave the products of addition, albeit in more modest yields than observed in the corresponding reactions of the cinnamyl alcohols (Scheme 3).

These results appear to tentatively support the proposals outlined in Scheme 1. The reaction is possible through both mixed-aggregate and coordinated base mechanisms, but the mixed-aggregate route appears more facile, based on the higher yields using the free alcohol, and the fact that **13** is not formed at room temperature.

In summary, we have shown for the first time that cinnamyl alcohols are substrates for hydroamination using the aminolithiation approach, and have assessed the scope and limitations of the process. The chemistry may provide a useful access to aromatic aminoalcohols, that is, *N*-alkylated phenylalaninol derivatives, albeit in racemic form so far.

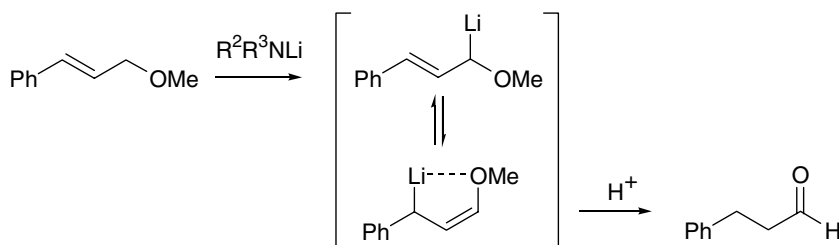
Acknowledgement

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- Additions to styrenes have been carried out under quite mild conditions, see: (a) Seijas, J. A.; Vazquez-Tato, M. P.; Entenza, C.; Martinez, M. M.; Onega, M. G.; Veiga, S. *Tetrahedron Lett.* **1998**, *39*, 5073; (b) Hartung, C. G.; Breindl, C.; Tillack, A.; Beller, M. *Tetrahedron* **2000**, *56*, 5157.
- This presumably arises via a competing metallation as shown below.



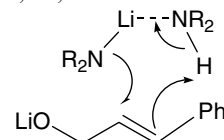
7. A two-necked round-bottomed flask fitted with a rubber septum and a reflux condenser was charged with cinnamyl alcohol (3.0 mmol) and dry tetrahydrofuran (15 mL) under an atmosphere of nitrogen. The solution was cooled to $-78\text{ }^{\circ}\text{C}$ and primary amine (3.0 mmol) was added, followed by dropwise addition of *n*-butyllithium (2.5 M hexanes, 6.0 mmol). The cold bath was removed and the reaction mixture was allowed to warm to room temperature over 0.5 h, then warmed to reflux over 0.5 h and reflux maintained until all cinnamyl alcohol was consumed as determined by TLC analysis (1–4 h). The mixture was then cooled to room temperature and partitioned between 2 M NaOH_{aq} (30 mL) and dichloromethane (100 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo to give the crude product.

Aminoalcohol 6a: Purification was done by column chromatography on silica gel, eluting with 10% ethanol/petroleum ether and then with 20% ethanol/petrol (2% NEt₃ added) to give pure aminoalcohol **6a** as a white crystalline solid (740 mg, 51%); mp 68–70 °C; ν_{max} (neat)/cm⁻¹ 3285, 3023, 2919, 2861, 1603, 1495, 1467, 1456, 1442; δ_{H} (270 MHz, CDCl₃) 2.20 (2H, br s, OH, NH), 2.77 (1H, dd, *J* 13.6, 6.9, 3-*HH*), 2.85 (1H, dd, *J* 13.6, 6.9, 3-*HH*), 2.98 (1H, tdd, *J* 6.9, 5.3, 3.9, 2-H), 3.36 (1H, dd, *J* 10.7, 5.3, 1-*HH*), 3.66 (1H, dd, *J* 10.7, 3.9, 1-*HH*), 3.79 (2H, s, 1'-H₂), 7.15–7.35 (10H, m, 10 × Ar-H); δ_{C} (70 MHz, CDCl₃) 38.2 (C-3), 51.1 (C-1'), 59.4 (C-2), 62.5 (C-1), 126.6 (C-Ar_{para}), 127.2 (C-Ar_{para}), 128.2, 128.6, 128.7, 129.3, 138.5 (C-Ar_{ipso}), 139.9 (C-Ar_{ipso}); Found (ESI): 242.1532 [MH]⁺, ([C₁₆H₂₀NO]⁺ requires 242.1545); *m/z* (ESI) 242.1511 ([MH]⁺, 81%), 264.1359 ([MNa]⁺, 17%).

Aminoalcohol 6d: Purification was done by column chromatography on silica gel, eluting with 80% ethyl acetate/petrol (2% NEt₃ added) to give pure aminoalcohol **6d** as a pale yellow solid (311 mg, 50%); mp 55–57 °C; ν_{max} (neat)/cm⁻¹ 3396, 3027, 2927, 2893, 1651, 1603, 1455, 1112; δ_{H} (270 MHz, CDCl₃) 2.65–2.80 (4H, m, 3-H₂, 1'-H₂), 2.82–2.91 (1H, m, 2-H), 3.27 (3H, s, -OMe), 3.30 (1H, dd, *J* 10.7, 5.5, 1-*HH*), 3.42 (2H, t, *J* 5.5, 2'-H₂), 3.57 (1H, dd, *J* 10.7, 3.8, 1-*HH*), 7.15–7.23 (3H, m, 3 × Ar-H), 7.24–7.31 (2H, m, 2 × Ar-H); δ_{C} (70 MHz, CDCl₃) 38.2 (C-3), 46.5 (C-1'), 58.8, 60.4, 62.6 (C-1), 72.3 (C-2'), 126.4 (C-Ar_{para}), 128.6, 129.3, 138.7 (C-Ar_{ipso}); Found (ESI): 232.1300 [MNa]⁺, ([C₁₂H₁₉NNaO₂]⁺ requires 232.1308); *m/z* (ESI) 232.1300 ([MNa]⁺).

8. It is possible that a concerted addition and protonation takes place, most likely involving a lithium amide solvated by neutral amine as shown below (this somewhat overlooks the complications of lithium amide aggregates and possible mixed aggregates involving the alkoxide). This type of idea originates from one of the earliest reports in this area, see:

Clossen, R. D.; Napolitano, J. P.; Ecke, G. G.; Kolka, A. J. *J. Org. Chem.* **1957**, 22, 646



9. A two-necked round-bottomed flask fitted with a rubber septum and a reflux condenser was charged with cinnamyl alcohol (3.0 mmol) and dry tetrahydrofuran (15 mL) under an atmosphere of nitrogen. The solution was cooled to $-78\text{ }^{\circ}\text{C}$ and secondary amine (30.0 mmol) was added, followed by dropwise addition of *n*-butyllithium (2.5 M hexanes, 6.0 mmol). The cold bath was removed and the reaction mixture was allowed to warm to room temperature over 0.5 h, and then warmed to reflux over 0.5 h and maintained at reflux until all cinnamyl alcohol was consumed as determined by TLC analysis. The mixture was then cooled to room temperature and partitioned between 2 M NaOH_{aq} (30 mL) and dichloromethane (100 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo to give the crude 1,2-amino alcohol.

Aminoalcohol 11b: Purification was done by column chromatography on silica gel, eluting with 15% ethanol/petrol (2.5% NEt₃ added) to give pure **11b** as a pale yellow solid (459 mg, 69%); mp 44–46 °C; ν_{max} (neat)/cm⁻¹ 3443, 2919, 2881, 1604, 1496, 1455, 1377; δ_{H} (270 MHz, CDCl₃) 1.39–1.71 (6H, m, 3'-H₂, 4'-H₂, 5'-H₂), 2.30 (1H, dd, *J* 13.0, 9.4, 3-*HH*), 2.37–2.47 (2H, m, 2'-H_{ax}, 6'-H_{ax}), 2.67–2.77 (2H, m, 2'-H_{eq}, 6'-H_{eq}), 2.80–2.91 (1H, m, 2-H), 2.94 (1H, dd, *J* 13.0, 4.4, 3-*HH*), 3.32 (2H, d, *J* 7.6, 1-H₂), 7.09–7.30 (5H, m, 5 × Ar-H); δ_{C} (70 MHz, CDCl₃) 24.9 (C-4'), 26.8 (C-3', C-5'), 32.0 (C-3), 49.5 (C-2', C-6'), 59.9 (C-2), 67.6 (C-1), 126.2 (C-Ar_{para}), 128.6, 129.0, 139.6 (C-Ar_{ipso}); Found (ESI): 220.1674 [MH]⁺, ([C₁₄H₂₂NO]⁺ requires 220.1701); *m/z* (ESI) 220.1674 ([MH]⁺, 94%).

Aminoalcohol 11c: Purification was done by column chromatography on silica gel, eluting with 15% ethanol/petrol (2.5% NEt₃ added) to give pure **11c** as a white crystalline solid (372 mg, 56%); mp 85–87 °C; ν_{max} (neat)/cm⁻¹ 3062, 2925, 2853, 1563, 1157; δ_{H} (270 MHz, CDCl₃) 2.37 (1H, dd, *J* 13.0, 9.2, 3-*HH*), 2.53 (2H, ddd, *J* 11.0, 6.1, 3.2, 2'-H_{ax}, 6'-H_{ax}), 2.77 (2H, ddd, *J* 11.0, 6.1, 3.2, 2'-H_{eq}, 6'-H_{eq}), 2.80–2.90 (1H, m, 2-H), 2.97 (1H, dd, *J* 13.0, 4.5, 3-*HH*), 3.30–3.40 (2H, m, 1-H₂), 3.69 (2H, ddd, *J* 11.0, 6.1, 3.2, 3'-H_{ax}, 5'-H_{ax}), 3.76 (2H, ddd, *J* 11.0, 6.1, 3.2, 3'-H_{eq}, 5'-H_{eq}), 7.09–7.31 (5H, m, 5 × Ar-H); δ_{C} (70 MHz, CDCl₃) 32.0 (C-3), 48.6 (C-2', C-6'), 59.7 (C-2), 64.75 (C-1), 64.55 (C-3', C-5'), 126.4 (C-Ar_{para}), 128.7, 129.0, 139.1 (C-Ar_{ipso}); Found (ESI): 222.1475 [MH]⁺, ([C₁₃H₂₀NO₂]⁺ requires 222.1494); *m/z* (ESI) 222.1475 ([MH]⁺, 42%).