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Hydroamination of cinnamyl alcohol using lithium amides

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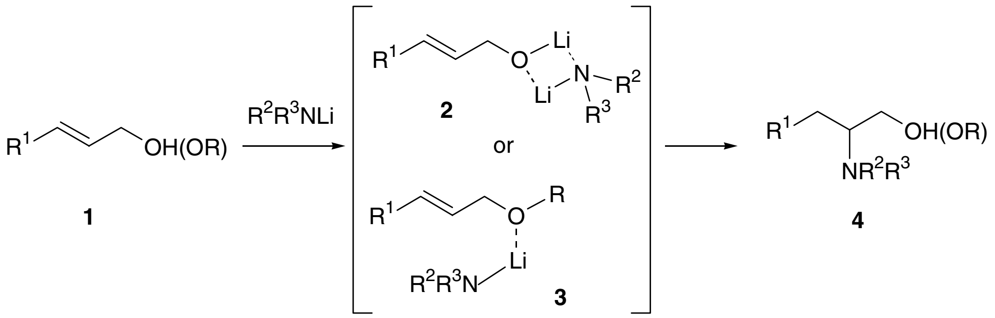
Abstract—Hydroamination of cinnamyl alcohol is possible by reaction with lithium amides derived from primary or cyclic secondary amines.

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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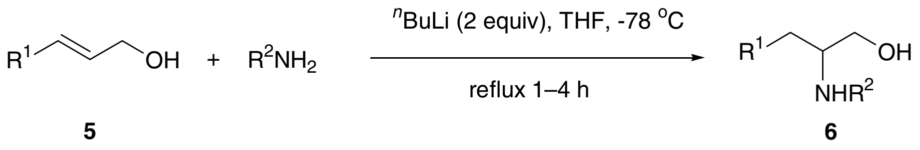
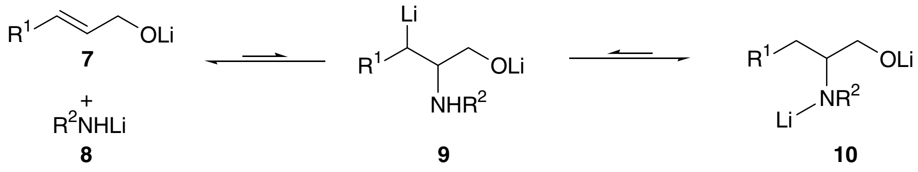
Table 1. Addition of primary amines to cinnamyl alcohol



Entry	R^1	Amine	Product	Yield (%)
1	Ph	$PhCH_2NH_2$	**6a**	51
2	Ph	$MeNH_2$	**6b**	40
3	Ph	$BuNH_2$	**6c**	55
4	Ph	$MeO(CH_2)_2NH_2$	**6d**	50
5	Ph	$Ph(CH_2)_2NH_2$	**6e**	57
6	Ph	*o*-MeO–$PhCH_2NH_2$	**6f**	37
7	*m*-MeO–Ph	$PhCH_2NH_2$	**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 ($R^1 = Ph$) to give products of type **4** in moderate yields, but other types of allylic alcohol (e.g., $R^1 = H$, Me, etc.) did not react. Under these conditions, which employed equimolar amounts of amine and alkene, the corresponding cinnamyl ether ($R^1 = Ph$, $R = Me$) 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.



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

Therefore, we focused on the combination of equimolar amounts of cinnamyl alcohol with primary amines by use of ^{n}BuLi (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 (entry 7) also participated. However, we also identified problematic reaction partners, such as hindered amines (e.g., ^{t}BuNH$_2$) 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).

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