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LETTERS

# Enantiodivergent conversion of chiral secondary alcohols into tertiary alcohols

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**From receptors in the nose to supramolecular biopolymers, nature shows a remarkable degree of specificity in the recognition of chiral molecules, resulting in the mirror image arrangements of the two forms eliciting quite different biological responses[1,2]. It is thus critically important that during a chemical synthesis of chiral molecules only one of the two three-dimensional arrangements is created. Although certain classes of chiral molecules (for example secondary alcohols[3,4]) are now easy to make selectively in the single mirror image form, one class—those containing quaternary stereogenic centres (a carbon atom with four different non-hydrogen substituents)—remains a great challenge[5–8]. Here we present a general solution to this problem which takes easily obtainable secondary alcohols in their single mirror image form and in a two-step sequence converts them into tertiary alcohols (quaternary stereogenic centres). The overall process involves removing the hydrogen atom (attached to carbon) of the secondary alcohol and effectively replacing it with an alkyl, alkenyl or aryl group. Furthermore, starting from a single mirror image form of the secondary alcohol, either mirror image form of the tertiary alcohol can be made with high levels of stereocontrol. Thus, a broad range of tertiary alcohols can now be easily made by this method with very high levels of selectivity. We expect that this methodology could find widespread application, as the intermediate tertiary boronic esters can potentially be converted into a range of functional groups with retention of configuration.**

We live in a chiral world. Indeed, chirality and life are so inextricably linked that the detection of chirality outside our planet is used as a test for extraterrestrial life itself[9,10]. Nature's inherent chirality results in extraordinary specificity in the recognition of chiral molecules. For example, the different smell of oranges and lemons comes from two molecules identical except for their three-dimensional spatial arrangement. The classic example of the drug 'thalidomide' further illustrates the difference in biological response: one of the two enantiomers caused fetal birth defects (it restricted the development of blood vessels in rapidly dividing tissues and as such is now being used against certain forms of cancer[11]) whereas the mirror image form had the desired sedative properties[12]. However, in this case the tragedy could not have been avoided by administering the enantiomer with the desired properties, as the drug readily racemizes *in vivo*.

Because of the established importance of the three-dimensional spatial relationship between a small molecule (for example a drug) and its site of action (for example a protein), it has become necessary to test individual enantiomers and not mixtures of the two forms. A mixture of enantiomers can be difficult to separate, so it is important to control which mirror image form of a chiral molecule is created during its synthesis. This field, known as asymmetric synthesis, has grown over the past half century to a point where the synthesis of certain classes of compounds (for example diols[13] and secondary alcohols[3,4]) is now facile. However, chiral molecules containing quaternary stereogenic centres (for example tertiary alcohols)[5–8] remain difficult to make with high enantioselectivity.

Tertiary alcohols are commonly obtained by addition of an organometallic reagent to a ketone (Fig. 1, paths a and b). Although such a process can be rendered asymmetric through the use of chiral ligands[14–16], the process does not often lend itself to high asymmetric induction as it invariably relies on the steric difference between the substituents flanking the carbonyl group. When this difference is small, as in the case of ketones, the ratio of enantiomers formed is often low.

We therefore considered a very different concept to prepare quaternary stereogenic centres that makes use of the 1,2-metallate rearrangement of boronate complexes. We recognized that reaction of a chiral carbenoid bearing an alkyl and an aryl group should react stereoselectively with a boron reagent to give a chiral 'ate' complex. This species would subsequently undergo a stereospecific 1,2-metallate rearrangement to give a homologated boron intermediate bearing a quaternary stereogenic centre. Oxidation would then furnish a tertiary alcohol. As the process no longer relies on the different steric properties of similar-sized groups, but on whether the reaction of the chiral carbenoid occurs with retention or inversion[17,18], the potential for high enantioselectivity is greatly increased (Fig. 2).

A similar strategy has been previously attempted through reactions of chiral α-chloroboronic esters with Grignard reagents and α-chlorolithium reagents with chiral boronic esters[19]. Although such reaction partners can be successfully combined with high enantioselectivity in the synthesis of secondary alcohols[20], generation of sterically more demanding tertiary alcohols was much less rewarding: variable levels of selectivity were obtained and even the sense of asymmetric induction was unpredictable[19]. Clearly, the choice of the chiral carbenoid is critical. Our earlier studies had shown that Hoppe's lithiated carbamates[21] derived from primary alcohols reacted efficiently with boranes and boronic esters furnishing secondary alcohols and amines with high enantiomeric ratios[22]. We therefore considered the possibility of extending this process to the use of chiral carbenoids derived from secondary alcohols (many are commercially available in enantiomerically enriched form but otherwise are easily made by Noyori transfer hydrogenation[23]) to prepare tertiary alcohols.

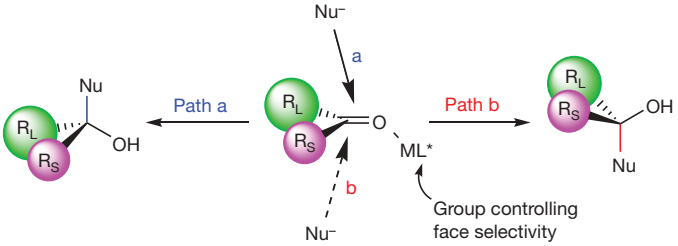


**Figure 1 | Common strategy for preparing chiral tertiary alcohols through face selective addition of nucleophiles to ketones.** Nu⁻, nucleophile.

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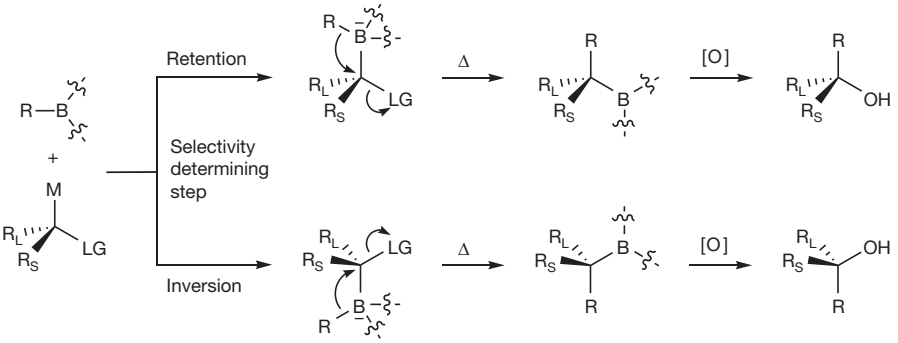
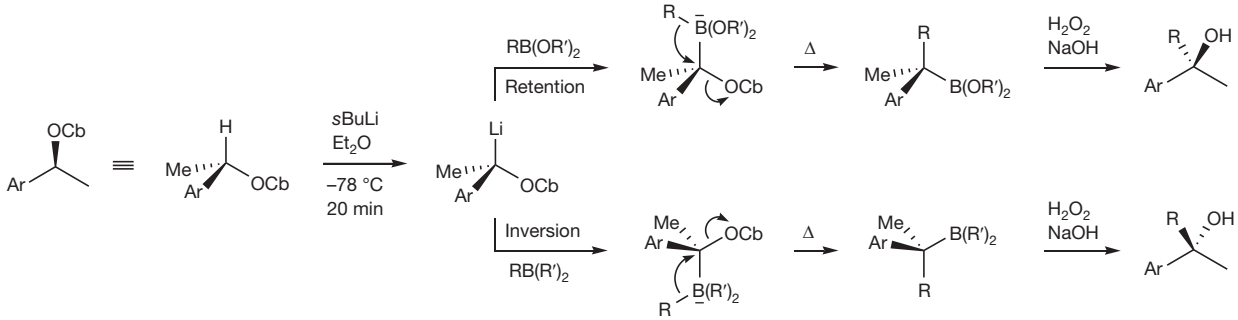



**Figure 2 | Proposed synthesis of tertiary alcohols through addition of chiral carbenoids to boron reagents.** Selectivity determined by degree of retention versus inversion in addition step. LG, leaving group; M = Li or Mg.

To test the concept, commercially available (*S*)-1-phenylethanol was converted into the corresponding *N*,*N*-diisopropyl carbamate. This carbamate had previously been deprotonated with *s*BuLi-TMEDA complex and reacted with a range of electrophiles[17]. During our investigation we found that *s*BuLi in $Et_2O$ was sufficient on its own to effect deprotonation of the carbamate. Subsequent addition of the borane or boronic ester followed by oxidation gave the tertiary alcohol in good yield and very high enantiomeric ratio (Table 1). The enantiomeric

**Table 1 | Lithiation–borylation of chiral secondary carbamates leading to tertiary alcohols**



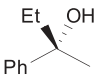
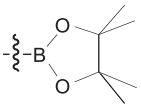
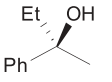
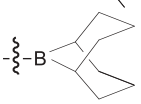
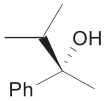
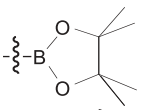
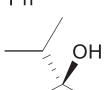
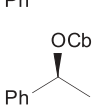
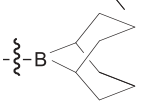
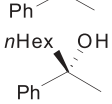
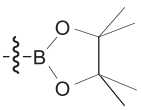
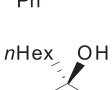
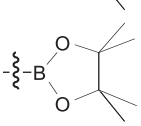
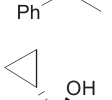
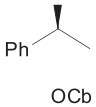
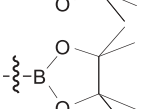
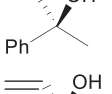
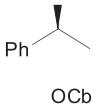
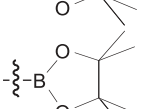
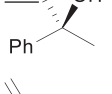
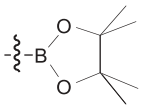
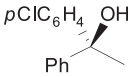
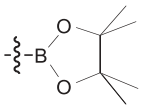
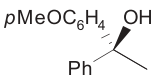
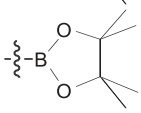
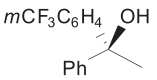
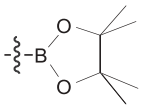
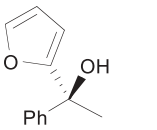
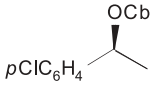
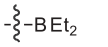
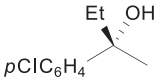
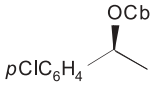
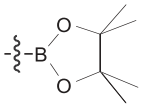
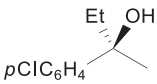
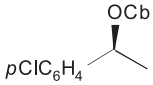
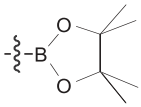
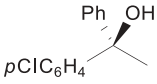
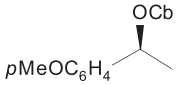
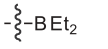
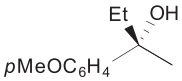
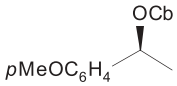
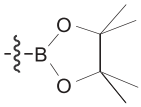
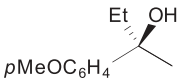
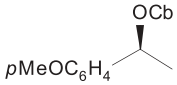
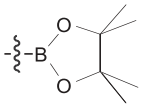
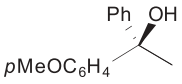
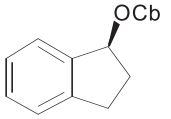
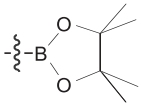
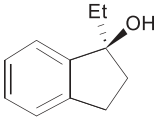
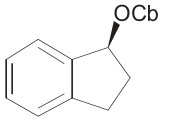
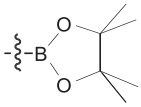
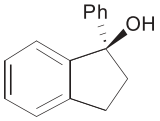
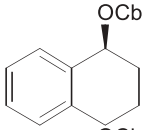
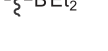
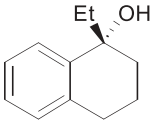
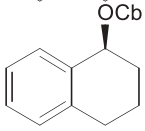

| Entry | Carbamate (e.r.) | Migrating group, R | Borane/boronic ester component | Product | Yield (%) (e.r., S:R) |
|---|---|---|---|---|---|
| 1 |  (99:1) | Et |  |  | 91 (99:1) |
| 2 |  (99:1) | Et |  |  | 95 (1:99) |
| 3 |  (99:1) | *i*Pr |  |  | 91 (98:2)* |
| 4 |  (99:1) | *i*Pr |  |  | 80 (4:96) |
| 5 |  (99:1) | *n*Hex |  |  | 60 (98:2)* |
| 6 |  (99:1) | *n*Hex |  |  | 85 (4:96) |
| 7 |  (99:1) | *c*Pr |  |  | 85 (3:97) |
| 8 |  (99:1) | vinyl |  |  | 75 (2:98) |
| 9 |  (99:1) | allyl |  |  | 95 (1:99)† |

**Table 1 | (Continued)**

| Entry | Carbamate (e.r.) | Migrating group, R | Borane/boronic ester component | Product | Yield (%) (e.r., S:R) |
|---|---|---|---|---|---|
| 10 |  (99:1) | *p*Cl-$C_6H_4$- |  |  | 97 (99:1)‡ |
| 11 |  (99:1) | *p*MeO-$C_6H_4$- |  |  | 92 (98:2)‡ |
| 12 |  (99:1) | *m*$CF_3$-$C_6H_4$- |  |  | 92 (99:1)‡ |
| 13 |  (99:1) | 2-furyl |  |  | 94 (98:2)‡ |
| 14 |  (98:2) | Et |  |  | 82 (95:5) |
| 15 |  (98:2) | Et |  |  | 92 (4:96)§ |
| 16 |  (98:2) | Ph |  |  | 89 (4:96)† |
| 17 |  | Et |  |  | 87 (96:4)‖ |
| 18 |  | Et |  |  | 97 (2:98)‖ |
| 19 |  | Ph |  |  | 81 (4:96)‡‖ |
| 20 |  | Et |  |  | 69 (99:1)§‖ |
| 21 |  | Ph |  |  | 73 (6:94)‡‖ |
| 22 |  | Et |  |  | 90 (5:95)‖ |
| 23 |  | Et |  |  | 98 (91:9)§‖¶ |
| 24 |  | Ph |  |  | 97 (4:96)†‖ |

The reactions were carried out in $Et_2O$ in the presence of 1.1 equivalents of *s*BuLi, 1.1 equivalents of borane or 1.5 equivalents of boronic ester at the initial substrate concentration of 0.25 mol $l^{-1}$ (method A). The following abbreviations are used: Me, methyl; Et, ethyl; *i*Pr, isopropyl; *n*Hex, *n*-hexyl; Ph, phenyl; Cb, *N*,*N*-diisopropylcarbamoyl.

* Method B was used in the oxidative work-up.

† Two equivalents of boronic ester were used.

‡ 1.1 equivalents of boronic ester were used.

§ Three equivalents of boronic ester were used.

‖ Deprotonation was carried out over 5 min in the presence of 1.1 equivalents of TMEDA (method C).

¶ One equivalent of $LaCl_3$·2LiCl (ref. 30) was added at −78 °C before warming up to ambient temperature. Use of three equivalents of EtB(pin) gave ~80:20 enantiomeric ratio (e.r.) with or without $LaCl_3$·2LiCl.

ratio of the starting carbamate is given to show the maximum enantiomeric ratio of the tertiary alcohol that is attainable.

In the case of boranes, both symmetrical trialkyl boranes and 9-BBN derivatives were examined, and good yields and high enantiomeric ratios were observed in all cases (Table 1, entries 1, 3 and 5). Interestingly, when the 9-BBN derivatives were used (entries 3 and 5), the boron substituent, rather than the boracycle, migrated exclusively, as was observed in the case of the less hindered primary carbamates[24,25].

We explored a broader range of boronic esters, including alkyl (entries 2, 4 and 6), cyclopropyl (entry 7), vinyl (entry 8), allyl (entry 9), aryl (entries 10, 11 and 12) and heterocyclic substrates (entry 13), as many of these are commercially available. In all cases high levels of selectivity were observed. Interestingly, the 1,2-metallate rearrangement of the boronate complex (established for the example in entry 2) readily occurred at 0 °C whereas related reactions involving lithiated carbamates derived from primary alkyl alcohols required higher temperatures (35 °C) and an additional Lewis acid ($MgBr_2$) to trigger the rearrangement[22].

Perhaps the most intriguing outcome was that in all cases the reactions occurred with almost complete inversion of stereochemistry when boranes were used but almost complete retention of stereochemistry when boronic esters were used. For a broad set of reactions to occur with such complete and yet opposite selectivity for the two sets of related reagents is unique. The consequence is that from a single enantiomer of a secondary alcohol, either enantiomer of a tertiary alcohol can now be prepared in high yield with very high enantioselectivity.

The origin of this difference in selectivity between the two reagents can be rationalized as follows (Fig. 3)[17,18]. In the case of boronic esters, the oxygen of the ester complexes with the lithium of the metallated carbamate and so is delivered on the same face as the metal. In the absence of such complexation, as in the case of the boranes, reaction occurs on the face opposite to the metal where there is significant electron density owing to the partially flattened nature of the carbanion. However, it should be noted that reactions of lithiated alkylcarbamates derived from non-benzylic primary alcohols occur with complete retention of stereochemistry with both boranes and boronic esters, presumably because in this case the non-mesomerically stabilized carbanion is essentially $sp^3$ hybridized and has very little electron density opposite the metal.

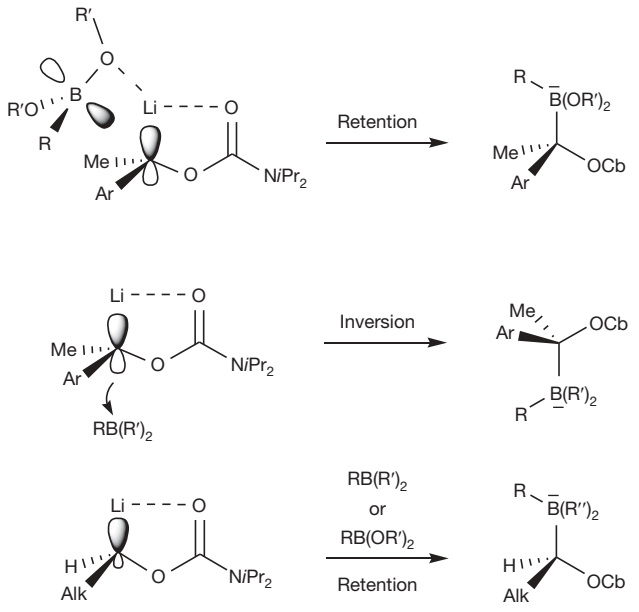



**Figure 3 | Rationalization of the inversion versus retention of stereochemistry observed in reactions of lithiated carbamates with boranes and boronic esters respectively.** Me, methyl; *i*Pr, isopropyl; Cb, *N*,*N*-diisopropylcarbamoyl.

In addition to the broad range of boron reagents tested, we examined alternative secondary alcohols bearing both electron-rich (*p*MeO-$C_6H_4$-) and electron-deficient (*p*Cl-$C_6H_4$-) aromatics. These were prepared by Noyori asymmetric transfer hydrogenation[23] of the corresponding ketones and subsequently converted into the required carbamates. These substrates worked just as well with both boranes and boronic esters (entries 14–19), demonstrating the scope of this sequence. Once again, reactions with boranes occurred with inversion whereas boronic esters occurred with retention; both sets of reactions proceeding with high and opposite selectivity. The process was also applied to carbamates derived from the commercially available cyclic secondary alcohols, (*S*)-1-indanol and (*S*)-1-tetralol with a range of boranes and boronic esters (entries 20–24), thus extending the scope of the methodology to this additional class of substrates.

Two points are worth noting. First, aryl boranes, such as Ph-9-BBN, could not be used with these carbamates because protodeboronation of the resulting homologated boranes occurred extensively during the aqueous oxidative work-up. In contrast, no protodeboronation occurred during oxidative work-up of aryl boronic ester-derived homologated products, thus leading to diarylsubstituted tertiary alcohols in good yields (entries 10–13, 16, 19, 21 and 24). Second, in the case of the indanol-derived carbamate, reaction with triethylborane or the corresponding boronic ester lead to the same enantiomer. This was not unexpected as this substrate had been shown to react consistently with retention of stereochemistry with a range of electrophiles, as a result of increased pyramidalization of the geometrically constrained carbanion[26] (as discussed above). In any case, opposite enantiomers of the indanyl-based tertiary alcohols are easily obtained from (*R*)-1-indanol which is also commercially available.

Although some of the tertiary alcohols presented in Table 1 can also be made with high enantioselectivity by titanium-catalysed addition of diorganozinc reagents to ketones[27–29], its scope is not as broad as that presented here. Tertiary alcohols with branched alkyl, vinyl and heteroaryl groups (entries 3–8 and 13), which are easily accessible in high enantiomeric ratio by our method, cannot be easily made by the alternative route. Furthermore, although a few diorganozinc reagents are commercially available, the vast number of commercially available boronic esters greatly aids the application of the current methodology.

The simple methodology that we have described converts the simplest and most readily accessible chiral functional group (secondary alcohols) into the most difficult to obtain chiral entities—quaternary stereogenic centres (tertiary alcohols)—with very high enantioselectivity. The process shows very broad substrate scope in terms of both the secondary alcohols and the boranes or boronic esters used, thus allowing access to a very broad range of tertiary alcohols. Furthermore, either enantiomer of the tertiary alcohol can be obtained with high enantioselectivity from the same enantiomer of the secondary alcohol, simply depending on whether a borane or boronic ester is used. The plethora of functional groups into which the intermediate boranes/boronic esters can potentially be converted adds considerably to this new methodology.

## METHODS SUMMARY

Enantioenriched secondary alcohols were obtained from commercial sources or prepared from the corresponding acetophenones by Noyori asymmetric transfer hydrogenation. These were converted into *N*,*N*-diisopropyl carbamates, deprotonated with *s*BuLi in $Et_2O$ at –78 °C, and then reacted with a borane or boronic ester (–78 °C). On warming, the intermediate 'ate' complexes underwent 1,2-migration to give the corresponding homologated boranes/boronic esters, which were oxidized *in situ* with an excess of alkaline hydrogen peroxide to afford chiral tertiary alcohols in good yields and high enantioselectivities.

**Full Methods** and any associated references are available in the online version of the paper at www.nature.com/nature.

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**Supplementary Information** is linked to the online version of the paper at www.nature.com/nature.

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**Author Information** Reprints and permissions information is available at www.nature.com/reprints. Correspondence and requests for materials should be addressed to V.K.A. (v.aggarwal@bristol.ac.uk).

## METHODS

**Method A.** To a stirred solution of the respective carbamate (1.00 mmol) in anhydrous $Et_2O$ (4.0 ml) at –78 °C (dry ice/acetone bath) under argon, *s*BuLi (0.82 ml of 1.3 M solution, 1.06 mmol) was added dropwise over 2 min. This mixture was allowed to stir at –78 °C for 20 min, and then 1 M solution of the respective borane (1.06 ml, 1.06 mmol) or boronic ester (1.1–3 ml, 1.1–3.0 mmol, see Table 1) in diethyl ether was added dropwise over 2 min with vigorous stirring. The reaction mixture was kept at –78 °C for an additional 30 min, then the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was diluted with anhydrous THF (4 ml) containing ~5 mg of 2,6-di-*tert*-butyl-4-methylphenol, cooled to ~2 °C (water-ice bath), and an ice-cold degassed mixture of 3 M NaOH (1.4 ml) and 30% aqueous $H_2O_2$ (0.8 ml) per 1 mmol of borane or boronic ester used was added all at once. The cooling bath was removed and the reaction mixture was stirred at ambient temperature for 2 h, then diluted with water (5 ml) and extracted with diethyl ether (3 × 10 ml). The combined organic phases were washed with brine (30 ml), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (PE/EtOAc) to afford pure tertiary alcohol.

**Method B.** Method A was followed, except that after the $NaOH/H_2O_2$ mixture was added, the reaction flask was fitted with a reflux condensor and stirring was continued at 60 °C (bath temperature) for 1 h, after which 1 ml of 30% $H_2O_2$ was added, and the mixture was refluxed for an additional 2 h. The remaining work-up was as described above.

**Method C.** Method A was followed, except that the deprotonation of a carbamate was performed in the presence of 1.1 equiv. of TMEDA (165 μl, 1.1 mmol) within 5 min.