

# Stereoselective preparation of quaternary benzylic centres using chiral imidazolines†

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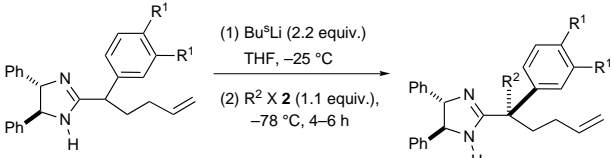
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Dianions derived from  $C_2$  symmetric chiral imidazolines provide good to excellent stereocontrol in alkylation reactions affording fully substituted benzylic centres.

Stereoselective preparation of quaternary centres, particularly in benzylic positions, remains a challenge. Carbometallation followed by nucleophilic substitution is seemingly a simple method, however, difficulties arise in both the preparation of the organometallic intermediate and also in the control of the stereoselectivity of the carbometallation in an inherently crowded position. Reports of the asymmetric preparation of vicinal heteroatom-stabilized tertiary organolithium compounds<sup>1,2</sup> are still scarce, although it is being actively studied by a number of groups.<sup>2</sup> Furthermore, stereoselective formation of fully  $C$ -substituted carbons *via* deprotonative carbolithiation remains elusive.<sup>3</sup>

In the wake of other studies on five-membered heterocycles as chiral auxiliaries,<sup>4</sup> we were interested in testing imidazolines in asymmetric substitution reactions. We observed that dianions derived from  $C_2$  symmetric chiral imidazoline **1**§ undergo diastereoselective alkylation in the presence of 1.1 equiv. of alkyl halides **2a–d** and afforded the corresponding fully  $C$ -substituted centres **3a–e** in good yield. The reaction was performed in THF and the dimetallated intermediate was formed without addition of supplementary complexing agents such as TMEDA or other additives.<sup>5</sup> Some representative examples are given in Table 1. Quaternary centres were obtained with good acyclic diastereoselectivity¶ and in good yield, as illustrated in entries 1–4. The presence of electron-donating substituents on the aryl side chain resulted in a drop in selectivity (entry 5).

**Table 1** Alkylation of dianions derived from  $C_2$  symmetric imidazolines using alkyl halides as electrophiles



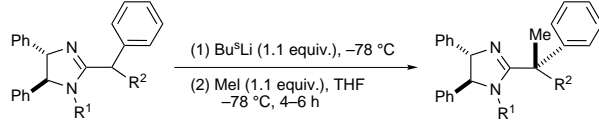
**1a** R<sup>1</sup> = H  
**b** R<sup>1</sup> = OMe

**3a** R<sup>1</sup> = H, R<sup>2</sup> = Me  
**b** R<sup>1</sup> = H, R<sup>2</sup> = CH<sub>2</sub>CH<sub>2</sub>OBu<sup>t</sup>  
**c** R<sup>1</sup> = H, R<sup>2</sup> = allyl  
**d** R<sup>1</sup> = H, R<sup>2</sup> = Bn  
**e** R<sup>1</sup> = OMe, R<sup>2</sup> = Me

Entry	1	2	Yield (%)	De (%)	3
1	<b>1a</b>	<b>2a</b> MeI	86	> 95	<b>3a</b>
2	<b>1a</b>	<b>2b</b> Bu <sup>t</sup> OCH <sub>2</sub> CH <sub>2</sub> I	79	> 95	<b>3b</b>
3	<b>1a</b>	<b>2c</b> Allyl I	79	92	<b>3c</b>
4	<b>1a</b>	<b>2d</b> BnBr	75	> 95	<b>3d</b>
5	<b>1b</b>	<b>2a</b> MeI	85	80	<b>3e</b>

Alkylation of monoanions derived from  $N$ -alkylated imidazolines such as **4a** proceeded with slightly lower diastereoselectivity. However, good stereocontrol was observed using the conformationally restrained bicyclic imidazoline **4b** (Table 2). Surprisingly, the diastereoselectivity in these reactions was the opposite to the observed for non-substituted  $C_2$  symmetric imidazolines **3a–e**, as was ascertained by chemical correlation between **3a** and **5a**: imidazoline **3a** was  $N$ -methylated using 1.1 equiv. of Bu<sup>n</sup>Li and 1.1 equiv. of MeI at  $-78$  °C, and the <sup>1</sup>H and <sup>13</sup>C MNR spectra of the resultant product were compared with that of **5a**.

**Table 2** Alkylation of monoanions derived from  $N$ -substituted imidazolines using methyl iodide

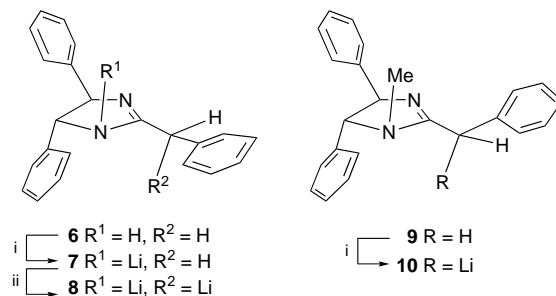


**4a** R<sup>1</sup> = Me, R<sup>2</sup> = CH<sub>2</sub>allyl  
**b** R<sup>1</sup>–R<sup>2</sup> = CH<sub>2</sub>CH<sub>2</sub>

**5a** R<sup>1</sup> = Me, R<sup>2</sup> = CH<sub>2</sub>allyl  
**b** R<sup>1</sup>–R<sup>2</sup> = CH<sub>2</sub>CH<sub>2</sub>

Entry	4	Yield (%)	De (%)	5
1	<b>4a</b>	86	72	<b>5a</b>
2	<b>4b</b>	21	> 95	<b>5b</b>

In order to provide a structural basis for the stereodifferentiation, the question of the  $C$ -*versus*  $N$ -lithiation dichotomy was addressed. A <sup>13</sup>C NMR study<sup>6</sup> of selected compounds **6** and **9** was undertaken (Scheme 1). The <sup>13</sup>C NMR spectrum at  $-69$  °C of the monolithiated intermediate **7** shows in a single set of well-resolved signals which were in accord with the expected  $N$ -lithiated product [ $C_{\alpha}$   $\delta$  40.2 (t, <sup>1</sup> $J_{C-H}$  125 Hz)]. Dimetallation using the standard procedure afforded a single, unsymmetrical product whose <sup>13</sup>C NMR signals at  $-69$  °C were in accord with those of the  $N$  and  $C_{\alpha}$  bis-lithiated compound **8**. The lithiated carbon [ $C_{\alpha}$   $\delta$  64.2 (d)] was shown to be slightly pyramidalised (<sup>1</sup> $J_{C-H}$  157 Hz)<sup>7</sup> and thus is stereogenic. The two *ortho* carbons of the benzylic side chain were found to be magnetically non-equivalent at this temperature, which indicates restrained conformational freedom of the side chain.



**Scheme 1** Reagents and conditions: i, Bu<sup>n</sup>Li (1.1 equiv.),  $-69$  °C; ii, Bu<sup>n</sup>Li (1.1 equiv.),  $-25$  °C, 25 min, then  $-69$  °C

Monolithiation of **9** under standard conditions afforded a single product whose  $^{13}\text{C}$  NMR signals at  $-69\text{ }^\circ\text{C}$  were in accord with those of the *C*-lithiated compound **10** [ $\text{C}_\alpha$   $\delta$  66.4 (d,  $^1J_{\text{C-H}}$  158 Hz)], structurally similar to the dimetallated counterpart **8** (Scheme 1). These results suggest in both cases the presence of carbometallated species prior to alkylation rather than the formation of *N*-metallated aza-enolates. The stereoselectivity of the alkylation reaction is thus dependent to the stereochemistry of this carbolithiated species<sup>1a,1b,8</sup> and is currently being investigated in our laboratory.||

In summary, the method described here allows the stereoselective preparation of either stereoisomeric quaternary benzylic centre independently of the stereochemistry of the inducting chiral auxiliary, using non-complexing alkyl halides.<sup>8</sup> Beyond the perspective of building fully *C*-substituted benzylic quaternary carbons<sup>9</sup> the method could also be useful in providing access to other, covalently linked stereodefined tertiary organometallic compounds useful in asymmetric synthesis.

## Notes and References

† Dedicated to Professor Yoshito Kishi on the occasion of his 60th birthday.

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§ Racemic imidazolines were used as starting materials for the alkylation reactions. Starting materials were prepared by classical condensation of the corresponding imino ether hydrochloride, itself obtained from arylacetone nitrile, and *trans*-1,2-diphenylethylenediamine, see ref. 4(c).

¶ The diastereoselectivity of the reaction was measured by  $^1\text{H}$  NMR analysis by integrating the  $\alpha$ -methyl or other characteristic signals.

|| The configuration of the newly formed stereocentre was established by chemical correlation. This synthesis will be presented in due course.

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