

## $\alpha$ -Metallation of Tetrahydroquinoline and Indoline *via* their Lithium Carbamates: A Versatile One-Pot Procedure<sup>1</sup>

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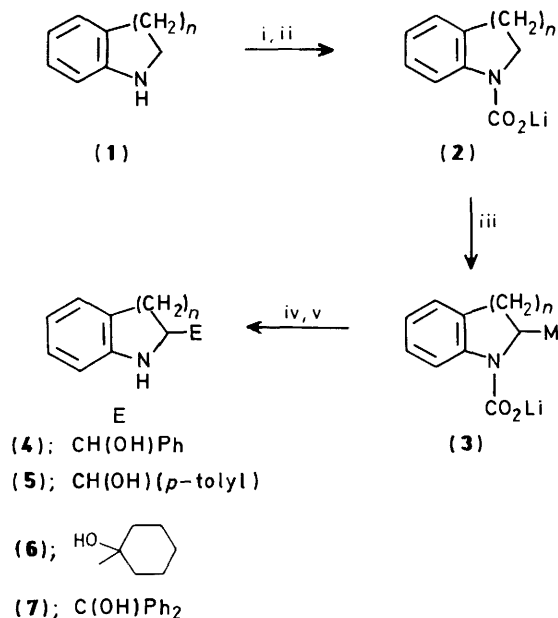
1,2,3,4-Tetrahydroquinoline and indoline as their lithium carbamates undergo  $\alpha$ -metallation with a  $\text{Bu}^t\text{Li-KO}^t\text{Bu}^t$  mixture. The resulting  $\alpha$ -metallo species react with carbonyl electrophiles to give the  $\alpha$ -alkylated secondary amines in an overall one-pot procedure.

The generation of  $\alpha$ -organolithium synthons for  $\alpha$ -carbanions derived from secondary amines is a subject of active synthetic pursuit.<sup>2</sup> *N*-Nitrosoamines,<sup>3</sup> formamidines,<sup>4</sup> phosphoramides<sup>5</sup> and hindered amides<sup>6</sup> have been developed as efficient synthons for  $\alpha$ -lithio secondary amines: each enables electrophilic substitution at the  $\alpha$ -carbon and each can be deprotected to yield an  $\alpha$ -substituted secondary amine. Very recently, asymmetric  $\alpha$ -alkylations of secondary amines have been achieved in high enantiomeric excesses.<sup>7</sup> However, the  $\alpha$ -alkylation of a secondary amine by each of these methods requires a sequence of three distinct steps: protection of the more acidic NH,  $\alpha$ -lithiation and subsequent alkylation, and finally, deprotection to liberate the  $\alpha$ -alkylated secondary amine. It is believed that the N-protecting group plays a crucial role in this sequence and most often, is instrumental in directing the lithiation onto the  $\alpha$ -carbon.<sup>8</sup> However, the protecting groups employed so far<sup>3</sup> suffer from certain disadvantages, *e.g.*, *N*-nitrosamines are highly toxic whereas others require moderate to very harsh conditions for deprotection, which is virtually impossible for the hindered amides.

We recently introduced  $\text{CO}_2$  as a novel protecting group for lithiation  $\alpha$  or  $\beta$  to heteroatoms.<sup>9</sup> Particularly attractive features of the  $\text{CO}_2$ -protection method are that the protecting group can be attached to the heteroatom very easily and that deprotection occurs spontaneously during the work-up stage. This allows the multi-step sequences of previous methods to be simplified into a one-pot procedure. Such a procedure has been used for a secondary amine, namely tetrahydroisoquinoline, the lithium carbamate of which (derived from the *N*-lithio amine and  $\text{CO}_2$ ) was smoothly lithiated at the 1-position with  $\text{Bu}^t\text{Li}$  in THF.<sup>10a</sup> Recently, Seebach has extended this methodology to provide a highly diastereoselective  $\alpha$ -alkylation of tetrahydroisoquinoline.<sup>10b</sup>

Successful  $\alpha$ -lithiation (at C-1) of tetrahydroisoquinoline *via* its lithium carbamate is aided by the fact that the methylene group in question is activated towards proton loss, being benzylic in nature. Extension of the  $\text{CO}_2$ -protection method to secondary amines devoid of such additional activation has now been achieved after extensive experimentation. We report that the  $\alpha$ -metallation of the non-benzylic secondary amines tetrahydroquinoline (**1a**) and indoline (**1b**) occurs *via* their lithium carbamates under slightly modified reaction conditions.

The desired lithium carbamates (**2a,b**) are formed readily from the amines by sequential addition of  $\text{BuLi}$  (1 equiv.) in tetrahydrofuran (THF) followed by  $\text{CO}_2$  gas. Despite considerable effort,<sup>11</sup>  $\alpha$ -lithiation of these lithium carbamates could not be realized with  $\text{Bu}^t\text{Li}$  alone, under a variety of reaction conditions. However, exposure of THF solutions of (**2a,b**) to an equimolar mixture of  $\text{Bu}^t\text{Li-KO}^t\text{Bu}^t$  (1 equiv.) ( $-78^\circ\text{C}$ — $-50^\circ\text{C}$ ) produced a wine-red solution of the  $\alpha$ -metallated species (**3a,b**), which could be trapped with various electrophiles



**Scheme.** Series *a*: tetrahydroquinoline ( $n = 2$ ) and series *b*: indoline ( $n = 1$ ). Reagents and conditions: i,  $\text{Bu}^t\text{Li}$ ; ii,  $\text{CO}_2$ ; iii,  $\text{Bu}^t\text{Li-KO}^t\text{Bu}^t$ , THF,  $-50^\circ\text{C}$ ; iv, Electrophile (EX); v,  $\text{H}^+ - \text{H}_2\text{O}$ .

(see Scheme). Hydrolytic work-up (2M HCl at  $20^\circ\text{C}$ ) afforded directly the  $\alpha$ -alkylated products (**4**)—(**7**) (Table).

The benzaldehyde  $\alpha$ -adduct (**4a**) from tetrahydroquinoline comprised a 40:60 mixture of the *syn:anti* diastereoisomers which were separated by column chromatography (silica gel, 10% EtOAc in hexane containing 10%  $\text{Et}_3\text{N}$ ); both isomers were isolated as crystalline solids. The stereochemical assignments for the two isomers are based, tentatively, on their  $^1\text{H}$  n.m.r. (200 MHz) data and are in analogy to those already reported<sup>12,13</sup> for similar compounds. In the *anti*-isomer (m.p.  $147$ — $149^\circ\text{C}$ , from benzene–light petroleum),  $\text{CHOH}$  showed a doublet ( $J$  10 Hz) at  $\delta$  4.65 whereas the corresponding proton for the *syn*-isomer (m.p.  $105$ — $107^\circ\text{C}$ , from ether–light petroleum) appeared at a more downfield region,  $\delta$  4.97 and with a smaller coupling constant (*d*,  $J$  6 Hz). In their  $^{13}\text{C}$  n.m.r. spectra, both isomers showed the requisite number of carbons, the  $\alpha$ -hydroxy carbons being found at 75.1 and 76.0 p.p.m. whereas the  $\alpha$ -amino carbons appeared at 41.6 and 43.0 p.p.m., respectively for the *anti* and the *syn* adducts.

The reaction of the  $\alpha$ -metallo indoline carbamate (**3b**) with *p*-tolualdehyde similarly produced the  $\alpha$ -adduct (**5b**) as a mixture of two diastereoisomers (52%, *syn:anti* = 55:45), which could also be separated on silica gel (15% EtOAc in hexane containing

**Table.** Reactions of  $\alpha$ -metallo lithium carbamates (**3**) with electrophiles

Amine ( <b>1a</b> )	Electrophile	Product ( <b>4a</b> )	E in product	% Yield <sup>a</sup>	M.p.(°C)
( <b>1a</b> )	PhCHO	( <b>4a</b> )	PhCHOH	55 <sup>b,c</sup>	<i>anti</i> 147–149 <i>syn</i> 105–107
( <b>1a</b> )	Cyclohexanone	( <b>6a</b> )	(CH <sub>2</sub> ) <sub>5</sub> COH	52	Viscous oil
( <b>1a</b> )	Ph <sub>2</sub> CO	( <b>7a</b> )	Ph <sub>2</sub> COH	55	128–129
( <b>1b</b> )	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CHO	( <b>5b</b> )	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CHOH	52 <sup>b,d</sup>	<i>anti</i> 130–133 <i>syn</i> 123–125
( <b>1b</b> )	Cyclohexanone	( <b>6b</b> )	(CH <sub>2</sub> ) <sub>5</sub> COH	57	108–110

<sup>a</sup> Isolated overall yields after column chromatography of products. <sup>b</sup> Diastereoisomers separated by flash chromatography and independently characterized, <sup>c</sup> *anti*:*syn* = 60:40, <sup>d</sup> *anti*:*syn* = 45:55.

15% Et<sub>3</sub>N). Here again, CHOH of the *syn*-isomer appeared at a more downfield region [ $\delta$  4.85 (d, *J* 6 Hz)] than that [ $\delta$  4.6 (d, *J* 8 Hz)] of the *anti*-isomer. In their <sup>13</sup>C n.m.r. spectra the  $\alpha$ -hydroxy carbons appeared at  $\delta$  75.2 and 75.6 p.p.m. whereas the  $\alpha$ -amino carbons were assigned to the methine signals at 48.6 and 49.3 p.p.m., respectively for the *anti* and the *syn* isomers of (**5b**).

Both of the  $\alpha$ -metallo species (**3a**) and (**3b**) reacted with cyclohexanone affording the corresponding products (**6a**) and (**6b**) in 52 and 57% yields, respectively. Additionally, (**3a**) was successfully treated with benzophenone to produce (**7a**) in 55% yield. Unfortunately, other electrophiles like alkyl halides (BuI or C<sub>6</sub>H<sub>13</sub>I), acid chlorides (PhCOCl), or esters (PhCO<sub>2</sub>Me, ClCO<sub>2</sub>Me) gave either complex reaction mixtures or very poor yields of the  $\alpha$ -alkylation products. Presumably, during acylation studies the desired products were not stable to the highly basic reaction medium (K/Li-OBu<sup>t</sup>) and succumbed to further reactions *via* enolization and/or further alkylation producing complex mixtures.

We are presently unsure of the nature of 'M' in the  $\alpha$ -metallo species (**3**). On the basis of Schlosser's studies of KOBu<sup>t</sup>-RLi systems,<sup>14</sup> we tentatively assign it as potassium; \* as such, (**3**) failed to react with highly lithiophilic electrophiles like PhSeSePh, PhSSPh, or DMF. Also, the role of CO<sub>2</sub> in the  $\alpha$ -metallation step is not completely understood. Presumably, it increases the kinetic acidity of the  $\alpha$ -hydrogens by electron withdrawal (partial dipole creation), apart from protecting the N-centre. This is suggested by the fact<sup>11</sup> that bistetrahydroisoquinolinylmethane<sup>15</sup> or *N*-(*t*-butyldimethylsilyl)indoline, systems without an electron withdrawing N-protecting group, could not be  $\alpha$ -metallated with Bu<sup>t</sup>Li-KOBu<sup>t</sup>. However, in all the successful cases listed in the Table, some starting amine was invariably recovered, possibly as a result of partial cleavage of the protecting group in the  $\alpha$ -metallation step.

The advantages of the methodology discussed in this report can be seen by a detailed comparison with that previously available. There is only a single previous report of the successful  $\alpha$ -lithiation of tetrahydroquinoline and indoline which was achieved *via* their formamidines.<sup>12</sup> We note the following. (i) The formamidine method apparently needs four steps: conversion of the secondary amine into the formamide (yield unstated but the reference<sup>16</sup> quoted by Meyers gives yields of 62–84% in analogous cases), transformation to the formamidine, lithiation/reaction with electrophile, and deprotection.

(ii) In the formamidine case the following electrophiles were used successfully: for tetrahydroquinoline: MeI (53%), BuI (68%), PhCHO (52%); for indoline: MeI (61%), EtI (48%),

PhCHO (53%) (these yields assume 84% yields in the conversions of the amines to their formamides). No attempts were reported with cyclohexanone or benzophenone as electrophiles.

(iii) For deprotection, the formamidine method required refluxing 2M KOH or, N<sub>2</sub>H<sub>4</sub>-HOAc at 50 °C, and for the benzaldehyde adducts, the particularly harsh conditions of prolonged reflux with LiAlH<sub>4</sub> in THF.

(iv) In the formamidine method the products of the reaction with benzaldehyde were described only as the HCl salts of the mixtures of diastereoisomers.

In summary, we have described a novel procedure for  $\alpha$ -metallation of 1,2,3,4-tetrahydroquinoline and indoline. Our method is highlighted by an easy protection–easy deprotection protocol which offers a convenient one-pot procedure for  $\alpha$ -alkylation of secondary amines. We are currently looking into the possible extension of this methodology to other secondary amine substrates.†

## Experimental

M.p.s were determined on a Bristoline hot-stage microscope and are uncorrected. <sup>1</sup>H N.m.r. spectra were recorded at 200 MHz on a Varian XL200 spectrometer and chemical shifts are reported in  $\delta$  (p.p.m.) downfield from Me<sub>4</sub>Si. <sup>13</sup>C N.m.r. spectra were recorded at 50 MHz with a Varian XL200 instrument using the solvent peaks (CDCl<sub>3</sub>,  $\delta$  77.0 or [<sup>2</sup>H<sub>6</sub>]DMSO,  $\delta$  39.5) as references. The nature of the respective carbons were determined by the Attached Proton Test. Elemental Analyses (C, H, N) were performed by Dr. R. W. King of this department. THF was freshly distilled from sodium–benzophenone. Column chromatography was carried out on MCB (230–400) silica gel with predistilled solvents.

*Experimental Procedure.*—BuLi (2.5M in hexane; 2 ml, 5 mmol) was added dropwise at –78 °C, under argon, to a solution of the amine (5 mmol) in dry THF (35 ml) in a 250 ml Schlenk type reactor. It was then slowly warmed to room temperature and dry CO<sub>2</sub> gas rapidly bubbled through it. The solution turned colourless (a colourless solution at this stage is vital for ultimate success; poor yields were obtained otherwise). All volatile contents were removed at 0.5 mmHg to leave a white powdery residue of the lithium carbamates (**2**). A preheated (140 °C, 0.5 mm, 2 h) sample of KOBu<sup>t</sup> (5 mmol) was then quickly added to (**2**) under argon. After adding dry THF (40 ml), Bu<sup>t</sup>Li (1.7M in pentane, 3 ml, 5 mmol) was introduced dropwise at –78 °C and the resulting wine-red solution was stirred for 2 h at –50 °C. The appropriate electrophile was then added at –78 °C and the mixture stirred at room temperature for 8 h; all the solvent was then removed at 0.5 mmHg. The residue was treated with 2M HCl (10 ml) at 20 °C, after gas evolution ceased, it was basified with solid Na<sub>2</sub>CO<sub>3</sub> and

\* Addition of LiBr to solutions of (**3**), before adding the electrophiles, produced poor yields of products.

† Preliminary results with lithium piperidinylcarbamate and KOBu<sup>t</sup>-Bu<sup>t</sup>Li show promise and will be reported in due course.

extracted with EtOAc or  $\text{CH}_2\text{Cl}_2$  ( $3 \times 15$  ml). The combined organic layers were washed with brine and dried ( $\text{Na}_2\text{SO}_4$ ). Removal of solvent followed by flash chromatography (silica gel, 5–15% gradient of EtOAc in hexane containing 10–15%  $\text{Et}_3\text{N}$ ) gave the products which [except (6a)] were further purified by recrystallization from appropriate solvents. According to this general procedure, the following products were prepared:

*anti*-(4a):  $R_F$  0.5 (silica gel, 10% EtOAc in hexane containing 10%  $\text{Et}_3\text{N}$ ); m.p. 147–149 °C (needles from benzene–light petroleum) (Found: C, 80.5; H, 7.0; N, 5.8.  $\text{C}_{16}\text{H}_{17}\text{NO}$  requires C, 80.30; H, 7.16; N, 5.85%);  $\delta_{\text{H}}(\text{CDCl}_3/[\text{T}_2\text{H}_6]\text{DMSO}/\text{D}_2\text{O})$  1.6 (2 H, m), 3.1 (3 H, m), 4.65 (1 H, d,  $J$  10 Hz), 6.4–6.6 (2 H, m), 7.0 (1 H, m), and 7.2–7.5 (6 H, m);  $\delta_{\text{C}}$  (50 MHz) 22.0 ( $\text{CH}_2$ ), 36.6 ( $\text{CH}_2$ ), 41.6 (CHN), 75.1 (CHOH), 112.4 (aromatic CH), 113.7 (aromatic CH), 119.6 (aromatic C), 125.6 (aromatic CH), 125.7 (aromatic CH), 125.8 (aromatic CH), 126.7 (aromatic CH), 130.1 (aromatic CH), 142.8 (aromatic C), and 143.6 (aromatic C).

*syn*-(4a):  $R_F$  0.4 (silica gel, 10% EtOAc in hexane containing 10%  $\text{Et}_3\text{N}$ ); m.p. 105–107 °C (needles from ether–light petroleum) (Found: C, 80.3; H, 7.3; N, 5.55.  $\text{C}_{16}\text{H}_{17}\text{NO}$  requires C, 80.30; H, 7.16; N, 5.85%);  $\delta_{\text{H}}(\text{CDCl}_3/\text{D}_2\text{O})$  1.65 (1 H, m), 2.2 (1 H, m), 3.0 (1 H, m), 3.2 (1 H, m), 3.4 (1 H, m), 4.97 (1 H, d,  $J$  6 Hz), 6.4–6.7 (3 H, m), 6.9 (1 H, m), and 7.2–7.3 (5 H, m);  $\delta_{\text{C}}$  21.7 ( $\text{CH}_2$ ), 39.2 ( $\text{CH}_2$ ), 43.0 (CHN), 76.0 (CHOH), 114.3 (aromatic CH), 116.7 (aromatic CH), 120.4 (aromatic C), 126.3 (aromatic CH), 127.1 (aromatic CH), 127.4 (aromatic CH), 128.1 (aromatic CH), 129.2 (aromatic CH), 142.5 (aromatic C), and 145.6 (aromatic C).

*anti*-(5b):  $R_F$  0.4 (silica gel, 15% EtOAc in hexane containing 15%  $\text{Et}_3\text{N}$ ); m.p. 130–133 °C (microcrystals from chloroform–hexane); (Found:  $M^+$  239.1313.  $\text{C}_{16}\text{H}_{17}\text{NO}$  requires  $M$ , 239.1310);  $\delta_{\text{H}}(\text{CDCl}_3/\text{D}_2\text{O})$  2.3 (3 H, s), 3.0–3.3 (2 H, m), 3.55 (1 H, m), 4.6 (1 H, d,  $J$  8 Hz), 6.5–6.7 (2 H, m), and 7.0–7.4 (6 H, m);  $\delta_{\text{C}}$  20.4 ( $\text{CH}_3$ ), 48.6 (CHN), 49.1 ( $\text{CH}_2$ ), 75.2 (CHOH), 108.9 (aromatic CH), 117.6 (aromatic CH), 125.4 (aromatic CH), 126.0 (aromatic CH), 126.9 (aromatic CH), 128.0 (aromatic CH), 129.9 (aromatic C), 136.0 (aromatic C), 139.9 (aromatic C), and 151.3 (aromatic C).

*syn*-(5b):  $R_F$  0.3 (silica gel, 15% EtOAc in hexane containing 15%  $\text{Et}_3\text{N}$ ); m.p. 123–125 °C (microcrystals from benzene–light petroleum) (Found:  $M^+$ , 239.1316.  $\text{C}_{16}\text{H}_{17}\text{NO}$  requires  $M$ , 239.1310);  $\delta_{\text{H}}(\text{CDCl}_3/\text{D}_2\text{O})$  2.35 (3 H, m), 3.5–3.7 (3 H, m), 4.85 (1 H, d,  $J$  6 Hz), 6.5–6.65 (2 H, m), and 7.0–7.3 (6 H, m);  $\delta_{\text{C}}$  21.1 ( $\text{CH}_3$ ), 49.3 (CHN), 49.7 ( $\text{CH}_2$ ), 75.6 (CHOH), 110.0 (aromatic CH), 118.5 (aromatic CH), 125.0 (aromatic CH), 126.5 (aromatic CH), 128.1 (aromatic CH), 128.6 (aromatic C), 129.0 (aromatic CH), 137.3 (aromatic C), 139.5 (aromatic C), and 152.2 (aromatic C).

(6a):  $R_F$  0.5 (silica gel, 12% EtOAc in hexane containing 10%  $\text{Et}_3\text{N}$ ); viscous oil; (Found:  $M^+$ , 231.1632.  $\text{C}_{15}\text{H}_{21}\text{NO}$  requires  $M$ , 231.1624);  $\delta_{\text{H}}(\text{CDCl}_3/\text{D}_2\text{O})$  1.4–1.7 (11 H, m), 2.2–2.3 (1 H, m), 2.7 (1 H, m), 3.3 (1 H, m), 3.55 (1 H, m), 6.4–6.6 (2 H, m), and 6.9–7.0 (2 H, m);  $\delta_{\text{C}}$  22.0 ( $\text{CH}_2$ ), 22.2 ( $\text{CH}_2$ ), 25.8 ( $\text{CH}_2$ ), 34.1 ( $\text{CH}_2$ ), 37.6 ( $\text{CH}_2$ ), 39.2 ( $\text{CH}_2$ ), 44.5 (CHN), 73.8 (COH), 113.9 (aromatic CH), 115.6 (aromatic CH), 119.8 (aromatic C), 127.6 (aromatic CH), 131.5 (aromatic CH), and 145.3 (aromatic C).

(6b):  $R_F$  0.5 (silica gel, 15% EtOAc in hexane containing 15%  $\text{Et}_3\text{N}$ ); m.p. 108–110 °C (needles from ether–hexane) (Found: C, 77.35; H, 9.05; N, 6.15.  $\text{C}_{14}\text{H}_{19}\text{NO}$  requires C, 77.38; H, 8.81; N, 6.45%);  $\delta_{\text{H}}(\text{CDCl}_3/\text{D}_2\text{O})$  1.3–1.8 (10 H, m), 3.25 (1 H, t,  $J$  7 Hz), 3.6 (2 H, d,  $J$  7 Hz), 6.6–6.7 (2 H, m), and 7.0–7.3 (2 H, m);  $\delta_{\text{C}}$  21.6 ( $\text{CH}_2$ ), 25.7 ( $\text{CH}_2$ ), 33.8 ( $\text{CH}_2$ ), 34.4 ( $\text{CH}_2$ ), 48.8 ( $\text{CH}_2$ ), 52.9 (CHN), 73.6 (COH), 109.6 (aromatic CH), 118.1 (aromatic

CH), 126.3 (aromatic CH), 127.9 (aromatic CH), 128.5 (aromatic C), and 152.5 (aromatic C).

(7a):  $R_F$  0.5 (silica gel, 10% EtOAc in hexane containing 10%  $\text{Et}_3\text{N}$ ); m.p. 128.129 °C (plates from ether–hexane) (Found: C, 83.8; H, 6.95; N, 4.1.  $\text{C}_{22}\text{H}_{21}\text{NO}$  requires C, 83.78; H, 6.71; N, 4.44%);  $\delta_{\text{H}}(\text{CDCl}_3/\text{D}_2\text{O})$  1.8 (1 H, m), 2.1 (1 H, m), 3.0 (1 H, m), 3.4 (1 H, m), 4.05 (1 H, m), 6.2–6.55 (3 H, m), 6.95 (1 H, m), and 7.1–7.8 (10 H, m);  $\delta_{\text{C}}$  24.1 ( $\text{CH}_2$ ), 39.6 ( $\text{CH}_2$ ), 43.9 (CHN), 81.5 (COH), 114.4 (aromatic CH), 116.4 (aromatic CH), 118.9 (aromatic C), 125.8 (aromatic CH), 126.1 (aromatic CH), 126.2 (aromatic CH), 127.8 (aromatic CH), 128.0 (aromatic CH), 130.8 (aromatic CH), 145.3 (aromatic C), 146.3 (aromatic C), and 147.8 (aromatic C).

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