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Asymmetric Synthesis of α-Amino Acid Derivatives *via* an Electrophilic Amination of Chiral Amide Cuprates with Li *t*-Butyl-N-Tosyloxycarbamate

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Abstract: *The utility of lithium t-butyl-N-tosyloxycarbamate (LiBTOC) as a (+)NHBOC synthon in highly diastereoselective reactions with chiral cis-aminoindanol derived amide cuprates is described. The diastereoselectivities of these reactions ranged from 96% to greater than 99%. The subsequent transformation of these adducts to α-amino acids is also described.*

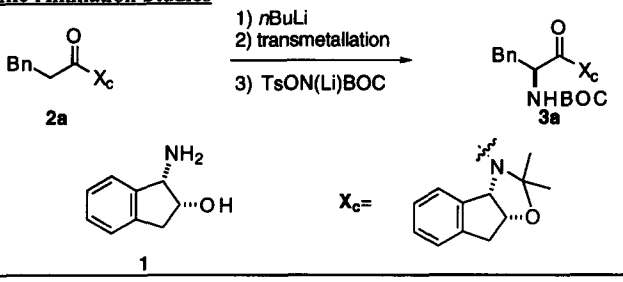
The importance of α-amino acids has stimulated the development of numerous methods for their synthesis.[1] Among these, the electrophilic amination of chiral enolates possesses a broader degree of generality than the alkylation of chiral glycine derivatives, since the latter process is subject to the limitations of alkyl halide reactivity.[2] Unfortunately, only a few suitable reagents capable of electrophilic amination have thus far been identified, for example, di-*t*-butyl azodicarboxylate[3], trisyl azide[4], 1-chloro-1-nitrosocyclohexane[5] and hydroxyamine derivatives.[6] Genet *et al.* have shown that lithium *t*-butyl-N-tosyloxycarbamate (LiBTOC) reacts with various organometallics to afford N-BOC-protected amine derivatives.[7] The commercially available 1S,2R-*cis* aminoindanol **1** makes it an attractive template for developing new methods in asymmetric synthesis, for example, as an auxiliary or as a component of chiral ligands.[8] As an extension of our recent work on the 1,2-migration of chiral enolate zincates[9], a highly diastereoselective electrophilic amination of chiral amide cuprates has been developed, based on the use of lithium *t*-butyl-N-tosyloxycarbamate (LiBTOC) as a "+NHBOC" synthon.

The amide substrates **2a-g** chosen for this study were prepared from the corresponding acid chlorides. The acid chlorides were reacted with 1S,2R-*cis* aminoindanol **1** in the presence of triethylamine to afford the hydroxyamides, which were subsequently treated with 2-methoxypropene and PPTS to give the desired amides **2a-g**. Using this highly efficient one-pot procedure, various amides **2a-g** have been prepared in high yields (91%-98%).[10]

Initial electrophilic amination studies were conducted on the dihydrocinnamate derivative **2a** (Table 1). LiBTOC was freshly prepared by deprotonation of *t*-butyl-N-tosyloxycarbamate with *n*BuLi. The direct reaction of the lithium amide enolate of **2a** with LiBTOC did not yield the expected α-BOC-protected amino amide **3a** (entry 5). Similarly, amination under conditions which were presumed to generate diorganozinc (entries 1 and 6), organozinc chloride (entry 2), and higher order zincate species (entries 3 and 4) were also unsuccessful. In contrast, after transmetallation of the

lithium enolate of **2a** with CuCN (1.1 equiv.), the resultant amide cuprate reacted rapidly with LiBTOC at -78 °C to afford the α-BOC-protected amino amide **3a** in 77% yield.

Table 1. Electrophilic Amination Studies



Entry	Li enolate (equiv.)	M /equiv.	TsON(Li)BOC (equiv.)	BnOLi (equiv.)	Temp. (°C)	Product (3a)
1	1.0	$ZnCl_2$/0.5	1.1	-	-78 -> 0	0%
2	1.0	$ZnCl_2$/1.0	1.1	-	-78 -> 0	0%
3	1.0	$ZnCl_2$/1.0	1.1	3.0	-78 -> 0	0%
4	1.0	$ZnCl_2$/0.5	1.1	3.0	-78 -> 0	0%
5	1.0	-	1.1	-	-78 -> 0	0%
6	1.0	MeZnCl/1.0	1.1	-	-78 -> 0	0%
7	1.0	CuCN/1.0	1.1	-	-78 -> 0	77%[a]

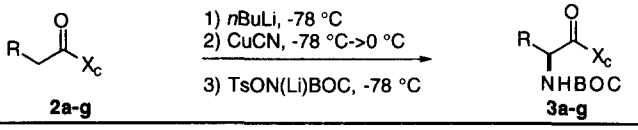
[a] isolated yield.

A controlled study of deprotonation was examined on the isobutyric derivative **2f**. The lithium amide enolate, generated with *n*BuLi (1.1 equiv.) in THF at -78 °C, was quenched by the addition of AcOH in MeOH at -78 °C and only 85% of the amide was recovered (determined by HPLC). During deprotonation, two major by-products were formed: (1) the indeneamide **4** derived from benzylic deprotonation followed by β-elimination of acetone and (2) the acetone-aldol product **5** of the lithium enolate and the liberated acetone.[11] The lithium enolate, generated as described above, was transferred *via* cannula into a slurry of CuCN (1.1 equiv.) in THF at -78 °C. The slurry was allowed to warm until dissolution was complete (ca. -5 °C). The resulting cuprate was cooled to -78 °C, and quenched by the addition of AcOH in MeOH at -78 °C. HPLC analysis showed that there was no further decomposition during the transmetallation.

Having established a viable route to the amide cuprates, several amides **2a-g** were examined for amination via the amide cuprate protocol (Table 2). The amide cuprates, generated as described above, were allowed to react with the freshly prepared LiBTOC (1.1 equiv.) at -78 °C for 30 min. After the solution was quenched at -78 °C with MeOH (5 equiv.), followed by the addition of a saturated NH_4Cl solution (aq), the reactions were allowed to warm to ambient temperature. The resultant α-BOC-protected amino amides **3a-g** were isolated as single diastereomers by simple flash chromatography. From the data in Table 3 it is evident that this amination process enjoys considerable generality while displaying excellent diastereoselectivity. As expected, diminished reactivity towards LiBTOC was

observed with more sterically hindered substrates. The assignment of absolute configuration to the major product diastereomers was made by correlation with α-amino acids of known configuration *via* a two step sequence.[12] As in the analogous alkylation[8a, 11] and 1,2-migration of enolate zincate studies[9], the sense of asymmetric induction observed in this amination process was consistent with preferential approach of LiBTOC from the least hindered face of the M-enolate rotamer.[11] Procedures for removal of the auxiliary were very straightforward. Hydrolysis with 6N HCl afforded α-amino acids in good yields (high ee) and proved to be generally effective for *cis*-aminoindanol amide hydrolysis (Table 3). After the pH of the reaction mixture was adjusted to 11, *cis*-aminoindanol was recovered by extraction of the aqueous solution with dichloromethane (80%).

Table 2. Electrophilic Amination of Amide Cuprates

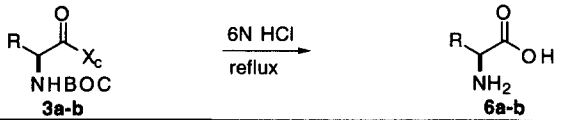


2a-g **3a-g**

entry	amide	R	product	% isolated yield	% de	config.
1	2a	$PhCH_2$	3a[13]	77 (79)[a]	≥99	S
2	2b	Ph	3b	51 (56)[a]	≥99	S
3	2c	CH_3	3c	63 (72)[a]	≥99	S
4	2d	$CH_3(CH_2)_3$	3d	68 (76)[a]	96.3	S
5	2e	$(CH_3)_2CHCH_2$	3e	72 (80)[a]	≥99	S
6	2f	$(CH_3)_2CH$	3f	67[b]	≥99	S
7	2g	$(CH_3)_3C$	3g	52 (80)[a]	≥99	S

[a] based on recovered sm. [b] based on BOCNHOTs. 2equiv. amide was used.

Table 3. Hydrolysis of *cis*-Aminoindanol Amides



3a-b **6a-b**

entry	substrate	R	product	%yield[a]	%ee[b]
1	3a	$PhCH_2$	6a	86.1	98.2
2	3b	Ph	6b	81.2	89.4

[a] based on HPLC assay yield. [b] determined by HPLC analysis using a Crownpak CR(+) column.

In conclusion, the electrophilic amination of chiral amide cuprates with LiBTOC, where "$^{+}$NHBOC" was directly transfered to a wide range of amides with predictable absolute configuration in high enantiomeric purity and good yield, provides an expedient approach to the asymmetric synthesis of α-amino acid derivatives.

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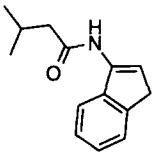
10. **2g** was prepared via a two-step sequence. The mixed pivalic acid anhydride, which was generated *in situ* from the corresponding carboxylic acid, reacted with *cis*-aminoindanol to give the hydroxyamide. After workup, the isolated hydroxyamide was treated with 2-methoxypropene and PPTS to afford the desired amide **2g**.
11. Askin et al. also observed the indeneamide by-product derived from benzylic deprotonation in a similar system. Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771.



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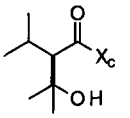

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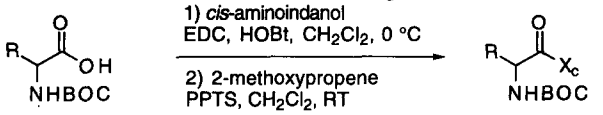
12. The absolute stereochemistry of the compounds as well as their structures were determined unequivocally by the following protocol. The commercially available N-BOC-protected amino acids were coupled with 1S,2R-*cis* aminoindanol **1** according to the scheme below. The resulting diastereomers were baseline-resolved by HPLC using a Zorbax Rx-C8 reversed-phased column. Conditions for amide formation see: Ho, G. J.; Emerson, K. M.; Mathre, D.; Shuman, R. F.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 3569.



13. [3aS-[3(R*), 3aα, 8aα]]-[2-(8, 8a-dihydro-2,2-dimethyl-2*H*-indeno[1,2-*d*]oxazol-3(3a*H*)-yl)-2-oxo-1-(phenylmethyl)ethylcarbamic acid 1,1-dimethylethyl ester (**3a**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.16 (m, 7H), 6.93-6.87 (m, 1 H), 6.22 (d, J=7.5 Hz, 1H), 5.85 (d, J=4.3 Hz, 1H), 5.11 (d, J=9.6 Hz, 1H), 4.94-4.82 (m, 2H), 3.48 (dd, J=13.4, 8.0 Hz, 1H), 3.08-3.06 (m, 2H), 2.99 (dd, J=13.5, 6.4 Hz, 1H), 1.64 (s, 3H), 1.40 (s, 9H), 1.33 (s, 3H): ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 168.5, 155.4, 140.7, 140.4, 137.0, 129.9, 128.7, 128.1, 127.1, 127.0, 125.5, 123.9, 96.7, 80.0, 79.3, 65.7, 54.8, 38.6, 36.2, 28.2, 26.3, 23.8.; Analysis calc'd for $C_{26}H_{32}N_2O_4$: C, 71.54 H, 7.39; N, 6.42; found: C, 71.75; H, 7.36; N, 6.34.

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