J|A|C|S
COMMUNICATIONS

Published on Web 07/25/2006

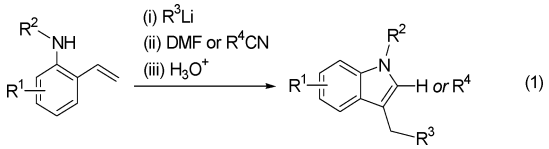
Enantioselective Carbolithiation Initiated Cascade Reactions

Anne-Marie L. Hogan and Donal F. O'Shea*

Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland

Received January 5, 2006; E-mail: donal.f.oshea@ucd.ie

The synthetic power of the intermolecular alkene carbolithiation transformation lies in its ability to construct a carbon−carbon bond and generate a new organolithium species in a single step. This has been accomplished for the unactivated carbon−carbon double bonds of ethene and styrene, following which the newly formed organolithium species could be further reacted with electrophiles.[1] We have previously expanded the synthetic utility of this transformation for *ortho*-amino-substituted styrenes.[2] Our methodology involved a cascade reaction sequence of alkyllithium addition to the styrene double bond, subsequent trapping of the intermediate organolithium with a suitable electrophile, followed by an in situ ring closure and dehydration to generate the substituted indole ring (eq 1).



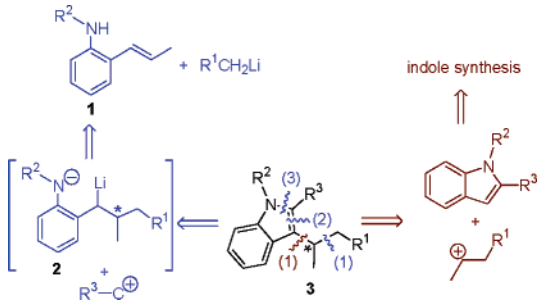
(1)

Our current goal is to advance this methodology for 2-propenylarylamines **1**, which could establish a new asymmetric route to the indole scaffold **3** (Scheme 1).[3] As the chiral center of **3** is generated at the beginning of the reaction sequence by formation of the exocyclic carbon−carbon bond via the carbolithiation (disconnection 1, blue) and is not involved in subsequent steps (disconnection 2 and 3, blue), any asymmetric influence exerted on this C−C bond formation should be carried through to the final cascade products (Scheme 1).[4] If successful, this approach could facilitate the stereoselective generation of a structurally diverse product set from the common intermediate **2**, by changing the electrophile chosen to react with this intermediate. This retrosynthetic analysis contrasts with the more orthodox approach, which indicates a Friedel−Crafts alkylation of a presynthesized indole ring with an activated carbon−carbon double bond (disconnection 1, brown). Recent examples of this approach have successfully employed imidazolidinone[5] in conjunction with α,β-unsaturated aldehydes, $Sc(OTf)_3$-pybox[6] controlled reaction with acyl phosphonates, and bis(oxazoline)-$Cu(OTf)_2$[7] with α′-hydroxy enones.

The starting substrates, (*E*)-benzyl-(2-propenylaryl)amines **1a**,**b** were prepared by a high-yielding Suzuki−Miyaura cross-coupling of benzyl-(2-bromoaryl)amines with (*E*)-propenyl boronic acid (Supporting Information). Our objective was to exploit the inexpensive commercially available natural product (−)-sparteine as the selectivity mediator for our cascade reactions.[8] The carbolithiation of β-methylstyrene with *n*-butyllithium has been accomplished with high enantioselectivity using (−)-sparteine to induce asymmetry in the reaction.[9]

Carbolithiation reaction conditions were optimized in cumene as solvent for the formation of benzyl-[2-(2-methylhexyl)phenyl]-amine **4a** obtained by protonation of intermediate **2a** with methanol (Table 1). The reaction sequence involves initial NH deprotonation

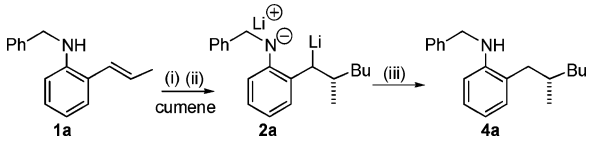
Scheme 1. Retrosynthetic Analysis of Indole **3**



of **1a** with phenyllithium[10] followed by carbolithiation with *n*-BuLi in the presence of (−)-sparteine for 4 h under varying reaction conditions. We observed that for a ratio of PhLi:*n*-BuLi:(−)-sparteine of 1:2:3 the optimal temperature for combined isolated yield and enantiomeric ratio (er) was −15 °C, with a lower temperature reducing isolated yield and a higher temperature reducing er (Table 1, entries 1−3). The use of 2 equiv of BuLi was adopted as it was found to result in improved isolated yields when compared to a lower stoichiometric ratio (entry 4). A study of the quantity of (−)-sparteine additive employed revealed its crucial role in gaining selectivity. The best results were obtained when an equal ratio of organolithium (PhLi + *n*-BuLi) to (−)-sparteine was used (entry 2). A slight reduction in er was observed when (−)-sparteine was reduced to 2 equiv (entry 5).

Further reduction in levels of (−)-sparteine resulted in a significant loss of enantioselectivity (entries 6 and 7). We also recorded a lowering of isolated yield for each reduction in (−)-sparteine used. When no (−)-sparteine is added, the reaction does not proceed and starting material is isolated upon reaction workup (entry 8). All er's were determined using chiral HPLC and compared

Table 1. Optimization of Carbolithiation Conditions[a]

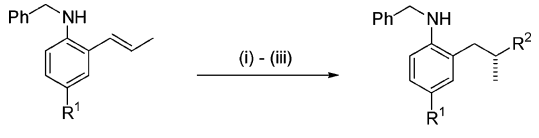


entry	temp (°C)	*n*-BuLi (equiv)	(−)-sparteine (equiv)	yield (%)	er[b]
1	−25	2	3	70	93:7
2	−15	2	3	89	92:8
3	0	2	3	74	90:10
4	−15	1.2	1.2	56	85:15
5	−15	2	2	75	91:9
6	−15	2	1	44	82:18
7	−15	2	0.1	20	71:29
8	−15	2	0	0	

[a] Conditions: (i) PhLi, rt, 15 min; (ii) *n*-BuLi, (−)-sparteine, 4 h; (iii) MeOH. [b] Determined using chiral HPLC.

10.1021/ja060076g CCC: $33.50

Table 2. Scope of Carbolithiation[a]



entry	substrate	product	R^1	R^2	yield (%)	er[b]
1	**1a**	**4b**	H	Et[c]	52	93:7
2	**1a**	**4c**	H	*n*-Hex	76	92:8
3	**1b**	**4d**	OCH_3	*n*-Bu	60	nd[d]

[a] Conditions: (i) PhLi, rt, 15 min, cumene; (ii) R^2Li, (−)-sparteine, −15 °C, 4 h; (iii) MeOH. [b] Determined by chiral HPLC. [c] Reaction with 5 equiv of EtLi and (−)-sparteine. [d] Chiral HPLC separation was not achieved.

to a racemic mixture generated using tetramethylethylenediamine (TMEDA) as additive (Supporting Information). The absolute configuration was assigned based upon the generation of (*S*)-3-methyl heptanoic acid from **4a**.[9b,c]

We next applied the reaction of **1a** with ethyl- and *n*-hexyllithium and found both generated the desired products **4b**,**c** in good yields with er's of 93:7 and 92:8 (Table 2, entries 1 and 2). In addition, we tested benzyl-(4-methoxy-2-propenylphenyl)amine **1b** as a starting substrate and found that it underwent efficient carbolithiation with *n*-BuLi to provide **4d**.

To demonstrate the potential generality of this reaction, the carbolithiation conditions were applied to a series of cascade reactions utilizing different electrophiles (Scheme 2). The reaction of **2a** with DMF, Weinreb base *N*-methoxy-*N*-methyl acetamide, benzonitrile, 2,2-diethoxypropionitrile,[11] or γ-butyrolactone followed by acidification gave rise to the 1,3- and 1,2,3-substituted indoles **3a**−**e** in acceptable yields, all with an er of 92:8 (±1%) (Table 3, entries 1−5). The tolerance of the reaction sequence to incorporation of functional groups by varying the electrophile is exceptional with alkyl, aryl, keto, and alcohol groups being successfully introduced at the C-2 position of the indole products. We were pleased to discover that the indole cascade reaction sequence was also successful with a variety of electrophiles for ethyl- and *n*-hexylithium (entries 6 and 7) and the starting substrate **1b** (entries 8 and 9).

In summary, our results exemplify the power of reversing the order of bond formation, so that selectivity control is achieved in the first step of the reaction to generate a chiral intermediate of

Scheme 2. Synthetic Potential of Lithiated Intermediate **2**

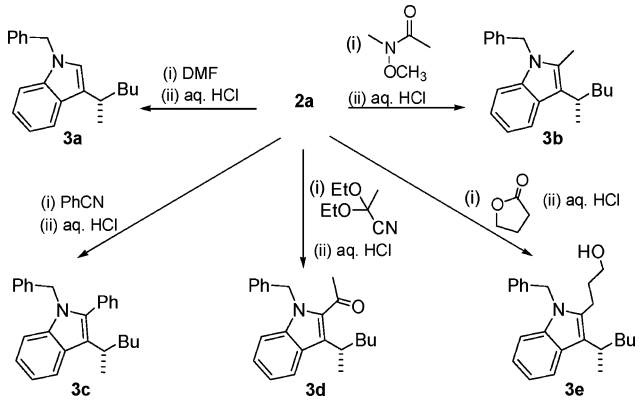
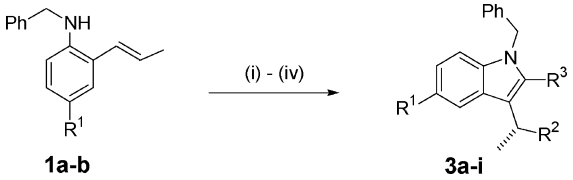


Table 3. Scope of Indole Synthesis[a]



entry	3	R^1	R^2	R^3	yield (%)	er[b]
1	**3a**	H	*n*-Bu	H	60	92:8
2	**3b**	H	*n*-Bu	CH_3	30	93:7[c]
3	**3c**	H	*n*-Bu	Ph	38	93:7
4	**3d**	H	*n*-Bu	$COCH_3$	51	92:8
5	**3e**	H	*n*-Bu	$(CH_2)_3OH$	45	92:8
6	**3f**	H	Et[d]	H	40	nd[e]
7	**3g**	H	*n*-Hex	H	58	92:8
8	**3h**	OCH_3	*n*-Bu	H	43	93:7
9	**3i**	OCH_3	*n*-Bu	$(CH_2)_3OH$	31	92:8

[a] Conditions: (i) PhLi, rt, 15 min, cumene; (ii) R^2Li, (−)-sparteine, −15 °C, 4 h; (iii) electrophile; (iv) 2 M HCl. [b] Determined using chiral HPLC. [c] An increased er of 99:1 was obtained after one recrystallization from pentane. [d] Reaction with 5 equiv of EtLi and (−)-sparteine. [e] Chiral HPLC separation was not achieved.

high synthetic potential, which can then be converted into a range of products simply by changing the electrophile. As organolithium chemistry is ubiquitous in synthetic chemistry the applications of this approach could be far-reaching.

Acknowledgment. This work was supported by Science Foundation Ireland. A.-M.L.H. thanks IRCSET for funding.

Supporting Information Available: All experimental procedures, compound characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Bartlett, P. D.; Tauber, S. J.; Weber, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6362. (b) Wei, X.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1996**, 187. (c) Wei, X.; Johnson, P.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1109. (d) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: Oxford, U.K., 2002; pp 273−335.

(2) (a) Coleman, C. M.; O'Shea, D. F. *J. Am. Chem. Soc.* **2003**, *125*, 4054. (b) Kessler, A.; Coleman, C. M.; Charoenying, P.; O'Shea, D. F. *J. Org. Chem*. **2004**, *69*, 7836.

(3) Several natural products and medicinal applications of this structural class are known: (a) Rawson, D. J.; Dack, K. N.; Dickinson, R. P.; James, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 125. (b) Chang-Fong, J.; Rangisetty, J. B.; Dukat, M.; Setola, V.; Raffay, T.; Roth, B.; Glennon, R. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 1961. (c) Christian, O. E.; Compton, J.; Christian, K. R.; Mooberry, S. L.; Valeriote, F. A.; Crews, P. *J. Nat. Prod*. **2005**, *68*, 1592.

(4) Intramolecular asymmetric carbolithiation routes to indolines have been described: (a) Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 6787. (b) Gil, G. S.; Groth, U. M. *J. Am. Chem. Soc*. **2000**, *122*, 6789.

(5) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2002**, *124*, 1172.

(6) (a) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780. (b) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942.

(7) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc*. **2005**, *127*, 4154.

(8) For reviews of (−)-sparteine in organolithium chemistry, see: (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res*. **1996**, *29*, 2283. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2282.

(9) (a) Klein, S.; Marek, I.; Poisson, J. F.; Normant, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 8853. (b) Norsikian, S.; Marek, I.; Normant, J. F. *Tetrahedron Lett*. **1997**, *38*, 7523. (c) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem.—Eur. J.* **1999**, *5*, 2055.

(10) Phenyllithium ensured complete deprotonation prior to carbolithiation. Cottineau, B.; O'Shea, D. F. *Tetrahedron Lett.* **2005**, *46*, 1935.

(11) Acetal protecting group was also removed during acidification step.

JA060076G