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Regioselective Carbolithiation of *o*-Amino-(*E*)-Stilbenes: Cascade Route to the Quinoline Scaffold

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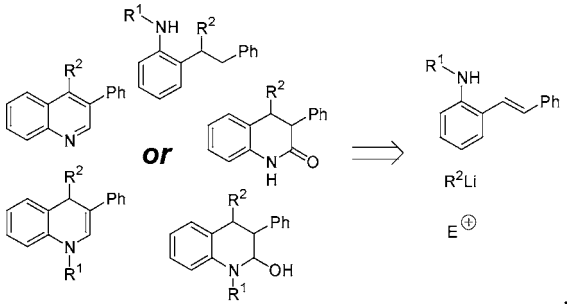
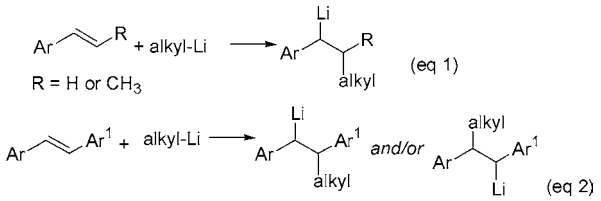
ABSTRACT



The regioselective carbolithiation of substituted *ortho*-amino-(*E*)-stilbenes can be exploited to initiate cascade reaction sequences that can be utilized as new routes to substituted 3,4-dihydro-1*H*-quinolin-2-ones, 1,2,3,4-tetrahydroquinolines, 1,4-dihydroquinolines, and quinolines.

Carbolithiation of alkenes offers a unique means of creating a carbon−carbon bond and a new organolithium species in a single step. The carbolithiation of unactivated alkenes such as ethene, styrene, β-methylstyrene, and stilbene has been described.[1] Carbolithiation of styrene and β-methylstyrene is regiospecific, exclusively generating the more stabilized benzylic lithiated compounds in both cases (Scheme 1, eq 1). In contrast, the relatively unstudied carbolithiation of unsymmetrical stilbenes poses a considerable selectivity challenge, as two possible benzylic lithiated regioisomers could be generated from the reaction (Scheme 1, eq 2). For the specific case of *o*-amino-stilbenes, it was anticipated that

Scheme 1. Regioselectivity of Alkene Carbolithiation



if reaction conditions could be identified in which one regioisomer was favored, then the resulting benzylic lithiated species would be a very synthetically versatile intermediate that could be applied to further in situ transformations. We have recently advanced the carbolithiation of *o*-amino-styrenes as an effective methodology for initiating a cascade reaction sequence to generate the functionalized indole and 7-azaindole ring systems.[2] The cascade methodology involves a regiospecific alkyllithium addition to the alkene, subsequent trapping of the intermediate organolithium with a suitable

(1) (a) Bartlett, P. D.; Friedman, S.; Stiles M. *J. Am. Chem. Soc.* **1953**, *75*, 1771. (b) Bartlett, P. D.; Tauber, S. J.; Weber, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6362. (c) Wei, X.; Taylor, R. J. K. *Chem. Commun.* **1996**, 187. (d) Wei, X.; Johnson, P.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans 1* **2000**, 1109. (e) Klein, S.; Marek, I.; Poisson, J. F.; Normant, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 8853. (f) Norsikian, S.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1997**, *38*, 7523. (g) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem.—Eur. J.* **1999**, *5*, 2055. (h) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: Oxford, U.K., 2002; pp 273−335.

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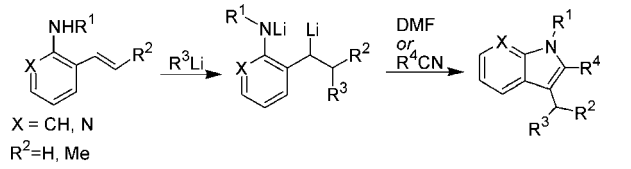
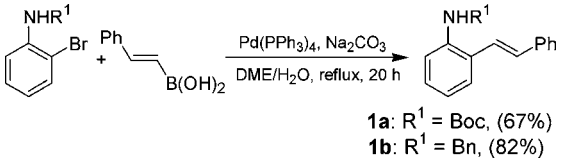
electrophile, followed by an in situ ring closure and dehydration to provide fused ring systems (Scheme 2).

Scheme 2. Indole and 7-Azaindole Synthesis



In this report, we outline our initial results to develop regioselective carbolithiations of *o*-amino-substituted stilbenes and the exploitation of this transformation for initiating cascade reaction sequences from which complex structural architectures can be generated in an efficient manner. The starting substrates *t*-butoxycarbonyl and benzyl *N*-substituted *o*-amino-(*E*)-stilbenes **1a** and **1b** were synthesized stereoselectively by Suzuki−Miyaura cross-coupling of the corresponding functionalized *o*-bromo-anilines with commercially available *trans*-2-phenylvinylboronic acid (Scheme 3).

Scheme 3. Synthesis of *N*-Substituted *o*-Amino-(*E*)-stilbenes

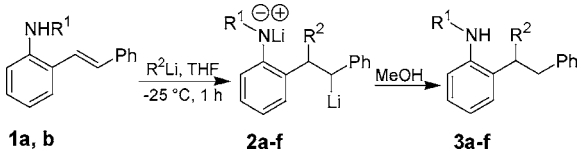


An extensive study of the carbolithiation reaction conditions of **1a** and **1b** was undertaken to identify an optimal regio outcome for a series of alkyllithiums (*t*-Bu-, *n*-Bu-, *s*-Bu-, and EtLi). The carbolithiation selectivity was determined by reacting the lithiated intermediates with methanol, and the crude reaction products were analyzed by NMR and HPLC. Encouragingly, it was found that when THF was employed as the reaction solvent at −25 °C, a single regioisomer **3a**−**f** was formed in high yields from the reaction of the four different alkyllithiums with the substrates **1a** and **1b** (Table 1). For *n*-Bu and EtLi, the inclusion of the additive *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDTA) was found to give improved conversions to **2** with good isolated yields of **3b**, **3c**, and **3e** obtained following protonation with methanol (entries 2, 3, and 5). Significantly, in all cases, the regioisomer formed had the alkyl group exclusively on the carbon α to the aniline ring, which would be consistent with the formation of the benzylic intermediates **2a**−**f** in the carbolithiation step (Table 1).

This is the opposite carbolithiation pattern from our previously reported styrene examples, as shown in Scheme 2, in which the lithiated carbon is α to the aniline ring. The subtlety of this selectivity achievement was highlighted by the fact that mixtures of both possible regioisomers were obtained when reactions were carried out using diethyl ether as solvent. For example, the reaction of **1a** and **1b** with *t*-BuLi provided a mixture of **3a**/**4a** and **3d**/**4d** in a 9:1 and 6:4 ratio, respectively (Table 2). The regioisomer assignments were confirmed by independently synthesizing compounds **4a** and **4d** (Supporting Information). During the course of this work, we became aware of a similar finding in which carbolithiation of *o*-methoxy-stilbene with *n*-BuLi in cumene and (−)-sparteine gave a 94:6 ratio of regioisomers, with the major isomer having the butyl group substituted at the carbon α to the *o*-methoxy functionalized benzene ring.[3]

Having established conditions for a regioselective alkyllithium addition, our next aim was to demonstrate the utility of lithiated compounds **2a**−**f** in cascade reaction sequences, to provide a new entry to the quinoline scaffold at a range of oxidation levels. Polysubstituted quinolinones, dihydroquinolines, tetrahydroquinolines, and quinolines are common

Table 1. Carbolithiation of *o*-Amino Stilbenes **1a** and **1b**

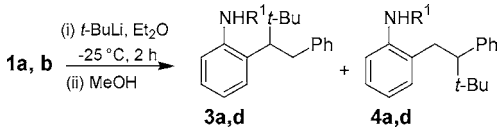


1a, b **2a-f** **3a-f**

entry	sm	R^1	product	R^2	yield[a] (%)
1	**1a**	Boc	**3a**	*t*-Bu	87
2	**1a**	Boc	**3b**	*n*-Bu[b]	62[c]
3	**1a**	Boc	**3c**	Et[b]	76[d]
4	**1b**	Bn	**3d**	*t*-Bu	79
5	**1b**	Bn	**3e**	*n*-Bu[b]	61[e]
6	**1b**	Bn	**3f**	*s*-Bu	81

[a] Isolated purified yield. [b] PMDTA added. [c] Compound **5b** was also isolated in 10% yield (see Table 3). [d] Compound **5c** was also isolated in 7% yield (see Table 3). [e] Starting material recovered in 29% yield.

Table 2. Regioisomer Ratios for Carbolithiation in Diethyl Ether



entry	substrate	products	ratio 3:4[a]	yield[b] (%)
1	**1a**	**3a**, **4a**	9:1	72
2	**1b**	**3d**, **4d**	6:4	30[c]

[a] Ratios determined by HPLC and ^{1}H NMR. [b] Combined yield of both isomers. [c] Starting material recovered in 41% yield.

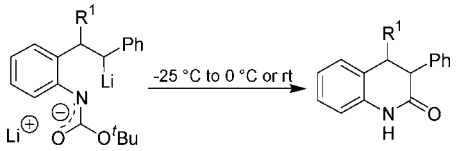
(2) (a) Coleman, C. M.; O'Shea, D. F. *J. Am. Chem. Soc.* **2003**, *125*, 4054. (b) Kessler, A.; Coleman, C. M.; Charoenying, P.; O'Shea, D. F. *J. Org. Chem.* **2004**, *69*, 7836. (c) Cottineau, B.; O'Shea, D. F. *Tetrahedron Lett.* **2005**, *46*, 1935.

(3) (a) Norsikian, S. Ph.D. Thesis, Université Pierre et Marie Curie, Paris, France, 1999. (b) Prof. I. Marek, Department of Chemistry, Technion-Israel Institute of Technology, Israel, private communication.

motifs found in important natural products and pharmaceutical agents.[4] As such, a common cascade route to each class would be of significant synthetic value.

It was envisioned that the lithiated intermediates **2a**−**c** could provide access to 3,4-dihydro-1*H*-quinolin-2-ones by intramolecular nucleophilic substitution of the benzylic lithium center at the Boc group.[5] The susceptibility of the Boc group to intermolecular nucleophilic attack by alkyllithiums has previously been reported.[6] The intramolecular cyclization was readily achieved following the carbolithiation of **1a** in THF at −25 °C by raising the reaction temperature to either 0 °C or room temperature for 1 to 6 h, thereby providing direct access to the 3,4-dihydro-1*H*-quinolin-2-ones **5a**−**c** (Table 3). It was found that cyclization proceeded more efficiently in the absence of PMDTA additive and, as such, it was omitted from the reaction for the formation of quinolin-2-ones **5b** and **5c**.

Table 3. Synthesis of 3,4-Dihydro-1*H*-quinolin-2-ones



2a-c **5a-c**

entry	temp (°C)	time (h)	R^1	product	yield[a] (%)
1	rt	6	*t*-Bu	**5a**	22[b]
2	0	1	*n*-Bu	**5b**	90
3	0	2	Et	**5c**	84

[a] Isolated purified yield. [b] Compound **3a** also isolated in 51% yield.

Compound **5a** was isolated as a single diastereoisomer, which was assigned a relative stereochemistry of 3,4-*trans*, as both the C-3 and C-4 proton signals appeared as two singlets in the ^{1}H NMR spectrum. Compounds **5b** and **5c** were isolated crude as a 6:4 ratio mixture of two isomers with the predominant being the 3,4-*trans* (J = 1.2 and 1.8 Hz, respectively) and the minor isomer assigned as 3,4-*cis* (J = 5.3 and 5.4 Hz, respectively). During purification on silica gel chromatography, the isomer mixture of **5b** and **5c** converted to a 9:1 and 8:2 ratio, respectively, in favor of the thermodynamic *trans* isomer. The relative stereochemistry of the major *trans* isomer of **5b** was confirmed by X-ray crystallography (Figure 1, Supporting Information). The

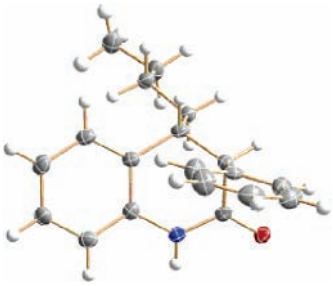


Figure 1. X-ray crystal structure of the major 3,4-*trans*-diastereoisomer of **5b**.

source of the *cis* isomers could be attributed to the strongly basic reaction conditions, as resubjecting the purified *trans* isomer of **5b** to the reaction conditions resulted in the isolation of product in a *trans*/*cis* isomer ratio of 3:7. It was observed that cyclization of the *tert*-butyl-substituted **2a** into **5a** required a higher temperature, with the product isolated in lower yield, possibly due to geometrical restrictions imposed by the *t*-Bu group on the conformation necessary for cyclization (Table 3, entry 1). As a result of the higher temperature required for cyclization, significant quantities of **3a** were also isolated due to competing deprotonation of the THF solvent by **2a** (entry 1). However, it was possible to achieve an improved 68% yield of **5a** (as the *trans* isomer) by the reaction of **2a** with CO_2, followed by acidification with aqueous 12 M HCl (Supporting Information).

To further extend the synthetic utility of the lithiated intermediates **2a**−**c**, treatment with DMF as electrophile, followed by acidification with aqueous acid, provided a versatile synthesis of the 1,2,3,4-tetrasubstituted tetrahydroquinolines **6a**−**c** in good isolated yields (Table 4).

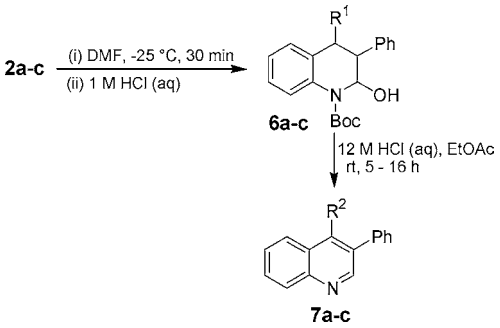
Two diastereomeric products were observed in each case, and for **6a**, separation by column chromatography was achieved and the relative stereochemistry determined by NMR and X-ray crystallography (Figure 2, Supporting Information). Both diastereoisomers gave the *tert*-butyl and the phenyl group *trans* to each other (J = 4.0 Hz for both diastereoisomers), differing in the relative stereochemistry of the phenyl and alcohol groups. The *n*-butyl- and ethyl-substituted tetrahydroquinolines **6b** and **6c** were also successfully isolated in good yields from the cascade reaction sequence. In each case, it was possible to readily convert **6a**−**c** into the fully aromatic 3- and 3,4-substituted quinolines **7a**−**c** by treatment with aqueous hydrochloric acid (Table 4). Compounds **6b** and **6c** dehydrated and in situ air-oxidized as expected to yield the 2,3-disubstituted quinolines, **7b** and **7c**, respectively. Interestingly, the *tert*-butyl-substituted

(4) For examples, see quinolin-2-ones: (a) Carling, R. W.; Leeson, P. D.; Moore, K. W.; Smith, J. D.; Moyes, C. R.; Mawer, I. M.; Thomas, S.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, I. M.; Marshall, G. R.; Tricklebank, M. D.; Saywell, K. L. *J. Med. Chem.* **1993**, *36*, 3397. (b) Rowley, M.; Kulagowski, J. J.; Watt, A. P.; Rathbone, D.; Stevenson, G. I.; Carling, R. W.; Baker, R.; Marshell, G. R.; Kemp, J. A.; Foster, A. C.; Grimwood, S.; Hargreaves, R.; Hurley, C.; Saywell, K. L.; Tricklebank, M. D.; Leeson, P. D. *J. Med. Chem.* **1997**, *40*, 4053. (c) Foucaud, B.; Laube, B.; Schemm, R.; Kreimeyer, A.; Goeldner, M.; Betz, H. *J. Biol. Chem.* **2003**, *278*, 24011. Tetrahydroquinolines: (d) Katritzky, A.; Rachwal, S.; Rachwal, B. *Tetrahedron*, **1996**, *52*, 15031. Dihydroquinolines: (e) Michne, W. F.; Guiles, J. W.; Treasurywala, A. D.; Castonguay, L. A.; Weigelt, C. A.; Oconnor, B.; Volberg, W. A.; Grant, A. M.; Chadwick, C. C.; Krafte, D. S.; Hill, R. J. *J. Med. Chem.* **1995**, *38*, 1877. (f) Gaillard, S.; Papamicael, C.; Marsais, F.; Dupas, G.; Levacher, V. *Synlett* **2005**, 441. (g) van Straten, N. C. R.; van Berkel, T. H. J.; Demont, D. R.; Karstens, W.-J. F.; Merkx, R.; Oosterom, J.; Schulz, J.; van Someren, R. G.; Timmers, C. M.; van Zandvoort, P. M. *J. Med. Chem.* **2005**, *48*, 1697. Quinolines: (h) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 476.

(5) For a review of the synthetic exploitation of the Boc protecting group, see: Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701.

(6) (a) Stanetty, P.; Koller, H.; Mohovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833.

Table 4. Synthesis of 3,4-Disubstituted and 3-Substituted Quinolines and 1,2,3,4-Tetrasubstituted tetrahydroquinolines



entry	product	R^1	yield[a] **6**	product	R^2	yield[a] **7**
1	**6a**	*t*-Bu	76%	**7a**	H	78%
2	**6b**	*n*-Bu[b]	63%	**7b**	*n*-Bu	78%
3	**6c**	Et[b]	71%	**7c**	Et	61%

[a] Isolated purified yield. [b] PMDTA added.

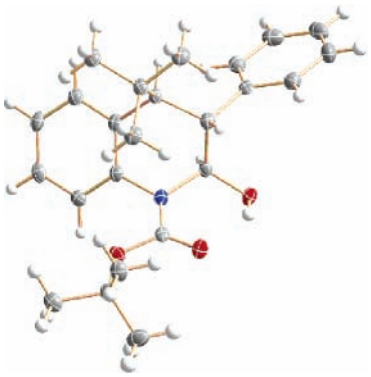


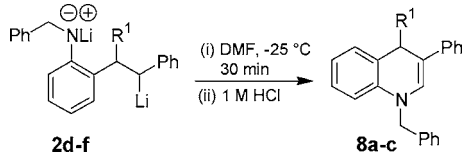
Figure 2. X-ray crystal structure of the minor 2,3-*trans*-3,4-*trans* diastereoisomer of **6a** (see Supporting Information for major diastereoisomer).

analogue **6a** yielded only the monosubstituted 3-phenylquinoline **7a,** indicating that the aromatic ring was generated by an elimination of the *tert*-butyl group. The elimination of a *tert*-butyl group from dihydroquinolines has been observed.[7]

(7) Anne, A.; Fraoua, S.; Moiroux, J.; Savéant, J.-M. *J. Am. Chem. Soc.* **1996**, *118*, 3938.

In additon, synthetic access to the 1,4-dihydroquinoline class was achieved by the treatment of the *N*-benzyl-substituted dilithiated intermediates **2d**−**f** with DMF, followed by aqueous acidic workup, to effect a dehydration. This provided a new route to the medicinally important 1-benzyl-4-alkyl-3-phenyl-1,4-dihydro-quinolines **8a**−**c** in good yields (Table 5).

Table 5. Synthesis of 1,3,4-Trisubstituted 1,4-Dihydroquinolines



entry	product	R^1	yield[a] (%)
1	**8a**	*t*-Bu	82%
2	**8b**	*n*-Bu	51%
3	**8c**	*s*-Bu	84%

[a] Isolated purified yield.

In summary, a regioselective carbolithiation of *o*-amino-substituted stilbenes can be utilized to provide lithiated intermediates of high synthetic potential from which new synthetic routes to substituted dihydroquinolin-2-ones, tetrahydroquinolines, 1,4-dihydroquinolines, and aromatic quinolines are possible. The synthetic scope of this methodology and the mechanism of carbolithiation regioselectivity is currently being investigated in terms of substituent diversity and routes to other fused-ring systems.

Acknowledgment. A.-M.L.H. thanks the Irish Research Council for Science, Engineering and Technology for studentship. Funding support from the Program for Research in Third-Level Institutions administered by the HEA. Thanks to Dr. D. Rai of the CSCB Mass Spectrometry Centre and Dr. H. Mueller-Bunz of the UCD Crystallographic Centre for analysis.

Supporting Information Available: Synthetic procedures, analytical data, and NMR spectra for all new compounds. X-ray crystallographic data of **5b** and **6a** as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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