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Carbolithiation of *o*-Amino-(*E*)-Stilbenes: Diastereoselective Electrophile Substitution with Applications to Quinoline Synthesis

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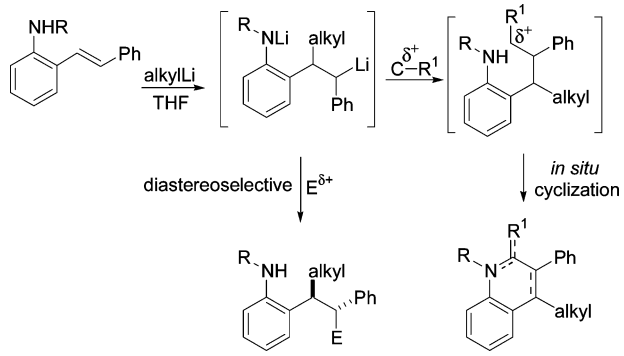

A regioselective carbolithiation of *o*-amino-(*E*)-stilbenes has been achieved with a series of alkyllithiums when THF is employed as the reaction solvent. The use of other solvents, such as diethyl ether or hydrocarbons, leads to a pronounced loss in regioselectivity. Moreover, high levels of diastereoselectivity have been obtained following reaction of the lithiated intermediate in THF with different electrophiles such as MeOD, CO_2, and Bu_3SnCl. It was shown that diastereoselectivity was influenced by the *ortho*-amino substituent and the alkyllithium utilized for carbolithiation with *N*-Boc substituent and *t*-BuLi proving optimal. In the case of carbolithiated intermediate **3a**, obtained from the reaction of *N*-Boc substituted stilbene with *t*-BuLi, ^1H and ^{13}C NMR analysis revealed predominantly one diastereoisomer which was stable at room temperature. Application of the carbolithiation/electrophile reaction methodology to the synthesis of six-membered quinoline ring systems is demonstrated with substituted 3,4-dihydroquinolin-2-ones, 1,2,3,4-tetrahydroquinolines, 1,4-dihydroquinolines, and quinolines all prepared by a common cascade route.

Introduction

Intermolecular alkene carbolithiation facilitates the generation of a carbon−carbon bond and carbon−lithium center in a single transformation. The synthetic utility of this transformation lies in the fact that the tandem formation of C−C and C−Li bonds allows for further *in situ* reactions. Indeed, one of the first uses for alkene carbolithiation was in the anionic polymerization of styrene.[1] The development of carbolithiation chemistry for nonpolymer applications can be traced to the reports of Bartlett et al. in which the intermolecular carbolithiation of the simplest unactivated alkene, ethene, was achieved.[2] Subsequently, the carbolithiation of other substituted alkenes such as styrene, β-methylstyrene, and *trans*-stilbene has been described in detail.[3]

(1) Ziegler, K.; Gellert, H. G. *Justus Liebigs Ann. Chem.* **1950**, *567*, 195.

(2) (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.

(3) (a) Okamoto, Y.; Kato, M.; Yuki, H. *Bull. Chem. Soc. Jpn* **1969**, *42*, 760. (b) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720. (c) Superchi, S.; Sotomayor, N.; Miao, G.; Joseph, B.; Campbell, M. G.; Snieckus, V. *Tetrahedron Lett.* **1996**, *37*, 6061. (d) Wei, X.; Taylor, R. J. K. *Chem. Commun.* **1996**, 187. (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) Marek, I. *J. Chem. Soc., Perkin Trans 1* **1999**, 535. (i) Wei, X.; Johnson, P.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans 1* **2000**, 1109. (j) Peters, J. G.; Seppi, M.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synthesis* **2002**, 381. (k) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: Oxford, U.K., 2002; pp 273−335. (l) Normant, J. F. *Topics Organomet. Chem.* **2003**, *5*, 287.

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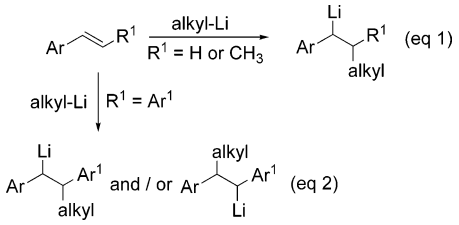
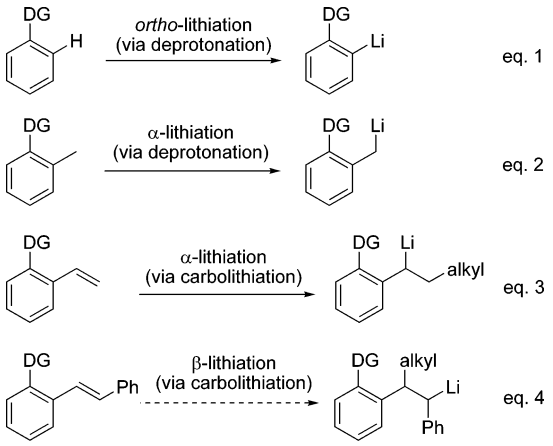
SCHEME 1. Regioselectivity of Alkene Carbolithiation



It has been shown that carbolithiation of unsymmetrical alkenes such as styrene and β-methylstyrene, which offer two potential regioisomer products, is regiospecific, with the more stabilized benzylic lithiated species generated exclusively in both cases (eq 1, Scheme 1). In contrast, the carbolithiation of unsymmetrical stilbenes (Ar $\neq$ Ar^1) poses a considerable selectivity challenge as two possible benzylic lithiated regioisomers could be generated from the reaction (eq 2, Scheme 1). We were attracted to investigate this issue for the specific case of *ortho*-aryl-substituted stilbenes to determine if selective carbolithiation could be achieved and to utilize it for the synthesis of fused ring systems.

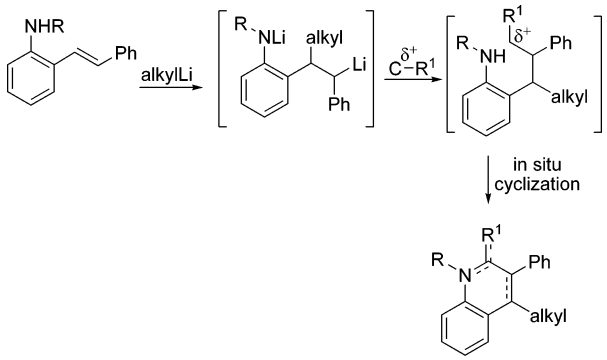
The value of lithiated compounds (generated by deprotonation) as synthetic intermediates for heterocyclic systems is indisputable, with the motifs of *ortho* hetero-substituted aryl- and benzylic-lithium species being common intermediates in the synthesis of fused ring systems (eqs 1 and 2, Scheme 2).[4−6]

SCHEME 2. Approaches to Lithiated Aryls and Benzylic Compounds (DG = Directing Group)



Heteroatom containing functional groups which have shown the ability to direct lithiations include methoxy, amines, and amides as well as oxygen and nitrogen carbamates.[7] For example, taking the specific case of *N*-Boc as the directing group (DG = *N*-Boc, Scheme 2), *ortho*-lithiation of phenylcarbamic acid *tert*-butyl ester can be achieved using *t*-BuLi in THF to generate the aryl lithium species (eq 1, Scheme 2),[4] while treatment of *o*-tolylcarbamic acid *tert*-butyl ester with *s*-BuLi in the same solvent results in lithiation at the α-benzylic position (eq 2).[5] Electrophile reaction at the aryl or benzylic lithium center and subsequent cyclization with the *ortho*-substituent has been reported for the synthesis of five-, six-, seven-, and eight-membered fused ring systems, the ring size being dependent upon the electrophile employed, the *ortho*-substituent, and whether the lithium is at the *ortho* or α position.

SCHEME 3. Carbolithiation Initiated Quinoline Synthesis



A less common approach, developed in our laboratory, is the generation of benzylic lithiated species via alkene carbolithiation followed by *in situ* reaction to provide routes to heterocycles (eq 3, Scheme 2). We have recently reported the carbolithiation of *ortho*-amino substituted styrenes, β-methylstyrenes, and vinylpyridines with applications to indole[8] and 7-azaindole synthesis.[9] Carbolithiation offers improved atom efficiency over utilizing the alkyllithium as a base as the product includes an additional functionality incorporated from the carbolithiation step.

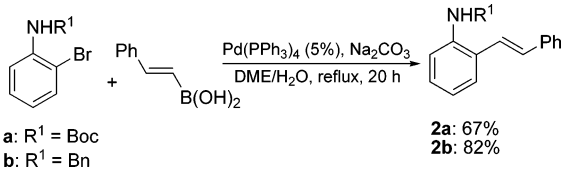
What is more unusual and synthetically more challenging to achieve is lithiation at the position β to the *ortho*-substituted aryl ring especially via a directed deprotonation reaction (eq 4, Scheme 2). Yet, if this lithiation pattern could be achieved it would provide access to a different series of ring systems following electrophile reaction. Herein we report our findings on achieving this lithiation pattern via carbolithiation for the specific case of *ortho*-amino-(*E*)-stilbenes (DG = NR, eq 4) and its subsequent application to a new synthetic entry into the quinoline ring system at various oxidation levels (Scheme 3).[10]

Results and Discussion

Synthesis of Starting Substrates. The required *N*-substituted *ortho*-bromoanilines **1a, b** were both prepared from commercially available 2-bromoaniline. Reaction with di-*tert*-butyl dicarbonate at reflux in THF for 24 h yielded (2-bromophenyl)-carbamic acid *tert*-butyl ester **1a**, while introduction of the benzyl group was accomplished by reductive amination with benzaldehyde in a methanol/sodium borohydride mixture.[8b] Our method of choice for the synthesis of the starting substrates *tert*-butoxycarbonyl and benzyl *N*-substituted *ortho*-amino-(*E*)-stilbenes **2a** and **2b** was the stereoselective Suzuki-Miyaura

(4) (a) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798. (b) Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833.
(5) Clark, R. D.; Muchowski, J. M.; Souchet, M.; Repke, D. B. *Synlett* **1990**, *4*, 207.
(6) (a) Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511. (b) Smith, K.; El-Hiti, G. A.; Pritchard, G.; Hamilton, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2299. (c) Clark, R. D.; Jahangir. *Tetrahedron* **1993**, *49*, 1351. (d) Wender, P. A.; White, A. W. *Tetrahedron* **1983**, *39*, 3767. (e) Wender, P. A.; White, A. W. *Tetrahedron Lett.* **1981**, *22*, 1475.
(7) (a) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: Oxford, U.K., 2002; p28−59.
(8) (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) Hogan, A.-M. L.; O'Shea, D. F. *J. Am. Chem. Soc.* **2006**, *128*, 10360.
(9) (a) Cottineau, B.; O'Shea, D. F. *Tetrahedron Lett.* **2005**, *46*, 1935. (b) Cottineau, B.; O'Shea, D. F. *Tetrahedron* **2007**, *63*, 10354.
(10) (a) Hogan, A.-M. L.; O'Shea, D. F. *Org. Lett.* **2006**, *8*, 3769. (b) For the directed deprotonation of *o*-amino-(*Z*)-stilbenes, see; Cotter, J.; Hogan, A.-M. L.; O'Shea, D. F. *Org. Lett.* **2007**, *9*, 1493.

SCHEME 4. Synthesis of *N*-Substituted *o*-Amino-(*E*)-Stilbenes



cross-coupling of **1a, b** with commercially available *trans*-2-phenylvinylboronic acid (Scheme 4). Using the cross-coupling conditions of 5% $Pd(PPh_3)_4$ as catalyst, Na_2CO_3 as base, and a 4:1 ratio of DME/water as solvent, **2a** was isolated in a low yield of 38%, yet **2b** was obtained in a good yield of 82%. The poor yield for the case of **2a** was in part due to competitive homocoupling of the boronic acid to generate *trans*,*trans*-1,4-diphenylbuta-1,3-diene in significant amounts. We found that homocoupling of the boronic acid could be reduced, and a higher 67% isolated yield of **2a** achieved, by changing the solvent ratio to 2:1 DME/water.

Regioselectivity of Carbolithiation. Our first aim was to determine conditions to provide optimal regioselectivity of alkyllithium addition to starting substrates **2a, b**. As a convenient method of studying the effect of temperature, solvent, and additive on the carbolithiation regioselectivity, the intermediate lithiated species were treated with methanol and the crude reaction products were analyzed by ^{1}H NMR and HPLC (Table 1).

Initial studies of the reaction of *t*-BuLi with **2a** revealed that the carbolithiation was regioselective in THF across the temperature range from −78 to −25 °C. The optimal temperature was determined as −25 °C (entry 2, Table 1) with lower temperatures such as −78 °C resulting in a poor conversion to product for the same reaction time of 1 h (entry 1). As such all other reactions were performed at −25 °C. To test the scope and limitations of the reaction, carbolithiation with five alkyllithiums of varying reactivity and steric bulk from tertiary to primary were investigated, in combination with the two *ortho*-substituted stilbenes **2a, b**. The *ortho*-substituents chosen were NBoc, which is a moderately strong directing group, and NBn, which to the best of our knowledge has not been reported to have any directing effect.[11]

We were pleased to discover that, with THF as solvent, a single regioisomer **5a**−**f** was generated from the reaction across the range of alkyllithiums: *t*-Bu, *s*-Bu, *n*-Bu, and EtLi (entries 1−7, Table 1). Significantly, in all cases the regioisomer formed had the alkyl group on the carbon α to the aniline ring, which would be consistent with the formation of the lithiated intermediates **3a**−**f** in the carbolithiation step. This carbolithiation selectivity is opposite from that observed for our previously reported corresponding styrene and *β*-methylstyrene substrates.[8,12] Reaction of methyllithium with **2a** resulted only in the recovery of starting material (entry 8).

While the reactions with *n*-Bu and EtLi were regioselective, the isolated yields of **5b** and **c** were low due to a competing intramolecular cyclization of intermediates **3b, c** to form the 3,4-dihydro-1*H*-quinolin-2-ones **11b** and **11c** in 45% and 26% yields, respectively (see later for a more detailed discussion). The additive *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDTA) was utilized to retard the intramolecular cyclization of **3b, c**, and improved yields of **5b** and **5c** (62 and 76%, respectively) were obtained (compare entries 3 and 4 with 9 and 10, respectively).[13] In both cases the addition of PMDTA significantly reduced the isolated yields of **11b, c** to 10% and 7%. The addition of PMDTA to the reaction of **2b** with *n*-BuLi improves the carbolithiation reactivity of the alkyllithium giving a higher yield of **5e** (compare entries 6, 11). It is noteworthy that in each case the use of PMDTA did not alter the regioselectivity of the addition.

The remarkable solvent dependency of this regioselectivity is illustrated by entries 12−18 (Table 1). When reactions were carried out using diethyl ether or the hydrocarbon cumene as solvent, mixtures of both regioisomers were obtained. For these solvents the degree of regioselectivity varied for different stilbene derivatives, alkyllithiums, and additives. For example the reaction of **2a** and **2b** with *t*-BuLi in diethyl ether provided a mixture of **5a/6a** and **5d/6d** in ratios of 90:10 and 60:40, respectively (entries 12, 13). Interestingly, when PMDTA was added a greater loss in selectivity was observed when compared to ether alone, with **5a/6a** obtained in a ratio of 75:25 (entry 14). A further decrease in selectivity was noted when the reaction was performed in cumene/PMDTA (entry 15). No carbolithiation products were obtained for the reaction of **2b** with *t*-BuLi in either diethyl ether/PMDTA or cumene/PMDTA (entries 16, 18). However carbolithiation was achieved when diethyl ether/(−)-sparteine was employed but with poor regioselectivity (entry 17).

The regioisomer assignments were confirmed by independently synthesizing compounds **6a**, **b**, **d**, and **e** as outlined in Scheme 5. Lithiation of *o*-tolylcarbamic acid *tert*-butyl ester **7**, followed by addition of 2,2-dimethylpropiophenone or valerophenone, afforded the alcohol products **8a** (R^1 = *t*-Bu) and **8b** (R^1 = *n*-Bu) in 67% and 81% yields, respectively. Reaction with thionyl chloride provided the trisubstituted alkenes **9a, b**, which following olefin hydrogenation yielded the regioisomers, **6a, b**. Nitrogen benzylation of **6a, b** was achieved by treatment with NaH/benzyl bromide, and subsequent removal of the Boc group with TFA gave the authentic samples of the regioisomers **6d, e**.

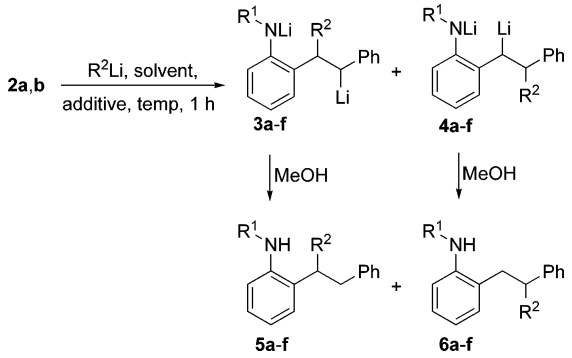
Diastereoselectivity of Carbolithiation-Electrophile Substitution Sequence. The carbolithiation of unsymmetrical 1,2-disubstituted alkenes such as stilbenes (Scheme 1, Ar ≠ Ar^1) generates an organolithium species with two contiguous stereocenters; therefore the possibility of introducing diastereo and/or enantioselectivity into the reaction sequence was explored. Treatment of lithiated intermediate **3a** (formed by the carbolithiation of **2a** with *t*-BuLi) with a series of electrophiles was investigated for diastereoselectivity of the electrophile substitution reaction. We were pleased to discover that

(11) Lithiation of *N*-monoalkylanilines has been achieved by first generating the *N*-alkyl-carbamate. The carbamate acts as an intermediate carbanion stabilizing group which is removed following lithiation. Katritzky, A. R.; Fan, W-Q.; Akutagawa, K. *Tetrahedron* **1986**, *42*, 4027.

(12) During the course of this work we became aware of a similar finding in which carbolithiation of *o*-methoxystilbene 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. (a) Norsikian, S. Ph.D. Thesis, 1999, Université Pierre et Marie Curie, Paris, France. (b) Prof. I. Marek, Department of Chemistry, Technion-Israel Institute of Technology, Israel, private communication.

(13) For examples of the use of PMDTA as additive in organolithium reactions, see: (a) Fukuda, T.; Mine, Y.; Masatomo, I. *Tetrahedron* **2001**, *57*, 975. (b) Barluenga, J.; Alonso, J.; Fananas, F. J. *J. Am. Chem. Soc.* **2003**, *125*, 2610. (c) Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. O.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201. (d) Reich, H. J.; Goldenberg, W. S.; Sanders, A. W.; Jantzi, K. L.; Tzschucke, C. C. *J. Am. Chem. Soc.* **2003**, *125*, 3509.

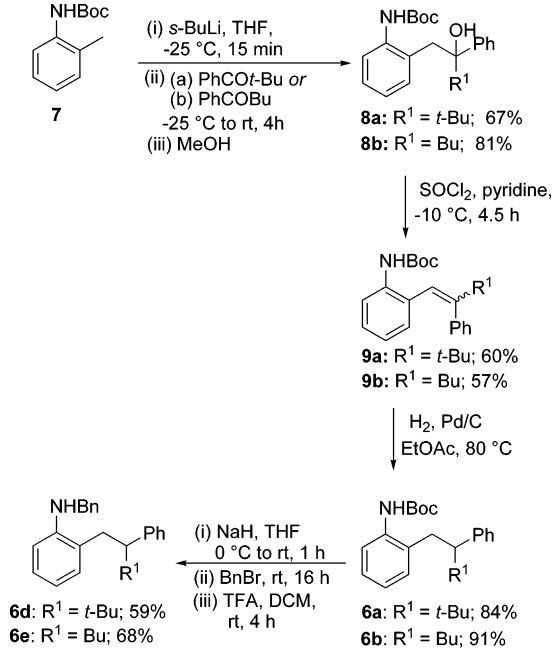
TABLE 1. Investigation of Regioselectivity of Carbolithiation of 2a, b



entry	sm	temp, °C	R^2	solvent	additive	product	ratio **5**:**6**[a]	yield,[b] %
1	**2a**	−78	*t*-Bu	THF	−	**5a/6a**	99:1	20[c]
2	**2a**	−25	*t*-Bu	THF	−	**5a/6a**	99:1	87
3	**2a**	−25	*n*-Bu	THF	−	**5b/6b**	99:1	40[d]
4	**2a**	−25	Et	THF	−	**5c/6c**	99:1	43[e]
5	**2b**	−25	*t*-Bu	THF	−	**5d/6d**	99:1	79
6	**2b**	−25	*n*-Bu	THF	−	**5e/6e**	99:1	33[f]
7	**2b**	−25	*s*-Bu	THF	−	**5f/6f**	99:1	81
8	**2a**	−25	Me	THF	PMDTA	−	−	−[g]
9	**2a**	−25	*n*-Bu	THF	PMDTA	**5b/6b**	99:1	62[h]
10	**2a**	−25	Et	THF	PMDTA	**5c/6c**	99:1	76[i]
11	**2b**	−25	*n*-Bu	THF[j]	PMDTA	**5e/6e**	99:1	61[k]
12	**2a**	−25	*t*-Bu	Et_2O[j]	−	**5a/6a**	90:10	72
13	**2b**	−25	*t*-Bu	Et_2O[j]	−	**5d/6d**	60:40	30[l]
14	**2a**	−25	*t*-Bu	Et_2O[j]	PMDTA	**5a/6a**	75:25	72
15	**2a**	−25	*t*-Bu	cumene[j]	PMDTA	**5a/6a**	45:55	71
16	**2b**	−25	*t*-Bu	Et_2O[j]	PMDTA	−	−	−[m]
17	**2b**	−25	*t*-Bu	Et_2O[j]	(−)-sparteine	**5d/6d**	40:60	39[n]
18	**2b**	−25	*t*-Bu	cumene[j]	PMDTA	−	−	−[o]

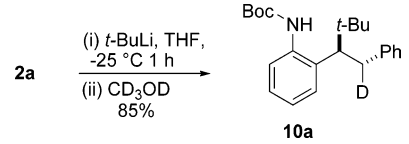
[a] Ratios determined by ^{1}H NMR and confirmed by HPLC (220 nm); a ratio of 99:1 indicates that only a single regioisomer was observed. [b]Isolated purified yield (combined yield of both isomers where relevant). [c]Remainder was unreacted starting material. [d]Compound **11b** was also isolated in 45% yield (see Table 4). [e]Compound **11c** was also isolated in 26% yield. [f]Starting material recovered in 50% yield. [g]Reaction at 0 °C, 87% starting material recovered. [h]Compound **11b** was also isolated in 10% yield. [i]Compound **11c** was also isolated in 7% yield. [j]Reaction time 2 h. [k]Starting material recovered in 29% yield. [l]Starting material recovered in 41% yield. [m]Starting material recovered in 83% yield. [n]Starting material recovered in 37% yield. [o]Starting material recovered in 94% yield.

SCHEME 5. Synthesis of Regioisomers 6a, b, d, and e



deuteration of **3a** with MeOD gave **10a** as a single diastereoisomer by ^{1}H NMR, with a C*H*^{t}Bu−C*H*D coupling constant of 2.5 Hz, and the electrophile and *t*-Bu group *anti* (Scheme 6, Table 2, entry 1).

SCHEME 6



X-ray crystal structure analysis of **10a** (Figure 1) shows the two aromatic rings in a *gauche* conformation in the solid state, and comparison of the ^{1}H NMR spectra and coupling constants of **10a** with the nondeuterated analogue **5a** indicates the Newman projection shown for the product. The interesting diaryl *gauche* conformation has been previously observed for other 1,2-diarylethanes containing *ortho*-substituted aryl rings.[14] The chemical shift of the *t*-Bu substituent (1.0 ppm) would indicate that this conformer also predominates in solution at room temperature (a deshielding of the *t*-Bu group by the neighboring phenyl ring, as reflected by an upfield shifted *t*-Bu resonance, is not observed).[15]

In addition, utilizing the electrophiles CO_2 or Bu_3SnCl in reaction with **3a** resulted in the formation of compounds **10b**

(14) Antolini, L.; Folli, U.; Iarossi, D.; Mucci, A.; Sbardellati, S.; Taddei, F. *J. Chem. Soc., Perkin Trans 2* **1995**, 1007 and references therein.
(15) Davies, H. M. L.; Ren, P. *Tetrahedron Lett.* **2001**, *42*, 3149.

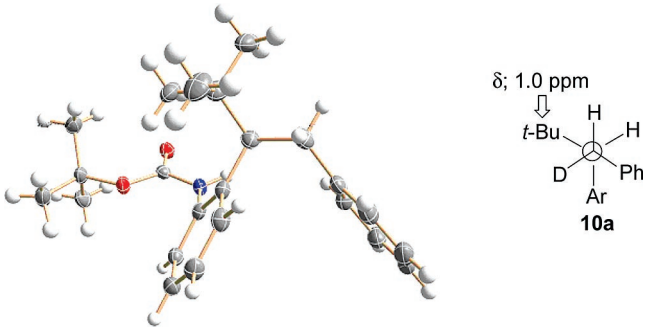


FIGURE 1. X-ray crystal structure (thermal ellipsoids drawn at the 50% probability level) and Newman projection of **10a**.

and **10c** as single diastereoisomers as judged by ^{1}H NMR (Figure 2, Table 2, entries 2, 3). The products **10b** and **10c** were characterized with C*H*−C*H* coupling constants of 11.6 and 11.5 Hz and upfield shifted *t*-Bu resonances at 0.6 and 0.7 ppm, respectively. The variation in the C*H*−C*H* coupling constant and *t*-Bu chemical shift of **10b** and **10c** in comparison to those of the deuterated example **10a** can be explained by the favored conformations of the products. In the case of the 1,1,2,2-tetra-substituted ethanes **10b** and **c**, the favored conformer placed the two aryl rings *antiperiplanar* resulting in an increased dihedral angle between the alkane protons and a deshielding effect of the phenyl ring on the *t*-Bu group accounting for the chemical shift difference from **10a** (Figure 2). As such, the electrophilic substitution with CD_3OD, CO_2, and Bu_3SnCl all occurred with retention of configuration. The use of ^{1}H NMR chemical shifts has been previously reported for conformational analysis and stereochemical assignment of tetra-substituted ethanes.[15]

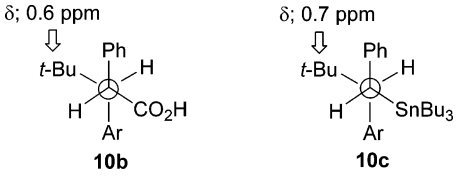
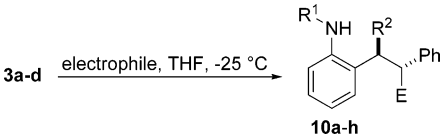


FIGURE 2. Newman projections of **10b, c**.

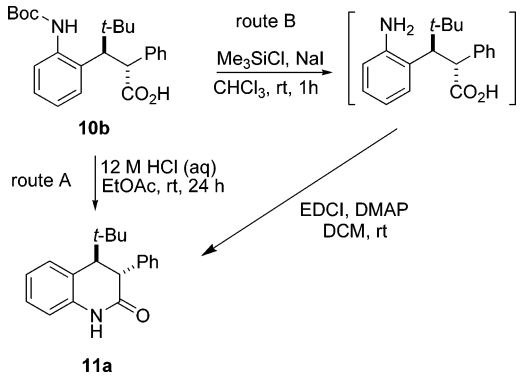
TABLE 2. Scope of Diastereoselective Substitution



entry	carbolithiated intermediate	R^1	R^2	E	product	yield,[a] %	dr[b]
1	**3a**	Boc	*t*-Bu	D	**10a**	85[c]	95:5
2	**3a**	Boc	*t*-Bu	CO_2H	**10b**	78	95:5
3	**3a**	Boc	*t*-Bu	$SnBu_3$	**10c**	34[d]	95:5
4	**3b**	Boc	*n*-Bu	D	**10d**	61[e]	95:5
5	**3c**	Boc	Et	D	**10e**	75[f]	95:5
6	**3b**	Boc	*n*-Bu	CO_2H	**10f**	56[g]	50:50
7	**3d**	Bn	*t*-Bu	D	**10g**	70[h]	95:5
8	**3d**	Bn	*t*-Bu	CO_2H	**10h**	64	60:40

[a] Isolated purified yield. [b]Diastereomeric ratios determined by ^{1}H NMR. [c]91% deuterium incorporation. [d]Compound **5a** was also recovered in 61% yield. [e]94% deuterium incorporation. [f]71% deuterium incorporation. [g]Compound **11b** was also isolated in 16% yield. [h]81% deuterium incorporation.

SCHEME 7. Cyclization of Compound 10b to 3,4-*trans* Quinolinone 11a



Confirmation of this assignment was achieved by intramolecular cyclization of compound **10b** to generate the quinolinone **11a** (Scheme 7, route A). The reaction was performed under acidic conditions using aqueous HCl to Boc deprotect and effect the intramolecular cyclization with **11a** isolated exclusively as the 3,4-*trans* isomer, which is consistent with the formation of the diastereoisomer as shown in the Newman projection (Figure 2). As interconversion of 3,4-*cis* and 3,4-*trans* quinolinone isomers can occur under acidic conditions (see later), the Boc deprotection of **10b** was also carried out under the neutral conditions of trimethylsilyl chloride/sodium iodide followed by intramolecular coupling with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) which exclusively provided the same *trans* isomer of **11a** (Scheme 7, route B).[16]

To further explore the scope of this diastereoselective transformation the effect of variation in alkyllithium and *ortho*-*N*-substituent on the selectivity obtained was determined (Table 2). Carbolithiation of **2a** with the less sterically bulky *n*-BuLi and EtLi, followed by deuteration of the lithiated intermediates **3b** and **3c**, gave the same excellent diastereoselectivity as observed for the *t*-Bu example (Table 2, entries 4, 5). The stereochemistry of deuterated products **10d** and **10e** was assigned by comparison with their corresponding protonated compounds **5b** and **5c** and was found to be the same as that observed for **10a**. However, when CO_2 was employed as the electrophile in reaction with **3b** (from carbolithiation of **2a** with *n*-BuLi), no diastereoselectivity was observed and the substitution products were isolated as an equal mixture of diastereoisomers **10f-(i)** and **10f-(ii)**. ^{1}H NMR analysis showed similar C*H*−C*H* coupling constants of 11.9 and 11.1 Hz for the two isomers indicating differences in conformations of the two diastereoisomers. This was supported by a variation in the chemical shift of the $CH_3(CH_2)_2CH_2$ protons for the two isomers with **10f-(i)** at 1.29−1.06 ppm and **10f-(ii)** at 1.89−1.72 ppm. As such, one of the isomers, **10f-(i)**, with a coupling constant of 11.9 Hz and deshielded CH_2 signal at 1.29−1.06 ppm, is assigned the same relative configuration and conformation of the aryl rings as the *t*-Bu example **10b**, while the other isomer, **10f-(ii)**, has the opposing relative configuration and a *gauche* conformation of the aryl rings. In addition an X-ray crystal structure of **10f-(ii)** was obtained to support this structural

(16) (a) Kato, T.; Marumoto, S.; Sato, T.; Kuwajima, I. *Synlett* **1990**, 671. (b) Mück-Lichtenfeld, C.; Ahlbrecht, H. *Tetrahedron* **1996**, *52*, 10025. (c) Mück-Lichtenfeld, C.; Ahlbrecht, H. *Tetrahedron* **1999**, *55*, 2609. (d) For review see; Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716.

(17) (a) Schade, S.; Boche, G. *J. Organomet. Chem.* **1998**, *550*, 359.

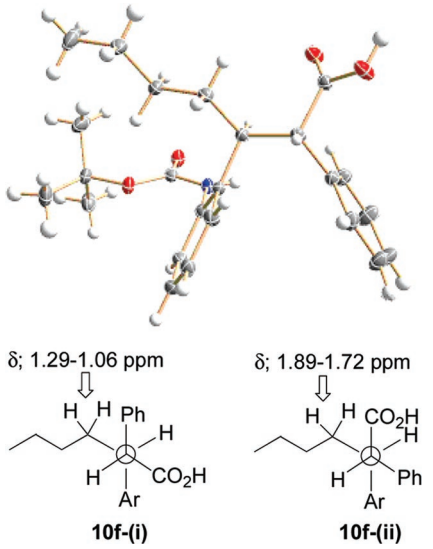


FIGURE 3. Newman projections of diastereoisomers **10f-(i)** and **10f-(ii)** with X-ray crystal structure (thermal ellipsoids drawn at the 50% probability level) of **10f-(ii)**.

assignment (Figure 3). Cyclization of a diastereoisomer mixture of **10f-(i)** and **-(ii)** to the quinolinone **11b** by Boc deprotection with trimethylsilyl chloride/sodium iodide and subsequent amide coupling with EDCI (as per Scheme 7, route B) gave the product as the corresponding mixture of 3,4-*trans* and 3,4-*cis* isomers which is consistent with the Newman projections shown in Figure 3.

The influence of the *N*-substituent upon diastereoselectivity was examined by reaction of the *N*-benzyl substituted lithiated intermediate **3d** with MeOD and CO_2 as electrophiles. Deuteration provided the product **10g** as a single diastereoisomer by ^{1}H NMR (J = 2.6 Hz and chemical shift of *t*-Bu group at 1.04 ppm) with the stereochemistry assigned by analogy to be the same as that of **10a** (Table 2, entry 7). However, reaction with CO_2 resulted in a lower selectivity and isolation of **10h** as a 60:40 mixture of diastereoisomers (entry 8). The C*H*−C*H* coupling constants of the two isomers had similar values of 11.1 and 10.4 Hz, but significant differences in the chemical shifts of the *t*-Bu groups were observed at 0.57 and 1.02 ppm for major and minor isomers, respectively. Comparison of the *t*-Bu chemical shift of the major isomer with that of **10b** (Figure 2) indicates that the same diastereoisomer is favored in both cases. As might be expected, reducing the temperature of the solution to −78 °C prior to addition of CO_2 resulted in an improved diastereoselectivity of 70:30. Overall these results indicate that a combination of the *t*-Bu group and *N*-Boc *ortho*-substituent is optimal for achieving the highest diastereoselectivities with a broad range of electrophiles.

The variation in diastereoselectivity observed for the two *ortho*-substituents (*N*-Boc and *N*-Benzyl) prompted an examination of the lithiated compounds **3a** and **3d** by NMR. Figure 4 shows the ^{1}H NMR and the gCOSY spectra of **3a** in THF-d_8 at −15 °C at the same concentration as the reaction conditions. The ^{1}H NMR of **3a** shows remarkable resolution for a lithiated species at this temperature indicating a highly conformationally organized compound, and in fact the spectrum remained virtually unchanged up to 20 °C (Supporting Information). The key CH protons, C*H*Ph and C*H*^{t}Bu, appear as sharp doublets at 2.68 and 3.73 ppm, respectively, with a coupling constant of 10.7 Hz. Their corresponding carbon atoms resonate at 61.7 and 45.4

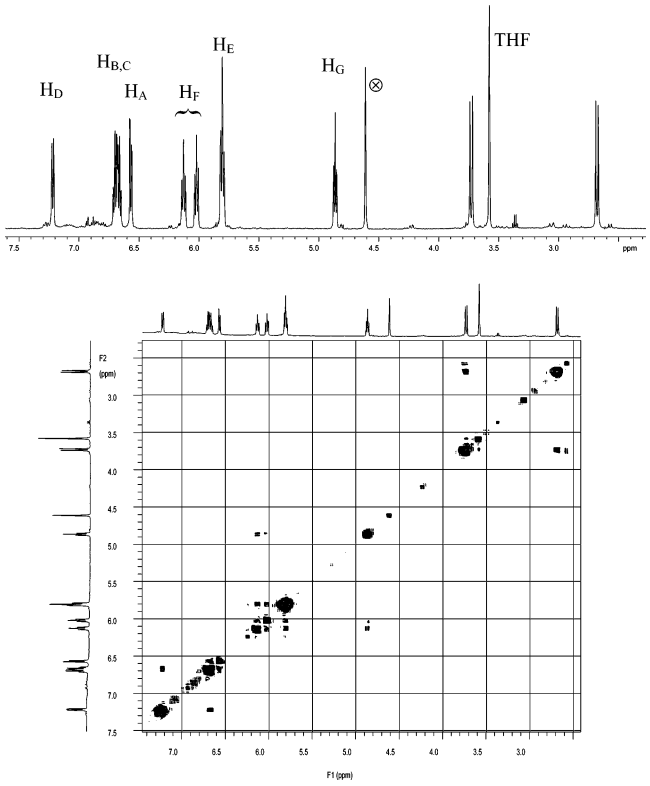


FIGURE 4. ^{1}H NMR and gCOSY spectrum of **3a** at −15 °C in THF-d_8 (⊗ unknown).

ppm. Examination of the gCOSY spectrum reveals the coupling between aromatic protons H_A, H_B, H_C, and H_D of the *ortho*-substituted aryl ring with H_D showing an heteronuclear multiple-bond correlation (HMBC) to C*H*^{t}Bu. The five hydrogens of the unsubstituted phenyl ring, labeled H_E, H_F, and H_G are assigned by coupling in the gCOSY spectrum. The informative aromatic signal shifted upfield to 4.87 ppm represents H_G (corresponding carbon signal at 98.6 ppm) and is indicative of charge delocalization into the ring which is a characteristic of a benzylic lithium species.[17] The inequivalence of the two H_F protons (chemical shifts) suggests that the molecule may be conformationally fixed with restricted rotation of some of the bonds. The ^{1}H NMR spectrum indicates that the lithiated intermediate **3a** exists predominantly in a stabilized conformation and, while not conclusive, does support the proposed formation of a heterochelated ring as shown in Figure 5. The Newman projection

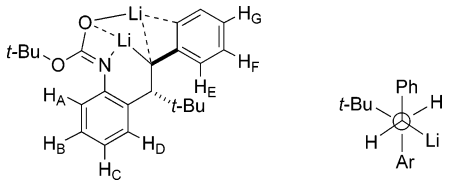


FIGURE 5. Proposed structure (solvent coordinations not shown) and Newman projection of **3a**.

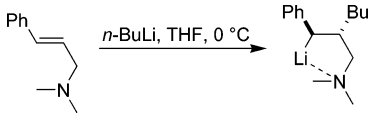
would be analogous to that of the carboxylic acid derivative **10b** which would facilitate the intramolecular chelation between the benzylic lithium and *ortho N*-Boc substituent. Diastereoselectivity could be envisaged by this arrangement due to a locking of the benzylic lithium in a preferred configuration. As the recorded coupling constant of **3a** is not conclusive for this

conformation and assignment of the *t*-Bu group could not be achieved due to masking by solvents, alternative dimeric structures cannot be ruled out at this time.

In contrast the ^{1}H NMR spectrum (THF-d_8, −15 °C) of the corresponding *N*-benzyl compound **3d** is considerably more complex containing a mixture of broad and well-defined peaks (Supporting Information). Significantly, the well resolved portions of the spectrum show an alkane C*H*Ph proton of the major component at 2.67 ppm with a coupling constant of 11.7 Hz, which is comparable to that observed for **3a**. These spectral characteristics would be consistent with the lower recorded diastereoselectivity following electrophilic substitution (Table 2, compare entries 2 and 8).

Related diastereoselectivities from electrophilic substitution of hetero-substituted benzyllithium compounds (generated via carbolithiation) are known within the literature.[3g,17] Selectivity is attributed to intramolecular heteroatom locked conformations within five-membered rings from which diastereoselective substitutions can be achieved. For example carbolithiation of dimethyl-(3-phenylallyl)amine with *n*-BuLi provides a heteroatom locked conformation from which highly diastereoselective substitutions are obtained (Scheme 8).[3g]

SCHEME 8. Carbolithiation of Dimethyl-(3-phenylallyl)amine

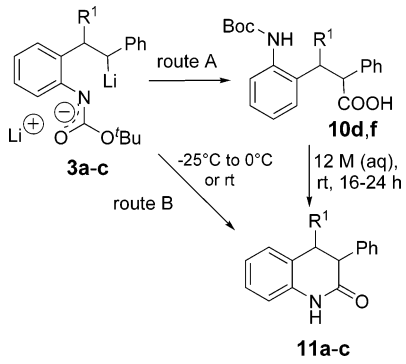


Having studied the regio- and diastereoselectivity of the reaction sequence, attempts to achieve enantioselectivity were carried out. The chiral diamine (−)-sparteine is a common chiral additive used in conjunction with alkyllithiums for asymmetric transformations.[18] Unfortunately (−)-sparteine mediated asymmetric carbolithiations are typically not successful in achieving high enantioselectivities in the presence of a strongly coordinating solvent such as THF. As it was determined that THF is essential for regioselective carbolithiation of our stilbenes, we anticipated that this would be incompatible with achieving enantioselective carbolithiations. As expected, the reaction of *n*-BuLi with either **2a** or **2b** in THF with 3 equiv of (−)-sparteine at −25 °C generated racemic products.

Synthesis of Quinolinone and Quinoline Ring Systems. Substituted quinolinones, dihydroquinolines, tetrahydroquinolines, and quinolines are common motifs found in natural products and pharmaceutical agents and as such continue to attract considerable attention from synthetic and medicinal chemists.[19] Thus, preparation of each structural class (quinolinones, dihydroquinolines, tetrahydroquinolines, and quinolines) via a common route would be of high synthetic value. As such the application of our regio- and diastereoselective carbolithiation−electrophile substitution reaction sequence was investigated for the synthesis of quinolinone and quinoline ring systems.

As previously demonstrated treatment of the acyclic carboxylic acids **10d, f** with aqueous 12 M HCl, effecting deprotection of the Boc group and intramolecular cyclization, allowed the isolation of 3,4-dihydro-1*H*-quinolin-2-ones **11a** and **11b**, respectively (Table 3, entries 1 and 2, route A). Compound **11a** was isolated exclusively as the 3,4-*trans* isomer while the *n*-alkyl derivative **11b** was obtained as a 60:40 mixture of the 3,4-*trans*/3,4-*cis* isomers. It was found that generation of the carboxylic acids **10d, f** was not necessary for access to this ring system, as intramolecular nucleophilic substitution of the benzylic lithium center of **3a**−**c** at the Boc group was readily achieved by raising the reaction temperature to either 0 °C or room temperature for 1 to 6 h (Table 3, entries 3−5, route B).

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



entry	sm	route	temp, °C	time, h	R^1	product	yield,[a] %
1	**10d**	A	rt	24	*t*-Bu	**11a**	76
2	**10f**	A	rt	16	*n*-Bu	**11b**	68
3	**3a**	B	rt	6	*t*-Bu	**11a**	22[b]
4	**3b**	B	0	1	*n*-Bu	**11b**	90
5	**3c**	B	0	2	Et	**11c**	84

[a] Isolated purified yield. [b]Compound **5a** was also isolated in 51% yield.

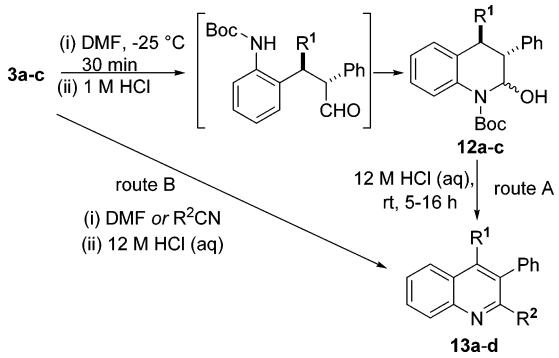
The reactivity of the Boc protecting group has previously been exploited for the synthesis of fused ring systems,[4a,20] and the intermolecular nucleophilic substitution of the Boc group of phenylcarbamic acid *tert*-butyl ester with *n*-BuLi has been reported.[4b] However, to the best of our knowledge this is the first example of formation of a six-membered ring by nucleophilic substitution of a benzylic lithium center on a Boc group. Following this intramolecular cyclization the 3,4-dihydro-1*H*-quinolin-2-one **11a** was obtained solely as the 3,4-*trans* isomer with compounds **11b, c** isolated crude as a 60:40 ratio of 3,4-*trans* (J = 1.2 and 1.8 Hz, respectively)/3,4-*cis* (J = 5.3 and 5.4 Hz, respectively). During purification by silica gel chro-

(18) 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*, 552. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282.

(19) 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.; O'Connor, 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.

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

TABLE 4. Synthesis of 1,2,3,4-Tetra-Substituted Tetrahydroquinolines, 2,3- and 3,4- Disubstituted and 3-Substituted Quinolines



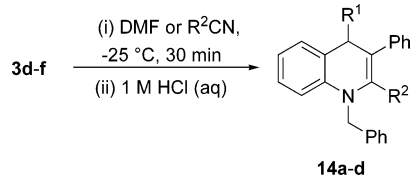
entry	sm	route	product	R^1	R^2	yield,[a] %
1	**3a**	−	**12a**	*t*-Bu	−	76
2	**3b**	−	**12b**	*n*-Bu	−	63
3	**3c**	−	**12c**	Et	−	71
4	**12a**	A	**13a**	H	H	78
5	**12b**	A	**13b**	*n*-Bu	H	78
6	**12c**	A	**13c**	Et	H	61
7	**3a**	B	**13a**	H	H	63
8	**3b**	B	**13b**	*n*-Bu	H	51
9	**3c**	B	**13c**	Et	H	36
10	**3a**	B	**13d**	H	4-$MeOC_6H_4$	21

[a] Isolated purified yield.

matography, the isomer mixture of **11b** and **11c** converted to a 90:10 and 80:20 ratio, respectively, in favor of the thermodynamic *trans* isomer. The acidity of the C-3 proton adjacent to the amide bond (C*H*Ph) creates a potential site for deprotonation thus allowing interconversion of *cis* and *trans* isomers.[19a,21] Notably, resubjecting the purified *trans* isomer of **11b** to the reaction conditions ((i) *n*-BuLi in THF at 0 °C for 1 h, (ii) MeOH) resulted in the isolation of **11b** in a *trans*/*cis* isomer ratio of 30:70.

To further extend the synthetic utility of the carbolithiation reaction we found that treatment of lithiated intermediates **3a**−**c** with DMF followed by acidification with aqueous acid provided a versatile synthesis of the 1,2,3,4-tetrasubstituted-tetrahydroquinolines **12a**−**c** in purified yields of 63−76% (Table 4, entries 1−3). Two diastereomeric products were isolated, 2,3-*cis*-3,4-*trans* and 2,3-*trans*-3,4-*trans*; however in all cases the alkyl and phenyl groups were *trans* to each other with the difference being in the relative orientation of the phenyl and alcohol groups. This result is consistent with generation of the aldehyde intermediate with *anti* selectivity, which following acidification and *in situ* cyclization affords the tetrahydroquinoline as the 3,4-*trans* isomer. Both isomers of **12a** showed a coupling constant between the C-3 and C-4 protons of 4.0 Hz. The corresponding coupling constants for the *n*-Bu derivative are 11.5 and 9.4 Hz for 2,3-*cis*-3,4-*trans*-**12b** and 2,3-*trans*-3,4-*trans*-**12b**, respectively. The differences in the coupling constants for the *t*-Bu and *n*-alkyl derivatives can be explained by differing conformations of the nitrogen containing ring as evidenced by X-ray crystal structure (Supporting Information). The ratio of isomers obtained was dependent on the acidification temperature, with low temperatures (−78 °C) favoring the 2,3-*trans*-3,4-*trans* isomer and increased temperatures yielding 2,3-*cis*-3,4-*trans* as the major isomer. A single isomer, 2,3-*cis*-3,4-*trans*, of **12a** was isolated when the reaction mixture was brought to room temperature before acidification. Alternatively

TABLE 5. Synthesis of 1,3,4-Tri- and 1,2,3,4-Tetra-Substituted 1,4-Dihydroquinolines



entry	lithiated intermediate	R^1	R^2	product	yield,[a] %
1	**3d**	*t*-Bu	H	**14a**	82
2	**3e**	*n*-Bu	H	**14b**	51
3	**3f**	*s*-Bu	H	**14c**	84
4	**3d**	*t*-Bu	$COCH_3$	**14d**	50[b]

[a] Isolated purified yield. [b]Acidification with saturated NH_4Cl followed by 5 M HCl for 30 min.

complete conversion from 2,3-*trans*-3,4-*trans*-**12a** to 2,3-*cis*-3,4-*trans*-**12a** could be achieved by treatment with 2 M HCl in THF at room temperature for 6 h.

Dehydration of **12a**−**c** by treatment with aqueous HCl (12 M) enabled the preparation of substituted quinoline rings (Table 4, route A, entries 4−6). Compounds **12b** and **12c** were dehydrated and *in situ* oxidized to yield as expected the 3,4-disubstituted quinolines, **13b** and **13c**, respectively. Surprisingly, the *t*-Bu substituted analogue **12a** yielded only the monosubstituted 3-phenylquinoline **13a**, indicating that the aromatic ring was generated by loss of the *t*-Bu group. Even when milder acidification conditions were employed (5 M HCl in THF), only **13a** was isolated with the 3,4-di-substituted quinoline again not observed. A similar loss of a *t*-Bu group from dihydroquinolines and porphyrins has been previously observed.[22]

Compounds **13a**−**c** could also be prepared directly from intermediates **3a**−**c** in similar overall yields without the isolation of **12a**−**c** (Table 4, route B, entries 7−9). The use of 4-methoxybenzonitrile as electrophile in reaction with **3a** with subsequent acidification demonstrated the use of this approach for the direct generation of the quinoline **13d** with a 2,3-di-substitution pattern following *in situ* loss of the *t*-Bu group (entry 10).

Reaction of the *N*-benzyl substituted di-lithiated intermediates **3d**−**f** with the electrophile DMF or diethoxypropionitrile provided a direct entry into the 1,4-dihydroquinoline class. Treatment of **3d**−**f** with DMF, followed by a mild aqueous acidification, resulted in ring closure and an *in situ* dehydration to the 1,4-dihydroquinolines **14a**−**c** without isolation of their tetrahydro precursors (Table 5, entries 1−3). A representative example of a nitrile electrophile, diethoxypropionitrile, was utilized in reaction with **3d** to generate the C-2 keto substituted 1,2,3,4-tetra-substituted-1,4,-dihydroquinoline **14d**. In this example, following the reaction cascade sequence to generate the 1,4-dihydroquinoline ring, a further *in situ* deprotection of the acetal protecting group occurred thereby generating the 2-keto substituent.

Conclusion

In summary, we have shown that a general carbolithiation of *ortho*-amino-(*E*)-stilbenes can be achieved in THF to provide

(21) Kim, Y.; Shin, E.; Beak, P.; Park, Y. S. *Synthesis*, **2006**, *22*, 3805.
(22) (a) Anne, A.; Fraoua, S.; Moiroux, J.; Savéant, J.-M. *J. Am. Chem. Soc.* **1996**, *118*, 3938. (b) Neya, S.; Funasaki, N. *Tetrahedron Lett.* **2002**, *43*, 1057.

single regioisomers containing carbon-lithium centers at the β position from the *ortho*-substituted aryl ring. Subsequent electrophile substitution reactions show exceptional diastereoselectivity with a range of electrophiles and investigation of the lithiated intermediates by NMR permitted an insight into the source of this selectivity. The scope of this regio- and diastereoselective reaction methodology has been demonstrated by the development of new synthetic routes to substituted quinolin-2-ones, 1,2,3,4-tetrahydroquinolines, 1,4-dihydroquinolines, and quinolines from common lithiated reaction intermediates. Utilization of this approach for the generation of other heterocycles by modification of the reacting pair of *ortho*-substituent and electrophile is ongoing.

Experimental Section

NMR Analysis of 3a. *t*-BuLi (0.10 mL, 0.17 mmol) was added to a solution of **2a** (17.1 mg, 0.06 mmol) in THF-d_8 (0.75 mL) at −20 °C. The temperature was increased to −15 °C, and the mixture was transferred to an NMR tube. NMR data were collected at −15 °C on a Varian 500 MHz instrument. ^{1}H NMR (THF-d_8, 500 MHz, −15 °C) δ: 7.22 (dd, 1H, J = 7.8/2.0 Hz, H_D), 6.72−6.65 (m, 2H, H_B and H_C), 6.57 (dd, 1H, J = 7.8/2.0 Hz, H_A), 6.15−6.11 (m, 1H, H_F), 6.04−6.01 (m, 1H, H_F), 5.82−5.79 (m, 2H, H_E), 4.88−4.85 (m, 1H, H_G), 3.73 (d, 1H, J = 10.7 Hz, C*H*^{t}Bu), 2.68 (d, 1H, J = 10.7 Hz, C*H*Ph). The signals for the *t*-Bu groups were not identified due to the presence of pentane in the sample (from the *t*-BuLi). [Note: Spectrum referenced from THF signal at 3.58 ppm.] ^{13}C NMR (THF-d_8, 125 MHz, −15 °C) δ: 151.6, 149.1, 143.8, 129.7, 129.7, 128.4, 126.1, 123.6, 121.1, 115.7, 111.2, 109.0, 98.6, 74.8, 61.7, 45.4. The signals corresponding to the two *t*-Bu groups were not identified. Variable temperature NMR was performed on the sample from −15 to 20 °C following which the sample was treated with methanol and compound **5a** was isolated.

[2-(1-Benzyl-2,2-dimethylpropyl)phenyl]carbamic Acid *tert*-Butyl Ester, 5a. A solution of **2a** (247.8 mg, 0.84 mmol) in THF (10 mL) was cooled to −25 °C. *t*-BuLi (1.70 mL, 2.53 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and treated with methanol (1 mL). The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and washed with water (10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 8/2 pentane/diethyl ether) gave the purified product as a colorless solid (257.8 mg, 87%), mp 63−64 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.40−7.37 (m, 1H), 7.34 (bs, 1H), 7.13−7.04 (m, 5 H), 6.90−6.88 (m, 2H), 5.61 (bs, 1H), 3.18 (dd, 1H, J = 12.9/2.7 Hz), 2.96−2.80 (m, 2H), 1.43 (s, 9H), 1.00 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.9, 141.7, 136.8, 128.7, 128.4, 128.2, 126.4, 125.9, 124.7, 80.2, 51.2, 37.2, 35.2, 28.5, 28.5. IR (KBr disk): 1366, 1690, 2947, 3431 cm^{-1}. ES-MS: *m*/*z* 352.2 [M − H]$^-$. HRMS [M − H]$^-$: 352.2290, $C_{23}H_{30}NO_2$ requires 352.2277. Analysis calcd for $C_{23}H_{31}NO_2$: C, 78.15; H, 8.84; N, 3.96. Found: C, 78.41; H, 8.92; N, 3.97.

[2-(1-Benzylpentyl)phenyl]carbamic Acid *tert*-Butyl Ester, 5b. A solution of **2a** (150.0 mg, 0.51 mmol) in THF (6 mL) was cooled to −25 °C, and PMDTA was (0.32 mL, 1.53 mmol) added. *n*-BuLi (0.60 mL, 1.54 mmol) was added dropwise over 30 min, during which time a red color developed. The reaction mixture was stirred for 1 h at −25 °C and treated with methanol (1 mL). The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and washed with hydrochloric acid (1 M, 10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 1/1 cyclohexane/diethyl ether) gave the purified product as a colorless solid (112 mg, 62%), mp 51−54 °C. (Note: compound **11b** was also isolated in 10% yield.) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45 (bs, 1H), 7.25−7.12 (m, 6H), 6.99−6.96 (m, 2H), 5.56 (bs, 1H), 3.00−2.92 (m, 2H), 2.74−2.68 (m, 1H), 1.80−1.61 (m, 2H), 1.45 (s, 9H), 1.29−1.20 (m, 2H), 1.19−1.12 (m, 2H), 0.82 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.9, 140.7, 136.0, 129.2, 129.2, 128.6, 126.7, 126.5, 126.4, 125.4, 80.1, 43.9, 41.8, 35.2, 30.0, 28.5, 23.0, 14.2. IR (KBr disc): 1450, 1522, 1674, 2860, 2926, 2949, 3026, 3226 cm^{-1}. ES-MS: *m*/*z* 376.2 [M + Na]$^+$. HRMS [M + Na]$^+$: 376.2249, $C_{23}H_{31}NO_2Na$ requires 376.2252. Analysis calcd for $C_{23}H_{31}NO_2$:C, 78.15; H, 8.84; N, 3.96. Found: C, 78.20; H, 8.94; N, 3.76.

[2-(1-Benzylpropyl)phenyl]carbamic Acid *tert*-Butyl Ester, 5c. A solution of **2a** (146.9 mg, 0.50 mmol) in THF (6 mL) was cooled to −25 °C, and PMDTA (0.31 mL, 1.48 mmol) was added. EtLi (0.92 mL, 1.50 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and treated with methanol (1 mL). The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in diethyl ether (10 mL) and washed with hydrochloric acid (1 M, 10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Chromatography on alumina (eluent: 1/1 pentane/diethyl ether) gave the purified product as a colorless solid (123.7 mg, 76%), mp 70−73 °C. (Note: compound **11c** was also isolated in 7% yield.) ^{1}H NMR (400 MHz) δ: 7.46 (bs, 1H), 7.25−7.13 (m, 6H), 7.00−6.98 (m, 2H), 5.61 (bs, 1H), 2.97−2.88 (m, 2H), 2.74−2.69 (m, 1H), 1.85−1.74 (m, 1H), 1.73−1.63 (m, 1H), 1.46 (s, 9H), 0.81 (t, 3H, J = 7.4 Hz). ^{13}C NMR (100 MHz) δ: 153.8, 140.7, 136.1, 129.2, 128.6, 126.7, 126.6, 126.4, 125.4, 80.1, 43.6, 43.5, 28.6, 28.2, 12.3. IR (neat): 1514, 1697, 1730, 2873, 2937, 2966, 3027, 3062, 3394 cm^{-1}. ES-MS: *m*/*z* 326.2 [M + H]$^+$. HRMS [M + H]$^+$: 326.2135, $C_{21}H_{28}NO_2$ requires 326.2120. Analysis calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.67; H, 8.38; N, 4.21.

Benzyl-[2-(1-benzyl-2,2-dimethylpropyl)phenyl]amine, 5d. A solution of **2b** (144.0 mg, 0.50 mmol) in THF (6 mL) was cooled to −25 °C. *t*-BuLi (1.15 mL, 1.51 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and treated with methanol (1 mL). The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in diethyl ether (10 mL) and washed with hydrochloric acid (1 M, 10 mL). The organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 9/1 pentane/diethyl ether) gave the product as a colorless solid (136.4 mg, 79%), mp 103−106 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30−7.28 (m, 1H), 7.26−7.19 (m, 3H), 7.13−7.08 (m, 3H), 7.01−6.97 (m, 2H), 6.96−6.93 (m, 3H), 6.73−6.69 (m, 1H), 6.41−6.39 (m, 1H), 4.18 (d, 1H, J = 14.8 Hz), 4.10 (d, 1H, J = 14.8 Hz), 3.80 (bs, 1H), 3.15 (dd, 1H, J = 13.1/ 2.6 Hz), 2.94−2.87 (m, 1H), 2.78 (dd, 1H, J = 11.4/ 2.6 Hz), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.9, 142.2, 139.9, 129.0, 128.7, 128.4, 128.2, 127.5, 127.3, 127.0, 126.8, 125.7, 117.0, 111.6, 50.2, 48.5, 37.4, 35.7, 28.5. IR (KBr disc): 1510, 1603, 2864, 2900, 2956, 3464 cm^{-1}. ES-MS: *m*/*z* 344.2 [M + H]$^+$. HRMS [M + H]$^+$: 344.2378, $C_{25}H_{30}N$ requires 344.2369. Analysis calcd for $C_{25}H_{29}N$: C, 87.41; H, 8.51; N, 4.08. Found: C, 87.21; H, 8.38; N, 3.87.

Benzyl-[2-(1-benzylpentyl)phenyl]amine, 5e. A solution of **2b** (143.9 mg, 0.50 mmol) in THF (6 mL) was cooled to −25 °C, and PMDTA (0.31 mL, 1.48 mmol) was added. *n*-BuLi (0.61 mL, 1.51 mmol) was added dropwise over 15 min, during which time red color developed. The reaction mixture was stirred at −25 °C for 2 h and treated with methanol (1 mL). The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in diethyl ether (10 mL) and washed with hydrochloric acid (1 M, 10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 99/1 pentane/diethyl

ether) gave the purified product as a colorless oil (105.1 mg, 61%). (Note: Starting material **2b** was also recovered in 29% yield.) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32−7.23 (m, 3H), 7.21−7.13 (m, 6H), 7.07−7.03 (m, 1H), 6.99−6.96 (m, 2H), 6.78−6.74 (m, 1H), 6.55−6.53 (m, 1H), 4.19 (d, 1H, J = 14.1 Hz), 4.07 (d, 1H, J = 14.1 Hz), 3.67 (bs, 1H), 2.92−2.79 (m, 3H), 1.73−1.67 (m, 2H), 1.29−1.17 (m, 4H), 0.82 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.1, 141.1, 139.8, 129.7, 129.3, 128.8, 128.4, 127.7, 127.3, 126.9, 126.7, 126.2, 117.9, 111.4, 48.8, 43.3, 40.7, 34.8, 30.0, 23.1, 14.3. IR (neat): 1506, 1603, 2856, 2927, 2954, 3028, 3061, 3444 cm^{-1}. ES-MS: m/z 344.2 [M + H]$^+$. HRMS [M + H]$^+$: 344.2365, $C_{25}H_{30}N$ requires 344.2378. Analysis calcd for $C_{25}H_{29}N$: C, 87.41; H, 8.51; N, 4.08. Found: C, 87.66; H, 8.43; N, 4.15.

Benzyl-[2-(1-benzyl-2-methylbutyl)phenyl]amine, 5f. A solution of **2b** (144.5 mg, 0.51 mmol) in THF (6 mL) was cooled to −25 °C. *s*-BuLi (1.09 mL, 1.49 mmol) was added dropwise over 15 min, during which time red color developed. The reaction mixture was stirred at −25 °C for 1 h and treated with methanol (1 mL). The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in diethyl ether (10 mL) and washed with hydrochloric acid (1 M, 10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 95/5 pentane/diethyl ether) gave the purified product as a colorless oil (142.2 mg, 81%). (Note: The product was analyzed as an equal mixture of diastereoisomers.) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.29−7.21 (m, 3H), 7.15−7.08 (m, 6H), 7.01−6.98 (m, 1H), 6.93−6.91 (m, 2H), 6.73−6.70 (m, 1H), 6.46−6.44 (m, 1H), 4.16−4.11 (m, 1H), 4.02−3.97 (m, 1H), 3.58 (bs, 1H), 3.18−3.14 (m, 1H), 2.79−2.73 (m, 2H), 1.79−1.75 (m, 1H includes both isomers, 0.5H, isomer 1), 1.43−1.37 (m, 0.5H, isomer 2), 1.32−1.24 (m, 0.5H, isomer 1), 1.08 (d, 1.5H, J = 6.7 Hz, isomer 1), 1.09−1.04 (m, 0.5H, isomer 2), 0.96−0.87 (m, 1.5H, isomer 1), 0.86−0.80 (m, 3H, isomer 2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.6, 146.4, 141.6, 141.5, 139.9, 139.8, 129.2, 129.1, 128.9, 128.7, 128.3, 128.2, 127.6, 127.5, 127.2, 127.1, 126.7, 125.9, 125.8, 117.6, 111.5, 111.4, 48.7, 39.6, 39.4, 39.2, 38.8, 27.6, 27.3, 17.2, 17.1, 11.7, 11.6. IR (neat): 1452, 1506, 1603, 2873, 2927, 2958, 3026, 3062, 3438 cm^{-1}. ES-MS: m/z 344.2 [M + H]$^+$. HRMS [M + H]$^+$: 344.2374, $C_{25}H_{30}N$ requires 344.2378. Analysis calcd for $C_{25}H_{29}N$: C, 87.41; H, 8.51; N, 4.08. Found: C, 87.46; H, 8.50; N, 4.10.

[2-(1-Benzyl-2,2-dimethylpropyl)phenyl]carbamic Acid *tert*-Butyl Ester-d_1, 10a. A solution of **2a** (94.1 mg, 0.32 mmol) in THF (3.8 mL) was cooled to −25 °C. *t*-BuLi (0.56 mL, 0.95 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and treated with methanol-d_4 (0.7 mL). The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and washed with water (10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 8/2 pentane/diethyl ether) gave the purified product as a colorless solid (96.9 mg, 85%), mp 61−62 °C. 95:5 dr. (Deuterium incorporation: 91%, determined by ^{1}H NMR.) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.41−7.38 (m, 1H), 7.35 (bs, 1H), 7.14−7.05 (m, 5H), 6.90−6.88 (m, 2H), 5.61 (bs, 1H), 3.17 (d, 1H, J = 2.5 Hz), 2.93 (s, 1H, J = 2.5 Hz), 1.43 (s, 9H), 1.00 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.6, 141.6, 136.7, 128.7, 128.4, 128.2, 126.4, 125.9, 124.7, 80.2, 51.1, 36.8 (t, J_{CD} = 19.5 Hz), 35.2, 28.5, 28.5. IR (neat): 1366, 1450, 1693, 1733, 2871, 2971, 3027, 3062, 3451 cm^{-1}. ES-MS: m/z 355.3 [M + H]$^+$. HRMS [M + H]$^+$: 355.2502, $C_{23}H_{33}NO_2$ requires 355.2511. Analysis calcd for $C_{23}H_{30}DNO_2$: C, 77.92; H, 9.10; N, 3.95. Found: C, 77.63; H, 8.83; N, 3.94.

3-(2-*tert*-Butoxycarbonylaminophenyl)-4,4-dimethyl-2-phenylpentanoic Acid, 10b. A solution of **2a** (150.7 mg, 0.51 mmol) in THF (6 mL) was cooled to −25 °C. *t*-BuLi (0.90 mL, 1.53 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and treated with solid carbon dioxide. The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and washed with water (10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Chromatography on alumina (eluent: diethyl ether followed by methanol) gave the purified product as a colorless solid (158.5 mg, 78%), mp 145−147 °C. 95:5 dr. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45−7.43 (m, 2H), 7.27−7.24 (m, 1H), 7.21−7.13 (m, 4H), 6.96−6.92 (m, 1H), 6.88−6.84 (m, 1H), 3.81 (d, 1H, J = 11.6 Hz), 3.56 (d, 1H, J = 11.6 Hz), 3.09 (bs, 1H), 1.57 (s, 9H), 0.60 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 180.3, 155.2, 142.6, 140.0, 136.1, 129.2, 128.3, 127.8, 126.7, 126.1, 125.2, 80.5, 59.3, 50.3, 35.3, 29.8, 28.7. IR (neat): 1367, 1574, 1684, 2932, 2959, 3389 cm^{-1}. ES-MS: m/z 398.2 [M + H]$^+$. HRMS [M + H]$^+$: 398.2332, $C_{24}H_{32}NO_4$ requires 398.2331.

{2-[2,2-Dimethyl-1-(phenyltributylstannanylmethyl)propyl]-phenyl}carbamic Acid *tert*-Butyl Ester, 10c. A solution of **2a** (105.5 mg, 0.36 mmol) in THF (4.3 mL) was cooled to −25 °C. *t*-BuLi (0.64 mL, 1.09 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and treated with tributyltin chloride (0.29 mL, 1.07 mmol). Stirring continued at −25 °C for 10 min before the reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in diethyl ether (10 mL) and washed with water (10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 99/1 pentane/diethyl ether) gave the purified product as a colorless oil (77.6 mg, 34%). 95:5 dr. (Note: Compound **5a** was also recovered in 61% yield.) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.78−7.76 (m, 1H), 7.26−7.14 (m, 6H), 7.10−7.06 (m, 1H), 7.02−6.98 (m, 1H), 6.42 (bs, 1H), 3.49 (d, 1H, J = 11.5 Hz), 3.35 (d, 1H, J = 11.5 Hz), 1.56 (s, 9H), 1.12−1.07 (m, 12H), 0.79−0.75 (m, 9H), 0.70 (s, 9H), 0.32−0.19 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.4, 148.1, 135.5, 128.8, 128.5, 128.5, 127.9, 126.8, 124.1, 123.9, 123.8, 80.7, 49.5, 40.4, 38.6, 29.6, 29.2, 28.7, 27.6, 13.8, 10.5. IR (neat): 1694, 1738, 2871, 2927, 2955, 3061, 3467 cm^{-1}. ES-MS: m/z 644.3 [M + H]$^+$. HRMS [M + H]$^+$: 644.3517, $C_{35}H_{58}NO_2Sn$ requires 644.3490.

2-(1-Benzylpentyl)phenyl]carbamic Acid *tert*-Butyl Ester-d_1, 10d. A solution of **2a** (80.8 mg, 0.27 mmol) in THF (3 mL) was cooled to −25 °C, and PMDTA (0.17 mL, 0.81 mmol) was added. *n*-BuLi (0.58 mL, 0.80 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred for 1 h at −25 °C and treated with methanol-d_4 (0.5 mL). The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in diethyl ether (10 mL) and washed with hydrochloric acid (1 M, 10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 1/1 cyclohexane/diethyl ether) gave the purified product as a colorless solid (58.7 mg, 61%), mp 49−50 °C. 95:5 dr. (Deuterium incorporation: 94%, determined by ^{1}H NMR.) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44 (bs, 1H), 7.25−7.13 (m, 6H), 6.99−6.96 (m, 2H), 5.56 (bs, 1H), 3.00−2.95 (m, 1H), 2.92 (d, 1H, J = 5.6 Hz), 1.79−1.63 (m, 2H), 1.45 (s, 9H), 1.30−1.20 (m, 2H), 1.20−1.12 (m, 2H), 0.82 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.8, 140.7, 136.0, 129.2, 129.2, 128.6, 126.7, 126.5, 126.4, 125.4, 80.1, 43.6 (t, J_{CD} = 19.1 Hz), 41.7, 35.2, 30.0, 28.5, 23.0, 14.2. IR (neat): 1451, 1514, 1675, 1730, 2859, 2930, 2958, 3402. ES-MS: m/z 355.3 [M + H]$^+$. HRMS [M + H]$^+$: 355.2508, $C_{23}H_{33}NO_2$ requires 355.2511. Analysis calcd for $C_{23}H_{30}DNO_2$: C, 77.92; H, 9.10; N, 3.95. Found: C, 77.65; H, 8.84; N, 3.84.

[2-(1-Benzylpropyl)phenyl]carbamic Acid *tert*-Butyl Ester-d_1, 10e. A solution of **2a** (98.6 mg, 0.33 mmol) in THF (4 mL)

was cooled to −25 °C, and PMDTA (0.21 mL, 1.00 mmol) was added. EtLi (0.58 mL, 0.99 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and treated with methanol-d_4 (0.5 mL). The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in diethyl ether (10 mL) and washed with hydrochloric acid (1 M, 10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Chromatography on alumina (eluent: 1/1 pentane/diethyl ether) gave the purified product as a colorless solid (81.3 mg, 75%), mp 68−69 °C. 95:5 dr. (Deuterium incorporation: 71%, determined by ^{1}H NMR.) ^{1}H NMR (400 MHz) δ: 7.46 (bs, 1H), 7.25−7.13 (m, 6H), 7.00−6.98 (m, 2H), 5.61 (bs, 1H), 2.94−2.88 (m, 2H), 1.85−1.74 (m, 1H), 1.73−1.64 (m, 1H), 1.46 (s, 9H), 0.81 (t, 3H, J = 7.4 Hz). ^{13}C NMR (100 MHz) δ: 153.8, 140.7, 136.1, 129.2, 128.5, 126.7, 126.5, 126.4, 125.4, 80.1, 43.4, 43.2 (t, J_{CD} = 19.1 Hz), 28.6, 28.1, 12.3. IR (neat): 1517, 1699, 1730, 2874, 2931, 2966, 3026, 3335, 3402 cm^{-1}. ES-MS: m/z 325.2 [M − H]$^-$. HRMS [M − H]$^-$: 325.2018, $C_{211}H_{25}DNO_2$ requires 325.2026. Analysis calcd for $C_{21}H_{26}DNO_2$: C, 77.26; H, 8.64; N, 4.29. Found: C, 77.15; H, 8.37; N, 4.16.

3-(2-*tert*-Butoxycarbonylaminophenyl)-2-phenylheptanoic Acid, 10f. A solution of **2a** (149.2 mg, 0.51 mmol) in THF (6 mL) was cooled to −25 °C, and PMDTA (0.32 mL, 1.53 mmol) was added. *n*-BuLi (0.71 mL, 1.54 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred for 1 h at −25 °C and treated with solid carbon dioxide. The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in dichloromethane (15 mL) and washed with hydrochloric acid (1 M, 10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. The impurities were removed by tritration with pentane to give the purified product as a colorless solid (102.8 mg, 56%), mp 149−150 °C. 50:50 dr. (Note: Compound **11b** was also isolated in 16% yield.) ^{1}H NMR (CD_3OD, 500 MHz) δ: 7.48−7.46 (m, 1H, *anti* isomer), 7.39−7.36 (m, 2H, *anti* isomer), 7.32−6.99 (m, 9H *syn* isomer, 6H *anti* isomer), 3.82 (d, 1H, J = 11.1 Hz, *syn* isomer), 3.77 (d, 1H, J = 11.9 Hz, *anti* isomer), 3.72−3.67 (m, 1H, *syn* isomer), 3.61−3.57 (m, 1H, *anti* isomer), 1.89−1.84 (m, 1H, *syn* isomer), 1.76−1.72 (m, 1H, *syn* isomer), 1.54 (s, 9H, *anti* isomer), 1.51 (s, 9H, *syn* isomer), 1.29−1.06 (m, 4H *syn* isomer, 6H *anti* isomer), 0.81 (t, 3H, J = 7.3 Hz, *syn* isomer), 0.64 (t, 3H, J = 7.4 Hz, *anti* isomer). [**10f-(i)** *anti* isomer; **10f-(ii)** *syn* isomer.] ^{13}C NMR (CD_3OD, 100 MHz) δ: 176.4, 176.3, 155.2, 155.1, 138.4, 138.0, 136.3, 136.2, 129.8, 128.6, 128.4, 128.3, 127.9, 127.4, 126.8, 126.4, 126.1, 125.8, 125.3, 80.0, 79.8, 29.0, 27.5, 23.3, 22.6, 21.9, 13.1, 13.0. [Note: Peaks under solvent signal could not be identified.] IR (neat): 1660, 1712, 2872, 2932, 2952, 3299 cm^{-1}. ES-MS: m/z 396.1 [M − H]$^-$. HRMS [M + H]$^+$: 398.2330, $C_{24}H_{32}NO_4$ requires 398.2331. Suitable crystals were grown by the slow evaporation of a solution of **10f** in diethyl ether.

Benzyl-[2-(1-benzyl-2,2-dimethylpropyl)phenyl]amine-d_1, 10g. A solution of **2b** (82.8 mg, 0.29 mmol) in THF (3.6 mL) was cooled to −25 °C. *t*-BuLi (0.61 mL, 0.87 mmol) was added dropwise over 15 min, during which time a red/brown color developed. The reaction mixture was stirred at −25 °C for 1 h and treated with methanol-d_4 (1 mL). The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in diethyl ether (10 mL) and washed with hydrochloric acid (1 M, 10 mL). The organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 9/1 pentane/diethyl ether) gave the purified product as a colorless solid (69.1 mg, 70%), mp 106−108 °C. 95:5 dr. (Deuterium incorporation: 81%, determined by ^{1}H NMR.) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.31−7.28 (m, 1H), 7.26−7.20 (m, 3H), 7.14−7.08 (m, 3H), 7.02−6.98 (m, 2H), 6.96−6.94 (m, 3H), 6.73−6.70 (m, 1H), 6.41−6.39 (m, 1H), 4.18 (d, 1H, J = 14.8 Hz), 4.11 (d, 1H, J = 14.8 Hz), 3.81 (bs, 1H), 3.14 (d, 1H, J = 2.6 Hz), 2.78 (d, 1H, J = 2.6 Hz), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.9, 142.1, 139.9, 128.9, 128.7, 128.3, 128.2, 127.4, 127.3, 127.0, 126.7, 125.7, 117.0, 111.5, 50.2, 48.5, 37.0 (t, J_{CD} = 19.1 Hz), 35.7, 28.5. IR (neat): 1506, 1602, 2868, 2905, 2958, 3027, 3062, 3458 cm^{-1}. ES-MS: m/z 345.2 [M + H]$^+$. HRMS [M + H]$^+$: 345.2427, $C_{25}H_{29}DN$ requires 345.2441. Analysis calcd for $C_{25}H_{28}DN$: C, 87.16; H, 8.78; N, 4.07. Found: C, 86.93; H, 8.48; N, 4.08.

3-(2-Benzylaminophenyl)-4,4-dimethyl-2-phenylpentanoic Acid, 10h. A solution of **2b** (161.3 mg, 0.56 mmol) in THF (6 mL) was cooled to −25 °C. *t*-BuLi (1.12 mL, 1.68 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and treated with solid carbon dioxide. The reaction mixture was allowed to warm to room temperature, and the THF was removed under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and washed with water (10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Chromatography on alumina (eluent: diethyl ether followed by methanol) gave the purified product as a colorless oil (138.7 mg, 64%). 60:40 dr. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.36−7.07 (m, 10H *syn* isomer, 9H *anti* isomer), 6.91−6.85 (m, 2H *anti* isomer), 6.74−6.67 (m, 1H *syn* isomer, 1H, *anti* isomer), 6.63−6.61 (m, 1H *syn* isomer), 6.44−6.41 (m, 1H *anti* isomer), 6.33−6.30 (m, 2H *syn* isomer), 6.24−6.21 (m, 1H *anti* isomer), 4.84 (bs, 1H *syn* isomer), 4.51 (bs, 1H *anti* isomer), 4.39 (d, 1H, J = 15.7 Hz, *syn* isomer), 4.33 (d, 1H, J = 15.7 Hz, *syn* isomer), 4.17 (d, 1H, J = 13.4 Hz, *anti* isomer), 4.05 (d, 1H, J = 13.4 Hz, *anti* isomer), 3.88 (d, 1H, J = 10.4 Hz, *syn* isomer), 3.78−3.76 (m, 1H *syn* isomer, 1H *anti* isomer), 3.22 (d, 1H, J = 11.1 Hz, *anti* isomer), 1.02 (s, 9H, *syn* isomer), 0.57 (s, 9H, *anti* isomer). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 182.7, 181.3, 146.8, 146.3, 142.4, 140.6, 139.6, 131.4, 130.7, 129.2, 128.9, 128.7, 128.5, 127.9, 127.7, 127.6, 127.5, 127.2, 127.0, 126.9, 126.6, 126.0, 125.8, 117.3, 116.0, 112.8, 110.9, 59.7, 57.6, 49.2, 48.9, 48.5, 48.1, 36.2, 35.6, 29.7, 29.0. IR (neat): 1383, 1505, 1581, 1600, 2869, 2954, 3391, 3601 cm^{-1}. ES-MS: m/z 388.2 [M + H]$^+$. HRMS [M + H]$^+$: 388.2283, $C_{26}H_{30}NO_2$ requires 388.2277.

***trans*-4-*tert*-Butyl-3-phenyl-3,4-dihydro-1*H*-quinolin-2-one, 11a. Method A:** Compound **10b** (21.5 mg, 0.05 mmol) was dissolved in ethyl acetate (2.25 mL), and hydrochloric acid (12 M, 1 mL) was added. The mixture was stirred at room temperature for 24 h. Sodium hydrogen carbonate (1 M, 20 mL) was added slowly (*caution: CO_2 evolved*), and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate, and the solvent was evaporated to dryness. Silica gel chromatography (eluent: diethyl ether) gave the purified product (10.6 mg, 76%). **Method B:** A solution of **10b** (52.9 mg, 0.13 mmol), sodium iodide (77.8 mg, 0.52 mmol), and chlorotrimethylsilane (0.06 mL, 0.47 mmol) in chloroform (3 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane (5 mL) and washed with water (5 mL). The organic layer was separated, dried over sodium sulfate, and concentrated to dryness. The crude reaction mixture was dissolved in dichloromethane (2 mL) and treated with EDCI (27.4 mg, 0.14 mmol) and DMAP (22.2 mg, 0.18 mmol). The reaction was stirred at room temperature for 3 h. The reaction mixture was diluted with dichloromethane (5 mL) and washed with water (5 mL). The organic layer was separated, dried over sodium sulfate, and concentrated to dryness. Crude ^{1}H NMR showed the product, **11a**, exclusively as the 3,4-*trans* isomer. After washing with hydrochloric acid (1 M) **11a** was obtained as a pale yellow oil (24.2 mg, 67%). **Method C:** A solution of **2a** (150.6 mg, 0.51 mmol) in THF (6 mL) was cooled to −25 °C. *t*-BuLi (1.00 mL, 1.49 mmol) was added dropwise over 15 min, during which time a red/brown color developed. The mixture was allowed to warm to room temperature and stirred for 6 h, by which time the color had faded to orange/red, and treated with methanol (1 mL). The THF was removed under reduced pressure. The residue was dissolved in dichloromethane

(10 mL) and washed with water (10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 3/1 diethyl ether/pentane) gave the purified product as a pale yellow oil (31.9 mg, 22%). (Note: Compound **5a** was also isolated in 51% yield.) ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.57 (bs, 1H), 7.26−7.10 (m, 6H), 7.09−7.07 (m, 1H), 7.00−6.94 (m, 1H), 6.84−6.80 (m, 1H), 4.11 (s, 1H), 2.77 (s, 1H), 1.02 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.6, 139.7, 136.9, 132.2, 128.7, 127.9, 127.1, 127.0, 122.7, 122.5, 115.6, 55.4, 48.2, 35.6, 27.8. IR (KBr disc): 1493, 1593, 1672, 2868, 2914, 2956, 3406 cm^{-1}. ES-MS: *m*/*z* 280.2 $[M + H]^+$. HRMS $[M + H]^+$: 280.1688, $C_{19}H_{22}NO$ requires 280.1701.

***trans*/*cis*-4-Butyl-3-phenyl-3,4-dihydro-1*H*-quinolin-2-one, 11b. Method A:** Compound **10f** (56.9 mg, 0.14 mmol) was dissolved in ethyl acetate (4 mL), and hydrochloric acid (12 M, 2 mL) was added. The mixture was stirred at room temperature for 24 h. Sodium hydrogen carbonate (1 M, 20 mL) was added slowly (*caution: CO_2 evolved*), and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate, and the solvent was removed under reduced pressure to give the pure product as a pale yellow solid (26.4 mg, 68%). **Method B:** A solution of **2a** (100.9 mg, 0.34 mmol) in THF (5 mL) was cooled to −25 °C. *n*-BuLi (0.51 mL, 1.02 mmol) was added dropwise over 15 min, during which time a red color developed. The mixture was allowed to warm to 0 °C and stirred for 1 h by which time the color had faded to pale yellow, and treated with methanol (1 mL). The THF was removed under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and washed with water (10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: diethyl ether) gave the purified product as a pale yellow solid (86.1 mg, 90%), mp 78−82 °C. [The product was analyzed as a 90:10 mixture of *trans*/*cis*-**11b**.] ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.32 (bs, 1H, *trans* isomer), 8.13 (bs, 1H, *cis* isomer), 7.19−7.14 (m, 6H, *trans* isomer), 7.10−7.07 (m, 1H, *trans* isomer), 7.05−7.02 (m, 1H, *cis* isomer), 7.00−6.97 (m, 1H, *trans* isomer), 6.83−6.81 (m, 1H, *cis* isomer), 6.78−6.77 (m, 1H, *trans* isomer), 4.03 (d, 1H, J = 5.3 Hz, *cis* isomer), 3.84 (d, 1H, J = 1.2 Hz, *trans* isomer), 3.10−3.06 (m, 2H, both isomers), 1.76−1.68 (m, 1H, *trans* isomer), 1.68−1.60 (m, 1H, *trans* isomer), 1.45−1.38 (m, 1H, *trans* isomer), 1.35−1.28 (m, 3H, *trans* isomer), 0.88 (t, 3H, J = 7.1 Hz, *trans* isomer), 0.79 (t, 3H, J = 7.1 Hz, *cis* isomer). ^{13}C NMR ($CDCl_3$, 150 MHz) of *trans* isomer δ: 171.3, 138.4, 135.7, 129.2, 128.7, 127.6, 127.3, 127.2, 126.4, 123.4, 115.5, 52.1, 44.3, 35.5, 29.0, 22.6, 13.9. IR (KBr disc): 1489, 1597, 1676, 2856, 2920, 2947, 3246 cm^{-1}. ES-MS: *m*/*z* 280.2 $[M + H]^+$. HRMS $[M + H]^+$: 280.1702, $C_{19}H_{22}NO$ requires 280.1701.

***trans*/*cis*-4-Ethyl-3-phenyl-3,4-dihydro-1*H*-quinolin-2-one, 11c.** A solution of **2a** (148.7 mg, 0.50 mmol) in THF (6 mL) was cooled to −25 °C. EtLi (0.94 mL, 1.50 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was warmed to 0 °C and stirred for 2 h, by which time the color had faded to pale orange, and treated with methanol (1 mL). The THF was removed under reduced pressure. The residue was dissolved in diethyl ether (10 mL) and washed with hydrochloric acid (1 M, 10 mL). The organic layer was dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: diethyl ether) gave the product as a pale yellow oil (106.1 mg, 84%). (The product was analyzed as an 80:20 mixture of *trans*:*cis*-**11c**; ^{13}C NMR signals quoted refer to the *trans* isomer unless otherwise stated.) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.51 (bs, 1H, *trans* isomer), 8.28 (bs, 1H, *cis* isomer), 7.33−7.25 (m, 1H, *trans* isomer), 7.22−7.15 (m, 5H, *trans* isomer), 7.11−7.09 (m, 1H, *trans* isomer), 7.06−7.02 (m, 1H, *cis* isomer), 7.00−6.97 (m, 1H, *trans* isomer), 6.84−6.82 (m, 1H, *cis* isomer), 6.80−6.78 (m, 1H, *trans* isomer), 4.06 (d, 1H, J = 5.4 Hz, *cis* isomer), 3.85 (d, 1H, J = 1.8 Hz, *trans* isomer), 3.03−2.95 (m, 2H, both isomers), 1.84−1.72 (m, 1H, *trans* isomer), 1.71−1.60 (m, 1H, *trans* isomer), 0.98 (t, 3H, J = 7.4 Hz, *trans* isomer), 0.84 (t, 3H, J = 7.4 Hz, *cis* isomer). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.6, 138.7, 135.9, 129.5, 128.9, 127.9, 127.6, 127.4, 126.1, 123.6, 115.8, 52.1, 51.0 (*cis* isomer), 46.0, 44.5 (*cis* isomer), 28.8, 20.9 (*cis* isomer), 11.9 (*cis* isomer), 11.6. IR (KBr disc): 1491, 1593, 1678, 2872, 2918, 2966, 3061, 3215 cm^{-1}. ES-MS: *m*/*z* 252.1 $[M + H]^+$. HRMS $[M + H]^+$: 252.1396, $C_{17}H_{18}NO$ requires 252.1388.

4-*tert*-Butyl-2-hydroxy-3-phenyl-3,4-dihydro-2*H*-quinoline-1-carboxylic Acid *tert*-Butyl Ester, 12a. A solution of **2a** (409.1 mg, 1.38 mmol) in THF (18 mL) was cooled to −25 °C. *t*-BuLi (2.75 mL, 3.47 mmol) was added dropwise over 15 min, during which time a brown color developed. The reaction mixture was stirred at −25 °C for 1 h and DMF (1.0 mL, 12.9 mmol) was added. Stirring continued at −25 °C for 15 min. Hydrochloric acid (1M, 10 mL) was added, and the reaction mixture was warmed to room temperature over 10 min. The THF was removed under reduced pressure, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 95/5 cyclohexane/diethyl ether) gave the purified product as two diastereoisomers. 2,3-*cis*-3,4-*trans*-**12a** was isolated as a colorless solid (258.1 mg, 49%), mp 154−155 °C; 2,3-*trans*-3,4-*trans*-**12a** was isolated as a colorless solid (141.0 mg, 27%), mp 71−72 °C. (Combined yield of both isomers 76%.) (Note: The ratio of isomers obtained was dependent on the acidification temperature, with lower temperatures giving higher yields of 2,3-*trans*-3,4-*trans*-**12a** and increased temperatures resulting in improved yields of 2,3-*cis*-3,4-*trans*-**12a**.) 2,3-*cis*-3,4-*trans*-**12a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.43 (d, 1H, J = 8.1 Hz), 7.28−7.16 (m, 6H), 7.12−7.07 (m, 2H), 6.00−5.97 (m, 1H), 3.79−3.76 (m, 1H), 2.83 (d, 1H, J = 4.0 Hz), 2.36 (d, 1H, J = 4.7 Hz), 1.52 (s, 9H), 0.88 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 152.9, 142.0, 136.9, 132.0, 131.1, 129.2, 128.3, 126.7, 126.6, 125.9, 123.8, 81.3, 79.2, 53.8, 49.9, 36.3, 28.4, 27.8. IR (KBr disk): 3465, 2963, 1671 cm^{-1}. ES-MS *m*/*z* 380.2 $[M - H]^-$. HRMS $[M - H]^-$: 380.2212, $C_{24}H_{30}NO_3$ requires 380.2226. Analysis calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.27; H, 7.94; N, 3.65. 2,3-*trans*-3,4-*trans*-**12a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.34−7.12 (m, 9H), 6.38 (d, 1H, J = 9.2 Hz), 4.72 (t, 1H, J = 8.9 Hz), 3.50 (dd, 1H, J = 8.9/4.0 Hz), 2.88 (d, 1H, J = 4.0 Hz), 1.48 (s, 9H), 0.89 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 154.9, 144.7, 140.7, 132.4, 131.3, 128.5, 128.3, 126.5, 126.5, 125.8, 124.7, 88.9, 82.0, 57.6, 51.9, 36.8, 28.4, 27.8. IR (KBr disk): 3446, 2963, 1675 cm^{-1}. ES-MS *m*/*z* 382.2 $[M + H]^+$. HRMS $[M + H]^+$: 382.2364, $C_{24}H_{32}NO_3$ requires 382.2382. Analysis calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.26; H, 7.99; N, 3.69.

4-Butyl-2-hydroxy-3-phenyl-3,4-dihydro-2*H*-quinoline-1-carboxylic Acid *tert*-Butyl Ester, 12b. A solution of **2a** (398.6 mg, 1.35 mmol) in THF (15 mL) was cooled to −25 °C. PMDTA (0.85 mL, 4.06 mmol) was added followed by *n*-BuLi (2.40 mL, 4.10 mmol), added dropwise over 15 min. The reaction mixture was stirred at −25 °C for 1 h and DMF (1.05 mL, 13.55 mmol) was added. Stirring continued at −25 °C for 15 min. Hydrochloric acid (1 M, 10 mL) was added, and the reaction mixture warmed to room temperature over 10 min. The THF was removed under reduced pressure, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 9/1 cyclohexane/diethyl ether) gave the purified product as a colorless solid (326.9 mg, 63%), mp 95−103 °C. (The product was isolated and characterized as a 1:1 mixture of two diastereoisomers 2,3-*cis*-3,4-*trans*-**12b** and 2,3-*trans*-3,4-*trans*-**12b**.) ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.63 (d, 1H, J = 8.0 Hz, 2,3-*trans*-3,4-*trans* isomer), 7.45−7.44 (m, 1H, 2,3-*cis*-3,4-*trans* isomer), 7.36−7.17 (m, 7H 2,3-*cis*-3,4-*trans* isomer, 7H 2,3-*trans*-3,4-*trans* isomer), 7.14−7.11 (m, 1H, 2,3-*cis*-3,4-*trans* isomer), 7.07−7.04 (m, 1H, 2,3-*trans*-3,4-*trans* isomer), 5.98−5.97 (m, 1H, 2,3-*trans*-3,4-*trans* isomer), 5.77 (dd, 1H, J = 7.6/3.6 Hz, 2,3-*cis*-3,4-*trans* isomer), 3.42 (bs, 1H, 2,3-*cis*-3,4-*trans* isomer), 3.37−3.34 (m, 1H, 2,3-*trans*-3,4-*trans* isomer), 3.23 (dd, 1H, J = 9.4/3.6 Hz, 2,3-*trans*-

3,4-*trans* isomer), 2.85−2.81 (m, 1H, 2,3-*cis*-3,4-*trans* isomer), 2.71 (d, 1H, J = 4.4 Hz, 2,3-*trans*-3,4-*trans* isomer), 2.67 (dd, 1H, J = 11.5/7.6 Hz, 2,3-*cis*-3,4-*trans* isomer), 1.81−1.79 (m, 1H, 2,3-*trans*-3,4-*trans* isomer), 1.59−1.54 (m, 2H 2,3-*cis*-3,4-*trans* isomer, 1H 2,3-*trans*-3,4-*trans* isomer), 1.54 (s, 9H, 2,3-*trans*-3,4-*trans* isomer), 1.51 (s, 9H, 2,3-*cis*-3,4-*trans* isomer), 1.43−1.08 (m, 4H 2,3-*cis*-3,4-*trans* isomer, 4H 2,3-*trans*-3,4-*trans* isomer), 0.79 (t, 3H, J = 7.2 Hz, 2,3-*cis*-3,4-*trans* isomer), 0.77 (t, 3H, J = 7.2 Hz, 2,3-*trans*-3,4-*trans* isomer). ^{13}C NMR ($CDCl_3$, 125 MHz) of both isomers δ: 154.5, 153.1, 141.3, 140.5, 136.7, 135.8, 134.9, 131.9, 129.3, 128.7, 128.6, 128.3, 127.9, 127.8, 127.0, 126.1, 126.0, 124.7, 124.6, 124.4, 124.2, 123.9, 85.3, 81.9, 81.8, 79.4, 54.8, 49.8, 39.0, 38.6, 32.4, 28.6, 28.5, 28.4, 27.7, 27.3, 22.9, 22.8, 13.9, 13.9. IR (KBr disc): 1676, 2929, 2960, 3464 cm^{-1}. ES-MS m/z 404.2 [M + Na]$^+$. HRMS [M + Na]$^+$: 404.2220, $C_{24}H_{31}NO_3Na$ requires 404.2202. Analysis calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.47; H, 8.09; N, 3.72. Suitable crystals were grown by the slow evaporation of a solution of **12b** in dichloromethane.

4-Ethyl-2-hydroxy-3-phenyl-3,4-dihydro-2*H*-quinoline-1-carboxylic Acid *tert*-Butyl Ester, 12c. A solution of **2a** (148.3 mg, 0.50 mmol) in THF (6 mL) was cooled to −25 °C. PMDTA (0.31 mL, 1.48 mmol) was added followed by EtLi (1.00 mL, 1.50 mmol), added dropwise over 15 min. The reaction mixture was stirred at −25 °C for 1 h and DMF (0.39 mL, 5.03 mmol) was added. Stirring continued at −25 °C for 15 min. Hydrochloric acid (1 M, 10 mL) was added, and the reaction mixture warmed to room temperature over 10 min. The THF was removed under reduced pressure, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 9/1 pentane/diethyl ether) gave the purified product as two diastereoisomers. 2,3-*cis*-3,4-*trans*-**12c** was isolated as a colorless solid (67.4 mg, 54%), mp 117−118 °C; 2,3-*trans*-3,4-*trans*-**12c** was isolated as a colorless solid (29.3 mg, 17%), mp 119−121 °C. (Combined yield of both isomers 71%.) 2,3-*cis*-3,4-*trans*-**12c**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.45 (d, 1H, J = 8.0 Hz), 7.37−7.33 (m, 2H), 7.29−7.21 (m, 5H), 7.14−7.11 (m, 1H), 5.77 (dd, 1H, J = 7.6/3.6 Hz), 3.44 (bs, 1H), 2.85−2.80 (m, 1H), 2.70 (dd, 1H, J = 11.7/7.6 Hz), 1.75−1.67 (m, 1H), 1.63−1.54 (m, 1H), 1.52 (s, 9H), 0.91 (t, 3H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 154.5, 141.2, 136.7, 134.4, 128.7, 128.7, 127.1, 126.0, 124.7, 124.6, 124.2, 85.3, 82.0, 54.3, 39.6, 28.4, 20.6, 10.5. IR (KBr disc): 1344, 1496, 1678, 2933, 2978, 3064 cm^{-1}. ES-MS m/z 352.2 [M − H]$^-$. HRMS [M − H]$^-$: 352.1897, $C_{22}H_{26}NO_3$ requires 352.1913. 2,3-*trans*-3,4-*trans* **12c**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.65 (d, 1H, J = 8.3 Hz), 7.37−7.29 (m, 4H), 7.27−7.17 (m, 3H), 7.08−7.05 (m, 1H), 5.99−5.98 (m, 1H), 3.41−3.40 (m, 1H), 3.21 (dd, 1H, J = 10.0/ 3.1 Hz), 2.64 (d, 1H, J = 4.3 Hz), 1.93−1.86 (m, 1H), 1.62−1.56 (m, 1H), 1.54 (s, 9H), 0.73 (t, 3H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 153.0, 140.5, 136.0, 131.2, 129.3, 128.3, 127.8, 127.0, 126.1, 124.3, 123.9, 81.8, 79.4, 48.9, 39.3, 28.4, 24.8, 9.2. IR (KBr disc): 1369, 1495, 1666, 2924, 2981, 3032 cm^{-1}. ES-MS m/z 352.2 [M − H]$^-$. HRMS [M − H]$^-$: 352.1906, $C_{22}H_{26}NO_3$ requires 352.1913. Suitable crystals were grown by the slow evaporation of a solution of 2,3-*cis*-3,4-*trans*-**12c** in ethanol.

3-Phenylquinoline,[23] **13a. Method A:** A solution of **12a** (50.4 mg, 0.13 mmol) in ethyl acetate (9 mL) and hydrochloric acid (12 M, 4 mL) was stirred at room temperature for 5 h. Sodium hydrogen carbonate (1 M, 60 mL) was added slowly (*caution: CO_2 evolved*), and the aqueous layer extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to give the pure product as a yellow oil (20.7 mg, 78%). **Method B:** A solution of **2a** (146.2 mg, 0.50 mmol) in THF (6 mL) was cooled to −25 °C. *t*-BuLi (0.85 mL, 1.50 mmol) was added dropwise over 15 min, during which time a brown color developed. The reaction mixture was stirred at −25 °C for 1 h and DMF (0.39 mL, 5.03 mmol) was added. Stirring continued at −25 °C for 15 min. Hydrochloric acid (1 M, 1 mL) was added, and the reaction mixture warmed to room temperature. The THF was removed under reduced pressure, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The residue was dissolved in ethyl acetate (6 mL), treated with hydrochloric acid (12 M, 3 mL), and stirred at room temperature for 16 h. Sodium hydrogen carbonate (1 M, 30 mL) was added slowly (*caution: CO_2 evolved*), and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Chromatography on alumina (eluent: 9/1 to 1/1 pentane/diethyl ether) gave the purified product as a yellow oil (64.9 mg, 63%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.19 (d, 1H, J = 2.3 Hz), 8.31 (d, 1H, J = 2.3 Hz), 8.15 (d, 1H, J = 8.4 Hz), 7.90−7.87 (m, 1H, J = 8.1 Hz), 7.76−7.71 (m, 3H), 7.70−7.51 (m, 3H), 7.46−7.42 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 150.2, 147.6, 138.2, 134.1, 133.5, 129.6, 129.5, 129.4, 128.4, 128.3, 128.2, 127.7, 127.2. IR (neat): 1493, 2868, 2972, 3032, 3059 cm^{-1}. ES-MS m/z 206.1 [M + H]$^+$. HRMS [M + H]$^+$: 206.0974, $C_{15}H_{12}N$ requires 206.0970.

4-Butyl-3-phenylquinoline, 13b. Method A: A solution of **12b** (51.4 mg, 0.13 mmol) in ethyl acetate (5 mL) and hydrochloric acid (12 M, 2 mL) was stirred at room temperature for 16 h. Sodium hydrogen carbonate (1 M, 20 mL) was added slowly (*caution: CO_2 evolved*), and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to give the pure product as a colorless oil (26.6 mg, 78%). **Method B:** A solution of **2a** (146.6 mg, 0.50 mmol) in THF (6 mL) and PMDTA (0.31 mL, 1.48 mmol) was cooled to −25 °C. *n*-BuLi (0.85 mL, 1.50 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and DMF (0.39 mL, 5.03 mmol) was added. Stirring continued at −25 °C for 15 min. Hydrochloric acid (1 M, 1 mL) was added, and the reaction mixture warmed to room temperature. The THF was removed under reduced pressure, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The residue was dissolved in ethyl acetate (6 mL), treated with hydrochloric acid (12 M, 3 mL) and stirred at room temperature for 16 h. Sodium hydrogen carbonate (1 M, 30 mL) was added slowly (*caution: CO_2 evolved*), and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Chromatography on alumina (eluent: 3/1 to 1/1 pentane/diethyl ether) gave the purified product as a colorless oil (66.8 mg, 51%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.79−8.76 (m, 1H), 8.16−8.10 (m, 2H), 7.74−7.70 (m, 1H), 7.64−7.58 (m, 1H), 7.52−7.45 (m, 3H), 7.43−7.35 (m, 2H), 3.06−2.99 (m, 2H), 1.66−1.60 (m, 2H), 1.38−1.28 (m, 2H), 0.83 (t, 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 151.7, 147.6, 145.6, 139.0, 134.3, 130.3, 129.7, 128.8, 128.4, 127.6, 127.1, 126.7, 124.3, 33.4, 28.6, 23.2, 13.6. IR (neat): 1499, 2870, 2928, 2957, 3061 cm^{-1}. ES-MS m/z 262.2 [M + H]$^+$. HRMS [M + H]$^+$: 262.1607, $C_{19}H_{20}N$ requires 262.1596.

4-Ethyl-3-phenylquinoline, 13c. Method A: A solution of **12c** (12.4 mg, 0.04 mmol) in ethyl acetate (1 mL) and hydrochloric acid (12 M, 0.4 mL) was stirred at room temperature for 16 h. Sodium hydrogen carbonate (1 M, 10 mL) was added slowly (*caution: CO_2 evolved*), and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to give the pure product as a colorless solid (5.0 mg, 61%), mp 87−88 °C. **Method B:** A solution of **2a** (146.4 mg, 0.50 mmol) in THF (6 mL) and PMDTA (0.31 mL, 1.48 mmol) was cooled to −25 °C. EtLi (0.94 mL, 1.50 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and DMF (0.39 mL, 5.03 mmol) was added. Stirring continued at −25 °C for 15 min. Hydrochloric acid (1 M, 1 mL) was added, and the reaction mixture warmed to room temperature. The THF was

(23) Mongin, F.; Mojovic, L.; Guillamet, B.; Trecourt, F.; Quegiuner, G. *J. Org. Chem.* **2002**, *67*, 8991.

removed under reduced pressure, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The residue was dissolved in ethyl acetate (6 mL), treated with hydrochloric acid (12 M, 3 mL), and stirred at room temperature for 16 h. Sodium hydrogen carbonate (1 M, 30 mL) was added slowly (*caution: CO_2 evolved*), and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Chromatography on alumina (eluent: 3/1 pentane/diethyl ether) gave the purified product as a colorless oil (41.5 mg, 36%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.76 (s, 1H), 8.16−8.11 (m, 2H), 7.74−7.70 (m, 1H), 7.63−7.59 (m, 1H), 7.52−7.44 (m, 3H), 7.40−7.38 (m, 2H), 3.05 (q, 2H, J = 7.6 Hz), 1.27 (t, 3H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 151.9, 147.9, 146.8, 139.1, 134.3, 130.5, 129.8, 129.0, 128.7, 127.8, 127.0, 126.9, 124.5, 22.3, 15.7. IR (neat): 1616, 2927, 2958, 3232 cm^{-1}. ES-MS m/z 234.2 $[M + H]^+$. HRMS $[M + H]^+$: 234.1289, $C_{17}H_{16}N$ requires 234.1283.

2-(4-Methoxyphenyl)-3-phenylquinoline, 13d. A solution of **2a** (145.1 mg, 0.49 mmol) in THF (6 mL) was cooled to −25 °C. *t*-BuLi (0.88 mL, 1.48 mmol) was added dropwise over 15 min, during which time a brown color developed. The reaction mixture was stirred at −25 °C for 1 h and 4-methoxybenzonitrile (0.60 mL, 4.91 mmol) was added. Stirring continued at −25 °C for 15 min. Hydrochloric acid (1M, 10 mL) was added, and the reaction mixture warmed to room temperature over 10 min. The THF was removed under reduced pressure, and the residue was dissolved in ethyl acetate (5 mL) and treated with hydrochloric acid (12 M, 2 mL). The solution was stirred at room temperature for 16 h. Sodium hydrogen carbonate (1 M, 20 mL) was added slowly (*caution: CO_2 evolved*), and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Chromatography on alumina (eluent: 95/5 pentane/diethyl ether) gave the purified product as a colorless oil (32.1 mg, 21%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.22−8.18 (m, 2H), 7.88−7.86 (m, 1H), 7.76−7.72 (m, 1H), 7.59−7.55 (m, 1H), 7.33−7.25 (m, 5H), 7.20−7.16 (m, 1H), 7.04−7.00 (m, 2H), 6.85−6.82 (m, 1H), 3.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.4, 158.4, 147.5, 141.9, 140.3, 137.8, 134.8, 129.9, 129.8, 129.7, 129.2, 128.5, 127.7, 127.5, 127.4, 127.0, 122.9, 115.2, 114.8, 55.3. IR (neat): 1600, 1728, 2858, 2926, 2954, 3024, 3060 cm^{-1}. ES-MS m/z 312.1 $[M + H]^+$. HRMS $[M + H]^+$: 312.1390, $C_{22}H_{18}NO$ requires 312.1388.

1-Benzyl-4-*tert*-butyl-3-phenyl-1,4-dihydroquinoline, 14a. A solution of **2b** (144.8 mg, 0.51 mmol) in THF (6 mL) was cooled to −25 °C. *t*-BuLi (0.79 mL, 1.52 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and DMF (0.40 mL, 5.16 mmol) was added. Stirring continued at −25 °C for 30 min. Hydrochloric acid (1 M, 10 mL) was added, and the reaction mixture was allowed to warm to room temperature over 10 min. The THF was removed under reduced pressure, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Chromatography on alumina (eluent: 99/1 pentane/diethyl ether) gave the purified product as a colorless solid (145.6 mg, 82%), mp 98−101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44−7.41 (m, 2H), 7.31−7.22 (m, 7H), 7.18−7.16 (m, 1H), 7.10−7.06 (m, 2H), 6.95−6.92 (m, 1H), 6.73−6.71 (m, 1H), 6.68 (s, 1H), 4.81 (d, 1H, J = 16.8 Hz), 4.75 (d, 1H, J = 16.8 Hz), 3.91 (s, 1H), 0.75 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.9, 142.0, 137.9, 132.4, 131.4, 128.9, 128.8, 127.4, 126.9, 126.7, 125.1, 125.0, 123.4, 120.4, 113.2, 111.8, 54.5, 50.9, 39.7, 28.0. IR (KBr disc): 1487, 1595, 1633, 2864, 2899, 2949, 3022, 3381, 3460 cm^{-1}. ES-MS m/z 206.2 base peak $[M + H - (C_{11}H_{16})]^+$ (loss of *t*-Bu and Bn groups). Analysis calcd for $C_{26}H_{27}N$: C, 88.34; H, 7.70; N, 3.96. Found: C, 88.04; H, 7.85; N, 3.91.

1-Benzyl-4-butyl-3-phenyl-1,4-dihydroquinoline, 14b. A solution of **2b** (143.1 mg, 0.50 mmol) in THF (6 mL) was cooled to −25 °C, and PMDTA (0.31 mL, 1.48 mmol) was added. *n*-BuLi (0.60 mL, 1.51 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 2 h and DMF (0.39 mL, 5.03 mmol) was added. Stirring continued at −25 °C for 30 min. Hydrochloric acid (1 M, 10 mL) was added, and the reaction mixture was allowed to warm to room temperature over 10 min. The THF was removed under reduced pressure, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Chromatography on alumina (eluent: 95/5 pentane/diethyl ether) gave the purified product as a colorless oil (90.0 mg, 51%). (Note: Starting material was also recovered in 24% yield.) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44−7.42 (m, 2H), 7.32−7.22 (m, 7H), 7.15−7.12 (m, 2H), 7.06−7.02 (m, 1H), 6.92−6.88 (m, 1H), 6.72 (s, 1H), 6.68−6.66 (m, 1H), 4.88 (d, 1H, J = 16.9 Hz), 4.77 (d, 1H, J = 16.9 Hz), 4.10−4.06 (m, 1H), 1.61−1.57 (m, 2H), 1.29−1.16 (m, 4H), 0.82−0.78 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 139.9, 139.6, 138.1, 130.1, 129.5, 129.0, 128.8, 127.4, 126.7, 126.7, 125.9, 125.3, 124.2, 121.1, 112.6, 111.9, 54.5, 39.9, 37.3, 28.1, 23.1, 14.4. IR (neat): 1597, 1743, 2868, 2927, 2954, 3028, 3061 cm^{-1}. ES-MS m/z 352.2 $[M + H]^+$. HRMS $[M + H]^+$: 352.2059, $C_{26}H_{26}N$ requires 352.2065. The nominal and accurate masses measured are of the oxidized quinoline cation.

1-Benzyl-4-*sec*-butyl-3-phenyl-1,4-dihydroquinoline, 14c. A solution of **2b** (142.1 mg, 0.50 mmol) in THF (6 mL) was cooled to −25 °C. *s*-BuLi (1.09 mL, 1.49 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and DMF (0.39 mL, 5.03 mmol) was added. Stirring continued at −25 °C for 30 min. Hydrochloric acid (1 M, 10 mL) was added, and the reaction mixture was allowed to warm to room temperature over 15 min. The THF was removed under reduced pressure, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Chromatography on alumina (eluent: 99/1 pentane/diethyl ether) gave the purified product as a colorless oil (147.9 mg, 84%). (The product was analyzed as an equal mixture of diastereoisomers.) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45−7.41 (m, 2H), 7.34−7.22 (m, 7H), 7.15−7.06 (m, 2H), 7.05−7.02 (m, 1H), 6.92−6.87 (m, 1H), 6.77 (s, 0.5H), 6.72 (s, 0.5H), 6.67−6.65 (m, 1H), 4.84−4.73 (m, 2H), 4.16 (d, 0.5H, J = 3.1 Hz), 4.11 (d, 0.5H, J = 3.4 Hz), 1.62−1.59 (m, 1H), 1.58−1.50 (m, 0.5H), 1.49−1.43 (m, 0.5H), 1.22−1.17 (m, 0.5H), 0.94−0.86 (m, 3H), 0.74−0.67 (m, 3.5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 141.3, 140.9, 138.1, 138.0, 131.3, 130.8, 130.3, 130.2, 129.2, 129.2, 129.0, 129.0, 128.8, 128.7, 128.7, 127.6, 127.4, 126.9, 126.8, 126.7, 125.3, 125.3, 124.8, 124.5, 124.4, 122.9, 120.9, 120.8, 112.3, 112.1, 111.9, 111.8, 54.7, 54.6, 45.8, 44.4, 43.6, 41.9, 27.0, 25.7, 16.4, 15.1, 12.5, 12.5. IR (neat): 1489, 1597, 1647, 2872, 2931, 2956, 3030, 3062 cm^{-1}. ES-MS m/z 352.2 $[M + H]^+$. HRMS $[M + H]^+$: 352.2054, $C_{26}H_{26}N$ requires 352.2065. The nominal and accurate masses measured are of the oxidized quinoline cation.

1-(1-Benzyl-4-*tert*-butyl-3-phenyl-1,4-dihydroquinolin-2-yl) ethanone, 14d. A solution of **2b** (143.1 mg, 0.50 mmol) in THF (6 mL) was cooled to −25 °C. *t*-BuLi (0.85 mL, 1.50 mmol) was added dropwise over 15 min, during which time a red color developed. The reaction mixture was stirred at −25 °C for 1 h and 2,2-diethoxypropionitrile (0.78 mL, 5.00 mmol) was added. Stirring continued at −25 °C for 2 h. Saturated ammonium chloride solution (10 mL) was added, and the reaction mixture was allowed to warm to room temperature over 10 min. The organic layer was separated; hydrochloric acid (5 M, 10 mL) was added, and the mixture stirred at room temperature for 30 min. The reaction mixture was diluted with diethyl ether (10 mL), and the organic layer was separated, dried over sodium sulfate, and concentrated to dryness. Chromatography on alumina (eluent: 9/1 pentane/diethyl ether) gave the purified product as a yellow solid (98.7 mg, 50%),

mp 123−125 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32−7.24 (m, 6H), 7.25−7.14 (m, 6H), 7.04−6.99 (m, 1H), 6.94−6.91 (m, 1H), 5.10 (d, 1H, J = 17.4 Hz), 4.82 (d, 1H, J = 17.4 Hz), 3.65 (s, 1H), 1.42 (s, 3H), 0.73 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 204.6, 142.8, 142.4, 139.6, 138.5, 130.7, 129.4, 128.7, 128.7, 127.3, 127.0, 126.6, 124.7, 120.9, 114.3, 113.5, 54.9, 50.3, 39.1, 31.7, 27.9. IR (neat): 1489, 1697, 2951, 3029, 3062 cm^{-1}. ES-MS: *m*/*z* 396.2 $[M + H]^+$. HRMS $[M + H]^+$: 396.2338, $C_{28}H_{29}NO$ requires 396.2327. Analysis calcd for $C_{28}H_{29}NO$: C, 85.02; H, 7.39; N, 3.54. Found: C, 84.73; H, 8.53; N, 3.45.

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Supporting Information Available: Experimental procedures for preparation of compounds **2a**, **2b**, **6a**, **6b**, **6d**, **6e**, **8a**, **8b**, **9a**, and **9b**. ^{1}H and ^{13}C NMR spectra of all compounds. Variable temperature ^{1}H NMR of **3a** from −15 to 20 °C and ^{1}H NMR of **3d** at −15 °C. X-ray crystallographic data of **10a**, **10f**, **10g**, **12b**, and **12c** (CCDC 656706−656710) as CIF files. This material is free of charge via the Internet at http://pubs.acs.org.

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