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Asymmetric Cascade Reaction Sequences via Chiral Lithiated Intermediates

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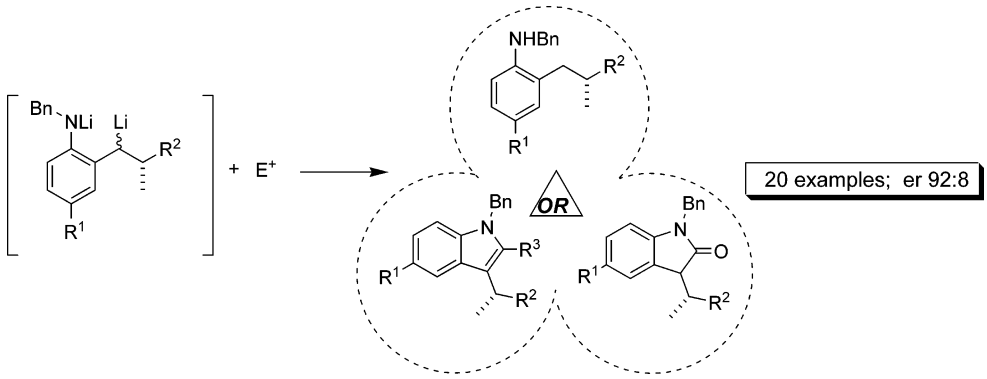


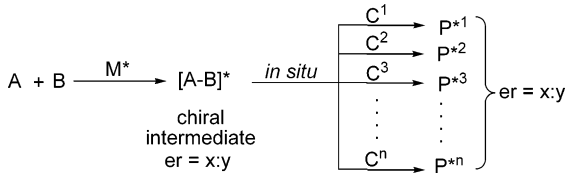
The (−)-sparteine-mediated enantioselective intermolecular carbolithiation of (*E*)-2-propenylarylamines allows for the generation of chiral lithiated intermediates which have broad synthetic potential. These intermediates have been exploited in a series of further in situ reactions with electrophiles to generate a collection of products each containing a common stereogenic center. The stereogenic center, formed in high enantiomeric ratio in the first carbolithiation step, is carried through the cascade reaction sequence to the final products and is independent of electrophile used. The methodology is demonstrated by the synthesis of structurally diverse chiral anilines, indoles, and indolones all with an er of 92:8 (±1). The heterocyclic syntheses involve an enantioselective alkene carbolithiation and subsequent trapping of the intermediate organolithium with a suitable electrophile, followed by an in situ ring closure and dehydration to generate the indole or indolone rings.

Introduction

The facile generation of chiral intermediates which could be utilized in a range of further in situ transformations to produce a diverse collection of chiral products is synthetically attractive. For example, the reaction of substrate A with reagent B, mediated by a chiral source, could generate a reactive chiral intermediate [A−B]*, which could be in situ converted to chiral products (P^{*1-n}) by subsequent reaction with additional reagents C^{1-n} (Scheme 1). Advantageously, all products derived from this intermediate would be generated with identical selectivity provided the stereogenic center in [A−B]* is configurationally stable. This approach could be anticipated to have application to combinatorial library generation.

The key to a successful implementation of this approach is the enantioselective generation of a reactive intermediate of broad synthetic potential from which a collection of chiral products can be readily obtained. Alkene carbolithiation provides a practical methodology for this as it allows the construction of a new C−C bond and organolithium center in a single transformation.[1] In addition, the carbolithiation of 1,2-disub-

SCHEME 1. Product Independent Enantioselectivities



(1) (a) Bartlett, P. D.; Tauber, S. J.; Weber, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6362. (b) Bartlett, P. D.; Friedman, S.; Stiles, M. *J. Am. Chem. Soc.* **1953**, *75*, 1771. (c) Ziegler, K.; Gellert, H. G. *Justus Liebigs Ann. Chem.* **1950**, *567*, 195. (d) Clayden. J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: Oxford, U.K., 2002; pp 273−335.

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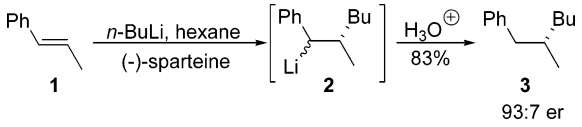
SCHEME 2. Enantioselective Carbolithiation of β-Methylstyrene

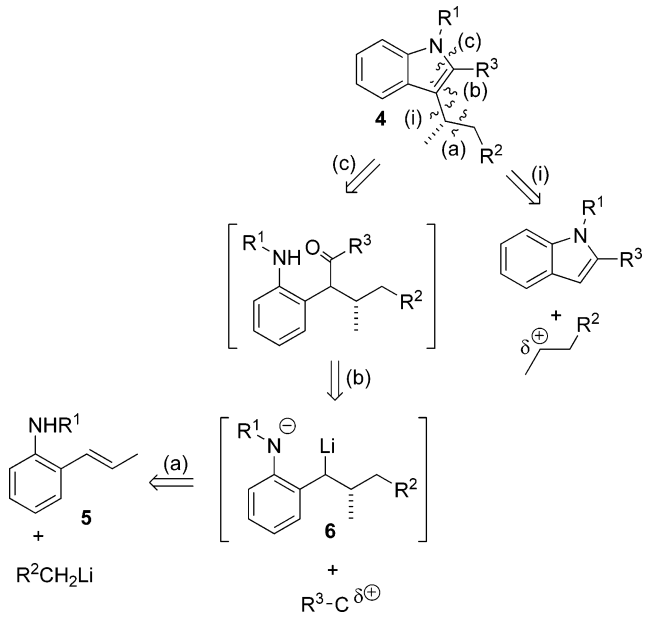


stituted alkenes generates an organolithium intermediate with two contiguous stereocenters.[2] For example, the enantioselective carbolithiation of the 1,2-disubstituted alkene β-methylstyrene **1** with *n*-BuLi has been previously reported utilizing (−)-sparteine to induce asymmetry in the product.[3] Following protonation of the lithiated intermediate **2**, 2-methylhexylbenzene **3** was isolated in good yield and er (Scheme 2). In this case, the chiral center created as a result of the C−C bond formation is configurationally stable, but the benzylic C−Li center has low configurational stability.[4] Our goal was to exploit a related carbolithiation reaction to provide one configurationally stable stereogenic center which would be incorporated into all products and utilize in situ reaction with electrophiles at the C−Li center to allow access to a collection of products. It is noteworthy that enantioselective substitution of configurationally unstable benzylic lithium centers is achievable via kinetic or thermodynamic resolution.[5]

To maximize synthetic potential of the intermediate, we chose to investigate *o*-substituted β-methylstyrenes as our starting substrates, therefore allowing the opportunity for the *o*-substituent to participate in further in situ steps. Specifically, one application of this methodology to *o*-amino β-methylstyrenes would provide a new route to the indole scaffold **4** with a chiral substituent at C-3 (Scheme 3).[6] Synthesis of this structural motif is attractive as a demonstration of this concept due to its prominence in many natural products and medicinal chemistry targets.[7] The known approach to such a structure entails a Friedel−Crafts alkylation of a presynthesized indole ring with an activated C−C double bond (disconnection (i), Scheme 3). Recent examples include the $Sc(OTf)_3$-pybox-controlled reaction with acyl phosphonates,[8] reaction of bis(oxazoline)-$Cu(OTf)_2$ with α′-hydroxy enones,[9] and the use of an imidazolidinone in conjunction with α,β-unsaturated aldehydes.[10] Both metal- and organo-catalyzed methodologies have resulted in the successful synthesis of this scaffold in high yields and enantioselectivities.

Our proposed methodology differs from the previous approaches in the order of bond formation. The first step involves

SCHEME 3. Contrasting Approaches to Chiral C-3 Substituted Indoles



asymmetric carbolithiation of the prochiral substrate **5** to provide lithiated intermediate **6** containing the key stereogenic center. Following reaction with specific electrophiles, a subsequent reaction sequence could occur between the reacted electrophile and *o*-substituent, facilitating an in situ ring closure to generate indole **4**.[11] This sequence of bond formation also allows for the inclusion of further substituent diversity (R^3) from the electrophile. Previous reports from our laboratory have shown that a carbolithiation/electrophile reaction sequence can be employed for the synthesis of achiral indoles, 7-azaindoles and quinolines from *o*-substituted styrenes, vinylpyridines, and stilbenes, respectively.[12]

Results and Discussion

The starting substrates **5a**−**d** were screened to determine the effect of *o*-substituents upon carbolithiation selectivity (see the Supporting Information for preparation). To assist cross-comparison of results, a uniform set of previously optimized reaction conditions were employed as follows: 1 equiv of PhLi to ensure complete NH deprotonation, followed by 2 equiv of *n*-BuLi and 3 equiv of (−)-sparteine at −15 °C for 4 h.[6] In addition, the influence of two solvent conditions (non-coordinating and coordinating) was investigated by duplicating the reactions in the hydrocarbon cumene and diethyl ether. Following carbolithiation of **5a**−**d** with *n*-BuLi, the intermediate

(2) Normant, J. F. *Top. Organomet. Chem*. **2003**, *5*, 287.
(3) (a) Norsikian, S.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1997**, *38*, 7523. (b) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem. Eur. J.* **1999**, *5*, 2055.
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(6) For preliminary report, see: Hogan, A.-M. L.; O'Shea, D. F. *J. Am. Chem. Soc.* **2006**, *128*, 10360.
(7) (a) Rawson, D. J.; Dack, K. N.; Dickinson, R. P.; James, K. *Biorg. Med. Chem. Lett.* **2002**, *12*, 125. (b) Chang-Fong, J.; Rangisetty, J. B.; Dukat, M.; Setola, V.; Raffay, T.; Roth, B.; Glennon, R. *Biorg. Med. Chem. Lett.* **2004**, *14*, 1961. (c) Christian, O. E.; Compton, J.; Christian, K. R.; Mooberry, S. L.; Valeriote, F. A.; Crews, P. *J. Nat. Prod*. **2005**, *68*, 1592.
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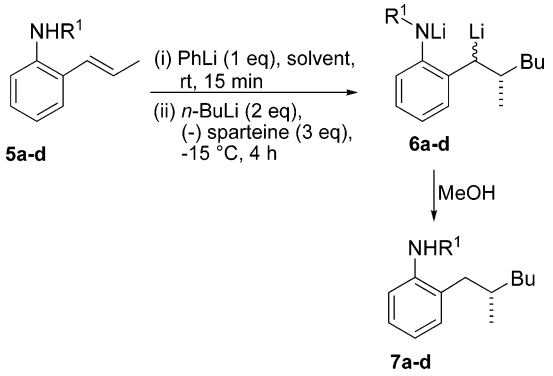
TABLE 1. Carbolithiation of 5a−d



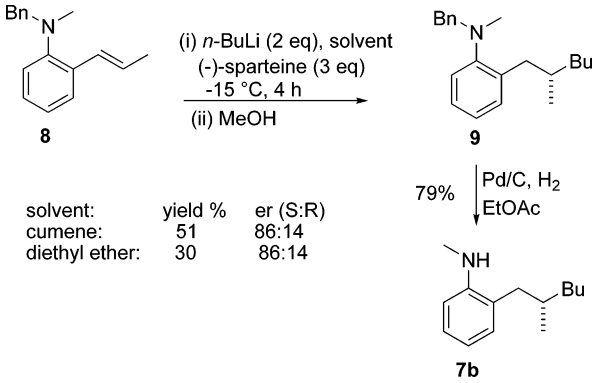
entry	sm	R^1	solvent	product	yield,[a] %	er[b] (*S*/*R*)
1	**5a**	Boc	cumene	**7a**	57	53:47
2	**5a**	Boc	Et_2O	**7a**	39[c]	57:43
3	**5b**	Me	cumene	**7b**	60	62:38
4	**5b**	Me	Et_2O	**7b**	40[d]	63:37
5	**5c**	Et	cumene	**7c**	47[e]	50:50
6	**5c**	Et	Et_2O	**7c**	30[f]	52:48
7	**5d**	Bn	cumene	**7d**	89	92:8
8	**5d**	Bn	Et_2O	**7d**	65	92:8

[a] Isolated purified yield. [b] Determined by chiral HPLC and compared to the racemic product generated with TMEDA as additive. [c] Starting material recovered in 36% yield. [d] Starting material recovered in 53% yield. [e] Starting material recovered in 21% yield. [f] Starting material recovered in 53% yield.

organolithium species **6a−d** were treated with methanol, generating the substituted 2-(methylhexyl)phenylamines **7a−d** and providing a convenient method of determining the selectivity of the reaction (Table 1). As expected, the *o*-substituent had a significant impact as the selectivities ranged from very poor for the *N*-Boc and *N*-alkyl analogues **7a−c** (Table 1, entries 1−6) to a high er of 92:8 for the *N*-benzyl substituted **7d**. Encouragingly, an identical er of 92:8 was obtained for carbolithiation of **5d** using either cumene or diethyl ether as the reaction solvent with **7d** isolated in yields of 89 and 65% respectively (entries 7 and 8). This solvent independent selectivity contrasts with other studies of enantioselective intermolecular carbolithiation reactions in which a hydrocarbon solvent is essential to achieve optimal er.[3] The absolute configuration of the stereocenter was determined by conversion of **7d** to 3-methylheptanoic acid, via $NaIO_4/RuCl_3$ mediated oxidation and comparison of the optical rotation with that reported for the enantiopure compound (Supporting Information).[13]

The results in Table 1 indicate the influence of a combination of factors on the enantioselectivity of the reaction, including a steric effect and the coordinating ability of the *o*-substituent. Use of the stronger coordinating *N*-Boc group as the *o*-substituent had a detrimental effect on the reaction selectivity, as did the *N*-alkyl substituted derivatives **5b**,**c**. Interestingly, the highest selectivity was recorded from the reaction with the *N*-benzyl derivative **5d**, which is more sterically demanding than the other alkyl substituents tested. As the lithium amide formed from the deprotonation of **5d** (prior to carbolithiation) could exist in solution as a monomer or dimer, a further study was carried out to investigate if this amide was essential to obtaining a high er. The tertiary amine **8** provided a suitable substrate for this investigation as it eliminates the lithium amide from the reaction sequence and combines the effects of a poor (Me) and good (Bn) selectivity group within the same molecule (Scheme 4, Supporting Information). Carbolithiation of **8** with *n*-BuLi/(−)-sparteine, followed by treatment of the lithiated intermediate with MeOH gave compound **9** in unoptimized yields of 51% and 30% from reaction in cumene and diethyl ether respectively. Hydrogenation of the benzyl group provided **7b** for er determination (Scheme 4). In both solvents, **9** was obtained with an identical er of 86:14 (*S*/*R*), only marginally inferior to that of *N*-benzyl derivative **7d**. Therefore, it could be concluded that the *N*-benzyl group is optimal for achieving high enantioselectivity, yet the presence of the lithium amide does not appear to be essential.

SCHEME 4. Carbolithiation of 8



In order to confirm (−)-sparteine as the optimal agent for promoting enantioselective carbolithiation of **5d**, we screened a selection of known chiral amines and amino alcohols as potential ligands for the reaction. The ligands tested included lithium alkoxides **10**, **11**, and **12**,[14] lithium amides **13** and **14**,[15] binaphthal **15**,[16] and bisoxazoline **16**,[17] all of which have previously been successfully employed in organolithium transformations (Figure 1).

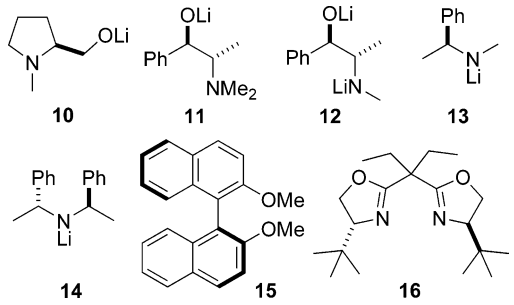


FIGURE 1. Chiral Ligand Screening.

Under our standard set of reaction conditions, the only alternative ligand which resulted in product formation was lithium amide **14** derived from [*S*-(*R*,*R*)]-(−)-bis(α-methylbenzyl)amine, which facilitated the generation of **7d** in a low 9% yield with respectable enantioselectivity of 13:87 (*S*/*R*) er. For

(13) Meyers, A. I.; Kamata, K. *J. Org. Chem.* **1974**, *39*, 1603.

(14) (a) Fort, Y.; Gros, P.; Rodriguez, A. L. *Tetrahedron: Asymmetry* **2001**, *12*, 2631. (b) Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2002**, 3375. (c) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773. (d) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Patel, J.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2006**, *128*, 10943.

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(16) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266.

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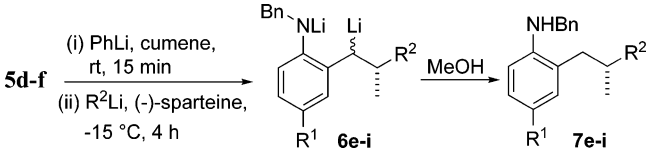
TABLE 2. Carbolithiation of Aryl Substituted Derivatives



entry	sm	R^1	R^2	product	yield,[a] %	er[b]
1	**5d**	H	Et	**7e**	52	93:7
2	**5d**	H	*n*-Hex	**7f**	76	92:8
3	**5e**	OCH_3	*n*-Bu	**7g**	60	nd[c]
4	**5f**	F	*n*-Bu	**7h**	63	92:8
5	**5f**	F	*n*-Hex	**7i**	61	93:7

[a] Isolated purified yield. [b] Determined by HPLC and compared to the racemic product generated with TMEDA as additive. [c] Chiral HPLC separation not achieved.

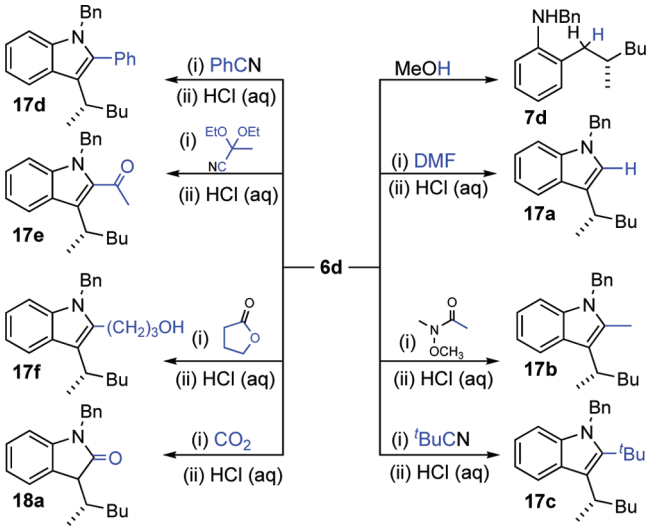
all other ligands tested starting material was recovered following reaction workup. Thus, the results of the ligand screen highlight the exceptional complementary relationship of carbolithiation reactions with (−)-sparteine and justifies its selection.[18]

In order to further explore the scope of the carbolithiation reaction we investigated the consequence of variation in alkyllithium and aryl substituents on the starting substrates **5d**−**f** upon reaction outcome. Application of both EtLi and *n*-HexLi to the carbolithiation of **5d** resulted in the formation of products **7e** and **7f** with the same high er as the *n*-Bu example (entries 1 and 2, Table 2). The carbolithiation reaction was also successful for both electron donating and electron withdrawing substituents in the aromatic ring of the substrates **5e**,**f** (entries 3−5, Table 2). Introduction of a methoxy group at the *para* position led to the isolation of **7g** in 60% yield and although chiral HPLC separation was not achieved for this example, a comparable er to that of **7d** was observed when an alternative electrophile was employed (see entries 9 and 10, Table 3). Carbolithiation of the 4-fluoro derivative **5f** with both *n*-Bu and *n*-HexLi yielded the expected products **7h** and **7i** in respectable yields and high er's of 92:8 and 93:7, respectively (entries 4 and 5).

Having established optimized conditions for chiral organolithium intermediate formation, the next goal was to exploit these compounds by reaction with a series of electrophiles thereby generating a diverse product set with a common er (Scheme 5). For example, starting from intermediate **6d**, the synthesis of aniline **7d**, 1,3- and 1,2,3-substituted indoles **17a**−**f**, or indolone **18a** was achieved by reaction with the electrophiles methanol, DMF, *N*-methoxy-*N*-methylacetamide, 2,2-dimethylpropionitrile, benzonitrile, 2,2-diethoxypropionitrile, γ-butyrolactone, and CO_2, respectively (Scheme 5). Since all products are generated from a common chiral intermediate **6d**, all have an identical er of 92:8 (±1), within experimental error (Table 1, entry 7; Table 3, entries 1−6; Table 4, entry 1). For indole synthesis, the substituent at C-2 on the ring is determined by the choice of electrophile. Thus, DMF generates an indole which is unsubstituted at C-2, while alkyl or aryl substituents can be introduced at this position using a Weinreb base or a nitrile as the electrophile. When 2,2-diethoxypropionitrile was used as electrophile, acidification resulted in cyclization, dehydration and deprotection of the acetal to provide a ketone at C-2. The organolithium intermediate causes ring opening of γ-butyrolactone, which following acidification undergoes cyclization,

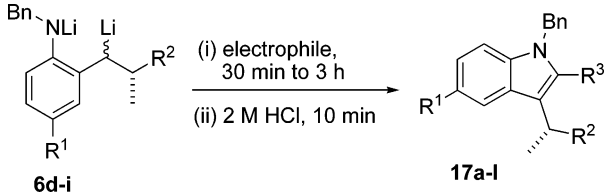
(18) Mealy, M. J.; Ludered, M. R.; Bailey, W. F.; Sommer, M. B. *J. Org. Chem.* **2004**, *69*, 6042.

SCHEME 5. Diverse Product Set from 6d



dehydration and protonation of the alkoxide generating an alkyl alcohol at C-2. The use of CO_2 as the electrophile allows synthetic access to the indolone ring **18a** following acid induced ring closure and dehydration. The one-pot production of this diverse product set of chiral anilines, indoles and indolones from a common starting material and chiral mediator highlights the advantage of this approach.

TABLE 3. Synthesis of 1,3-, 1,2,3-, 1,3,5-, and 1,2,3,5-Substituted Indoles

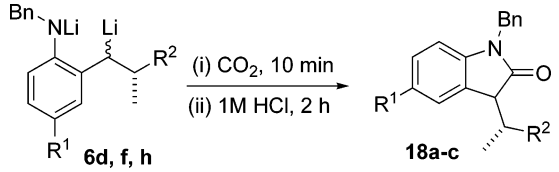


entry		R^1	R^2	R^3	product	yield,[a] %	er[b]
1	**6d**	H	*n*-Bu	H	**17a**	60	92:8
2	**6d**	H	*n*-Bu	CH_3	**17b**	30[c]	93:7[d]
3	**6d**	H	*n*-Bu	*t*-Bu	**17c**	50	91:9
4	**6d**	H	*n*-Bu	Ph	**17d**	38	93:7
5	**6d**	H	*n*-Bu	$COCH_3$	**17e**	51	92:8
6	**6d**	H	*n*-Bu	$(CH_2)_3OH$	**17f**	45	92:8
7	**6e**	H	Et	H	**17g**	40	nd[e]
8	**6f**	H	*n*-Hex	H	**17h**	58	92:8
9	**6g**	OCH_3	*n*-Bu	H	**17i**	43	93:7
10	**6g**	OCH_3	*n*-Bu	$(CH_2)_3OH$	**17j**	31	92:8
11	**6h**	F	*n*-Bu	$(CH_2)_2CH(CH_3)OH$	**17k**	15[f]	92:8
12	**6i**	F	*n*-Hex	$COCH_3$	**17l**	37	91:9

[a] Isolated purified yield. [b] Determined by HPLC and compared with racemic sample generated with TMEDA as additive. [c] Compound **7d** was also isolated in 62% yield. [d] An increased er of 99:1 was obtained after one recrystallization from pentane. [e] Chiral HPLC separation not achieved. [f] Compound **7h** was also isolated in 77% yield.

The carbolithiation initiated cascade reaction sequence is also tolerant to variations in alkyllithium, with both Et and *n*-HexLi successfully employed (Table 3, entries 7, 8, and 12). In addition, methoxy and fluoro substituents have been included in the aryl ring without affecting the er of the indole products **17i**−**l** (Table 3, entries 9−12). Introduction of an alkyl alcohol at C-2, by employing γ-butyrolactone as the electrophile, gave indole **17j** in 31% yield and 92:8 er. Carbolithiation of fluoro-

TABLE 4. Indolone Synthesis



entry		R^1	R^2	product	yield,[a] %	er[b]
1	**6d**	H	*n*-Bu	**18a**	64	92:8
2	**6f**	H	*n*-Hex	**18b**	55	92:8
3	**6h**	F	*n*-Bu	**18c**	32	nd[c]

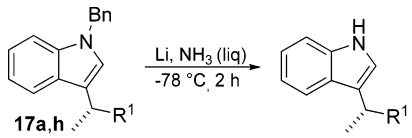
[a] Isolated purified yield. [b] Determined by HPLC and compared with racemic sample generated with TMEDA as additive. [c] Chiral HPLC separation not achieved.

substituted **5f** with both *n*-Bu and *n*-HexLi, followed by electrophile reaction (γ-valerolactone and 2,2-diethoxypropionitrile), resulted in isolation of indoles **17k** and **17l** with comparable selectivity (entries 11 and 12).

Further examples were provided by the treatment of the lithiated species **6d**,**f**,**h** with CO_2 generating the corresponding carboxylic acids which were effectively cyclized with 1 M HCl (aq) to form the indolones **18a**−**c** in a one-pot operation (Table 4). Indolones **18a**−**c** were isolated as a mixture of diastereoisomers due to the presence of the second stereogenic center in the 5-membered ring, however the asymmetric generation of quaternary centers on indolone rings has been the subject of several recent reports.[19]

Use of the *N*-benzyl group is a requirement for high enantioselectivity, however debenzylation of the final products can be achieved by treatment with lithium and ammonia, as illustrated for indoles **17a** and **17h** (Scheme 6). Following reduction, the deprotected indoles **19a**,**b** were isolated in yields of 92% and 57%, respectively.

SCHEME 6. Deprotection of Indoles 17a,h



19a; R^1 = Bu; 92% yield; 93:7 er
19b; R^1 = Hex; 57% yield; 93:7 er

In summary, enantioselective cascade reaction sequences are very powerful synthetic protocols for the efficient assembly of complex architectures. We have shown that by exploiting an asymmetric carbolithiation of (*E*)-2-propenylarylamines, chiral lithiated intermediates of broad synthetic potential can be readily generated with the asymmetric induction being governed by the organic natural product (−)-sparteine. Application of these intermediates to further in situ transformations provides access to a diverse product set with all final products having a common stereogenic center and identical selectivity. The methodology is exemplified by the synthesis of chiral substituted anilines, indoles and indolones. Utilization of this synthetic methodology for the generation of other heterocycles from alternatively *o*-substituted β-methylstyrenes is currently underway and will be reported in due course.

(19) For examples, see: (a) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308. (b) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164. (c) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043.

Experimental Section

Representative Synthesis of Anilines 7.

Benzyl-[4-fluoro-2-(2-methylhexyl)phenyl]amine, **7h.** PhLi (0.30 mL, 0.51 mmol) was added to a solution of **5f** (121.9 mg, 0.51 mmol) in cumene (2 mL) and stirred at room temperature for 15 min. This solution was added dropwise, over 15 min, to a premixed solution of *n*-BuLi (0.47 mL, 1.03 mmol) and (−)-sparteine (0.35 mL, 1.52 mmol) in cumene (2 mL) at −15 °C. The mixture was stirred at −15 °C for a further 4 h and treated with methanol (1 mL). The reaction mixture was washed with HCl (aq) (1 M, 10 mL) and the aqueous layer extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 99/1 pentane/diethyl ether) gave the purified product as colorless oil (96.0 mg, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36−7.35 (m, 4H), 7.31−7.27 (m, 1H), 6.80−6.75 (m, 2H), 6.54−6.50 (m, 1H), 4.32 (s, 2H), 3.77 (bs, 1H), 2.51 (dd, 1H, J = 14.2, 5.8 Hz), 2.21 (dd, 1H, J = 14.2, 8.5 Hz), 1.82−1.71 (m, 1H), 1.40−1.15 (m, 6H), 0.89 (d, 3H, J = 6.4 Hz), 0.88−0.84 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 155.7 (d, $^1J_{CF}$ = 236.3 Hz), 142.3 (d, J_{CF} = 1.7 Hz), 139.6, 128.9, 127.6, 127.5, 127.4, 117.2 (d, $^2J_{CF}$ = 22.0 Hz), 113.0 (d, $^2J_{CF}$ = 21.6 Hz), 111.5 (d, $^3J_{CF}$ = 7.5 Hz), 49.2, 39.4, 37.1, 32.5, 29.6, 23.1, 20.1, 14.3. IR (neat): 1509, 2857, 2926, 2956, 3031, 3454 cm^{-1}. ES-MS: *m*/*z* 300.2 $[M + H]^+$. HRMS $[M + H]^+$: 300.2125, $C_{20}H_{27}NF$ requires 300.2128. Anal. Calcd for $C_{20}H_{26}FN$: C, 80.22; H, 8.75; N, 4.68; F, 6.34. Found: C, 80.20; H, 8.66; N, 4.70; F, 6.52. $[\alpha]_D$ = +3.1 (*c* = 1.6, CH_2Cl_2, 20 °C). The enantiomeric ratio was determined using a Chiracel OD column (95/5 pentane/2-propanol, 0.3 mL/min), retention times of isomers: 21.0 min (7%) and 22.0 min (93%). A racemic mixture generated with TMEDA gave a 1:1 ratio.

Benzyl-[4-fluoro-2-(2-methyloctyl)phenyl]amine, 7i. PhLi (0.29 mL, 0.50 mmol) was added to a solution of **5f** (119.9 mg, 0.50 mmol) in cumene (2 mL) and stirred at room temperature for 15 min. This solution was added dropwise, over 15 min, to a premixed solution of *n*-HexLi (0.43 mL, 1.00 mmol) and (−)-sparteine (0.35 mL, 1.52 mmol) in cumene (2 mL) at −15 °C. The mixture was stirred at −15 °C for a further 4 h and treated with methanol (1 mL). The reaction mixture was washed with HCl (aq) (1 M, 10 mL) and the aqueous layer 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 colorless oil (99.0 mg, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36−7.33 (m, 4H), 7.30−7.27 (m, 1H), 6.80−6.75 (m, 2H), 6.54−6.50 (m, 1H), 4.32 (s, 2H), 3.76 (bs, 1H), 2.51 (dd, 1H, J = 14.3, 5.8 Hz), 2.21 (dd, 1H, J = 14.3, 8.5 Hz), 1.78−1.74 (m, 1H), 1.33−1.20 (m, 10H), 0.90−0.85 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155.7 (d, $^1J_{CF}$ = 230.5 Hz), 142.3 (d, J_{CF} = 1.7 Hz), 139.6, 128.9, 127.6, 127.5, 127.4, 117.2 (d, $^2J_{CF}$ = 21.7 Hz), 113.0 (d, $^2J_{CF}$ = 21.7 Hz), 111.5 (d, $^3J_{CF}$ = 7.5 Hz), 49.2, 39.4, 37.4, 32.6, 32.1, 29.7, 27.4, 22.9, 20.1, 14.3. IR (neat): 1509, 2854, 2925, 3031, 3454 cm^{-1}. ES-MS: *m*/*z* 328.2 $[M + H]^+$. HRMS $[M + H]^+$: 328.2445, $C_{22}H_{31}NF$ requires 328.2441. Anal. Calcd for $C_{22}H_{30}FN$: C, 80.69; H, 9.23; N, 4.28. Found: C, 80.34; H, 9.16; N, 4.10. $[\alpha]_D$ = −2.1 (*c* = 1.6, CH_2Cl_2, 20 °C). The enantiomeric ratio was determined using a Chiracel OD column (95/5 pentane/2-propanol, 0.3 mL/min), retention times of isomers: 22.2 min (7%) and 23.1 min (93%). A racemic mixture generated with TMEDA gave a 1:1 ratio.

Representative Synthesis of Indoles 17.

1-Benzyl-2-*tert*-butyl-3-(1-methylpentyl)-1*H*-indole, 17c. PhLi (0.39 mL, 0.49 mmol) was added to a solution of **5d** (109.5 mg, 0.49 mmol) in cumene (2 mL) and stirred at room temperature for 15 min. This solution was added dropwise, over 15 min, to a

premixed solution of *n*-BuLi (0.46 mL, 0.98 mmol) and (−)-sparteine (0.34 mL, 1.48 mmol) in cumene (2 mL) at −15 °C. The mixture was stirred at −15 °C for a further 4 h and treated with 2,2-dimethylpropionitrile (0.81 mL, 7.34 mmol) in THF (4 mL). Stirring was continued for 3 h, during which time the temperature was gradually increased to room temperature. HCl (aq) (2 M, 10 mL) was added and stirring continued at room temperature for 10 min. The organic layer was separated and the aqueous layer 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 colorless oil (85.1 mg, 50%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.81−7.77 (m, 1H), 7.26−7.16 (m, 3H), 7.02−7.00 (m, 3H), 6.84−6.81 (m, 2H), 5.60 (s, 2H), 3.67−3.55 (m, 1H), 2.07−1.95 (m, 1H), 1.93−1.81 (m, 1H), 1.53−1.47 (m, 2H), 1.49 (s, 9H), 1.38−1.17 (m, 5H), 0.86 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 141.7, 139.1, 138.4, 128.5, 127.1, 126.7, 125.6, 121.2, 120.9, 118.4, 118.3, 110.0, 49.3, 36.5, 34.8, 32.6, 31.8, 31.1, 23.0, 21.1, 14.2. IR (neat): 2870, 2926, 2957, 3028 cm^{-1}. ES-MS: *m*/*z* 348.2 [M + H]$^+$. HRMS [M + H]$^+$: 348.2695, $C_{25}H_{34}N$ requires 348.2691. $[\alpha]_D$ = −5 (*c* = 0.1, CH_2Cl_2, 20 °C). The enantiomeric ratio was determined using a Chiracel OD column (99.75/0.25 pentane/2-propanol, 0.6 mL/min), retention times of isomers: 17.1 min (91%) and 18.5 min (9%). A racemic mixture generated with TMEDA gave a 1:1 ratio.

1-[1-Benzyl-5-fluoro-3-(1-methylheptyl)-1*H*-indol-2-yl]ethanone, 17l. PhLi (0.31 mL, 0.53 mmol) was added to a solution of **5f** (127.6 mg, 0.53 mmol) in cumene (2 mL) and stirred at room temperature for 15 min. This solution was added dropwise, over 15 min, to a premixed solution of *n*-HexLi (0.46 mL, 1.06 mmol) and (−)-sparteine (0.37 mL, 1.61 mmol) in cumene (2 mL) at −15 °C. The mixture was stirred at −15 °C for a further 4 h and treated with 2,2-diethoxypropionitrile (0.83 mL, 5.32 mmol). Stirring continued for 3 h, during which time the temperature was gradually increased to room temperature. Saturated ammonium chloride solution (10 mL) was added and stirring continued at room temperature for 10 min. The aqueous layer was removed; HCl (aq) (5 M, 10 mL) was added to the organic layer and the mixture stirred at room temperature for 30 min. The organic layer was separated and the aqueous layer extracted with diethyl ether (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 pale yellow oil (74.0 mg, 37%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.50−7.47 (m, 1H), 7.25−7.19 (m, 4H), 7.05−7.00 (m, 1H), 6.94−6.92 (m, 2H), 5.51 (s, 2H), 3.42−3.31 (m, 1H), 2.50 (s, 3H), 1.96−1.87 (m, 1H), 1.85−1.78 (m, 1H), 1.48 (d, 3H, J = 7.1 Hz), 1.28−1.19 (m, 8H), 0.88−0.82 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 194.9, 157.4 (d, $^1J_{CF}$ = 238.8 Hz), 138.5, 136.0, 135.7, 128.8, 127.5, 127.4, 126.4, 125.3 (d, $^3J_{CF}$ = 10.8 Hz), 114.2 (d, $^2J_{CF}$ = 26.5 Hz), 112.1 (d, $^3J_{CF}$ = 9.5 Hz), 107.6 (d, $^2J_{CF}$ = 23.6 Hz), 48.4, 37.1, 32.6, 32.0, 31.9, 29.5, 28.6, 22.8, 21.4, 14.3. ^{19}F NMR ($CDCl_3$, 376 MHz) δ: −123.7−123.8 (m). IR (neat): 1452, 1661, 2855, 2927, 2959, 3031 cm^{-1}. ES-MS: *m*/*z* 378.2 [M − H]$^-$. HRMS [M − H]$^-$: 378.2248, $C_{25}H_{29}NOF$ requires 378.2233. $[\alpha]_D$ = +2.6 (*c* = 0.6, CH_2Cl_2, 20 °C). The enantiomeric ratio was determined using a Chiracel OD column (95/5 pentane/2-propanol, 0.4 mL/min), retention times of isomers: 14.3 min (9%) and 15.1 (91%). A racemic mixture generated with TMEDA gave a 1:1 ratio.

Representative Synthesis of Indolones 18.

1-Benzyl-3-(1-methylpentyl)-1,3-dihydroindol-2-one, 18a. PhLi (0.31 mL, 0.47 mmol) was added to a solution of **5d** (101.8 mg, 0.46 mmol) in cumene (2 mL) and stirred at room temperature for 15 min. This solution was added dropwise, over 15 min, to a premixed solution of *n*-BuLi (0.42 mL, 0.91 mmol) and (−)-sparteine (0.32 mL, 1.39 mmol) in cumene (2 mL) at −15 °C. The mixture was stirred at −15 °C for a further 4 h and treated with solid carbon dioxide. The cooling bath was removed, HCl (aq) (1 M, 10 mL) was added, and stirring was continued at room temperature for 2 h. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 3/2 pentane/diethyl ether) gave the purified product as colorless oil (90.3 mg, 64%) [NMR data for product as an equal mixture of diastereoisomers]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30−7.28 (m, 4H), 7.26−7.23 (m, 2H), 7.16−7.13 (m, 1H), 7.01−6.99 (m, 1H), 6.72−6.70 (m, 1H), 5.02 (dd, 1H, J = 15.5, 3.3 Hz), 4.78 (dd, 1H, J = 15.5, 6.7 Hz), 3.53 (dd, 1H, J = 13.3, 3.4 Hz), 2.45−2.38 (m, 0.5H, isomer 1), 2.37−2.30 (m, 0.5H, isomer 2), 1.59−1.43 (m, 2H), 1.41−1.26 (m, 4H), 0.99 (d, 1.5H, J = 6.9 Hz, isomer 2), 0.94−0.85 (m, 3H), 0.78 (d, 1.5H, J = 6.8 Hz, isomer 1). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 178.2, 177.6, 144.3, 144.2, 136.5, 136.4, 129.0, 128.8, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 124.9, 124.4, 122.5, 122.4, 109.3, 109.2, 51.0, 50.6, 44.1, 44.0, 36.4, 35.9, 34.5, 33.0, 31.3, 30.2, 23.1, 23.1, 17.3, 15.9, 14.4, 14.4. IR (neat): 1358, 1466, 1488, 1613, 1713, 2858, 2928, 2958, 3032, 3060 cm^{-1}. ES-MS: *m*/*z* 308.2 [M + H]$^+$. HRMS [M + H]$^+$: 308.2005, $C_{21}H_{26}NO$ requires 308.2014. $[\alpha]_D$ = +12.1 (*c* = 1.4, CH_2Cl_2, 20 °C). The enantiomeric ratio was determined using a Chiracel OD column (99.8/0.2 pentane/2-propanol + 0.1% TFA, 0.6 mL/min), retention times of isomers: 26.2 min (4%), 27.2 min (4%), 28.4 min (44%) and 29.4 min (48%). A racemic mixture generated with TMEDA gave retention times 26.2 min (27%), 27.2 min (23%), 28.4 min (22%) and 29.4 min (28%). 92:8 er.

1-Benzyl-5-fluoro-3-(1-methylpentyl)-1,3-dihydroindol-2-one, 18c. PhLi (0.31 mL, 0.47 mmol) was added to a solution of **5f** (112.8 mg, 0.47 mmol) in cumene (2 mL) and the mixture stirred at room temperature for 15 min. This solution was added dropwise, over 15 min, to a premixed solution of *n*-BuLi (0.43 mL, 0.93 mmol) and (−)-sparteine (0.32 mL, 1.39 mmol) in cumene (2 mL) at −15 °C. The mixture was stirred at −15 °C for a further 4 h and treated with solid carbon dioxide. The cooling bath was removed, HCl (aq) (1 M, 10 mL) was added, and stirring was continued at room temperature for 2 h. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated to dryness. Silica gel chromatography (eluent: 3/2 pentane/diethyl ether) gave the purified product as a colorless oil (48.8 mg, 32%) [NMR data of product as an equal mixture of diastereoisomers]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33−7.24 (m, 5H), 7.01−6.98 (m, 1H), 6.88−6.82 (m, 1H), 6.62−6.58 (m, 1H), 5.01 (dd, 1H, J = 15.7, 3.2 Hz), 4.77 (dd, 1H, J = 15.7, 6.7 Hz), 3.53 (dd, 1H, J = 11.5, 3.0 Hz), 2.42−2.38 (m, 0.5H, isomer 1), 2.35−2.28 (m, 0.5H, isomer 2), 1.55−1.41 (m, 2H), 1.40−1.25 (m, 4H), 0.99 (d, 1.5H, J = 7.0 Hz, isomer 2), 0.94−0.86 (m, 3H), 0.79 (d, 1.5H, J = 6.7 Hz, isomer 1). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 177.7, 177.0, 159.2 (d, $^1J_{CF}$ = 238.8 Hz), 159.1 (d, $^1J_{CF}$ = 238.8 Hz), 140.1, 139.9, 136.1, 136.0, 129.3, 129.2, 129.0, 127.8, 127.6, 127.5, 114.1 (d, $^2J_{CF}$ = 23.2 Hz), 114.0 (d, $^2J_{CF}$ = 26.5 Hz), 112.9 (d, $^2J_{CF}$ = 26.5 Hz), 112.4 (d, $^2J_{CF}$ = 23.2 Hz), 109.4 (d, $^3J_{CF}$ = 8.3 Hz), 109.3 (d, $^3J_{CF}$ = 9.1 Hz), 51.2, 50.8, 44.1, 44.0, 36.2, 35.8, 34.2, 32.8, 30.0, 30.0, 23.0, 22.9, 17.0, 15.8, 14.3, 14.3. IR (neat): 1489, 1712, 2859, 2929, 2959, 3033, 3065 cm^{-1}. ES-MS: *m*/*z* 326.2 [M + H]$^+$. HRMS [M + H]$^+$: 326.1927, $C_{21}H_{25}NOF$ requires 326.1920. Anal. Calcd for $C_{21}H_{24}FNO$: C, 77.51; H, 7.43; N, 4.30; F, 5.84. Found: C, 77.46; H, 7.51; N, 4.30; F, 5.35. $[\alpha]_D$ = +15.9 (*c* = 0.5, CH_2Cl_2, 20 °C). Chiral HPLC separation not achieved.

Synthesis of Indoles 19.

3-(1-Methylpentyl)-1*H*-indole, 19a. Lithium wire (17.3 mg, 2.49 mmol) was added to liquid ammonia (75 mL) at −78 °C and stirred for 30 min. A solution of **17a** (24.1 mg, 0.08 mmol) in THF (1 mL) was added and stirring continued at −78 °C for 2 h. Solid ammonium chloride was added, the bath removed, and the ammonia allowed evaporate. Water (15 mL) was added and the aqueous layer extracted with diethyl ether (2 × 25 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 product as a colorless oil (14.8 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.87 (bs, 1H), 7.64 (d, 1H, J = 7.9 Hz), 7.34 (d, 1H, J = 8.1 Hz), 7.19−7.15 (m, 1H), 7.11−7.07 (m, 1H), 6.94 (s, 1H), 3.07−2.98 (m, 1H), 1.83−1.75 (m, 1H), 1.65−1.57 (m, 1H), 1.34 (d, 3H, J = 7.0 Hz), 1.33−1.27 (m, 4H), 0.90−0.85 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 136.7, 127.2, 123.2, 122.0, 120.0, 119.7, 119.1, 111.3, 37.6, 31.0, 30.2, 23.1, 21.7, 14.4. IR (neat): 1457, 1619, 2857, 2927, 2957, 3057, 3418 cm^{-1}. ES-MS: *m*/*z* 202.2 $[M + H]^+$. HRMS $[M + H]^+$: 202.1596, $C_{14}H_{20}N$ requires 202.1596. The enantiomeric ratio was determined using a Chiracel OD column (99/1 pentane/2-propanol, 0.4 mL/min), retention times of isomers: 63.8 min (7%) and 66.1 min (93%).

3-(1-Methylheptyl)-1*H*-indole,[20] 19b. Lithium wire (17.3 mg, 2.49 mmol) was added to liquid ammonia (75 mL) at −78 °C and stirred for 30 min. A solution of **17h** (38.6 mg, 0.12 mmol) in THF (1 mL) was added and stirring continued at −78 °C for 2 h. Solid ammonium chloride was added, the bath removed, and the ammonia allowed evaporate. Water (15 mL) was added and the aqueous layer extracted with diethyl ether (2 × 25 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 product as colorless oil (15.6 mg, 57%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.85 (bs, 1H), 7.64 (d, 1H, J = 8.0 Hz), 7.33 (d, 1H, J = 8.0 Hz), 7.18−7.15 (m, 1H), 7.11−7.07 (m, 1H), 6.94 (s, 1H), 3.07−2.98 (m, 1H), 1.81−1.75 (m, 1H), 1.64−1.57 (m, 1H), 1.34 (d, 3H, J = 6.9 Hz), 1.31−1.19 (m, 8H), 0.90−0.84 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 136.8, 127.2, 123.2, 122.0, 120.0, 119.7, 119.2, 111.3, 37.9, 32.1, 31.1, 29.7, 27.9, 22.9, 21.6, 14.3. IR (neat): 1457, 1619, 2855, 2926, 2957, 3057, 3418 cm^{-1}. ES-MS: *m*/*z* 230.2 $[M + H]^+$. HRMS $[M + H]^+$: 230.1900, $C_{16}H_{24}N$ requires 230.1909. The enantiomeric ratio was determined using a Chiracel OD column (99/1 pentane/2-propanol, 0.6 mL/min), retention times of isomers: 38.9 min (7%) and 40.2 min (93%).

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Supporting Information Available: Analysis and experimental procedures for starting materials **7a**−**g**, **8**, **9**, **17a**,**b**,**d**−**k**, and **18b**. ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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