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Amines Bearing Tertiary Substituents by Tandem Enantioselective Carbolithiation–Rearrangement of Vinylureas

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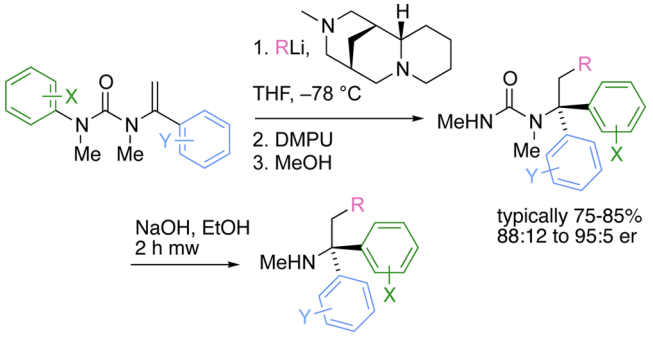
ABSTRACT



In the presence of (−)-sparteine or a (+)-sparteine surrogate, organolithiums add to *N*-alkenyl-*N*′-arylureas to give benzylic organolithiums in an enantioselective manner. Under the influence of DMPU, these organolithiums undergo rearrangement with migration of the *N*′-aryl ring from N to C, leading to the urea derivatives of enantiomerically enriched amines bearing tertiary substituents. Basic hydrolysis returns the functionalized amine, providing a new synthetic route to compounds with quaternary stereogenic centers bearing nitrogen.

Chiral amines bearing tertiary substituents (tertiary carbinamines) are widespread in naturally occurring and synthetic bioactive molecules.[1] Nonetheless, the synthesis of the quaternary stereogenic center carrying a nitrogen atom at the core of these molecules remains a challenge.[2] Successful approaches include nucleophilic additions to imines,[3] stereospecific rearrangements of chiral precursors,[2,5] or stereospecific functionalization of precursors containing tertiary stereogenic centers.[4,5] We have previously shown that migration of an *N*-aryl substituent within a lithiated urea (for example, **2Li** to **3Li**) allows the stereospecific construction of quaternary centers bearing nitrogen.[5] We have also shown that lithiated ureas such as **2Li** may be generated not only by deprotonation but also by carbolithiation.[6] We now report an asymmetric method whereby amines bearing tertiary substituents may be

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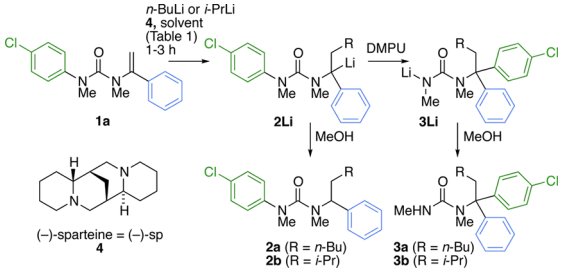
constructed in enantiomerically enriched form from achiral precursors by using a tandem carbolithiation–aryl migration in the presence of a chiral additive, forming two new C–C bonds with control of absolute configuration.

Styrenes, including those bearing α-N[6,7] or -O[8] substituents, undergo nucleophilic attack by organolithiums at the β-position to generate benzyllithiums.[9] The addition of (−)-sparteine **4** to such carbolithiations may induce enantioselectivity.[10] By using **4** or a similar chiral lithium-coordinating ligand, we proposed to impose enantioselectivity on the carbolithiation of ureas such as **1a**, generating a configurationally stable, enantiomerically enriched organolithium **2Li** which would be trapped in situ by stereospecific aryl migration to give **3Li** and hence the tertiary carbinamine derivatives **3** (Scheme 1).

Scheme 1. Optimization of Solvent and Conditions



Trial reactions were carried out using the vinylurea **1a**.[11] Treatment of **1a** with *n*-BuLi in a range of solvents at −78 °C resulted in rapid racemic carbolithiation, giving **2a** on protonation after 1 h in Et_2O and a mixture of **2a** and **3a** in THF (Table 1, entries 1 and 2). In toluene (entry 3), the racemic reaction was slower, reaching only 35% completion in 6 h and therefore giving an opportunity for an asymmetric ligand-accelerated reaction.

Addition of (−)-sparteine to the addition in Et_2O or toluene gave, after protonation, mixtures of simple carbolithiation product **2a** and tandem carbolithiation–aryl migration product **3a**, complicating the analysis (entry 4). With the aim of accelerating rearrangement of the carbolithiation product **2aLi** to **3aLi**, the reactions were therefore terminated by addition of DMPU, an additive known to accelerate the N to C aryl migration[5,6] probably by favoring the formation of solvated ion pairs.[12] By adding DMPU after 1 h at −78 °C, a carbolithiation–rearrangement product was formed in moderate yield and in low er from **1a** with *n*-BuLi and (−)-sparteine in toluene (entry 5). However, on delaying the addition of DMPU to 6 h (entry 6), the er was significantly improved. This suggested that carbolithiation was still incomplete after 1 h and that DMPU was promoting an unwanted rapid, racemic carbolithiation of any remaining unreacted alkyllithium.

We therefore sought conditions that would allow asymmetric carbolithiation to reach completion fast enough to avoid racemization or epimerization of the organolithium product. Using *i*-PrLi, we were able to obtain **3b** with encouraging er's in toluene after 1 h, but only with a large excess of (−)-sparteine (entry 7). In cumene or in *t*-BuOMe, similar er's were obtained but without the need for a large excess of (−)-sparteine (entries 8, 11), with cumene giving the better yields. Interestingly, yields (but not er) improved as the temperature was raised to −50 °C (entries 9 and 10), perhaps because the increased rate of carbolithiation was offset by the increased rate of racemization of **2Li**. However, carbolithiation–rearrangement of **1a** with *i*-PrLi in cumene in the presence of (−)-sparteine gave the product **3b** in high yield and in 92:8 er (entry 12). We ascribe the exceptional performance of cumene to its resistance to deprotonation at a temperature sufficiently high to allow complete carbolithiation prior to addition of DMPU, coupled with the high configurational stability of the intermediate organolithium **2Li** in such a noncoordinating solvent.[13] It was not possible to use (−)-sparteine catalytically (entry 13) without statistical loss of er, but good results were obtained with 2 equiv of alkyllithium and 1 equiv (−)-sparteine.

With optimized conditions in hand, a range of vinylureas **1**[11] were treated with commercially available organolithiums in the presence of (−)-sparteine at −50 °C in cumene (Scheme 2). Both electron-rich and electron-poor aromatic rings underwent the tandem addition–rearrangement reaction in good yield and with good to excellent er. With phenyllithium and with methyllithium (which underwent carbolithiation only in THF), racemic products **3g** and **3h** were formed.[14]

With *tert*-butyllithium, only carbolithiation (without tandem rearrangement) was observed, giving **2c**. More

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Table 1. Conditions for Carbolithiation–Rearrangement of **1a**

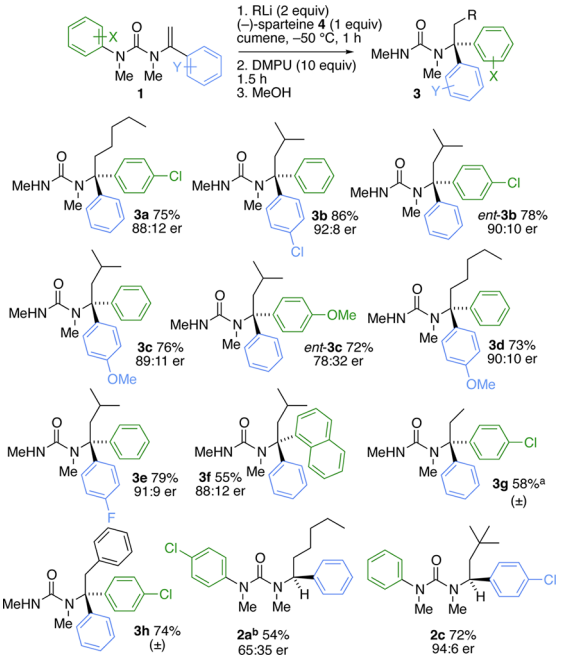
entry	R	**4**–**7** (equiv)	DMPU (equiv)	solvent	temp (°C)	yield of **2** (%)	yield of **3** (%)	er of **3**
1	*n*-Bu	0	0	THF	−78	49	21	
2	*n*-Bu	0	0	Et_2O	−78	47	0	
3	*n*-Bu	0	0	tol	−78	0, 35[a]	0	
4	*n*-Bu	**4**, 1	0	Et_2O	−78	32	12	[b]
5	*n*-Bu	**4**, 1	10[c]	tol	−78	0	53	62:38
6	*n*-Bu	**4**, 1	10[d]	tol	−78	0	45	76:24
7	*i*-Pr	**4**, 6	10[c]	tol	−78	0	56	80:20
8	*i*-Pr	**4**, 2	10[e]	mtbe	−78	0	60	80:20
9	*i*-Pr	**4**, 2	10[c]	mtbe	−50	0	70	80:20
10	*i*-Pr	**4**, 2	10[c]	Et_2O	−50	0	85	80:20
11	*i*-Pr	**4**, 1	10[c]	cum[f]	−78	0	85	75:25
12	*i*-Pr	**4**, 1	10[c]	cum[f]	−50	0	86	92:8
13	*i*-Pr	**4**, 0.5	10[c]	cum[f]	−50	0	81	70:30
14	*i*-Pr	**6**, 1	10[c]	tol	−78	0	0	[b]
15	*i*-Pr	**7**, 1	10[c]	tol	−78	0	0	[b]
16	*i*-Pr	**5**, 1	10[c]	cum[f]	−78	0	62	35:65
17	*i*-Pr	**5**, 1	10[c]	THF	−78	0	74	5:95

[a] After 6 h. [b] Not determined. [c] Added after 1 h. [d] Added after 6 h. [e] Added after 3 h. [f] cum = cumene = Ph*i*-Pr.

generally, unrearranged products **2** could be isolated when DMPU was not added to the reaction mixture: **2a** was formed in 65:35 er under these conditions and had $[\alpha]_D$ = +12.8. Comparison with an authentic enantiomerically pure sample of (*S*)-(−)-**2a**[15] allowed us to confirm that (−)-sparteine induces the formation of **2a** with (*R*) absolute configuration. Since both protonation and aryl migration are stereochemically retentive,[16] and carbolithiation is *syn* selective,[6] we deduce that (−)-sparteine leads to aryl migration to the *Re* face of the alkenyl group, the back face as drawn, of vinylureas **1**.

Despite the dominance of (−)-sparteine as a director of asymmetric organolithium chemistry over the last 20 years,[17] other lithium-complexing agents, especially the "(+)-sparteine surrogate" **5**,[18] show promising activity as alternative or improved ligands. We screened **5**,[18] BPox **6**,[19] and *trans*-cyclohexanediamine **7**[20] in the addition of *i*-PrLi to **1a**.

Scheme 2. Asymmetric Carbolithiation–Rearrangement Using (−)-Sparteine **4**



[a] Reaction carried out in THF. [b] Without addition of DMPU.

No carbolithiation was observed using **6** or **7** in toluene (Table 1, entries 14 and 15), but in a test reaction with **5** the product **3b** was obtained in excellent er, even in THF (Table 1, entries 16 and 17).[14]

When applied to a wider range of substrates **1** (Scheme 3), carbolithiation with organolithiums in the presence of the (+)-sparteine surrogate **5** behaved distinctively differently from reactions using (−)-sparteine **4** as the chiral ligand. As expected, the products had the opposite absolute configuration using **5** in place of **4**. The reactions also performed best in THF. In general, carbolithiation and rearrangement proceeded with good er using *i*-PrLi. However, with *n*-BuLi the products **3j** and **3l** were close to racemic.[21] Other noncommercial organolithiums gave varying results: *p*-methoxyphenyllithium led to racemic **3m**, while cyclopentyllithium resulted in only slight enantioenrichment in **3n**. An attempted reaction employing in situ halogen–lithium exchange of (*Z*)-1-iodohex-3-ene resulted in the formation of **3o** in good yield, evidently via ethylation of *t*-BuLi by ethylene generated on decomposition of THF.[22]

Ureas related to **3** are readily converted to amines **8** bearing tertiary substituents by solvolysis under neutral or basic conditions.[5b] Thus, treatment of **3k** with ethanolic sodium hydroxide gave the amine **8k** in excellent yield (Scheme 4) and without loss of enantiomeric purity.

(15) (*S*)-(−)-**2a** ($[\alpha]_D$ = −59.7) was made using the method of: Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. See the Supporting Information.

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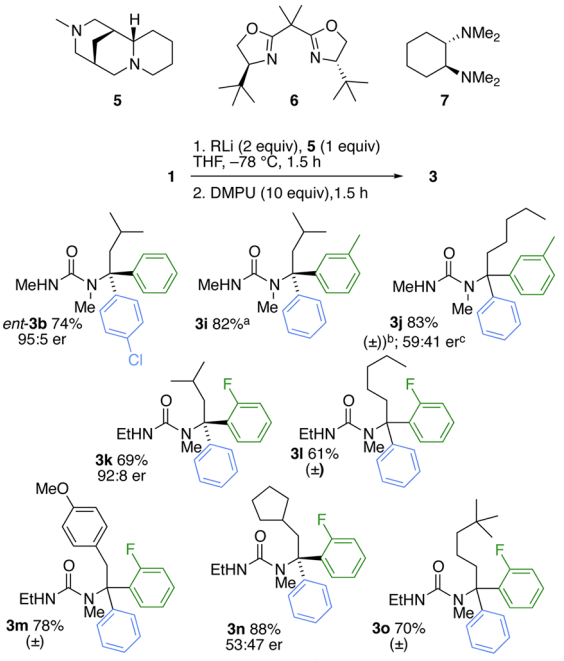
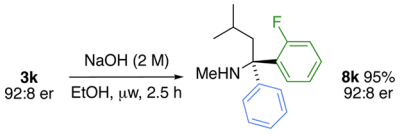
(21) Increasing the concentration of the reaction mixture from 0.1 to 0.3 M made a marginal improvement to the er of **3j**, suggesting that the coordination of **5** to *n*-BuLi in THF may be concentration dependent. Concentration-dependent values for er have been observed in other lithiations using *n*-BuLi + **5** in THF. Nonetheless, NMR indicated coordination between *n*-BuLi + **5** in THF even at 0.07 M: Carbone, G.; O'Brien, P. Unpublished results.

Scheme 3. Asymmetric Carbolithiation–Rearrangement Using (+)-Sparteine Surrogate **5**



[a] Enantiomeric ratio not determined. [b] At 0.1 M. [c] At 0.3 M.

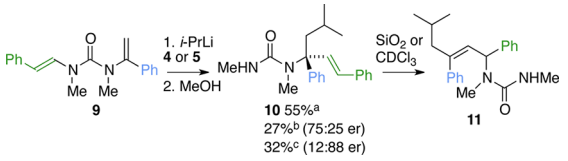
Scheme 4. Solvolysis of the Product Urea To Liberate the Amine



Lithiated ureas will not only trap *N*-aryl groups by intramolecular migration but also *N*-alkenyl groups.[12] In THF, the *N*-alkenylurea **9** underwent regioselective carbolithiation followed by vinyl migration to yield **10**, whose isolation was complicated by a strong tendency to undergo rearrangement to **11** in acid. However, both **4** and **5** induced asymmetric carbolithiation–vinylation to give **10** in enantiomerically enriched form (Scheme 5).

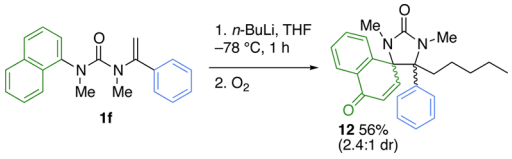
We assume that the reactions begin with an asymmetric carbolithiation, in which the diamine-complexed organolithium attacks one enantiotopic face of the alkene (*Re* for **4**; *Si* for **5**) to form a stereodefined organolithium formed under kinetic control. We know from other work that such urea-stabilized organolithiums are configurationally stable on the time scale of the rearrangement,[5,13] so it seems unlikely that asymmetry is induced by any form of equilibration of the organolithium.[23] Migration of the aromatic ring then occurs via an intramolecular nucleophilic aromatic substitution whose mechanism has been discussed elsewhere[24] and which may or may not involve a dearomatized intermediate. In the case of the 1-naphthyl migration to form **3f**, a dearomatized intermediate[5a] may, however, be trapped to give the enone **12** by allowing dry air into the reaction flask (Scheme 6).

Scheme 5. Asymmetric Carbolithiation–Vinylation



[a] In THF (–78 °C, 90 min then –30 °C, 90 min) with neither **4** nor **5**. [b] **4**, cumene, –35 °C, 2 h. [c] **5**, Et_2O, –45 °C, 4 h.

Scheme 6. Trapping a Dearomatized Intermediate



In summary, carbolithiation in the presence of chiral diamines of vinylic ureas bearing an *N*-aryl group leads to tandem formation of two new C–C bonds and allows the formation of amines bearing α-tertiary substituents in good enantiomeric ratios.

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Supporting Information Available. Full experimental details and characterization of new compounds.This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.