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Substituted Diarylmethylamines by Stereospecific Intramolecular Electrophilic Arylation of Lithiated Ureas

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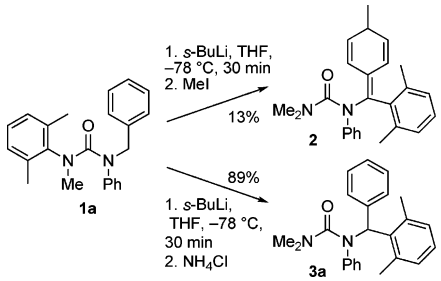
Diarylmethylamine derivatives form an important class of pharmacologically active compounds (including for example the non-sedative antihistamine levocetirizine and the anti-emetic meclizine) and are generally made in enantiomerically pure form[1] by reagent-controlled addition to imines[2] or by substrate-controlled addition to *N*-sulfinylimines.[3] While studying the regioselective lithiation of *N*-aryl ureas,[4,5] we uncovered a mechanistically remarkable stereospecific intramolecular aryl transfer, and in this communication, we detail this new and strategically complementary route to diarylmethylamine derivatives. Importantly, the rearrangement offers a new asymmetric synthesis of the much less readily accessible α-alkylated analogues of the simple diarylmethylamines, compounds which retain important biological activity.[6]

N-Aryl ureas undergo efficient ortho-[4] and lateral lithiation,[5] and *N*-benzyl urea **1a** was treated with *sec*-BuLi and methyl iodide with the aim of determining the site of deprotonation. The reaction mixture became deeply colored, and purification of the product mixture yielded an unstable, deep indigo compound, identified as **2**, in low yield. The N→C migration of the aryl group is remarkable, though related rearrangements of lithiated benzylamines and their derivatives are known.[7]

By replacing the final methylation with an aqueous quench, the rearranged product **3a** was obtained in a satisfying 89% yield. Under similar conditions, a series of *N*-benzyl-*N*′-aryl ureas **1** rearranged to **3** in good yield irrespective of the electronic or steric nature of the substituents borne by the migrating ring (Scheme 2), as shown in Table 1. The substitution patterns of the products showed the reaction to be, formally, an *ipso* S_NAr displacement of the urea nitrogen by the lithiobenzyl group. The products **3** are derivatives of diarylmethylamines, and reductive cleavage of the urea with DIBAL, or hydrolysis of its *N*-nitroso derivative, returned diarylmethylamines **4** in excellent yield, confirming the method as a plausible synthetic route to diarylmethylamines.

Excess base was needed for good yields, and quenching the rearrangement of **1a** with CD_3OD gave a product **3a** deuterated at the acidic doubly benzylic position α to nitrogen. Evidently, **3** is deprotonated under the reaction conditions, ruling out the synthesis of enantiomerically pure diarylmethylamines by an asymmetric variant of the rearrangement of **1**. However, treatment of α-methylbenzylurea **5a** under similar conditions showed that tertiary benzyllithiums rearrange similarly, though rather more slowly than **1**. After 2 h at −78 °C, significant amounts of starting material remained, and raising the temperature or lengthening the reaction time gave rise to olefinic products arising from elimination of the urea. Deuteration after just 10 min showed that lithiation was complete, so DMPU was added to increase the reactivity of the resulting organolithium.[8] Rearrangement was much faster, and ureas **6** were obtained, generally in good yield, on quenching the reactions after 2 or 6 h, as shown in Table 2, entries 1−17. Migration of both electron-rich and electron-deficient rings occurred, though yields of some fluorinated ureas were compromised by decomposition (entries 6−8). In all cases where measurement was possible, there was minimal loss of enantiomeric purity in the products of the rearrangement: the N→C aryl transfer proceeds with almost complete stereospecificity. The rearrangement can furthermore be used as a method for the synthesis of α,α-diarylethylamines **7**—N-nitrosation makes the urea susceptible to hydrolysis in good yield over 3 days in refluxing THF−H_2O (Scheme 3). If required, N-nitrosation can be carried out simply by terminating the rearrangement with an excess of *tert*-butyl nitrite (entry 3).

Scheme 1. Rearrangement of a Lithiated Urea



Scheme 2. Synthesis of Diarylmethylamines

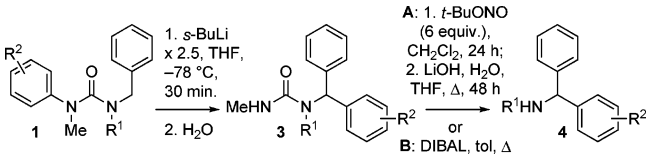


Table 1. Aryl Transfers in Lithiated *N*-Benzyl Ureas

entry	**1**	R^1	R^2	**3**, yield % (remaining **1**, %)	yield of **4**, % (method)
1	**1a**	Ph	2,6-diMe	**3a**, 89	
2	**1b**	Ph	4-Me	**3b**, 85	
3	**1c**	*p*-Tol	H	**3c**, 85	
4	**1d**	Me	H	**3d**, 78 (8)	84 (**B**)
5	**1e**	Me	2-Me	**3e**, 76 (15)	72 (**A**)
6	**1f**	Me	2-OMe	**3f**, 75 (21)	78 (**A**)
7	**1g**	Me	2,6-di-Me	**3g**, 82 (14)	84 (**A**)
8	**1h**	Me	4-Cl	**3h**, 69 (4)[a]	
9	**1i**	Me	4-OMe	**3i**, 76 (4)[a]	

[a] Reaction time was 2 h.

We propose that the rearrangements of **1** and **5** proceed via a mechanism approximating to that outlined in Scheme 4—benzylic lithiation of **5** gives **8**, whose organolithium center adds to the "distal" aryl ring[9] to give dearomatized intermediate **9**. Where **8** is chiral, it is evidently configurationally stable on the time scale of this addition.[10] Ring opening, either under the reaction conditions or on work up, returns urea **6**. Treating a mixture of **1a** and **1e** with *sec*-BuLi proved that the rearrangement is intramolecular: only **3a** and **3e** were obtained, with no evidence by mass spectrometry of "crossover" products. Evidence for the existence of a dearomatized intermediate **9** was obtained by allowing the rearrangements

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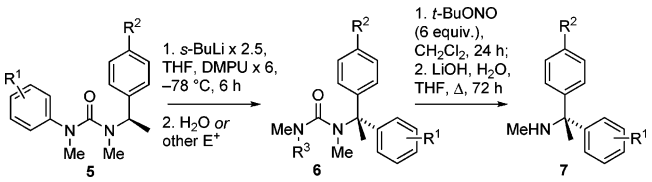
Table 2. Stereospecific Aryl Migration

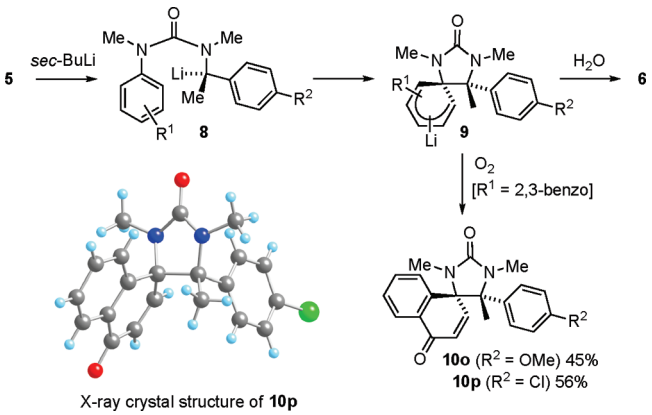
entry	5	R^1	R^2	R^3	6, yield % (5, %)[a]	6, er (5, er)[a]	7, yield %
1	**5a**	H	H	H	**6a**, 95[b]	–	72
2	(*R*)-**5b**	4-OMe	H	H	**6b**, 82[b]	97:3	
3	(±)-**5b**	4-OMe	H	NO[c]	**6b′**, 65	–	82
4	(±)-**5c**	2-OMe	H	H	**6c**, 84[b]	–	–
5	(*S*)-**5d**	3,4-OMe	H	H	**6d**, 76	98:2	–
6	(±)-**5e**	2-F	H	H	**6e**, 34[b]	–	–
7	(±)-**5f**	3-F	H	H	**6f**, 40	–	–
8	(*S*)-**5g**	4-F	H	H	**6g**, 34	99:1	–
9	(*S*)-**5h**	4-Cl	H	H	**6h**, 51[b] (17)	98:2 (50:50)	–
10	(*S*)-**5i**	3-Cl, 4-F	H	H	**6i**, 69	>99:1	75
11	(*S*)-**5j**	2,3-benzo	H	Me[d]	**6j**, 88	97:3	–
12	(*S*)-**5j**	2,3-benzo	H	H	n/d	95:5[e]	68[e]
13	(*S*)-5k	3,4-benzo	H	H	**6k**, 88	>97:3	–
14	(*R*)-**5l**	H	MeO	H	*ent*-**6b**, 73	>98:2	–
15	(*S*)-**5m**	2-Me	MeO	H	**6m**, 64	99:1	–
16	(*S*)-**5n**	4-Me	MeO	H	**6n**, 79	>97:3	–
17	(*R*)-**5o**	2,3-benzo	MeO	Me[d]	**6o**, 65	>98:2	–
18	(*R*)-**5p**	2,3-benzo	Cl	Me[d]	**6p**, 78	97:3	–
19	(*R*)-**5b**	4-OMe	H	H[f]	**6b**, 84 (16, >95% *d*)[g]	96:4 (42:58)	–
20	(*R*)-**5b**	4-OMe	H	H[h]	**6b**, 95 (5, >95% *d*)[g]	95:5 (74:26)	–
21	(*R*)-**5l**	H	MeO	H[f]	*ent*-**6b**, <5 (95, 80% *d*)[i]	n/d (91:9)	–
22	(*R*)-**5l**	H	MeO	H[h]	*ent*-**6b**, 6 (94, 92% *d*)[i]	n/d (89:11)	–

[a] Remaining starting material. [b] Quenched after 2 h. [c] Quenched with *t*-BuONO. [d] Quenched with MeI. [e] Yield over three steps from **5**. Er is of *N*-nitroso derivative. [f] Quenched with CD_3OD. [g] Quenched after 25 min; yields determined by NMR. [h] Quenched with $(CD_3)_2SO$. [i] Quenched after 5 min.

Scheme 3. Rearrangement of Ureas Derived from α-Methylbenzylamines



Scheme 4. Evidence for a Dearomatized Intermediate



X-ray crystal structure of **10p**

of **5o** and **5p** to proceed for 2 h and then exposing the reaction mixture to dry air. Oxidation of an intermediate presumed to be **9** yielded crystalline enones **10** in both cases: X-ray crystallography confirmed the absolute stereochemistry of **10p** and provides evidence for stereochemically retentive (rather than invertive) rearrangement.[11]

Interestingly, while the rearranged products were essentially enantiomerically pure, starting material remaining after the reaction of **5** was generally recovered with a diminished enantiomeric ratio (entries 9 and 19−22). When (*R*)-**5b** was lithiated and allowed to stir at −78 °C for only 25 min before quenching with either CD_3OD or $(CD_3)_2SO$, the small amount of **5b** remaining was fully deuterated but had only 42:58 or 74:26 er (*R*:*S*), respectively (entries 19 and 20). Deuteration of lithiated (*R*)-**5l** after only 5 min with CD_3OD or $(CD_3)_2SO$ returned material with 89:11 or 88:12 er (*R*:*S*) after accounting for incomplete lithiation (entries 21 and 22). These observations suggest that, while *rearrangement* of **8** is stereospecific, *reprotonation* of **8** is not, with stereospecificity dependent on protonating agent: methanol protonates **8b** with a slight preference for inversion, while DMSO protonates with a 3:1 preference for retention.[12]

Overall, the three-step sequence of urea synthesis, rearrangement, and urea cleavage amounts to a stereospecific electrophilic arylation of α-methylbenzylamines and thus provides a powerful way of making otherwise inaccessible enantiomerically pure amines bearing heavily substituted chiral substituents.

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Supporting Information Available: X-ray crystallography data for **10p**. Experimental and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For a discussion of the effect of HMPA and DMPU on dearomatizing cyclization reactions of benzyllithiums, see: (a) Ahmed, A.; Clayden, J.; Yasin, S. A. *Chem. Commun.* **1999**, 231. (b) Clayden, J.; Knowles, F. E.; Menet, C. J. *Synlett* **2003**, 1701.

(9) Comparison of Table 1, entries 2 and 3, shows that when both urea nitrogen atoms bear an aryl substituent ring location and not ring substitution determines which rearranges.

(10) Tertiary organolithiums α to nitrogen are generally configurationally stable over periods of minutes to hours at −78 °C (Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561) and acyl transfers in α-methylbenzyl carbamates are stereospecific (Hara, O.; Ito, M.; Hamada, Y. *Tetrahedron Lett.* **1998**, *39*, 5537). For a discussion, see: Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: New York, 2002; pp 193−194.

(11) Tertiary organolithiums α to nitrogen seem to *alkylate* with inversion but *acylate* with retention (see ref 10a and ref 10c, pp 252−253). Although the reaction we present here may be formalized as a kind of [1,4]-aza-Wittig rearrangement, we have not pursued this interpretation first because of evidence for a dearomatized intermediate **9** and second because Wittig rearrangements usually proceed with *inversion* at a chiral organolithium center (see ref 10c, pp 247−249 and 346−360).

(12) Protonation/deuteration reactions of benzylic organolithiums are in general retentive; see ref 10c, p 249, and: (a) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J.-F.; Normant, J.-F. *Chem.—Eur. J.* **1999**, *5*, 2055. For related examples of diastereoselectivity of protonation varying with proton source, see: (b) Rein, K.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211. (c) Meyers A. I.; Dickman, D. I. *J. Am. Chem. Soc.* **1987**, *109*, 1263. **8l** has a greater propensity to protonate with retention, but loss of er on protonation is still significant.

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