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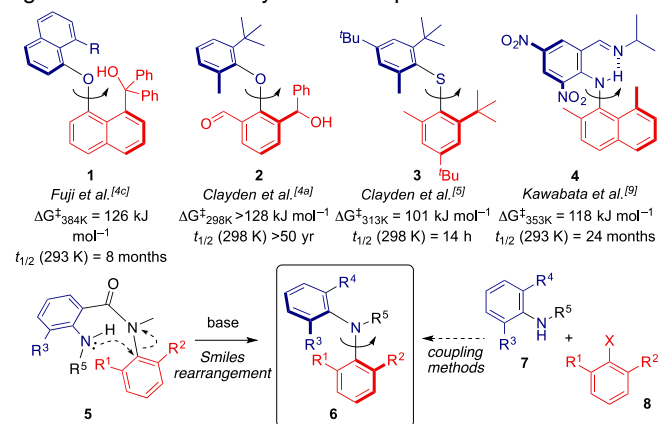
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Heavily Substituted Atropisomeric Diarylamines by Unactivated Smiles Rearrangement of *N*-Aryl Anthranilamides

Romain Costil, Harvey J. A. Dale, Natalie Fey, George Whitcombe, Johnathan V. Matlock*, Jonathan Clayden*^[a]

Abstract: Diarylamines find use as metal ligands and as structural components of drug molecules, and are commonly made by metal catalyzed C–N coupling. However, the limited tolerance to steric hindrance of these couplings restricts the synthetic availability of more substituted diarylamines. Here we report a remarkable variant of the Smiles rearrangement that employs readily accessible *N*-aryl anthranilamides as precursors to diarylamines. Conformational predisposition of the anthranilamide starting material brings the aryl rings into proximity and allows the rearrangement to take place despite the absence of electron-withdrawing substituents, and even with sterically encumbered doubly *ortho*-substituted substrates. Some of the diarylamine products are resolvable into atropisomeric enantiomers, and are the first simple diarylamines to display atropisomerism.

Atropisomers form a pivotal class of chiral ligands for asymmetric catalysis,^[1] are found in many families of natural products,^[2] and are of emerging importance in medicinal chemistry.^[3] Although the stereochemistry of most atropisomers derives from slow rotation about a C–C single bond, C–O,^[4] C–S^[5] and C–N atropisomers are also known,^[6] and they too show great promise as new families of ligands or as medicinally active compounds.



Scheme 1. Atropisomerism in diaryl ethers, sulfides and amines.

The diarylamine motif is a privileged pharmacophore, present in major drugs such as the analgesic diclofenac and the diuretic torasemide.^[7] Diarylamines have also been used

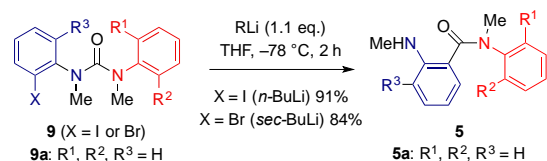
as a scaffold for the design of a variety of XNY pincer ligands and have found application in a variety of metal-catalyzed reactions.^[8] Nonetheless, despite the existence of atropisomeric diaryl ethers **1** and **2** and diaryl sulfides **3**, the potential for atropisomerism in diarylamines has hardly been explored. In 2009, Kawabata reported the atropisomeric diarylamine **4**, chiral by virtue of a rotationally restricted C–N axis,^[9] in which an intramolecular hydrogen bond maintains the planarity of the nitro-substituted ring. We now report the first example of an unelaborated diarylamine atropisomer **6**, whose synthesis was made possible by the discovery of a remarkable unactivated Smiles rearrangement of anthranilamides **5**. This rearrangement allows the construction of diarylamines with exceptionally high steric hindrance.

Stable C–O or C–S stereogenic axes in diarylethers and diarylsulfides require 2,6-disubstitution on both aryl rings to create rotational barriers sufficiently high that separable atropisomers exist.^[4a, 5] Expecting similar steric demands in atropisomeric diarylamines, we sought synthetic methods allowing the construction of Ar–N bonds between 2,6-disubstituted anilines **7** and 2,6-disubstituted coupling partners **8** (Scheme 1). The challenging *N*-arylations of 2,6-disubstituted anilines by 2,6-substituted aryl halides (which require specialist ligands and techniques^[10]) and the lack of generality in structures available by nucleophilic aromatic substitution (S_NAr) reactions prompted us to explore an alternative approach to **6**.

Smiles rearrangement allows *N*-arylation, under basic conditions, of amides,^[11] carbamates,^[12] anilines^[13] and indoles.^[14] The classical Smiles rearrangement proceeds by intramolecular S_NAr :^[13, 15] an activated, electron-deficient aryl ring migrates from O or S to N, with the heteroatoms in a 1,4-^[11a-c, 15d] or 1,5-relationship.^[11d, 14, 15a, 16] However, recent explorations of N to C aryl migrations in ureas,^[17] have suggested that conformational preorganization^[18] may promote intramolecular S_NAr reactions of even unactivated or electron-rich rings. *N*-Methylated benzaniilides related to **5** prefer conformations in which the aryl rings lie *cis*,^[19] and anthranilamide **5a** was made to test the possibility that intramolecular *N*-arylation might proceed in such a compound by Smiles rearrangement, even of an unactivated ring.^[20]

The gram-scale synthesis of **5a** was achieved by applying Snieckus' conditions for the 'anionic *ortho*-Fries' rearrangement of carbamates^[21, 22] to urea^[23] **9a**. Treatment of **9a** (X = I and Br) with *n*- or *sec*-butyllithium gave anthranilamide **5a** in excellent yield (Scheme 2, see SI for optimization table). The same approach was used to provide a number of other anthranilamide substrates for further Smiles rearrangements (see SI for details).

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Scheme 2. Anthranilamides by anionic *ortho*-Fries rearrangement of ureas.

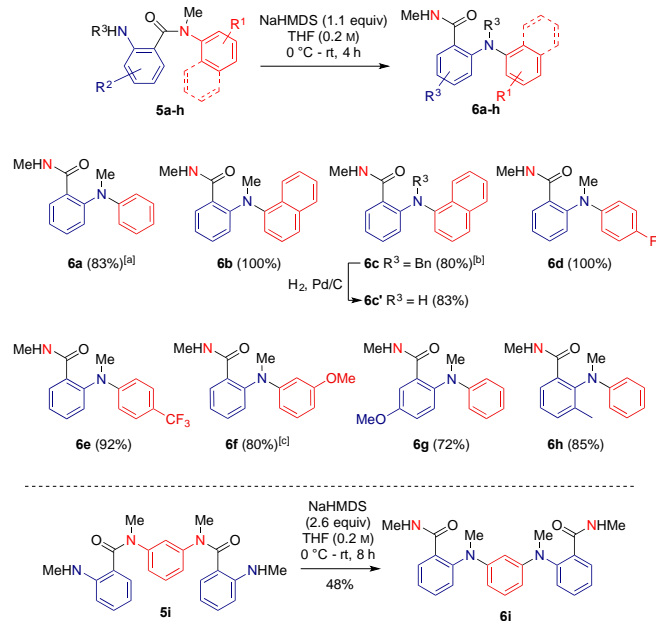
Model substrate **5a** was subjected to the range of bases shown in Table 1 (entries 1-7). Smiles rearrangement to diarylamine **6a** occurred in good to excellent yields under several different sets of conditions, with sodium hexamethyldisilazide at 20 °C providing the best yields (entry 4). KHMDS (entry 5) performed slightly less well, and LiHMDS required heating to 66 °C to give comparable yields (entries 2, 3). The weaker bases KO t -Bu and Cs $_2$ CO $_3$ still promoted rearrangement, but in substantially lower yield. The migration of the aryl ring from the amide to the aniline nitrogen to form a diarylamine was confirmed by $^3\text{J}_{\text{C-H}}$ *N*-methyl HMBC correlations to two quaternary aromatic carbon atoms. This correlation, along with the appearance of the $^3\text{J}_{\text{NH-CH}}$ coupling in the amide group, was used to confirm the structures of the products isolated from subsequent Smiles rearrangements (see SI).

Table 1. Optimisation of the Smiles rearrangement.^[a]

Entry	Base ^[b]	Temp. (°C)	Time (h)	Conversion of 5a (%) ^[c]	Yield 6a (%) ^[c]
1	<i>n</i> -BuLi	20	3	0	0
2	LiHMDS	20	4	25	6
3	LiHMDS	66	16	>95	70
4	NaHMDS	20	4	>95	87, 86 ^[d]
5	KHMDS	20	4	>95	57
6	KO t -Bu	20	4	86	21
7	Cs $_2$ CO $_3$ ^[e]	80	16	44	19
8	<i>n</i> -BuLi + DMPU ^[f]	20	3	85	48
9	LiHMDS + DMPU ^[f]	20	4	>95	83

[a] Optimisation was carried out on a 0.2 mmol scale. [b] Temperature of deprotonation: *n*-BuLi was added at -78 °C, LiHMDS/KHMDS/NaHMDS were added at 0 °C and KO t -Bu/Cs $_2$ CO $_3$ were added at 20 °C. *n*-BuLi (1.44 m in hexanes), KHMDS (1.0 m in THF) = potassium bis(trimethylsilyl)amide, NaHMDS (1.0 m in THF) = sodium bis(trimethylsilyl)amide, LiHMDS (1.0 m in THF) = lithium bis(trimethylsilyl)amide, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone. [c] Calculated using 1,3,5-trimethoxybenzene as an internal standard. [d] Isolated yield. [e] *N,N*-dimethylformamide as solvent. [f] DMPU (5.0 equiv.) added at 20 °C.

The Smiles rearrangement of **5a** to **6a** has two notable features. Firstly, rather than the more common oxygen or sulfur-based leaving group, the reaction proceeds by substitution of an amide nitrogen atom.^[24] Secondly, and most significantly, **5a** has no electronic activation of the migrating phenyl ring: typical Smiles rearrangements require an activated migrating aryl ring carrying an *ortho*- or *para*-electron withdrawing group^[13] to promote intramolecular S $_N$ Ar. This insensitivity to the electronic nature of the migrating ring turned out to be a general feature of Smiles rearrangements of related anthranilamides. Excellent to quantitative yields of diarylamines were obtained for a range of substrates **5b-i** (Scheme 3) irrespective of whether the migrating ring was electron-deficient (e.g. **6e**) or electron-rich (e.g. **6f**). With a *para*-methoxyphenyl migrating ring (the *para* regioisomer of **6f**) the migration failed, with products from amide hydrolysis instead being isolated. Changing the amide nitrogen substituent to Bn allowed the secondary diarylamine **6c'** to be formed by hydrogenolysis of **6c**, although **5c** required heating to reflux in order to effect rearrangement in good yield. The straightforward incorporation of substituents into the anthranilamide ring made the *para*-OMe-substituted and *ortho*-Me-substituted diarylamines **6g** and **6h** readily accessible. Double Smiles rearrangement of **5i** was used to prepare **6i** in good yield, demonstrating the potential of the method for the synthesis of extended arylamine structures.



Scheme 3. Smiles rearrangement of variously substituted anthranilamides. [a] Prepared on 1.4 g scale; [b] Heated to reflux for 24 h. This reaction failed with R 3 = *t*-Bu; [c] This reaction failed with the MeO in the *para* position.

The remarkable ease with which this Smiles rearrangement occurs, even with electron-rich rings, along with the evident importance of the metal counteraction (particularly Na $^+$ vs Li $^+$: see Table 1, entries 4 and 2) prompted us to explore possible reaction pathways computationally, using density functional theory (DFT). Pathways for the rearrangement of deprotonated **5a** to **6a** mediated by (a) a lithium counteraction coordinated to two molecules of THF solvent, or a sodium counteraction coordinated to (b) two (entry 2) or

(c) three (entry 3) molecules of THF solvent were compared.^[25]

We found that the smaller lithium cation can form a very stable chelate (Li_A Figure S1) requiring considerable conformational change to access a conformer that is competent for the rearrangement reaction (Li_B). Calculations suggest that the larger sodium cation can accommodate an additional solvent molecule in its coordination sphere, but even assuming the same coordination of two THF molecules, the sodium-mediated reaction is thermodynamically and kinetically more favourable than the lithium-mediated reaction. Coordination to Na⁺ is weaker than to Li⁺ in the chelating conformer Na_B, facilitating access to the transition state by rotation around the C-C(=O) bond. A single transition state for a concerted reaction could be located for the lithium-mediated reaction (Li_TS1), whereas with sodium the reaction proceeds in two steps, by way of a high-energy intermediate with near-symmetrical C-N bonding distances to the migrating phenyl group (Na_C) (Figure 1). Despite the lack of anion-stabilising substituents, this intermediate has some characteristics of the 'Meisenheimer' intermediate of a classical S_NAr reaction, with localized single and double bonds and a substantially more negative NBO charge on the migrating ring (from Na_B +0.2 to -0.3 in Na_C).^[25]

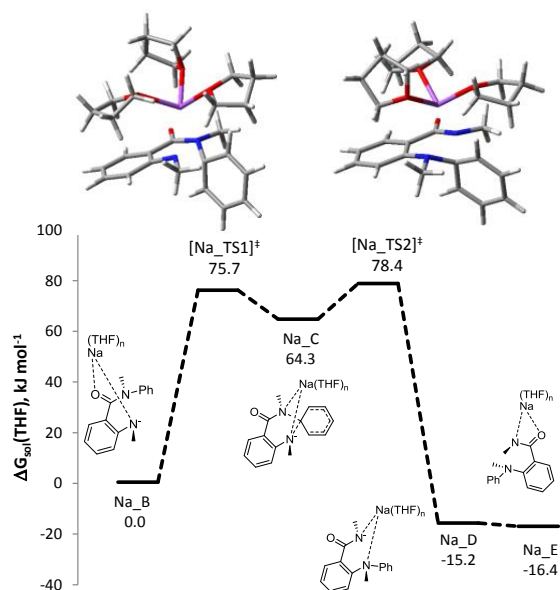
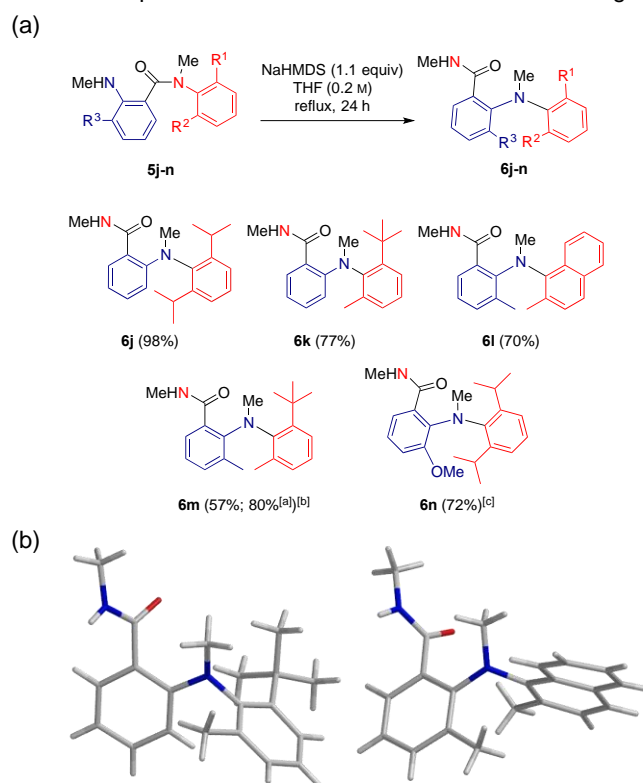


Figure 1: Energy profile for the Na(THF)₃ pathway, along with key calculated geometries. See supporting information for structural data.

The computational results suggest that destabilisation of the lithium chelate by a coordinating ligand might increase reactivity in lithium-mediated reactions. Adding the powerful lithium-coordinating co-solvent DMPU to the reactions in Table 1, entries 8 and 9, did indeed substantially improve the yield of **6a**.^[26] The use of a lithium counterion in the Smiles rearrangement also raised the possibility that both the anionic *ortho*-Fries rearrangement used to make the starting materials and the Smiles rearrangement could be carried out under the same strongly basic conditions, with a lithium counterion. This approach succeeded in some cases, but

was less than optimal: **6b** was formed in 58% yield on treatment of **9b** with *n*-BuLi at -78 °C followed by DMPU, while under equivalent conditions **6c** was formed in 25% yield and **6a** only in trace quantities.

This electronically versatile Smiles rearrangement turned out also to be remarkably insensitive to steric bulk. The substituted anthranilamides **5j-n** were prepared, and each was treated with base. Although the reactions were slower than those of their less hindered congeners, all were successfully transformed into diarylamine products **6j-n** (Scheme 4) having remarkably high levels of steric encumbrance about the central N atom. X-ray crystal structures of **6k** and **6l** showed bond angles around this nitrogen atom of *ca.* 360°, indicating a planar nitrogen atom whose lone pair is delocalized into the anthranilamide ring.

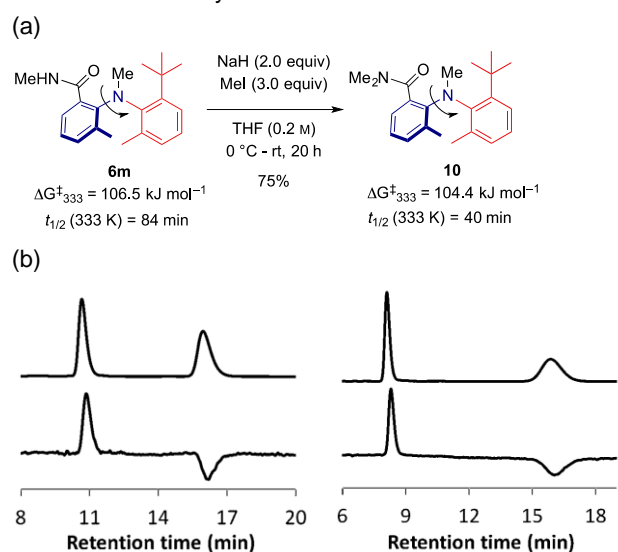


Scheme 4. (a) Smiles rearrangement leading to sterically encumbered diarylamines; (b) X-ray crystal structures of **6k** and **6l** (CCDC deposition numbers 1557197 and 1557204). ^[a]Yield based on recovered starting material. ^[b]Reaction time: 96 h. ^[c]Reaction conditions: 150 °C (μw), 16 h.

The steric hindrance around the central nitrogen atom of **6j-n** is comparable to that of related atropisomeric diaryl ethers and sulfides (Scheme 1),^[4a, 5] raising the possibility that these compounds may provide the first structurally simple examples of chiral, atropisomeric diarylamines. Amine **6j** showed in its room temperature ¹H NMR spectrum two well-resolved CHMe₂ doublets which did not coalesce even at 100 °C in toluene-*d*₈. An EXSY experiment allowed us to estimate the barrier to rotation about the (red) Ar-N bond to be 79 kJ mol⁻¹ at 25 °C, suggesting that atropisomeric diamines could be accessible with greater steric hindrance around the central nitrogen. Indeed, HPLC of **6k** showed two resolved enantiomers using a chiral stationary phase at 0 °C. The four different *ortho* substituents^[4a] of **6l** and **6m** were the

key feature leading to atropisomerism. The enantiomers of diarylamine **6m** were resolved by HPLC, and by following the first order decay of enantiomeric excess we evaluated a barrier to C–N rotation of 106.5 kJ mol⁻¹ at 333 K in toluene (Scheme 5, see SI for details).

The only previous example of an atropisomeric diarylamine **4** featured an intramolecular hydrogen bond, locking rotation about one of the Ar–N bonds.^[9] To confirm that the atropisomerism of **6m** results solely from steric hindrance and not intramolecular hydrogen bonding, compound **10** was made by alkylation of the secondary amide of **6m**. As a result, the barrier to rotation decreased only marginally to 104.4 kJ mol⁻¹. By contrast, methylation of **4** reduced the barrier to rotation by 15.5 kJ mol⁻¹.^[9b]



Scheme 5. (a) Atropisomeric diarylamines **6m** and **10** and (b) their resolution by HPLC on chiral stationary phase (Chiralpak OD-H, eluent 95:5 hexane–isopropanol, 1.0 mL/min. UV detector above; optical rotation detector below).

In conclusion, sterically hindered diarylamines can display atropisomerism as a consequence of restricted rotation around highly encumbered Ar–N bonds. Both hindered and unhindered diarylamines may be made using an unprecedentedly versatile Smiles rearrangement in which the migrating ring requires no electronic activation. This transition metal-free route to diarylamines is particularly remarkable for its tolerance of a range of functionalities and its compatibility even with the very hindered aryl rings, and provides a valuable alternative to metal-catalysed coupling chemistry for the synthesis of challenging diarylamines.

Acknowledgements

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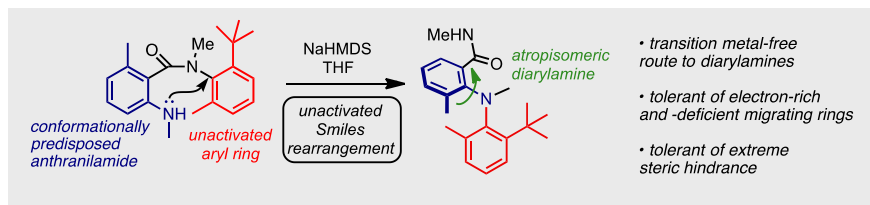
Keywords: diarylamine • Smiles rearrangement • atropisomer

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- [25] Full computational details, including a discussion of different coordination environments of the metal cations, may be found in the supporting information.
- [26] The use of a lithium counterion in the Smiles rearrangement also raised the possibility that both the anionic *ortho*-Fries rearrangement used to make the starting materials and the subsequent Smiles rearrangement could be carried out in tandem under the same strongly basic conditions with a lithium counterion. This approach succeeded in some cases, but was less than optimal: **6b** was formed in 58% yield on treatment of **9b** with *n*-BuLi at $-78\text{ }^{\circ}\text{C}$ followed by DMPU (5 equiv., warming to rt), while under equivalent conditions **6c** was formed in 25% yield and **6a** only in trace quantities.

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COMMUNICATION



Smiles rearrangement of conformationally predisposed anthranilamides provides a valuable method for the synthesis of diarylamines, even with unactivated or heavily substituted migrating rings.

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