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Enantiomerically enriched atropisomeric *N,N′*-diaryl ureas by oxidative kinetic resolution of their 2-sulfanyl derivatives

Jonathan Clayden *, Hazel Turner

School of Chemistry, University of Manchester, Oxford Rd., Manchester M13 9PL, UK

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ABSTRACT

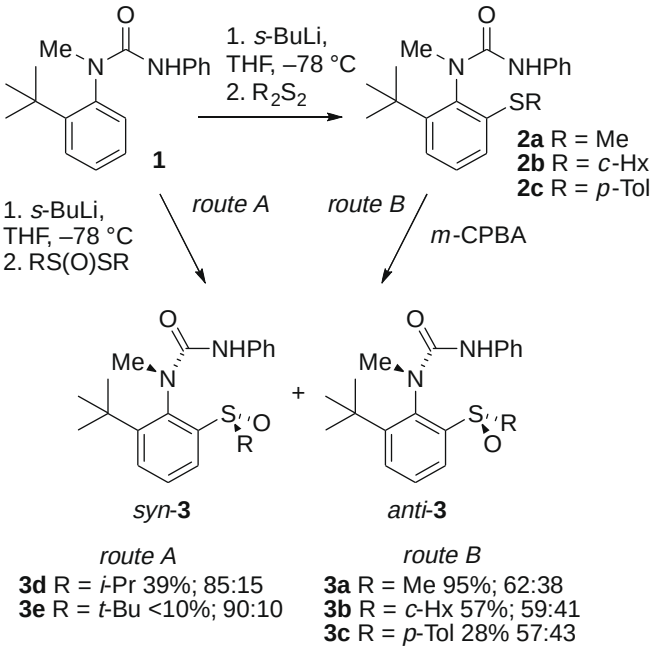
Atropisomeric *N*-methyl-*N,N′*-diaryl ureas may be obtained in enantiomerically enriched form by oxidative kinetic resolution of their sulfide derivatives. The atropisomeric sulfides may be obtained in up to 97:3 er and display high stability to racemisation (half-lives at 25 °C of up to 500 years). Unlike related fully alkylated ureas, the product sulfoxides exhibit relatively weak thermodynamic conformational selectivity.

The last 50 years has seen biaryl atropisomers emerge as a class of compounds rich in utility for the development of valuable chiral ligands and chiral catalysts.[1] More recently, families of atropisomers based on structures other than biaryls[2] have come to the fore as potential new sources of such structures, and atropisomeric anilides, benzamides and naphthamides have been used as chiral ligands, catalysts, auxiliaries and starting materials.[3,4]

The conformational properties of aryl ureas prompted us to investigate them as a further potential class of atropisomers, and we recently reported that hindered ureas not only display atropisomerism,[5] but also show high diastereoselectivity in their reactions.[6] Moreover, their rich lithiation chemistry makes their derivatisation and conversion to other related compound classes particularly straightforward.[7,8]

This work was all carried out in the racemic series, and in order to widen the potential utility of atropisomeric ureas, we sought a method for their asymmetric synthesis. Non-classical resolution methods have been particularly successful when applied to non-biaryl atropisomers,[9–12] and in this Letter, we report the first asymmetric synthesis of atropisomeric ureas, using the strategy of kinetic resolution.

We have previously made use of dynamic resolution under thermodynamic control for the asymmetric synthesis of atropisomeric amides[4,10,13] and ethers,[11] and in a preliminary attempt to extend our methods employing sulfoxide controlling groups to atropisomeric ureas, we synthesised the sulfoxides *syn*- and *anti*-**3a–e** by ortholithiation[7] of urea **1**, either quenching the lithio derivative directly with a thiosulfinate ester RS(O)SR[11] or by first forming the sulfide **2** then oxidising to the sulfoxide (Scheme 1). Mixtures of diastereoisomers of **3** were formed in the ratios indicated.



Scheme 1. Kinetic diastereoselectivity in the formation of sulfinyl-substituted 2-*t*-butyl ureas. Yields are from **1**.

Diastereoisomeric ratios were greater when **3** was made by Route A, but yields were low. Ratios obtained by oxidation with *m*-CPBA were poor, and remained unchanged on heating in refluxing toluene for extended periods of time (>24 h). We therefore assume that these product ratios represent selectivity under kinetic control, with the steric encumbrance of the *t*-butyl substituent

* Corresponding author.
E-mail address: j.p.clayden@manchester.ac.uk (J. Clayden).

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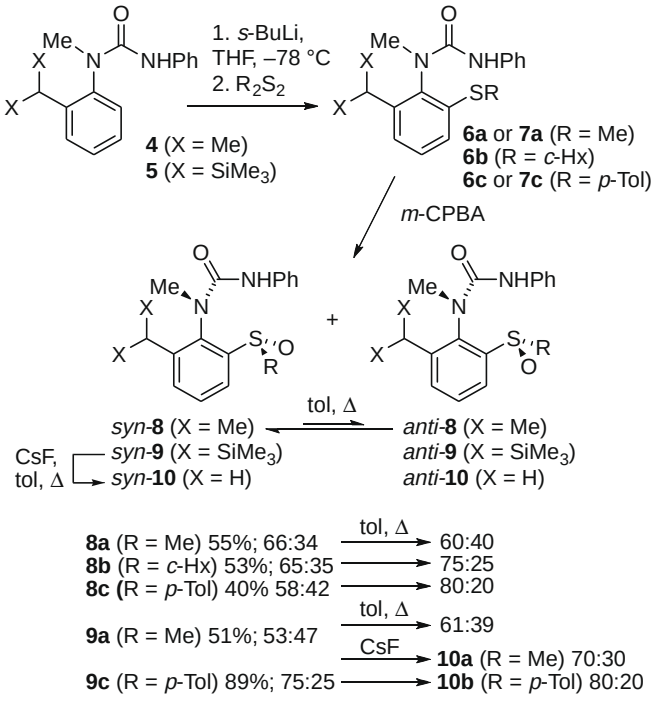
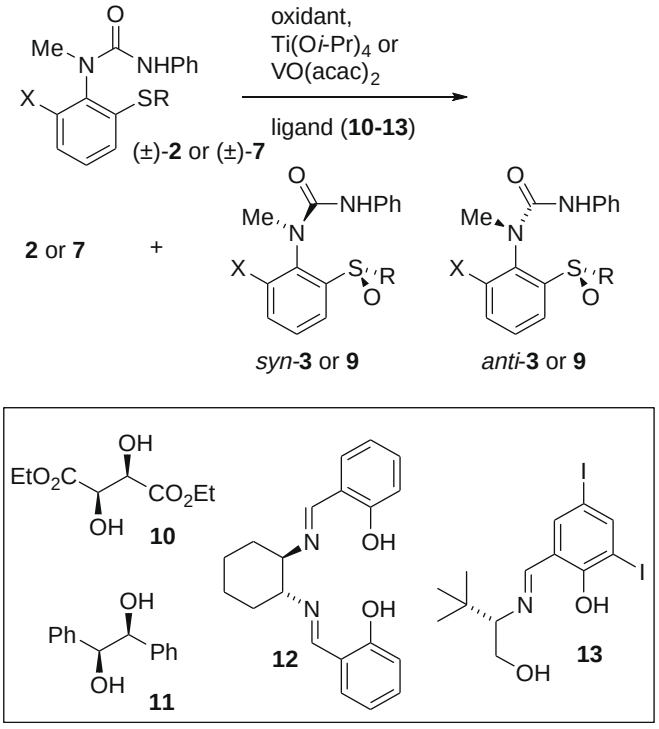


Scheme 2. Kinetic and thermodynamic diastereoselectivity in the formation of sulfinyl-substituted ureas. Yields are from **4** or **5**.



Scheme 3. Kinetic resolution of 2-sulfanyl ureas.[1]

presenting a large barrier to Ar–N rotation and consequent epimerisation.[14]

Given previous successes with asymmetric synthesis by dynamic resolution under thermodynamic control,[4,9–11,13] we next investigated oxidation of the less hindered analogues **6a–c** and **7a, c** made from the ureas **4** and **5**. The structure of **5** was chosen on the basis that the silyl groups would assist selectivity for ortholithiation to yield **7**,[15] and would also allow simpler methyl substituted derivatives to be formed later by desilylation. On oxidation of **6** or **7**, mixtures of diastereoisomeric sulfoxides **8a–c** and **9a, c** were initially obtained with low selectivity. However, on this occasion heating **8a, 8b** and **8c** in refluxing toluene led to epimerisation to a 1.5:1–4:1 mixture of diastereoisomers (Scheme 2), with a clear dependence of the ratio on the size of R. Desilylation of **9a** and **9c** with caesium fluoride in refluxing toluene returned the methyl substituted sulfoxides **10a** and **10c** likewise with relatively poor thermodynamic selectivity.

The diastereoisomers of **8a** were separated by chromatography, and an Eyring analysis of the change in *anti*:*syn* ratio of **8a** with time at 65 °C in toluene allowed us to deduce a barrier to epimerisation by N–Ar rotation $\Delta G^{\ddagger}_{\text{epim}} = 114\ \text{kJ mol}^{-1}$ for *syn*-**6a** and 117 kJ mol^{-1} for *anti*-**6a**.[16] These figures are broadly in accord with barriers to rotation of related compounds.[5]

2-Sulfinyl derivatives **3**, **8** and **9** of these *N*-alkyl-*N*,*N*′-diarylureas evidently display relatively poor thermodynamic selectivity, making dynamic resolution under thermodynamic control using sulfoxide substituents an unsuitable method for their asymmetric synthesis. Instead, we therefore turned to asymmetric oxidation of **2** or **7** as a potential method for kinetic resolution (Scheme 3). Trial oxidations of **2a** were attempted with peroxides in the presence of one of four ligands **10-13**[17] and the results are detailed in Table 1, entries 1–5. High diastereoselectivity in the oxidation was obtained by vanadium-catalysed oxidation with the (*S*)-*tert*-leucinol derived imine ligand **10**,[17i] and despite the presence of 1.2 equiv oxidant, this reaction which reached no further than 50% completion and also provided the major product diastereoisomer *anti*-**3a** in good enantiomeric excess. The remaining sulfide **2a** was isolated from this reaction in 30% yield and with 97:3 er, constituting the first isolation of an enantiomerically enriched atropisomeric urea (entry 5). From these results, we calculate[18] a selectivity factor (*S* factor) of >300 for kinetic resolution of **2a**.[14]

A similar kinetic resolution occurred when **2b** was used as a starting material: *anti*-**3b** was formed with good diastereoselectivity and with good er, but it was not possible to determine the er of the remaining starting material (entry 6). In contrast, *p*-tolylsulfide **2c** (entry 7) oxidised slowly and unselectively under these conditions (*S* factor = 2). An alternative methylsulfide, **7a**, was also oxidised selectively (*S* factor = 8) to give remaining **7a** in good er when driven to 63% completion (entry 8).

Incubation of recovered (+)-**2a** in toluene at 110 °C, resulted in slow first order loss of enantiomeric purity with time, and an Eyring analysis[16] of the decay allowed us to determine a barrier to racemisation $\Delta G^{\ddagger}_{\text{rac}} = 132\ \text{kJ mol}^{-1}$, corresponding to an estimated[19] half-life for racemisation at 25 °C of 500 years (Scheme 4).

Similar treatment of (+)-**7a** led to much faster racemisation: at 65 °C racemisation was almost complete within three days, and analysis for the decay gave $\Delta G^{\ddagger}_{\text{rac}} = 112\ \text{kJ mol}^{-1}$, corresponding to an estimated half-life for racemisation at 25 °C of 8 weeks. Removal of the silyl groups from (+)-**5a** with CsF in refluxing toluene returned a 2-methyl substituted urea but in racemic form, presumably because the barrier to racemisation is even lower.

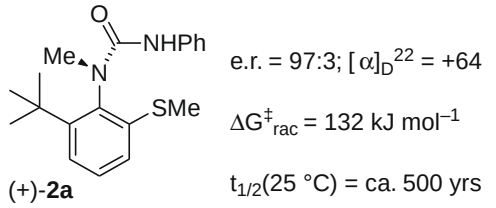
It is interesting that the thermodynamically determined conformational selectivities observed for sulfinyl-substituted *N*-alkyl-*N*,*N*′-diaryl ureas **3**, **8**, **9** and **10** are significantly poorer than those reported previously for (synthetically less versatile) *N*,*N*′-dialkyl-*N*,*N*′-diaryl ureas.[20] Indeed, when we methylated the mixture of atropisomers **10b** we observed, after equilibration, an increase in the ratio of conformers from 80:20 to

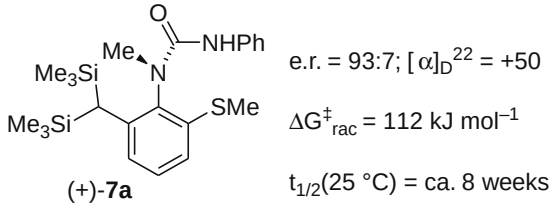
[1] For identity of X, see Table 1.

Table 1
Kinetic resolution in the oxidation of sulfanyl ureas under the conditions of Scheme 3

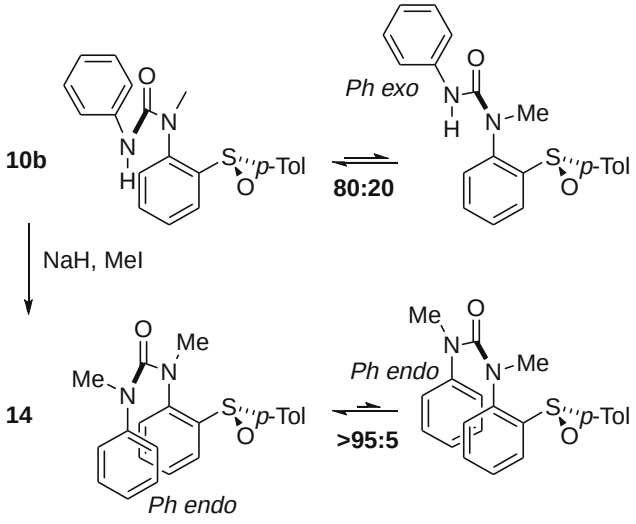
Entry	S.M.	X=	R=	Catalyst	Oxidant, equiv	Extent of reaction (%)	er remaining S.M	Product, ratio *syn*:*anti*	er of *syn* sulfoxide	Cacld *S* factor
1	**2a**	*t*-Bu	Me	**10** + $Ti(Oi\text{-}Pr)_4$	*t*-BuOOH, 2	81	—	**3a**, 33:67	—	—
2	**2a**	*t*-Bu	Me	**10** + $Ti(Oi\text{-}Pr)_4$	$PhMe_2COOH$, 2	79	—	**3a**, 38:62	—	—
3	**2a**	*t*-Bu	Me	**11** + $Ti(Oi\text{-}Pr)_4$	*t*-BuOOH, 2	41	—	**3a**, 46:54	—	—
4	**2a**	*t*-Bu	Me	**12** + $VO(acac)_2$	H_2O_2, 2	39	—	**3a**, 58:42	—	–
5	**2a**	*t*-Bu	Me	**13** + $VO(acac)_2$	H_2O_2, 1.2	49	97:3[a]	**3a**, 95:5	86:14	300
6	**2b**	*t*-Bu	*c*-Hx	**13** + $VO(acac)_2$	H_2O_2, 1.2	43	—	**3b**, 84:13	89:11	—
7	**2c**	*t*-Bu	*p*-Tol	**13** + $VO(acac)_2$	H_2O_2, 2.4	24	55:45	**3c**, 55:45	—	2
8	**7a**	$(Me_3Si)_2CH$	Me	**13** + $VO(acac)_2$	H_2O_2, 1.2	63	93:7[b]	**9a**, 59:41	—	8

[a] Isolated in 30% yield.
[b] Isolated in 25% yield.





Scheme 4. Kinetic stability of atropisomeric ureas. Absolute stereochemistry assumed *P* as shown, but unconfirmed: see Ref. 14.



Scheme 5. Contrasting N–CO and N–Ar thermodynamic conformational selectivities in differently substituted ureas.

>95:5 (Scheme 5). We assume this outcome is due to the contrasting conformations of the two classes of urea: X-ray crystal structures and NMR suggest that 'NH' ureas **3**, **8**, **9** and **10** adopt an 'exo' conformation shown in Scheme 5, while fully alkylated *N,N′*-diaryl ureas such as **14** are known to prefer an "endo" conformation (as shown in Scheme 5),[5,21] which places the sulfinyl substituent in a more hindered environment and thus leads to higher selectivity.

In summary, we present the first method for the asymmetric synthesis of atropisomeric ureas, employing kinetic resolution of a sulfide. Stable atropisomeric ureas were obtained in up to 97:3 er.

Acknowledgements

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14. We have been unable to determine with complete certainty the relative or absolute stereochemistry of the compounds in this Letter, but from the known conformational preference of related ureas (see Ref. 20) we deduce *syn* stereochemistry for the more thermodynamically stable of each pair of sulfoxides. The major product of *m*-CPBA oxidation turns out also to be the more stable, where both were determined. Absolute stereochemistry is deduced from the fact that (*S*)-**13** gives (*S*) sulfoxides (Ref. 17i), and if the *syn* (=*M, S*) sulfoxide is formed faster the remaining sulfanylurea should be *P*.
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