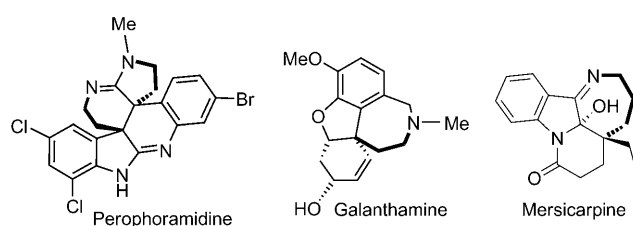


## Catalytic Enantio- and Diastereoselective Alkylations with Cyclic Sulfamides\*\*

Thomas A. Moss, Beatriz Alonso, David R. Fenwick, and Darren J. Dixon\*

The enantioselective construction of derivatives of  $\gamma$ -amino butyric acid and  $\delta$ -amino pentanoic acid from simple starting materials using asymmetric catalysis provides convenient access to a range of structurally diverse natural products, pharmaceutical compounds, and potential building blocks for  $\gamma$ -peptides and foldamer chemistry.<sup>[1]</sup> Several natural products containing the aminoethylene and aminopropylene scaffolds attached to a quaternary stereocenter have been isolated. Developments in the field of enantioselective Michael



additions of carbonyl compounds to nitroolefins and acrylonitriles have been significant, with highly enantioselective examples reported in both cases.<sup>[2,3]</sup>

We recognized that structures containing aminoethylene or aminopropylene moieties could be accessed rapidly and stereoselectively if suitable two-carbon or three-carbon nitrogen-containing electrophiles could be utilized. To this end, we recently described both the base-catalyzed,<sup>[4a]</sup> and the phase-transfer catalyzed enantio- and diastereoselective<sup>[4b]</sup> ring-opening reactions of nitrogen-protected aziridines as a method for the direct construction of  $\gamma$ -amino butyric acid derivatives. During the course of that study, we found that sulfonyl protection of the nitrogen atom was necessary to achieve acceptable levels of reactivity. Although the sulfonyl

group could be cleaved under mild conditions in some cases, we believed that a method which encompassed a wider range of nitrogen-protecting groups would be more desirable. Furthermore, access to the aminopropylene unit ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{NHP}$ ) remained elusive. Anticipating that azetidines would lack the required reactivity to be used as three-carbon electrophiles,<sup>[5]</sup> we considered cyclic sulfamides as potential two- or three-carbon electrophile candidates.<sup>[6,7]</sup> Seminal work by Lubell and Wei<sup>[8]</sup> and extensive studies by Gallagher and co-workers<sup>[9,10]</sup> have found that five-membered and six-membered cyclic sulfamides are useful precursors for the synthesis of pyrrolidine and piperidinone alkaloids. In those studies, methylene carbon acids were typically used as the nucleophile, with chiral enantiopure electrophiles. To the best of our knowledge, there have been no reports of a catalytic enantioselective nucleophilic ring-opening of cyclic sulfamides with carbon-centered nucleophiles, despite the synthetic advantages of such an approach. We reasoned that a base-catalyzed reaction would be challenging, owing to the low basicity of sulfamic acid salts that can be formed from the ring opening of cyclic sulfamides. Accordingly, we believed that an enantioselective ring-opening of cyclic sulfamides could be realized using asymmetric phase-transfer catalysis with a stoichiometric base.<sup>[11,12]</sup> Attracted by the simplicity of the approach, and the synthetic potential of the methodology, we began our investigations. Herein, we report our findings into the direct enantioselective catalytic alkylation reaction of methine pro-nucleophiles with *N*-protected five-membered and six-membered cyclic sulfamides. Extension of the procedure to include diastereoselective variants is also described.

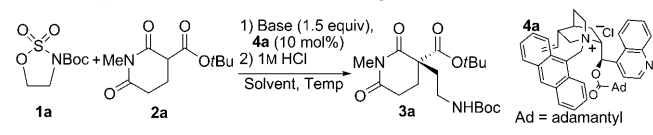
Preliminary studies were carried out using *N*-Boc-protected cyclic sulfamide **1a** and *tert*-butyl-1-methyl-2,5-dioxopiperidine-3-carboxylate (**2a**) as a representative pro-nucleophile (Boc = *tert*-butoxycarbonyl). Pleasingly, complete consumption of the pro-nucleophile was observed after 24 h at room temperature when powdered  $\text{Cs}_2\text{CO}_3$  was used as the base and tetrabutylammonium bromide (TBAB) as the catalyst (Table 1, entry 1). Lower conversions were generally observed when aqueous base mixtures were employed (for example, Table 1, entry 2); in these cases a larger excess of electrophile was required for completion of the reaction, which is presumably due to partial hydrolysis of the electrophile in the aqueous phase. As expected, when the phase-transfer catalyst was omitted, reactivity was significantly reduced (Table 1, entry 3). Interestingly, very low conversions were observed when solid  $\text{K}_2\text{CO}_3$  or  $\text{K}_3\text{PO}_4$  were used as the base (Table 1, entries 4 and 5), highlighting the importance of cesium carbonate in this reaction. Cinchona-derived phase-transfer catalyst **4a**,<sup>[13]</sup> which we have

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**Table 1:** Optimization studies on **2a** using **1a**


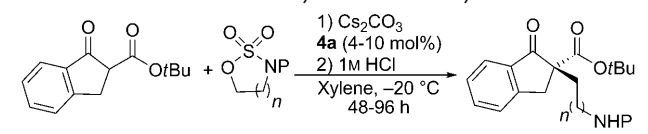
Entry	Solvent	T [°C]	Conversion 48 h	Base	Catalyst (mol %)	ee [%]
1	9:1 Tol/ CHCl <sub>3</sub>	25	100	Cs <sub>2</sub> CO <sub>3</sub>	TBAB (10)	0
2	9:1 Tol/ CHCl <sub>3</sub>	25	80	50% aq Cs <sub>2</sub> CO <sub>3</sub>	TBAB (10)	0
3	9:1 Tol/ CHCl <sub>3</sub>	25	35	Cs <sub>2</sub> CO <sub>3</sub>	-	0
4	9:1 Tol/ CHCl <sub>3</sub>	25	< 10	K <sub>2</sub> CO <sub>3</sub>	TBAB (10)	0
5	9:1 Tol/ CHCl <sub>3</sub>	25	< 10	K <sub>3</sub> PO <sub>4</sub>	TBAB (10)	0
6	9:1 Tol/ CHCl <sub>3</sub>	0	60	Cs <sub>2</sub> CO <sub>3</sub>	<b>4a</b> (10)	78
7	Toluene	0	57	Cs <sub>2</sub> CO <sub>3</sub>	<b>4a</b> (10)	81
8	9:1 Xy/ CHCl <sub>3</sub>	0	58	Cs <sub>2</sub> CO <sub>3</sub>	<b>4a</b> (10)	80
9	Xylene	0	54	Cs <sub>2</sub> CO <sub>3</sub>	<b>4a</b> (10)	85
10	Xylene	0	41	Cs <sub>2</sub> CO <sub>3</sub>	<b>4a</b> (5)	84
11	Xylene	0	30	Cs <sub>2</sub> CO <sub>3</sub>	<b>4a</b> (2.5)	79

[a] Reactions were performed on a 0.4 mmol scale in 2 mL of solvent. Conversion determined by <sup>1</sup>H NMR spectroscopy. Enantiomeric excess determined by HPLC analysis using a Chiralpak AD column.

previously reported as giving high levels of enantiocontrol in aziridine ring-opening reactions,<sup>[4b]</sup> performed well, giving alkylation adduct **3a** following acidic workup in 78% *ee* (Table 1, entry 6). Less-polar solvents were more successful for high levels of enantiocontrol; for example, xylene gave an 85% *ee* (Table 1, entry 9). Catalyst loading could be dropped to 2.5 mol% without considerably affecting enantioinduction (Table 1, entry 11), although reaction rates were decreased. Accordingly, and for convenience, further reactions were conducted at 10 mol% catalyst loading.

With the optimal reaction conditions established, we sought to probe the scope of nitrogen-protecting groups that are amenable to this procedure (Table 2). In this case, representative pro-nucleophile *tert*-butylindanone carboxylate (**2b**) was treated under mild phase-transfer conditions with five-membered and six-membered cyclic sulfamidates that bore a range of nitrogen-protecting groups (**1a–1e**). Carbamate-protected (Table 2, entries 1 and 2), sulfonyl-protected (Table 2, entry 3) and phosphonate-protected (Table 2, entry 4) electrophiles were screened, and in every case but one, a highly stereoselective alkylation was observed (up to 96% *ee*) following mild acid hydrolysis. In some cases, competitive oxygen alkylation also occurred (Table 2, entries 1, 2, 4, 5). We were pleased to observe that the six-membered electrophile **1e** (Table 2, entry 5) gave an alkylation adduct containing the protected aminopropylene scaffold in 65% yield and in an excellent 92% *ee*; this opens up a potential route to a wide spectrum of potential synthetic targets. To test the scale-up potential of our methodology, *tert*-butyl indanone carboxylate **2b** was reacted with sulfamidate

**Table 2:** Enantioselective ring-opening of various *N*-protected cyclic sulfamidates **1a–1e** with *tert*-butylindanone carboxylate **2b**.



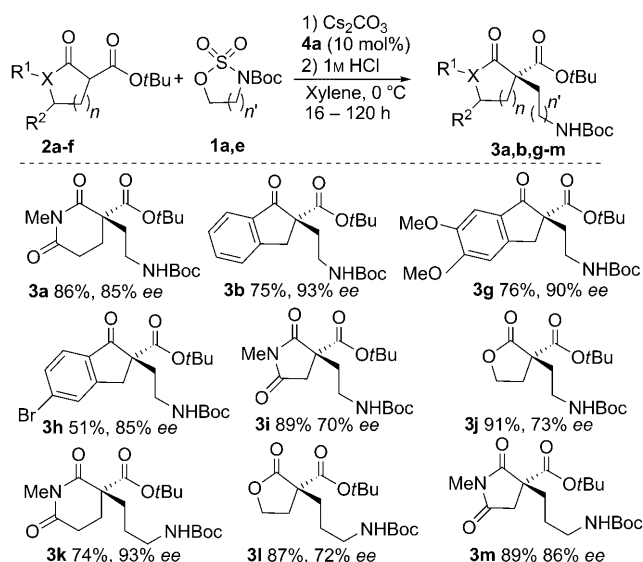
Entry	PG	<i>n</i>	<b>3</b>	Yield [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	Boc	1 ( <b>1a</b> )	<b>b</b>	75 (18)	93
2	Cbz	1 ( <b>1b</b> )	<b>c</b>	54 (31)	94
3 <sup>[c]</sup>	<i>o</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>	1 ( <b>1c</b> )	<b>d</b>	80	96 <sup>[d]</sup>
4	PO(OEt) <sub>2</sub>	1 ( <b>1d</b> )	<b>e</b>	55 (33)	45
5	Boc	2 ( <b>1e</b> )	<b>f</b>	65 (20)	92

[a] Yield of isolated product (yield of isolated oxygen alkylation adduct shown in parentheses). [b] Determined by HPLC analysis. [c] Reaction performed at 0°C due to low solubility of the electrophile. [d] > 99% *ee* after recrystallization; absolute stereochemistry determined by single crystal X-ray crystallography (see the Supporting Information).<sup>[14]</sup> PG = protecting group, Cbz = carboxybenzyl.

**1a** on a gram-quantity scale and at reduced catalyst loading (4 mol%). Pleasingly, after 24 h at 0°C the alkylation adduct was obtained in 65% yield and in 82% *ee* (see the Supporting Information for details).

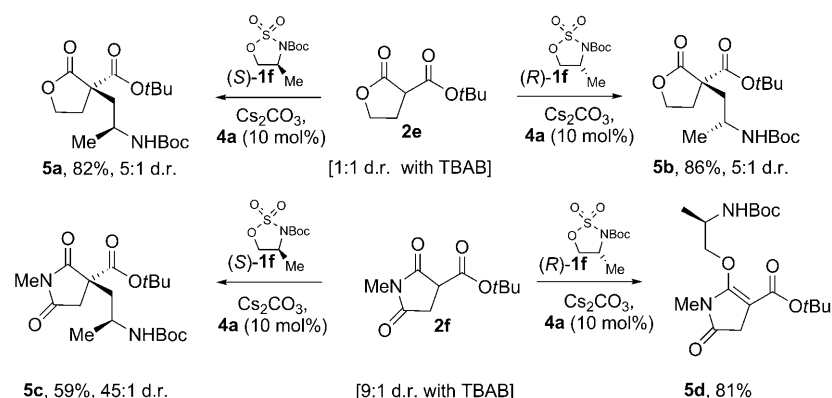
The scope of the reaction with respect to the pro-nucleophile was then investigated. Previous reports<sup>[4b,c,13]</sup> have shown that cinchona-derived phase-transfer catalyst **4a** reacts well with cyclic β-keto esters bearing a *tert*-butyl ester substituent. Wanting to expand the synthetic utility of the reaction, we subjected various cyclic<sup>[15]</sup> pro-nucleophiles to our optimal reaction conditions. Pleasingly, good to high enantioselectivities<sup>[16]</sup> were observed for a range of both five-membered and six-membered cyclic systems, several of which are novel substrates in asymmetric phase-transfer catalysis. Substituents were introduced onto the indanone scaffold (Scheme 1, **3g** and **3h**) without considerably affecting stereoinduction (90 and 85% *ee*, respectively; cf. **3b**, 93% *ee*). Succinimide (**3i** and **3m**) and lactone (**3j** and **3l**) pro-nucleophiles performed well, giving the alkylation products in high yields (87–91%) and in up to 86% *ee*. As has been previously demonstrated, glutarimide-derived pro-nucleophile **2a** was an effective substrate, affording high levels of stereoinduction; when **1e** was used as the electrophile, the product **3k** was obtained in good yield and in an impressive 93% *ee*. The variety of ring sizes tolerated for both the nucleophile and electrophile reactants, along with the mild reaction conditions, allows for the facile synthesis of a diverse range of products, with generally good stereocontrol (Scheme 1).

To extend the procedure to diastereoselective reactions, we employed enantiopure cyclic sulfamidates as electrophiles. Using alanine as a convenient source of chirality, both enantiomers of sulfamidate **1f** were synthesized in the hope of observing “matched” and “mismatched” combinations of substrate and catalyst control. Using achiral phase-transfer catalyst TBAB, substrate control from (*S*)-alanine-derived sulfamidate electrophile (*S*)-**1f** was found to be highly nucleophile dependent,<sup>[17,18]</sup> varying from poor with lactone



**Scheme 1.** The enantioselective ring opening of unsubstituted cyclic sulfamidates by asymmetric phase-transfer catalysis. Reactions performed on a 0.4 mmol scale in 2 mL xylene. ee determined by HPLC analysis. For **3h**, the reaction was performed at –20 °C in 2 mL of a 9:1 Xylene/ $\text{CHCl}_3$  solution (see the Supporting Information).

**2e** (1:1 d.r.), to good with succinimide **2f** (9:1 d.r.; Scheme 2). Lactone-derived pro-nucleophile **2e**, which had displayed no substrate control with TBAB, afforded diastereomeric alky-

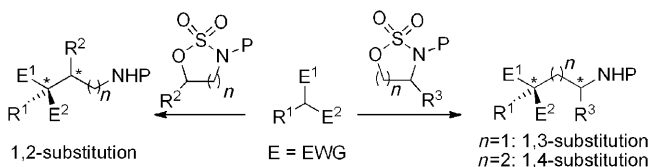


**Scheme 2.** The diastereoselective ring opening of chiral cyclic sulfamidates by phase-transfer catalysis. Reactions were performed on a 0.4 mmol scale in 2 mL xylene. For the complete catalyst screen, see the Supporting Information. The relative stereochemistry of **5c** was determined by X-ray crystallography.

lation adducts **5a** and **5b** with catalyst **4a** in high yields, and in a moderate 5:1 d.r. in both cases. This level of diastereoselectivity was anticipated in light of the enantioselective alkylation result (Scheme 1). With succinimide pro-nucleophile **2f**, the matched pair of **4a** with sulfamidate (*S*)-**1f** resulted in excellent diastereoselection towards **5c** (45:1 d.r.) and a minor amount of *O*-alkylation side-product, whereas, interestingly, the mismatched pair of **4a** with sulfamidate (*R*)-**1f** afforded the *O*-alkylation product **5d** almost exclusively (Scheme 2). The relative stereochemistry of **5c** was unambig-

uously assigned by single crystal X-ray diffraction (see the Supporting Information for details).<sup>[14]</sup>

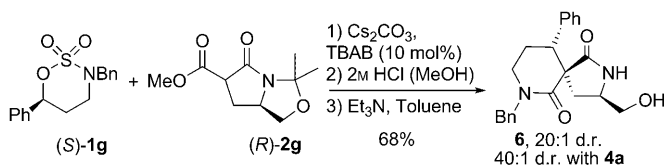
The ring-opening reaction of substituted cyclic sulfamidates is known to be completely regioselective.<sup>[6]</sup> Exploiting this, alkylation products which have 1,2- or 1,3-substitution patterns could be accessed depending on the position of the substituent on the sulfamidate ring. Having established that C2-substituted cyclic sulfamidates were reactive, C1-substituted analogues were then investigated (Scheme 3).



**Scheme 3.** Divergent synthetic strategies available from cyclic sulfamidate electrophiles. EWG = electron withdrawing group.

Accordingly, chiral sulfamidate **1g** was synthesized both as a racemate and as the single (*S*)-enantiomer. We chose chiral pro-nucleophile (*R*)-**2g** as a model system, with the intention of obtaining a measure of substrate control from the nucleophile. Pleasingly, treatment of (*R*)-**2g** with one equivalent of sulfamidate (*S*)-**1g** in the presence of a catalytic amount of TBAB and cesium carbonate for 24 h at 40 °C, followed by acid hydrolysis and thermal lactamization (as demonstrated by Gallagher and co-workers),<sup>[9,10]</sup> afforded the deprotected spirolactam **6** in good yield and in 20:1 d.r. Pleasingly, the use of catalyst **4a** improved the diastereoselectivity of the reaction to 40:1, this suggested a “matched” pairing of nucleophile and catalyst (Scheme 4). When the pseudo-enantiomer of catalyst **4a** was used, lactam **6** was obtained in a lower 10:1 d.r. (see the Supporting Information).<sup>[19]</sup>

In conclusion, we have developed the first enantioselective phase-transfer-catalyzed ring-opening of five-membered and six-membered cyclic sulfamidates. Under mild conditions, good to excellent selectivities have been obtained for a range of electrophiles and several novel pro-nucleophile systems. Using single enantiomer cyclic sulfamidates, moderate to high catalyst controlled diastereoselectivities can be observed. Finally, functionalized spirolact-



**Scheme 4.** Nucleophile-controlled and phase-transfer-catalyst-controlled alkylation/lactamization.

tams have been synthesized using this procedure. Further work to probe the scope of this method and its application in total synthesis is currently ongoing and will be reported in due course.

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- [14] CCDC 753701 (**3d**) and 753702 (**5c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- [15] Subjection of acyclic pro-nucleophile *tert*-butyl-2-methylacetoacetate to our optimal conditions resulted in a 2:3 inseparable mixture of *O*- and *C*-alkylated products, respectively.
- [16] The stereochemistry of indanone adducts **3b**, **3c**, **3e–3h** were assigned by analogy to compound **3d** (absolute configuration determined by X-ray crystallography). Compounds **3j** and **3l** were assigned by analogy to the cyclopentanone system (see Ref. [13c]). Succinimide products **3i** and **3m** were assigned by analogy to compound **5c** in the matched system with (*S*)-**1f** and catalyst **4a** (relative configuration determined by X-ray crystallography). Glutarimide adducts **3a** and **3k** were assigned by analogy to the succinimide, and cyclohexanone systems (Ref. [13]).
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