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Catalytic Asymmetric Alkylation Reactions for the Construction of Protected Ethylene-Amino and Propylene-Amino Motifs Attached to Quaternary Stereocentres

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Abstract: An efficient catalytic and stereoselective method for the direct construction of protected ethylene-amino and propylene-amino scaffolds attached to quaternary stereocentres is reported. Preliminary investigations revealed a mild base catalysed nucleophilic ring opening of *N*-sulfonyl aziridines using the commercially available phosphazene base 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) was possible and resulted in highly efficient alkylation reactions with a range of methine carbon acids. This reaction could be rendered highly asymmetric (up to 97% *ee*) by employing phase-transfer catalysis to control stereoinduction. Incorporation of alkyl substituents onto the aziridine electrophile, resulted in a highly diastereoselective (up to 30:1 d.r.) variant of this methodology. A further extension using N-protected cyclic sulfamidates as the electrophilic component was successful with a range of pro-nucleophiles (up to 96% *ee* and 45:1 d.r.) and allowed a range of nitrogen protecting groups (carbamate, sulfonyl, phosphonyl, benzyl) to be incorporated into the alkylation adducts. Finally, the utility of the products have been demonstrated in the synthesis of useful heterocycles and compounds bearing structural components of natural products.

Keywords: alkylation · asymmetric synthesis · aziridines · phase-transfer catalysis · sulfamidates

Introduction

Compounds containing the ethylene-amino and propylene-amino group attached to a stereogenic quaternary carbon[1] are widespread amongst natural products (Figure 1), and

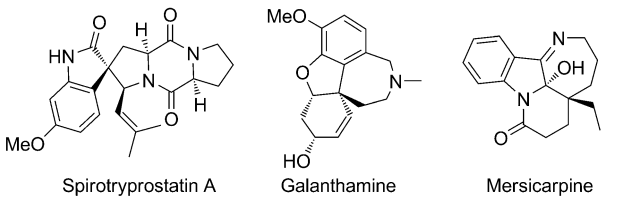

Figure 1. Natural products containing the ethylene-amino and propylene-amino scaffolds bonded to a quaternary carbon.

form the basis of potential building blocks for γ-peptides and foldamer chemistry.[2] Despite its prevalence, there is a dearth of methods to introduce this important structural motif catalytically and asymmetrically. To this end, developments in the field of enantioselective Michael additions of carbonyl compounds to nitro-olefins and acrylonitriles have been significant with highly enantioselective examples known in both cases.[3,4] The impressive bioactivities of many of these compounds encouraged us to investigate a synthetic strategy that was simple in concept but broad in applicability. We recognised a synthetically powerful route to these compounds could involve a catalytic, and potentially enantioselective alkylation reaction of a carbon acid with a protected amino ethylene synthon, such as an N-protected aziridine.[5] Furthermore, such a reaction would install directly a protected amino group and allow γ-substituents to be incorporated into the produced γ-amino acid backbone.

Results and Discussion

Base catalysed alkylation using aziridines: Our synthetic strategy (Scheme 1) required the base catalysed addition of various pro-nucleophiles **1** to a suitably protected form of aziridine **2**. The proposed alkylation reaction would afford the desired products **3** in a quick and efficient manner, whilst also using relatively simple starting materials. *N*-Substituted aziridines have previously been employed as mildly electrophilic reagents for the homologation of a range of carbon and heteroatom nucleophiles. Their simple synthesis

Scheme 1. Concept of a catalysed aziridine ring opening reaction.

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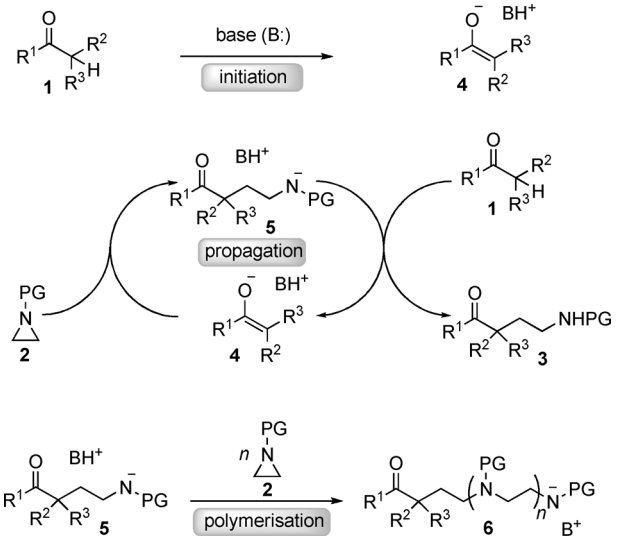
from readily available and inexpensive commercial materials,[6] as well as their ease of handling makes them important synthetic building blocks. Due to their modest reactivity, and ability to polymerise under certain reaction conditions, the synthetic community has focused on using harsh reagents when using aziridine electrophiles. These include stoichiometric amounts of organometallics or reactive metal enolates when employing a carbon-centred nucleophile. Exceptionally little attention has been dedicated to finding mild and catalytic conditions for the ring opening of protected aziridine precursors.[7,8] It should be noted that until this study, there were no reports of using carbon acids under base catalysed conditions to facilitate the ring opening of aziridines, enantioselective or otherwise.[5]

For the proposed reaction to be catalytic in base, the reactivity of the aziridine electrophile and the pK_a values of all the reaction components is critical; following the union of aziridine **2** with carbanion **4**, the resulting adduct **5** must be basic enough to deprotonate another molecule of pro-nucleophile **1**, thus completing the catalytic cycle (Scheme 2).

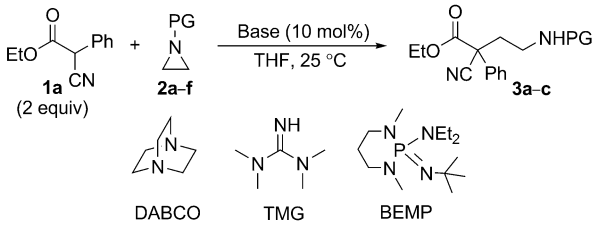


Scheme 2. Initiation, propagation and polymerisation pathways in the base catalysed alkylation of carbon acids with aziridine electrophiles.

As adduct **5** is also nucleophilic at the nitrogen atom, the equilibrium must favour carbanion **4** to suppress the possible polymerisation pathway of aziridine **2**. We postulated that by careful choice of aziridine N-protecting group, pro-nucleophile and base catalyst, a mild aziridine alkylation reaction would be possible using base catalysis. Preliminary studies using a range of *N*-sulfonyl aziridines (**2a–f**) with ethyl phenylcyanoacetate **1a** as a representative pro-nucleophile were performed to assess the feasibility of our concept (Table 1). Using catalytic DABCO, the alkylation adduct **3a** was furnished in an encouraging 69% yield, but only after 72 h at 25°C (Table 1, entry 1). To address the need for higher reactivity, we screened more basic catalytic systems. TMG afforded the product in an improved yield and shortened reaction time (Table 1, entry 2). Employing the even more basic phosphazene reagent BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine)[9] led to almost quantitative formation of product **3a** in 19 h at 25°C (Table 1, entry 3). *N*-*p*-Nosyl aziridine (**2d**) was found to have poor solubility whilst *N*-diethylphosphonate aziridine (**2e**) was unreactive under our conditions; both gave no observable alkylation products. Interestingly, when the *o*-(trifluoromethyl)benzenesulfonyl aziridine (**2f**) was used as the electrophile under base catalysed conditions, only polymerisation products were obtained (Table 1, entry 8). The various reaction pathways presented in Scheme 2 can rationalise this observation. If the ring opened adduct **5** is reasonably stable (as one could envisage due to the *ortho* placement of the trifluoromethyl group on the arylsulfonyl protecting group), then proton transfer between adduct **5** and the parent acid **1** is disrupted, thus allowing the polymerisation of the aziridine to become the dominant reaction pathway. Successful alkylation using the carbamate protected aziridine **2c** was observed, however, the reaction was prohibitively slow (Table 1, entry 5). Despite the long reaction time, no significant polymerisation of aziridine **2c** was observed, this suggests that proton transfer in the catalytic cycle was fast, the lethargic reaction presumably being caused by the weaker inductive activation of the carbamate protected aziridine in comparison to its sulfonyl analogues. The reaction efficiency was further enhanced when *N*-mesitylsulfonyl aziridine (**2b**) was employed (Table 1, entry 4), possibly due to a suppression of the aziridine polymerisation pathway through steric effects. Overall, the optimal conditions employed aziridine **2b** (1 equiv), pro-nucleophile **1a** (2 equiv) with BEMP (10 mol%) in THF at 25°C.

With the optimal conditions in hand, the scope of the aziridine alkylation reaction was probed by modifying the pro-

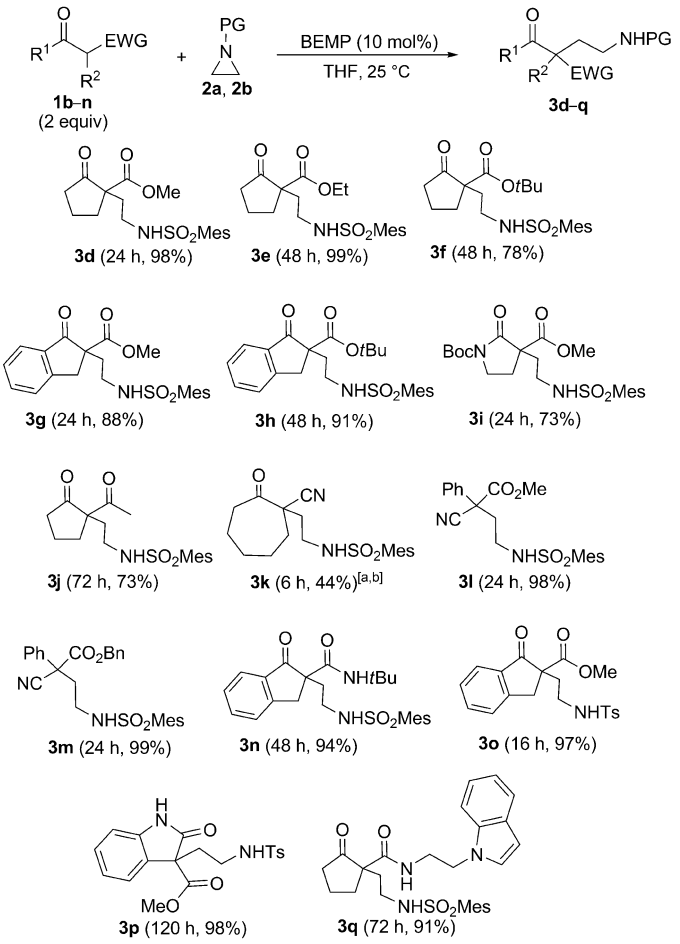
Table 1. Preliminary studies into a base catalysed alkylation of ethyl phenylcyanoacetate **1a**.



Entry[a]	PG	Base	*t* [h]	Product	Yield [%][b]
1	*p*-tosyl (**2a**)	DABCO	72	**3a**	69
2	*p*-tosyl (**2a**)	TMG	36	**3a**	83
3	*p*-tosyl (**2a**)	BEMP	19	**3a**	93
4	SO_2Mes (**2b**)	BEMP	24	**3b**	98
5	Cbz (**2c**)	BEMP	672	**3c**	83
6	*p*-nosyl (**2d**)	BEMP	24	–	0[c,d]
7	$PO(OEt)_2$ (**2e**)	BEMP	168	–	0[d]
8	*o*-$CF_3C_6H_4SO_2$ (**2f**)	BEMP	1	–	0[e]

[a] Reactions were performed on a 0.36 mmol scale in THF (0.8 mL) at 25°C. [b] Isolated yield after purification. [c] Aziridine **2d** was insoluble in THF at 25°C. [d] No reaction occurred. [e] Polymeric products were obtained.

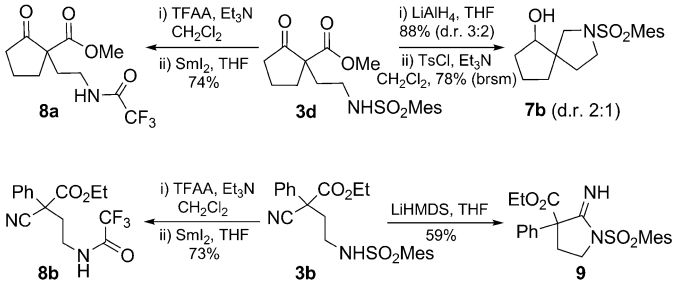
nucleophile coupling partner. A range of carbonyl compounds **1b–n** including esters, lactams, acetates and nitriles, in addition to cyanoacetates, amides and oxindoles were screened. Pleasingly, the nature of the electron withdrawing substituent had little bearing on the reaction, with acetates, amides, nitriles and a range of esters all reacting efficiently (Scheme 3). Yields ranged from 73–99% and in many cases



Scheme 3. Base catalysed alkylation reactions with *N*-sulfonyl aziridines **2a** and **2b**. Reactions were performed on a 0.36 mmol scale in THF (0.8 mL) at 25°C. Isolated yield after purification. [a] Reaction was performed at 65°C. [b] 23% Oxygen-alkylation product was isolated.

were quantitative, with the exception of **3k** (44%); in this case appreciable oxygen-alkylation was also observed when conducting the reaction at 65°C. Pleasingly, oxindole nucleophiles reacted efficiently furnishing the product **3p** in 98% yield. Other reactive functional groups, such as the indole substituted **3q**, did not affect the chemical yield (91%).

With the scope of the reaction established, the synthetic potential of the alkylation products was investigated (Scheme 4). Firstly, adducts **3d** and **3b** were synthesised on gram scale with no reduction in chemical yield. Direct lactamisation of cyclic derivatives, such as **3d**, proved to be challenging, however, azaspirocycles could be accessed in a



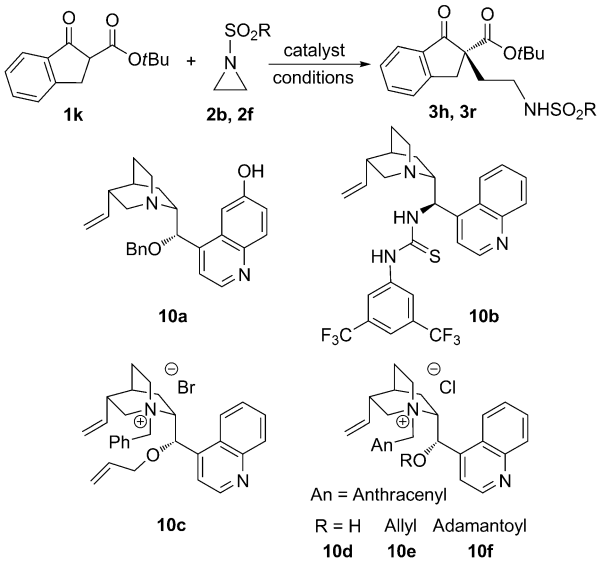
Scheme 4. Manipulation of alkylation adducts **3d** and **3b**.

two-step process; first by reduction of **3d** to the corresponding diol **7a**, which was then transformed into the N-protected spiro adduct **7b** (d.r. 2:1) by a one-pot tosylation/cyclisation reaction. Cyclisation of acyclic adducts was somewhat more facile; treatment of cyanoacetate **3b** with LiHMDS resulted in smooth cyclisation onto the nitrile affording functionalised amidine **9** in good yield.

Sulfonamide protecting groups are notoriously difficult to cleave, but as sulfonyl protection was necessary for acceptable levels of reactivity, we began investigations into its cleavage under non-destructive conditions. Of the various methods reported,[10] we found the trifluoroacetamide exchange protocol of Moussa and Romo to be the most productive (Scheme 4). Subjection of adducts **3b** and **3d** to a one-pot activation/cleavage reaction using TFAA and SmI_2,[11] resulted in smooth substitution of the sulfonamide protecting group to the synthetically useful trifluoroacetamide protected compounds **8a** and **8b** in good yields (74 and 73%, respectively).

Enantioselective alkylation using aziridines: The construction of enantioenriched γ-amino butyric acid derivatives through the nucleophilic ring opening of aziridines is a barely explored field,[5] and thus with parameters for a base catalysed reaction established,[12] we next sought to develop an asymmetric variant of our methodology. Preliminary studies were conducted using *N*-mesitylsulfonyl aziridine (**2b**) and *tert*-butyl indanone carboxylate **1k** as a representative pro-nucleophile (Table 2). Initially, we screened for activity in the alkylation reaction using the bifunctional cinchona derived catalysts **10a** and **10b** (Table 2, entries 1 and 2).[13] Pleasingly, at room temperature, using CH_2Cl_2 as solvent, both catalysts **10a** and **10b** were observed to afford the desired adduct **3h**. However, the reactions were found to be prohibitively slow with only 15% conversion (Table 2, entry 1) and 10% conversion (Table 2, entry 2) after 48 h. The alkylation adducts were also obtained in low enantioselectivity (10 and 6% *ee*, respectively). This led us to conclude that aziridines bearing a *N*-sulfonyl protecting group were unsuitable electrophiles for use with the bifunctional organocatalysts **10a** and **10b**. In an attempt to enhance the reactivity of the alkylation reaction, we screened a variety of bases in conjunction with a selection of phase-transfer catalysts (**10c–f**).[14–17] Initially, pro-nucleophile **1k** was treated with aziridine **2b** using 10 mol% of phase-transfer cata-

Table 2. Preliminary studies into the enantioselective alkylation of *tert*-butyl indanone carboxylate **1k** with aziridine electrophiles.



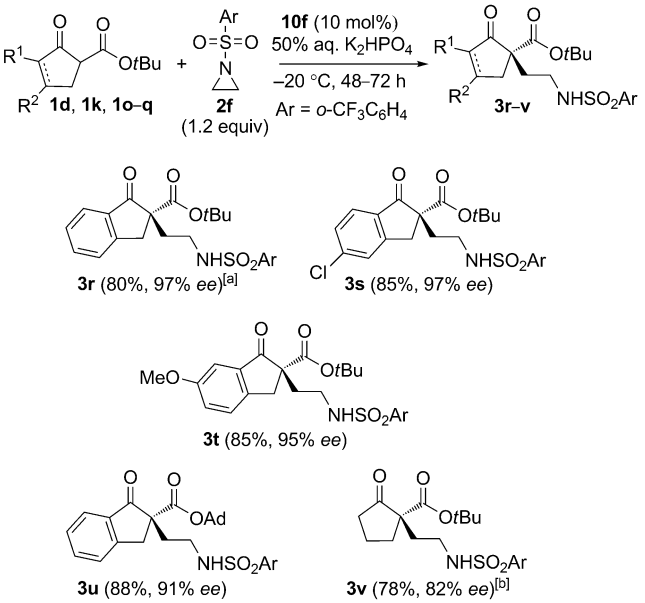
Entry[a]	Aziridine	Cat.	Conditions[b]	Conv.[c]	*ee* [%][d]
1	**2b**	**10a**	RT, CH_2Cl_2	15	10
2	**2b**	**10b**	RT, CH_2Cl_2	10	6
3	**2b**	**10f**	BEMP (10 mol%), RT	100	33
4	**2b**	**10f**	50% aq. Cs_2CO_3, RT	35	91
5	**2f**	**10c**	50% aq. Cs_2CO_3, 0°C	100	24
6	**2f**	**10d**	50% aq. Cs_2CO_3, 0°C	80	21
7	**2f**	**10e**	50% aq. Cs_2CO_3, 0°C	100	51
8	**2f**	**10f**	50% aq. Cs_2CO_3, 0°C	100	94
9	**2f**	**10f**	50% aq. Cs_2CO_3, −20°C	100	95
10	**2f**	**10f**	50% aq. K_2HPO_4, −20°C	100[e]	97
11	**2f**	**10f**	50% aq. K_3PO_4, −20°C	100	86

[a] Reactions were performed on a 0.13 mmol scale. [b] Entries 4–11 were performed with base (1.5 equiv) and catalyst (10 mol%) in toluene/$CHCl_3$ (9:1, 1.0 mL). [c] Determined by ^1H NMR spectroscopy after 48 h. [d] Determined by HPLC analysis. [e] Conversion after 72 h.

lyst **10f**[18] in the presence of 10 mol% BEMP,[17] and indanone adduct **3h** was afforded in an encouraging 33% *ee* (Table 2, entry 3). Anticipating a prevalent background reaction using the strongly basic BEMP, we opted to use the more mildly basic Cs_2CO_3 as a 50% aq. solution. Gratifyingly, the alkylation reaction was found to have excellent stereocontrol, forming adduct **3h** in 91% *ee* (Table 2, entry 4), although the reaction was slow (35% conversion after 2 days).

The ability to tune the reactivity of the electrophilic aziridine motif by judicious choice of the N-protecting group adds to the versatility of aziridine chemistry. By modifying the mesityl protected aziridine **2b** to the *o*-(trifluoromethyl) benzenesulfonyl substituted aziridine **2f**, a dramatic increase in reactivity was observed, with complete conversion to alkylation adduct **3r** in 48 h at 0°C whilst also exhibiting excellent enantioselectivity (94% *ee*; Table 2, entry 8). The *o*-(trifluoromethyl)benzenesulfonyl protecting group offers significant advantages over other sulfonamide groups commonly employed to protect aziridines. These 2-carbon electrophiles are highly reactive compared to *N*-*p*-tosyl protected aziridines, they do not suffer from low solubility and are stable at room temperature, whereas more reactive systems such as *N*-triflimide aziridines are known to be susceptible to self-polymerisation. In a screen of various cinchona alkaloid-derived phase-transfer catalysts (**10c–f**; Table 2, entries 5–8), **10f** bearing the bulky adamantoyl ester was found to be the most selective affording the alkylation adduct **3r** in good yield, and in 94% *ee* when the reaction was conducted at 0°C with 50% aq. Cs_2CO_3 as the base. A slight increase in the selectivity of the alkylation was observed by cooling the reaction mixture to −20°C (95% *ee*; Table 2, entry 9). A further enhancement of stereocontrol was found when using a milder 50% aq. K_2HPO_4 solution as the base (97% *ee*; Table 2, entry 10). Conversely, when the more strongly basic 50% aq. K_3PO_4 solution was used, reduced reaction times but diminished enantioselectivity was observed (86% *ee*; Table 2, entry 11).

With optimal conditions in hand, the scope of the reaction was then probed (Scheme 5). A range of substituted indanone pro-nucleophiles bearing bulky ester moieties were



Scheme 5. Enantioselective ring opening of unsubstituted aziridines with phase-transfer catalyst **10f**. Reactions were performed on a 0.13 mmol scale in toluene/$CHCl_3$ (9:1, 1 mL) at −20°C. Isolated yield after purification. Enantiomeric excess was determined by HPLC analysis. [a] For deprotection of **3r**, see the Supporting Information. [b] Reaction was performed at 0°C using 50% aq. Cs_2CO_3 as the base.

subjected to the alkylation conditions, with high enantioselectivities and good yields being obtained in all cases (91–97% *ee*; **3r–u**). The indanone pro-nucleophile could easily tolerate both electron-withdrawing (**3s**, 85%, 97% *ee*) and electron-donating (**3t**, 85%, 95% *ee*) substituents on the aromatic ring. The *tert*-butyl ester group could also be exchanged for the bulky adamantly group with only a small decrease in enantioselectivity. *tert*-Butyl cyclopentanone carboxylate was also found to be a good substrate leading to

the alkylated product **3v** in good yield and enantiomeric excess (78%, 82% *ee*) when using 50% aq. Cs_2CO_3 at 0°C. In order to determine the absolute stereochemistry imparted by phase-transfer catalyst **10f**, the reaction between *tert*-butyl indanone carboxylate **1k** and aziridine **2f** was scaled up and the product **3r** recrystallised (>99% *ee*). Single crystal X-ray analysis revealed the absolute stereochemistry of **3r** to be *S*, which was consistent with the stereochemical outcomes for related systems (Figure 2).[18] Accordingly, the related indanone structures **3s–u** and cyclopentanone adduct **3v** were assigned by analogy assuming the presence of a bulky *tert*-butyl ester was the major factor in governing the facial selectivity.

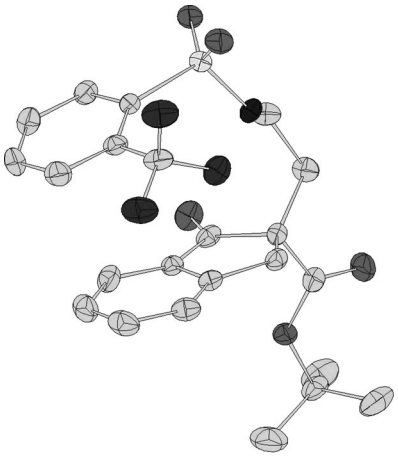
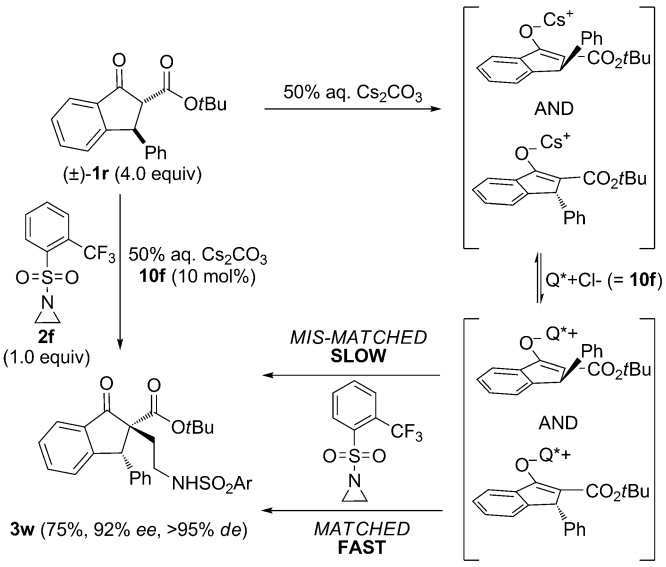


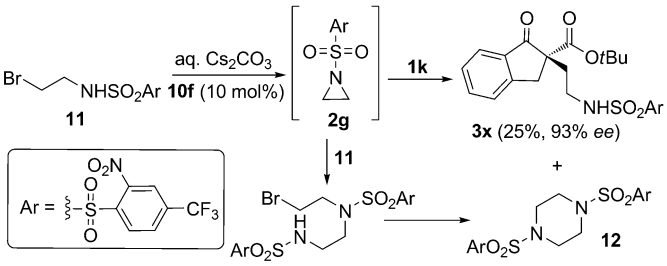
Figure 2. Absolute stereochemistry of **3r** determined to be *S* by single crystal X-ray crystallography (see the Supporting Information).

To extend this methodology, a pro-nucleophile bearing an additional stereocentre was employed in the alkylation reaction (Scheme 6). Due to the presence of the extra stereocentre in the pro-nucleophile, effective molecular recognition was observed. Using an excess (4 equiv) of racemic *tert*-butyl 3-phenylindanone-2-carboxylate (**1r**) as the pro-nucleophile, predominantly one enantiomer was reactive toward **2f** and resulted in the efficient production of **3w** in high enantioselectivity (92% *ee*) as a single diastereoisomer. We propose that a high level of substrate control directs addition of the aziridine electrophile to the face of the enolate opposite to the phenyl group.[19] When a chiral catalyst ($Q^{*+}Cl^-$) is employed, the diastereofacial selectivity arising from the substrate can be *matched* or *mis-matched* to the enolate–catalyst ion pair formed. In the *matched* case alkylation is fast; in the *mis-matched* case the alkylation is blocked by the bulky phenyl group and is significantly slower. As formation of the ammonium enolate ion pair is reversible, one enantiomer of the nucleophile is more reactive than the other, affording the alkylation product in high diastereo- and enantioselectivity.

Although activated aziridine **2f** proved to be a suitable electrophile for reactive indanone and cyclopentanone systems, the reaction turnover was poor in other cases. However, attempts to synthesise even more reactive electrophiles, such as **2g**, led to problems of dimerisation in the aziridine formation step (Scheme 7). Anticipating that dimerisation occurred via aziridine formation, we reasoned that if a suitable aziridine precursor **11** was used as the electrophile, forming the reactive aziridine **2g** in situ, and trapping with a pro-nucleophile could give the alkylation adduct without the need to isolate the aziridine electrophile. Pleasingly, this was indeed found to be the case, treatment of *tert*-butyl indanone carboxylate **1k** with **11** and catalyst **10f** (10 mol%) led to the formation of the alkylation adduct **3x** in high enantioselectivity (93% *ee*) but in poor yield due to the formation of dimer **12**.



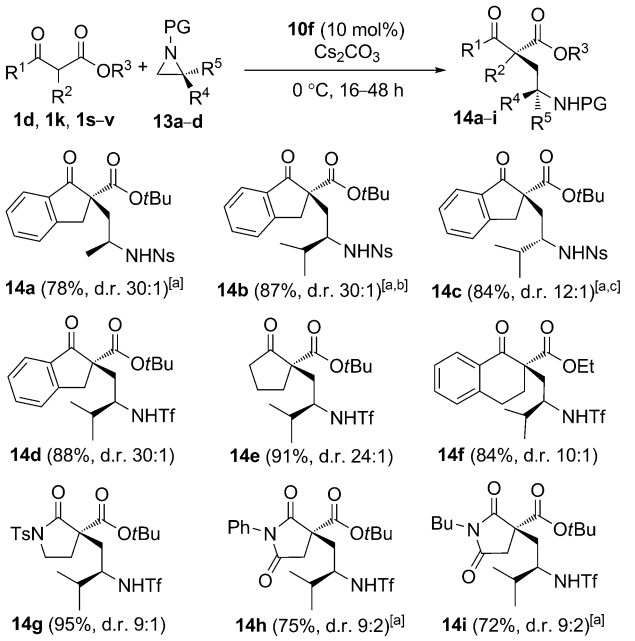
Scheme 6. Proposed origin of stereoselectivity through a catalyst controlled *matched* and *mis-matched* pathway. Reactions were performed on a 0.25 mmol scale in toluene/$CHCl_3$ (9:1, 2 mL) at 0°C. Isolated yield after purification. Yield based on **2f**.



Scheme 7. In situ aziridine formation/nucleophilic trapping.

Nucleophilic ring opening of aziridines is generally regioselective towards the less hindered carbon of the aziridine. Thus, if suitably substituted chiral aziridines were used as electrophiles, product substitution patterns could be obtained that would not normally be accessible by the commonly employed β-substituted nitro-olefin Michael reactions.[3,4] Furthermore, we envisaged that if the chiral elec-

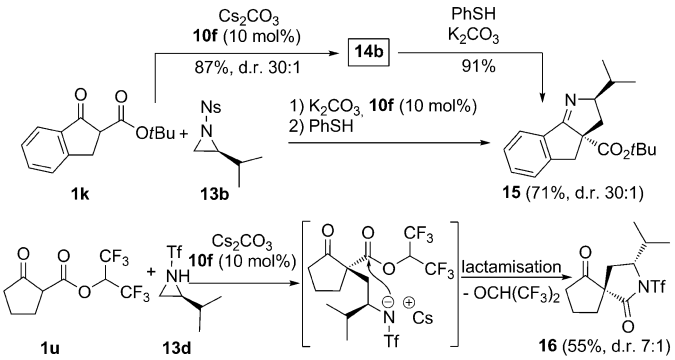
trophiles themselves imparted a degree of substrate controlled diastereoselectivity, finding *matched* pairs of electrophile/phase-transfer catalyst could result in higher diastereoselectivities in the products than might be expected from the enantioselective reaction with the same pro-nucleophile.[20] In an initial proof-of-concept, indanone **1k** was treated with *N*-*p*-nosyl aziridines bearing both small (**13a**, PG = *p*-Ns, R^4 = Me, R^5 = H) and bulky (**13b**, PG = *p*-Ns, R^4 = *i*Pr, R^5 = H; **13c**, PG = *p*-Ns, R^4 = H, R^5 = *i*Pr; **13d**, PG = Tf, R^4 = *i*Pr, R^5 = H) substituents, with solid Cs_2CO_3 and 10 mol% of phase-transfer catalyst **10f** (Scheme 8). Pleasingly, we were



Scheme 8. Diastereoselective ring opening of chiral aziridines **13a–d** with phase-transfer catalyst **10f**. Reactions were performed on a 0.25 mmol scale in toluene/$CHCl_3$ (9:1, 1 mL) at 0°C. Isolated yield after purification. Diastereomeric ratio was determined by ^1H NMR spectroscopy of the crude product. [a] Reaction performed at 25°C. [b] Product obtained in d.r. 2:1 when **10f** was replaced with TBAB (10 mol%). [c] Relative stereochemistry of **14c** was determined by single crystal X-ray crystallography (see the Supporting Information).

able to obtain the *matched* enantiopure alkylation adducts (**14a** and **14b**) in good yields and high diastereoselectivities (d.r. 30:1 in both cases). In the *mis-matched* case, catalyst control outweighed the weak natural substrate control and **14c** was afforded in good diastereomeric excess (d.r. 12:1). *N*-*p*-Nosyl protected aziridine **13b** was found to exhibit poor reactivity with pro-nucleophiles that were not indanone based. By substituting the *N*-*p*-nosyl group with the corresponding *N*-trifluoromethylsulfonyl aziridine **13d**, we were able to significantly enhance the reactivity of the alkylation reaction when using indanones (**14d**), cyclopentanones (**14e**), tetralones (**14f**) lactams (**14g**) and succinimides (**14h** and **14i**) as the pro-nucleophiles, giving the alkylation products in high yields and in moderate to high diastereoselectivities (d.r. 9:2 to 30:1).

N-*p*-Nosyl substituted sulfonamides can be readily cleaved under mildly nucleophilic conditions.[21] Alkylation adduct **14b** was treated with thiophenol and K_2CO_3, which underwent smooth desulfonylation at room temperature, followed by intramolecular condensation to give tricyclic imine **15** in high yield (Scheme 9). We reasoned that as the deprotection

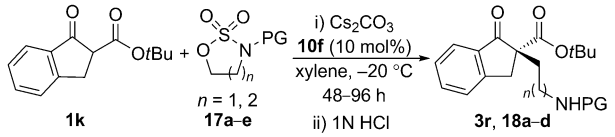


Scheme 9. One-pot alkylation/cyclisation sequences for the synthesis of functionalised cyclic imines and spiro-lactams.

proceeds with weak inorganic bases, this process could be telescoped with the alkylation process, thus circumventing the purification of the alkylation intermediate. Accordingly we synthesised heterocyclic compound **15** in a one-pot sequence from the corresponding pro-nucleophile **1k** by an initial alkylation with **13b** followed by addition of thiophenol. Pleasingly the overall yield was comparable to the two-step process. Although direct lactamisation onto esters was challenging in cyclic examples, this incompatibility could be overcome by activating the nucleophile as the hexafluoroisopropyl ester. Treatment of activated cyclopentanone pro-nucleophile **1u** with aziridine **13d** and catalyst **10f** resulted in rapid and irreversible intramolecular lactamisation following initial diastereoselective alkylation, giving the spiro-lactam **16** in moderate yield but in good diastereomeric ratio.

Enantioselective alkylation using cyclic sulfamidates: Studies to this point had identified the sulfonyl protecting group as a vital component for acceptable levels of reactivity in aziridine electrophiles.[22] Although in some cases it was found that the sulfonyl group could be cleaved under mild conditions, we believed a method encompassing a wider range of nitrogen protecting groups would be desirable. Additionally, access to the "propylene-amino" unit ($CH_2CH_2CH_2NHPG$) remained elusive. Accordingly, we considered cyclic sulfamidates as potential 2- and 3-carbon electrophiles.[23,24] Seminal work by Lubell[25] and Gallagher[26] have demonstrated that 5- and 6-membered cyclic sulfamidates are valuable intermediates for the synthesis of alkaloid natural products. However, to the best of our knowledge, there have been no previous reports of opening sulfamidate electrophiles with carbon centred nucleophiles in a catalytic and enantioselective fashion.

Table 3. Enantioselective ring opening of N-protected cyclic sulfamidates **17a–e** with indanone nucleophile **1k**.



1k 17a–e 3r, 18a–d

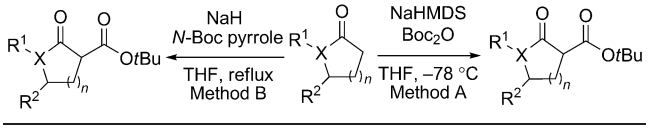
Entry[a]	17	PG	n	Product	Yield [%][b]	ee [%][c]
1	a	Boc	1	18a	75 (18)	93
2	b	Cbz	1	18b	54 (31)	94
3[d]	c	o-$CF_3C_6H_4SO_2$	1	3r	80	96
4	d	$PO(OEt)_2$	1	18c	55 (33)	45
5	e	Boc	2	18d	65 (20)	92

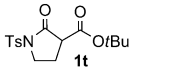
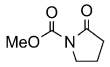
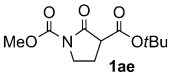
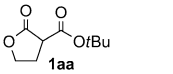
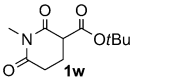
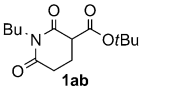
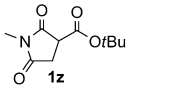
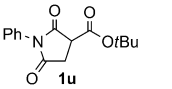
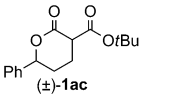
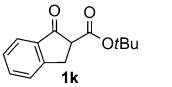
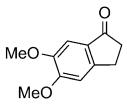
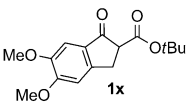
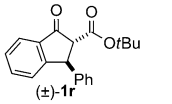
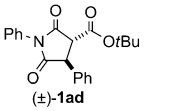
[a] Reactions were performed on a 0.40 mmol scale in xylene (2 mL) at −20 °C. [b] Isolated yield after purification (yield of oxygen-alkylation product shown in parentheses). [c] Determined by HPLC analysis. [d] Reaction performed at 0 °C due to low solubility of **17c**.

In an initial electrophile screen, *tert*-butyl indanone carboxylate (**1k**) was treated with 5- and 6-membered cyclic sulfamidates (**17a–e**) bearing a range of nitrogen protecting groups under phase-transfer catalysis (Table 3). Carbamate (Table 3, entries 1 and 2), sulfonyl (entry 3) and phosphonate (entry 4) protected electrophiles were screened for reactivity in the alkylation reaction, and in all but one case, the alkylation products were obtained in excellent enantioselectivity (up to 96% *ee*) following mild acid hydrolysis. In some cases, low to moderate degrees of competitive oxygen-alkylation was also observed (Table 3, entries 1, 2, 4 and 5). We were pleased to observe that the 6-membered electrophile reacted efficiently (entry 5) giving the alkylation adduct bearing the protected "propylene-amino" scaffold (previously unobtainable using our established methodology)[22] in good yield and with excellent stereocontrol (92% *ee*), thus giving access to a much wider spectrum of potential synthetic targets. In a test of the scale-up potential of our methodology, *tert*-butyl indanone carboxylate (**1k**) was treated on gram scale with sulfamidate **17a** at reduced catalyst loading (4 mol%). Pleasingly, the alkylation adduct **18a** was afforded in 65% yield and in 82% *ee*, after 24 h at 0 °C (see the Supporting Information).

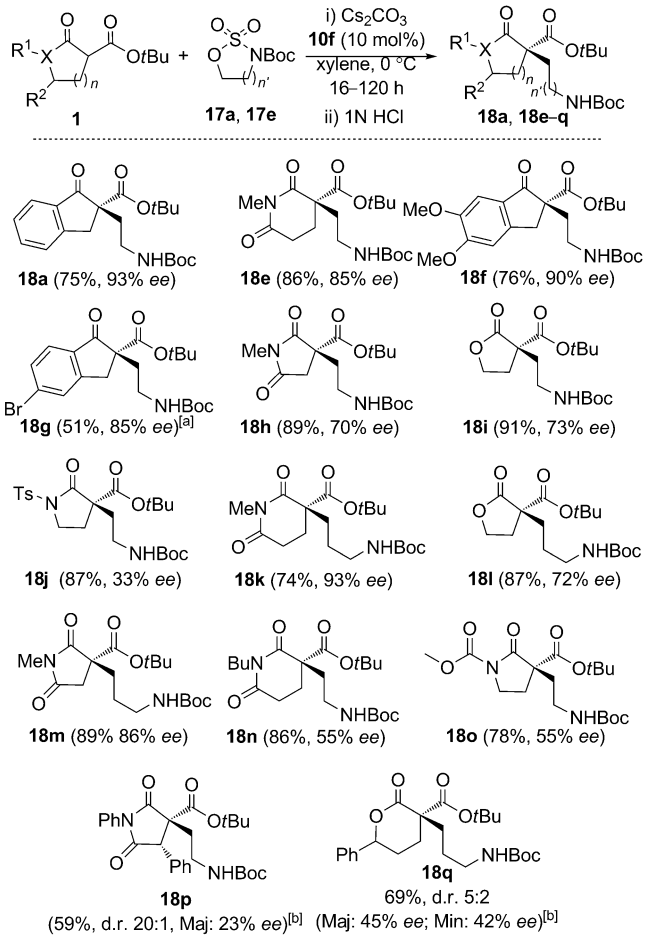
With optimal conditions established, the scope of this reaction was investigated with respect to the pro-nucleophile. Wishing to expand the general synthetic utility of our methodology, we synthesised a range of cyclic pro-nucleophiles bearing a *tert*-butyl ester substituent. On searching the literature, we found general methods for the direct introduction of *tert*-butyl esters were lacking; cyanoformate reagents have been used with some success,[18d] although the formation of cyanide by-products and the absence of a commercially available reagent makes this reaction potentially hazardous and impractical on large scale. Other methods, such as metal catalysed transesterification[27] and Dieckmann cyclisation,[28] have been used, but these are generally narrow in scope. After extensive optimisation, we found the combination of Boc_2O and NaHMDS (Table 4, Method A) generally gave highly efficient and selective mono-acylation for heterocyclic nucleophiles, even in cases such as succinimides and glutarimides in which there is more than one reactive carbonyl present. Under these conditions, indanone derived nucleophiles gave predominantly the oxygen-acylated products. However, in these cases direct esterification could be performed by using *N*-Boc pyrrole[29] as the electrophile and heating with NaH in THF (Table 4, Method B).

Table 4. Synthesis of various *tert*-butyl carboxylate substituted pro-nucleophiles.[a]



Starting material	Method	Product	Yield [%][b]
	A	 1t	70[c]
	A	 1ae	85
	A	 1aa	92
	A	 1w	82
	A	 1ab	88
	A	 1z	85
	A	 1u	90
	A	 (±)-1ac	73[d,e]
	B	 1k	85
	B	 1x	81
	B	 (±)-1r	88[d,f]
	B	 (±)-1ad	55[d,f]

[a] Method A: NaHMDS (2.0 equiv), Boc_2O (1.0 equiv), THF, −78 °C, 0.5–3 h. Method B: NaH (2.0 equiv), *N*-Boc pyrrole (1.2 equiv), THF, reflux, 3–6 h. [b] Isolated yield after purification. [c] Yield based on recovered starting material. [d] Diastereomeric ratio determined by ^1H NMR spectroscopy of the crude product. [e] d.r. 5:2. [f] d.r. > 20:1.



Scheme 10. Enantioselective ring opening of unsubstituted cyclic sulfamidates under phase-transfer catalysis. Reactions were performed on a 0.40 mmol scale in xylene (2 mL) at 0 °C. Isolated yield after purification. Enantiomeric excess was determined by HPLC analysis. [a] Reaction was performed at −20 °C in xylene/$CHCl_3$ (2 mL). [b] Reaction was performed on a 0.20 mmol scale. Yield based on the starting sulfamidate. Diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude product.

With a range *tert*-butyl ester pro-nucleophiles in hand, we subjected them to the optimal reaction conditions (Scheme 10). Pleasingly, the alkylation adducts were afforded in good to high enantioselectivities[30] using a range of 5- and 6-membered cyclic[31] systems, several of which are novel substrates in asymmetric phase-transfer catalysis. Substituents could be introduced onto the aryl ring of the indanone scaffold, with electron-rich (**18f**) and electron-poor (**18g**) substituents being tolerated without considerably affecting the stereocontrol (90% *ee* and 85% *ee*, respectively, cf. 93% *ee* in **18a**). The succinimide derived (**18h** and **18m**) and lactone derived (**18i** and **18l**) pro-nucleophiles were found to perform well, giving the alkylation products after 16 h at 0 °C in high yields (87–91%) and in good to high levels of enantioselectivity (up to 86% *ee*). *N*-Methyl glutarimide derived pro-nucleophile **1w** was an effective substrate with regard to generating high levels of stereoinduction (**18e** and **18k**). For example, using **17e** as the electrophile the product **18k** was obtained in good yield and in an impressive 93% *ee*. *N*-Butyl glutarimide **18n** showed diminished stereoinduction (55% *ee*) compared to the *N*-Me analogue **18e** (85% *ee*) using **10f** as the catalyst. Pro-nucleophiles bearing an additional stereocentre could also be utilised. By using 2 equiv of the pro-nucleophile to 1 equiv of the sulfamidate **17a**, 3-phenyl succinimide (**18p**) gave a high level of diastereocontrol (d.r. 20:1), but the yield was moderate and the enantioselectivity was low (59%, 23% *ee* for the major isomer). More remote stereogenic centres could also influence diastereoselectivity, albeit moderately. For example, lactone pro-nucleophile **1ac** gave the alkylation products **18q** as a mixture of diastereomers (d.r. 5:2) in good yield but with moderate enantioselectivity (69%, 45% *ee* for the major isomer). The combination of ring sizes available in both nucleophile and electrophile partners, and the mild reaction conditions allows a diverse range of products to be synthesised easily and with exceptional stereocontrol.

To extend our developed methodology to diastereoselective alkylation reactions, we wanted to implement enantiopure cyclic sulfamidates (Figure 3). Using alanine and phenylalanine as convenient chiral building blocks, both enantiomers of sulfamidates **17f** and **17g** were synthesised in the hope that *matched* and *mis-matched* combinations of substrate and catalyst could be observed. Using TBAB as an achiral phase-transfer catalyst (Table 5), substrate control from (*S*)-alanine-derived sulfamidate (*S*)-**17f** was found to be highly dependent on the nature of the nucleophile,[20] varying from good with succinimide **1z** (d.r. 9:1) to poor with lactone **1aa** (d.r. 1:1). Lactam derived nucleophile **1t** gave the alkylated product **19a** with moderate diastereoselectivity (d.r. 7:2) when TBAB was used as the catalyst, which in the *matched* case with sulfamidate (*R*)-**17g** and **10f** was enhanced (d.r. 7:1). In the *mis-matched* case using the enantiomeric electrophile (*S*)-**17g**, diastereoselectivity was eroded (d.r. 2:1), however, it could be boosted (d.r. 11:2) by employing the *matched* pseudoenantiomeric catalyst **10f′** (Figure 4). The lactone pro-nucleophile **1aa** had previously displayed no substrate control with TBAB, but when used in conjunction with catalyst **10f**, the alkylation adducts **19b** and **19c** were afforded in high yields and moderate diastereoselectivity (d.r. 5:1, in both cases). This level of diastereoselectivity was anticipated in light of the previous enantioselective alkylation result (Scheme 10). Using succinimide pro-nucleophile **1z** with the *matched* pair of catalyst **10f** and sulfamidate (*S*)-**17f** resulted in excellent diastereo-

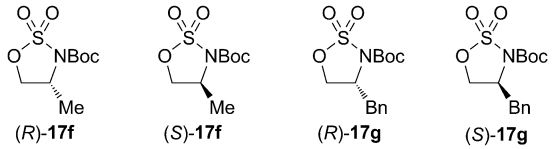
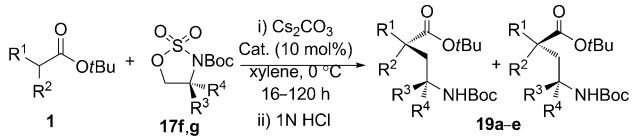
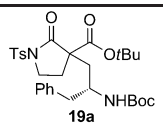
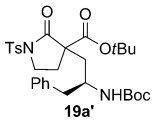
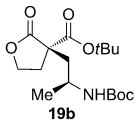
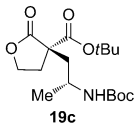
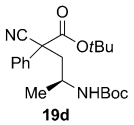
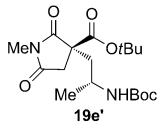
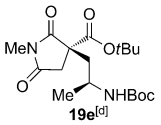


Figure 3. Enantiopure cyclic sulfamidates used in diastereoselective alkylation studies.

Table 5. Diastereoselective ring opening of chiral cyclic sulfamidates under phase-transfer catalysis.[a]



Sulfamidate	Product	Catalyst (10 mol%)	Yield [%][b]	d.r.[c]
(*R*)-**17g**	 **19a**	TBAB	82	7:2
		10f	80	7:1
(*S*)-**17g**	 **19a'**	TBAB	84	7:2
		10f	78	2:1
		10f'	81	11:2
(*S*)-**17f**	 **19b**	TBAB	84	1:1
		10f	82	5:1
(*R*)-**17f**	 **19c**	TBAB	83	1:1
		10f	86	5:1
(*S*)-**17f**	 **19d**	TBAB	85	1.1:1
		10f	84	3:2
		10g	82	1.3:1
(*R*)-**17f**	 **19e'**	TBAB	36	9:1
		10f	traces	n.d.
		10g	51	7:1
(*S*)-**17f**	 **19e**[d]	TBAB	41	9:1
		10f	59	45:1
		10g	65	9:1

[a] Reactions were performed on a 0.40 mmol scale in xylene (2 mL) at 0 °C. [b] Isolated yield of product, [c] Determined by ^{1}H NMR spectroscopy of the crude product. [d] The relative stereochemistry of **19e** was determined by single crystal X-ray crystallography (see the Supporting Information).

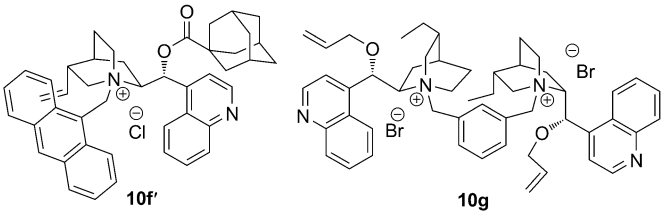
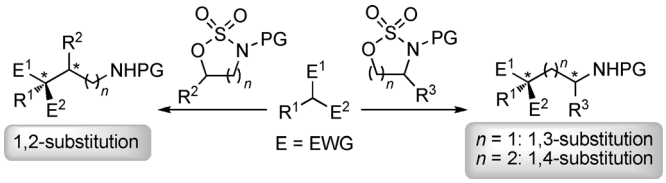


Figure 4. Other phase-transfer catalysts used in diastereoselective alkylation studies.

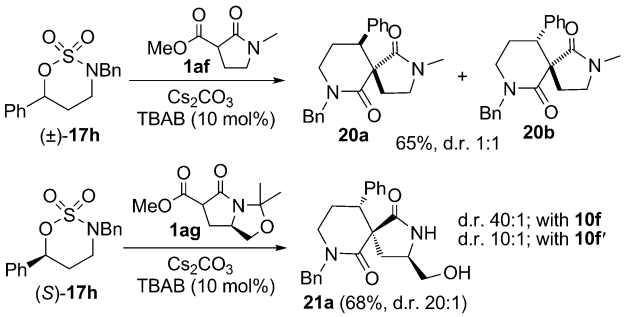
selectivity, furnishing **19e** (d.r. 45:1) with a minor amount of the oxygen-alkylation side-product. Interestingly, the *mismatched* pair of catalyst **10f** and sulfamidate (*R*)-**17f** resulted in almost exclusive oxygen-alkylation. The relative stereochemistry of **19e** was determined by single crystal X-ray diffraction (see the Supporting Information). Acyclic pro-nucleophile **1af** displayed both poor catalyst and substrate directed selectivity; with the alkylation adduct **19d** being obtained in good overall yield, but with disappointing diastereoselectivity (d.r. 3:2).

The ring-opening of substituted cyclic sulfamidates is known to be completely regioselective. Exploiting this, we postulated that we could access alkylation products that have 1,2- or 1,3-substitution patterns (Scheme 11). Having



Scheme 11. Divergent synthetic strategies available from cyclic sulfamidate electrophiles.

established that C2-substituted cyclic sulfamidates were reactive towards our conditions, C1-substituted variants were then investigated. Chiral sulfamidate **17h** was synthesised in racemic form and as single *S* enantiomer. Initial alkylation studies were carried out using NMP derived nucleophile **1af** (Scheme 12). Pleasingly, treatment of **1af** with sulfamidate



Scheme 12. Nucleophile controlled alkylation/lactamisation.

(±)-**17h** (1 equiv) in the presence of catalytic TBAB and Cs_2CO_3 for 6 h at 50 °C, followed by acid hydrolysis and subsequent lactamisation afforded the spiro-lactams **20a** and **20b** as a 1:1 mixture of diastereomers (d.r. 3:2, when **10f** was used in place of TBAB). In order to obtain a higher degree of stereocontrol we chose chiral pro-nucleophile (*R*)-**1ag** with the intention of obtaining a degree of substrate control from the nucleophile. Pleasingly, treatment of (*R*)-**1ag** with one equivalent of sulfamidate (*S*)-**17h** in the presence of catalytic TBAB and Cs_2CO_3 for 24 h at 40 °C, followed by acid hydrolysis and lactamisation[26] afforded the spiro-lactam **21** in good yield and diastereoselectivity (68%, d.r. 20:1). Pleasingly, using catalyst **10f** further enhanced the diastereoselectivity of the reaction (d.r. 40:1); this suggested a *matched* pairing of catalyst and nucleophile. In compari-

son, when the pseudoenantiomeric catalyst **10 f′** was used in the synthesis of lactam **21**, there was a decrease in the diastereoselectivity of the reaction (d.r. 10:1), thus suggesting that these were a *mis-matched* combination (see the Supporting Information).[32]

Conclusion

In conclusion, we have developed highly efficient catalytic and enantioselective alkylation methodologies for creating quaternary carbon stereogenic centres attached to ethylene-amino and propylene-amino motifs. Using commercially available phosphazene reagents, it is possible to perform base catalysed ring opening on a range of substrates in generally high yields. Then, through asymmetric phase-transfer catalysis this reaction can be rendered highly enantioselective and diastereoselective. To address the need for a wider variety of nitrogen protecting groups to be tolerated, we then applied the reaction to the ring opening of 1,2- and 1,3-cyclic sulfamidates with various substitution patterns and protecting groups.[33] Manipulation of the alkylation adducts, including spiro-cyclisation and intramolecular condensation for the efficient synthesis of multicyclic systems has also been demonstrated.

Experimental Section

General procedure for the BEMP catalysed aziridine ring opening reaction: BEMP (10.4 μL, 0.036 mmol) was added to a solution of pro-nucleophile (0.720 mmol) in THF (0.8 mL) and the resulting solution was stirred at 25°C for 10 minutes. The aziridine (0.360 mmol) was added and the mixture was stirred at 25°C until completion (usually 16–48 h). The solution was concentrated and the residue was purified by flash column chromatography to yield the desired product.

General procedure for the phase-transfer catalysed aziridine ring opening reaction: K_2HPO_4 (0.200 mmol in 35 μL H_2O) was added to a solution of pro-nucleophile (0.130 mmol), aziridine (0.160 mmol) and catalyst **10 f** (0.013 mmol) in a 9:1 toluene/$CHCl_3$ mixture (1 mL) at −20°C. Following completion of the reaction (usually 16–72 h), CH_2Cl_2 (5 mL) and 1 N HCl (2 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL), the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash column chromatography to yield the desired product.

General procedure for the synthesis of *tert*-butyl ester substituted pro-nucleophiles with Boc_2O (Method A): NaHMDS (2 M in THF, 10 mL) was added dropwise to a solution of carbonyl compound (10.0 mmol) in THF (40 mL) at −78°C. Following addition of base, Boc_2O (10.0 mmol) in THF (5 mL) was added and the mixture was stirred at −78°C until completion (usually 0.5–3 h). The reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc (25 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash column chromatography to yield the desired product.

General procedure for the synthesis of *tert*-butyl ester substituted indanone pro-nucleophiles with *N*-Boc pyrrole (Method B): Indanone (5.0 mmol) was added to a suspension of NaH (10.0 mmol, 60% in mineral oil washed with hexane) in THF (20 mL) at RT. Following warming to relux, *N*-Boc pyrrole (10.0 mmol) in THF (5 mL) was added dropwise and the solution was further warmed to reflux until completion (usually 3–6 h). The reaction mixture was cooled to RT, quenched with 1 N HCl and extracted with EtOAc (25 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash column chromatography to yield the desired product.

General procedure for the phase-transfer catalysed sulfamidate ring opening reaction: Solid Cs_2CO_3 (0.600 mmol) was added to a solution of pro-nucleophile (0.400 mol), sulfamidate (0.420 mmol) and catalyst **10 f** (0.040 mmol) in xylene (2.0 mL) at 0°C. Following completion of the reaction (usually 16–72 h), 1 N HCl (2 mL) was added and the mixture was stirred for 10 min. CH_2Cl_2 (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL), the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash column chromatography to yield the desired product.

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[1] For selected examples from our group of reactions forming quaternary stereocentres, see: a) A. W. Pilling, J. Boehmer, D. J. Dixon, *Angew. Chem.* **2007**, *119*, 5524–5526; *Angew. Chem. Int. Ed.* **2007**, *46*, 5428–5430; b) C. L. Rigby, D. J. Dixon, *Chem. Commun.* **2008**, 3798–3800; c) M. Li, D. J. Dixon, *Org. Lett.* **2010**, *12*, 3784–3787; d) P. Jakubec, D. M. Cockfield, P. S. Hynes, E. Cleator, D. J. Dixon, *Tetrahedron: Asymmetry* **2011**, *22*, 1147–1155.

[2] For a review, see: C. M. Goodman, S. Choi, S. Shandler, W. F. DeGrado, *Nat. Chem. Biol.* **2007**, *3*, 252–262.

[3] For selected reviews, see: a) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331; b) M. Santanu, J. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; c) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; d) Y. Takemoto, H. Miyabe, *Chimia* **2007**, *61*, 269–275.

[4] For recent examples of secondary amine catalysed Michael additions of aldehydes to nitro-olefins, see: a) Y. Chi, L. Guo, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608–5609; b) M. Wiesner, J. D. Revell, S. Tonazzi, H. Wennermers, *J. Am. Chem. Soc.* **2008**, *130*, 5610–5611; c) P. García-García, A. Lapépêche, R. Halder, B. List, *Angew. Chem.* **2008**, *120*, 4797–4799; *Angew. Chem. Int. Ed.* **2008**, *47*, 4719–4721; d) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4800–4802; *Angew. Chem. Int. Ed.* **2008**, *47*, 4722–4724; e) M. Durini, F. A. Sahr, M. Kuhn, M. Civera, C. Gennari, U. Piarulli, *Eur. J. Org. Chem.* **2011**, 5599–5607.

[5] For reviews on ring opening of aziridines, including asymmetric methods, see: a) X. E. Hu, *Tetrahedron* **2004**, *60*, 2701–2743; b) I. D. G. Watson, L. Yu, A. K. Yudin, *Acc. Chem. Res.* **2006**, *39*, 194–206; c) M. Pineschi, *Eur. J. Org. Chem.* **2006**, 4979–4988; d) C. Schneider, *Angew. Chem.* **2009**, *121*, 2116; *Angew. Chem. Int. Ed.* **2009**, *48*, 2082; e) S. Stanković, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. V. Speybroeck, N. D. Kimpe, H.-J. Ha, *Chem. Soc. Rev.* **2012**, *41*, 643–665.

[6] For methodologies in aziridine synthesis, see: a) J. E. G. Kemp, in *Comprehensive Organic Synthesis, Vol. 7* (Eds.: B. M. Trost, I. Fleming, L. Lwowski), Pergamon, Oxford, **1991**, p. 469; b) K. M. L. Rai, A. Hassner, *Adv. Strain. Interest. Org. Mol.* **2000**, *8*, 187–257; c) S. S. Murphree, A. Padwa, *Prog. Heterocycl. Chem.* **2001**, *13*, 52–70; d) A. L. Williams, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*,

1612–1613; e) X. Zeng, X. Zeng, Z. Xu, M. Lu, G. Zhong, *Org. Lett.* **2009**, *11*, 3036–3039; f) L. D. S. Yadav, R. Kapoor, Garima, *Synlett* **2009**, 3123–3126.

[7] a) H. Stamm, V. Gailius, *Chem. Ber.* **1981**, *114*, 3599–3608; b) T. Baumann, B. Buckholz, H. Stamm, *Synthesis* **1995**, 44–46.

[8] For a phase-transfer catalysed example, see: a) E. V. Blyumin, H. J. Gallon, A. K. Yudin, *Org. Lett.* **2007**, *9*, 4677–4680. For a Lewis base catalysed example, see: b) S. Minakata, Y. Okada, Y. Oderaotoshi, M. Komatsu, *Org. Lett.* **2005**, *7*, 3509–3512. For a Lewis acid catalysed example, see: c) I. Ungureanu, P. Klotz, A. Mann, *Angew. Chem.* **2000**, *112*, 4790–4792; *Angew. Chem. Int. Ed.* **2000**, *39*, 4615–4617; d) J. S. Yadav, B. V. S. Reddy, S. Abraham, G. Sabitha, *Tetrahedron Lett.* **2002**, *43*, 1565–1567.

[9] R. Schwesinger, J. Willaredt, H. Schlemper, M. Keller, D. Schmitt, H. Fritz, *Chem. Ber.* **1994**, *127*, 2435–2454.

[10] D. A. Alonso, P. G. Andersson, *J. Org. Chem.* **1998**, *63*, 9455–9461, and references cited therein.

[11] Z. Moussa, D. Romo, *Synlett* **2006**, 3294–3298.

[12] T. A. Moss, A. Alba, D. Hepworth, D. J. Dixon, *Chem. Commun.* **2008**, 2474–2476.

[13] For seminal work on bifunctional cinchona-derived organocatalysis, see: a) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; b) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525–6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; c) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969; d) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483; e) B. Li, L. Jiang, M. Liu, Y. Chen, L. Ding, Y. Wu, *Synlett* **2005**, 603–606.

[14] For reviews of phase-transfer catalysis, see: a) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013–3028; b) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518–525; c) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506–517; d) T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *119*, 4300–4345; *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266; e) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2007**, *107*, 5656–5682.

[15] For selected examples of phase-transfer catalysis, see: a) R. He, X. Wang, T. Hashimoto, K. Maruoka, *Angew. Chem.* **2008**, *120*, 9608–9610; *Angew. Chem. Int. Ed.* **2008**, *47*, 9466–9468; b) D. Uraguchi, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 14088–14089; c) V. Rauniyar, A. D. Lackner, G. L. Hamilton, F. D. Toste, *Science* **2011**, *334*, 1681–1684; d) E. E. Maciver, P. C. Knipe, A. P. Cridland, A. L. Thompson, M. D. Smith, *Chem. Sci.* **2012**, *3*, 537–540; e) K. M. Johnson, M. S. Rattley, F. Sladojevich, D. M. Barber, M. G. Nuñez, A. M. Goldys, D. J. Dixon, *Org. Lett.* **2012**, *14*, 2492–2495; f) C. D. Fiandra, L. Piras, F. Fini, P. Disetti, M. Moccia, M. F. A. Adamo, *Chem. Commun.* **2012**, *48*, 3863–3865.

[16] For selected examples of phase-transfer catalysed alkylation reactions forming a quaternary stereocentre, see: a) T. B. K. Lee, G. S. K. Wong, *J. Org. Chem.* **1991**, *56*, 872–875; b) T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, K. Maruoka, *Angew. Chem.* **2003**, *115*, 3926–3928; *Angew. Chem. Int. Ed.* **2003**, *42*, 3796–3798; c) E. J. Park, M. H. Kim, D. Y. Kim, *J. Org. Chem.* **2004**, *69*, 6897–6899; d) S.-S. Jew, Y.-J. Lee, J. Lee, M. J. Kang, B.-S. Jeong, J.-H. Lee, M.-S. Yoo, M.-J. Kim, S.-H. Choi, J.-M. Ku, H.-G. Park, *Angew. Chem.* **2004**, *116*, 2436–2439; *Angew. Chem. Int. Ed.* **2004**, *43*, 2382–2385; e) T. Ooi, K. Fukumoto, K. Maruoka, *Angew. Chem.* **2006**, *118*, 3923–3926; *Angew. Chem. Int. Ed.* **2006**, *45*, 3839–3842; f) D. Uraguchi, Y. Asai, T. Ooi, *Angew. Chem.* **2009**, *121*, 747–751; *Angew. Chem. Int. Ed.* **2009**, *48*, 733–736; g) K. Ohmatsu, M. Kiyokawa, T. Ooi, *J. Am. Chem. Soc.* **2011**, *133*, 1307–1309; h) S. Hong, J. Lee, M. Kim, Y. Park, C. Park, M.-H. Kim, S.-S. Jew, H.-G. Park, *J. Am. Chem. Soc.* **2011**, *133*, 4924–4929.

[17] a) M. J. O'Donnell, F. Delgado, R. Hostettler, R. Schwesinger, *Tetrahedron Lett.* **1998**, *39*, 8775–8778; b) Y.-J. Lee, J. Lee, M.-J. Kim, B.-S. Jeong, J.-H. Lee, T.-S. Kim, J. Lee, J.-M. Ku, S.-S. Jew, H.-G. Park, *Org. Lett.* **2005**, *7*, 3207–3209.

[18] For seminal work, see: a) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415; b) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595–8598; c) T. B. Poulsen, L. Bernardi, M. Bell, K. A. Jørgensen, *Angew. Chem.* **2006**, *118*, 6701–6704; *Angew. Chem. Int. Ed.* **2006**, *45*, 6551–6554; d) T. B. Poulsen, L. Bernardi, J. Aleman, J. Overgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 441–449; e) L. Bernardi, J. Cantarero, B. Neiss, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 5772–5778.

[19] H.-F. Cui, K.-Y. Dong, G.-W. Zhang, L. Wang, J.-A. Ma, *Chem. Commun.* **2007**, 2284–2286.

[20] For electrophile directed diastereoselective alkylation, see: a) L. Overman, J. F. Larrow, B. A. Stearns, J. M. Vance, *Angew. Chem.* **2000**, *112*, 219–221; *Angew. Chem. Int. Ed.* **2000**, *39*, 213–215; b) S. B. Hoyt, L. Overman, *Org. Lett.* **2000**, *2*, 3241–3244; c) T. Emura, T. Esaki, T. Kazutaka, M. Shimizu, *J. Org. Chem.* **2006**, *71*, 8559–8564; d) S. P. Marsden, R. Newton, *J. Am. Chem. Soc.* **2007**, *129*, 12600–12601.

[21] T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373–6374.

[22] a) T. A. Moss, D. R. Fenwick, D. J. Dixon, *J. Am. Chem. Soc.* **2008**, *130*, 10076–10077; b) M. W. Paixão, M. Nielsen, C. B. Jacobsen, K. A. Jørgensen, *Org. Biomol. Chem.* **2008**, *6*, 3467–3470.

[23] For a review on the synthesis and reactions of cyclic sulfamidates, see: R. E. Meléndez, W. D. Lubell, *Tetrahedron* **2003**, *59*, 2581–2616.

[24] For seminal work in this area, see: a) J. E. Baldwin, A. C. Spivey, C. J. Schofield, *Tetrahedron: Asymmetry* **1990**, *1*, 881–884; b) G. J. White, M. E. Garst, *J. Org. Chem.* **1991**, *56*, 3178–3181; c) G. F. Cooper, K. E. McCarthy, M. G. Martin, *Tetrahedron Lett.* **1992**, *33*, 5895–5896; d) L. T. Boulton, H. T. Stock, J. Raphy, D. C. Horwell, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1421–1430; e) J. J. Posakony, T. J. Tewson, *Synthesis* **2002**, 859–864.

[25] L. Wei, W. D. Lubell, *Can. J. Chem.* **2001**, *79*, 94–104.

[26] a) J. F. Bower, J. Svenda, A. J. Williams, J. P. H. Charmant, R. M. Lawrence, P. Szeto, T. Gallagher, *Org. Lett.* **2004**, *6*, 4727–4730; b) J. F. Bower, P. Szeto, T. Gallagher, *Chem. Commun.* **2005**, 5793–5795; c) J. F. Bower, S. Chakthong, J. Svenda, A. J. Williams, R. M. Lawrence, P. Szeto, T. Gallagher, *Org. Biomol. Chem.* **2006**, *4*, 1868–1877; d) J. F. Bower, T. Riis-Johannessen, P. Szeto, A. J. Whitehead, T. Gallagher, *Chem. Commun.* **2007**, 728–730; e) J. F. Bower, A. J. Williams, H. L. Woodward, P. Szeto, R. M. Lawrence, T. Gallagher, *Org. Biomol. Chem.* **2007**, *5*, 2636–2644; f) J. F. Bower, P. Szeto, T. Gallagher, *Org. Lett.* **2007**, *9*, 4909–4912.

[27] M. Nakajima, S. Yamamoto, Y. Yamaguchi, S. Nakamura, S. Hashimoto, *Tetrahedron* **2003**, *59*, 7307–7313.

[28] M. E. Bunnage, S. G. Davies, R. M. Parkin, P. M. Roberts, A. D. Smith, J. M. Withey, *Org. Biomol. Chem.* **2004**, *2*, 3337–3354.

[29] For examples of reactions using pyrrole reagents, see: a) M. S. Scott, C. A. Luckhurst, D. J. Dixon, *Org. Lett.* **2005**, *7*, 5813–5816; b) R. D. Richardson, F. A. Hernandez-Juan, D. J. Dixon, *Synlett* **2006**, 77–80.

[30] The stereochemistry of indanone adducts **18a–d**, **18f** and **18g** were assigned by analogy to compound **3r** (absolute configuration determined by X-ray analysis). Compounds **18i** and **18l** were assigned by analogy to the cyclopentanone system (see ref. [18c]). Succinimide products **18h** and **18m** were assigned by comparison to compound **19e** in the matched system with (*S*)-**17f** and catalyst **10f** (relative configuration determined by X-ray analysis). Glutarimide adducts **18e** and **18k** were assigned by analogy to the succinimide and cyclohexanone (see ref. [18c]) systems.

[31] Subjection of acyclic pro-nucleophile *tert*-butyl-2-methylacetoacetate to our optimal conditions resulted in a 2:3 inseparable mixture of oxygen- and carbon-alkylated products, respectively.

[32] When the reaction was conducted with (±)-**17h**, a 1:1 mixture of major diastereomers were obtained, in a 20:1 ratio with their respective minor diastereomers (d.r. 20:1:20:1).

[33] T. A. Moss, B. Alonso, D. Fenwick, D. J. Dixon, *Angew. Chem.* **2010**, *122*, 578–581; *Angew. Chem. Int. Ed.* **2010**, *49*, 568–571.

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