Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 3756

www.rsc.org/obc

PAPER

Asymmetric α-oxyacylation of cyclic ketones†

Deborah A. Smithen,*[a] Christopher J. Mathews[b] and Nicholas C. O. Tomkinson*[c]

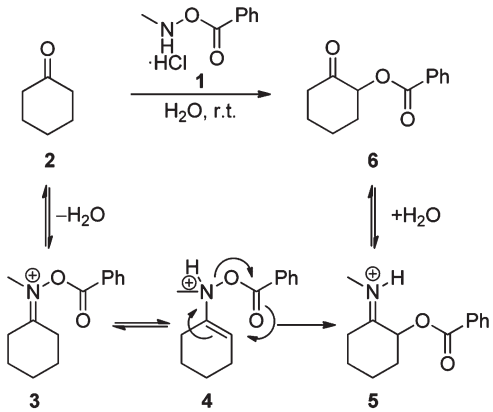
Received 9th February 2012, Accepted 9th March 2012
DOI: 10.1039/c2ob25293g

Reaction of cyclic ketones with chiral *N*-alkyl-*O*-acyl hydroxylamines leads to the corresponding α-oxyacylated carbonyl compound in up to 89% ee. The levels of asymmetric induction were influenced by solvent polarity, acid strength and, to a lesser extent, temperature. Increasing the steric bulk around the nitrogen atom of the hydroxylamine reagent led to increased levels of asymmetric induction, which was also found to be detrimental to the yield observed for the transformation. Examination of N- and O-substituents along with substrates revealed the scope and limitations of the procedure.

Introduction

The [3,3]-sigmatropic rearrangement as a method for the formation of C–C and C–heteroatom bonds has a rich history in the synthesis of complex natural products and molecules of biological significance.[1] The ordered and often predictable transition state for the rearrangement has permitted development of several asymmetric variants providing robust methods for the formation of challenging stereogenic centres with high levels of enantiomeric excess.[2,3]

We recently described a series of hydroxylamine reagents for the oxyacylation,[4,5] oxycarbonylation,[6] oxycarbamoylation[7] and oxysulfonylation[8] of carbonyl compounds, providing a simple and highly practical family of reagents for the α-oxygenation of carbonyl compounds. It is believed that each of these reactions proceeds *via* a similar mechanistic pathway involving condensation of a reagent (*e.g.* **1**) with a carbonyl substrate **2** to give an iminium ion **3**, which is converted to the protonated enamine **4** under the acidic reaction conditions. [3,3]-Sigmatropic rearrangement of **4**,[9,10] cleaving the weak N–O bond[11] and forming a stronger C–O bond, gives the α-functionalised iminium ion **5** which is hydrolysed to give the product **6** (Scheme 1). The ease with which these reactions can be carried out, with many of the transformations proceeding at room temperature in the presence of both moisture and air with bench stable reagents, suggested that development of an asymmetric variant would be of great use. Within this paper we describe chiral hydroxylamine reagents for this purpose and examine their reactivity with cyclic ketone substrates.



Scheme 1 Proposed mechanism for α-functionalisation with hydroxylamine reagents.

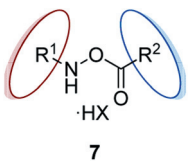
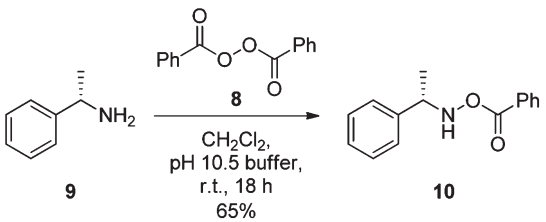


Fig. 1 Opportunities for introduction of chirality in generic reagent **7**.

Examination of the generic structure of the reagent **7** suggested two places for the introduction of chirality: The nitrogen substituent (R^1) or the acyl substituent (COR^2) (Fig. 1). Within these studies we have examined the nitrogen substituent (R^1) as this would not be incorporated into the product, providing the opportunity for amine recovery and future development of a catalytic asymmetric protocol.

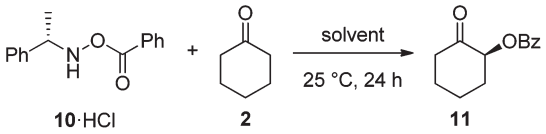
[a]*School of Chemistry, Main Building, Cardiff University, Park Place, Cardiff, CF10 3AT, UK*
[b]*Chemistry Department, Syngenta, Jealotts Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, UK*
[c]*WestCHEM, Department of Pure and Applied Chemistry, Thomas Graham Building, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, UK. E-mail: Nicholas.Tomkinson@strath.ac.uk; Fax: +44(0)141 548 5743; Tel: +44(0)141 548 2276*

†Electronic supplementary information (ESI) available: Experimental procedures and analytical data for chiral and achiral reagents together with copies of all ^1H, ^{13}C spectra and HPLC traces. See DOI: 10.1039/c2ob25293g



Scheme 2 Preparation of reagent **10**.

Table 1 Effect of solvent on asymmetric α-oxybenzoylation of cyclohexanone[a]



Entry	Solvent	% Yield **11**[b]	% ee[c]
1	H_2O	95	0
2	DMSO	53	0
3	CH_3CN	38	3
4	Acetone	37	3
5	$CHCl_3$	29	0
6	THF	32	0
7	CH_2Cl_2	38	0
8	PhMe	51	5[d]

[a] All reactions carried out with **10**·HCl (1 equiv), cyclohexanone (1 equiv), [0.5] M, 25 °C, 24 h. [b] Isolated yield. [c] Determined by HPLC, Chiracel OD. [d] (*S*)-Enantiomer of product obtained in excess.

The target α-oxyacylated carbonyl compounds are important functional groups present in many natural products, pharmaceuticals and synthetic intermediates of broad utility. Shi has reported the catalytic asymmetric introduction of the oxybenzoyl group α- to ketones by a low temperature epoxidation of preformed enol esters followed by rearrangement under acidic reaction conditions, to give the products with good yield and excellent enantioselectivity.[12] Very recently, List has described a direct method for the α-benzoyloxylation of cyclic ketones using a primary amine organocatalyst with outstanding levels of enantioselectivity providing a simple and effective method for the preparation of this class of compound.[13]

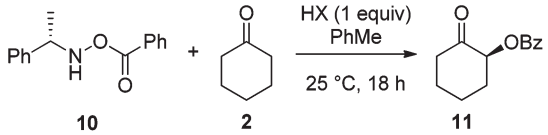
Results and discussion

Investigations began with the preparation of **10** derived from (*S*)-α-methyl benzylamine (Scheme 2). Treatment of **9** with one equivalent of benzoyl peroxide (**8**) under basic conditions as originally described by Phanstiel[14] for the oxidation of primary amines, provided a simple, scalable and efficient method for the preparation of reagent **10** (65%).

Having prepared quantities of **10** it was converted to the corresponding HCl salt (95%) and examined for reactivity in the α-functionalisation of cyclohexanone (**2**) (Table 1).

A series of solvents with decreasing polarity were examined in the α-functionalisation of cyclohexanone (Table 1). In previous investigations with achiral reagent **1**, the cleanest and most efficient reactions took place in polar solvent mixtures (DMSO, THF–H_2O).[4,5] Once again, this proved to be the case with **10**·HCl, water providing the product **11** in an excellent 95% isolated yield under the standard reaction conditions adopted (entry 1). With less polar solvents the reaction tended to proceed at a slower rate with substantially lower isolated yields being obtained under the conditions examined (entries 3–8). No significant enantiomeric excess was observed in the product for the majority of solvents examined (entries 1–7); however, toluene delivered the product with a small, but repeatable 5% ee, with the (*S*)-enantiomer of the product **11** in excess (entry 8).[12] Although small, the use of toluene clearly influenced the stereochemical outcome of the transformation. Repeating the transformation in toluene for 24, 48 and 72 hours led to the same levels of asymmetric induction being observed (5% ee) suggesting that no racemisation was taking place under the reaction conditions and the ee observed was a genuine reflection of asymmetric induction obtained within the proposed rearrangement.

Table 2 Effect of co-acid on asymmetric α-oxybenzoylation of cyclohexanone[a]



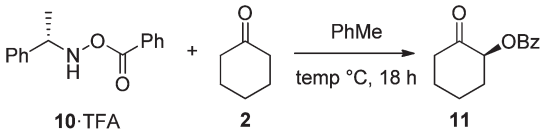
Entry	HX	% Yield **11**[b]	% ee[c]
1	HCl	51	5
2	$MeSO_3H$	53	5
3	TFA	51	35
4	TCA	53	38
5	DPP	51	10
6	$PhCO_2H$	2	0

[a] All reactions carried out with **10**·HX (1 equiv), cyclohexanone (1 equiv), [0.5] M, 25 °C, 18 h. [b] Isolated yield. [c] Determined by HPLC, Chiracel OD, (*S*)-enantiomer of product obtained in excess. TFA: trifluoroacetic acid; TCA: trichloroacetic acid; DPP: diphenyl phosphate.

The next variable examined was the acid HX (Table 2). A variety of acids were chosen, ranging in p*K*a, to determine if the relative p*K*a or the counter-ion were affecting the reaction. Having established that toluene was the most promising solvent for the transformation it was adopted within this screen. Under standard reaction conditions, the acid had a significant effect on both the yield and the asymmetric induction observed. Near identical yields were observed for a range of stronger acids (entries 1–5; 51–53%), whereas the weaker benzoic acid resulted in a slower reaction and substantial recovery of starting materials (entry 6). The most dramatic influence of the acid was observed in the ee of the product. The stronger acids HCl and $MeSO_3H$ gave (*S*)-**11** in just 5% ee, whereas trifluoroacetic acid (TFA) and trichloroacetic acid (TCA) gave the product (*S*)-**11** in a significantly higher ee (35% and 38% respectively). Decreasing the strength of the acid further (diphenyl phosphonate; DPP) gave (*S*)-**11** in similar yield but substantially lower ee (entry 5; 10% ee).

Using the most promising conditions of toluene as the solvent and TFA as the co-acid we briefly examined the effect of temperature on the reaction of **10** with cyclohexanone (Table 3).

Table 3 Effect of temperature on asymmetric α-oxybenzoylation of cyclohexanone[a]

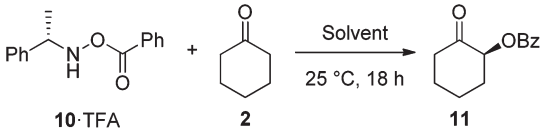


10·TFA **2** **11**

Entry	Temp °C	% Yield **11**[b]	% ee[c]
1	30	54	7
2	25	51	35
3	20[d]	51	37
4	10[e]	41	41
5	0	27	43

[a] All reactions carried out with **10**·TFA (1 equiv), cyclohexanone (1 equiv), [0.5] M, 18 h, at stated temperature. [b] Isolated yield. [c] Determined by HPLC, Chiracel OD, (*S*)-enantiomer of product obtained in excess. [d] Temperature range 20–22 °C. [e] Temperature range 7–10 °C.

Table 4 Re-examination of reaction solvent[a]



10·TFA **2** **11**

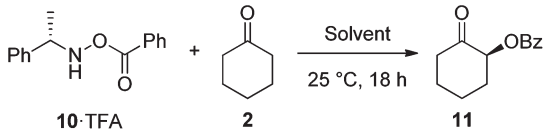
Entry	Solvent	% Yield **11**[b]	% ee[c]
1	DMSO	72	0
2	Acetone	41	0
3	EtOH	65	0
4	CH_2Cl_2	45	13
5	Et_2O	49	9
6	PhMe	51	37
7	Hexane	53	17

[a] All reactions carried out with **10**·TFA (1 equiv), cyclohexanone (1 equiv), [0.5] M, 25 °C, 18 h. [b] Isolated yield. [c] Determined by HPLC, Chiracel OD, (*S*)-enantiomer of product obtained in excess.

Unsurprisingly, higher ee's were observed at lower temperatures (up to 43% ee at 0 °C); however, the decrease in temperature also reduced the rate of reaction such that under a standard set of conditions the isolated yield of the product reduced to 27% (entry 5). At temperatures above 25 °C, the ee rapidly deteriorated (entry 1). It was therefore decided to continue with reaction optimisation at room temperature, which gave a favourable balance between yield and level of asymmetric induction along with providing the most convenient reaction conditions (entry 3). Encouragingly, mass balance for these transformations was achieved through recovered starting materials and not accompanying side reactions–decomposition products. This observation was consistent throughout the work.

Prior to examination of the amine substituent it was decided to re-examine the effect of solvent on the transformation (Table 4). Within the initial solvent screen (Table 1), we were conscious of the fact that all ee's measured were <5%. Due to potential error margins associated with these measurements, it was considered appropriate to confirm that toluene was indeed the most appropriate solvent for the transformation. As can be seen from Table 4, toluene remained the optimal solvent for the reaction (entry 6; 51% yield, 37% ee). Interestingly, highly polar solvents capable of accepting a H-bond gave the product **11** in 0% ee (entries 1–3). Within this screen we also examined hexane as the reaction medium, in order to determine whether the higher ee's observed with toluene were a result of the aromatic nature or the polarity (or both) of this solvent (entry 7). Despite giving the product in comparable yield (53%), the ee was significantly lower; therefore we concluded that the higher ee's obtained were influenced by aromatic hydrocarbons.

Table 5 Effect of aromatic solvents on asymmetric α-oxybenzoylation[a]



10·TFA **2** **11**

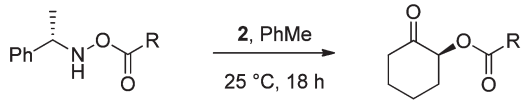
Entry	Solvent	% Yield **11**[b]	% ee[c]
1	Benzene	49	42
2	Toluene	51	37
3	Xylene	48	33
4	Anisole	38	32
5	Hexafluorobenzene	48	23
6	2-Nitrotoluene	35	15
7	Nitrobenzene	41	14

[a] All reactions carried out with **10**·TFA (1 equiv), cyclohexanone (1 equiv), [0.5] M, 25 °C, 18 h, in solvent stated. [b] Isolated yield. [c] Determined by HPLC, Chiracel OD, (*S*)-enantiomer of product obtained in excess.

Driven by this finding, a range of electron poor (entries 5–7) and electron rich (entries 2–4) aromatic solvents along with benzene were examined as the reaction medium (Table 5). This showed that for the proposed [3,3]-sigmatropic rearrangement, electron rich aromatics gave the product in significantly higher ee's than electron poor aromatic solvents. Benzene proved to be the optimal reaction solvent (entry 1) giving the product in comparable yield and marginally higher ee than our previous best result (49% yield; 42% ee).

It was clear that significant influence on the diastereomeric transition states of the rearrangement could be exerted by both the reaction medium and the acid used. Encouraged by these findings we went on to examine the effect of both the *O*-acyl and N-substituent on the rearrangement process (Tables 6 and 7). Introduction of alternative acyl groups onto the reagent scaffold was achieved through use of the Geffken method,[15] which has previously been applied to the preparation of related hydroxylamine derivatives.[16] Reaction of a carboxylic acid **12** with carbonyl diimidazole (CDI) at 0 °C for 15 minutes, followed by addition of *N*-(*S*)-α-methyl benzyl hydroxylamine **13**[17] gave the products **15–18** (Scheme 3). Achiral reagents derived from *N*-methyl hydroxylamine hydrochloride were also prepared by the same method in order to evaluate levels of asymmetric induction, if any, within the reactions of **15–18**. In the preparation of both the achiral and chiral series of reagents the transformations were not optimised (5–68%), but did provide adequate amounts of material to allow for examination of *O*-substitution on the stereochemical outcome of α-functionalisation (Table 6).

Table 6 α-Functionalised cyclohexanone derivatives from reagents **15–18**[a]



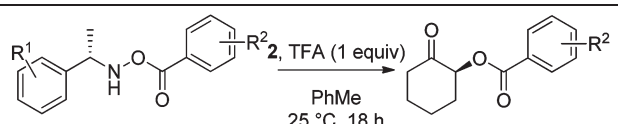
10·TFA R = Ph
15·TFA R = ^{t}Bu
16·TFA R = 3,5-(^{t}Bu)$_2$C$_6$H$_3$
17·TFA R = 2,4,6-(Me)$_3$C$_6$H$_2$
18·TFA R = Me

11 R = Ph
20 R = ^{t}Bu
21 R = 3,5-(^{t}Bu)$_2$C$_6$H$_3$
22 R = 2,4,6-(Me)$_3$C$_6$H$_2$
23 R = Me

Entry	Reagent	Product	% Yield[b]	% ee
1	**10**	11	51	37[c]
2	**15**	20	28	35[d]
3	**16**	21	37	25[e]
4	**17**	22	40	9[f]
5	**18**	23	50	14[g]

[a] All reactions carried out with hydroxylamine reagent (**15–18**) (1 equiv), TFA (1 equiv), cyclohexanone (1 equiv), [0.5] M, 25 °C, 18 h, in PhMe. [b] Isolated yield. [c] Determined by HPLC, Chiracel OD, (*S*)-enantiomer of product obtained in excess. [d] Determined by ^{1}H NMR spectroscopy, using 0.1 equivalents of shift reagent Eu(hfc)$_3$. [e] Determined by ^{1}H NMR spectroscopy, using 1.3 equivalents of shift reagent Eu(hfc)$_3$. [f] Determined by HPLC, Chiracel OD column, 5% IPA–Hexane, 1.0 mL min^{-1} (t_1 = 9.7 min; t_2 = 12.1 min). [g] Determined by ^{1}H NMR spectroscopy, using 0.3 equivalents of shift reagent Eu (hfc)$_3$.

Table 7 Effect of modifying electronics on α-functionalisation[a]



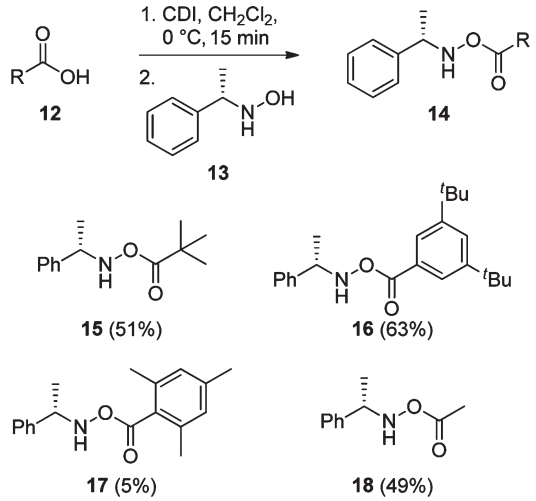
24 R^1 = H; R^2 = 4-F
25 R^1 = H; R^2 = 4-OMe
26 R^1 = H; R^2 = 4-NMe$_2$
27 R^1 = H; R^2 = 3,4,5-(OMe)$_3$
28 R^1 = 4-F; R^2 = H
29 R^1 = 4-Me; R^2 = H
30 R^1 = 4-OMe; R^2 = H

31 R^2 = 4-F
32 R^2 = 4-OMe
33 R^2 = 4-NMe$_2$
34 R^2 = 3,4,5-(OMe)$_3$
11 R^2 = H
11 R^2 = H
11 R^2 = H

Entry	Reagent	R^1	R^2	% Yield[b]	% ee[c]
1	**10**	H	H	51	37[d]
2	**24**	H	4-F	48	22
3	**25**	H	4-OMe	38	33
4	**26**	H	4-NMe$_2$	44	32
5	**27**	H	3,4,5-(OMe)$_3$	39	17
6	**28**	4-F	H	43	22[d]
7	**29**	4-Me	H	42	56[d]
8	**30**	4-OMe	H	N/A[e]	N/D

[a] Reactions carried out with hydroxylamine reagent (**24–30**) (1 equiv), TFA (1 equiv), cyclohexanone (1 equiv), [0.5] M, 25 °C, 18 h, in PhMe. [b] Isolated yield. [c] Determined by HPLC, Chiracel OD. [d] (*S*)-Enantiomer of product obtained in excess. [e] Decomposition of reagent observed.

Results from this study demonstrated that increasing the steric bulk of the *O*-acyl group did not improve the level of asymmetric induction in the reaction (entries 2–4), as compared to the parent reagent **10** (entry 1). A significantly lower ee obtained from use of an *O*-2,4,6-trimethyl benzoyl group (entry 4; 9% ee) prompted examination of the acetyl group (entry 5), but was found to be less efficient in promoting asymmetry (14% ee).



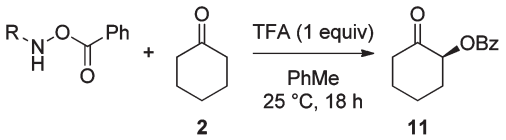
Scheme 3 Variation of acyl group using Geffken method.

With the reaction proceeding *via* a concerted pericyclic rearrangement it was believed the electronics of the system was a factor that could impact results and thus warranted investigation. We therefore prepared a series of reagents **24–30**[14,15] which probed this feature on both the nitrogen and oxygen substituents (Table 7). Once again achiral reagents derived from *N*-methyl hydroxylamine hydrochloride were also prepared by standard methods to establish methods for ee determination.

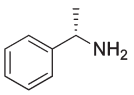
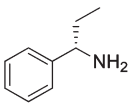
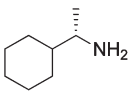
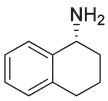
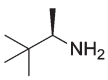
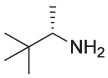
Although an appreciable decrease in asymmetric induction was observed as a direct result of an electron-withdrawing substituent on the *O*-acyl group (entry 2), attempts made to bring about the reverse effect through incorporation of electron-donating groups (entries 3–5) did not offer any enhancement to the benchmark result (entry 1). Examining substituent effects of the benzylamine portion of the reagent revealed a significant influence on the stereochemical outcome of the transformation (entries 6–8). It was again found that an electron-withdrawing group brought about a decrease in the level of asymmetric induction (entry 6), however, an electron-donating group provided a notable increase in the measured ee of the product **11** (entry 7; 56% ee). A small decrease in isolated yield was also observed; nevertheless the combined values for ee and yield had now surpassed that previously established. In an attempt to exploit this trend further, an amine bearing a *p*-methoxybenzyl substituent was incorporated into the reagent. This reagent **30** was unstable under the acidic reaction conditions (entry 8), attributed to the presence of a lone-pair of electrons on the methoxy group. As this would undoubtedly be the case for other strong electron-donating substituents, this avenue of investigation was not pursued further.

Insight gained from this study led us to believe that it was the amine portion of the reagent that had greatest influence over the stereochemical outcome of the reaction, as opposed to the *O*-acyl group that was our initial focus. For this reason we elected to examine variation of both the size and nature of the N-substituent (Table 8).

Table 8 Influence of amine structure on α-functionalisation process[a]



2 11

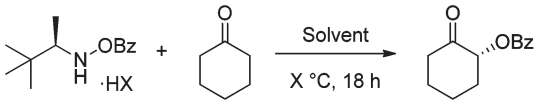
Entry	Reagent	Amine	% Yield **11**[b]	% ee[c]
1	**10**		51	37[d]
2	**38**		58	40[d]
3	**39**		46	22[d]
4	**40**		38	55[e]
5	**41**		35	75[e]
6	**42**		34	75[d]

[a] All reactions carried out with hydroxylamine reagent (**38**–**42**) (1 equiv), TFA (1 equiv), cyclohexanone (1 equiv), [0.5] M, 25 °C, 18 h, in solvent stated. [b] Isolated yield. [c] Determined by HPLC, Chiracel OD. [d] (*S*)-Enantiomer of product obtained in excess. [e] (*R*)-Enantiomer of product obtained in excess.

Continuing with commercially available chiral amines, the first reagent to be synthesised in this series was derived from (*S*)-α-ethyl benzylamine, whereby only a slight change in steric environment surrounding the reactive nitrogen atom was introduced (entry 2). This reagent **38** was found to generate the corresponding α-oxybenzoyl cyclohexanone product **11** in marginally better yield and ee, compared to the (*S*)-α-methyl benzylamine derived reagent **10** (entry 1). From here, a series of chiral amines, both aliphatic and benzylic, were incorporated into the reagent and examined for their effectiveness in the α-functionalisation reaction (entries 3–6). Results from this series of experiments showed a definite correlation between the size of the N-substituent and level of asymmetric induction, with the best result obtained from reagent **41**, derived from (*R*)-3,3-dimethyl-2-butylamine, giving the product **(*R*)-11** in a pleasing 75% ee (entry 5). It was also observed that an increase in steric demand of the N-substituent of these reagents was accompanied by a decrease in conversion. Whilst not ideal, we continued in our pursuit of a highly asymmetric transformation, with the hope of resolving the issue of low yields at a later stage.

Following identification of a structurally optimised chiral hydroxylamine reagent **41**, final screens were carried out to confirm the reaction conditions were still optimal for the asymmetric rearrangement process.

Table 9 Optimisation of α-oxybenzoylation reaction of cyclohexanone using reagent **41**[a]



41 2 11

Entry	Solvent	HX	Temp °C	% Yield[b]	% ee[c,d]
1	Toluene	TFA	20	35	75
2	Acetone	TFA	20	11	77
3	CH_2Cl_2	TFA	20	27	81
4	Hexane	TFA	20	16	79
5	Toluene	HCl	20	12	12
6	Toluene	MsOH	20	10	70
7	Toluene	TCA	20	25	70
8	Toluene	DPP	20	18	73
9	Toluene	TFA	35	51	67
10	Toluene	TFA	10	28	82
11	Toluene	TFA	0	20	83
12[e]	Toluene	TFA	10	55	82

[a] All reactions carried out with **41**·HX (1 equiv), cyclohexanone (1 equiv), [0.5] M, 18 h, unless otherwise stated. [b] Isolated yield. [c] Determined by HPLC, Chiracel OD. [d] (*R*)-Enantiomer of product obtained in excess. [e] Two equivalents of reagent used with reaction time of 48 h.

Variation of the reaction medium showed consistent ee's were observed with each solvent examined (entries 2–4), suggesting a defined transition state with less dependence on relative solvent effects. Toluene, however, remained the optimal solvent for combined ee and yield (entry 1). The effect of the acid showed less dependence on the acidity of the acid than in earlier investigations (*cf.* Table 9 entries 5–8 and Table 2). It was noted, however, that strong acid (HCl; entry 5) still had a negative impact on the level of asymmetry observed. Altering the reaction temperature (entries 9–11) resulted in an increased yield and decreased ee at higher temperature (entry 9) and a lower yield with significantly improved ee at lower temperature (entries 10 and 11). As a high level of enantioselectivity was the foremost goal of our efforts, the optimum temperature appeared to be 10 °C (entry 10), with lower temperatures showing minimal further enhancement (entry 11). In order to improve the overall yield the reaction at 10 °C was conducted over 48 hours using two equivalents of reagent **41**·TFA. This produced our best result to date for the asymmetric α-oxybenzoylation of cyclohexanone (entry 12; 55% yield; 82% ee). Once again, the mass balance was accounted for with unreacted starting materials. Leaving the reaction for longer or increasing the amount of reagent did not improve this outcome.

A transition state model consistent with the sense of asymmetry observed is shown in Fig. 2. We believe the reaction is proceeding through a 6-membered chair-like transition state with the bulky nitrogen substituent adopting an equatorial position. Steric interaction between the methyl group of the auxiliary and the cyclohexane ring disfavours approach of the oxybenzoyl group from the *Si*-face of the enamine (**43**). Approach of the oxybenzoyl group from the *Re*-face of the enamine (**44**) removes this steric interaction and leads to the observed product (*R*)-**11** when using reagent (*R*)-**41**·TFA.

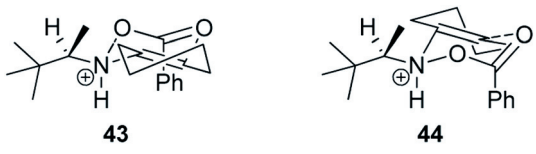
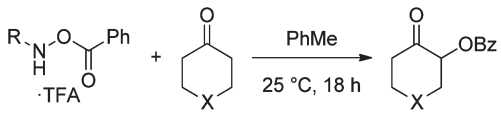
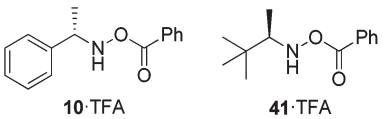


Fig. 2 Proposed transition state model.

Table 10 Application of optimised reaction conditions to various cyclic ketones[a]





Entry	X	% Yield[b]	% ee	% Yield[b]	% ee
1[e]	CH_2	51	37[c]	55	82[d]
2	—	28	24	Not Isolated	
3	CH_2CH_2	35	25[c]	9	55[d]
4	O	24	22	15	49
5	S	8	23	Not Isolated	
6	N-Boc	34	26	4	45
7	$C(CH_3)_2$	49	28	44	62
8	$C(CO_2Et)_2$	51	30	28	67
9[e]	$C(OCH_2CH_2O)$	51	39	35	89
10	CH^tBu	50	>98[f]	Not performed	

[a] All reactions carried out with **10**·TFA or **41**·TFA (1 equiv), cycloalkanone (1 equiv), [0.5] M, 18 h, unless otherwise stated. [b] Isolated yield. [c] (*S*)-Enantiomer of the product produced in excess. [d] (*R*)-Enantiomer of the product produced in excess. [e] Reactions performed at 10 °C for 48 hours with 2 equivalents of reagent. [f] Diastereomeric excess.

Having examined reagent structure and reaction conditions we went on to study a series of alternative ketone substrates with both **10**·TFA and **41**·TFA to evaluate some of the scope and limitations of the transformation (Table 10). As observed with cyclohexanone as the substrate, variation of the chiral reagent from **10**·TFA to **41**·TFA resulted in significantly higher levels of asymmetry for each product isolated, by a factor of around 2, which suggested a direct correlation between the size of the N-substituent and the stereochemical outcome of the reaction. In addition, with each product isolated (*S*)-**10** led to the opposite enantiomer compared to that generated by (*R*)-**41**, suggesting a consistent transition state for each transformation. Use of cyclopentanone (entry 3) or cycloheptanone (entry 4) led to lower yields and ee's being observed for each of the products isolated suggesting the reagents described have been optimised for 6-membered ring substrates. In instances where the cyclohexanone skeleton was retained (entries 7–10), the yields and ee's were significantly higher and closer in value to those of cyclohexanone (entry 1). For example, reaction of **41**·TFA with cyclohexane-1,4-dione monoethylene ketal gave the product in 89% ee. Examination of the effect of substitution of the cycloalkanone ring with the *meso*-compound 4-*tert*-butyl cyclohexanone provided a particularly interesting result. When reacted with achiral *N*-methyl-*O*-benzoyl hydroxylamine hydrochloride under standard conditions the product was isolated as a 2 : 1 mixture of diastereoisomers (69% combined yield), the major isomer being the expected *cis*-product. Reaction of 4-^{t}butyl cyclohexanone with chiral reagent **10**·TFA (entry 10) gave the product with complete stereoselectivity, generating the *cis*-isomer in 50% yield.

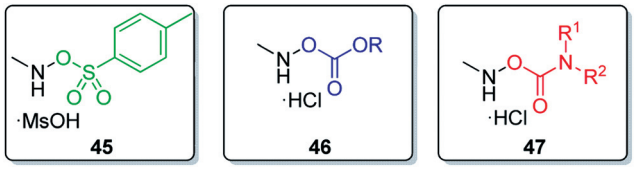
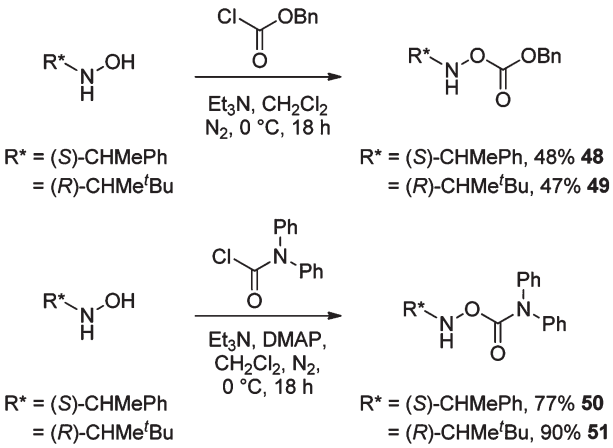


Fig. 3 Achiral reagents for the α-oxytosylation, oxycarbonoylation and oxycarbamoylation of carbonyl compounds.



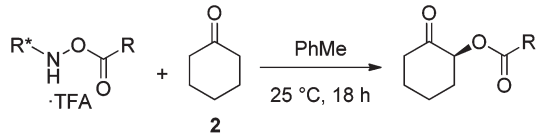
Scheme 4 Synthesis of chiral carbonoyl and carbamoyl reagents.

Previous work within the group had involved development of hydroxylamine derived reagents **45–47** as alternatives to the oxybenzoylation process for the direct α-oxytosylation,[8] α-oxycarbonoylation[6] and α-oxycarbamoylation[7] of carbonyl compounds (Fig. 3).

In an effort to determine if the technology developed within this work could also be applied to alternative migrating groups we prepared reagents for asymmetric oxycarbonoylation and oxycarbamoyl **48–51** directly from the corresponding hydroxylamine precursor by treatment with the appropriate acyl chloride under basic reaction conditions (47–90% yield) (Scheme 4).

Having prepared reagents **48–51** they were each reacted with cyclohexanone under standard conditions: toluene, TFA, room temperature, 18 hours (Table 11). The results obtained displayed similar trends to those observed for reagents **10** and **41**, consistent with similar mechanisms operating within each of these transformations. Yields observed for each reagent used were similar in each case (entries 2 and 3), with consistently higher ee's observed with reagents derived from *N*-(*R*)-3,3-dimethyl-2-butyl hydroxylamine. Whilst the ee's were not as high as those observed in the α-oxybenzoylation process (entry 1), it should be noted that these reactions are unoptimised at this stage.

Table 11 Asymmetric α-oxycarbonoylation and oxycarbamoylation of cyclohexanone[a]



Entry	R	R* % Yield[b]	R* % ee	R* % Yield[b]	R* % ee
1[e]	Ph	51	37[c]	55	82[d]
2	OCH_2Ph	54	33	46	58
3	NPh_2	51	39	44	63

[a] All reactions carried out with cyclohexanone (1 equiv), [0.5] M, 18 h, unless otherwise stated. [b] Isolated yield. [c] (*S*)-Enantiomer of the product produced in excess. [d] (*R*)-Enantiomer of the product produced in excess. [e] Reaction performed at 10 °C for 48 hours with 2 equivalents of reagent.

Conclusions

In summary, we have described efficient methods for the preparation of a series of hydroxylamine salts that can be used for the asymmetric α-oxygenation of carbonyl compounds in up to 89% ee. The levels of asymmetric induction were influenced by solvent polarity, acid strength and, to a lesser extent, temperature. Increasing the steric bulk around the nitrogen atom of the hydroxylamine reagent led to increased levels of asymmetric induction, which was also found to be detrimental to conversion. In addition, a transition state consistent with the sense of asymmetric induction observed and with experimental findings has been proposed. The direct and regular correlation between ee of products and the nitrogen substituent suggests a consistent transition state for each carbonyl compound examined although optimisation for each substrate would be necessary. The ease with which these transformations can be carried out together with the stability and simplicity of reagent synthesis suggest this to be an effective alternative method with which to access this important class of substrate.

Experimental section

General procedure 1 for hydroxylamine reagent synthesis using Phanstiel method[14]

A solution of benzoyl peroxide **8** (75% solution in water, 6.66 g, 0.021 mol) in CH_2Cl_2 (103 mL) was added quickly to a mixture of an amine (0.021 mol) and pH 10.5 buffer solution (103 mL) (prepared by mixing aqueous $NaHCO_3$ (222 mL, 0.75 M) with aqueous sodium hydroxide (78 mL, 1.5 M)). Vigorous stirring was continued at room temperature for 18 hours. The reaction mixture was then extracted with CH_2Cl_2 (3 × 50 mL), washed with brine (50 mL), dried (Na_2SO_4) and concentrated to give the crude product. Conversion to the HCl salt was achieved by passing HCl gas through a solution of the crude hydroxylamine (1 mmol) in diethyl ether (25 mL). The precipitated hydrochloride salt was collected by filtration under reduced pressure, washing with ether, and then drying under reduced pressure.

General procedure 2 for hydroxylamine reagent synthesis using Geffken method[15]

Carbonyl diimidazole (1.04 g, 6.40 mmol) was added slowly (over 5 min) to a cooled solution (0 °C) of a carboxylic acid (6.40 mmol) in CH_2Cl_2 (20 mL) and stirring was continued for 15 min until evolution of CO_2 ceased. The appropriate hydroxylamine (1.2 equiv, 7.68 mmol) was then added quickly, and stirring was continued for 1 hour. The reaction mixture was then diluted with CH_2Cl_2 (10 mL), washed with ice-cold 1M HCl (13 mL), saturated $NaHCO_3$ solution (13 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated to give the crude product, which was purified by column chromatography.

General procedure 3 for α-functionalisation of carbonyl compounds

The ketone (1 mmol) was added dropwise (over 5 min) to a stirred solution of the hydroxylamine salt (1 mmol, 1 equiv) in the indicated solvent (2 mL). Stirring was continued at 25 °C for 18 hours. The reaction mixture was diluted with brine (10 mL) and extracted with ethyl acetate (4 × 10 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated to give the crude product which was purified on silica.

Acknowledgements

The authors thank the EPSRC and Syngenta for financial support and the Mass Spectrometry Service, Swansea for high-resolution spectra.

Notes and references

1 For a recent review in the area, see: E. Ilardi, C. E. Stivala and A. Zakarian, *Chem. Soc. Rev.*, 2009, **38**, 3133.
2 A. M. M. Castro, *Chem. Rev.*, 2004, **104**, 2939.
3 U. Nubbemeyer, *Synthesis*, 2003, 961.
4 C. S. Beshara, A. Hall, R. L. Jenkins, K. L. Jones, T. C. Jones, N. M. Killeen, P. H. Taylor, S. P. Thomas and N. C. O. Tomkinson, *Org. Lett.*, 2005, **7**, 5729.
5 C. S. Beshara, A. Hall, R. L. Jenkins, T. C. Jones, R. T. Parry, S. P. Thomas and N. C. O. Tomkinson, *Chem. Commun.*, 2005, 1478.
6 A. Hall, K. L. Jones, T. C. Jones, N. M. Killeen, R. Porzig, P. H. Taylor, S. C. Yau and N. C. O. Tomkinson, *Synlett*, 2006, 3435.
7 A. Hall, E. P. Huguet, K. L. Jones, T. C. Jones, N. M. Killeen, S. C. Yau and N. C. O. Tomkinson, *Synlett*, 2007, 293.
8 O. R. S. John, N. M. Killeen, D. A. Knowles, S. C. Yau, M. C. Bagley and N. C. O. Tomkinson, *Org. Lett.*, 2007, **9**, 4009.
9 H. O. House and F. A. Richey Jr., *J. Org. Chem.*, 1969, **34**, 1430.
10 C. H. Cummins and R. M. Coates, *J. Org. Chem.*, 1983, **48**, 2070.
11 The N–O bond strength in hydroxylamine has been calculated to be 63 kcal mol^{-1}:K. B. Wiberg, *J. Phys. Chem.*, 1992, **96**, 5800.
12 Y. Zhu, K. J. Manske and Y. Shi, *J. Am. Chem. Soc.*, 1999, **121**, 4080.
13 O. Lifchits, N. Demoulin and B. List, *Angew. Chem., Int. Ed.*, 2011, **50**, 9680.
14 Q. X. Wang, J. King and O. Phanstiel IV, *J. Org. Chem.*, 1997, **62**, 8104.
15 D. Geffken, *Chem. Ber.*, 1986, **119**, 744.
16 T. C. Jones and N. C. O. Tomkinson, *Org. Synth.*, 2007, **84**, 233.
17 Prepared by hydrolysis of **10** under standard conditions: L. Wang and O. Phanstiel IV, *J. Org. Chem.*, 2000, **65**, 1442.

