Accessible sugars as asymmetric olefin epoxidation organocatalysts: glucosaminide ketones in the synthesis of terminal epoxides†

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A systematically varied series of conformationally restricted ketones, readily prepared from *N*-acetyl-D-glucosamine, were tested against representative olefins as asymmetric epoxidation catalysts showing useful selectivities against terminal olefins and, in particular, typically difficult 2,2-disubstituted terminal olefins.

Introduction

Chiral epoxides are found in many natural products[1] and are highly versatile electrophilic intermediates which can be manipulated into a large variety of related functional groups. Asymmetric epoxidations[2] have long been performed using metal-mediated methodology such as the powerful transformations developed by Sharpless[3] and Jacobsen.[4] Other important methods involve the use of chiral dioxiranes and oxaziridines, typically derived from precursor ketones, aldehydes and imines as versatile organocatalysts[5] with increasingly broad olefin substrate specificities allowing normally high conversions and selectivities. Among these methods, heterocyclic ketones, including fructose- and oxazolidinone-bearing ketones **1–4**, have been successfully employed for the epoxidation of a certain range of olefins such as unfunctionalised *trans*-, trisubstituted and terminal olefins[5a] (Fig. 1).

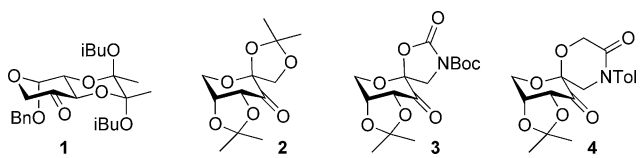

Fig. 1 Selected examples of carbohydrate-based asymmetric epoxidation organocatalysts.

However, certain motifs and especially 2,2-disubstituted terminal olefinic systems remain challenging substrates for epoxidation with high stereoselectivity[6] (*e.g.* 30% and 58% ee for α-methylstyrene and α-isopropylstyrene, respectively, with catalyst **3**).[7] As a solution to these problems, alternative methods have been reported for the synthesis of 2,2-disubstituted terminal epoxides such as the use of stoichiometric amounts of keto bile acids[8] as asymmetric inducers (30–76% ee for α-methylstyrene) and chloroperoxidases[9] (20–89% ee). Although the last method provides excellent selectivities, this specialist biocatalytic method is most successful for 2,2-disubstituted aliphatic alkenes and only some 2-aryl olefins such as α-methylstyrene derivatives have been employed to date. During the preparation of this manuscript, Shibasaki and co-workers[10] revealed the addition of dimethyloxosulfonium methylide to ketones catalysed by chiral multimetallic complexes (up to 97% ee) and a procedure reported by Shi[6] employed a new lactam ketone system which enhances the enantioselectivity for the epoxidation of 2,2-disubstituted terminal olefins up to 88% ee. Since 2,2-disubstituted terminal epoxides are implicated in the synthesis of various α-arylpropionic acids (non-steroidal antiinflammatory drugs–NSAIDs and household pain killers) and these analogues are commonly prepared *via* enzymatic resolution procedures,[11] the development of a new catalytic system able to synthesise 2,2-disubstituted terminal epoxides *via* chemical asymmetric epoxidation of the corresponding alkenes would be highly desirable.

With a view to addressing this goal and some prior limitations,[12] we present here a novel class of chiral ketones readily derived from an abundant, chiral pool carbohydrate, *N*-acetyl-D-glucosamine. Carbohydrates are a naturally occurring, inexpensive, renewable, readily available source of chirality which contain a high density of stereogenic centres and may provide advantageously rigid frameworks.[13] Due to these favourable properties, they have already proven to be effective scaffolds for organocatalysts in asymmetric epoxidations.[5a] In our choice of scaffold **I** (Fig. 2), we considered key advantages to be the often powerful directing effect of α-substituents,[14] and conformational rigidity afforded by the *trans*-decalin-like benzylidene-4,6-*O*-acetal. Indeed, it has been noted previously that conformational flexibility in such epoxidising organocatalysts may have dramatically detrimental effects on stereoselectivity.[5a] Moreover, we considered that the use of an α-substituent with the potential to act as Lewis base (C-2 carboxamide) would allow scope for wide-ranging tuning of

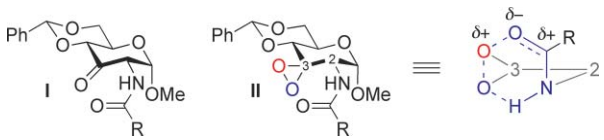

Fig. 2 Putative interactions between dioxirane at C-3 and carboxamide at C-2.

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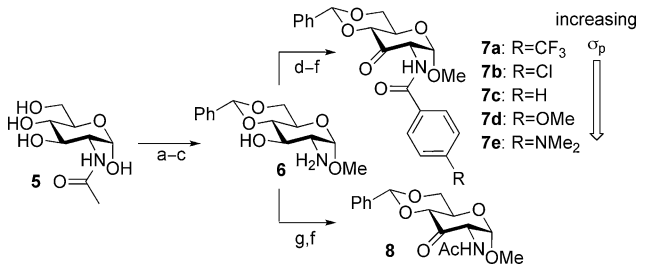
† Electronic supplementary information (ESI) available: Synthesis and characterization of ketones **7a–e** and **8**, epoxidation procedures, optimization studies, proposed model for the stereochemical outcome, characterization of epoxides **10**, **15–18** and **24–28** along with the data for the determination of the enantiomeric excess. See DOI: 10.1039/b911675c

a putative dioxirane at C-3 **II** (Fig. 2), through substituent (R) alteration.

Results and discussion

Putative dioxirane precursors, ketonic amides **7a–e** and **8** containing just such a vicinal functional group pattern, were synthesised over 5–6 steps from commercially available *N*-acetylglucosamine in overall yields up to 59% giving simple and robust access to these potential catalysts on gram scales (Scheme 1). Thus, anomeric protection as methyl pyranoside using acetyl chloride in methanol, regioselective 4,6-*O*-protection as benzylidene acetal and base-mediated deamidation of *N*-2 gave versatile aminoalcohol intermediate **6**. Amidation of the alpha anomer of **6** with either acetic anhydride or appropriate *para*-substituted benzoyl chloride afforded the corresponding amide which was then oxidised under Swern conditions to give **7a–e** and **8**, displaying a representative range of electronic properties (varied σ_p).

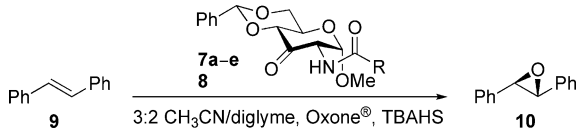


Scheme 1 Synthesis of carbohydrate ketone catalyst precursors based on scaffold **I**. *Reagents and conditions*: (a) AcCl, MeOH; (b) $PhCH(OMe)_2$, *p*-TsOH, DMF, 70 °C, 80% from **5**; (c) KOH, EtOH, 80 °C, 76%; (d) *p*-R-BzCl, 0 °C, pyridine, DCM; (e) NaOH, MeOH; (f) DMSO, $(COCl)_2$, Et_3N, DCM/THF, –78 °C to rt, 45–97% (yields quoted over 3 steps, see ESI† for full details); (g) Ac_2O, NaOMe, MeOH, 81%.

With these putative ketone organocatalysts in hand, suitable conditions for the epoxidation of a testing model olefin, *trans*-stilbene **9**, using *p*-Cl benzamide **7b** were investigated with respect to: solvent system; temperature; volume of organic solvent; pH; equivalents of co-oxidant Oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$); reaction time; and duration of Oxone® addition. Promising reaction conditions were found: 3 : 2 CH_3CN/diglyme at pH 10.6 using 1 equivalent of **7b** at 25 °C over 2.5 h reaction in the presence of 3 equivalents of Oxone® added over 30 min. These conditions were then screened against *trans*-stilbene as a substrate using the full range of ketones **7a–e** and **8** to test both potential activity and selectivity of such ketones (Table 1).

Although some conversions were found to be low under these conditions, for *trans*-stilbene **9** as a difficult substrate (Table 1, entries 2–7) the across-the-board activity with all ketones and broadly reasonable stereoselectivities (56–76% ee) showed the initial potential of the keto glucosaminide scaffold. Conversions could be improved to usable levels without too severe a loss of selectivity (Table 1, entries 8–12) using a greater excess of Oxone®. The desired ability to tune reactivity through substituent (R) was also confirmed and gave insight into mechanism. For benzamide ketones **7a–e**, a clear trend relating ee to Lewis basicity was also observed. Thus, variation of the *para*-substituent tuned ee from 56% for *para*-CF_3 benzamide ($\sigma_p = +0.53$) up to 76% for *para*-NMe_2 ($\sigma_p = -0.63$). A correlation ($R^2 = 0.88$) was

Table 1 Screening of ketones **7a–e** and **8** in *trans*-stilbene **9** epoxidation[a]

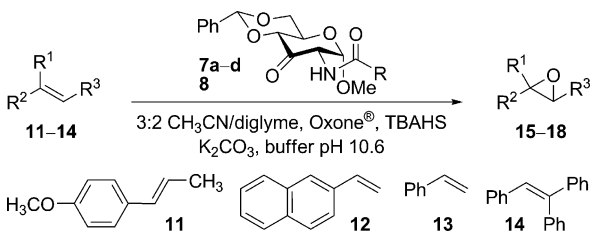


Entry	Catalyst	R	Oxone (equiv)	Conv. (%)[b]	ee (%)[c]
1	α-Me-GlcNAc	n/a	1.4	0	nd
2	**7a**	*p*-$CF_3C_6H_4$	1.4	3	56 (*R*,*R*)
3	**7b**	*p*-ClC_6H_4	1.4	19	65 (*R*,*R*)
4	**7c**	C_6H_5	1.4	26	69 (*R*,*R*)
5	**7d**	*p*-$MeOC_6H_4$	1.4	39	73 (*R*,*R*)
6	**7e**	*p*-$Me_2NC_6H_4$	1.4	7	74 (*R*,*R*)
7	**8**	Me	1.4	43	61 (*R*,*R*)
8	**7a**	*p*-$CF_3C_6H_4$	3	10	nd
9	**7b**	*p*-ClC_6H_4	3	51	67 (*R*,*R*)
10	**7d**	*p*-$MeOC_6H_4$	3	64	66 (*R*,*R*)
11	**7e**	*p*-$Me_2NC_6H_4$	3	10	76 (*R*,*R*)
12	**7d**	*p*-$MeOC_6H_4$	6	57	69 (*R*,*R*)

[a] *General conditions*: 3 : 2 CH_3CN/diglyme, Oxone® added over 30 min, TBAHS (0.1 equiv), K_2CO_3 (5.8 equiv), buffer pH 10.6, catalyst (1 equiv), 2.5 h, rt (see ESI† for full details). [b] Determined by ^1H NMR analysis. [c] Determined by chiral HPLC (Chiralcel OD column).

observed yielding a relative reaction coefficient ($\log(k_R/k_S)$ *vs.* σ_p) of $\rho = -0.28$ consistent with differential development of greater partial positive charge within the amide (Fig. 2) during the more diastereoselective epoxidation modes.[15] Encouraged by these initial results, we screened several other representative olefin substrates such as bis-substituted **11**, terminal **12** and **13**, and tri-substituted **14** (Table 2).

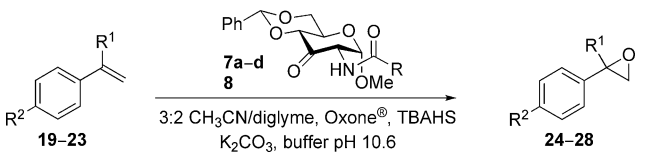
Table 2 Screening of ketones **7a–d** and **8** against other olefin substrates[a]



Entry	Ketone	R	Substrate	Conv. (%)[b]	ee (%)[c]
1	**7a**	*p*-$CF_3C_6H_4$	*trans*-anethole **11**	95	41
2	**7b**	*p*-ClC_6H_4	*trans*-anethole **11**	87	45
3	**8**	Me	*trans*-anethole **11**	> 98	50
4[d]	**8**	Me	*trans*-anethole **11**	> 98	49
5	**7a**	*p*-$CF_3C_6H_4$	vinylnaphthalene **12**	33	25 (*R*)
6	**7b**	*p*-ClC_6H_4	vinylnaphthalene **12**	30	26 (*R*)
7	**7a**	*p*-$CF_3C_6H_4$	styrene **13**	67	67 (*R*)
8	**7c**	C_6H_5	styrene **13**	95	66 (*R*)
9	**7d**	*p*-$MeOC_6H_4$	styrene **13**	76	81 (*R*)
10[d]	**8**	Me	styrene **13**	85	74 (*R*)
11	**7c**	C_6H_5	triphenylethene **14**	40	58 (*R*)

[a] *General conditions*: 3 : 2 CH_3CN/diglyme, Oxone® (1.4 equiv) added over 30 min, TBAHS (0.1 equiv), K_2CO_3 (5.8 equiv), buffer pH 10.6, ketone (1 equiv), 2.5 h, rt (see ESI† for full details). [b] Determined by ^1H NMR analysis. [c] Determined by chiral HPLC (Chiralcel OD column). [d] 0.3 equiv of ketone used.

Table 3 Asymmetric epoxidation of 2,2-disubstituted terminal olefins with ketones **7a–d** and **8**[a]



Entry	Ketone	R	R_1	R_2	Substrate	Conv. (%)[b]	ee (%)[c]
1[d]	**7a**	*p*-$CF_3C_6H_4$	Me	H	**19**	92	4 (*S*)
2[d]	**7b**	*p*-ClC_6H_4	Me	H	**19**	33	23 (*S*)
3[d]	**7c**	C_6H_5	Me	H	**19**	60	30 (*S*)
4[d]	**7d**	*p*-$MeOC_6H_4$	Me	H	**19**	53	19 (*S*)
5[d]	**8**	Me	Me	H	**19**	98	40 (*S*)
6[e]	**8**	Me	Me	H	**19**	98	40 (*S*)
7	**8**	Me	Me	Me	**20**	> 99	42[f] (*S*)
8	**8**	Me	Me	Cl	**21**	> 99	36[f] (*R*)[g]
9	**8**	Me	Me	*i*-Bu	**22**	70	42[f] (*S*)
10	**8**	Me	*i*-Pr	H	**23**	98	24[f]

[a] *General conditions*: 3 : 2 CH_3CN/diglyme, Oxone® (1.4 equiv) added over 30 min, TBAHS (0.1 equiv), K_2CO_3 (5.8 equiv), buffer pH 10.6, ketone (0.06 equiv), 2.5 h, 0 °C. [b] Determined by ^1H NMR analysis. [c] Determined by chiral HPLC (Chiralcel OD column). [d] 1 equiv of ketone used at rt. [e] 0.3 equiv of ketone used at rt. [f] Determined by chiral GC (Cydex B column). [g] Opposite enantiomer obtained (see ESI† for full details).

Ready alteration of reactivity and selectivity of the organocatalysts in the substituent (R) allowed tuning towards substrate. In all cases, good to excellent conversions (67–98%) were possible except with more difficult substrates, terminal 2-vinylnaphthalene **12** (33% with ketone **7a**) and the most hindered, triphenylethene **14** (40% with ketone **7c**).[16] Ketone **8** was an all-round performer and consistently gave high conversions with comparable selectivities across all substrates tested, with little loss of activity even down to 0.06 equiv. Representative epoxidations of notoriously difficult substrate styrene **13** (Table 2, entry 9) complement existing methods (81% ee with catalyst **3**).[17] These epoxidation organocatalysts were then applied to key target 2,2-disubstituted terminal olefins (Table 3). Such substrates might allow direct asymmetric access to NSAID scaffolds, an approach not previously explored. Thus, a variety of 2-alkyl-2-aryl olefins **19–23** were effectively epoxidised in fair to excellent conversions (up to >99%) albeit in moderate selectivity (Table 3, entries 5–8 and 10). In particular, the 70% conversion observed in alkene **22** with ketone **8** (Table 3, entry 9) is, to the best of our knowledge, the highest conversion reported for this substrate, (*S*)-ibuprofen[18] precursor, using an asymmetric organocatalytic epoxidation strategy. Finally, catalyst loading was successfully reduced to 0.3 and 0.06 equiv, with the same enantioselectivity being maintained (Table 3, entries 6–10).

Conclusions

In summary, the keto glucosaminide scaffold **I** made in expeditious, high yielding syntheses from renewable, low cost starting materials gives access to tuneable robust epoxidation organocatalysts which were readily recovered. Until now, single examples of such catalysts have emerged based on single scaffolds with little intended design or scope for substituent tuning of reactivity or selectivity. Although some stereoselectivities were modest, their ability to handle typically challenging terminal olefin substrates (*e.g.* styrene **13**, 76% conv., 81% ee) and including relevant substrates for the first time (*e.g.* NSAID precursor **22**, 70% conv., 42% ee) in a manner that outstrips other strategies[19] may prove usefully complementary. To this end, we continue to focus on the development of these readily created and tuned catalysts under the mild conditions investigated here with other putative substrate types.

Experimental section

General epoxidation procedure

Trans-stilbene **9** (54 mg, 0.3 mmol) and the chosen ketone catalyst (0.3 mmol) were dissolved in the chosen solvent system (4.5 mL). The phase transfer agent, NBu_4HSO_4 (TBAHS), (5 mg, 0.1 mmol) and chosen buffer solution (3 mL in 4×10^{-4} M Na_2EDTA) were added to the solution. Oxone® (254 mg, 0.41 mmol) in aqueous Na_2EDTA (4×10^{-4} M, 2 mL) and a solution of K_2CO_3 in water[20] (2 mL) were added dropwise over a period of 30 min using two separate plastic syringes with teflon needles. The mixture was stirred at room temperature for 2.5 hours. The reaction progress was followed by TLC (20 : 1 petrol : diethyl ether) showing consumption of the starting material (R_f 0.7) and formation of product (R_f 0.5). The reaction was quenched with water (10 mL) and the resulting precipitate was filtered off and washed with a 5 : 1 petrol : diethyl ether solution (30 mL). The remaining precipitate was found to be the pure ketone (40–95%). The epoxide and corresponding olefin were found to be entirely within the petrol solution. The epoxide was separated from the olefin using column chromatography (97 : 2 : 1, petrol : diethyl ether : triethylamine) after conversion had been determined by crude ^1H NMR (calculated from the integration of the olefinic and oxiranic protons of the crude reaction mixture). In the cases where a low conversion was observed, a small portion was purified using semi-prep TLC.

Acknowledgements

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