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Influence of α-methyl substitution of proline-based organocatalysts on the asymmetric α-oxidation of aldehydes

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ABSTRACT

The direct asymmetric organocatalytic α-oxidation of aldehydes using *trans*-2-(*p*-methylphenylsulfonyl)-3-phenyloxaziridine is reported. This method affords the *S* isomer of α-hydroxy aldehydes, thereby complementing the selectivity for the *R* isomer observed using the two-step nitrosobenzene method. Use of α-methylproline and α-methylproline tetrazole significantly increases the enantioselectivity observed for the α-oxidation of aldehydes compared to analogous unsubstituted organocatalysts.

1. Introduction

The direct enantioselective organocatalytic α-oxidation of carbonyl compounds provides a valuable synthetic tool to prepare α-hydroxy compounds, which are important building blocks in organic synthesis.[1,2] One-way to synthesise these is the α-hydroxylation of enolates using chiral oxaziridines.[3] There are several asymmetric catalytic methods, including Sharpless dihydroxylation of enol ethers,[4] epoxidation of silyl enol ethers with chiral dioxiranes,[5] epoxidation of enol ethers with chiral Mn–salen catalysts,[6] and more recently, Yamamoto's BINAP–AgOTf catalytic system generating α-aminoxy ketones from tin enolates and nitrosobenzene,[7] which are then converted to α-hydroxy ketones using $CuSO_4$.[8] In parallel to this indirect α-aminoxylation of enolates, several groups have also reported a direct proline-catalysed variant of this α-aminoxylation, in which preformation of the enolate is not required. The research groups of Zhong,[9] Hayashi[10,11] and MacMillan[12] have reported the direct proline-catalysed α-aminoxylation of aldehydes whilst Hayashi[2,11] and Cordova[1] have reported a similar reaction using ketones.

All these studies differ in the nature of the reaction conditions used, such as the ratio of starting material to nitrosobenzene, catalyst loading, solvent, reaction temperature and reaction time.

MacMillan et al.[12] performed reactions in an aerobic atmosphere with wet solvent ($CHCl_3$). Use of as little as 2 mol % of proline provided the α-aminoxylated aldehydes with high reaction efficiency and enantioselectivity, whilst a loading of 0.5 mol % did not destroy the enantioselectivity. Zhong[9] used DMSO as the solvent and a higher catalyst loading (20 mol %) affording shorter reaction times (10–20 min) with the same excellent enantioselectivities using several aliphatic aldehydes. Hayashi et al.,[10] however, conducted their reactions in acetonitrile with an even higher catalyst loading (30 mol %) for a longer time (24 h) at low temperature (−20 °C) in an attempt to suppress side reactions (homo-dimerisation of nitrosobenzene and self-aldolisation of aldehydes). Nevertheless, similarly moderate yields and excellent enantioselectivities were obtained.

With regards to ketone oxidation, Cordova et al.[1] carried out the reactions with 20 mol % of proline **1** and 10 equiv of ketone in DMSO for 2–3 h, whilst Hayashi et al.[2,11] performed their reactions with 10 mol % of proline **1** with only 2 equiv of ketone in DMF for 4 h, with slow addition of nitrosobenzene to eliminate side reactions. In either case, excellent enantioselectivities were observed.

Meanwhile, Yamamoto et al.[13] demonstrated the efficient α-aminoxylation of ketones and aldehydes using as little as 5 mol % proline-tetrazole **2** in DMSO to afford good yields and excellent enantioselectivities. They also showed that a higher yield of α-aminoxylated cyclohexanone was obtained with proline-tetrazole **2** as compared to that with proline **1**.

Although this α-aminoxylation of carbonyl compounds catalysed by proline **1** and proline-tetrazole **2** provides excellent enantioselectivities, the α-aminoxylated carbonyl compounds are only obtained over two steps, and in certain cases (mainly acyclic ketones), the formation of α-hydroxyamino carbonyl compounds is a side reaction.[1,2,11] Cordova et al.,[14] however, have reported the one-step direct asymmetric α-oxidation of ketones using an oxazidirine as oxidant catalysed by proline **1** and proline-related organocatalysts to afford α-hydroxy ketones directly. Use of nitrosobenzene as the oxidant posed problems due to side reactions[11,12] and the instability of the reagent.[10] This oxaziridine methodology provided an operationally simple method to prepare α-hydroxy ketones, albeit with low enantioselectivities and moderate yields using a limited range of organocatalysts.

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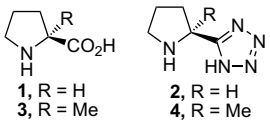


Figure 1. Structures of proline-based organocatalysts **1**–**4**.

Continuing our efforts to probe the effects of α-substitution on the selectivity of proline-based organocatalysts, we have previously reported our results on the use of α-methylproline **3** and α-methylproline tetrazole **4**.[15] We demonstrated that the selectivity of aldol reactions was improved when α-methylproline tetrazole **4** was used rather than the more well known proline-tetrazole **2** (Fig. 1).[15] Therefore, we envisaged that α-substituted organocatalysts **3** and **4**, may improve the enantioselectivity of aldehyde α-oxidation reactions and the results of this study are reported herein.

2. Results and discussion

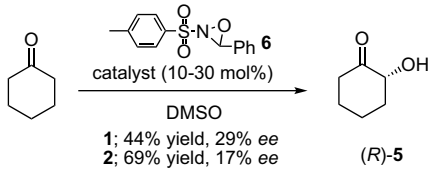
Cordova et al.[14] reported that the oxidation of cyclohexanone to (*R*)-2-hydroxycyclohexanone **5** using proline **1** or tetrazole **2** proceeded with 29% and 17% ee's, respectively, using *trans*-2-(*p*-methylphenylsulfonyl)-3-phenyloxaziridine **6**[16] as the oxidant. (Scheme 1) Whilst these authors did try (*S*)-α-methylproline **3** as a catalyst, they found it resulted in no selectivity.

When we first attempted to repeat this asymmetric α-oxidation using proline **1** and oxaziridine **6** under the conditions reported by Cordova et al.,[14] we were surprised to find that the reaction formed a complex mixture of products. More surprisingly, none of the desired product **5** formed despite several attempts. Oxidant **6** was in fact prepared in the attempted reaction (Scheme 2) from *p*-toluenesulfonimine **8**[16,17] and its oxidant properties demonstrated by the successful oxidation of triphenylphosphine to triphenylphosphine oxide.[16]

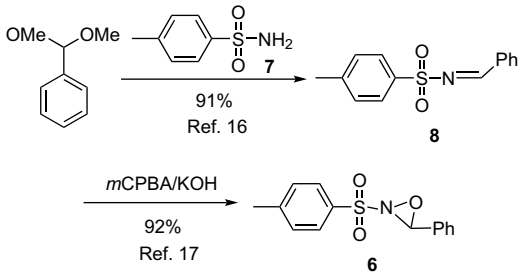
Satisfied that generation of the oxidant **6** was not responsible for the lack of any α-oxidation reaction, we decided to isolate some of the many reaction products. Surprisingly, several of the products were more commonly found in the aldol reaction, in particular β-hydroxyketone **9**, isolated in a 1.3:1 *syn*:*anti* ratio, its dehydration product α,β-unsaturated ketone **10**, and diphenyloxapyrrolizidine **11** (Scheme 3).

Oxapyrrolizidine **11** is a known compound formed by the condensation of proline **1** and benzaldehyde[18] whilst β-hydroxyketone **9** is the aldol product formed between cyclohexanone and benzaldehyde. The only source of benzaldehyde is from the breakdown of oxidant **6** during the reaction. Another interesting by-product isolated was sulfonamide **12**, isolated as a 4.4:1 (*anti*/*syn*) mixture of diastereomers. The structure of sulfonamide **12**[19] was established using X-ray crystallography.[20]

To increase our understanding of oxidation reactions utilising oxaziridine **6**, a number of reactions were carried out where one or more of the reagents were removed. Firstly, cyclohexanone was reacted with oxaziridine **6** without proline **1** being added, affording a mixture of benzaldehyde, *p*-toluenesulfonamide **7** and sulfonimine **8**. Benzaldehyde and sulfonimine **8** were observed by



Scheme 1. Previously reported α-oxidation of cyclohexanone.[14]

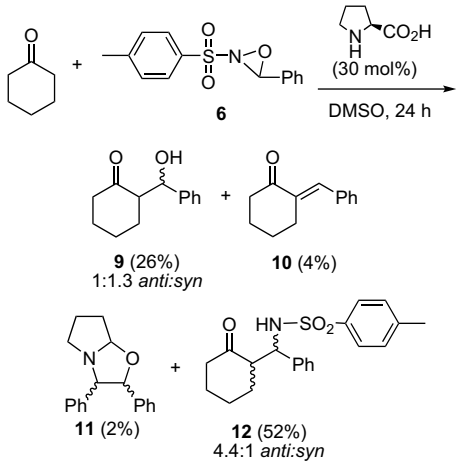


Scheme 2. Synthesis of oxaziridine **6**.

TLC after one hour and were isolated in reasonable yield after 24 h. Secondly, proline **1** and oxaziridine **6** were reacted together. In this case oxaziridine **6** decomposed to give benzaldehyde, *p*-toluenesulfonamide **7** and sulfonimine **8** as observed by TLC after one hour, but no sulfonimine **8** was seen by TLC after 7 h and none by ^{1}H NMR of the crude product after 24 h suggesting proline **1** catalyses the hydrolysis of sulfonimine **8**.[21] Finally oxidant **6** was stirred alone in DMSO establishing that oxaziridine **6** quickly (within 1 h) decomposed to sulfonimine **8** with some benzaldehyde also present. This could result from the oxidation of DMSO to the corresponding dimethyl sulfone with oxaziridine **6** being reduced to sulfonimine **8**. Cordova et al.[22] noted that DMSO was oxidised to dimethyl sulfone in the organocatalytic α-oxidation of cyclohexanone with molecular oxygen as the oxidant.

Given that in DMSO oxaziridine **6** quickly decomposes to form sulfonimine **8** but products **9**–**12** are not formed in the absence of proline **1** we postulated that sulfonamide **12** is formed by either a proline **1** catalysed Mannich reaction of cyclohexanone with sulfonimine **8** or the Michael reaction of *p*-toluenesulfonamide **7** with α,β-unsaturated ketone **10**, which in turn requires proline **1** to access the precursor aldol adduct **9**.

To explore whether the proline-catalysed Mannich or Michael reaction was more likely to have afforded sulfonamide **12**, the formation of sulfonamide **12** was monitored when 1 equiv of ketone **10**[23] was reacted with 1 equiv of *p*-toluenesulfonamide **7** in the presence of proline **1** and DMSO under ambient conditions. After 3 days, TLC analysis showed only starting material, with no sulfonamide **12** formed. When 1 equiv of sulfonimine **8** and 2 equiv of cyclohexanone were stirred with proline **1** in DMSO at room temperature for 17 h, a significant amount of sulfonamide **12** was observed by TLC, together with small amounts of other unidentified



Scheme 3. Products formed during the proline **1** catalysed oxidation of cyclohexanone with oxaziridine **6**.

compounds. Notably, sulfonimine **8** appeared to have been totally consumed. As a result, we conclude that the proline-catalysed Mannich reaction between cyclohexanone and sulfonimine **8** furnishes sulfonamide **12** as a side product in the attempted proline-catalysed α-oxidation of cyclohexanone in DMSO.

The fact that *anti* sulfonamide **12** was obtained as the major isomer in the unexpected proline **1**-catalysed Mannich reaction was not clearly understood. β-Amino carbonyl compounds arising from proline **1**-catalysed Mannich reactions between aromatic imines and ketones or aldehydes have the *syn* configuration.[24] A proline **1**-catalysed Mannich reaction of 2-butanone and an *E*-*p*-toluenesulfonimine in DMSO has also been reported to be *syn* diastereoselective.[25] It is thought that oxaziridine **6** has the *E* configuration[16,17] and sulfonimine **8**, supposedly also with the *E* configuration, should react with cyclohexanone to give *syn* sulfonamide **12** when catalysed by proline **1**. The formation of more *anti*-**12** than *syn*-**12** suggests that oxaziridine **6** decomposes in DMSO to form more of the *Z* isomer of sulfonimine **8**.

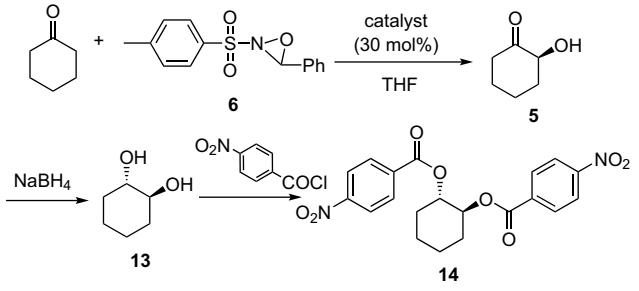
The lack of information in the original report[14] into the production of these significant by-products **9**–**12** is somewhat surprising especially in light of the fact that none of the desired 2-hydroxycyclohexanone **5** was formed in our hands. Given that the key problem appeared to be the rapid decomposition of oxidant **6** in DMSO, we decided to investigate other solvents.

To the best of our knowledge, there have been only several examples of stereoselective α-oxidation of carbonyl compounds using oxaziridine **6**. In all cases, the stereoselectivity was substrate-controlled and THF was used as the solvent.[26,27] Therefore, we envisaged that proline-catalysed α-oxidation of cyclohexanone should proceed in THF. After confirming that oxaziridine **6** remained intact after stirring the oxidant in THF overnight, we attempted the α-oxidation of cyclohexanone with proline in THF. To our delight, all oxaziridine **6** was reduced to sulfonimine **8** with the product 2-hydroxyketone **5** visible by TLC after stirring overnight. Isolation of the product by flash chromatography provided 2-hydroxyketone as a yellow oil, whose ^{1}H NMR data were consistent with literature values.[11] As the purified 2-hydroxyketone **5** appeared to oligomerise on standing, it was converted *in-situ* into 1,2-cyclohexanediol for determination of the stereoselectivity. Thus the *trans* diol **13** was isolated and converted to the bis-*p*-nitrobenzoyl ester derivative **14** thus allowing the enantiomeric excess to be determined using chiral HPLC. Using this method, the efficiency and stereoselectivity of the four catalysts **1**–**4** to effect the asymmetric α-oxidation of cyclohexanone were examined (Table 1).

Our results indicated that the α-methyl substituted catalysts were much less efficient than their parent catalysts. All oxaziridine **6** was consumed after 3 h when proline **1** and tetrazole **2** were used, providing 67% of the isolated diols. In contrast, when α-methylproline **3** and α-methyl tetrazole **4** were used, a significant amount of oxaziridine **6** still remained after 5 days, with the latter catalyst being more effective. In terms of enantioselectivity, a 10% ee was obtained with proline **1**, whereas a 16% ee in favour of the opposite enantiomer was observed with tetrazole **2**. This result is surprising given that the two catalysts usually lead to the same absolute configuration of adducts in many organocatalytic reactions. Whilst α-methyl tetrazole **4** did not improve the enantioselectivity over the unsubstituted catalysts, surprisingly α-methylproline **3** gave 36% ee. This improved stereoselectivity of α-methylproline **3** over α-methyl tetrazole **4** was in contrast to our previous comparison of their relative performance in the catalytic aldol reaction.[15]

Our results are consistent with previous results[22] on the α-oxidation of cyclohexanone with molecular oxygen, in terms of the effects of α-substitution on the organocatalysis, where α-methylproline **3** decreased the yield but increased the enantioselectivity to 48% ee from the 18% ee obtained with proline **1**. On the other hand, acyclic α-methylvaline reduced both the yield and enantioselectivity.

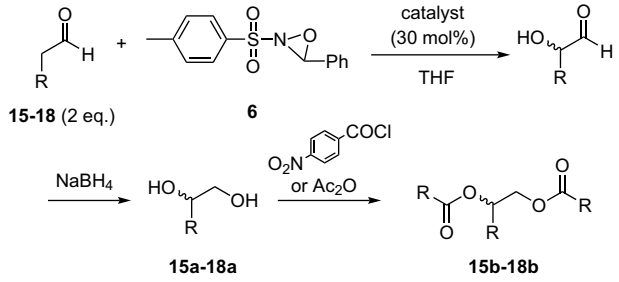
Table 1
Results of the organocatalysed α-oxidation of cyclohexanone with oxaziridine **6**



Catalyst	Time[a]	Yield[b]	ee[c]
1	3 h	67%	10%
2	3 h	67%	16%[d]
3	5 days	7%	36%
4	5 days	25%	9%

[a] Duration of the α-oxidation before sodium borohydride was added.
[b] The isolated combined yields of the *cis* and *trans* diols.
[c] The ee of the *trans* diester derivative determined by chiral HPLC. The absolute configuration of the major enantiomer was determined by comparison of HPLC trace with an enantiopure authentic sample.
[d] The absolute configuration of the major enantiomer was 1*R*, 2*R*, the opposite to the other three experiments.

Table 2
Results of the organocatalysed α-oxidation of aldehydes with oxaziridine **6**



Aldehyde	Catalyst	Time[a]	Yield[b]	$[\alpha]_D$[c]	ee[d]
Ph **15**	**1**	1 h	35%	0	1%
	2	1 h	33%	+2.57	5% (*S*)
	3	2 h	23%	−6.64	12% (*R*)
	4	2 h	59%	+11.75	28% (*S*)
16	**1**	69 h	60%	n.d.	3% (*S*)
	2	77 h	56%	−1.35	15% (*R*)
	3	23 h	49%	+1.38	25% (*S*)
	4	4 h	58%	n.d.	20% (*S*)
Bn **17**	**1**	22 h	67%	n.d.	5% (*S*)
	2	19 h	58%	−3.42	5% (*S*)
	3	19 h	64%	−14.53	48% (*S*)
	3[e]	55 h	63%	−12.31	39% (*S*)
	4	4 h	63%	−11.79	37% (*S*)
*n*Bu **18**	**1**	21 h	66%	n.d.	1% (*S*)
	2	28 h	59%	−3.95	0% (*S*)
	3	22 h	67%	−13.95	45% (*S*)
	4	4 h	64%	−7.94	28% (*S*)

[a] Duration of the α-oxidation before sodium borohydride was added.
[b] The isolated yields of diols **15a**–**18a**.
[c] The $[\alpha]_D$ of the diols **15a**–**18a**.
[d] The ee of the diester derivatives **15b**–**18b** as measured by chiral HPLC.
[e] The reaction was carried out at 0 °C.

These results, together with ours, suggest that the α-methyl group has a detrimental effect on the efficiency of the reaction, probably due to the increased steric hindrance around the secondary amine that precluded the formation of the enamine species. On the other hand, the increase in the enantioselectivity is specific to proline, which supports the postulation that the α-methyl group alters the conformation of the pyrrolidine ring such that the amine and acid functionalities are in the optimal positions to effect catalysis.[15] The lower efficiency yet improved selectivity observed using α-methylproline **3** prompted us to extend our α-oxidation procedure to aldehydes, which are more reactive than ketones. Table 2 summarises the results of the α-oxidation of various aldehydes.

It is noteworthy that the formation of by-products was observed in two of these reactions. In the α-oxidation of phenylacetaldehyde **15** catalysed by proline **1**, a significant quantity (~6%) of the sulfonamide **19** (Fig. 2), the reduced Mannich product between phenylacetaldehyde **15** and sulfonimine **8**, was isolated as a mixture of diastereomers after $NaBH_4$ reduction. On the other hand, in the α-oxidation of hydrocinnamaldehyde **17** catalysed by all catalysts **1**–**4**, a significant amount of diol **20** (Fig. 2), the reduced self-aldolisation adduct of hydrocinnamaldehyde **17**, was isolated after $NaBH_4$ reduction. Proline **1** was found to give diol **20** as a 1:1 mixture of diastereomers.

The production of sulfonamide **19** and diol **20** as by-products illustrates the high reactivity of the aldehyde substrates, with which the α-methyl substituted catalysts can proceed reasonably efficiently. Our studies suggested that a small excess (2 equiv) of the aldehyde was enough to provide a reasonable yield of the α-hydroxyl adduct, albeit with concomitant formation of the side products noted above.

One remarkable finding is that α-methyl tetrazole **4** exhibited superior efficiency in all of the aldehyde α-oxidations studied. With isovaleraldehyde **16**, hydrocinnamaldehyde **17** and hexanal **18**, complete consumption of the oxaziridine **6** within 4 h was observed using **4** whilst the other three catalysts required 5–20 times longer. Comparable yields of the isolated diols were obtained using all four catalysts.

To see whether a lower temperature would improve the enantioselectivity further, the α-oxidation of hydrocinnamaldehyde **17** catalysed by α-methylproline **3** was also carried out at 0 °C. Disappointingly, this led to a lower ee than that observed at room temperature. This is in line with the findings of Cordova et al.[14] who reported that the α-oxidation of cyclohexanone with oxaziridine **6** in THF catalysed by (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine at 0 °C provided a lower ee than at room temperature.

The stereochemistry observed in our studies represents an interesting outcome. All reported α-oxidations of ketones or aldehydes catalysed by organocatalysts **1**–**3** using either nitrosobenzene[1,2,9–12] or molecular oxygen[22] gave (*R*)-α-hydroxy adducts as the major isomer, and the reported oxidations of ketones using oxaziridine **6** catalysed by proline **1** or tetrazole **2** (in DMSO) also favoured the formation of the *R* isomer.[14] In contrast, we found the *S* isomer to be predominant in reactions catalysed by organocatalysts **1**–**4**, with just a few exceptions.

The *R* configuration reportedly arises from the nucleophilic *re*-facial attack of *anti*-enamine on the electrophilic oxygen in the oxidant. Such a transition state is favoured due to the lower energy of the *anti*-enamine, and the chirality at the asymmetric carbon of the catalyst. The *S* acid (or tetrazole) favours the approach of the oxidant to the *re*-face of the *anti*-enamine, either by forming a hydrogen bond with nitrosobenzene (**A**, Fig. 3), or by protonation of the resultant α-hydroxyl group in the oxidation with molecular oxygen (**B**, Fig. 3). The observed *S* configuration can only arise from either nucleophilic *si*-facial attack of an *anti*-enamine on oxaziridine **6** (**C**, Fig. 3), or *si*-facial attack of a *syn*-enamine with potential hydrogen bond formation (**D**, Fig. 3). At this preliminary stage, we postulate that the latter case is more likely to lead to the (*S*)-isomer. Our results indicate that α-substituted proline catalysts give higher stereoinduction, which will be unlikely if the former stereochemical course **C** is followed. In this transition state, with no hydrogen bonding, steric factors may be the major driving force, whereby repulsion from the acid group may preclude the approach of oxaziridine **6** to the *re*-face. Based on this assumption, the α-methyl group should lower this facial selectivity affording less (*S*)-isomer than the non-methyl catalysts. We therefore propose that the favoured transition state **D** involves a *syn*-enamine and a hydrogen bond with oxaziridine **6**.

The *syn* configuration could be more favoured over the *anti*, given an earlier example of a similar phenomenon in the proline-catalysed enantioselective α-alkylation of aldehydes.[28a] A density functional study on the alkylation reaction has shown that the *syn* transition state benefits from a greater proximity of the leaving group to the acid proton, and from a more planar iminium moiety.[29] In fact, the planarity of the iminium transition state has also been identified as one of the main contributors to the formation of the major stereoisomer in the proline-catalysed intramolecular aldol reaction between two keto groups.[28b,c] It is reasonable therefore to assume that iminium planarity may also be critical in *syn* transition state **D**, even though the catalysis of alkylation, intramolecular aldol and oxidation reactions may be mechanistically different. To rationalise the increase in enantioselectivity when using α-methyl catalysts, we propose that replacement of the α-hydrogen with a methyl group, which gives rise to a tetrasubstituted asymmetric

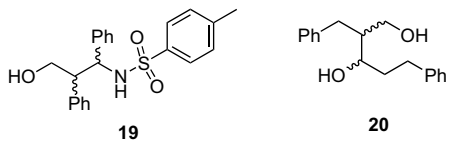


Figure 2. Structures of by-products **19** and **20** formed in the α-oxidations of aldehydes.

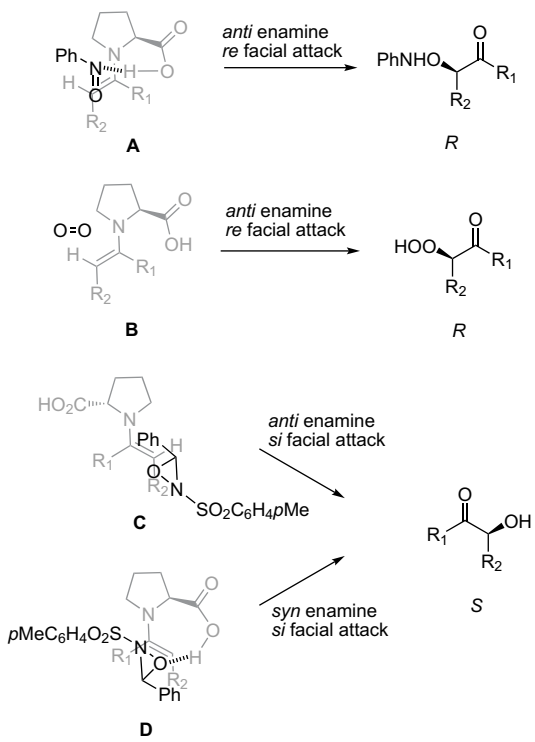


Figure 3. Transition states leading to *R* or *S* configurations of α-hydroxy adducts.

carbon, possibly changes the conformation of the amino acid derived enamine intermediate.[30] As such, the altered conformation of the α-methyl enamine intermediate in the *anti* configuration may proceed to an iminium that deviates from planarity,[28] while the *syn* iminium could still be relatively planar and hence the more favoured transition state **D**.

3. Conclusion

This report provides the first example of a direct organocatalytic α-oxidation of aldehydes using *trans*-2-(*p*-methylphenylsulfonyl)-3-phenyloxaziridine **6** as the oxidant to afford the α-hydroxy adducts favouring the (*S*)-isomer. More significantly, the positive effects of α-methyl substitution in proline-based organocatalysts are also demonstrated. α-Methylproline **3** and α-methyl tetrazole **4** dramatically increase the enantioselectivity of the α-oxidation compared to the unsubstituted catalysts and α-methyl tetrazole **4** provides superior reaction efficiency over catalysts **1**–**3**.

4. Experimental

4.1. General

Reactions were monitored by TLC, using pre-coated silica gel TLC plates obtained from Merck. Flash chromatography was carried out on silica gel (Riedel–de Haën, particle size 0.032–0.063 mm). Hexane for flash chromatography was distilled before use. HPLC analysis was performed on a Dionex Instrument (multi-wavelength absorbance detector with a binary HPLC pump). The Chiralpak AD-RH column was purchased from Daicel Chemical Industries Ltd. Optical rotations were measured on a Perkin–Elmer 341 polarimeter (λ=589 nm, 0.1 dm cell). Melting point determinations were performed on an Electrothermal® melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance DRX 300 MHz or 400 MHz spectrometers at ambient temperatures. Chemical shifts δ are expressed in parts per million and coupling constants *J* are reported in hertz. TMS served as internal standard (δ=0 ppm) for ^{1}H NMR, and $CDCl_3$ served as internal standard (δ=77.0 ppm) for ^{13}C NMR. Infrared spectra were recorded on a Perkin–Elmer spectrum one FT-IR spectrometer.

4.2. Procedure for the preparation of *trans*-2-(*p*-methylphenylsulfonyl)-3-phenyloxaziridine (6)[16,17]

To a round-bottomed flask equipped with a short-path distillation head was charged *p*-toluenesulfonamide **7** (10 mmol, 1.7 g) and benzaldehyde dimethylacetal (10 mmol, 1.5 g). The mixture was heated at 180 °C for 45 min, during which methanol (~0.2 mL) was distilled from the mixture. The mixture was then cooled at reduced pressure by which time the yellow liquid had turned into a creamy white solid, which was re-dissolved in warm DCM and hexane was added to precipitate the product. Sulfonimine **8** was collected and washed with hexane to afford a white shiny powdery solid (2.4 g, 91%), which was used directly in the next step without further purification. A mixture of *m*-chloroperoxybenzoic acid (4.2 mmol, 0.95 g) and powdered potassium hydroxide (13.5 mmol, 0.76 g) in DCM (10 mL) was stirred vigorously at room temperature for 5 min. The mixture was further diluted with DCM (10 mL) and sulfonimine **8** (3.9 mmol, 1 g) was added. The white suspension was vigorously stirred for another 5 min. The resultant white salt was filtered off and the filtrate was concentrated in vacuo to furnish *trans*-2-(*p*-methylphenylsulfonyl)-3-phenyloxaziridine **6** as a white solid (0.98 g, 92%). The ^{1}H NMR data of **6** was consistent with literature data.[17]

4.3. Procedure for the α-oxidation of cyclohexanone

To a solution of oxaziridine **6** (1 equiv) in distilled THF was added, under ambient atmosphere, the catalyst (**1**–**4**). The mixture was stirred for 5 min, after which cyclohexanone (3 equiv) was added and the mixture was stirred at room temperature for the reported time. Excess $NaBH_4$ was added to the mixture at 0 °C and reaction was stopped when TLC showed full consumption of 2-hydroxycyclohexanone (R_f=0.6, 3:1 EtOAc/hexane). Solvent was then removed and silica gel and EtOAc were added to the residue. The mixture was stirred for an hour, after which elution of the compounds from the silica with EtOAc afforded the crude *cis* and *trans* diol (*cis* diol: R_f=0.3; *trans* diol: R_f=0.2, 3:1 EtOAc/hexane). Column chromatography with 2:1 EtOAc/hexane as the eluent as eluent provided pure *trans* diol. To allow for chiral HPLC analysis, the *trans* diol was then esterified: to a solution of the diol (1 equiv) in DCM was added triethylamine (18 equiv), DMAP (catalytic amount) and *p*-nitrobenzoyl chloride (5 equiv). The mixture was stirred at room temperature overnight, after which it was quenched with pH 7 phosphate buffer. The organic phase was separated and the aqueous phase was extracted with EtOAc (×3). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The crude was purified by flash chromatography with 4:1 hexane/EtOAc as the eluent to yield the bis-*p*-nitrobenzoate as a brown oil.[17]

*4.3.1. (1R,2R)-Cyclohexane-1,2-diyl bis(4-nitrobenzoate) (**14**)*

Compound **14** was obtained as a yellow crystal.[31] R_f=0.7, 4:1 hexane/EtOAc. Mp=107–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42–1.56 (m, 2H, $4H_{ax}$ and $5H_{ax}$), 1.56–1.73 (m, 2H, $3H_{eq}$ and $6H_{eq}$), 1.82–1.95 (m, 2H, $4H_{eq}$ and $5H_{eq}$), 2.20–2.33 (m, 2H, $3H_{ax}$ and $6H_{ax}$), 5.23–5.33 (m, 2H, 1H and 2H), 8.11 (d, *J*=8.9 Hz, 4H, $CHCO_2$), 8.21 (d, *J*=9.0 Hz, 4H, $CHCNO_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.43 (C-4 and C-5), 60.18 (C-3 and C-6), 75.35 (C-1 and C-2), 123.50 ($CHCNO_2$), 130.63 ($CHCO_2$), 135.19 (quat. CCO_2), 150.54 (quat. CNO_2), 164.01 (CO_2). IR: $\bar{\nu}$ = 2941 (C–H), 1725 (ester C=O stretching), 1523 (asymmetric $(N=O)_2$ stretching), 1321 (symmetric $(N=O)_2$ stretching), 1262 (C(=O)–O stretching), 1117 (O–C–C stretching), 870 (C–N stretching) cm^{-1}. *m*/*z* (CI+, NH_3) 432 (0.44, $M+NH_4^+$), 385 (0.13), 248 (0.14, $C_6H_{11}OCOC_6H_5NO_2^+$), 150 (0.62, $NO_2C_6H_4CO^+$), 138 (0.62), 120 (1.00). HRMS: found $M+NH_4^+$, 432.14142; $C_{20}H_{22}N_3O_8$ requires 432.14069. The enantiomeric excess of **14** was measured at 254 nm on Chiralpak AD-RH HPLC column (75:25 MeCN/H_2O, 0.4 mL/min), 15.70 min (1*S*,2*S*), 18.15 min (1*R*,2*R*).

4.4. General procedure for the α-oxidation of aldehydes

To a solution of oxaziridine **6** (1 equiv) in distilled THF was added, under ambient atmosphere, the catalyst (**1**–**4**). The mixture was stirred for 5 min, after which the aldehyde (2 equiv) was added and the mixture was stirred at room temperature for the reported time. $NaBH_4$ (2 equiv) was then added to the mixture at 0 °C and the mixture was stirred overnight. The mixture was poured onto a mixture of 1 N HCl and EtOAc and stirred for 10 min. The organic phase was separated, and the aqueous phase was further extracted with EtOAc. The combined organics were dried ($MgSO_4$) and evaporated to afford a crude mixture, which was purified by flash chromatography (2:1 → 1:1 hexane/EtOAc) to furnish the diol (Diols **15a**–**18a**: R_f=0.3, 1:1 EtOAc/hexane). To allow for chiral HPLC analysis, the diol was then esterified: To a solution of the diol (1 equiv) in DCM was added triethylamine (18 equiv), DMAP (catalytic amount) and *p*-nitrobenzoyl chloride or acetic anhydride (5 equiv). The mixture was stirred at room temperature overnight, after which it was quenched with pH 7 phosphate buffer. The organic phase was separated and the aqueous phase was extracted with EtOAc (×3). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The crude was purified

by flash chromatography with a mixture of hexane/EtOAc to yield the pure diester.

4.4.1. ^{1}H NMR and optical rotation data for diols **15a–18a**

Diols **15a–18a** were obtained as pure compounds. Their ^{1}H NMR data were consistent with literature values: **15a–17a** (Ref. 32) and **18a** (Ref. 33).

The stereochemistry of diols **15a–18a** were determined by comparison of their optical rotation data with literature values. (*S*)-**15a**: $[\alpha]_D^{23}$ +11.75 (*c* 1.11, $CHCl_3$), 28% ee; lit. (*R*)-**15a**: $[\alpha]_D^{20}$ −62.7 (*c* 0.11, $CHCl_3$), >99% ee.[34] (*S*)-**16a**: $[\alpha]_D^{23}$ +1.38 (*c* 2.89, $CHCl_3$), 25% ee; lit. (*S*)-**16a**: $[\alpha]_D$ +11.0 (*c* 0.6, $CHCl_3$), >99% ee.[32] (*S*)-**17a**: $[\alpha]_D^{23}$ −14.53 (*c* 2.00, EtOH), 48% ee; lit. (*S*)-**17a**: $[\alpha]_D^{24}$ −33.5 (*c* 0.93, EtOH), >98% ee.[35] (*S*)-**18a**: $[\alpha]_D^{21}$ −13.95 (*c* 0.43, EtOH), 45% ee; lit. (*S*)-**18a**: $[\alpha]_D$ −22.0 (*c* 0.9, EtOH), >99% ee.[32]

4.4.2. 1-Phenylethane-1,2-diyl bis(4-nitrobenzoate) (**15b**)

R_f=0.3, 6:1 hexane/EtOAc. Mp=110–113 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.74 (dd, *J*=12.0, 3.6 Hz, 1H, $2H_a$), 4.85 (dd, *J*=12.0, 8.1 Hz, 1H, $2H_b$), 6.48 (dd, *J*=8.1, 3.6 Hz, 1H, 1H), 7.35–7.49 (m, 3H, 3′H, 4′H and 5′H), 7.49–7.58 (m, 3H, 2′H and 6′H), 8.05–8.18 (m, 2H, 3‴H and 7‴H), 8.18–8.35 (m, 6H, 3″H, 7″H, 4″H, 6″H, 4‴H and 6‴H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 67.07 (C-2), 74.82 (C-1), 123.61 (C-4″ and C-6″ or C-4‴ and C-6‴), 123.65 (C-4″ and C-6″ or C-4‴ and C-6‴), 126.68 (C-2′ and C-6′), 129.01 (C-3′ and C-5′), 129.27 (C-4′), 130.73 (C-3‴ and C-7‴), 130.81 (C-3″ and C-7″), 134.81 and 134.98 (C-2″ and C-2‴), 135.36 (C-1′), 150.69 and 150.75 (C-5″ and C-5‴), 163.75 (C-1″), 164.23 (C-1‴). IR: $\bar{\nu}$ = 1721 (ester C=O stretching), 1520 (asymmetric $(N{=}O)_2$ stretching), 1347 (symmetric $(N{=}O)_2$ stretching), 1257 (C(=O)–O stretching), 1117 (O–C–C stretching of primary alcohol), 1101 (O–C–C stretching of secondary alcohol), 874 (C–N stretching) cm^{-1}. *m*/*z* (CI^+, NH_3) 454 (0.21, $M{+}NH_4^+$), 270 (0.25, $M{-}OCOC_6H_4NO_2^+$), 240 (0.17), 150 (0.78, $NO_2C_6H_4CO^+$), 138 (1.00), 120 (0.91, $C_6H_5CHCH_2O^+$). HRMS: found $M{+}NH_4^+$, 454.12575; $C_{22}H_{20}N_3O_8$ requires 454.12504. The enantiomeric excess of **15b** was measured at 254 nm on Chiralpak AD-RH HPLC column (65:35 MeCN/H_2O, 0.4 mL/min), 36.45 min (*S*), 42.27 (*R*).

4.4.3. 3-Methylbutane-1,2-diyl bis(4-nitrobenzoate) (**16b**)

R_f=0.5, 5:1 hexane/EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.107 (d, *J*=6.9 Hz, 3H, CH_3), 1.108 (d, *J*=6.6 Hz, 3H, CH_3), 2.10–2.39 (m, 1H, 3H), 4.55 (dd, *J*=7.7, 12 Hz, 1H, $1H_a$), 4.69 (dd, *J*=3, 12 Hz, $1H_b$), 5.35–5.46 (m, 1H, 2H), 8.05–8.15 (m, 2H, 3′H and 7′H), 8.15–8.35 (m, 6H, 4′H, 6′H, 3″H, 7″H, 4″H and 6″H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.98 (CH_3), 18.65 (CH_3), 29.66 (C-3), 65.21 (C-1), 77.29 (C-2), 123.59 (C-4′ and C-6′ or C-4″ and C-6″), 123.63 (C-4′ and C-6′ or C-4″ and C-6″), 130.71 (C-3′, C-7′, C-3″ and C-7″), 134.94 (C-2′ or C-2″), 135.26 (C-2′ or C-2″), 150.68 (C-5′ or C-5″), 164.27 (C-1′ or C-1″), 164.37 (C-1′ or C-1″). IR: $\bar{\nu}$ = 2968 (C–H), 1717 (ester C=O stretching), 1521 (asymmetric $(N{=}O)_2$ stretching), 1343 (symmetric $(N{=}O)_2$ stretching), 1258 (C(=O)–O stretching), 1115 (O–C–C stretching of primary alcohol), 1097 (O–C–C stretching of secondary alcohol), 871 (C–N stretching) cm^{-1}. *m*/*z* (FAB^+) 403 (0.05, $M{+}H^+$), 236 (0.07, $M{-}CO_2C_6H_4NO_2^+$), 165 (0.06), 150 (0.19, $COC_6H_4NO_2^+$), 120 (0.14), 89 (0.28). HRMS: found MH^+, 403.11430; $C_{19}H_{19}N_2O_8$ requires 403.11414. The enantiomeric excess of **16b** was measured at 210 nm on Chiralpak AD-RH HPLC column (55:45 MeCN/H_2O, 0.4 mL/min), 64.13 min (*R*), 69.73 (*S*).

4.4.4. 3-Phenylpropane-1,2-diyl diacetate (**17b**)

The ^{1}H NMR data of diacetate **17b** were consistent with literature data.[36] The diacetate of 3-phenylpropane-1,2-diol was used for the determination of ee via HPLC instead of the bis-*p*-nitrobenzoate derivative, i.e., 3-phenylpropane-1,2-diyl bis(4-nitrobenzoate) because the latter was found to give inconsistent ee over successive runs of the HPLC experiment. Increasing ee was obtained on repeating the HPLC experiment on the same sample, while the homogenous sample solution (made up by sonicating the solid bis-*p*-nitrobenzoate in a mixture of hexane and isopropanol) was found to show precipitation over time. These observations appeared to suggest that the minor enantiomer crashed out at a higher rate than the major enantiomer, giving the apparent increase in ee. This did not happen with the diacetate derivative **17b** and was thus employed for the HPLC analysis. The enantiomeric excess of **17b** was measured at 210 nm on Chiralpak AD-RH HPLC column (25:75 MeCN/H_2O, 0.3 mL/min), 77.43 min (*R*), 81.23 (*S*).

4.4.5. Hexane-1,2-diyl bis(4-nitrobenzoate) (**18b**)

R_f=0.4, 6:1 hexane/EtOAc. Mp=100–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, *J*=6.8 Hz, 3H, CH_3), 1.32–1.50 (m, 4H, $CH_3CH_2CH_2$), 1.73–1.92 (m, 2H, $CH_3CH_2CH_2CH_2$), 4.50 (dd, *J*=12, 7.2 Hz, 1H, $CH_{2a}O$), 4.64 (dd, *J*=12, 2.8 Hz, 1H, $CH_{2b}O$), 5.49–5.58 (m, 1H, CH), 8.09–8.22 (m, 4H, $CHCCO_2$), 8.22–8.31 (m, 4H, $CHCNO_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.82 (CH_3), 22.39 (CH_3CH_2), 27.25 ($CH_3CH_2CH_2$), 30.45 ($CH_3CH_2CH_2CH_2$), 66.36 (CH_2O), 73.20 (CH), 123.58 ($CHCNO_2$), 130.71 ($CHCCO_2$), 134.92, 135.24 (CCO_2), 150.62 (CNO_2), 164.22, 164.30 (C=O–O). IR: $\bar{\nu}$ = 2957 (C–H), 1715 (ester C=O stretching), 1523 (asymmetric $(N{=}O)_2$ stretching), 1347 (symmetric $(N{=}O)_2$ stretching), 1259 (C(=O)–O stretching), 1118 (O–C–C stretching of primary alcohol), 1100 (O–C–C stretching of secondary alcohol), 870 (C–N stretching) cm^{-1}. *m*/*z* (FAB^+) 417 (0.03, $M{+}H^+$), 400 (0.01), 250 (0.05, $M{-}OCOC_6H_4NO_2^+$), 165 (0.04), 150 (0.20, $NO_2C_6H_4CO^+$), 120 (0.13, $C_6H_4COO^+$), 89 (0.24). HRMS: found MH^+, 417.12985; $C_{20}H_{21}N_2O_8$ requires 417.12979. The enantiomeric excess of **18b** was measured at 254 nm on Chiralpak AD-RH HPLC column (75:25 MeCN/H_2O; 0.1% formic acid, 0.25 mL/min), 41.19 min (*R*), 45.49 min (*S*).

4.4.6. N-(3-hydroxy-1,2-diphenylpropyl)-4-methylbenzenesulfonamide (**19**)

Compound **19** was obtained as a colourless crystal.[37] R_f=0.2, 3:1 hexane/EtOAc. Mp=152–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3), 3.00–3.12 (m, 1H, $CHCH_2OH$), 3.64 (dd, *J*=5.6, 11.3 Hz, 1H, CH_aOH), 3.91 (dd, *J*=8.3, 11.3 Hz, 1H, CH_bOH), 4.76 (dd, *J*=6.2, 8.3 Hz, 1H, CHNH), 5.39 (d, *J*=8.4 Hz, 1H, NH), 6.79 (dd, *J*=1.4, 7.4 Hz, 2H, Ar′–H), 6.90 (dd, *J*=1.7, 7.4 Hz, 2H, Ar–H), 7.00 (d, *J*=8.1 Hz, 2H, $CHCCH_3$), 7.03–7.10 (m, 3H, Ar′-H), 7.13–7.24 (m, 3H, Ar-H), 7.39 (d, *J*=4.5 Hz, 2H, $CHCSO_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.32 (CH_3), 53.91 ($CHCH_2OH$), 58.40 (CHNH), 62.93 (CH_2OH), 126.38 (CHAr′), 126.94 ($CHCSO_2$), 127.03 (CHAr′), 127.17 (CHAr), 127.54 (CHAr′), 128.49 (CHAr), 128.58 ($CHCCH_3$), 128.96 (CHAr), 136.88 (CCH_3 or Cquat.–Ar′), 136.91 (CCH_3 or Cquat.–Ar′), 138.68 (Cquat.–Ar), 142.95 (Cquat.–SO_2). IR: $\bar{\nu}$ = 3668 (O–H stretching), 3322 (sulfonamide N–H stretching), 1494, 1455 (aromatic C–C stretching), 1317 (sulfonamide S=O stretching), 1148, 759, 698, 669 (aromatic C–H bending). *m*/*z* (FAB^+) 382 (0.04, $M{+}H^+$), 260 (0.12, $M{-}C_6H_5CHCH_2OH^+$), 181 (0.08), 172 (0.09), 149 (0.13), 120 (0.13), 91 (0.24, $C_6H_4CH_3$). HRMS: found MH^+, 382.14847; $C_{22}H_{24}NO_3S$ requires 382.14769.

4.4.7. 2-Benzyl-5-phenylpentane-1,3-diol (**20**)

R_f=0.3, 2:1 hexane/EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69–2.03 (m, 3H, 2H and 4H), 2.48–2.92 (m, 4H, 5H and 6H), 3.27 (bs, 2H, OHs), 3.50–3.60 (m, 1H, $1H_a$ of diastereomer A), 3.60–3.68 (m, 2H, $1H_a$ and $1H_b$ of diastereomer B), 3.68–3.78 (m, 2H, 3H of diastereomer B), 3.80–3.97 (m, 1H, $1H_b$ of diastereomer A and 3H of diastereomer A), 7.0–7.4 (m, 10H, Ar–Hs), as a 1:1 mixture of diastereomers A and B. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 31.60 and 32.20 (C-5), 32.52 and 35.04 (C-6), 35.27 and 37.49 (C-4), 45.97 and 46.39 (C-2), 62.74 and 63.96 (C-1), 73.82 and 74.26 (C-3), 125.79 and 125.82, 125.92 and 125.99, 128.32 and 128.34, 128.37 and 128.39, 128.89 and 129.02 (Ar–Cs), 140.13 and 140.29 (Ar C-quat.), 141.88 and 141.90 (Ar C-quat.). IR: $\bar{\nu}$ = 3241 (br d, O-H stretch), 2941, 1602,

1492 (aromatic C–C stretch), 1453 and 1331 (O-H bending), 1060, 1029 (alcohol C–O stretch), 742 (aromatic C–H bending), 694. *m*/z (EI^+) 252 (0.07, M^+-H_2O), 234 (0.16, M^+-2H_2O), 143 (0.21, $M^+-2H_2O-C_6H_5CH_2$), 117 (0.31,$M^+-H_2O-C_6H_5(CH_2)_2CHOH$), 104 (0.14, $C_6H_5CH_2CH^+$), 91 (1.00, $C_6H_5CH_2^+$), 77 (0.90, $C_6H_5^+$). HRMS: found $M-H_2O$, 252.15129; $C_{18}H_{20}O$ requires 252.15142.

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Supplementary data

Optical rotation data for diols **15a**–**18a** along with HPLC traces for diesters **15b**–**18b** can be found as Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.060.

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20. Whilst the X-ray crystal structure allowed confirmation of the structure of sulfonamide **12** the resolution is insufficient for addition to the Cambridge structural database. Data for compound 12: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50–2.01 (m, 6H, *c*-Hex), 2.15–2.40 (m, 5H, *c*-Hex and CH_3), 2.70–2.82 and 2.82–2.92 (m, 1H, COCH), 4.34–4.40 (dd, *J*=8.4, 4.8 Hz, 1H, CHPh) and 4.40–4.48 (dd, *J*=9.6, 5.6 Hz, 1H, CHPh), 5.90–5.96 (d, *J*=9.3 Hz, 1H, NH) and 5.96–6.06 (d, *J*=8.4 Hz, 1H, NH), 6.95–7.10 (m, 7H, Ar–H), 7.38–7.50 (m, 2H, Ar–H) as a mixture of diastereoisomers.^{13}C NMR (100 MHz, $CDCl_3$): δ 21.36, 24.51, 26.77 and 27.94, 30.63 and 32.38, 42.32 and 42.59, 55.51 and 56.78, 58.81 and 59.29, 126.99, 127.05, 128.03, 129.08, 127.98, 128.19 (quat. Ar–C), 137.59, 139.07, 142.74, (quat. Ar–C), 221.71 and 212.63, as a mixture of diastereoisomers. *m*/*z* (FAB) 358 (0.13, M+H), 260 (0.29), 187(0.25), 91 (0.27). HRMS: found MH^+, 358.14718; $C_{20}H_{24}NO_3S$ requires 358.14769.
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