

The semi-pinacol rearrangement of homochiral epoxyalcohols catalysed by rare earth triflates

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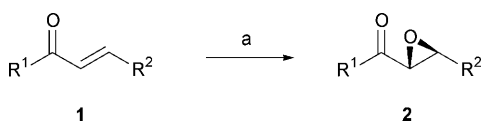
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α,β -Epoxy ketones, prepared using the poly-leucine catalysed asymmetric epoxidation of enones, can be converted into α -substituted β -hydroxy ketones via carbonyl alkylation with Grignard reagents followed by ytterbium triflate catalysed semi-pinacol rearrangement of the resulting epoxyalcohols.

Polyamino acids, such as poly-leucine, are able to catalyse the asymmetric epoxidation of α,β -unsaturated enones **1** by basic H_2O_2 , a transformation known as the Juliá-Colonna reaction (Scheme 1).¹ To date, most of the epoxides **2** prepared have been



Scheme 1 Reagents and conditions: (a) urea- H_2O_2 , DBU, poly-L-leucine or SiO_2 -poly-L-leucine, THF, rt.

of the type $\text{R}^1 = \text{aryl}$ or alkyl and $\text{R}^2 = \text{aryl}$ or vinyl, for which ees are generally $>80\%$.² The first part of this communication shows that enones **1** where $\text{R}^1 = \text{aryl}$ and $\text{R}^2 = \text{alkyl}$ can also be epoxidised with good stereocontrol, under the previously described biphasic reaction conditions.³

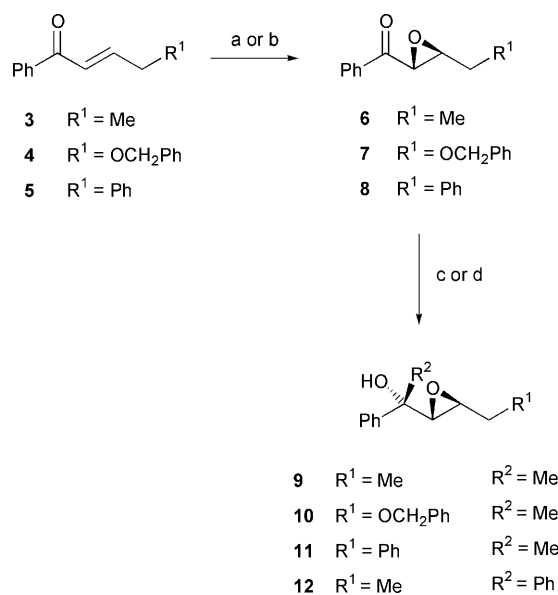
Grignard reagents add to the carbonyl group of α,β -epoxyketones in a highly stereoselective manner; diastereoselectivities $>99:1$ in favour of the product of Cram-chelate addition are typically observed in the generation of the tertiary alcohols.⁴ Such enantiomerically enriched epoxyalcohols have, in the past, been formed by a less efficient, five-step Sharpless asymmetric epoxidation-oxidation-alkylation-oxidation-alkylation strategy.^{5,6} It has been shown that when treated with stoichiometric quantities of certain Lewis acids such epoxyalcohols undergo a semi-pinacol rearrangement to afford aldols. A range of Lewis acids including TiCl_4 ,⁵ $\text{BF}_3 \cdot \text{OEt}_2$,⁶⁻⁸ alumina⁷ and SnCl_4 ⁹ has been used to this effect. The corresponding silyl ethers exhibit similar reactivity when treated with $\text{BF}_3 \cdot \text{OEt}_2$,¹⁰ TiCl_4 ⁵ and SnCl_4 .¹⁰ In the case of less reactive substrates, $\text{Ti}(i\text{-PrO})_2\text{Cl}_2$ ⁶ and $\text{Ti}(i\text{-PrO})_3\text{Cl}$ ¹⁰ have been used. Suzuki has reported a catalytic variant of the silyl protected epoxyalcohol rearrangement using 2–5 mol% TMSI or TMSOTf.¹¹ When this work was initiated no catalytic variant applicable to unprotected epoxyalcohols had been reported. However, recently Tu *et al.* have shown that ZnBr_2 can catalyse such semi-pinacol rearrangements.¹² In the second part of this paper we show that rare earth triflates can be employed as Lewis acid catalysts in a similar manner.

Rare earth triflates[†] have been shown to be viable alternatives to more conventional Lewis acids for a number of transformations, including a variety of epoxide opening reactions.¹³ The principal advantages of such triflates are their stability to moisture, low toxicity, ease of handling, recyclable nature and ability to function in a catalytic capacity.¹⁴ Poor reactivity, under previously reported rearrangement conditions, in the

case of some of our substrates, prompted an investigation into the utility of rare earth triflates as catalysts for epoxyalcohol semi-pinacol rearrangements.

A number of *trans*- β -alkylenones were prepared in order to provide substrates for developing the alkylation-rearrangement methodology. The β -ethylenone **3** was prepared via a Wittig reaction between propionaldehyde and benzoylmethylene triphenylphosphorane and the β -benzylenone **5** was synthesised as previously described.¹⁵ The γ -benzyloxyenone **4** was prepared by application of chemistry previously utilised for the ethyloxy-substituted analogue.¹⁶ Thus, 2-benzyloxyethanol was oxidised under Swern conditions and the resulting aldehyde was treated with benzoylmethylene triphenylphosphorane to afford the desired enone **4** in 38% yield over the two steps.

Oxidation of the β -ethylenone **3** under biphasic conditions,³ using urea- H_2O_2 and DBU in THF, catalysed by silica-immobilised¹⁷ poly-L-leucine (416 mg mmol^{-1} enone), gave the epoxide **6** in 64% yield and 60% ee after 17 hours (Scheme 2).



Scheme 2 Reagents and conditions: (a) urea- H_2O_2 , DBU, SiO_2 -poly-L-leucine, THF, rt; (b) urea- H_2O_2 , BEMP, SiO_2 -poly-L-leucine, THF, rt; (c) MeMgBr , THF, Et_2O , -78°C ; (d) PhMgBr , THF, Et_2O , -78°C .

The use of 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)¹⁸ instead of DBU allowed a sub-stoichiometric amount of base to be employed; under optimum conditions, using 3 mol% BEMP, the epoxide **6** was obtained in 86% yield and 77–79% ee. Further reduction in the amount of BEMP led to a significant loss in stereoselectivity, for example with 0.1 mol% the epoxide **6** was generated in only 74% ee. Treatment of the enone **4** under similar conditions (20 mol% BEMP) gave the epoxide **7** in 79% yield and 93% ee. On the other hand, epoxidation of the enone

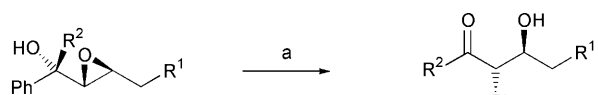
Table 1 The semi-pinacol rearrangement of **9** catalysed by various rare earth triflates.

Catalyst	Mol% catalyst	Time	Yield (%)
Sc(OTf) ₃	20	6 h	90
La(OTf) ₃	20	10 h	90
Yb(OTf) ₃	20	3 h	99
Yb(OTf) ₃	15	15 h	97
Yb(OTf) ₃	10	3 days	87
Yb(OTf) ₃	5	6 days	87

5 proceeded in a lower yield due to the formation of a dimeric side product, presumably *via* Michael addition of the anion generated by deprotonation of one molecule of **5** to a second molecule of the enone. However, when the reaction was performed with additional silica supported catalyst (2 g mmol⁻¹ enone) none of the dimeric material was generated, leading to an improved yield of the epoxide **8** (75%) with an ee > 90%.[‡]

Treatment of the epoxyketones **6–8** with methylmagnesium bromide or phenylmagnesium bromide furnished the corresponding alcohols **9–12** in 90 to 96% yield; in each case only a single diastereomer was observed in the ¹H NMR spectrum. The stereochemistry of the products was assigned by comparison with a previously reported example in which the configuration was determined by X-ray crystallography.¹⁹

Using epoxyalcohol **9**, three readily available metal triflates, Sc(OTf)₃, La(OTf)₃ and Yb(OTf)₃, were tested as rearrangement catalysts employing dichloromethane and acetonitrile as solvents. Initial reactions were performed using 20 mol% of the triflate catalysts. All three of the Lewis acids were found to catalyse the migration of the aryl group of **9** to afford the aldol **13** (Scheme 3). Dichloromethane was found to be the better



9	R ¹ = Me	R ² = Me	13	R ¹ = Me	R ² = Me
10	R ¹ = OCH ₂ Ph	R ² = Me	14	R ¹ = OCH ₂ Ph	R ² = Me
11	R ¹ = Ph	R ² = Me	15	R ¹ = Ph	R ² = Me
12	R ¹ = Me	R ² = Ph	16	R ¹ = Me	R ² = Ph

Scheme 3 Reagents and conditions: (a) Yb(OTf)₃ (20 mol%), CH₂Cl₂, rt.

solvent, with the product proving clean enough to obviate the need for additional purification (Table 1). The rate of reaction catalysed by the three Lewis acids was found to decrease in the order Yb(OTf)₃ > Sc(OTf)₃ > La(OTf)₃, with the former proving to be the most synthetically useful, generating the α -phenyl- β -hydroxy ketone **13** in 99% yield after 3 hours.

Further experiments were performed in order to determine the effect of reducing the molar percentage of Yb(OTf)₃. When less than 15 mol% Yb(OTf)₃ was employed the reaction took three or more days to run to completion and the crude product contained significant impurities. The optimised conditions of 20 mol% Yb(OTf)₃ in DCM were then applied to the enones **10**, **11** and **12** with the corresponding aldols **14**, **15** and **16** being formed in 82, 100 and 97% yield respectively.

Previous semi-pinacol rearrangements of epoxyalcohols have been reported to proceed with inversion of stereochemistry at the site of epoxide opening. X-Ray analysis of a single crystal of the aldol **16** demonstrated that this is also the case in the present study (Fig. 1).

Cyclic trisubstituted enones such as *trans*-2-benzylidene-1-tetralone§ can be epoxidised with good enantioselectivity under polyleucine catalysis.²⁰ Treatment of **17**, generated by such an epoxidation, with methylmagnesium bromide gave the tertiary alcohol **18** as expected. Unexpectedly, treatment of **18** with 20 mol% Yb(OTf)₃ in DCM furnished benzaldehyde (**20**) (identified by ¹H NMR and TLC) and an α -methyltetralone (40% yield). Analysis of the latter by ¹H NMR spectroscopy showed the material to be 1-methyl-2-tetralone (**19**) by com-

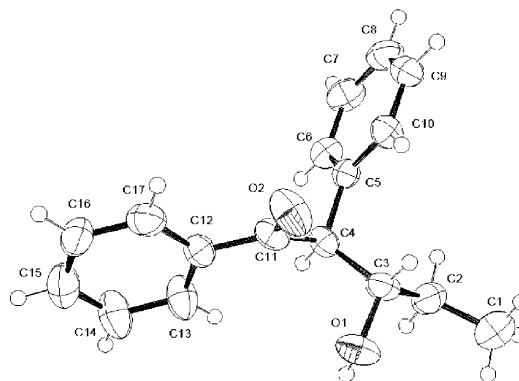
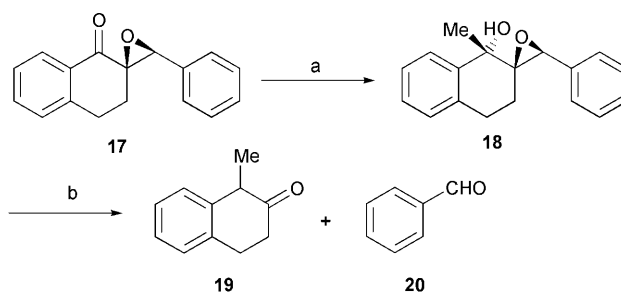


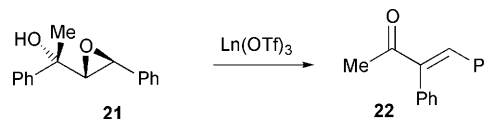
Fig. 1 X-Ray crystal structure of 3-hydroxy-1,2-diphenylpentan-1-one (**16**). Thermal ellipsoids drawn with 50% probability.

parison with literature data²¹ and with an authentic sample. In particular, a quartet at δ 3.53 (*J* 7 Hz), due to the benzylic proton coupling to the methyl group, is a distinctive feature of the spectrum and clearly excludes the possibility of having formed 2-methyl-1-tetralone (the product of methyl group migration and retro-aldol reaction) (Scheme 4).



Scheme 4 Reagents and conditions: (a) MeMgBr, THF, Et₂O, -78 °C; (b) Yb(OTf)₃ (20 mol%), CH₂Cl₂, rt.

The mechanism of this latter reaction is under investigation. At this point, we have established that open chain analogues behave differently; the epoxyalcohol **21** forms the enone **22** on treatment with rare-earth triflates (Scheme 5).



Scheme 5

In summary, we have demonstrated the applicability of modified Juliá-Colonna epoxidation conditions to β -alkyl substituted enones. The resultant epoxyketones have been converted into aldols by Grignard addition followed by semi-pinacol rearrangement catalysed by Yb(OTf)₃. The newly developed rearrangement conditions constitute an efficient, convenient and mild alternative to previously reported procedures.

Experimental

Representative experimental procedure: (2*S*,3*S*)-3-hydroxy-1,2-diphenylpentan-1-one (**16**)

To a solution of (2*R*,3*S*)-2,3-epoxy-1,1-diphenylpentan-1-ol (**12**) (300 mg, 1.18 mmol) in anhydrous DCM (6 cm³) was added ytterbium(III) trifluoromethanesulfonate (150 mg, 0.242 mmol). The reaction mixture was stirred at room temperature for 4 hours after which time water (10 cm³) was added and the product was extracted with diethyl ether (2 × 10 cm³). The combined ethereal extracts were dried (MgSO₄) and the solvent was removed *in vacuo* to afford (2*S*,3*S*)-3-hydroxy-1,2-diphenylpentan-1-one (**16**) (290 mg, 1.14 mmol, 97%) as yellow crystals; mp 87–88 °C; *R*_f [SiO₂; petroleum ether (40–60)–

diethyl ether, 1 : 1] 0.35 (Found: C, 80.0; H, 7.1. C₁₇H₁₈O₂ requires C, 80.3; H, 7.1%); δ_{H} (400 MHz; CDCl₃; Me₄Si) 0.96 (3 H, t, *J* 7.3 Hz, CH₃), 1.32–1.48 (2 H, m, CH₂), 2.89 (1 H, br s, OH), 4.27 (1 H, dt, *J* 8.3, 3.9 Hz, C(3)H), 4.58 (1 H, d, *J* 8.6 Hz, C(2)H), 7.19–7.50 (8 H, m, ArH) and 7.91–7.98 (2 H, m, ArH); *m/z* (CI⁺) 254 ([M – H₂O + NH₄]⁺, 1%), 237 (6), 214 (69), 197 (100), 105 (39).

X-Ray crystallography.¶ Crystallographic data were recorded on a STOE-IPDS diffractometer using graphite monochromated Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$, $T = 213 \text{ K}$). The structures were solved by Direct Methods and were refined by full matrix least squares against F^2 using all data.²²

Crystal data. C₁₇H₁₈O₂, $M = 254.35$, orthorhombic, $a = 5.6084(7)$, $b = 13.3595(17)$, $c = 19.118(3) \text{ \AA}$, $U = 1432.4(4) \text{ \AA}^3$, space group $P2_12_12_1$, $Z = 4$, $\mu(\text{Mo-K}\alpha) = 0.076 \text{ mm}^{-1}$, 9206 reflections measured, 2260 unique ($R_{\text{int}} = 0.0794$) which were used in all calculations. For $I \geq 2\sigma(I)$ $R_1 = 0.0333$. The final $wR(F^2)$ was 0.0661(all data). Absolute configuration was not determined, *Flack* parameter²³ = 1.5 (19).

Acknowledgements

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Notes and references

† The IUPAC name for triflate is trifluoromethanesulfonate.

‡ Complete resolution of the two enantiomers of **7** using chiral HPLC, chiral GC or chiral shift NMR was not achieved. The quoted ee of >90% is an estimate from the partly resolved HPLC analysis.

§ The IUPAC name for 1-tetralone is 3,4-dihydronaphthalen-2(1*H*)-one.

¶ CCDC reference number 160661. See <http://www.rsc.org/suppdata/p1/b1/b101838h/> for crystallographic files in .cif or other electronic format.

1 M. J. Porter, S. M. Roberts and J. Skidmore, *Bioorg. Med. Chem.*, 1999, **7**, 2145.

2 For a discussion of the different methods for epoxidising electron deficient double bonds and a comparison of their substrate ranges see M. J. Porter and J. Skidmore, *Chem. Commun.*, 2000, 1215.

3 B. M. Adger, J. V. Barkley, S. Bergeron, M. W. Cappi, B. E. Flowerdew, M. P. Jackson, R. McCague, T. C. Nugent and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3501.

4 A. T. Gillmore, S. M. Roberts, M. B. Hursthouse and K. M. Abdul Malik, *Tetrahedron Lett.*, 1998, **39**, 3315.

5 K. Maruoka, M. Hasegawa, H. Yamamoto, K. Suzuki, M. Shimazaki and G. Tsuchihashi, *J. Am. Chem. Soc.*, 1986, **108**, 3827.

6 M. Shimazaki, H. Hara, K. Suzuki and G. Tsuchihashi, *Tetrahedron Lett.*, 1987, **28**, 5891.

7 C. J. Cheer and C. R. Johnson, *J. Am. Chem. Soc.*, 1968, **90**, 178.

8 K. Suzuki, M. Miyazawa, M. Shimazaki and G. Tsuchihashi, *Tetrahedron*, 1988, **44**, 4061.

9 C. M. Marson, A. J. Walker, J. Pickering, A. D. Hobson, R. Wrigglesworth and S. J. Edge, *J. Org. Chem.*, 1993, **58**, 5944.

10 S. W. Baldwin, P. Chen, N. Nikolic and D. C. Weinseimer, *Org. Lett.*, 2000, **2**, 1193.

11 K. Suzuki, M. Miyazawa and G. Tsuchihashi, *Tetrahedron Lett.*, 1987, **28**, 3515.

12 Y. Q. Tu, C. A. Fan, S. K. Ren and A. S. C. Chan, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3791.

13 (a) H. Kotsuki, M. Teraguchi, N. Shimomoto and M. Ochi, *Tetrahedron Lett.*, 1996, **37**, 3727; (b) P. Crotti, V. Di Bussolo, L. Favero, F. Macchia and M. Pineschi, *Tetrahedron Lett.*, 1994, **35**, 6537; (c) J. T. Kohrt, J.-X. Gu and C. R. Johnson, *J. Org. Chem.*, 1998, **63**, 5088; (d) X.-L. Hou, J. Wu, L.-X. Dai, L.-J. Xia and M.-H. Tang, *Tetrahedron: Asymmetry*, 1998, **9**, 1747; (e) M. Meguro, N. Asao and Y. Yamamoto, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2597.

14 S. Kobayashi, *Synlett*, 1994, 689.

15 H. J. Reich, I. L. Reich and J. M. Renga, *J. Am. Chem. Soc.*, 1973, **95**, 5813.

16 P. C. Ray, PhD Thesis, Liverpool, 2000.

17 T. Geller and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1397.

18 BEMP is often the preferred base for Juliá–Colonna epoxidations; A. Burns, K.-H. Drauz, E. A. O'Connor, S. M. Roberts and J. Skidmore, unpublished results.

19 J. F. Bickley, A. T. Gillmore, S. M. Roberts, A. Steiner and J. Skidmore, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1109.

20 P. A. Bentley, J. F. Bickley, S. M. Roberts and A. Steiner, *Tetrahedron Lett.*, in press.

21 N. J. Harper and J. Raines, *J. Chem. Soc. (C)*, 1969, 1372.

22 G. M. Sheldrick, *SHELX97, Crystal structure determination program*, Gottingen, Germany, 1997.

23 H. D. Flack, *Acta Crystallogr. Sect. A Fundam. Crystallogr.*, 1983, **39**, 876.