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N-Alkyl salts derived from ephedrine do not promote enantioselective Corey–Chaykovsky reactions involving sulfonium methylides under phase-transfer conditions

Sarah A. Kavanagh, Stephen J. Connon *

Centre for Synthesis and Chemical Biology, School of Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland

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ABSTRACT

N-Alkyl salts derived from ephedrine have twice been reported to act as chiral phase-transfer catalysts in Corey–Chaykovsky reactions between sulfonium ylides and benzaldehyde; reportedly furnishing the terminal epoxide product in moderate–excellent enantiomeric excess. This study unequivocally demonstrates that these reactions proceed without measurable stereoinduction and explains how previous studies mistakenly attributed product optical activity to asymmetric catalysis.

1. Introduction

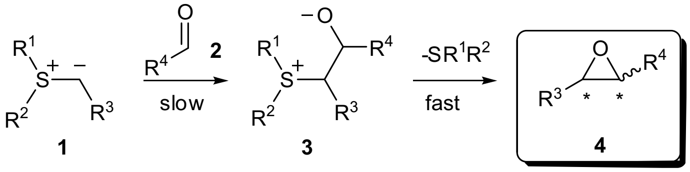
Over the past five decades, the Corey–Chaykovsky reaction[1] (Scheme 1) has been proven to be a robust and practical method for the synthesis of synthetically valuable epoxide derivatives from aldehydes. Whilst considerable progress towards a general, enantioselective variant of this alkylidene transfer reaction using chiral sulfides/sulfonium ylides has been made,[2,3] analogous catalytic processes using sulfonium methylides (i.e., **1**, $R^3 = H$, Scheme 1) which furnish terminal epoxides with high (>80% ee) enantioselectivity have thus far proven elusive.[4]

2. Results and discussion

Over the course of a research programme aimed at the design of novel organocatalysts for methylene transfer to aldehydes,[5] we were intrigued to discover two reports detailing the moderate-highly enantioselective synthesis of terminal epoxides using the Corey–Chaykovsky reaction under the influence of phase-transfer catalysis. In 1975, Hiyama et al.[6] disclosed that the reaction between benzaldehyde **5** and trimethylsulfonium iodide **6** in a biphasic $CH_2Cl_2/NaOH_{(aq)}$ solvent mixture in the presence of the ephedrine-derived salt **7** furnished styrene oxide **8** in moderate yield and excellent selectivity (Scheme 2).

Interestingly, although no background reaction in the absence of the catalyst was reported, the enantioselectivity of the process appeared to increase with increased catalyst loading (35% ee at 1 mol % loading, 97% ee at 20% loading). Over 20 years later, Zhang et al.[7] reported a similar study detailing the use of the lipophilic catalysts **9** and **10** designed to facilitate the formation of chiral micelles. Again significant enantioselectivity was reported to be achievable, in this instance a curious dependence of enantioselectivity on both temperature and reaction time was observed (in general product ee increased with temperature, up to 40 °C, and reaction time, up to 60 h). In both reports the product's specific rotation was used to both assign absolute configuration and determine ee.

Encouraged by what we saw as a significant opportunity to develop this hitherto underexploited methodology (particularly considering the general difficulties associated with the catalytic



Scheme 1. Mechanism of the Corey–Chaykovsky reaction.

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* Corresponding author.
E-mail address: connons@tcd.ie (S. J. Connon).

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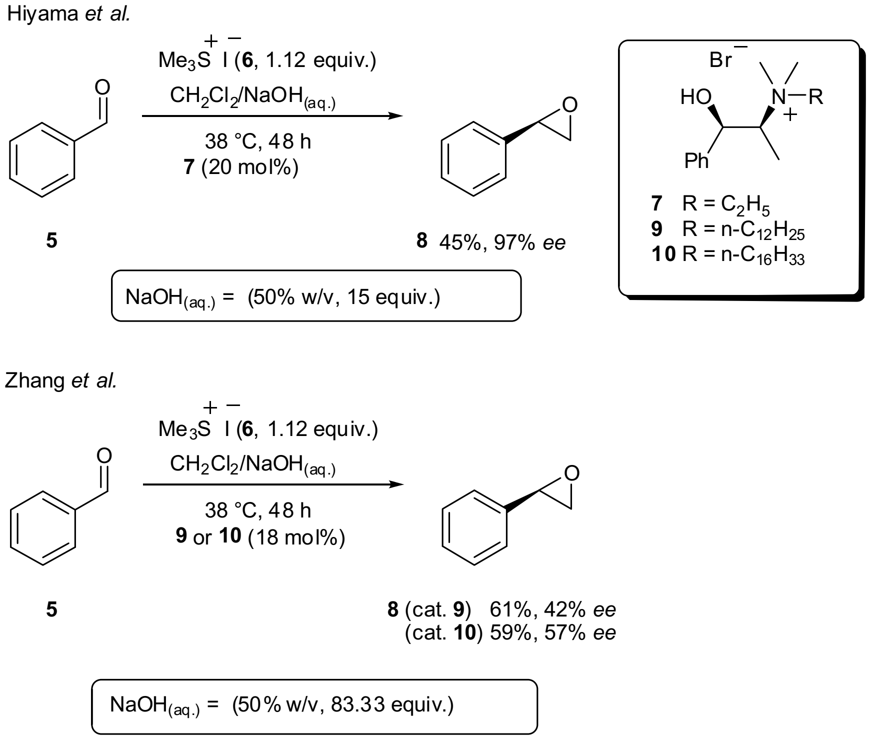
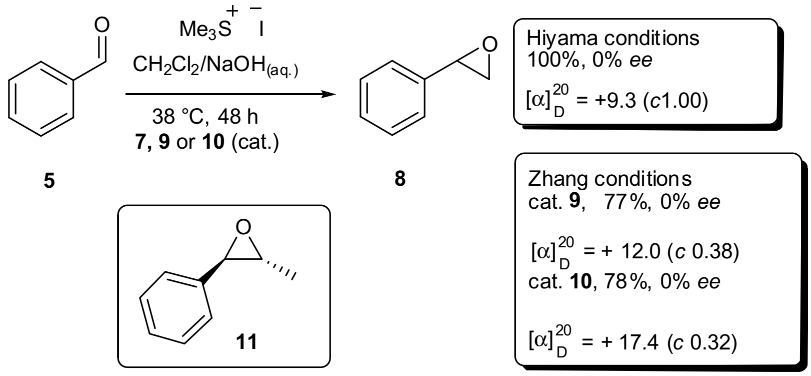


Scheme 2. Conditions employed and results obtained by Hiyama et al. and Zhang et al.



Scheme 3. Outcome of representative asymmetric Corey–Chaykovsky reactions carried out in our laboratory.

asymmetric synthesis of terminal epoxides from achiral starting materials[8]) through the design of new phase-transfer catalysts for these and related reactions—we repeated the key experiments detailed in both papers precisely. Whist we did observe some catalysis of the reaction by the ephedrinium salts[9] and product optical activity, in both cases CSP-HPLC analysis (Chiralcel OD-H column 4.6 × 250 mm, 99.9:0.1 hexane/*i*-PrOH solvent) of the product after chromatography indicated that **8** had been formed as a racemic mixture (Scheme 3). Several repetitions of the experiment gave reproducible results.

The CSP-HPLC chromatograms from these reactions along with those of *rac*-**8** are shown in Figure 1. It is noteworthy that a peak not derived from **8** at 15.6–16 min retention time is present in the catalysed reactions despite chromatographic purification of the product prior to HPLC analysis.[10] The presence and identity of the impurity was confirmed by ^{1}H NMR analysis to be epoxide **11**, presumably formed in high enantiomeric excess from the base-mediated ring closure of **7** and **9**–**10**. Figure 2 shows that this impurity (which is inseparable from **8** by either column chromatography or rudimentary vacuum distillation) is present both before and after chromatography in the reaction catalysed by **10**.[11] Very similar spectra were obtained from the other reactions outlined in Scheme 3.

To verify that **11** forms under these basic phase-transfer conditions and that it is responsible for the optical activity of the chromatographed product mixture—catalysts **7** and **9**–**10** were exposed to the reaction conditions outlined in Scheme 3 in the absence of either benzaldehyde or sulfonium salt (Scheme 4). Each of the three catalysts completely decomposed to form **11** in quantitative yield (Scheme 4 and Fig. 3). This would explain the strong dependence of the enantioselectivity on the reaction conditions (temperature, time, loading) in the earlier studies:[6,7] factors likely to afford greater decomposition of the catalyst to enantiopure/enantioenriched **11** would yield a 'product' of higher specific rotation.[12]

Isolated **11** possessed a large specific rotation {$[\alpha]_D = +64.6$ (c 0.71)} and an identical retention time (15.7 min) to the previously

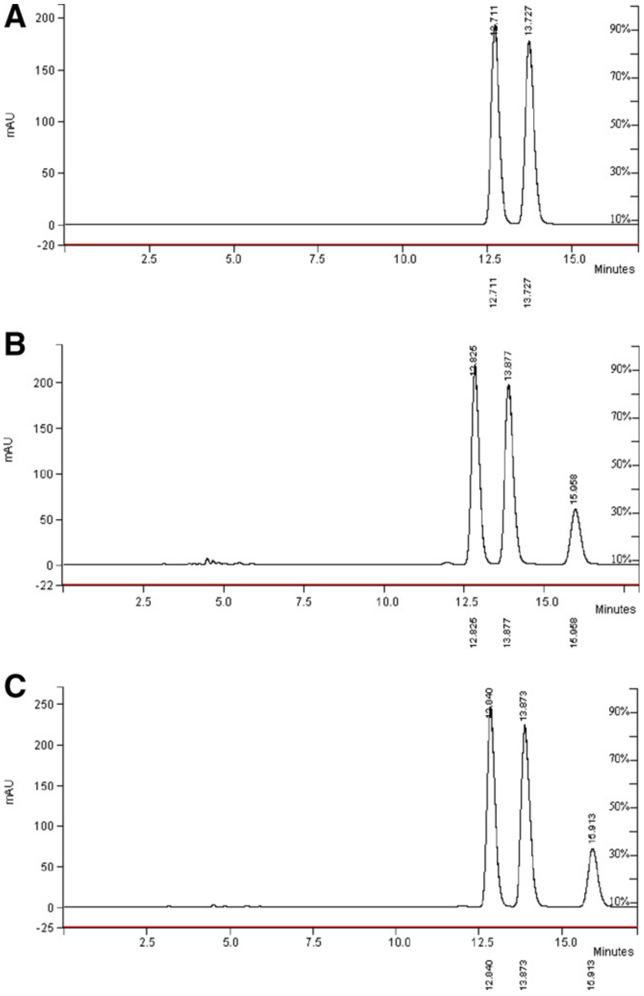


Figure 1. CSP-HPLC analysis of the reactions outlined in Scheme 3. (A) Racemic **8**. (B) Reaction catalysed by **7** under Hiyama's conditions. (C) Reaction catalysed by **9** under Zhang's conditions.

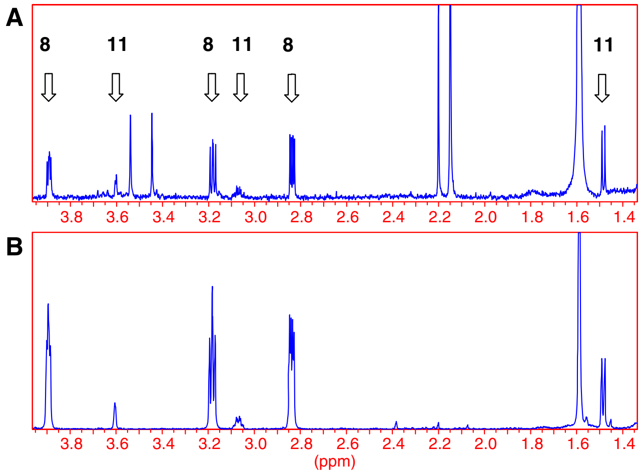


Figure 2. ^{1}H NMR spectroscopic analysis (400 MHz, $CDCl_3$, highfield expansion) of the reaction outlined in Scheme 3 catalysed by **10** under Zhang's conditions. (A) Spectrum of the crude material after 48 h. (B) Spectrum after chromatography.

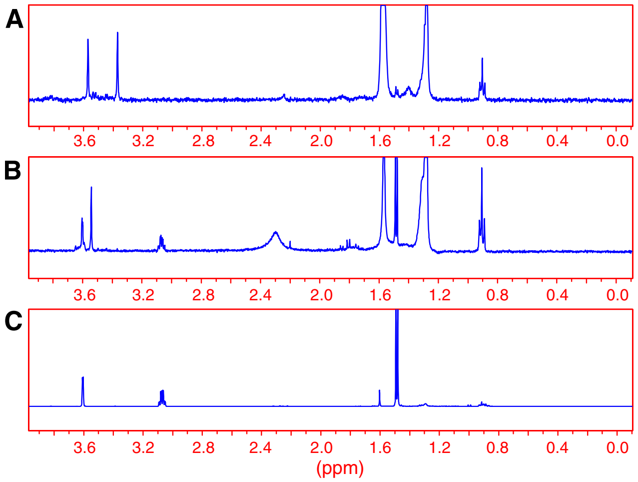
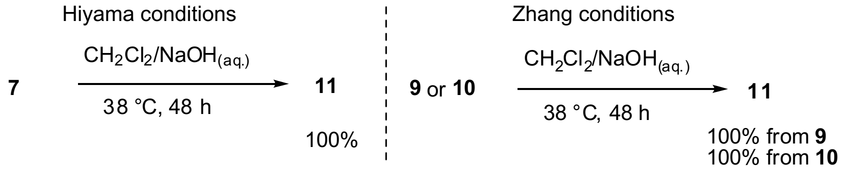


Figure 3. ^{1}H NMR spectroscopic analysis (400 MHz, $CDCl_3$, highfield expansion) of the reaction outlined in Scheme 4 catalysed by **10** under Zhang's conditions. (A) Spectrum of the reaction (organic phase) at $t = 0$ h. (B) Spectrum of the reaction (organic phase) at $t = 32.5$ h. (C) Isolated **11** from the same reaction after chromatography.

unidentified component in the chromatograms shown in Figure 1 (Fig. 4). To be certain that epoxide racemisation occurs neither during chromatography nor under the reaction conditions, a sample of commercially available enantiopure (*R*)-**8** was purified by the same column chromatography methodology used throughout this study, and in a second experiment, pure (*R*)-**8** (1.0 equiv) was added at $t = 0$ h to a Corey–Chaykovsky reaction and upon completion the products were isolated and analysed by CSP-HPLC. In both cases no evidence for racemisation was found.[13]

3. Conclusion

Thus, it is certain that the reliance of both earlier studies[6,7] on the specific rotation data led to the error in reporting **7** and **9**-**10** as being capable of asymmetric catalysis of the Corey–Chaykovsky reaction. The authors were unfortunate that the catalyst decomposition product, which is responsible for the optical activity that they observed, is an epoxide difficult to separate from the desired epoxide product. This impurity may well also have been difficult to identify at low levels (max. 20%) with lowfield NMR instrumentation. With the benefit of CSP-HPLC analysis and highfield NMR (400–600 MHz), it can be unequivocally shown that these ammonium salt-catalysed methylene transfer reactions furnish racemic products exclusively.



Scheme 4. Decomposition of catalysts **7** and **9**–**10** under the reaction conditions in the absence of **5** or **6**.

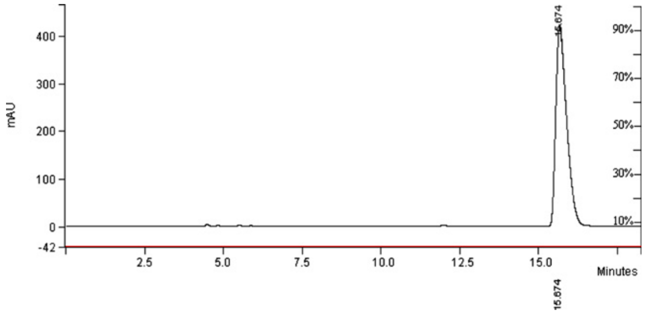


Figure 4. CSP-HPLC analysis of the reaction outlined in Scheme 4. The decomposition of catalyst **10** under Zhang's reaction conditions.

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8. For example, see: Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.
9. The control reaction without any catalyst afforded **8** in 16% yield under otherwise identical conditions.
10. Chromatography was carried out under conditions recommended in Ref. 7: silica gel, hexane/ether 10:1, R_f 0.5. The product was isolated as a single spot. Variation of the solvent composition and R_f always resulted in the observation of a single non-baseline spot.
11. Such base-mediated transformations are precedented. For recent examples see: (a) Couty, F.; David, O.; Durrat, F.; Evano, G.; Lakhdar, S.; Marrot, J.; Vargas-Sanchez, M. *Eur. J. Org. Chem.* **2006**, 3479; (b) Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1749; (c) Robiette, R.; Conza, M.; Aggarwal, V. K. *Org. Biomol. Chem.* **2006**, *4*, 621.
12. During the preparation of this manuscript, we were pleased to find that in 1980, Rosenberger had questioned Hiyama's results and suggested that **11** may be the cause of the observed specific rotation. Their proof was not unequivocal however and their work pre-dated that of Zhang et al. Rosenberger's work does not appear in a Scifinder Scholar search for papers which cite Hiyama's work (although it does in a Web of Science search)—which has no doubt contributed to a general misconception that the results outlined in Ref. 6 are still valid, see: (a) Rosenberger, M.; Jackson, W.; Saucy, G. *Helv. Chim. Acta* **1980**, *63*, 1665; for examples, of relatively recent papers which cite Refs. 6 and 7 as examples of enantioselective phase-transfer catalysis see: (b) Llewellyn, D. B.; Adamson, D.; Arndtsen, B. A. *Org. Lett.* **2000**, *2*, 4165; (c) Tohma, H.; Takizawa, S.; Watanabe, H.; Fukuoka, Y.; Maegawa, T.; Kita, Y. *J. Org. Chem.* **1999**, *64*, 3519; (d) Ramón, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149; (e) Yadav, A. K.; Singh, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 587.
13. In these experiments, epoxide **8** was detected in >99% ee and 53% ee, respectively.