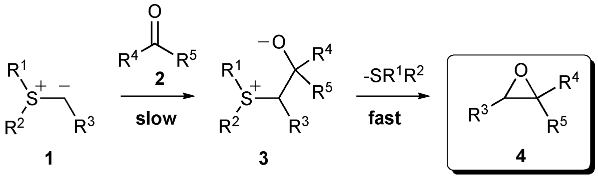
Urea derivatives are highly active catalysts for the base-mediated generation of terminal epoxides from aldehydes and trimethylsulfonium iodide†

Sarah A. Kavanagh, Alessandro Piccinini, Eimear M. Fleming and Stephen J. Connon*

Received 24th January 2008, Accepted 12th February 2008
First published as an Advance Article on the web 5th March 2008
DOI: 10.1039/b719767e

_N_,_N′_-Diarylureas have been shown to efficiently catalyse sulfonium ylide-mediated aldehyde epoxidation reactions for the first time. These processes are of broad scope and can be coupled with a subsequent Cu(II) ion-catalysed Meinwald rearrangement to give an efficient and convenient protocol for aldehyde homologation without intermediate purification.

Epoxides are among the most versatile and useful synthetic building blocks available to the organic chemist. One of the most straightforward non-oxidative methods for the synthesis of these compounds is the Corey–Chaykovsky (CC) reaction involving the base-mediated addition of sulf(ox)onium ylides to aldehydes.[1] The mechanism of this reaction involves the addition of the ylide **1** (formed from the deprotonation of the corresponding sulfonium salt by the dimsyl ion[1b,d] or the reaction of a sulfide with a Simmons–Smith reagent[2]) to the carbonyl electrophile **2** to form the zwitterionic intermediate **3**, which undergoes ring closure to afford the oxirane product **4** (Scheme 1). This reaction has received considerable attention and significant progress towards the development of general asymmetric variants of the process using chiral (often *in situ* formed) sulfonium ylides has been made.[3] While smooth, enantioselective alkylidene transfer from ylides to aldehydes has been demonstrated,[4] the corresponding methylene transfer to form terminal epoxides is characterised by (super)stoichiometric sulfide loadings and moderate yields/enantioselectivity;[5] with the most successful protocols involving a metal-mediated Simmons–Smith type carbenoid transfer.[5e,f]



Scheme 1 Mechanism of CC reaction.

Since it seems clear that the hitherto most common strategy involving the use of chiral sulfonium ions is unlikely to lead to highly enantioselective methylene transfer protocols, we became interested in developing an organocatalytic strategy based on the use of hydrogen bonding[6] to activate the aldehyde towards nucleophilic attack by the ylide, the idea being that if a catalyst capable of aldehyde activation under simple CC reaction conditions could be identified, it could be later modified to do the same in a face selective manner. In addition, such a strategy would not require the tedious multistep synthesis of enantiopure sulfide catalysts.

We were also intrigued by the lack of activity of the readily available and inexpensive[7] trimethylsulfonium iodide in CC reactions—for example this salt has been shown to be unreactive under convenient biphasic conditions (aq. NaOH–CH_2Cl_2, rt) and has been reported to give appreciable product yields only on heating in the presence of a phase transfer catalyst[5b–d,8]—conditions not conducive to either hydrogen-bond mediated catalysis or arguably hydrogen-bond directed asymmetric induction either. Likewise, solid–liquid two-phase systems have been developed (NaOH or KOH(s)/MeCN),[9–13] however heating is involved and the formation of cinnamonitrile can also be problematic.[14,15] We therefore considered the ability to promote efficient CC reactions between trimethylsulfonium iodide and benzaldehyde at room temperature under convenient phase transfer conditions to be the benchmark against which catalyst efficacy could be judged. Herein we report our preliminary results on the development of such an active catalyst system.

For the past four years our group has been interested in the design and exploitation of (thio)urea derivatives as robust and active hydrogen-bond donating catalysts for a variety of addition reactions characterised by an increase in basicity at a heteroatom in the reaction transition state.[6b,16] Curran[17a,b] and Schreiner[17d,e] were the first to recognise the potential of readily prepared, tunable and relatively rigid *N*,*N′*-diarylureas and -thioureas which possess two *syn*-periplanar N–H bonds available for hydrogen bond donation as catalysts for Claisen rearrangements and Diels–Alder reactions respectively. Since, these materials have been shown to serve as active and versatile promoters of the addition of cyanide and silyl ketene acetals to nitrones,[18a] the Baylis–Hillman reaction,[18b] Friedel–Crafts type reactions,[18c] acetalisations,[18d] Claisen rearrangements,[18b,e] ring-opening reactions of oxiranes,[18f,g] acyl Strecker reactions,[18h] tetrahydropyranylations[18i] and imine reductions.[18j,19]

One issue which we speculated may have been responsible for the dearth of studies on the use of hydrogen-bond donating catalysts in the CC reaction is the reasonably basic conditions required to form the ylide nucleophile, which precludes the use of catalysts of strong–medium acidity. We were therefore pleased to find that the pK_a (DMSO) of diarylurea **5**, its thiourea analogue **6** and trimethylsulfonium iodide **7** (Fig. 1) are 19.55, 13.4 and 18.2 respectively.[20] Thus at a minimum we expected urea derivatives to be compatible with the deprotonated sulfonium methylide.

Centre for Synthesis and Chemical Biology, School of Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland. E-mail: connons@tcd.ie; Fax: +353 1 671 2826; Tel: +353 1 8961306

† Electronic supplementary information (ESI) available: Experimental procedures for the catalysed epoxidation, ^{1}H and ^{13}C NMR spectra of all products and an example demonstrating the presence of the unidentified intermediate. See DOI: 10.1039/b719767e

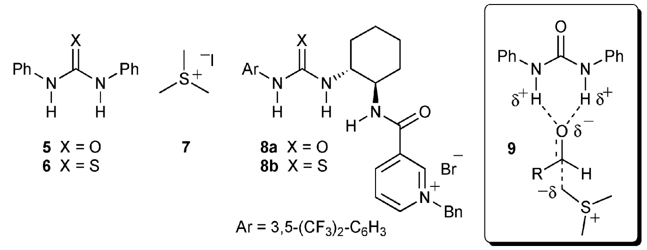


Fig. 1 Catalyst activity: rationale.

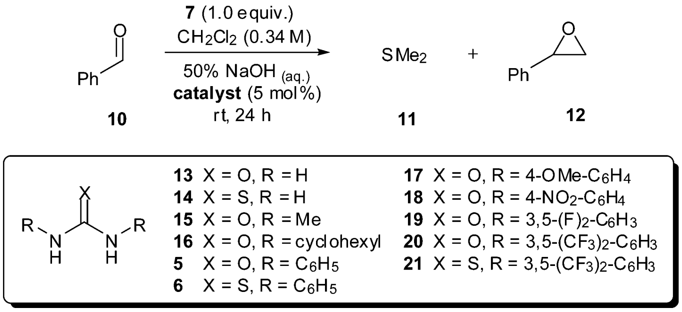
In addition, we have recently demonstrated that precatalysts **8a**,**b** could promote the reduction of diketones in the presence of aqueous base in a biphasic system without decomposition.[21] We therefore posited that (thio)urea derivatives could accelerate CC reactions under these conditions through the stabilisation of developing negative charge on the oxygen heteroatom in the rate-determining addition step[22] transition state (**9**, Fig. 1).

To test this hypothesis, a range of urea and thiourea derivatives **5–6** and **13–21** were prepared and evaluated as promoters of the CC reaction between benzaldehyde (**10**) and **7** in the presence of NaOH base under biphasic conditions at room temperature (Table 1). In the absence of catalyst no styrene oxide (**12**) was formed (entry 1), however we were surprised to detect trace amounts of an unidentified intermediate (the ^{1}H NMR spectrum of which indicates that it is not a β-hydroxysulfonium ion derived from attack of **7** on **10**) which was converted to **12** after extended reaction times. At low catalyst loadings of 5 mol%, urea (**13**), thiourea (**14**) and *N*-alkyl urea derivatives **15–16** failed to promote the formation of **12** effectively, although significant levels of the intermediate were observed using *N*,*N*′-dimethylurea **15**. Use of the more acidic *N*-phenylurea and thioureas (**5** and **6** respectively) resulted in substantial improvements in both rate and efficiency—allowing the formation of **12** in moderate yield (entries 6–7).

An electron-rich analogue of urea **5** (*i.e.* **17**, entry 8) proved inferior to more acidic analogues incorporating electron deficient aromatic substituents (even the insoluble **18**, entries 9–11). Gratifyingly, bis-fluoro- and bis-trifluromethylphenyl substituted ureas **19** and **20** proved to be highly active: both furnished excellent yields of **12** after 24 h at 5 mol% loading (entries 10 and 11). It is of interest that, as expected (*vide supra*), urea **20** is a more active catalyst than the more acidic thiourea **21** (entry 12), just as **5** is a better catalyst in this reaction than **6**. This superiority of urea over thiourea derivatives is unusual[23]—in this case we would propose that it is related to the high acidity of the thiourea derivatives relative to the sulfonium ion.

Reduction of the levels of base led to lower conversions (entries 13 and 14), while increased catalyst loadings of 10 mol% resulted in faster reactions and quantitative yields (entry 15). In addition, efficient catalysis was observed with loadings as

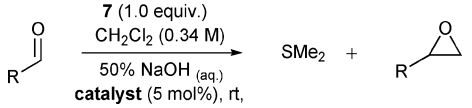
Table 1 (Thio)urea catalysis of the CC reaction: initial studies

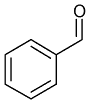
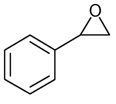
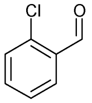
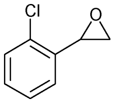
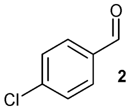
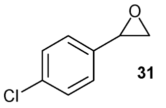
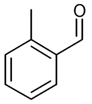
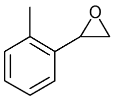
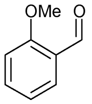
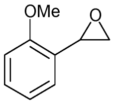
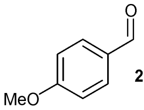
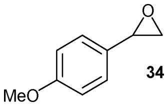
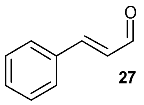
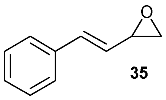
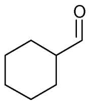
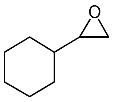
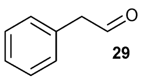
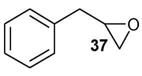


Entry	Cat.	Loading (mol%)	CH_2Cl_2 : NaOH (v/v)[a]	Conversion (%)[bc]	Yield (%)[d]
1	None	5	1.23 : 1	1.5	0
2	**13**	5	1.23 : 1	3	0
3	**14**	5	1.23 : 1	1	0
4	**15**	5	1.23 : 1	7	0
5	**16**	5	1.23 : 1	2	0
6	**5**	5	1.23 : 1	50	39
7	**6**	5	1.23 : 1	35	22
8	**17**	5	1.23 : 1	14	0
9	**18**[e]	5	1.23 : 1	22	11
10	**19**	5	1.23 : 1	99	99
11	**20**	5	1.23 : 1	97	97
12	**21**	5	1.23 : 1	67	50
13	**20**	5	7.37 : 1	42	29
14	**20**	5	14.7 : 1	15	0
15[f]	**20**	10	1.23 : 1	100	100
16	**20**	2	1.23 : 1	85	85
17	NBCC[g]	5	1.23 : 1	69	60
18[h]	NBCC[g]	5	1.23 : 1	95	83

[a] 2.18 cm^3 of CH_2Cl_2 used in all cases. [b] Determined by ^{1}H NMR spectroscopy. [c] In addition to the starting material, the only species detected by ^{1}H NMR spectroscopy were **12** and the intermediate. Integration of the resonances associated with the intermediate supports the assumption that its presence is responsible for the discrepancy between the conversion and yield in reactions involving inefficient catalysts. [d] Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [e] **18** was only partially soluble in the reaction medium. [f] 21 h reaction time. [g] NBCC = *N*-benzylcinchonidinium chloride. [h] NBCC and **20** (both at 5 mol% level) used together.

Table 2 Evaluation of the substrate scope



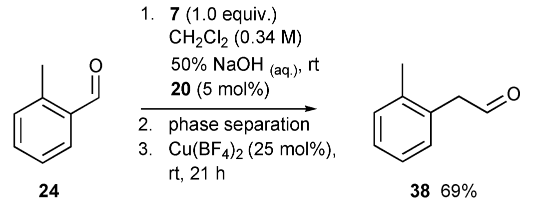
Entry	Substrate	Time/h	Product	Yield (%)[a]
1	 **10**	20	 **12**	93
2	 **22**	16	 **30**	93
3	 **23**	15	 **31**	91
4	 **24**	85	 **32**	96
5	 **25**	40	 **33**	57 (95)[b]
6	 **26**	92	 **34**	75 (98)[b]
7	 **27**	38	 **35**	91
8	 **28**	133[c]	 **36**	90
9	 **29**	40[d]	 **37**	0

[a] Isolated yield. [b] Crude epoxide decomposes during either Kugelrohr distillation or chromatography, the figure in parentheses represents the crude yield of spectroscopically pure product—see ref. 24 and the ESI. [c] 98% of **28** had been consumed after 69 h. [d] Time taken for complete consumption of **29**.

low as 2 mol% after 24 h (entry 16). We also found that **20** is superior to the cinchona alkaloid-derived phase transfer catalyst *N*-benzylcinchonidinium chloride (NBCC), however little synergy was observed when both catalysts were employed together (entries 11, 17 and 18).

With an active catalyst in hand, attention now turned to the question of substrate scope. Gratifyingly, the catalytic methodology proved robust—we found that catalyst **20**[24] promoted the smooth transformation of a range of aldehydes **10** and **22–28** into epoxides **12** and **30–36** at 5 mol% levels (Table 2). In addition to styrene oxide **12** (entry 1), epoxides derived from activated (entries 2 and 3), hindered (entry 4) and electron-rich (entries 5 and 6) aromatic aldehydes could be prepared in excellent yields.[25] α,β-Unsaturated and α-substituted aliphatic aldehydes (but not unbranched analogues which underwent competitive aldol reactions) were also amenable to epoxidation under these conditions (entries 7–9).

The clean catalysis observed in these reactions prompted us to exploit the electrophilicity of the oxirane products through the development of a tandem organocatalytic epoxidation–transition metal catalysed ring opening process (Scheme 2). The epoxidation could be combined with a Cu(II) ion-catalysed Meinwald rearrangement[26,27] to give a convenient and potentially useful protocol for the homologation of aldehydes. Organocatalysed epoxidation of **24** followed by separation of the phases and addition of $Cu(BF_4)_2$ (25 mol%, hydrate) to the organic portion



Scheme 2 Tandem epoxidation-ring opening reactions.

resulted in the isolation of the chain-extended phenyl acetaldehyde derivative **38** in good overall yield.

In summary we have shown for the first time that appropriately substituted *N*,*N*′-diarylureas and thioureas are capable of the efficient catalysis of the Corey–Chaykovsky reaction involving the inexpensive trimethylsulfonium iodide at ambient temperature. Rather unusually, urea derivatives are clearly superior catalysts to their thiourea analogues in these processes. These catalysed reactions are of wide scope with respect to the aldehyde component and clean formation of the epoxide is observed under optimal conditions—a property which was exploited in the development of an epoxidation–Meinwald rearrangement process which allows convenient aromatic aldehyde homologation without requiring intermediate purification steps. The efficient catalysis observed in this study (5 mol% catalyst loading is generally sufficient) offers the possibility of developing an enantioselective variant of the reaction using chiral urea derivatives. Investigations along these lines are under way.

Financial support from Science Foundation Ireland (SFI) and the Irish Research Council for Science Engineering and Technology (IRCSET) is gratefully acknowledged.

Notes and references

1 (*a*) A. W. Johnson and R. B. LaCount, *J. Am. Chem. Soc.*, 1961, **83**, 417; (*b*) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, **84**, 867; (*c*) V. Franzen and H.-E. Driesen, *Chem. Ber.*, 1963, **96**, 1881; (*d*) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.

2 V. K. Aggarwal, A. Ali and M. P. Coogan, *J. Org. Chem.*, 1997, **62**, 8628.

3 (*a*) For recent reviews see: A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341; (*b*) V. K. Aggarwal and J. Richardson, *Chem. Commun.*, 2003, 2644; (*c*) V. K. Aggarwal and C. L. Winn, *Acc. Chem. Res.*, 2004, **37**, 611; (*d*) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches and V. K. Aggarwal, *Chem. Rev.*, 2007, **107**, 5841.

4 (*a*) Representative recent examples: V. K. Aggarwal, E. Alonso, I. Bae, G. Hynd, K. M. Lydon, M. J. Palmer, M. Patel, M. Porcelloni, J. Richardson, R. A. Stenson, J. R. Studley, J.-L. Vasse and C. L. Winn, *J. Am. Chem. Soc.*, 2003, **125**, 10926; (*b*) M. Davoust, J.-F. Brière, P.-A. Jaffrès and P. Metzner, *J. Org. Chem.*, 2005, **70**, 4166; (*c*) X.-M. Deng, P. Cai, S. Ye, X.-L. Sun, W.-W. Liao, K. Li, Y. Tang, Y.-D. Wu and L.-X. Dai, *J. Am. Chem. Soc.*, 2006, **128**, 9730.

5 (*a*) B. M. Trost and R. F. Hammen, *J. Am. Chem. Soc.*, 1973, **95**, 962; (*b*) T. Hiyama, T. Mishima, H. Sawada and H. Nozaki, *J. Am. Chem. Soc.*, 1975, **97**, 1626; (*c*) L. Breau and T. Durst, *Tetrahedron: Asymmetry*, 1991, **2**, 367; (*d*) Y. Zhang and W. Du, *Tetrahedron: Asymmetry*, 1997, **8**, 2723; (*e*) V. K. Aggarwal, M. P. Coogan, R. A. Stenson, R. V. H. Jones, R. Fieldhouse and J. Blacker, *Eur. J. Org. Chem.*, 2002, 319; (*f*) B. R. Bellenie and J. M. Goodman, *Chem. Commun.*, 2004, 1076.

6 (*a*) Selected recent reviews on this topic: A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (*b*) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520; (*c*) S. J. Connon, *Chem.–Eur. J.*, 2006, **12**, 5418; (*d*) Y. Takemoto, *Org. Biomol. Chem.*, 2005, **3**, 4299; (*e*) P. M. Pihko, *Angew. Chem., Int. Ed.*, 2004, **43**, 2062; (*f*) P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289.

7 Trimethylsulfonium iodide is considerably less expensive than the methylsulfate and tetrafluoroborate analogues available from Aldrich. Their current prices in £ g^{-1} are 1.02, 7.48 and 74.30 respectively.

8 (*a*) A. Merz and G. Märk, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 845; (*b*) C. Bermand, A. Comel and G. Kirsch, *ARKIVOC*, 2000, **2**, 128.

9 (*a*) M. E. Borredon, M. Delmas and A. Gaset, *Tetrahedron Lett.*, 1982, **23**, 5283; (*b*) M. E. Borredon, M. Delmas and A. Gaset, *Tetrahedron*, 1987, **43**, 3945; (*c*) H. Bouda, M. E. Borredon, M. Delmas and A. Gaset, *Synth. Commun.*, 1987, **17**, 503; (*d*) C. Lemini, M. Ordonez, J. Pérez-Flores and R. Cruz-Almanza, *Synth. Commun.*, 1995, **25**, 2695; (*e*) A. Ahmed, E. K. Hoegenauer, V. S. Enev, M. Hanbauer, H. Kaehlig, E. Oehler and J. Mulzer, *J. Org. Chem.*, 2003, **68**, 3026.

10 (*a*) For a similar solvent-free protocol involving t-BuOK and heating at 60 °C see: F. Toda and K. Kanemoto, *Heterocycles*, 1997, **46**, 185; (*b*) F. Toda and N. Imai, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2674.

11 (*a*) For examples using clean deprotonation of the salt in DMSO using strong bases at room temperature see ref. 1*b*–*d* and: R. G. Harvey, M. Konieczny and J. Pataki, *J. Org. Chem.*, 1983, **48**, 2930; (*b*) S. Kulasegaram and R. J. Kulawiec, *J. Org. Chem.*, 1997, **62**, 6547; (*c*) J. A. Ciaccio, A. L. Drahus, R. M. Meis, C. T. Tingle, M. Smrtka and R. Geneste, *Synth. Commun.*, 2003, **33**, 2135; (*d*) S. Raghavan and T. Sreekanth, *Tetrahedron Lett.*, 2006, **47**, 5595.

12 (*a*) For useful ambient temperature reactions with the relatively expensive methylsulfate salt see: P. Mosset and R. Grée, *Synth. Commun.*, 1985, **15**, 749; (*b*) L. M. Harwood, G. Casy and J. Sherlock, *Synth. Commun.*, 1990, **20**, 1287; (*c*) M. M. Elenkov, B. Hauer and D. B. Janssen, *Adv. Synth. Catal.*, 2006, **348**, 579; (*d*) for the bromide salt see ref. 8*b* and: M. Purpura and N. Krause, *Eur. J. Org. Chem.*, 1999, 267.

13 Recently efficient CC reactions in ionic liquids have been reported: S. Chandrasekhar, C. Narasihmulu, V. Jagadeshwar and K. Venkatram Reddy, *Tetrahedron Lett.*, 2003, **44**, 3629.

14 K. Julienne, P. Metzner and V. Henryon, *J. Chem. Soc., Perkin Trans. 1*, 1999, 731.

15 In preliminary experiments we also found that cinnamonitrile formed rapidly in this ylide-generating system unless water was added—a requirement which was unlikely to be beneficial in a system involving a hydrogen-bond donating catalyst.

16 S. J. Connon, *Chem. Commun.*, 2008, DOI: 10.1039/b719249e.

17 (*a*) D. P. Curran and L. H. Kuo, *J. Org. Chem.*, 1994, **59**, 3259; (*b*) D. P. Curran and L. H. Kuo, *Tetrahedron Lett.*, 1995, **36**, 6647; (*c*) for the first chiral (thio)urea catalysts see: M. S. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 4901; (*d*) P. R. Schreiner and A. Wittkopp, *Org. Lett.*, 2002, **4**, 217; (*e*) P. R. Schreiner and A. Wittkopp, *Chem.–Eur. J.*, 2003, **9**, 407.

18 (*a*) T. Okino, Y. Hoashi and Y. Takemoto, *Tetrahedron Lett.*, 2003, **44**, 2817; (*b*) D. J. Maher and S. J. Connon, *Tetrahedron Lett.*, 2004, **45**, 1301; (*c*) G. Dessole, R. P. Herrera and A. Ricci, *Synlett*, 2004, 2374; (*d*) M. Kotke and P. R. Schreiner, *Tetrahedron*, 2006, **62**, 434; (*e*) M. Kirsten, J. Rehbein, M. Hiersemann and T. Strassner, *J. Org. Chem.*, 2007, **72**, 4001; (*f*) C. M. Kleiner and P. R. Schreiner, *Chem. Commun.*, 2006, 4315; (*g*) E. M. Fleming, C. Quigley, I. Rozas and S. J. Connon, *J. Org. Chem.*, 2008, **73**, 948; (*h*) S. C. Pan, J. Zhou and B. List, *Synlett*, 2006, 3275; (*i*) M. Kotke and P. R. Schreiner, *Synthesis*, 2007, **62**, 779; (*j*) Z. Zhang and P. R. Schreiner, *Synlett*, 2007, 1455.

19 (*a*) For reports concerning the reduction of imines/reductive amination of aldehydes/ketones using thiourea as a catalyst see: D. Menche, J. Hassfeld, G. Menche, A. Ritter and S. Rudolph, *Org. Lett.*, 2006, **8**, 741; (*b*) D. Menche and F. Arikan, *Synlett*, 2006, 841; (*c*) D. Menche, S. Böhm, J. Li, S. Rudolph and W. Zander, *Tetrahedron Lett.*, 2007, **48**, 365. However, it should be noted that the role of thiourea in these reactions has been recently brought into question, see ref. 18*j*.

20 F. D. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456.

21 B. Procuranti and S. J. Connon, *Chem. Commun.*, 2007, 1421.

22 For a very recent study on the mechanism of the CC reaction see: D. R. Edwards, P. Montoya-Peleaz and C. M. Crudden, *Org. Lett.*, 2007, **9**, 5481.

23 For other examples see ref. 17a, 18b and: P. Vachal and E. N. Jacobsen, *Org. Lett.*, 2000, **2**, 867.

24 Both **19** and **20** are highly active catalysts in this reaction. Urea **20** was chosen as the candidate for further study as it has already been shown to promote a range of transformations effectively whereas **19** is less widely used.

25 The ^{1}H NMR spectra of the crude material after the epoxidation of *o*- and *p*-anisaldehyde (**25** and **26** respectively) indicated that the epoxides are formed cleanly as the sole product under the reaction conditions

indicated in Table 2. These crude spectra are available in the ESI.† This is not reflected in the isolated yield as considerable decomposition is observed after either column chromatography (SiO_2 or Al_2O_3 with a mobile phase containing triethylamine) or Kugelrohr distillation. In any case the crude product was of sufficient purity to be used in subsequent transformations.

26 J. Meinwald, S. S. Labana and S. S. Chadha, *J. Am. Chem. Soc.*, 1963, **85**, 582.

27 Our choice of this catalyst for the Meinwald rearrangement was based on the availability of an excellent protocol reported recently by Graham *et al.*: M. W. C. Robinson, K. S. Pillinger and A. E. Graham, *Tetrahedron Lett.*, 2006, **47**, 5919.