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Efficient Catalytic Corey–Chaykovsky Reactions Involving Ketone Substrates

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Abstract: It has been demonstrated for the first time that a sulfide catalyst, utilised at 20 mol% loading, can promote methylene transfer to ketones in the presence of methyl triflate and an organic base. This metal-free methodology is of broad scope – both aliphatic and aromatic ketones (including trifluoromethyl ketones) can be converted to synthetically useful terminal epoxides in excellent yields at room temperature.

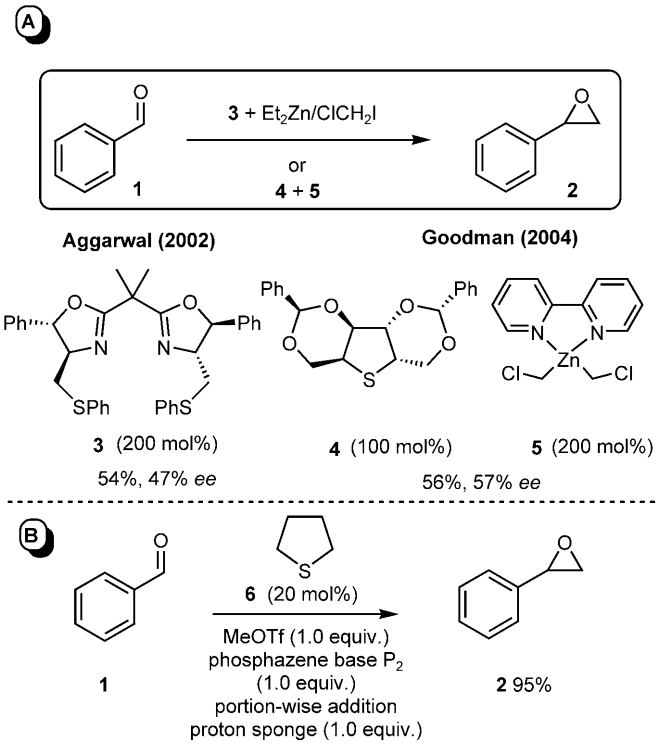
Keywords: Corey–Chaykovsky reaction; epoxides; methylene transfer; organocatalysis; sulfides

Epoxides are among the most valuable synthetic building blocks available to an organic chemist. Hence, the synthesis of these spring-loaded electrophiles in enantiomerically pure form is of great interest.[1] Although there are many distinguished protocols for the synthesis of optically active substituted/functionalised epoxides,[2] there is a dearth of methods for the catalytic synthesis of the corresponding unfunctionalised terminal epoxides.

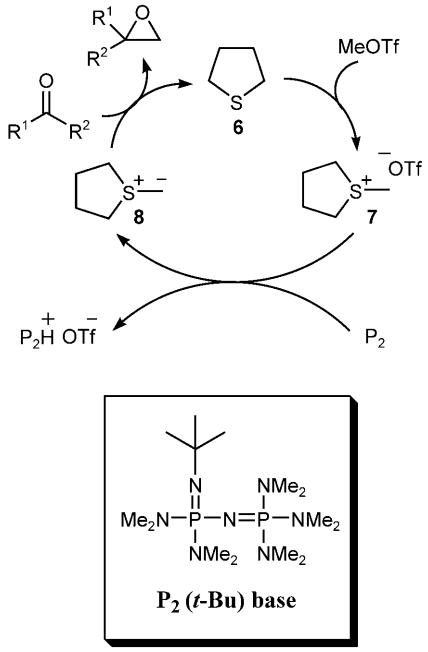
The Corey–Chaykovsky (CC) reaction[3] is a time-honoured and efficient methodology for the synthesis of these compounds. Initially this reaction involved the use of stoichiometric loadings of preformed sulf(ox)onium salts (in the presence of base) as the alkyl-transfer agent, which is naturally undesirable from an atom-economy perspective.

In a landmark series of studies, Furukawa,[4a] Aggarwal[4b–d,g–i,l,n] and others[4e,f,j,k,m] demonstrated that the (asymmetric) addition of semi-stabilised ylides to carbonyl compounds is possible using catalytic sulfide loadings. However, the corresponding asymmetric methylene transfer (i.e., *via* a chiral non-stabilised ylide) has been characterised by moderate yields/enantioselectivities and a requirement for (super)stoichiometric sulfide loadings.[5] For instance, Aggarwal's[5d] and Goodman's[5e] benchmark literature protocols for the asymmetric sulfonium ylide mediated methylene transfer to benzaldehyde (**1**) involve the use of 100–200 mol% of chiral sulfides **3–4** and produce **2** in *ca.* 50–60% yield and up to 57% *ee* (Scheme 1, A). It is also noteworthy that these protocols involved the use of a modified version of the classical CC reaction involving a metal-mediated Simmons–Smith type carbenoid transfer.[5e,6]

We recently reported an operationally simple catalytic procedure for metal-free methylene transfer to



Scheme 1. Protocols for chiral sulfide mediated terminal epoxidation.



Scheme 2. The CC reaction: catalytic cycle.

aldehydes under classical CC conditions using (for the first time) low loadings (20 mol%) of a sulfide catalyst **6**, which allows the synthesis of **2** in high yield (Scheme 1, B).[7]

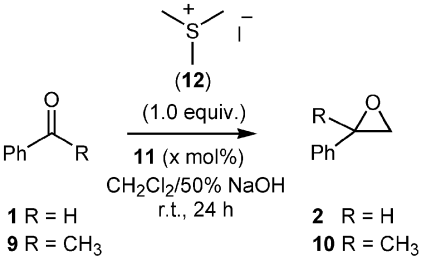
The key realisation which led to the development of a catalytic protocol was that alkylation of the sulfide (i.e., **6**→**7**, Scheme 2) by alkyl electrophiles is rate-determining. Thus, turnover is facilitated by the use of a powerful alkylating agent such as methyl triflate, which leads to the formation of the sulfonium salt **7** in a catalytically feasible time frame, which is cleanly deprotonated by a phosphazene base to form ylide **8**. Under these conditions **8** reacted rapidly with aldehydes to furnish a range of epoxides in excellent yields (Scheme 2).

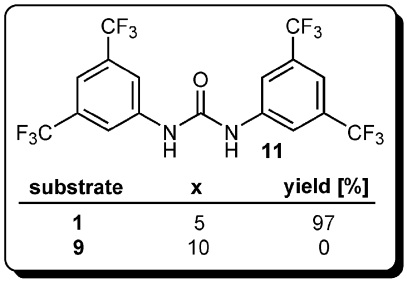
On completion of this study we realised that for this methodology to be considered genuinely useful it must be compatible with ketone substrates. Although there are numerous reported examples of methylene transfer to ketones, all of these procedures require (super)stoichiometric sulfide loadings.[8] For example, Shibasaki reported a very efficient protocol for the synthesis of enantioenriched terminal epoxides derived from ketones. This procedure requires a superstoichiometric amount of an achiral sulfoxonium ylide, the observed stereoinduction is derived from a metal complex catalyst.[9] Given that a catalytic protocol for methylene transfer to aldehydes has only recently been reported, the absence of a protocol for the catalytic (in sulfide) methylene transfer to ketones is perhaps unsurprising.

An obvious cause of concern in developing such a process is the greatly reduced electrophilicity of simple ketones relative to their aldehyde counterparts. Initial experimentation in this regard was not encouraging, for example, we previously reported the results of a study concerning the influence of hydrogen-bond donating catalysts on the CC reaction in a biphasic solvent system:[10] benzaldehyde (**1**) could be converted to **2** in excellent yield in the presence of catalyst **11**, trimethylsulfonium iodide and base. For the purposes of the current study this reaction was repeated using acetophenone (**9**) as the substrate. The difference in reaction rate was striking: no conversion to **10** was observed, even with elevated catalyst loadings of 10 mol% (Scheme 3).

While it was thus obvious that ketones represent a challenge from an electrophilicity standpoint,[7] the key question now was whether or not ketones would be unreactive enough towards ylide **8** under our optimised conditions (Scheme 1) to render C–C bond formation (as opposed to sulfide alkylation) the rate-determining step. If this were the case, it would be unlikely that a practical catalytic procedure would be possible. However, we envisaged that the homogeneous nature of the catalytic methodology (Scheme 1), which involves the rapid and clean formation of **8** in the same phase as the ketone electrophile (thus the concentration of both could be carefully controlled), could (at least partially) compensate for the inherent lack of electrophilicity associated with ketone substrates. To test this hypothesis we applied our catalytic protocol to the epoxidation of a variety of aromatic ketones (Table 1).

We were delighted to observe that under these conditions acetophenone (**9**) underwent smooth reaction in the presence of catalyst **6** (20 mol%) to furnish terminal epoxide **10** in high yield (entry 1). We were

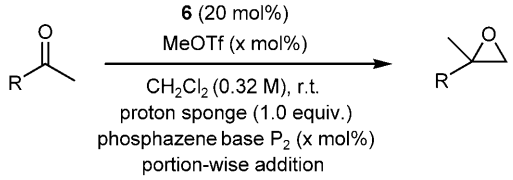


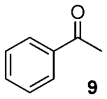
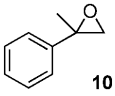
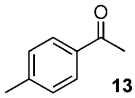
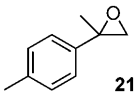
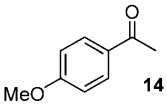
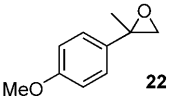
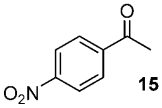
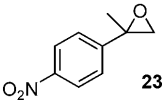
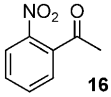
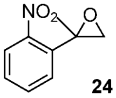
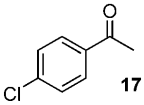
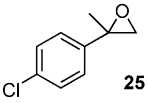
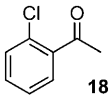
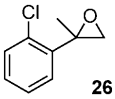
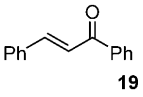
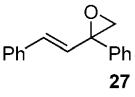
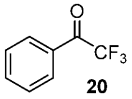
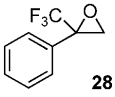


substrate	x	yield [%]
1	5	97
9	10	0

Scheme 3. Urea-catalysed epoxidation of **2** and the attempted epoxidation of **9**.

Table 1. Catalytic epoxidation of aromatic ketones.



Entry	Ketone	Product	X	Yield[a] [%]
1	 9	 10	100	85
2	 13	 21	100	89
3	 MeO 14	 MeO 22	115	94[b]
4	 O_2N 15	 O_2N 23	100	93
5	 NO_2 16	 NO_2 24	100	89
6	 Cl 17	 Cl 25	100	94
7	 Cl 18	 Cl 26	100	92
8	 Ph Ph 19	 Ph Ph 27	110	88
9	 CF_3 20	 F_3C 28	100	85

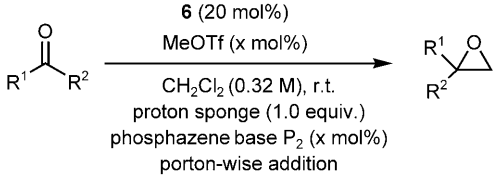
[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopy using an internal standard due to product decomposition during column chromatography.

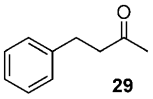
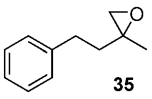
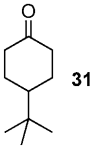
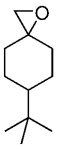
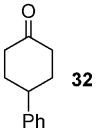
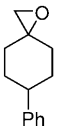
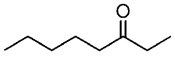
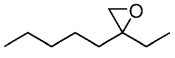
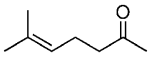
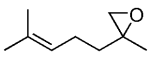
next interested in evaluating the performance of a range of ketones of variable steric and electronic characteristics in the catalytic CC reaction. The catalytic procedure proved robust – epoxide products **21**–**28** could be synthesised in excellent isolated yield using catalytic sulfide loadings in each case. Electron-rich substrates **13** and **14** (entries 2 and 3, respectively), in addition to activated ketones **15**–**18** (entries 4–7), afforded epoxide yields ranging between 89 and 93%.

Chalcone[1d] (**19**) (Table 1, entry 8) represented an interesting substrate from a chemoselectivity standpoint: despite the relatively hindered nature of the carbonyl moiety we observed complete conversion to **27** without any trace of the cyclopropanation adduct being detected. It is also noteworthy that the methodology can be utilised in the epoxidation of trifluoromethyl ketone **20** (for the first time to the best of our knowledge) Table 1, entry 9);[11] an interesting building block in the synthesis of biologically active compounds.[12]

Aliphatic ketones were also susceptible to catalytic epoxidation under these reaction conditions (Table 2). Benzylacetone (**29**, entry 1) proved to be a good substrate in this reaction, producing the corresponding epoxide **35** in high yield. Cyclohexanone and 4-substituted cyclohexanone derivatives (**30** and **31**–**32** respectively, entries 2–4) furnished the corresponding epoxide products **36**–**38** in excellent yield. Epoxides derived from long chain aliphatic ethyl (**33**, entry 5) and methyl (**34**, entry 6) ketones could also be pre-

Table 2. Catalytic epoxidation of aliphatic ketones.



Entry	Ketone	Product	X	Yield[a] [%]
1	 29	 35	100	89
2	 30	 36	144	95
3	 31	 37	118	93[b]
4	 Ph 32	 Ph 38	118	94
5	 33	 39	136	83[c]
6	 34	 40	118	90

[a] Isolated yield.
[b] *dr* (O-*ax*:O-*eq*) = 40:60.
[c] Determined by ^{1}H NMR spectroscopy using an internal standard.

pared without difficulty. Undesired aldol-derived side products were not detected in any of these reactions.

In summary, it has been shown, for the first time, that ketones can be converted to terminal epoxides *via* a CC reaction involving methylene transfer in the presence of substoichiometric loadings of a sulfide catalyst. The method is of broad scope: a diverse array of aromatic (including hindered, activated and deactivated analogues) and aliphatic aldehydes are amenable to epoxidation. Product yields are invariably high-excellent using a convenient, room temperature protocol. It should now be possible to develop chiral sulfide catalysts capable of promoting efficient asymmetric variants of this reaction. Studies along these lines are underway in our laboratory.

Experimental Section

Representative Procedure for the Catalytic Methylene Transfer to 17 using Sulfide 6

A 5-mL round-bottomed flask containing a stirring bar was charged with catalyst **6** (10 μL, 0.11 mmol), fitted with a septum and flushed with argon. CH_2Cl_2 (1.80 mL, 0.32 M) was added *via* syringe followed by styrene (65 μL, 0.57 mmol). Proton sponge (121.5 mg, 0.57 mmol) was added followed by *p*-chloroacetophenone (**17**) (73 μL, 0.57 mmol). The first aliquot of methyl triflate (11.6 μL, 0.10 mmol) was added *via* syringe and the resulting solution was allowed to stir at room temperature for 25 min. The first aliquot of P_2 base was then added (2.0 M in THF, 51 μL, 0.10 mmol) and allowed to stir for 25 min. The consecutive additions of methyl triflate and P_2 base were repeated in this fashion an additional four times at 25 min intervals. The remaining methyl triflate (6.4 μL, 0.06 mmol) and P_2 base (2.0 M in THF, 28 μL, 0.06 mmol) were then added (*vide supra*). After 25 min the reaction was analysed by ^{1}H NMR spectroscopy. After purification of the crude material by flash chromatography (8:2 hexane/CH_2Cl_2) the product **25** was obtained as a pale yellow liquid; yield: 90 mg (94%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.32$ (s, 4H), 2.99 (d, 1H, $J = 5.5$ Hz), 2.77 (d, 1H, $J = 5.5$ Hz), 1.72 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 139.3$, 132.8, 128.0, 126.3, 56.6, 55.8, 21.2; HR-MS-CI: $m/z = 169.0428$ $[M+H]^+$, calcd. for $C_9H_{10}OCl$: 169.0420.

Representative Procedure for the Catalytic Methylene Transfer to 29 using Sulfide 6

A 5-mL round-bottomed flask containing a stirring bar was charged with catalyst **6** (10 μL, 0.11 mmol), fitted with a septum and flushed with argon. CH_2Cl_2 (1.80 mL, 0.32 M) was added *via* syringe followed by styrene (65 μL, 0.57 mmol). Proton sponge (121.5 mg, 0.57 mmol) was added followed by 4-phenyl-2-butanone (**29**) (85 μL, 0.57 mmol). The first aliquot of methyl triflate (11.6 μL, 0.10 mmol) was added and the resulting solution was allowed to stir at room temperature for 25 min. The first aliquot of P_2 base was then added (2.0 M in THF, 51 μL, 0.10 mmol) and allowed to stir for 25 min. The consecutive additions of methyl triflate and P_2 base were repeated in this fashion an additional four times at 25 min intervals. The remaining methyl triflate (6.4 μL, 0.06 mmol) and P_2 base (2.0 M in THF, 28 μL, 0.06 mmol) were then added. After 25 min the reaction was analysed by ^{1}H NMR spectroscopy. After purification of the crude material by flash chromatography (7:3 hexane/CH_2Cl_2) the product **35** was obtained as a pale yellow liquid; yield: 81.9 mg (89%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$–7.26 (m, 2H), 7.21–7.18 (m, 3H), 2.76–2.68 (m, 2H), 2.61–2.58 (m, 2H), 1.97–1.80 (m, 2H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 141.6$, 128.5, 128.3, 126.0, 56.7, 54.0, 38.6, 31.5, 21.1; HR-MS-CI: $m/z = 163.1123$ $[M+H^+]$, calcd. for $C_{11}H_{15}O$: 163.1123

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