Catalytic (Asymmetric) Methylene Transfer to Aldehydes

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ABSTRACT

An investigation into the poor activity of sulfides as catalysts for sulfonium-ylide-mediated methylene transfer to aldehydes has indicated that ylide formation is the problematic catalytic cycle step. Alkylation with traditional electrophiles does not proceed with sufficient efficiency to allow the sulfide to be used catalytically. Methyl triflate rapidly alkylates cyclic thiolanes under mild conditions, allowing their use in efficient aldehyde epoxidation reactions (in conjunction with phosphazene bases) at loadings as low as 10 mol%.

Over the past 15 years the Corey–Chaykovsky (CC) epoxidation process involving the reaction between sulfonium ylides and aldehydes has evolved into a highly synthetically useful, catalytic asymmetric methodology. The use of semistabilized ylides such as those derived from the reaction of either benzyl halides or α-haloesters/amides with chiral sulfides at catalytic loadings (in conjunction with phosphazene bases) at loadings as low as 10 mol%


to us that betaine formation from a methyliide (7, R₁ = H, Scheme 1) should be more efficient (if anything) than the corresponding reaction using less nucleophilic (semi)-stabilized ylides (7, R₁ = aryl or COR). This leaves either ring closure of the betaine or the formation of the sulfonium ylide as the factor responsible for the low catalytic activity associated with methylene transfer.

Since it is also difficult to see how sterically unencumbered methyliide-derived betaines (8, R₁ = H) would fail to ring-close where more substituted (albeit aryl substituted) analogues succeed – we reasoned that inefficient formation of the sulfonium ylide (i.e. 6 → 7, Scheme 1) was the most plausible underlying cause of the observed sluggish catalysis of methylene transfer. This thesis was also supported by Goodman’s observation that treatment of 4 with Mel followed by base did not lead to the formation of 2 from 1.

To test this hypothesis, we initially treated benzaldehyde (1) with the unhindered sulfide 9 (20 mol%) in the presence of stoichiometric amounts of solid KOH and Mel in CH₂Cl₂ (Scheme 2). Under these conditions we observed the formation of 2 in 18% yield. A repeat of this experiment using 100 mol% of the pre-formed sulfonium salt 10 however, resulted in a 90% yield under otherwise identical conditions (Scheme 2). Thus it is clearly the rate of alkylation to form the sulfonium salt 10 which is problematic in this process.

With this in mind we carried out a screening study aimed at the identification of an agent which would methylate the sulfide at a rate conducive to smooth catalysis of the CC reaction under these conditions. The results of these experiments are outlined in Table 1. With the sulfide utilized at the same concentration as that used in the attempted catalytic CC reaction (see Scheme 2) we found that methyl iodide furnished the corresponding iodide salt in 25% yield after 24 h (entry 1). Methyl tosylate and methyl mesylate failed to alkylate 9 under these conditions (entries 2-3) and even powerful methyliating electrophiles such as Meerwein’s salt and

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**Scheme 1:** Benchmark literature procedures for the sulfonium-ylide mediated methylene transfer to benzaldehyde (1)

**Scheme 2:** Preliminary experiments: identification of sulfonium salt formation as the problematic step

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11 It is noteworthy that analysis of these reactions by ¹H NMR spectroscopy did not indicate the formation of methanol.
dimethylsulfate gave unsatisfactory alkylation rates in dichloromethane solvent (entries 4–5). However, use of commercially available MeOTf resulted in clean, rapid formation of salt 10f inside 15 min at ambient temperature (entries 6–7). MeOTf could be conveniently added to the reaction via syringe and could be also used in acetonitrile solvent; however its high reactivity renders it incompatible with THF (entries 8–9).

We were now ready to bring both efficient alkylation and deprotonation to bear on the methylene transfer process. Unfortunately treatment of 1 with stoichiometric amounts of MeOTf and P2 base in the presence of 20 mol% of sulfide 9 resulted in poor product yield, despite considerable conversion of the aldehyde. Interestingly, we also noted the presence of phenylacetaldehyde (presumably a Meinwald rearrangement\(^{14}\) product) in the crude \(^1\)H NMR spectrum of these reactions. This led us to speculate that a) the alkylation agent is not compatible with the P2 base when both are present together in solution and b) a protic species in solution (possibly due to the presence of adventitious water) is capable of catalyzing the deleterious Meinwald rearrangement.

To circumvent these two difficulties we developed a modified protocol: use of proton sponge additive avoids the Meinwald rearrangement, while addition of the alkylation agent and base in 5 portions (with a ca. 20 min interval) allows the consumption of the methyl triflate to occur prior to introduction of each portion of base. While portion-wise addition is obviously less desirable than a protocol involving initial addition of all reagents, the excellent efficiency of both the individual alkylation and deprotonation steps and the liquid nature of both added reagents (i.e. they can be injected via syringe) results in a convenient and remarkably reproducible catalytic protocol which can be executed in 5 hours and furnished an average of 95% product yield over 3 experiments.\(^ {15} \)

We now turn to the results of our base screening study. Commercially available P1 and P2 phosphazene organic bases fared significantly better and led to the formation of 2 in excellent yield, with the P2 base\(^ {13} \) proving superior.

With catalytically promising alkylation conditions in hand, we next required an appropriate base. Table 2 details the results of a screening study to identify an active and easily handled base which would transform triflate salt 10f into 2 in the presence of 1 in dichloromethane solvent.

## Table 2. Identification of a suitable base

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>yield (%)(^ a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOH (aq 50% v/v)</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>KHMDs (solution in PhMe)</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOK</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>P2 (t-Bu)</td>
<td>95</td>
</tr>
</tbody>
</table>

\(^{a}\)Determined by \(^1\)H NMR spectroscopy using an internal standard.

### Scheme 3: Use of the sulfide at catalytic loadings

We now turn to the results of our base screening study. Commercially available P1 and P2 phosphazene organic bases fared significantly better and led to the formation of 2 in excellent yield, with the P2 base\(^ {13} \) proving superior.

### Table 3. Evaluation of substrate scope


15 A key predictor of success in these experiments is having prior knowledge of the interval required to ensure complete alkylation of 9 (20 mol%) by MeOTf (20 mol%) at the concentration to be used in the epoxidation protocol.
We were next interested in investigating the issue of substrate scope (Table 3). We were pleased to observe that under these conditions 9 could promote methylene transfer to 1 (at either 10 or 20 mol\% loadings, entries 1-2), together with a range of hindered- (entry 3), deactivated (entries 4-5) and activated (entries 6-7) aromatic aldehydes to afford epoxides 2 and 19-23 in excellent yields. α,β-Unsaturated (entry 8) and α-branched aliphatic aldehydes (16 and 17 respectively, entries 8-9) are also good substrates, although an unbranched aldehyde did not furnish epoxide 26, presumably due to competitive homo-aldol reactions.

Finally, we then synthesized two novel chiral analogues of 9 (i.e. 27 and 28) with a view towards catalysis of an asymmetric CC reaction involving methylene transfer. Both materials proved capable of promoting the reaction efficiently; furnishing 2 in high yield. The isopropyl-substituted catalyst 27 provided the epoxide product with very modest levels of enantioselectivity, however use of the bulkier tert-butyl analogue 28 allowed the isolation of (R)-2 in 43% ee. While this is not on a par with the levels of selectivity achievable using semistabilized ylides, this methodology affords levels of product enantiomeric excess approaching those obtainable using the benchmark literature procedures for asymmetric methylene transfer, but requires 5-10 times less catalyst and provides the product in significantly higher yield (Schemes 1 and 4).

In summary, an investigation into the low catalyst activity in CC reactions involving methylene transfer resulted in the development of a methodology capable of converting aromatic, α,β-unsaturated and aliphatic aldehydes to the corresponding terminal epoxides in excellent yields using 10-20 mol\% of a simple sulfide catalyst. An asymmetric variant of this process was also developed which could produce styrene oxide in up to 43% ee. This field (enantioselective methylene transfer to aldehydes) has been relatively dormant over the past 5 years. We would be optimistic that this protocol – the first not to require (super)stoichiometric amounts of chiral sulfide (prepared via multistep syntheses) will facilitate the development of new sulfide catalyst systems, the methylides derived from which could be better able to discriminate between aldehyde faces in the betaine-forming reaction step.

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**Supporting Information Available** General experimental procedures, 1H and 13C NMR spectra, characterisation data, HPLC assays. This material is available free of charge via the Internet at http://pubs.acs.org