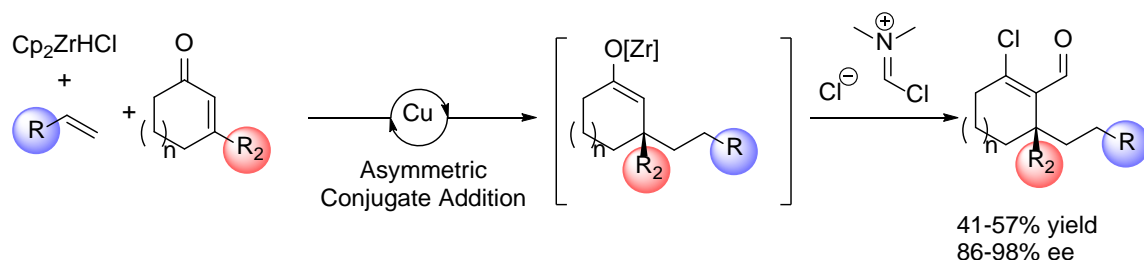


β -chloroaldehydes from trapping zirconium enolates produced in asymmetric 1,4-additions

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Supporting Information Placeholder



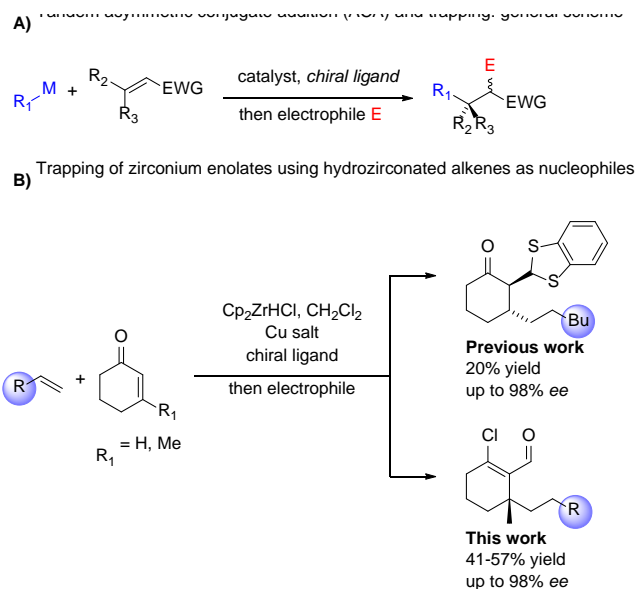
ABSTRACT: Zirconium enolates, derived from copper catalyzed asymmetric conjugate additions, are trapped with the Vilsmeier-Haack reagent. Asymmetric additions generate quaternary carbon centers with high enantioselectivity (generally ~90% ee) and the enolates are converted to unsaturated β -chloroaldehydes (41–57% yields). The reaction tolerates changes to the nucleophile, can be used to form five, six or seven membered ring products, is scalable to 5 mmol and the products are readily elaborated by condensation, cross coupling and addition reactions.

Asymmetric conjugate addition (ACA) is a staple of the organic chemist's toolkit for C-C bond formation. When performed in sequence with an electrophilic trapping reaction, the resulting tandem sequences are particularly powerful^{1a-d} (Scheme 1, A). As multiple bonds and stereocenters may be formed in one step, this strategy is frequently used in natural product synthesis.^{2a-g}

Many ACA/trapping reactions are initiated by organometallic nucleophiles such as Grignard, organoaluminum and organozinc reagents. The intermediate enolates generated from these ACAs have been trapped in a variety of ways¹, including with Mander's reagent,³ the Heller-Sarpong reagent,⁴ carbenium ions,⁵ nitro-olefins⁶ and Stork-Jung electrophiles.⁷ Trapping intermediate aluminium enolates has been extensively investigated by Alexakis and co-workers.^{8,9} Generally, tandem ACA/trapping reactions remain strongly substrate dependent^{3,8,10-12} and developing new trapping methods would facilitate chemists ability to rapidly access complex molecules.

Our group has developed ACAs that use alkylzirconium species as nucleophiles. These organometallics are made *in situ* from hydrozirconation of alkenes with Cp_2ZrHCl , tolerate a variety of functional groups, and can be generated and used at convenient temperatures. We have shown that these alkylzirconium reagents add to a variety of cyclic and acyclic enones to furnish ACA products bearing tertiary or quaternary stereocenters in high yield and enantioselectivity.¹³

Scheme 1. A) General scheme of the tandem ACA/trapping reaction B) Previous work¹⁵ and this work.



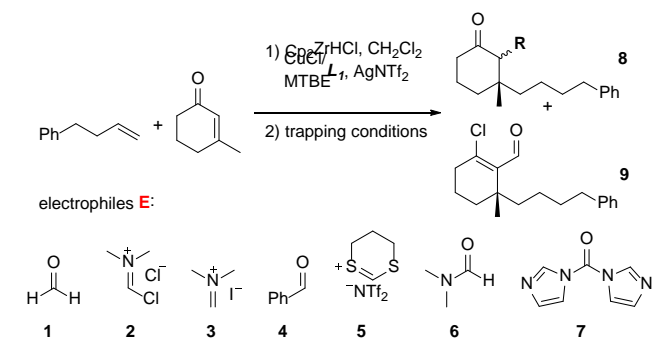
The development of tandem ACA/trapping reactions initiated by organozirconium reagents have been difficult to realize, possibly because of the strength of the Zr–O bond in the intermediate enolate¹⁴, however Nemethova et al. recently demonstrated that a few specialized electrophiles can be used to trap zirconium enolates

(Scheme 1, **B**).¹⁵ In that work, highly electrophilic carbenium ions gave trapped products in <20% yield.

Here, we report a synthetically useful tandem ACA/trapping procedure initiated by copper catalyzed ACA of alkylzirconium species to form quaternary centers¹³ followed by trapping of the intermediate enolate with the Vilsmeier-Haack reagent (VH) (Table 1, **2**).¹⁶ Unsaturated β -chloroaldehydes are the products of this sequence (Scheme 1, **B**) which (*vide infra*) can readily be elaborated in a number of ways. VH is well known as a strong formylating agent, and under certain conditions behaves as both a formylating and chlorinating agent.¹⁷

The use of highly reactive electrophiles was initially investigated to trap enolates generated in ACAs as shown in Table 1.^{13d,e} Although α -hydroxy ketone product **8** ($R=CH_2OH$) could be obtained using formaldehyde **1**, and **8** was potentially amenable to further functionalization, the yields were difficult to reliably reproduce, and there is procedural complexity in generating gaseous anhydrous formaldehyde (Table 1, entry 1).

Table 1.^a Investigation of electrophiles used in zirconium enolate trapping.



| entry | E | product | yield % | conditions |
|-------|----------|---------------------|----------|-------------------------------------|
| 1 | 1 | 8 $R=CH_2OH$ | Up to 50 | Freshly cracked, anhydrous CH_2O |
| 2 | 1 | 8 $R=CH_2OH$ | 0 | 35% wt. aqueous solution of CH_2O |
| 3 | 2 | 9 | 41 | '2' ($POCl_3$, DMF) |

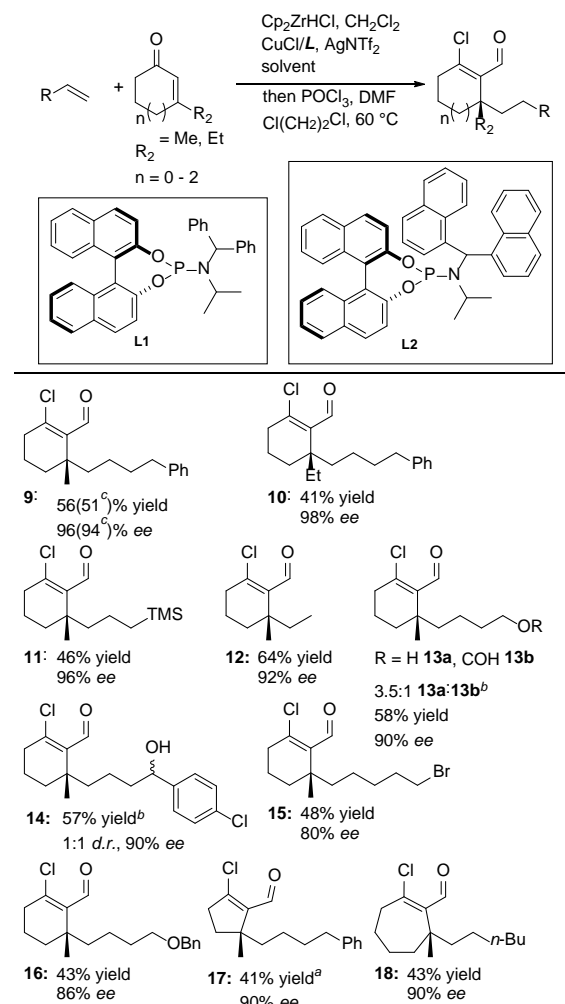
^aIsolated yields.

We found that the use of VH **2** resulted in the formation of unsaturated β -chloroaldehyde **9** as opposed to α -functionalized ketones (Table 1, entry 3). **2** is prepared by simply mixing phosphorous(V) oxychloride ($POCl_3$) and DMF in a solvent. The products present multiple functional groups for further elaboration, and are complementary to the α -functionalized ketones normally obtained in ACA/trapping protocols. We were unable to successfully trap this enolate with **3-9**.

The conditions found to provide the best yield use 20 equiv. of **2** at 60 °C. These conditions furnished the desired unsaturated β -chloroaldehydes in fair yields and require ~20 min for complete consumption of the ACA enolate, after which the reaction should be carefully quenched at 0 °C.

The trapping procedure shows tolerance (Scheme 2) to aromatic rings (examples **9**, **10**, **14**, **16**), an alkyl silane (example **11**), an alkyl bromide (**15**) and a benzyl protected alcohol (example **16**). When *tert*-butyldimethylsilyl protected alcohols were used (examples **13** and **14**), free alcohols were obtained as the major product. For product **13a**, formate ester **13b** is also obtained.

Scheme 2. ACA-chloroformylation of 3-substituted cyclic enones.



Isolated yields. Unless specified otherwise, ACA reactions were conducted using **L1** with MTBE as solvent. *ee*'s determined by HPLC or SFC. ^aACA reaction conducted using **L2**, Et_2O as solvent and $TMSCl$ (5.0 eq.). ^bAsymmetric addition using TBDMS protected alcohols. ^c5 mmol scale to give 0.79 g of **9**.

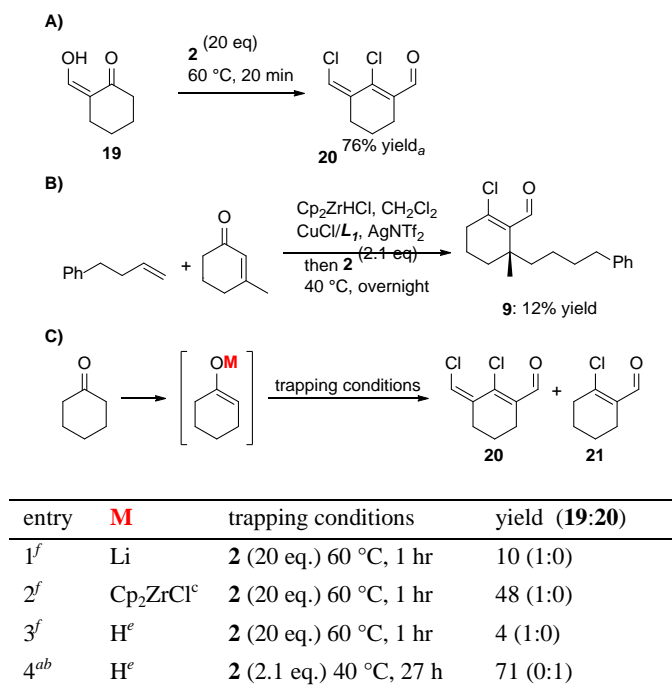
We performed the reactions on a 5 mmol scale to give 0.79 g of **9** in 51% yield with 94% *ee*. In this reaction, less **2** (10 rather than 20 equiv.) can be used without adversely affecting the yield, however 2 hours were required for complete consumption of the enolate.

The trapping procedure is suitable for the quaternary centre containing enolates to form six-, seven-^{13d} and five-membered^{13g} ring containing products. The five-membered ring example **17** is of particular interest because 1,2,3-trisubstituted cyclopentanes bearing a quaternary methyl stereocenter are common in natural products.^{2a,18}

Experiments to probe the trapping process were performed (Scheme 3). Treatment of hydroxymethylene cyclohexanone²¹ **19**, a simple model for a 1,3-dicarbonyl which might be formed through formylation gave doubly chlorinated $\alpha,\beta,\delta,\gamma$ -unsaturated aldehyde **20** in 76% isolated yield. No such dienes were observed in our reactions, suggesting against dicarbonyl (or tautomeric) intermediates (Scheme 3, **A**). Milder conditions¹⁹ as reported by a Genentech process group for the chlo-

ration of cyclohexanone led to decreased yield (12%, Scheme 3 B).

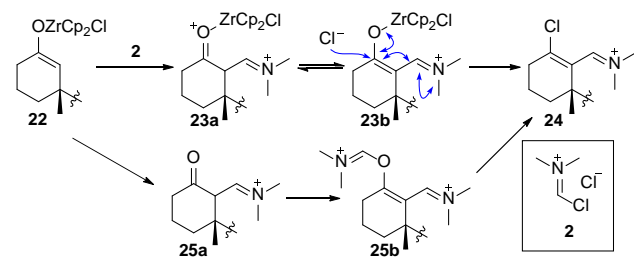
Scheme 3.^{c,d} Selected experiments for mechanistic studies



^aIsolated yield. ^bData consistent with literature.^{17a-c,19} ^cLithiation and transmetalation procedures carried out according to Evans and coworkers.²⁰ ^dUnless specified otherwise, yields determined by ¹H NMR spectroscopy using Cl(CH₂)₂Cl as internal standard. ^eCyclohexanone was used. ^fYield based on average over two experiments.

Next, different enolates were investigated. Use of the lithium enolate²⁰ gave only 10% yield of dichloride **20** and no mono-chloride **21** (Scheme 3, C, entry 1). Remarkably, the zirconium enolate²⁰ (formed via transmetalation of the lithium enolate with Cp₂ZrCl₂) gave 48% yield, exclusively of dichloride **20**. Treating cyclohexanone (drawn as the enol) under optimized trapping conditions gave dichloride **20** in 4% yield (Scheme 3, C, entry 3). Interestingly, Sandoval's conditions¹⁹ gave exclusively **21** in 71% yield (Scheme 3, C, entry 4).

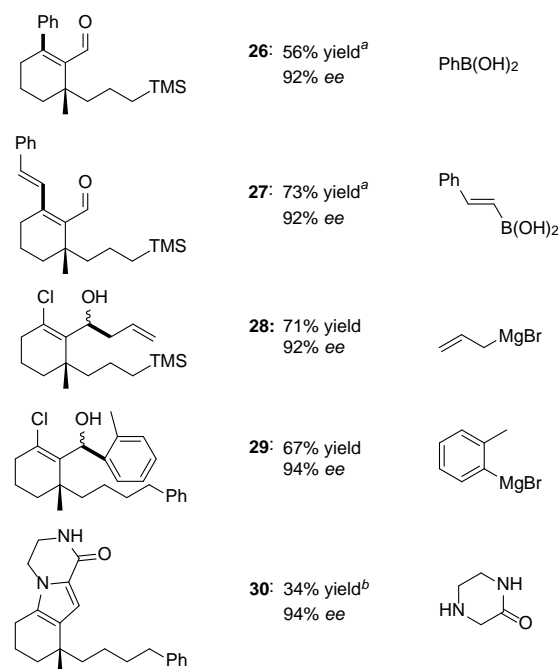
Scheme 4. Possible mechanisms for chloroformylation



Plausible mechanisms for trapping are suggested in Scheme 4. The zirconium enolate **22** may react with **2** to form **23a**. Loss of hydrogen to **23b**, followed by chloride addition / elimination of an O-Zr species would give iminium **24** and furnish the β-chloroaldehyde upon hydrolysis. Alternatively if **25a** is formed from reaction with **2**, another equivalent of **2** could activate the oxygen via formation of **25b**. This species could then undergo substitution with Cl⁻ as above to provide **24**.

The products obtained are well-suited for further functionalization (Scheme 5). The β-chloroaldehydes readily underwent Suzuki-Miyaura coupling with boronic acids to give products **26** and **27**. Treatment of the products with Grignard reagents gave 1,2-addition products **28** (71%) and **29** (67%) both as a 1:1 mixture of diastereomers. Unsaturated β-chloroaldehyde **9** was also subject to condensation with 2-piperazinone in the presence of *N*-methylmorpholine to give dihydropyrrolopyrazinone **30**.¹⁹

Scheme 5.^c Examples of functionalized products and their starting materials



^a5.0 mol % Pd(OAc)₂/XPhos, 3.0 eq. K₃PO₄, MeCN/H₂O 5 hrs. at 40 °C. ^b2-oxopiperazinone/NMM (*N*-methylmorpholine) in DMF, 5 hrs. at 115 °C. ^cIsolated yields.

In summary, zirconium enolates from ACA reactions to form quaternary stereocenters were trapped using the Vilsmeier-Haack reagent in synthetically useful yields and high enantioselectivity. The method was shown to be scalable and is tolerant to functional groups. The products from the reaction were subjected to further derivatization and investigations are currently underway to apply this trapping procedure in complex molecule synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. All procedures, characterization data, NMR spectra and chromatography traces (PDF)

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Notes

The authors declare no competing financial interests.

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