Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

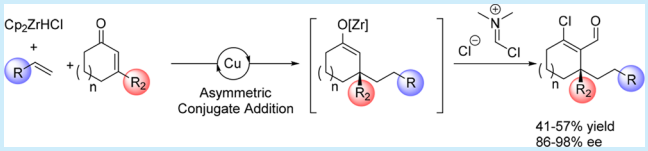
β-Chloroaldehydes from Trapping Zirconium Enolates Produced in Asymmetric 1,4-Additions

Jiao Yu Joseph Wang, Thomas Palacin, and Stephen P. Fletcher*

Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, U.K.

Supporting Information

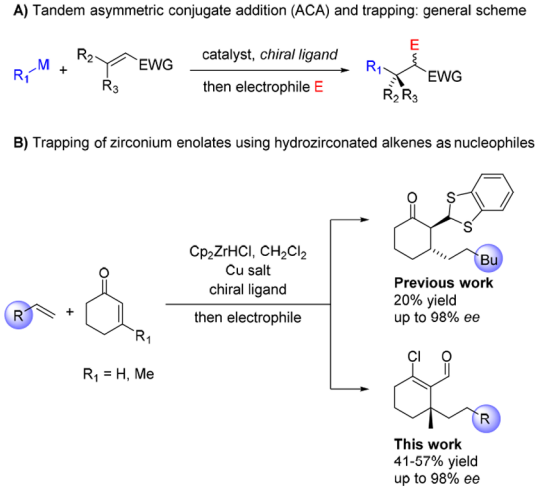
ABSTRACT: Zirconium enolates, derived from copper-catalyzed asymmetric conjugate additions, are trapped with the Vilsmeier−Haack reagent. Asymmetric additions generate quaternary carbon centers with high enantioselectivity (generally ∼90% ee), and the enolates are converted to unsaturated β-chloroaldehydes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



Downloaded via LUND UNIV on December 31, 2018 at 19:37:10 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

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−f]

Scheme 1. (A) General Scheme of the Tandem ACA/Trapping Reaction. (B) Previous Work[15] and This Work



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 ways,[1] including with Mander's reagent,[3] the Heller−Sarpong reagent,[4] carbenium ions,[5] nitro-olefins,[6] and Stork−Jung electrophiles.[7] Trapping of intermediate aluminum 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]

The development of tandem ACA/trapping reactions initiated by organozirconium reagents has been difficult to realize, and a variety of approaches examined in our laboratory did not lead to useful results, possibly because of the strength of the Zr−O bond in the intermediate enolate.[14] 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 centers[13] 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 (vida 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]

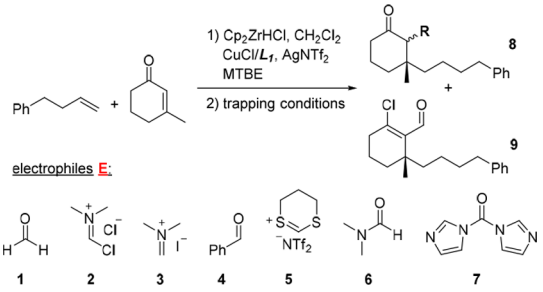
The use of highly reactive electrophiles was initially investigated to trap enolates generated in ACAs as shown in Table 1.[13d,e] Although α-hydroxy ketone product **8** (R = CH_2OH) could be obtained using formaldehyde **1**, and **8** was

Received: November 3, 2018

 © XXXX American Chemical Society

DOI: 10.1021/acs.orglett.8b03520
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Investigation of Electrophiles Used in Zirconium Enolate Trapping[a]



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)

[a]Isolated yields.

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).

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). Compound **2** is prepared by simply mixing phosphorus(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.

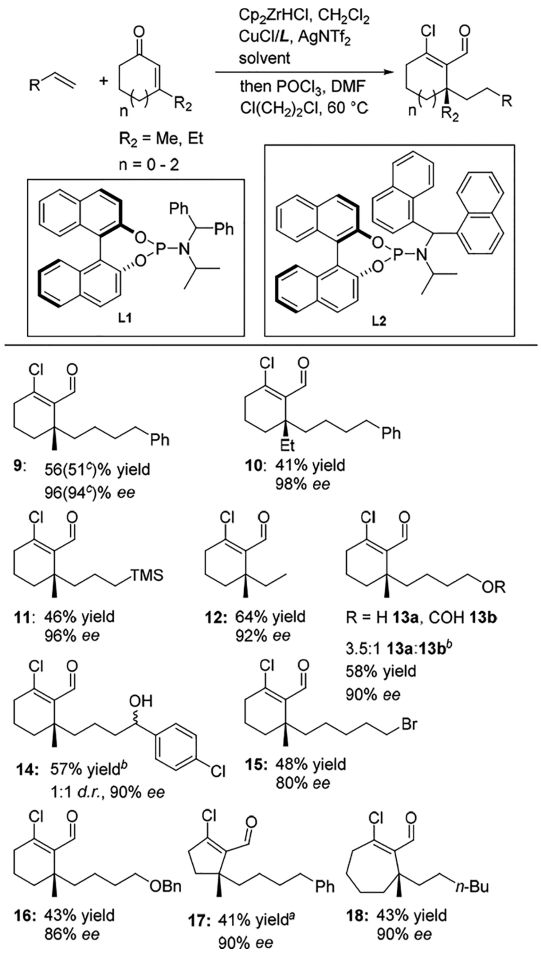
The trapping procedure shows tolerance (Scheme 2) to aromatic rings (examples **9**, **10**, **14**, and **16**), an alkyl silane (example **11**), an alkyl bromide (**15**), and a benzyl-protected alcohol (example **16**). When *tert*-butyldimethylsilyl-protected alcohols were used (examples **13**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

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 h was required for complete consumption of the enolate.

The trapping procedure is suitable for the quaternary center 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 cyclohexanone[21] **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. As no such dienes were observed in our reactions, it suggests against dicarbonyl (or tautomeric) intermediates (Scheme 3, A); however as shown below, other simple model systems also led to

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 were determined by HPLC or SFC. [a]ACA reaction conducted using **L2**, Et_2O as solvent, and TMSCl (5.0 equiv). [b]Asymmetric addition using TBDMS-protected alcohols. [c]5 mmol scale to give 0.79 g of **9**.

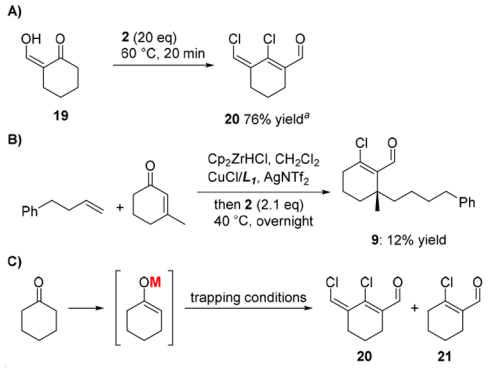
formation of compound **20**. Milder conditions[19] as reported by a Genentech process group for the chlorination of cyclohexanone led to a decreased yield of trapped product (12%, Scheme 3, B) and mostly simple 1,4-addition product.

Next, different enolates were investigated. Remarkably, use of the lithium enolate[20] gave only 10% yield of dichloride **20** (mostly recovered SM) and no monochloride **21** (Scheme 3, C, entry 1). Similarly, the zirconium enolate[20] (formed via transmetalation of the lithium enolate with Cp_2ZrCl_2) 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 conditions[19] gave exclusively **21** in 71% yield (Scheme 3, C, entry 4).

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 **VH** could activate the oxygen via formation of **25b**. This species

DOI: 10.1021/acs.orglett.8b03520
Org. Lett. XXXX, XXX, XXX–XXX

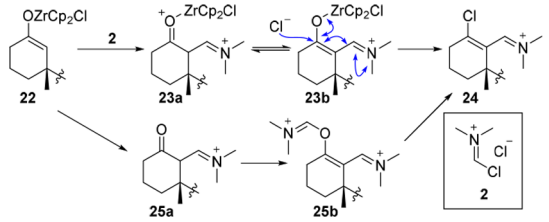
Scheme 3. Selected Experiments for Mechanistic Studies*



entry	M	trapping conditions	yield % (**19**:**20**)
1[e]	Li	**2** (20 eq.) 60 °C, 1 hr	10 (1:0)
2[e]	Cp_2ZrCl[c]	**2** (20 eq.) 60 °C, 1 hr	48 (1:0)
3[e]	H[d]	**2** (20 eq.) 60 °C, 1 hr	4 (1:0)
4[ab]	H[d]	**2** (2.1 eq.) 40 °C, 27 h	71 (0:1)

*Unless specified otherwise, yields determined by ^{1}H NMR spectroscopy using $Cl(CH_2)_2Cl$ as internal standard. [a]Isolated yield. [b]Data consistent with literature.[17a−c,19] [c]Lithiation and transmetalation procedures carried out according to the procedure of Evans and co-workers.[20] [d]Cyclohexanone was used. [e]Yield based on average over two experiments.

Scheme 4. Possible Mechanisms for Chloroformylation

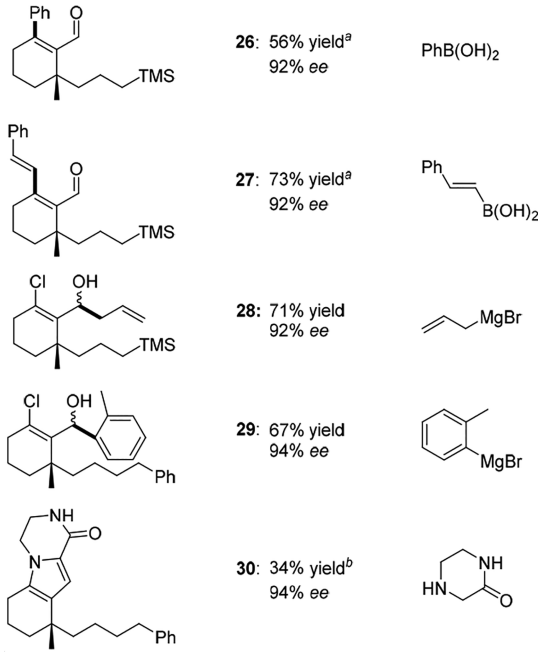


could then undergo substitution with Cl^- as above to provide **24**.

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%) as a 1:1 mixture of diastereomers. Unsaturated β-chloroaldehyde **9** was also subjected to condensation with 2-piperazinone in the presence of *N*-methylmorpholine to give dihydropyrrolopyrazinone **30**.[19]

In summary, zirconium enolates from ACA reactions to form quarternary 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.

Scheme 5. Examples of Functionalized Products and Their Starting Materials*



*Isolated yields. [a]5.0 mol % $Pd(OAc)_2$/XPhos, 3.0 eq. K_3PO_4, $MeCN/H_2O$ 5 h. at 40 °C. [b]2-oxopiperazinone/NMM (*N*-methylmorpholine) in DMF 5 h. at 115 °C.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03520.

All procedures, characterization data, NMR spectra, and chromatography traces (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: stephen.fletcher@chem.ox.ac.uk.

ORCID

Stephen P. Fletcher: 0000-0001-7629-0997

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EPSRC EP/H003711/1 and the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007−2013) under REA Grant Agreement 316955 for funding.

■ REFERENCES

(1) (a) Guo, H. C.; Ma, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354−366. (b) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, *2007*.1 (c) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039−1075. (d) Galestokova, Z.; Sebesta, R. *Eur. J. Org. Chem.* **2012**, *2012*, 6688−6695.

(2) For selected recent examples, see: (a) Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12904−12906. (b) Mendoza, A.; Ishihara, Y.; Baran, P. S. *Nat. Chem.* **2012**, *4*, 21−25. (c) Krasutsky, S. G.; Jacobo, S. H.; Tweedie, S. R.; Krishnamoorthy, R.; Filatov, A. S.

DOI: 10.1021/acs.orglett.8b03520
Org. Lett. XXXX, XXX, XXX−XXX

Org. Process Res. Dev. **2015**, *19*, 284−289. (d) Yu, X.; Su, F.; Liu, C.; Yuan, H.; Zhao, S.; Zhou, Z.; Quan, T.; Luo, T. *J. Am. Chem. Soc.* **2016**, *138*, 6261−6270. (e) Cottet, P.; Bleschke, C.; Capdevila, M. G.; Tissot, M.; Alexakis, A. *Adv. Synth. Catal.* **2016**, *358*, 417−425. (f) Zeng, M.; Murphy, S. K.; Herzon, S. B. *J. Am. Chem. Soc.* **2017**, *139*, 16377−16388.

(3) Murphy, S. K.; Zeng, M.; Herzon, S. B. *Org. Lett.* **2016**, *18*, 4880−4883.

(4) Murphy, S. K.; Zeng, M.; Herzon, S. B. *Org. Lett.* **2017**, *19*, 4980−4983.

(5) Drusan, M.; Rakovsky, E.; Marek, J.; Sebesta, R. *Adv. Synth. Catal.* **2015**, *357*, 1493−1498.

(6) Hung, Y. M.; Tseng, C. H.; Uang, B. J. *Tetrahedron: Asymmetry* **2015**, *26*, 1369−1374.

(7) Jarugumilli, G. K.; Zhu, C.; Cook, S. P. *Eur. J. Org. Chem.* **2012**, *2012*, 1712−1715.

(8) Germain, N.; Schlaefli, D.; Chellat, M.; Rosset, S.; Alexakis, A. *Org. Lett.* **2014**, *16*, 2006−2009.

(9) Bleschke, C.; Tissot, M.; Muller, D.; Alexakis, A. *Org. Lett.* **2013**, *15*, 2152−2155.

(10) Germain, N.; Guénée, L.; Mauduit, M.; Alexakis, A. *Org. Lett.* **2014**, *16*, 118−121.

(11) Germain, N.; Alexakis, A. *Chem. - Eur. J.* **2015**, *21*, 8597−8606.

(12) Gualandi, A.; Mengozzi, L.; Cozzi, P. G. *Synthesis* **2017**, *49*, 3433−3443.

(13) For relevant reviews, see: (a) Maksymowicz, R. M.; Bissette, A. J.; Fletcher, S. P. *Chem. - Eur. J.* **2015**, *21*, 5668−5678. (b) Pinheiro, D. L. J.; de Castro, P. P.; Amarante, G. W. *Eur. J. Org. Chem.* **2018**, *2018*, 4828−4844. For procedures used to form quaternary centers see: (c) Maksymowicz, R. M.; Roth, P. M. C.; Fletcher, S. P. *Nat. Chem.* **2012**, *4*, 649−654. (d) Sidera, M.; Roth, P. M. C.; Maksymowicz, R. M.; Fletcher, S. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7995−7999. (e) Roth, P. M. C.; Sidera, M.; Maksymowicz, R. M.; Fletcher, S. P. *Nat. Protoc.* **2014**, *9*, 104−111. (f) Gao, Z.; Fletcher, S. P. *Chem. Sci.* **2017**, *8*, 641−646. (g) Ardkhean, R.; Mortimore, M.; Paton, R. S.; Fletcher, S. P. *Chem. Sci.* **2018**, *9*, 2628−2632.

(14) Maciver, E. E.; Maksymowicz, R. M.; Wilkinson, N.; Roth, P. M. C.; Fletcher, S. P. *Org. Lett.* **2014**, *16*, 3288−3291.

(15) Nemethová, I.; Soradova, Z.; Sebesta, R. *Synthesis* **2017**, *49*, 2461−2469.

(16) Salmon, R. Oxalyl Chloride−Dimethylformamide. *Encyclopedia of Reagents for Organic Synthesis*; Wiley, 2001.

(17) (a) Reddy, C. P.; Tanimoto, S. *Synthesis* **1987**, *1987*, 575−577. (b) Mewshaw, R. E. *Tetrahedron Lett.* **1989**, *30*, 3753−3756. (c) Kuchenbeiser, G.; Shaffer, A. R.; Zingales, N. C.; Beck, J. F.; Schmidt, J. A. R. *J. Organomet. Chem.* **2011**, *696*, 179−187. (d) Usui, K.; Tanoue, K.; Yamamoto, K.; Shimizu, T.; Suemune, H. *Org. Lett.* **2014**, *16*, 4662−4665.

(18) For selected examples, see: (a) Trost, B. M.; Pissot-Soldermann, C.; Chen, I. *Chem. - Eur. J.* **2005**, *11*, 951−959. (b) Trost, B. M.; Dong, L.; Schroeder, G. M. *J. Am. Chem. Soc.* **2005**, *127*, 2844−2845. (c) Hong, A. Y.; Krout, M. R.; Jensen, T.; Bennett, N. B.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2756−2760. (d) Bennett, N. B.; Stoltz, B. M. *Chem. - Eur. J.* **2013**, *19*, 17745−17750. (e) Dai, J.; Yoshida, W. Y.; Kelly, M.; Williams, P. *J. Nat. Prod.* **2016**, *79*, 1464−1467.

(19) Sandoval, C.; Lim, N.-K.; Zhang, H. *Org. Lett.* **2018**, *20*, 1252−1255.

(20) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975−3978.

(21) Ainsworth, C. *Org. Synth.* **1959**, *39*, 27.

DOI: 10.1021/acs.orglett.8b03520
Org. Lett. XXXX, XXX, XXX−XXX