Asymmetric remote C-H functionalization: Use of internal olefins in tandem hydrometallation – isomerization – asymmetric conjugate addition sequences*

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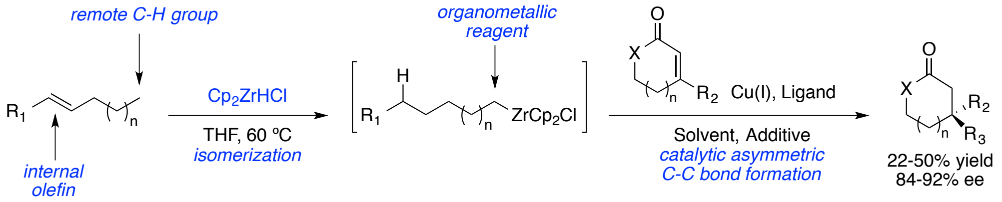
We describe catalytic asymmetric C-C formation using terminal alkyl-metal nucleophiles generated from internal olefins through a chain-walking isomerization mechanism. Hydrometallation of internal olefins with the Schwartz reagent gives the least hindered alkyl-zirconocene after thermal (60 °C in THF) isomerization. After switching the solvent from THF to dichloromethane, the alkyl-zirconocenes can be used in copper-catalyzed asymmetric conjugate additions. Addition to a variety of cyclic *α*,*β*-unsaturated species were achieved in modest (22-50%) yield with high (84-92% ee) enantioselectivity. This work demonstrates that remote C-H functionalization coupled with asymmetric C-C bond formation is possible, but the present procedures are limited in terms of yield and olefin scope.



Introduction

C-H Bond functionalization has been under development for over 50 years,[1] with the activation of remote C-H bonds typically relying on metal-mediated strategies.[2-6] The design of redox-efficient olefin isomerization reactions[7-9] is one approach to remote C-H activation. Here a position far from the original double bond is functionalized through a 'chain-walking' mechanism. Recent reports of Pd[10, 11] or Ru[12] catalyzed migration / C-C bond forming processes hint toward the tremendous potential of this strategy in remote C-H functionalization.[6]

A well-established method for olefin isomerization reactions involves hydrometallation of an internal olefin with the Schwartz reagent.[13-15] After initial hydrozirconation, internal olefins typically isomerize to the least sterically hindered primary alkyl-zirconocene product *via* *β*-hydride elimination and re-addition sequences.[16, 17] These methods allow the C-H functionalization of otherwise inert terminal methyl groups,[15, 18] and a number of synthetic applications have been reported.[19, 20] Zirconocene mediated chain-walking was also recently reported to initiate C-C bond activation,[21] demonstrating that there is tremendous breadth of reactivity still remaining to be found in zirconocene initiated isomerization processes. We note that despite the extensive previous work, processes which couple olefin migration with asymmetric C-C bond formation at sites remote from the initial olefin unit have not been reported. This is remarkable because such transformations represent a straightforward approach to remote asymmetric C-H functionalization, a major goal of contemporary synthetic chemistry.

Alkylzirconium reagents, generated *in situ* by hydrometallation of terminal alkenes, can be used in asymmetric conjugate addition (ACA) reactions[22-25] to cyclic Michael acceptors to form tertiary centres,[26-28] quaternary centres,[29, 30] and lactones.[31] Here we report that the combination of Schwartz reagent and internal alkenes can convert remote C-H bonds into terminal alkylzirconium reagents that can be used in ACA reactions.

Results and Discussion

Our studies began by examining the sequential hydrometallation – isomerization – ACA (HM-I-ACA) of *trans*-4-octene to 4,4-dimethylcyclohexen-2-one (Table 1). For simplicity we varied only the conditions for hydrometallation, keeping the reaction conditions previously reported for asymmetric addition to unsubstituted cyclic enones constant.[26] In the case of terminal alkenes we use CH_2Cl_2 as solvent for hydrozirconation, which is generally complete within 30 min at room temperature as judged by the appearance of a clear yellow solution. The hydrozirconation of internal alkenes is more energetically demanding than monosubstituted alkenes, and stirring *trans*-4-octene in CH_2Cl_2 at room temperature for more than 6 h provided no hydrozirconated product, and so we examined solvents with higher boiling points (Table 1). HM-I-ACA using chloroform at 60 °C, for the hydrozirconation, provided no ACA product. However, when using THF at the same temperature, **1** was obtained in moderate yield and low (50%) enantiomeric excess (entry 2). We then performed the hydrometallation in THF at 60 °C, and once judged finished by the appearance of a clear solution, the THF was removed under reduced pressure and CH_2Cl_2 added before adding the isomerization product to the copper-ligand solution (entry 3). This procedure increased the ee of the ACA product to 58%. The ee was dramatically increased by using a procedure where the THF was co-evaporated with CH_2Cl_2 before adding additional CH_2Cl_2, and we suspect that this procedure give higher enantioselectivity because it removes the vast majority of the THF from the reaction.

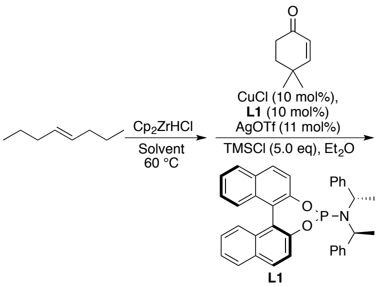


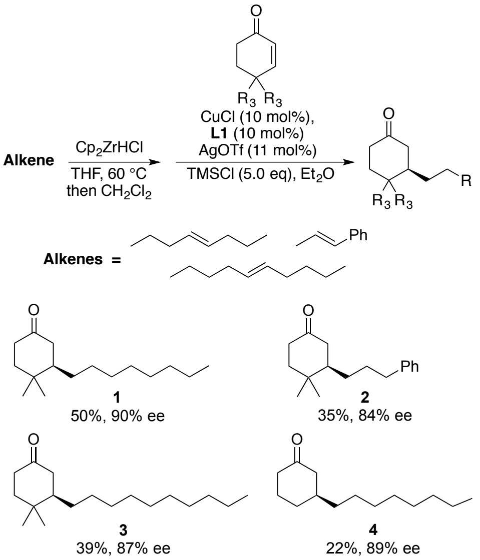
Table 1. Optimization of the conditions for hydrometallation - isomerization

Entry	Solvent	Yield (%)	ee (%)
1	$CHCl_3$	0	na
2	THF	53	50
3	THF then CH_2Cl_2	46	58
4[a]	THF then CH_2Cl_2	50	90

a. THF was removed under reduced pressure after the addition of CH_2Cl_2

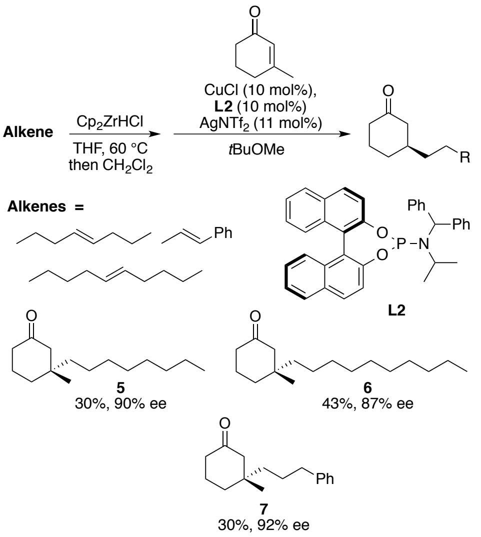
With optimized hydrozirconation-isomerization conditions in hand we explored the generality of the HM-I-ACA to cyclic enones to form tertiary centres (Scheme 1).

The method affords 3-substituted cyclohexenones with high enantioselectivity and moderate yields. The use of methyl styrene provided **2** in moderate yield (35%) and enantioselectivity (84% ee), NMR spectroscopy of the crude reaction mixture suggested the presence of branched side products that we were unable to isolate in pure form. Such products could arise from incomplete chain-walking migration or migration toward the aromatic ring. Regiomeric hydrometallation products have previously been observed[20] and likely contribute to the lower yield observed with **2**. The use *trans* 5-decene afforded **3** in 39% yield and 87% ee. When using 2-cyclohexenone instead of 4,4-dimethyl-2-cyclohexenone, **4** was obtained with comparable enantioselectivity (89% ee), but the yield was diminished (to 22%). We note that ACAs of alkylzirconiums to cyclohexenone typically gives lower yield than substituted cyclohexenones.[26]



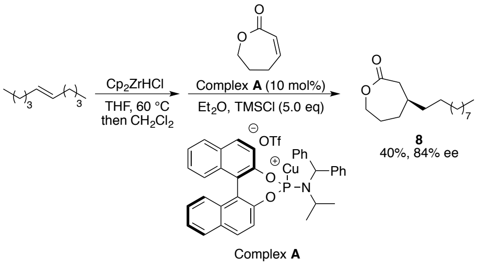
Scheme 1. Asymmetric Conjugate Addition to Cyclohexenones Using Internal Alkenes.

We next explored the formation of quaternary centres. In this case, ligand **L2** developed in our group, and copper triflimide (rather than copper triflate) in *tert*-butyl methyl ether generally provides the highest enantioselectivity.[29] The use of HM-I-ACA also worked in this case (Scheme 2) to provide **5**, **6** and **7** with excellent enantioselectivities despite low yields



Scheme 2. Formation of Quaternary Centres *via* ACA Using Internal Alkenes.

When performing HM-I-ACA with an α,β-unsaturated lactone (Scheme 3) we used our previously developed conditions (complex **A**, in Et_2O with 5 equiv. TMSCl),[31] after isomerization in THF followed by solvent exchange, to providing **8** in 40% yield and 84% ee.



Scheme 3. ACA of *trans*-5-Decene to 6,7-dihydrooxepin-2(5*H*)-one.

Conclusion

In conclusion, we report preliminary studies into a copper-catalyzed hydrometallation – isomerization – asymmetric conjugate addition reaction that serves as an asymmetric remote C-H activation sequence. Tertiary and all-carbon quaternary centers are formed with high levels of enantioselectivity by coupling unactivated methyl groups to cyclic Michael acceptors. The current system is limited to linear alkenes, and yields are generally low. Conceptually, this work allows internal alkenes to act as the equivalents of premade terminal organometallic nucleophiles in catalytic asymmetric reactions for the first time.

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Supporting Information
All procedures, characterization data, and NMR spectra. This material is available online free of charge?

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