Asymmetric Catalysis

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Formation of Quaternary Centers by Copper-Catalyzed Asymmetric Conjugate Addition of Alkylzirconium Reagents**

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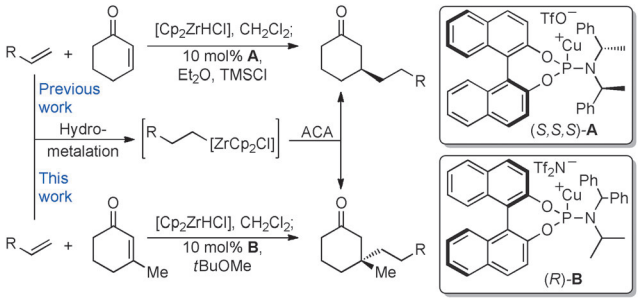
Alkenes are among the most readily available organic molecules, and are feedstocks for the preparation of many commodity chemicals.[1] Using alkenes as starting materials in synthesis is practical because they are inexpensive and easy to handle. We recently reported[2] that alkenes can be used as the equivalents to premade alkyl metal species in copper-catalyzed asymmetric conjugate additions (ACA).[3] In these reactions hydrometalation (HM) of terminal alkenes with the Schwartz reagent[4] generates alkylzirconocenes,[5] which undergo asymmetric 1,4-additions catalyzed by complex **A** (Scheme 1). These processes are currently limited to the formation of tertiary centers from ACA to unsubstituted cyclic enones.[2] Herein we report that this approach can be used to form quaternary centers.



Scheme 1. Hydrometalation/asymmetric conjugate addition of alkenes. Cp = cyclopentadienyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

The ability to construct all-carbon quaternary centers with high levels of enantioselectivity is widely regarded as one of the most significant and challenging goals in asymmetric catalysis.[6] An important approach to this problem, pioneered and developed by the groups of Hoveyda and Alexakis, involves transition metal catalyzed ACA reactions of organometallics to trisubstituted Michael acceptors.[7] In the case of alkyl nucleophiles, copper catalysis allows enantioselective addition of dialkylzincs,[8] trialkylaluminums,[9] and Grignard reagents[10] to trisubstituted enones.

The development of new synthetic methodology capable of coupling unactivated partners is a significant goal of contemporary chemistry. The premade alkyl metal nucleophiles which are currently used to form quaternary centers are not ideal and only a few are readily available. They are highly reactive and can present practical (and safety) issues,[11] and their use typically requires cryogenic reaction temperatures.[3b,7,12] These factors limit the options that are available in reaction design and present significant challenges to the incorporation of these procedures into large-scale or industrial processes.[11] Additionally, the sophistication of the alkyl groups which can be added in these procedures is quite restricted.[7] While simple groups can be used, nucleophiles containing stereogenic centers and even protected functional groups are essentially unknown. Below, we describe the development and use of a system which allows alkenes to be used as alkyl metal equivalents in highly enantioselective copper-catalyzed ACAs to trisubstituted cyclic enones. A wide variety of simple and functionalized alkenes are readily available, and allows easy variation in the alkyl groups which can be added. It is noteworthy that these reactions operate at room temperature, tolerate a wide range of reaction conditions, and use a new, readily available phosphoramidite[13] ligand. These results suggest that this new approach may be more general and practical than those requiring preformed organometallics.

Our studies began with evaluating the coupling of 4-phenyl-1-butene (**1**) and 3-methyl-2-cyclohexen-1-one (**2**) under reaction conditions that we had previously applied in 1,4- and 1,6-conjugate addition reactions.[2] Hydrometalation of **1** and subsequent asymmetric conjugate addition to **2** in the presence of the phosphoramidite (*S*,*S*,*S*)-**C**, $(CuOTf)_2$.PhH, and TMSCl (Table 1, entry 1) gave (*S*)-**3** in 45% yield and 60% *ee*. The use of the diastereomeric (*R*,*S*,*S*)-**D** gave (*R*)-**3** and improved the *ee* value to 70% (Table 1, entry 2) while isomeric (*R*)-**E** gave (*R*)-**3** with 61% *ee*. The use of $(CuOTf)_2$·PhH without TMSCl gave very low (<20%) conversion. Using (*R*,*S*,*S*)-**D** in combination with different copper sources (Table 1, entries 4, 5, 7, and 8) showed that the reaction was highly sensitive to the copper counterion and that triflimidate provided high levels of enantioselectivity. In the case of $CuNTf_2$ the enantioselectivity could be improved (to 88% *ee*) by omitting TMSCl from the procedure (entries 5 and 6), without affecting the conversion. We found that filtering off the AgCl byproduct from copper sources generated by silver exchange gave slightly higher (ca. 5–10% *ee*) enantioselectivity. Using ligand (*R*)-**E** with copper

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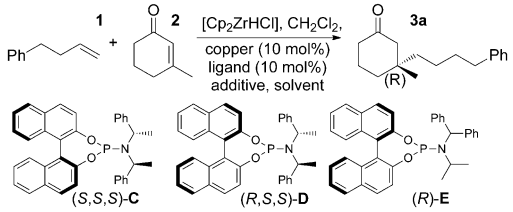
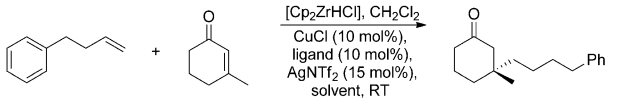
Table 1: Screening conditions for hydrometalation/asymmetric conjugate addition to trisubstituted enones.



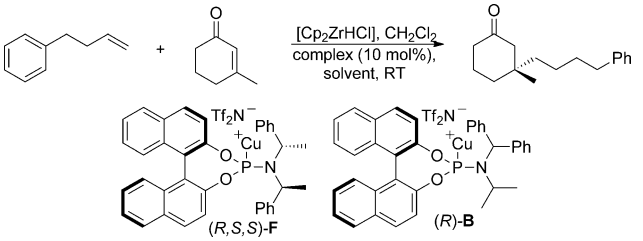
Entry	Copper source	Ligand	Additive	Solvent	*ee* [%][a]
1[b]	$(CuOTf)_2$·PhH	(*S*,*S*,*S*)-**C**	TMSCl	Et_2O	60
2	$(CuOTf)_2$·PhH	(*R*,*S*,*S*)-**D**	TMSCl	Et_2O	70
3	$(CuOTf)_2$·PhH	(*R*)-**E**	TMSCl	Et_2O	61
4	$[Cu(MeCN)_4]BF_4$	(*R*,*S*,*S*)-**D**	TMSCl	Et_2O	23
5[c]	CuCl + $AgNTf_2$	(*R*,*S*,*S*)-**D**	TMSCl	Et_2O	82
6[c]	CuCl + $AgNTf_2$	(*R*,*S*,*S*)-**D**	–	Et_2O	88
7[c]	CuCl + $AgSbF_6$	(*R*,*S*,*S*)-**D**	–	CH_2Cl_2	73
8[c]	CuCl + $AgClO_4$	(*R*,*S*,*S*)-**D**	–	CH_2Cl_2	69
9[c]	CuCl + $AgSbF_6$	(*R*)-**E**	–	CH_2Cl_2	41
10[c]	CuCl + $AgClO_4$	(*R*)-**E**	–	CH_2Cl_2	61
11[c]	CuCl + $AgNTf_2$	(*R*)-**E**	–	CH_2Cl_2	92

Reaction conditions: alkene (2.5 equiv), $[Cp_2ZrHCl]$ (2 equiv), 3-Me-2-cyclohexen-1-one (1 equiv), copper (10 mol%), ligand (10 mol%), room temperature. [a] Enantiomeric excess determined by HPLC. [b] The *S* enantiomer was obtained. Absolute configuration assigned by analogy to **3b** and **3o**; see the Supporting Information. [c] Silver (15 mol%), precipitate filtered before use.

Table 2: Effect of solvent and procedure.



Entry	Ligand/Complex	Solvent	Yield [%][a]	*ee* [%][b]
1[c]	(*R*,*S*,*S*)-**D**	CH_2Cl_2	66	78
2[c]	(*R*,*S*,*S*)-**D**	$ClCH_2CH_2Cl$	71	78
3[c]	(*R*,*S*,*S*)-**D**	Et_2O	64	88
4[c]	(*R*,*S*,*S*)-**D**	*t*BuOMe	83	86
5[c]	(*R*,*S*,*S*)-**D**	2-Me-THF	90	84
6[c]	(*R*,*S*,*S*)-**D**	toluene	62	91
7[c]	(*R*)-**E**	CH_2Cl_2	74	92
8[c]	(*R*)-**E**	$ClCH_2CH_2Cl$	92	90
9[c]	(*R*)-**E**	*t*BuOMe	66	94
10[c]	(*R*)-**E**	2-Me-THF	70	90



11[d]	(*R*,*S*,*S*)-**F**	2-Me-THF	83	78
12[d]	(*R*,*S*,*S*)-**F**	toluene	62	90
13[d]	(*R*)-**B**	CH_2Cl_2	68	89
14[d]	(*R*)-**B**	*t*BuOMe	72	90

Reaction conditions: alkene (2.5 equiv), $[Cp_2ZrHCl]$ (2 equiv), 3-Me-2-cyclohexen-1-one (1 equiv), room temperature, full conversion overnight. [a] Yield of isolated product. [b] Enantiomeric excess determined by HPLC. [c] (*R*,*S*,*S*)-**D** or (*R*)-**E** (0.10 equiv), CuCl (0.10 equiv) and $AgNTf_2$ (0.15 equiv) were stirred and the precipitate filtered before use; see the Supporting Information. [d] Using 10 mol% of (*R*)-**B** or (*R*,*S*,*S*)-**F** previously prepared in a batch by mixing phosphoramidite, CuCl and $AgNTf_2$ in a 1:1:1.1 ratio and filtration before use; see the Supporting Information.

salts also demonstrated that NTf_2 is an excellent counterion and **3a** was obtained in 92% *ee*.

We were pleased that the previously unreported ligand (*R*)-**E** provided levels of enantioselectivity comparable to those of the isomeric phosphoramidites (*S*,*S*,*S*)-**C** and (*R*,*S*,*S*)-**D**, which are extensively used.[13] Using (*R*)-**E** may be advantageous as it can be prepared in two steps from widely available starting materials. The amine moiety is easily prepared by reductive amination, and does not require starting with a chiral nonracemic amine or the separation of diastereomers during preparation.

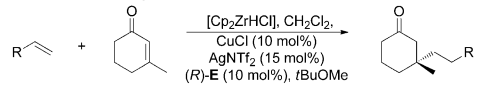
We next examined the effect of the solvent and method of catalyst preparation on the yield and enantioselectivity of **3a** by using the ligands (*R*,*S*,*S*)-**D** and (*R*)-**E** (Table 2). Experiments with copper ligand complexes generated in situ (entries 1–10) demonstrated that the reaction was remarkably tolerant to solvents. We also examined catalyst complexes which had previously been prepared in a batch. These procedures (entries 11–14) gave only slightly diminished *ee* values compared to freshly prepared materials and may be attractive in some instances because of their operational simplicity. While these experiments uncovered a whole range of potentially useful conditions, we chose to conduct the rest of the preliminary studies reported here using a single set of reaction conditions. The (*R*)-**E**/$CuNTf_2$ system was relatively insensitive to solvent effects (entries 7–10, all *ee* values >90%), thus suggesting that it is robust, and we used this combination in *t*BuOMe simply because it gave the highest levels of enantioselectivity.

Using these reaction conditions we found that a range of simple unactivated terminal alkenes participated in the HM/ACA to give all-carbon quaternary centers (Table 3). These reactions are comparable to those using premade organometallic reagents. Here, despite significant structural variation of the nucleophilic partner, the yields and enantioselectivities are uniformly high. In several cases (Table 3, entries 1–3) the alkenes are gases, and the reactions were performed under a balloon atmosphere of the relevant alkene. The absolute configuration of **3b** and **3m**[14] were determined to have an *R* configuration.

Examining the nucleophiles that were previously reported in ACA to form quaternary centers reveals that there are still major challenges to be overcome in the use of functionalized reagents. A complete list (as far as we are aware) of the *n*-alkyl nucleophiles which have been used is shown in Figure 1 and is currently limited to Grignard reagents bearing olefins[10] and a single dialkylzinc reagent used in the addition to specially activated enones[8b] and nitro-olefins.[8a]

We chose to examine the use of more elaborate nucleophiles (Table 4) in ACA reactions to form quaternary centers. We found that alkenes bearing aromatic rings (entries 1, 5, 7, and 10), additional alkenes (entries 2 and 3), halogens (entries 4 and 10), and ethers (entries 5, 6, 7, 8, and 10) all

Table 3: Addition of simple alkenes.



Entry	Substrate	Product	Yield [%][a]	*ee* [%][b]
1[c]		**3b**	81	91[d]
2[c]		**3c**	79	93
3[c]		**3d**	76	94
4		**3e**	97	95
5[e]		**3f**	62	86
6		**3g**	67	94

Reaction conditions: alkene (2.5 equiv), [Cp_2ZrHCl] (2 equiv), 3-Me-2-cyclohexen-1-one (1 equiv), CuCl (10 mol%), $AgNTf_2$ (15 mol%), precipitate filtered before use, (*R*)-**E** (10 mol%), room temperature overnight. [a] Yield of isolated product. [b] The *ee* value was determined by derivatization and ^{13}C NMR spectroscopy. [c] A balloon of alkene gas was used. [d] Absolute configuration determined by comparison of optical rotation and GC retention times. [e] Heated to 40°C at hydrometalation stage.

gave highly promising preliminary results. Formation of a quaternary center using electron-rich allylsilane (entry 9) gave excellent results and the sequence can also be used on alkenes bearing stereogenic centers (entries 3 and 10) and multiple functional groups (entry 10).

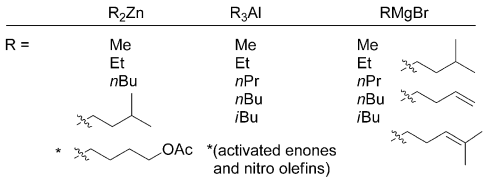
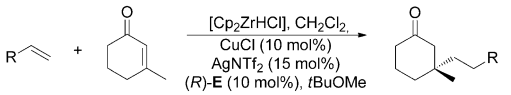


Figure 1. *n*-Alkyl nucleophiles previously used in ACA to form quaternary centres.

We also briefly examined the scope of the reaction using enones with different ring sizes and substitution patterns (Table 5). 3-Methyl-cyclopentenone, well known as an extremely challenging coupling partner for ACA reactions, whose use is essentially an unsolved problem,[9c,e,f,10a,15] gave **4** in only 4% yield using standard reaction conditions. However, we were able to increase the yield to 56% by using an excess of reagents and starting the reaction at 0°C (entry 1). 3-Ethyl-2-cyclohexen-1-one (entry 2) performed well in the coupling. Isophorone, also known to be troublesome in ACAs

Table 4: Addition of functionalized alkenes.



Entry	Substrate	Product	Yield [%][a]	*ee* [%]
1		**3h**	65	90[b]
2[c]		**3i**	75	78[d]
3		**3j**	48[e]	86[d]
4	Br	**3k**	53	79[d]
5		**3l**	53	89[b]
6	TBSO	**3m**	75	92[d]
7	TBDPSO	**3n**	61	ca. 90[b,f]
8	OTBS	**3o**	84	89[d]
9	Si	**3p**	82	>95[d]
10	OTBS, Cl	**3q**	82[e]	89[g]

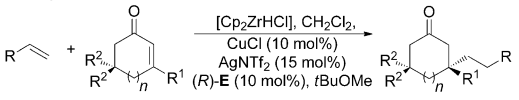
Reaction conditions: alkene (2.5 equiv), [Cp_2ZrHCl] (2 equiv), 3-Me-2-cyclohexen-1-one (1 equiv), CuCl (10 mol%), $AgNTf_2$ (15 mol%), precipitate filtered before use, (*R*)-**E** (10 mol%), room temperature overnight. [a] Yield of isolated product. [b] The *ee* value was determined by HPLC. [c] 10 equiv of alkene used. [d] The *ee* value was determined by derivatization and ^{13}C NMR spectroscopy. [e] Obtained as a 1:1 mixture of diastereomers. [f] ±5% *ee*. [g] HPLC analysis on the corresponding deprotected alcohol. TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

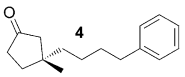
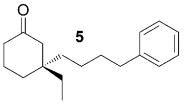
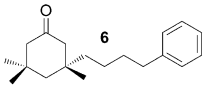
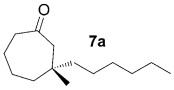
because of steric hindrance,[9c] gave 34% yield of the coupling product **6** when using an excess of reactants in the presence of TMSCl (entry 3). The use of a seven-membered β-substituted enone (entry 4) also gave promising preliminary results.

We also performed a single experiment on a preparative scale to examine if these procedures are suitable for scale-up (Scheme 2). On a gram scale, at room temperature, we obtained 1.46 g (94% yield, 92% *ee*) of **3a**.

In conclusion, we report preliminary studies into a copper-catalyzed hydrometalation/asymmetric conjugate addition approach which provides all-carbon quaternary centers by coupling alkenes with β-substituted enones. Conceptually, this

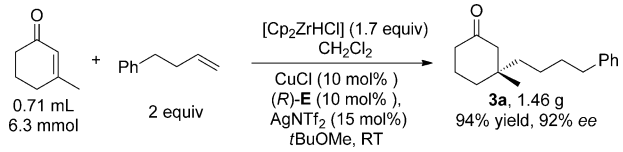
Table 5: Scope of enones.



Entry	Enone	Product	Yield [%][a]	*ee* [%]
1[b,c]		 **4**	56	65[d]
2		 **5**	58	ca. 92[d,e]
3[b,f]		 **6**	34	73[d]
4		 **7a**	70	90[g]

Reaction conditions: alkene (2.5 equiv), [Cp_2ZrHCl] (2 equiv), enone (1 equiv), CuCl (10 mol%), $AgNTf_2$ (15 mol%), precipitate filtered before use, (*R*)-**E** (10 mol%), room temperature overnight. [a] Yield of isolated product. [b] Used 5 equiv of alkene and 3 equiv of [Cp_2ZrHCl]. [c] 0°C to room temperature. [d] The *ee* value was determined by HPLC. [e] ±5% *ee*. [f] Used 5 equiv of TMSCl. [g] The *ee* value was determined by dehydrogenation of the product to the enone and then HPLC analysis.

approach allows alkenes to act as the equivalents to premade organometallic nucleophiles. This first-generation system uses a new readily available phosphoramidite ligand as the catalytic source of chirality. Practically, this system has the unusual advantage of working at room temperature and appears amenable to scale. A wide variety of alkenes are readily available, and the reaction conditions we report here demonstrate that much more elaborate alkyl units than previously reported can be added. Additional optimization, extension, and application of this chemistry is currently being investigated and will be reported in due course.



Scheme 2. Gram-scale catalytic asymmetric conjugate addition.

Experimental Section

CuCl (57 mg, 0.63 mmol, 0.10 equiv) and ligand (*R*)-**E** (340 mg, 0.63 mmol, 0.10 equiv) were dissolved in *t*BuOMe (31.5 mL) under an argon atmosphere and the resulting mixture stirred at room temperature. After 1 hour, $AgNTf_2$ (367 mg, 0.95 mmol, 0.15 equiv) was added and the resulting suspension stirred for another 15 min. In another flask, Cp_2ZrHCl (2.76 g, 10.7 mmol, 1.7 equiv) was added to a stirred, room temperature solution of 4-phenyl-1-butene (**1a**; 1.90 mL, 12.6 mmol, 2.0 equiv) in CH_2Cl_2 (6.0 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the clear-yellow solution containing the alkene/zirconium mixture. The resulting black mixture was stirred for an additional 10 min before 3-methyl-2-cyclohexenone (**2a**; 0.71 mL, 6.3 mmol, 1.0 equiv) was added by syringe over about 3 min. Stirring was continued for 12 h before the reaction was quenched by addition of Et_2O (ca. 10 mL) and then NH_4Cl (1M aq., ca. 20 mL). A precipitate was filtered off, the phases were partitioned, and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., ca. 20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash column chromatography of the yellow residue (1:9 Et_2O/petrol; SiO_2) gave (−)-(*R*)-3-methyl-3-(4-phenylbutyl)cyclohexanone (**3a**; 1.46 g, 5.97 mmol, 94%) as a colorless oil. HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak IC; flow: 1 mL min^{-1}; *n*-hexane/*i*PrOH: 98:2; $\lambda = 210$ nm; major enantiomer (−)-(*R*)-3-methyl-3-(4-phenylbutyl)cyclohexanone, $t_R = 17.0$ min; minor enantiomer (+)-(*S*)-3-methyl-3-(4-phenylbutyl)cyclohexanone, $t_R = 18.2$ min].

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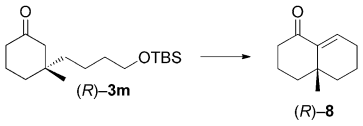
[14] Compound (*R*)-**3m** was converted in three steps into (*R*)-**8** which has known and meaningful optical rotation. See the Supporting Information.



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