Asymmetric catalysis

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Quaternary Centre Formation by Copper Catalyzed Asymmetric Conjugate Addition of Alkylzirconium Reagents

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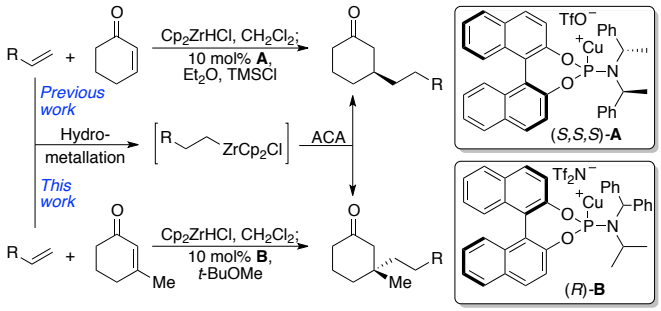
Alkenes are among the most readily available organic molecules, and are feedstocks for the preparation of many commodity chemicals.[1] Using alkenes as starting materials in synthesis is practical because they are inexpensive and easy to handle. We recently reported[2] that alkenes can be used as the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

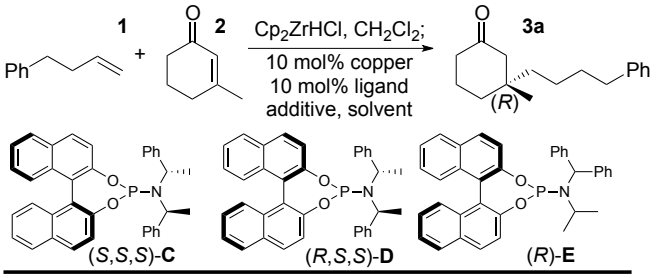


Scheme 1. Hydrometallation – asymmetric conjugate addition of alkenes.

The ability to construct all-carbon quaternary centres 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 Hoveyda and Alexakis groups, involves transition-metal catalyzed ACA reactions of organometallics to trisubstituted Michael acceptors.[7] In the case of alkyl nucleophiles, Cu-catalysis allows enantioselective addition of dialkylzincs,[8] trialkylaluminiums[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 that are currently used to form quaternary centres are not ideal; only a few are readily available, they are highly reactive which can present practical (and safety) issues,[11] 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 that can be added in these procedures is quite restricted.[7] While simple groups can be used, nucleophiles containing stereogenic centres and even protected functional groups are essentially unknown. Below, we describe the development and use of a system that allows alkenes to be used as alkyl-metal equivalents in highly enantioselective Cu-catalyzed ACAs to trisubstituted cyclic enones. A wide variety of simple and functionalized alkenes are readily available, which allows easy variation in the alkyl groups that 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.

Table 1. Screening conditions for hydrometallation - asymmetric conjugate addition to trisubstituted enones.



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

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

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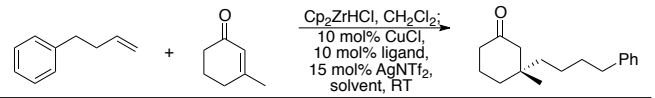
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

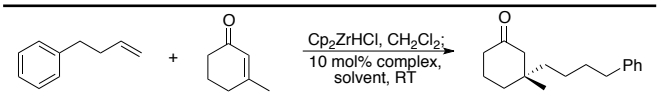
Our studies began by evaluating the coupling of 4-phenyl-1-butene (**1**) and 3-methyl-2-cyclohexen-1-one (**2**) under reaction conditions that we had previously applied in 1,4- and 1,6- conjugate addition reactions.[2] Hydrometallation of **1** followed by asymmetric conjugate addition to **2** in the presence of 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 diastereomeric (*R*,*S*,*S*)-**D** gave (*R*)-**3** and improved the ee 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 (*c.f.* 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 (~5-10% ee) enantioselectivity. Using ligand (*R*)-**E** with copper salts also demonstrated that NTf_2 is an excellent counterion and **3a** was obtained in 92% ee.

We were pleased that previously unreported ligand **E** provided comparable levels of enantioselectivity to isomeric phosphoramidites **C** and **D**, which are extensively used.[13] Using **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 non-racemic amine or the separation of diastereomers during preparation.

Table 2. Effect of solvent and procedure.



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



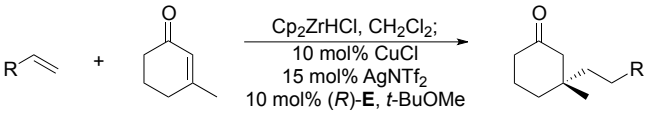
	Entry	Ligand/Complex	Solvent	Yield[a]	ee[b]
(*R*,*S*,*S*)-**F**	11[d]	**F**	2-Me-THF	83%	78%
	12[d]	**F**	Toluene	62%	90%
(*R*)-**B**	13[d]	**B**	CH_2Cl_2	68%	89%
	14[d]	**B**	*t*-BuOMe	72%	90%

Conditions: alkene (2.5 eq.), Cp_2ZrHCl (2 eq.), 3-Me-2-cyclohexen-1-one (1 eq.), room temperature, full conversion overnight. [a]Isolated yield. [b]Enantiomeric excess determined by HPLC. [c]**D** or **E** (0.10 eq.), CuCl (0.10 eq.) and $AgNTf_2$ (0.15 eq.) were stirred and the precipitate filtered before use, see Supporting Information. [d]Using 10 mol% of **B** or **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 Supporting Information.

We next examined the effect of solvent and method of catalyst preparation on the yield and enantioselectivity of **3a** with ligands **D** and **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 that had previously been prepared in a batch. These procedures (entries 11-14) gave only slightly diminished ee's compared to freshly prepared materials and may be attractive in some instances due to 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 **E**-$CuNTf_2$ system was relatively insensitive to solvent effects (entries 7-10, all ee's >90%) suggesting that it is robust, and we used this combination in *t*-BuOMe simply because it gave the highest levels of enantioselectivity.

Using these conditions we found that a range of simple unactivated terminal alkenes participated in the HM-ACA to give all carbon quaternary centres (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, 2 and 3) the alkenes are gasses, and the reactions were performed under a balloon atmosphere of the relevant alkene. The absolute configuration of (*R*)-**3b** and **3m**[14] (*vide infra*) were determined to have the *R*-configuration.

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%

Conditions: alkene (2.5 eq.), Cp_2ZrHCl (2 eq.), 3-Me-2-cyclohexen-1-one (1 eq.), CuCl (10 mol%), $AgNTf_2$ (15 mol%), precipitate filtered before use, (*R*)-**E** (10 mol%), room temperature overnight. [a]Isolated yield. [b]Ee 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 a hydrometallation stage.

Examining the nucleophiles that have previously been reported in ACA to form quaternary centres 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 that have been used in 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]

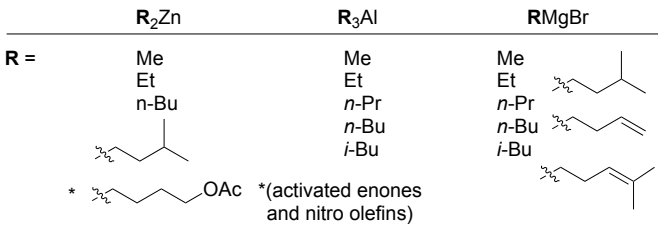


Figure 1. *n*-Alkyl nucleophiles previously used in ACA to form quaternary centres.

We chose to examine the use of more elaborate nucleophiles (Table 4) in ACA reactions to form quaternary centres. Using conditions that had previously been optimized for formation of **3a**, 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 gave highly promising preliminary results. Quaternary centre formation with electron rich allylsilane (entry 9) gave excellent results and the sequence can be also be used on alkenes bearing stereogenic centres (entries 3 and 10) and multiple functional groups (entry 10).

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, 9e, 9f, 10a, 15] gave **4** in only 4% yield using standard conditions, but we were able to increase the yield to 56% by using an excess of reagents and starting the reaction at 0 ºC (entry 1). 3-Ethyl-2-cyclohexen-1-one (entry 2) performed well in the coupling. Isophorone, also known to be troublesome in ACAs due to steric hindrance,[9c] gave 34% yield of coupling product **6** when using an excess of reactants in the presence of TMSCl (entry 3). The use of a 7-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 (Figure 2). On a gram scale, at room temperature, we obtained 1.46 g (94% yield, 92% ee) of **3a**.

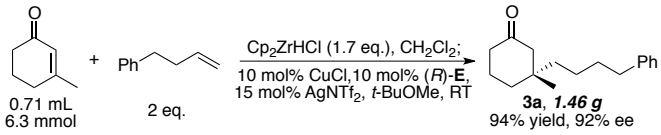
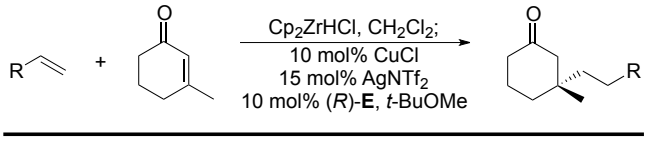
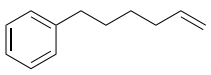
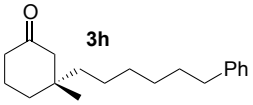
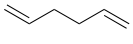
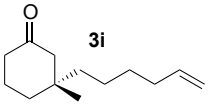
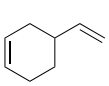
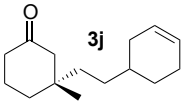
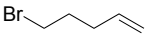
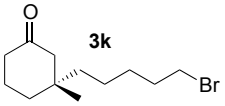
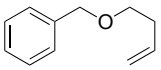
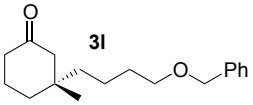
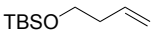
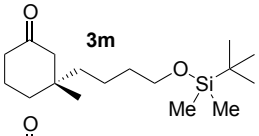
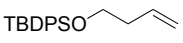
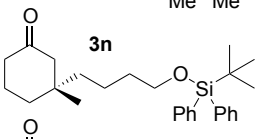
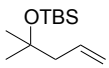
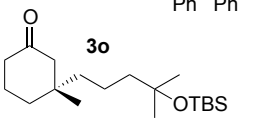
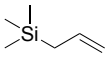
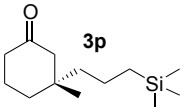
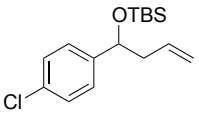
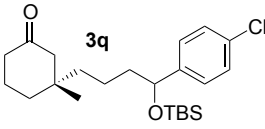


Figure 2. *Gram scale catalytic asymmetric conjugate addition.*

In conclusion, we report preliminary studies into a Cu-catalyzed hydrometallation – asymmetric conjugate addition approach that provides all-carbon quaternary centres by coupling alkenes with β-substituted enones. Conceptually, this 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 conditions we report here demonstrate that much more elaborate alkyl units can be added than previously reported. The further optimization, extension and application of this chemistry is currently being investigated and will be reported in due course.

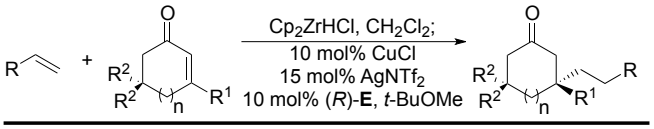
Table 4. Addition of functional alkenes.

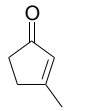
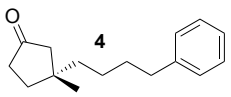
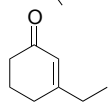
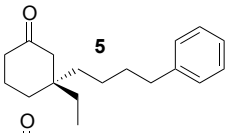
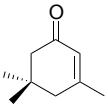
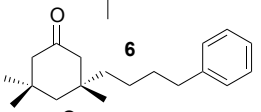
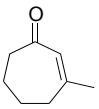
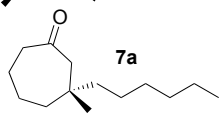


Entry	Substrate	Product	Yield[a]	ee
1		 **3h**	65%	90%[b]
2[c]		 **3i**	75%	78%[d]
3		 **3j**	48%[e]	86%[d]
4		 **3k**	53%	79%[d]
5		 **3l**	53%	89%[b]
6		 **3m**	75%	92%[d]
7		 **3n**	61%	~90%[b,f]
8		 **3o**	84%	89%[d]
9		 **3p**	82%	>95%[d]
10		 **3q**	82%[e]	89%[g]

Conditions: alkene (2.5 eq.), Cp_2ZrHCl (2 eq.), 3-Me-2-cyclohexen-1-one (1 eq.), CuCl (10 mol%), $AgNTf_2$ (15 mol%), precipitate filtered before use, (*R*)-**E** (10 mol%), room temperature overnight. [a]Isolated yield. [b]Ee determined by HPLC. [c]10 eq. of alkene used. [d]Ee 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.

Table 5. Scope of enones.



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

Conditions: alkene (2.5 eq.), Cp_2ZrHCl (2 eq.), 3-Me-2-cyclohexen-1-one (1 eq.), CuCl (10 mol%), $AgNTf_2$ (15 mol%), precipitate filtered before use, (*R*)-**E** (10 mol%), room temperature overnight. [a]Isolated yield. [b]5 eq. of alkene and 3 eq. of Cp_2ZrHCl. [c]0 ºC to room temperature. [d]Ee determined by HPLC. [e]±5%ee. [f]5 eq. of TMSCl was added. [g]Ee determined by dehydrogenation to the enone and HPLC.

Experimental Section

CuCl (57 mg, 0.63 mmol, 0.10 eq) and ligand (*R*)-**E** (340 mg, 0.63 mmol, 0.10 eq) were dissolved in *t*-BuOMe (31.5 mL) under an argon atmosphere and the resulting mixture allowed to stir at room temperature. After 1 hour, $AgNTf_2$ (367 mg, 0.95 mmol, 0.15 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (2.76 g, 10.71 mmol, 1.7 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene **1a** (1.90 mL, 12.6 mmol, 2.0 eq) 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 allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone **2a** (0.71 mL, 6.30 mmol, 1.0 eq) was added *via* 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 and then the phases were partitioned between the aqueous and Et_2O layers 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; hexane/i-PrOH: 98:2; λ = 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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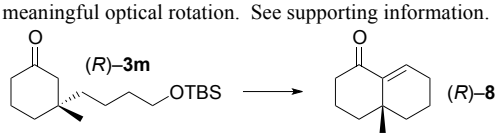
[14] Compound (*R*)-**3m** was converted in 3 steps to (*R*)-**8** which has known and meaningful optical rotation. See supporting information.



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Asymmetric Catalysis

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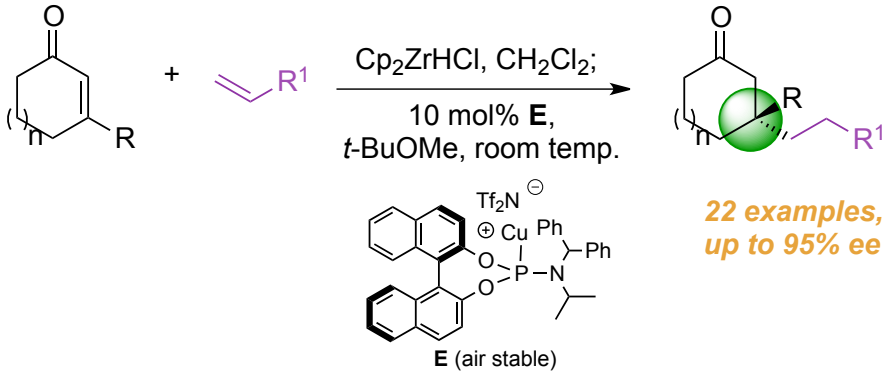
Page – Page

Quaternary Centre Formation by Copper Catalyzed Asymmetric Conjugate Addition of Alkylzirconium Reagents



E (air stable)

22 examples, up to 95% ee

Simply alkenes: Alkylzirconocenes generated *in situ* from alkenes are used in highly enantioselective copper-catalyzed 1,4-additon reactions to trisubstituted cyclic enones to give quaternary centres.

These reactions operate at room temperature under a range of conditions and tolerate many functional groups which has been a long-standing challenge in the formation of quaternary centres.