Asymmetric Catalysis

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Regiodivergent 1,4 versus 1,6 Asymmetric Copper-Catalyzed Conjugate Addition**

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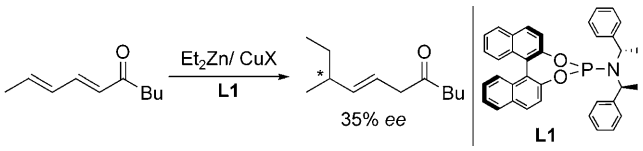
The conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl groups[1] is a powerful carbon-carbon bond-forming process, and catalytic asymmetric versions have become useful synthetic tools for the generation of tertiary[2] and quaternary carbon stereocenters.[3] Despite a large body of literature on 1,4-conjugate additions, analogous 1,6-addition methods are underdeveloped. In fact, the presence of three electrophilic sites and the difficulties in controlling the regioselectivity have limited the investigation of this reaction. Most often, copper reagents exclusively provided the 1,6-addition product,[4] and when we performed a reaction with diethylzinc and **L1** we observed only 1,6-addition compounds in 35% *ee* (Scheme 1).[5]



Scheme 1. 1,6 addition of diethyl zinc.

Recently Fillion et al. reported the asymmetric synthesis of benzylic tertiary and quaternary stereogenic centers in good yields and selectivities by using a 1,6-conjugate addition of dialkylzinc reagents to Meldrum's acid acceptors in the presence of **L1**.[6] Also, Feringa's group demonstrated that ferrocene-based diphosphine ligands, such as (*R*)-1-[(*S*)-2-diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine ((*R*,*S*)-josiphos), led to 1,6-conjugate addition to linear dienoates using Grignard reagents.[7] They obtained high enantioselectivities (up to 97% *ee*) and regioselectivities. By using Rh/binap (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) catalysis, Hayashi et al. described the 1,6-conjugate addition of aryl zinc reagents to 3-alkenyl cyclohexen-2-ones such as **1**, with up to 98% *ee*.[8] This class of substrates attracted our attention and we report herein our strange results on the regiodivergent 1,4 or 1,6 copper-catalyzed, asymmetric conjugate addition (ACA) of different alkyl metal sources (RMgX, R_2Zn, R_3Al) to α,β and γ,δ Michael acceptors.

We first examined the addition of diethylzinc to 3-(1-propenyl) 2-cyclohexen-1-one (**1**) using different ligands (Figure 1). Unsurprisingly, only the 1,6-addition compound was obtained as deconjugated isomer **2a′** (Scheme 2). To prevent the formation of oxidative byproducts,[9] hydrochloric acid that was degassed with argon was used for quenching the reaction. The isomerization of **2a′** using 1 equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under argon led to the totally reconjugated adduct **2a**. The best enantioselectivity (89% *ee*) was achieved with ligand **L2**. Triethylaluminum also gave 1,6-adduct **2a** (after reconjugation) but in a lower yield. Also, the best ligand in this case, **L1**, gave a lower enantioselectivity (68% *ee*).

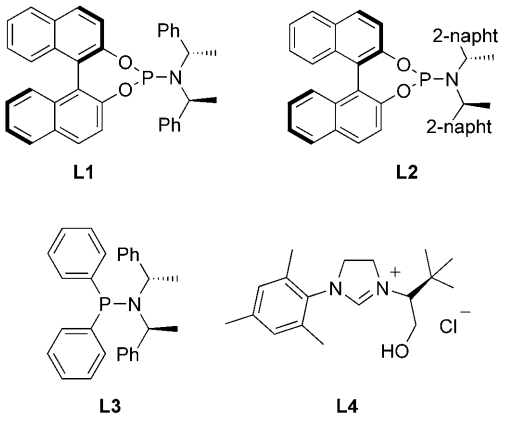


Figure 1. Selected ligands used for this study.

To examine the scope of the 1,6 ACA, we next studied the addition of Grignard reagents to **1**. Using chiral ligands **L1**–**L3**, as well as binap[10] or josiphos,[7] only led to the 1,6 adduct (after reconjugation) in low enantioselectivity. However, when N-heterocyclic carbene (NHC) ligand **L4**[11] was employed, the 1,4 adduct was obtained as the slightly major regioisomer! Surprisingly, this result corresponds to a conjugate addition at the most hindered position, thus generating an all-carbon quaternary center with high enantioselectivity (97% *ee*). After optimization of the reaction

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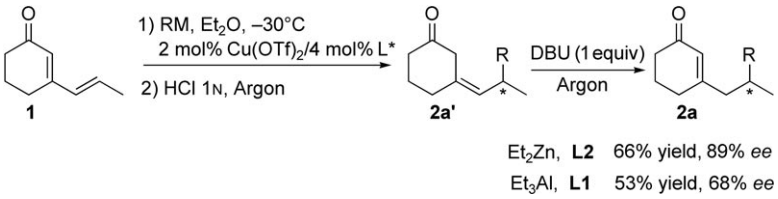
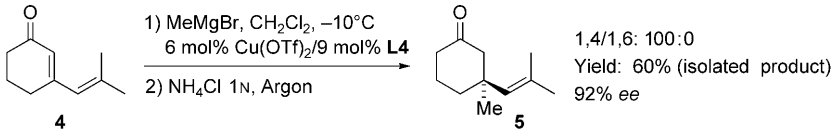


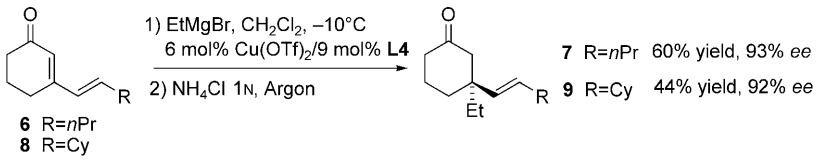
Scheme 2. Enantioselective 1,6-conugate addition of diethylzinc and trialkylaluminum reagents to compound **1**.

conditions, particularly the use of dichloromethane as the solvent, the 1,4 adduct became almost the exclusive product (Table 1).

*n*Alkyl Grignard reagents provided the 1,4 adducts with greater than 95% selectivity and *ee* values as high as 99% (Table 1, entries 1, 3, and 4). *iso*-Propyl and *iso*-butyl Grignard reagents afforded a separable mixture of both regioisomers, whereas methyl Grignard gave only the 1,6 adduct. It seems that the natural trend for 1,6 addition,[4] as well as the preference for the least substituted position,[2b] are difficult to overcome. A solution to this problem was to have a substrate with equally substituted positions, such as **4** (Scheme 3). Thus, methyl Grignard was now able to deliver 1,4 adduct **5** with excellent regioselectivity (100%) and enantioselectivity (92%). The hydrogenation of **5** provided the saturated analogue, whose absolute configuration is already known.[3c]



Scheme 3. Enantioselective 1,4-conjugate addition of methyl Grignard.



Scheme 4. Enantioselective 1,4-conjugate addition to other substrates. Cy = cyclohexyl.

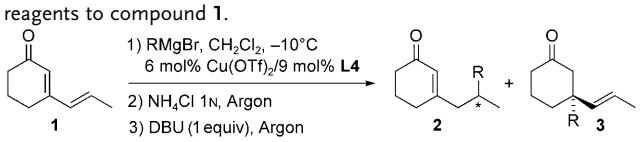
This regioselective 1,4 ACA was extended to other similar substrates having different substitution patterns (Scheme 4). Substrates **6** and **8** reacted in exactly the same way, affording the 1,4 adducts in high regio- and enantioselectivities.

Another interesting dienic substrate was bicyclic compound **10**, to which we applied our best conditions for 1,6 or 1,4 ACA (Table 2). Diethylzinc was not very reactive, and only the deconjugated 1,6 addition product **11** was observed with poor enantioselectivity. Attempts to reconjugate **11** using DBU failed. In contrast, triethylaluminum was a more reactive reagent and compound **11** was obtained with moderate enantioselectivity (Table 2, entry 2), with **L2** being the best ligand. We also examined the addition of trimethylaluminum to **10**; the best copper salt was CuTC (copper thiophene carboxylate) and the best ligand was SimplePhos (**L3**; Table 2, entry 3),[12] giving compound **11** with a moderate enantiomeric excess of 56%. Ethyl Grignard underwent a regioselective 1,4 ACA with **10** in the presence of **L4** to give **2a** with excellent enantioselectivity (Table 2, entry 4).

This regiodivergent ACA is quite intriguing. Experiments with simpler NHC's (Arduengo's carbene[13]) and Grignard reagents gave exclusively the 1,6 adduct. Only when an OH group was present on the NCH was the 1,4 adduct present. Other carbenes, similar to **L4**,[11] gave lower enantioselectivity, but good 1,4 selectivity. It is well known that the only observable π complex on such polyethylenic ketones is the one on the α,β position.[4] Although the ω adduct is usually obtained, it may be speculated that if the reductive elimination step is fast, the copper(III) intermediate may collapse readily to afford the 1,4 product. This is, for example, the case with Yamamoto's reagents (RCu/BF_3).[14]

Of synthetic interest is the olefinic appendage of the 1,4 adduct. For example, compound **3c** was cyclized by ring

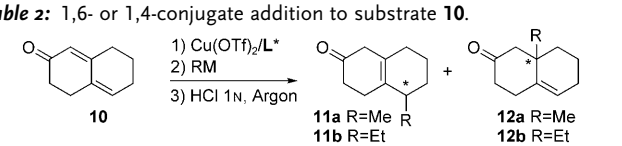
Table 1: Enantioselective 1,4-conjugate addition of several Grignard reagents to compound **1**.



Entry	R	Product	2/3[b]	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	Et	**3a**	<1:99	100	62	97
2	Me	**2b**	100:0	100	n.d.	–
3	Bu	**3b**	4:96	100	67	97
4	But-3-enyl	**3c**	5:95	100	65	>99
5	*i*Pr	**3d**	35:65	100	25	95
6	*i*Bu	**3e**	44:56	100	39	99

[a] All reactions were performed with **1** (0.5 mmol), RMgX (2 equiv), $Cu(OTf)_2$/**L4** 6/9 mol%, in CH_2Cl_2 at −10°C. [b] Determined by GC-MS methods. [c] Yield of isolated 1,4 adduct. [d] Determined by GC methods using a chiral stationary phase. n.d. = not determined.

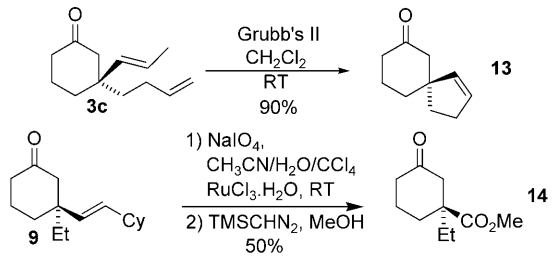
Table 2: 1,6- or 1,4-conjugate addition to substrate **10**.



Entry	RM	L*	Solvent	*T* [°C]	11/12[a]	Conv. [%][a,b]	*ee* [%][c]
1	Et_2Zn	**L2**	Et_2O	−10	100:0	11	11
2	Et_3Al	**L2**	Et_2O	−10	100:0	100 (45)	69
3	Me_3Al[d]	**L3**	Et_2O	−10	100:0	100 (54)	56
5	EtMgBr	**L4**	CH_2Cl_2	−10	2:98	100 (73)	96

[a] The product ratio **11**/**12** and the conversion were determined by GC-MS methods. [b] Yield of isolated products in parentheses. [c] Determined by GC analysis using a chiral phase. [d] Run with 2 equivalents of RM and with CuTC. RM = alkylmetal reagent.

closing metathesis (Scheme 5)[15] to afford spiro compound **13**. Alternatively, adduct **9** was oxidatively cleaved to afford ketoester **14**. Besides its synthetic versatility, this transformation allowed us to determine the *ee* value of adduct **9**.



Scheme 5. Synthetic transformations of the 1,4 adducts.

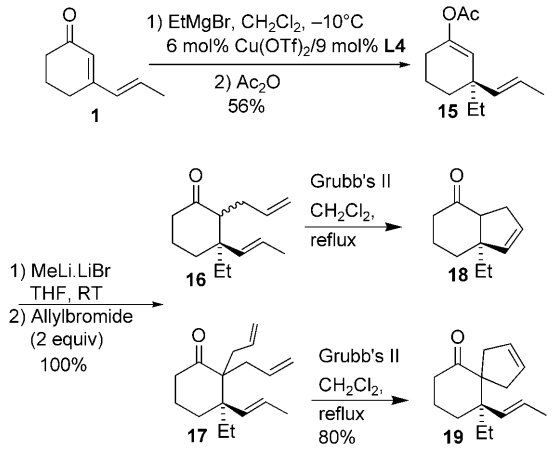
In addition, the resulting enolate from the 1,4 ACA could be trapped with Ac_2O (Scheme 6).[16] Enol acetate **15** was used to regenerate the lithium enolate,[17] which upon allylation gave a 3:1 ratio of monoallylated adduct **16** (as a *cis/trans* mixture) and bisallylated **17**. Both **16** and **17** underwent a facile ring closing metathesis to provide products **18** and **19**, respectively. Although **16** was a mixture of isomers, a single product,**19**, was obtained; presumably the one with the *cis* ring junction.

In summary, we have disclosed an unusual regiodivergent 1,4- or 1,6-asymmetric conjugate addition. Although the 1,6 adducts had moderate to good enantioselectivity, the 1,4 adducts had excellent *ee* values for an all-carbon quaternary stereocenter. Additional work is in progress for a better understanding of the mechanistic insights.

Experimental Section

Synthesis of **3a**: $Cu(OTf)_2$ (10.8 mg, 6 mol%) and **L4** (14.6 mg, 9 mol%) were dissolved in dry CH_2Cl_2 (1.5 mL) in a dried Schlenk tube equipped with septum and stirring bar under nitrogen. The mixture was cooled to −10 °C and EtMgBr (2 equiv in Et_2O) was added. The reaction mixture was stirred for an additional 5 min and then a solution of dienone **1** (0.5 mmol) in dry CH_2Cl_2 (5 mL) was added by syringe pump over 15 min. The reaction mixture was stirred for 1 h at −10 °C and then an NH_4Cl solution (1M, 0.5 mL) was added. The mixture was warmed to room temperature and then 5 mL of the NH_4Cl-solution and 5 mL of CH_2Cl_2 were added, after which the layers were separated. After extraction with CH_2Cl_2 (2 × 5 mL), the combined organic extracts were dried and evaporated. Flash chromatography (pentane/diethyl ether 90:10) afforded desired compound **3a**.

^{1}H NMR (100 MHz, $CDCl_3$): $\delta = 0.78$ (t, $J = 7.5$ Hz, 3H), 1.37 (q, $J = 7.5$, 2H), 1.61–1.69 (m, 6H), 1.76–1.84 (m, 1H), 2.12 (d, $J =$ 14.0 Hz, 1H), 2.16–2.33 (m, 2H), 2.46 (d, $J = 14.0$ Hz, 1H), 5.15 (d, $J = 16$ Hz, 1H), 5.34 ppm (dq, $J_1 = 6.0$ Hz et $J_2 = 16.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 7.9$ (CH_3), 18.3 (CH_3), 21.8 (CH_2), 34.2 (CH_2), 35.2 (CH_2), 41.2 (CH_2), 44.2 (C), 49.8 (CH_2), 125.3 (CH), 136.6 (CH), 212.0 ppm (CO). HRMS (EI): $[M]^+$ found 166.1360, calcd for $C_{11}H_{18}O$: 166. 1357. $[\alpha]_D^{20} = +72.24$ deg cm^3 g^{-1} dm^{-1} ($c =$ 1.4 g cm^{-3}, $CHCl_3$), 97% *ee*. The enantiomeric excess was determined on the hydrogenated compound by GC analysis employing LIPODEX-E (75-40-1-100): $Rt_1 = 36.88$ min (minor), $Rt_2 = 39.09$ (major). The corresponding racemic saturated compound was obtained by copper-catalyzed conjugate addition of *n*PrMgBr to 3-ethyl-2-cyclohexenone.



Scheme 6. Synthetic transformations of enol acetate **15**.

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