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ω-Ethylenic Allylic Substrates as Alternatives to Cyclic Substrates in Copper- and Iridium-Catalyzed Asymmetric Allylic Alkylation

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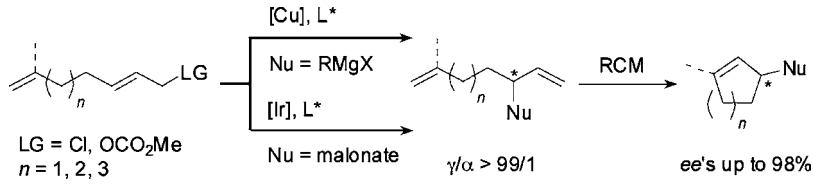
ABSTRACT



A new strategy to access highly enantioenriched cyclic compounds (up to 98%) is proposed using ω-ethylenic allylic substrates through a one-pot asymmetric allylic alkylation and ring-closing metathesis. Such starting compounds can be seen as synthetic equivalents of cyclic allylic substrates.

Asymmetric allylic alkylation (AAA) is one of the fundamental C−C bond-forming transformations used as an important tool in organic synthesis to achieve high regio- and enantioselectivity using different nucleophiles and different allylic electrophiles.[1] Many metals can catalyze this reaction and, among them, palladium has been extensively studied and successfully applied in this reaction using stabilized nucleophiles, such as malonates or amines.[2]

The low regioselectivity obtained in palladium-catalyzed allylic alkylation with nonsymmetrical (or monosubstituted) allylic substrates has hampered the general use of this reaction. In addition, only stabilized nucleophiles provided high selectivities, forcing many authors to explore other alternatives.

In recent years, more attention has turned to copper. Copper-catalyzed allylic alkylation could be considered complementary to palladium. In fact, copper catalysis allows the use of nonstabilized organometallic reagents for the direct introduction of alkyl groups into prochiral allylic substrates, and more interestingly, it proceeds with high S_N2' regioselectivity.[3]

In our laboratory, we were interested in cyclic allylic substrates as class of electrophiles because of the numerous biologically active compounds bearing a cyclic moiety in the scaffold, which could be obtained starting from an asymmetric allylic alkylation reaction.[4]

Many examples for the formation of enantioenriched cyclic compounds can be found in the literature using palladium as catalyst, as high enantioselectivity is reached using an appropriate chiral ligand which allows deracemization of the meso π-allyl intermediate formed upon displacement of the allylic leaving group.[2]

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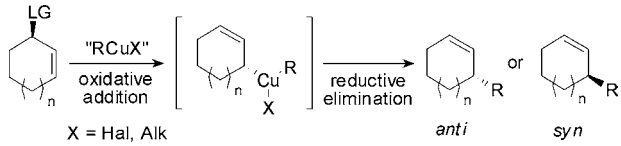
In contrast, there are some limitations to using copper as catalyst with cyclic compounds because of the different mechanism involved in this reaction, compared to the one of palladium.[5] Exclusively S_N2' (or γ) *syn* or *anti* adducts can be obtained by choosing a suitable chelating leaving group on a chiral allylic substrate (Scheme 1).[6] However,

Scheme 1. Copper-Mediated Allylic Alkylation

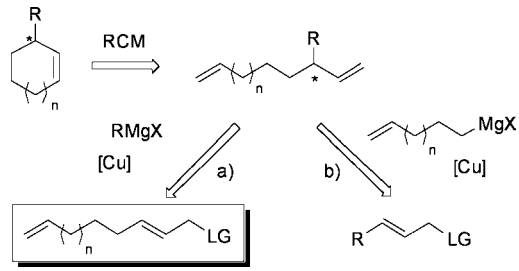


starting from a racemic allylic substrate the enantiodiscriminating step, namely the oxidative addition of copper, would generate both possible σ-allyl intermediate, producing after the reductive elimation step a mixture of enantiomers.[7]

For this reason we looked for an alternative way to obtain this important chiral synthons.

Here we propose the use of an ω-ethylenic allylic substrate as synthetic equivalent, which can undergo copper-catalyzed asymmetric allylic alkylation using Grignard reagents and bears a convenient functionality to be cyclized through a ring closing metathesis reaction (Scheme 2, pathway a). This

Scheme 2. Alternative Approach for the Synthesis of Enantioenriched Cyclic Systems



functionality can be also introduced through the allylic alkylation step from the nucleophile, as it has already been reported from our group (Scheme 2, pathway b).[8] Depending on the R group to be introduced, either pathway a or b can be chosen. For example, linear R alkyl groups on the allylic substrate usually afford lower enantioselectivities than aryl groups.[8d] On the other hand, aryl Grignard reagents are not very γ regioselective.[3] One key feature of our strategy is the possibility to perform the reaction in a one-pot procedure as we have already demonstrated the tolerance of Grubbs' catalyst toward the allylic alkylation's conditions.[8]

Initially, we considered three allylic chlorides, differing from each other for the length of the carbon chain between the allylic double bond and the ethylenic bond to have access to enantioenriched five-, six-, and seven-membered rings.

Copper-catalyzed asymmetric allylic alkylation was performed using 3 mol % of copper thiophene carboxylate (CuTC), 3.3 mol % of a chiral phosphoramidite-type ligand (Figure 1),

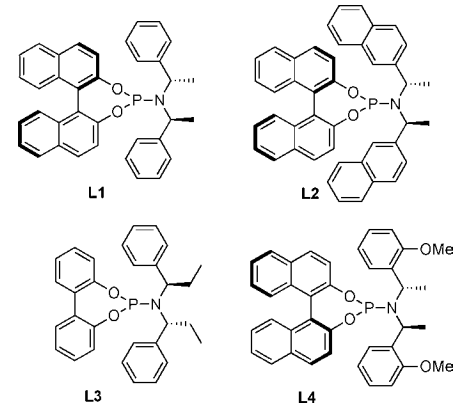


Figure 1. Chiral ligands used in this work.

and 1.3 equiv of Grignard reagent in dichloromethane at −78 °C. *Without* quenching the reaction, Grubbs' catalyst[9] was added and the flask was warmed to room temperature. The results reported in the schemes are the best obtained after a screening of different phosphoramidite-type ligands.

As shown in Table 1, regioselectivities were excellent in all cases and subsequent ring-closing metathesis, using 5 mol % of Grubbs' catalyst (first generation), allowed the determination of the enantiomeric excess when it was not possible after the alkylation step. Entries 1 and 2 of Table 1 show effectively that no loss of enantioselectivity takes place during the ring-closure step. Although the isolated yields over the two steps are good to moderate, it should be mentioned that the metathesis step is the most delicate, needing recently bought (or prepared) Grubbs' catalyst.

By looking more in detail at the results, bulky phosphoramidite ligand **L2**[10] gave the best enantiomeric excess of 93% for the formation of a six-membered ring with a (4-*tert*-butoxy)butyl substitution (Table 1, entry 6). **L2** was also effective for the formation of a phenethyl-substituted six-membered ring product in 86% ee, and the same level of enantioselectivity was obtained with the standard phosphoramidite ligand **L1**[11] for obtaining a phenethyl-substituted five-

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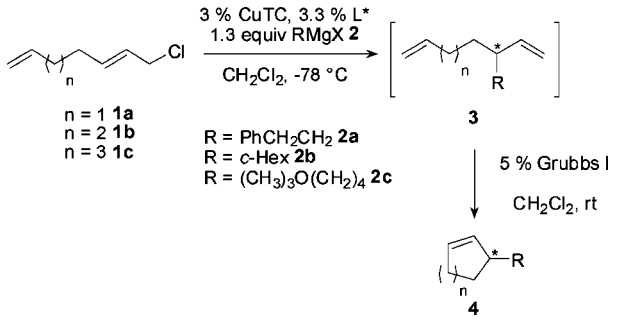
Table 1. Cu-AAA/RCM of Allylic Chlorides **1a**−**c**[a]



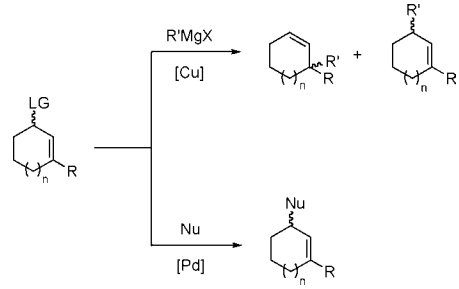
entry	substrate	R	L	γ/α[b]	ee of **3**[c] (%)	product **4**	yield[d] (%)	ee of **4**[c] (%)
1	**1a**	**2a**	**L1**	92/8	86	**4a**	62	86
2	**1a**	**2b**	**L3**	>99/1	82	**4b**	74	82
3	**1a**	**2c**	**L4**	>99/1		**4c**	52	73
4	**1b**	**2a**	**L2**	>99/1		**4d**	66	86
5	**1b**	**2b**	**L1**	94/6		**4e**	68	74
6	**1b**	**2c**	**L2**	>99/1		**4f**	68	93
7[e]	**1c**	**2a**	**L1**	>99/1		**4g**	62[f]	85
8[e]	**1c**	**2b**	**L3**	>99/1		**4h**	55[f]	80

[a] General conditions: 3 mol % of CuTC, 3.3 mol % of L*, 1.3 equiv of RMgX, in CH_2Cl_2, at −78 °C. [b] Determined by ^{1}H NMR or GC/MS. [c] Determined by chiral GC or SFC analysis. [d] Yield of isolated product after a flash column chromatography on SiO_2. [e] Reaction performed in a two-pot procedure. [f] Overall yield.

membered ring (Table 1, entry 4 and 1). An 85% ee was also obtained with this ligand for the corresponding seven-membered ring product (Table 1, entry 7). The introduction of a secondary alkyl group was also explored: a good 82% and 80% ee was achieved with the use of chiral ligand **L3**[12] to obtain five- and seven-membered ring products (Table 1, entry 2 and 8), while only 74% ee was obtained for the six-membered ring with ligand **L1** (Table 1, entry 5). Finally, it is worth mentioning the positive effect the ω double bond has on the enantioselecivity. The saturated analogue of **1a** gave, under the same conditions as entry 2, only 38% ee.

We then turned our attention to a challenging cyclic substrate for the asymmetric allylic alkylation reaction having a substitution on the γ-position (Scheme 3). In fact, this kind

Scheme 3. Allylic Alkylation on γ-Substituted Cyclic Systems



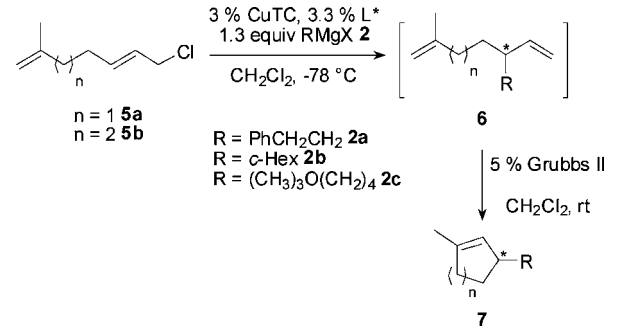
of allylic system is not accessible in a highly selective way from a direct asymmetric allylic alkylation on the corresponding allylic substrate.[13] To the best of our knowledge, no examples are reported in the literature about this transformation catalyzed either by copper or palladium. In fact, as already discussed for simple cyclic substrates, copper-catalyzed allylic alkylation would afford a mixture of enantiomers because of the formation of the two possible diastereomeric species. In addition, the presence of a substituent in the γ-position would afford a mixture of regioisomers because of the hindered position.

Furthermore, concerning palladium chemistry, it is well-known that this metal is generally regioselective for the least hindered position but the presence of a substituent in the γ position would lead to the formation of a nonmeso π-allyl intermediate, preventing deracemization of the substrates and thus resulting in the formation of a mixture of enantiomers.[1]

For these reasons, we wished to apply our strategy to synthesize these challenging compounds starting from an ω-ethylenic allylic substrate and performing the asymmetric allylic alkylation−ring-closing metathesis in a one-pot procedure.

Table 2 summarizes the results obtained for the copper-catalyzed asymmetric allylic alkylation for allylic chlorides **5a** and **5b**.

Table 2. Cu-AAA/RCM of Allylic Chlorides **5a**,**b**



entry	substrate	R	L	γ/α[a]	product **7**	yield[b] (%)	ee of **7**[c] (%)
1	**5a**	**2b**	**L3**	>99/1	**7a**	55	74
2	**5a**	**2c**	**L1**	>99/1	**7b**	60	68
3[d]	**5b**	**2a**	**L4**	92/8	**7c**	62[e]	67
4	**5b**	**2b**	**L3**	>99/1	**7d**	70	64
5[d]	**5b**	**2c**	**L1**	>99/1	**7e**	60[e]	53

[a] Determined by ^{1}H NMR or GC/MS. [b] Yield of isolated product after a flash column chromatography on SiO_2. [c] Determined by chiral GC or SFC analysis. [d] Reaction performed in a two-pot procedure. [e] Overall yield.

All the reactions proceeded in highly regioselective manner. Biphenol ligand **L3** was reasonably efficient for the cyclohexyl alkylation of both substrates with ee's up to 74% (Table 2, entry 1), while phosphoramidite ligand **L1** afforded

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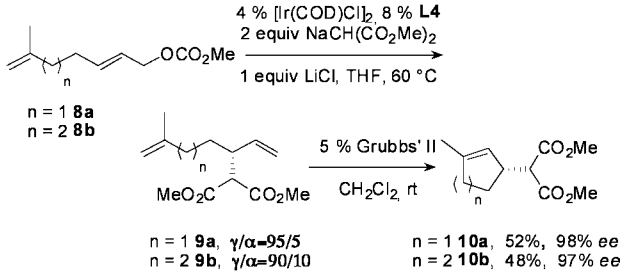
(13) Falciola, C. A.; Tissot-Croset, K.; Reyneri, H.; Alexakis, A. *Adv. Synth. Catal.* **2008**, *350*, 1090.

68% ee for the formation of a five-membered ring with a (4-*tert*-butoxy)butyl substitution but only 53% for the six-membered ring (Table 2, entries 2 and 5).

By comparing the results obtained on the allylic substrate without having a substituent on the terminal double bond we observed a decrease of the enantiomeric excess, especially in the case of the addition of a secondary Grignard reagent. We could assume that the ethylenic double bond could play a role in the enantiodetermining step and in particular during the coordination of copper to the substrate. Indeed the metal can coordinate to this terminal double bond before the formation of the σ-allyl complex so that the presence of the methyl group can modify by steric hindrance the chiral pocket.

Finally, we were interested in investigating the asymmetric allylic alkylation reaction using stabilized nucleophiles. Therefore, we performed the iridium-catalyzed asymmetric allylic alkylation on allylic carbonate **8a** and **8b** with dimethyl malonate (Scheme 4). The choice of using this metal as catalyst instead of palladium is due to the fact that iridium-mediated allylic alkylation reaction has recently emerged as highly regioselective, as reported by our group and other authors.[14]

Scheme 4. Ir-AAA/RCM of Allylic Carbonates **8a**,**b**



After optimization of the reaction conditions, high regio- and enantioselectivities with both substrates were obtained. It should be pointed out that because of the different reaction's conditions (i.e., different reaction's solvent) the whole process was performed in a two step procedure. Ligand **L4**[8b,c] afforded up to 95% γ-selectivity and up to 98% ee.

In conclusion, we have described a new strategy to access highly enantioenriched cyclic systems using ω-ethylenic allylic substrates as synthetic equivalent of cyclic allylic compounds. This is a complementary strategy to our previously described one,[8] as it allows an easy variation of the organometallic reagent instead of the substrate. It was applied in the copper-catalyzed enantioselective allylic alkylation by Grignard reagents and iridium-catalyzed enantioselective allylic alkylation with dimethyl malonate followed by a ring-closing metathesis reaction. Enantiomeric excesses up to 93% and 98% were obtained, respectively.

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C spectra, and chiral separations for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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