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Highly Enantioselective and Regioselective Copper-Catalyzed 1,4 Addition of Grignard Reagents to Cyclic Enynones

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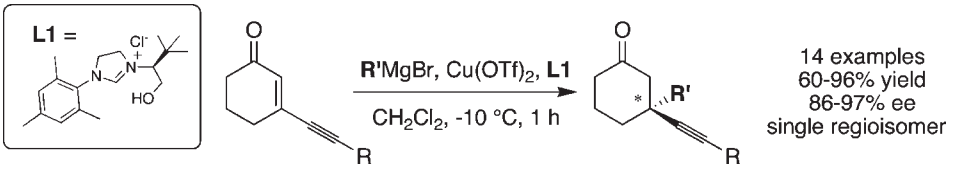
ABSTRACT



In this letter we describe an unusual result in terms of regioselectivity with respect to copper-catalyzed conjugate additions of various Grignard reagents to cyclic enynones. The use of $Cu(OTf)_2$ and NHC ligand L1 as the catalyst combination in CH_2Cl_2 led to the unique formation of the 1,4 adduct. This selectivity does not follow the general trend previously observed in the literature using extended Michael acceptors. Moreover these reactions allowed for the creation of a quarternary stereogenic center with enantioselectivities up to 97% ee.

The conjugate addition of carbon nucleophiles to electron-deficient olefins has become one of the most important methods for the formation of a C−C bond. The asymmetric version of this reaction has been extensively studied over the past few decades, highlighting Cu and Rh as the catalysts of choice for this transformation.[1] However, the conjugate addition to the vinylogous electron-deficient dienes has been much less developed due to the presence of various electrophilic sites, which, upon nucleophilic attack, can lead to several regioisomers.[2]

The use of copper reagents frequently result in 1,6 selectivity, as demonstrated extensively by Krause.[3] Over the past few years, copper-catalyzed 1,6 addition has emerged as a new and interesting field of research. In 2008, Fillion was the first to describe the copper-catalyzed enantioselective 1,6 addition employing diorganozinc reagents and Meldrum's acid as the substrate.[4] High enantioselectivities up to 84% were obtained. Subsequently, Feringa reported the addition of Grignard reagents to dienic esters using a catalyst combination of ferrocene-based phosphine ligands and $CuBr \cdot Me_2S$ exclusively affording the 1,6 adduct with high stereoselectivities.[5] Recently Mauduit and our group published the copper-catalyzed asymmetric conjugate addition (ACA) of diorganozinc reagents to cyclic dienones. 100% selectivities in favor of the 1,6 adduct were obtained with excellent

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(1) Reviews on asymmetric conjugate additions, see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221. (c) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796. (d) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (e) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354. (f) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (G) Chrisyoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279.

(2) Csáky, A. G.; de la Herrán, G.; Murcia, M. C. *Chem. Soc. Rev.* **2010**, *39*, 4080.

(3) Krause, N.; Thorand, S. *Inorg. Chim. Acta* **1999**, *296*, 1.

(4) Fillion, E.; Wilsily, A.; Liao, E. T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957.

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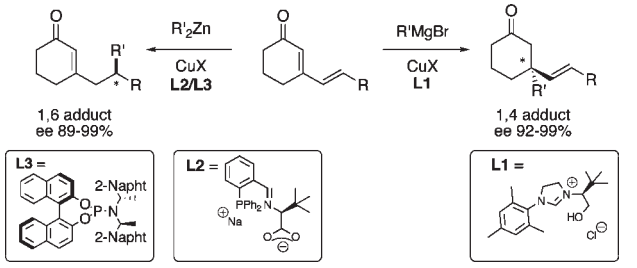
enantioselectivities up to 99% using a Cu−DiPPAM (**L2**) complex (Scheme 1).[6]

However, few examples have highlighted that this general trend, leading to a preferential 1,6 attack, could be unfavored depending on the substrate and/or the reaction conditions. The first example was described by Yamamoto who showed that a fine-tuning of the copper reagent allows regioselective 1,4 addition.[7] Recently, we developed the copper-catalyzed ACA of trialkyl aluminum reagents to extended nitro-Michael acceptors affording the 1,4 adducts only, with excellent stereocontrol.[8] In addition, our group disclosed that the selectivity can be altered in favor of the 1,4 addition by changing the nucleophile and the catalytic reaction conditions. Indeed by using a Grignard reagent in combination with *N*-heterocyclic carbene (NHC) **L1** we observed mainly 1,4 addition to the cylic dienone, resulting in the highly enantioselective formation of the 1,4 adduct on the most substituted position (Scheme 1).[9]

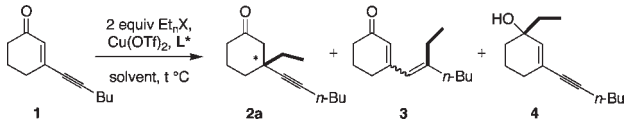
Scheme 1. Regiodivergent 1,4 versus 1,6 ACA



In this report, we detail an extension of this previous methodology using cyclic enynones. These types of extended Michael acceptors were first studied by Hulce[10] who observed only the 1,6 addition via addition of a copper reagent. Hayashi reported the rhodium-catalyzed 1,6 addition of aryltitanates to this family of substrates to afford chiral allenes.[11] We found two reports by Hoveyda in recent literature, including two isolated examples of copper-catalyzed 1,4 additions on this type of substrate using diethylzinc[12] and trimethylaluminium.[13]

We initially evaluated the addition of three different types of organometallic reagents to the enynone **1** using NHC ligand **L1** and phosphoramidite ligand **L3** under various reaction conditions (Table 1).

Table 1. Result of Initial Organometallic Screening for the Conjugate Addition to Enynone **1**



1 2a 3 4

entry	organometallic source	t [°C]	L*	conv [%][c]	2/3/4[c]	ee[d] 1,4
1[a]	EtMgBr	−10	**L1**	100	91.5:0:8.5	85
2[a,e,f]	EtMgBr	−10	**L1**	100	28:nd:nd[f]	93
3[a]	EtMgBr	−10	**L3**	100	0:100:0	–
4[a,e]	EtMgBr	−10	**L3**	100	nd[f]	–
5[a]	Et_2Zn	−10	**L1**	10	nd[f]	–
6[a,e]	Et_2Zn	−10	**L1**	100	75:25:0	99
7[b]	Et_2Zn	−10	**L3**	60	0:100:0	–
8[a,e]	Et_3Al	−30	**L1**	100	5:95:0	–
9[b]	Et_3Al	−30	**L3**	100	0:100:0	–

[a] Reaction performed with Cu(OTf)$_2$/**L*** = 6/9 mol % in CH_2Cl_2. [b] Reaction performed with Cu(OTf)$_2$/**L*** = 2/4 mol % in Et_2O. [c] Determined by GC-MS. [d] Determined by GC on a chiral phase. [e] Et_2O was used as solvent. [f] Messy reaction.

First, we performed the addition of EtMgBr using the reaction conditions previously published[9] for the 1,4 addition on cyclic dienone using the NHC ligand **L1** and Cu(OTf)$_2$ as the catalyst in CH_2Cl_2 (and a small amount of Et_2O from the Grignard solution) (Table 1, entry 1). We were delighted to observe that the 1,4 adduct was mainly formed with the enantioselectivity reaching 85%. This impressive selectivity, resulting in the formation of a stereogenic quaternary center, demonstrates that cyclic enynones react in a similar way as the corresponding dienones under the same reaction conditions. When pure Et_2O was used in place of CH_2Cl_2 (Table 1, entry 2), the 1,4 addition was observed in a minor amount, despite a messy reaction due to the large quantities of 1,2 and 1,6 addition products. This result highlights the detrimental effect of this solvent in terms of regioselectivity. The use of the phosphoramidite ligand **L3** in CH_2Cl_2 led to the formation of the 1,6 adduct exclusively and to a messy reaction in Et_2O (Table 1, entries 3 and 4).

Then, the use of diethylzinc was investigated under the initial reaction conditions (with NHC **L1**), which showed a very low conversion (Table 1, entry 5). However, when Et_2O was used, an enantioselectivity of 99% was detected in a ratio of 3:1 in favor of the 1,4 adduct **2a** (Table 1, entry 6). Under the same reaction conditions, **L3** afforded only the 1,6 adduct (Table 1, entry 7). Finally Et_3Al was also tested affording mainly the 1,6 adduct (Table 1, entries 8 and 9).

As a consequence of the high regioselectivity displayed with Grignard reagents, as shown in the previous table, and the various possibilities offered by this organometallic reagent, we investigated the scope of these nucleophiles on the reaction with enynone **1a** (Table 2, entries 1−5). After a slight modification in terms of dilution and addition time of the EtMgBr (see Supporting Information), the 1,4

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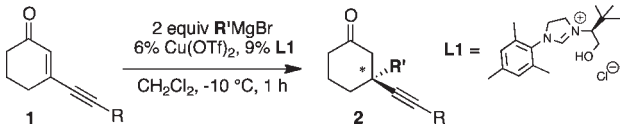
adduct **2a** was obtained as a single regioisomer with an enantioselectivity of 82% (Table 2, entry 1). On the other hand, but-3-enylmagnesium bromide afforded perfect selectivity and an excellent enantioselectivity of 95% under the initial reaction conditions (Table 2, entry 2). Isopropyl and -butyl Grignard reagents required slight modifications of reaction conditions, but also with the maximum of Et_2O contained within the Grignard reagent being replaced by CH_2Cl_2 to obtain the 1,4 adduct as the major isomer with high ee's (Table 2, entries 3 and 4).

Table 2. Conjugate Addition of Grignard Reagent to Enynones **4a**−**f**[a]



entry	1	R′	conv [%][b]	yield [%]	ee[%][c] 1,4
1[d]	**1a**	Et	100	72 (**2a**)	82
2	**1a**	But-3-enyl	100	90 (**2b**)	95
3[d,e]	**1a**	*i*Pr	100	60 (**2c**)	92
4[d,e,f]	**1a**	*i*Bu	100	88 (**2d**)	95
5[d,e]	**1a**	Me	100	nd (**2e**)	nd
6[g]	**1b**	Me	100	29 (**2f**)	83
7	**1b**	Et	100	82 (**2g**)	79
8	**1b**	*i*Pr	100	57 (**2h**)	87
9	**1b**	*i*Bu	100	87 (**2i**)	93
10	**1c**	*i*Bu	100	98 (**2j**)	95
11	**1c**	But-3-enyl	100	72 (**2k**)	91
12[h]	**1c**	Cy	100	74 (**2l**)	96
13	**1d**	*i*Bu	100	81 (**2m**)	94
14	**1d**	But-3-enyl	100	87 (**2n**)	93
15	**1e**	But-3-enyl	100	79 (**2o**)	96

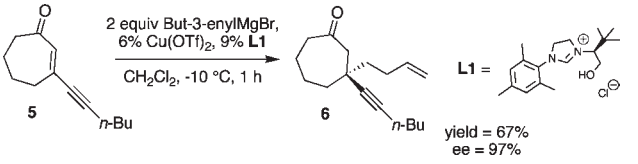
[a] All reactions performed with **1** (0.25 mmol), R′MgBr (2 equiv), $Cu(OTf)_2$/**L*** = 6/9 mol % in CH_2Cl_2 at −10 °C. [b] Determined by GC-MS. [c] Determined by GC on a chiral phase. [d] Solution was twice as diluted as under standards reaction conditions, substrate addition times of 30 min instead of 15 min. [e] Et_2O of the Grignard is replaced by CH_2Cl_2. [f] The product is isolated from a mixture 1,2/1,4/1,6 = 11:17:71. [g] The product is isolated from a mixture 1,2/1,4/1,6 = 4:93:3. [h] The product is isolated from a mixture 1,4/1,6 = 95:5.

Despite many attempts, the addition of MeMgBr remained problematic as with cyclic dienones since the 1,6 adduct was the major isomer (Table 2, entry 5). In order to drive the selectivity in favor of the 1,4 adduct we used substrate **1b** possessing a bulky *tert*-butyl group at the 1,6 position, and as expected, the selectivity went in favor of the 1,4 adduct with good enantioselectivity (Table 2, entry 6).

We also applied different Grignard reagents to substrate **1b**, always affording perfect regioselectivities with enantioselectivities up to 95% (entries 7−9). TMS- and phenyl-substituted substrates (**1c** and **1d**) also gave excellent results in terms of regio- and enantioselectivities (entries 10−14). We also tried to apply our methodology to enynone **1e**, affording an enantioselectivity of 96%. The correponding unprotected alcohol was also tried under our reaction conditions, but low conversion and a mixture of products were observed.

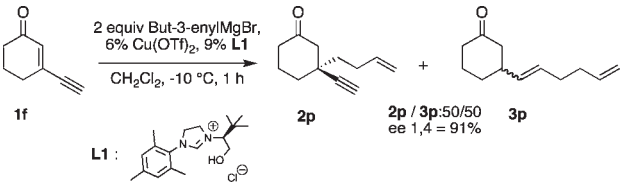
This regioselective 1,4 ACA was also extended to different ring sizes. The seven-membered ring displayed our best results in terms of enantioselectivity (97%) with perfect regioselectivity (Scheme 2), whereas the five-membered ring gave a very messy reaction, indicating very low control of the regioselectivity.

Scheme 2. Conjugate Addition of Grignard Reagent to Seven-Membered Ring

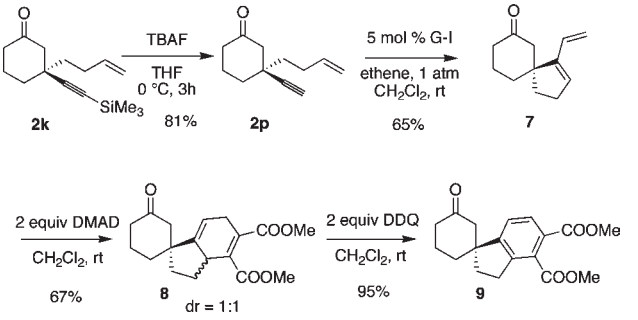


To determine the limitation of this methodology, we synthesized enynone **1f** possessing a terminal alkyne. Slight modifications of the methodology gave a very interesting result since we observed the formation of the 1,4 and 1,6 adducts in equal quantities. An enantioselectivity of 91% was detected for adduct **2p** (Scheme 3). This result highlighted the power of this catalytic system since even with the 1,6 position completely naked the 1,4 attack occurred.

Scheme 3



Scheme 4. Sequence Ene-Yne Methathesis/Diels−Alder/Aromatization Reaction



In order to illustrate the synthetic potential of the 1,4 adducts, possessing an acetylenic appendage, a sequence ene-yne methathesis/Diels−Alder/aromatization was

investigated (Scheme 4). After deprotection of **2k** under classical reaction conditions, **2p** was submitted to a Grubbs I catalyst in the presence of an ethylene atmosphere.[14] The spiro-bicyclic compound **7** was formed in 65% yield. This intermediate was applied to the Diels−Alder reaction using DMAD as a dienophile. Unfortunately, a 1:1 diastereomeric mixture was observed for compound **8**. Therefore this system has been easily rearomatized affording compound **9** in a quantitative yield.

In summary, we have developed a highly stereoselective and regioselective 1,4 addition of Grignard reagents to cyclic enynones with excellent ee values for an all-carbon quaternary stereocenter. Development of the 1,6 addition on this type of substrate is being pursued in our laboratories and will be published in the future.

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Supporting Information Available. Experimental procedures and spectral analyses of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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