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Enantioselective and Regiodivergent Copper-Catalyzed Conjugate Addition of Trialkylaluminium Reagents to Extended Nitro-Michael Acceptors

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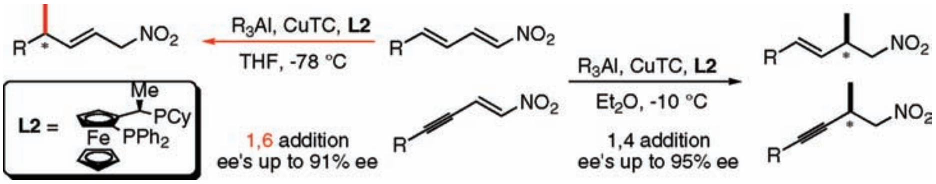
ABSTRACT



The first highly enantioselective and regiodivergent conjugate addition of trialkylaluminium reagents to nitrodienes and nitroenynes is described. By a design of the substrate and a fine-tuning of the reaction conditions, it is possible to selectively form the 1,4- or 1,6-adduct. The same combination of catalyst, copper source, and a ferrocene-based phosphine ligand afforded enantioselectivities up to 95% and 91%, respectively.

The conjugate addition has been widely studied in organic synthesis and has proven to be a very powerful tool for the generation of carbon−carbon bonds. The asymmetric 1,4-addition of organometallic reagents has been described with many catalysts, particularly Cu and Rh, and a wide range of Michael acceptors can react with high regioselectivity (1,4 versus 1,2) and stereoselectivity.[1] Recently, we turned our attention to extended Michael acceptors, which are more challenging substrates due to the presence of various electrophilic sites, which upon nucleophilic attack can lead to several regioisomers.[2] Copper reagents react preferentially in a 1,6-manner to $\alpha,\beta,\gamma,\delta$-unsaturated Michael acceptors as shown by Krause.[3] However, Yamamoto has shown that a fine-tuning of the copper reagent allows regioselective 1,4- or 1,6-addition.[4] In 2006, Fillion reported a copper-catalyzed 1,6-addition employing diorganozinc reagents and Meldrums acid as substrate. High enantioselectivities up to 84% were obtained.[5] Two years later, Feringa also demonstrated a highly enantioselective 1,6-asymmetric conjugate addition (ACA) to $\alpha,\beta,\gamma,\delta$-unsaturated esters using ferrocene-based phosphine ligands and $CuBr{\cdot}Me_2S$ as the catalyst combination.[6] Recently, our group has described a regiodivergent 1,4- versus 1,6-asymmetric copper-catalyzed conjugate addition to cyclic dienone, showing intriguing results.[2] Using a combination of Grignard reagent with N-heterocyclic carbene (NHC) resulted in the highly enantioselective formation of the 1,4-adduct on the most substituted position. This result contradicts the observed general trend that

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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) Henon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122.

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

(4) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119.

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

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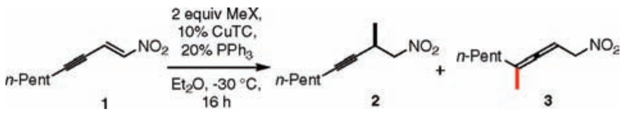
nucleophilic attack usually leads to the 1,6-addition. Other metals behave similarly. Thus, Hayashi reported the rhodium-catalyzed 1,6-addition of aryltitanates to cyclic enynones to afford chiral allenes.[7] The same group subsequently described the use of Rh/binap catalyst in the 1,6-addition of diarylzinc reagent to cyclic dienones.[8]

In this report, we detail an unprecedented regiodivergent and enantioselective copper-catalyzed conjugate addition of trialkylaluminium reagents to nitrodienes and nitroenynes as Michael acceptors. These kind of substrates have been recently employed in our group for organocatalyzed 1,4-addition.[9] Nitroalkenes are among the most reactive Michael acceptors and therefore have been extensively studied in the field of transition metal catalysis and organocatalysis.[10] Many groups have contibuted in the Cu-catalyzed asymmetric conjugate addition to nitroolefins.[11] From a synthetic point of view, the nitrogroup can act as a masked functionality and can be transformed into various functional groups, which enlarges its synthetic value.[12]

We first examined the addition of three different types of organometallic reagents to nitroenyne **1** catalyzed by a combination of CuTC (Copper Thiophene 2-Carboxylate) and PPh$_3$ (Table 1). This result demonstrated that the strength of the organometallic reagent has an important effect in terms of regioselectivity. Grignard reagents, the strongest nucleophiles, exclusively afforded compound **2** via the 1,4-addition (Table 1, entry 1). Conversely, the addition of dimethylzinc, the least reactive nucleophile, displayed a strong tendency for the 1,6-adduct formation (Table 1, entry 3). As an intermediate, trimethylaluminium mainly gave the 1,4-adduct (Table 1, entry 2). These observed trends show that the 1,4-addition regioselectivity is favored by strongly nucleophilic reagents.

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



entry	organometallic source	convn [%][a]	2/3[a]
1	MeMgBr	100	100/0
2	Me$_3$Al	100	68/31
3	Me$_2$Zn	100	18/82

[a] Determined by GC-MS.

To carry out this reaction in an asymmetric fashion, we screened various chiral ligands, using different reaction conditions and nucleophiles (Figure 1, Table 2).

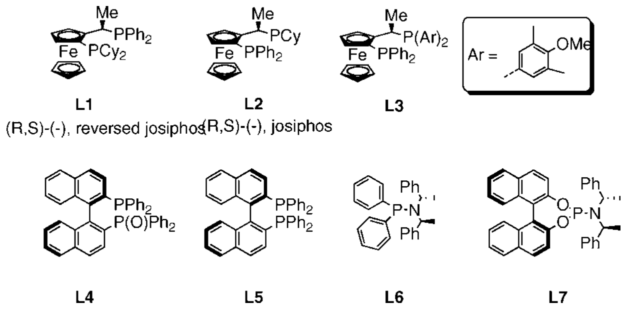
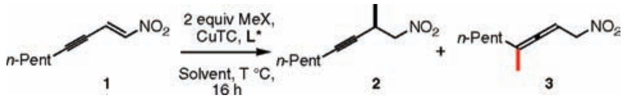


Figure 1. Chiral ligands used in this work.

We initially evaluated the reactivity of three different organometallic reagents in the presence of the ferrocene-based phosphine ligand **L1** and CuTC as catalyst. As expected, MeMgBr afforded the 1,4-adduct exclusively, but only racemic mixtures were obtained (Table 2, entry 1). The addition of Me$_2$Zn afforded the 1,4-adduct and the 1,6-adduct with a ratio close to 1:1 and an enantioselectivity of 86% for the 1,4-adduct (Table 2, entry 2). No enantioselectivity was detected for the 1,6-product. The ease of racemization of allenes in the presence

Table 2. Optimization for the Enantioselective 1,4-Addition of Trimethylaluminium to Nitroenyne **4**[a]



entry	reactant	t [°C]	L*	convn [%][b]	2/3[b]	ee[c] 1,4/1,6
1	MeMgBr	−30	**L1**	100	100:0	0/–
2	Me$_2$Zn	−30	**L1**	100	42:58	86/0
3	Me$_3$Al	−30	**L1**	27	100:0	87/–
4	Me$_3$Al	−10	**L1**	100	100:0	89/–
5	Me$_3$Al	−10	**L3**	100	100:0	14/–
6	Me$_3$Al	−10	**L2**	100	100:0	95/–
7[d]	Me$_3$Al	−10	**L2**	100	100:0	95/–
8[e]	Me$_3$Al	−10	**L2**	100	100:0	9/–
9[f]	Me$_3$Al	−10	**L2**	100	100:0	94/–
10[f]	Me$_3$Al	−30	**L2**	100	100:0	94/–

[a] Reaction performed with CuTC/**L** = 5/10 mol % in Et$_2$O. [b] Determined by GC-MS. [c] Determined by GC on a chiral phase. [d] Reaction performed with CuTC/**L** = 5/5.25 mol % in 10 min. [e] CH$_2$Cl$_2$ was used as solvent. [f] THF was used as solvent.

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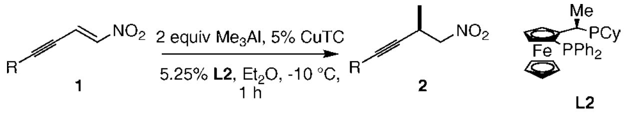
of copper may explain this result.[13] Using Me$_3$Al, we were pleased to observe a perfect regioselectivity in favor of the 1,4-adduct and high level of enantioselectivity (Table 2, entry 3), with, however, a low conversion at −30 °C. By increasing the temperature to −10 °C, the formation of the 1,4-adduct was quantitative, and the enantiomeric excess improved to 89% (Table 2, entry 4). Next, the stereochemical outcome was examined by screening various chiral ligands. Pleasingly, the ferrocene type ligand, Josiphos **L2**, was found to induce almost perfect levels of enantioselectivity (95% ee, Table 2, entry 6). Ligands **L4**−**L7** al gave inferior results. The catalyst/ligand ratio could be reduced to 5/5.25% without losing on enantioselectivity. Moreover, the reaction was complete within 10 min due to the high reactivity of this extended nitro Michael acceptor (Table 2, entry 7). A solvent screening was also performed: CH$_2$Cl$_2$ led to a significant drop in terms of enantioselectivity (Table 2, entry 8), whereas THF displayed similar levels of enantioselectivity as observed for diethylether, despite a longer reaction time of 16 h (Table 2, entry 9). Decreasing the reaction temperature to −30 °C did not afford any improvement in terms of enantiomeric excess (Table 2, entry 10). The general trend (1,6-addition), usually observed in copper catalysis, that commonly uses primary organometallics and chiral ligands with $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compounds seemed not to be applicable to this catalytic system. This less typical regioselectivity has already been noticed in some cases,[14,2] but Krause reported that nitroenynes react with lithium cuprates by exception, leading to the formation of the 1,4-adduct exclusively.[13c]

With the optimized condition in hand, we turned our attention to the scope of the reaction. First, several nitroenynes were tested with various alkyl and aromatic groups. A perfect regioselectivity was obtained in favor of the 1,4-adduct in every case with high enantioselectivity ranging from 88 to 95% and good isolated yields between 50 and 74% (Table 3). Phenyl-substituted nitroenyne (Table 3, entry 2) displayed a similar enantioselectivity as in the case of the alkyl-substituted species (Table 3, entries 1 and 4). However, when the aryl moiety possessed an electron-donating group in the para position, the enantioselectivity decreased to 83% (Table 3, entry 6). This is not the case when an electron-withdrawing group is on the same position (Table 3, entries 5 and 8). The aryl nitroenyne derivative bearing an isopropyl group at the ortho position showed a decrease in ee by comparison with the phenyl derivative, reflecting probably the influence of the steric hindrance (Table 3, entry 10). Among the alkyl groups it must be noticed that functionalized groups are perfectly tolerated (Table 3, entry 7).

Table 3. Conjugate Addition of Trimethylaluminium to Nitroenyne **1a**−**j**[a]

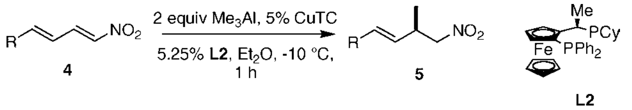


entry	1	R	convn [%][b]	yield [%]	ee 1,4 [%][c]
1	**1a**	*n*-pent	100	56 (**2a**)	95
2	**1b**	Ph	100	70 (**2b**)	94
3	**1c**	Cy	100	74 (**2c**)	90
4	**1d**	*t*-Bu	100	55 (**2d**)	95
5	**1e**	*p*-BrC$_6$H$_4$	100	64 (**2e**)	95
6	**1f**	*p*-OMeC$_6$H$_4$	100	54 (**2f**)	83
7	**1g**	CH$_2$OBn	100	65 (**2g**)	93
8	**1h**	*p*-CF$_3$C$_6$H$_4$	100	52 (**2h**)	90
9	**1i**	SiMe$_3$	100	69 (**2i**)	95
10	**1j**	*o*-*i*Pr C$_6$H$_4$	100	62 (**2j**)	88

[a] All reactions performed with **1** (0.5 mmol), Me$_3$Al (2 equiv), CuTC/**L2** = 5/5.25 mol % in Et$_2$O at −10 °C. [b] Determined by GC-MS. [c] Determined by GC or SFC on a chiral phase.

Then, we switched our attention to the addition of trimethylaluminium reagents to nitrodiene (Table 4). Here, also, the general trend in terms of regioselectivity was observed. MeMgBr afforded exclusively the 1,4-adduct without enantioselectivity (Table 4, entry 1), whereas Me$_3$Al displayed a perfect regioselectivity in favor of the 1,4-adduct with high levels of enantioselectivity of 88% (Table 4, entry 3). Dimethylzinc reacted sluggishly but only at room temperature, affording a mixture of the 1,4- and the 1,6-adduct (Table 4, entry 2). We then analyzed the scope of this reaction using different nitrodienes. The cyclohexyl-substituted nitrodiene **4e** gave the best enantioselectivity (90% ee, Table 4, entry 8), whereas the *para*-methoxy aryl-substituted derivative **4b** displayed the lowest (77%) as already observed with the nitroenyne analogue **1j** (Table 3, entry 6). In general, the stereoselectivity obtained with nitrodienes afforded slightly lower enantioselectivity than nitroenynes.

Table 4. Conjugate Addition of Trimethylaluminium to Nitrodiene **4a**−**f**[a]



entry	4	R	convn [%][b]	yield [%]	ee [%][c] 1,4
1[d]	**4a**	Ph	100	nd (**5a**)	0
2[e]	**4a**	Ph	70	nd (**5a**)	70
3	**4a**	Ph	100	70 (**5a**)	88
4	**4b**	*p*-OMeC$_6$H$_4$	100	50 (**5b**)	77
5	**4c**	*p*-Cl C$_6$H$_4$	100	55 (**5c**)	84
7	**4d**	*i*-Pr	100	67 (**5d**)	90
8	**4e**	Cy	100	59 (**5e**)	90

[a] All reactions performed with **1** (0.5 mmol), Me$_3$Al (2 equiv), CuTC/**L*** = 5/5.25 mol % in Et$_2$O at −10 °C. [b] Determined by GC-MS. [c] Determined by GC or SFC on a chiral phase. [d] MeMgBr used. [e] Me$_2$Zn used at room temp., ratio 1,4/1,6 = 72: 28 (see text).

To explore the scope of the nucleophiles for the reaction, we investigated the addition of different trialkylaluminium reagents to nitroenyne **1b** (Table 5).

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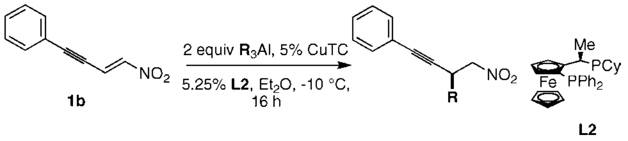
Table 5. Conjugate Addition of Trialkylaluminium to Nitroenynes **1b**[a]



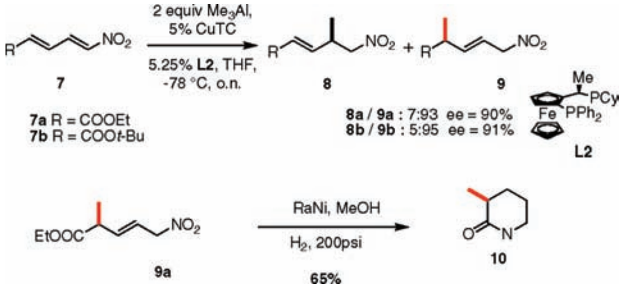
entry	R	product	convn [%][b]	ee [%][c] 1,4	yield [%]
1	Me	**2b**	100	94	70
2	Bu	**6b**	100	71	65
3	Et	**6c**	100	62	53
4	*n*Pr	**6d**	100	60	68
5	*i*Bu	**6e**	100	6	55

[a] All reactions performed with 1 (0.5 mmol), R_3Al (2 equiv), CuTC/**L*** 5/5.25 mol % in Et_2O at −10 °C during 16 h. [b] Determined by GC-MS. [c] Determined by GC or SFC on a chiral phase.

In contrast to the addition of Me_3Al, lower levels of enantioselectivity were obtained, and the reaction rate was slower. Linear trialkylaluminium species afforded moderate enantioselectivities (60−71%) (Table 5, entries 2−4). The very crowded triisobutylaluminum reagent lead to almost complete loss of asymmetric induction (Table 5, entry 5). The detrimental effect of bulky alkylaluminum reagents in the ACA employing nitroalkenes as Michael acceptors has already been observed by others.[15] At this point, we have uncovered a highly enantioselective and regioselective 1,4-addition to extended nitro Michael acceptors, opening up a range of methyl-substituted chiral nitro compounds bearing an unsaturation at the γ,δ position. A complementary approach to synthesizing chiral nitroalkyne adducts has also been described by Tomioka using the conjugate addition of arylalkynyl lithium reagents to nitroolefins.[16]

To explore the limitations in terms of regioselectivity, we synthesized substrates **7a** and **7b** which allow two possible 1,4-additions (Scheme 1). In line with the electron-withdrawing ability of esters versus nitro group, no conjugate addition toward the ester-acceptor group has been observed, and the major product turned out to be the 1,6-adduct with respect to the nitro group. This switch in regioselectivity from 1,4- to 1,6-addition has been unexpected but might be rationalized by invoking a coordination of the carbonyl moiety to the catalyst. This coordination would then facilitate the reductive elimination to proceed at the δ rather than the β position. For both adducts **9a**/**9b**, good regioselectivities and high ee’s have been obtained.

Scheme 1. 1,6-Addition to Nitrodienoate **7a**,**b**



To prove the versatility of the nitro group in synthesis, we performed a reduction/cyclization tandem reaction to afford lactam **10** containing a tertiary stereogenic center.

In conclusion, we have developed a highly enantioselective and regiodivergent 1,4/1,6-asymmetric conjugate addition of trimethylaluminium to $\alpha,\beta,\gamma,\delta$-unsaturated nitro compounds. Mechanistic studies and further applications of the hereby developed methodology are being pursued in our laboratories and will be published in due time.

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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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