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Catalytic Regio- and Enantioselective Alkylation of Conjugated Dienyl Amides

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Table 1: Optimization of the enantioselective 1,6-addition of EtMgBr to the substrate **1a**.^[a]

Entry	Solvent	T [°C]	Cu/L	LA	2a/3a ^[b,c]	ee [%] ^[d,e] 2a
1	CH ₂ Cl ₂	0	—	—	2:98 (38)	n.d.
2	CH ₂ Cl ₂	−78	—	—	—	—
3	CH ₂ Cl ₂	0	L1	—	9:91 (nd)	n.d.
4	CH ₂ Cl ₂	−78	L1	—	—	—
5	CH ₂ Cl ₂	−78	—	BF ₃ ·Et ₂ O	—	—
6	CH ₂ Cl ₂	−78	L1	BF ₃ ·Et ₂ O	94:6 (92)	85
7	CH ₂ Cl ₂	−78	L1	TMSOTf	33:67 (58)	72
8	CH ₂ Cl ₂	−78	L1	TMSBr	41:59 (nd)	n.d.
9	CH ₂ Cl ₂	−78	L1	TBSOTf	68:32 (nd)	n.d.
10	CH ₂ Cl ₂	−78	L2	BF ₃ ·Et ₂ O	99:1 (93)	54
11	CH ₂ Cl ₂	−78	L3	BF ₃ ·Et ₂ O	95:5 (90)	86
12	MTBE	−78	L1	BF ₃ ·Et ₂ O	90:10 (60)	90
13	Et ₂ O	−78	L3	BF ₃ ·Et ₂ O	87:13 (51)	86
14	Et ₂ O	−78	L1	BF ₃ ·Et ₂ O	93:7 (66)	93
15 ^[f]	Et ₂ O	−78	L1	BF ₃ ·Et ₂ O	96:4 (81)	95

[a] Reaction conditions: the LA (2 equiv), EtMgBr (2 equiv), ligand **L** (6 mol %), CuBr·SMe₂ (5 mol %), and **1a** (0.2 mmol) in 2 mL of solvent. [b] 1,6/1,4 ratio was determined by ¹H NMR spectroscopy. [c] The values in brackets are yields for the isolated products. [d] The ee values were determined by HPLC using a chiral stationary phase. [e] The absolute configuration was determined by conversion of **2a** into a known compound (see the Supporting Information). [f] 3 equiv of BF₃·Et₂O was used in this case. MTBE = methyl *tert*-butyl ether, TBS = *tert*-butyldimethyl silyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

crude reaction mixture revealed predominant formation of the 1,6-addition product **2a**. Furthermore, **2a** was obtained with a promising enantioselectivity of 85 %. Encouraged by these results we investigated the effect of the type of LA, the catalyst structure, and the nature of the solvent on the stereochemical outcome, and on the overall reactivity of the catalytic system. The silicon-based LA led to worse reaction outcomes with decreased regioselectivity, as well as reduced enantioselectivity (entries 7–9). A screening of chiral ligands for the copper catalyst (only selected examples are shown) revealed the ferrocenyl-based ligand **L1** to be the best choice in terms of enantioselectivity, while similarly high levels of regioselectivities were obtained for most other chiral ligands (entries 6, 10, and 11). Importantly, switching from dichloromethane to ethereal solvents was detrimental for the reactivity, leading to lower substrate conversion, but it was beneficial for the stereochemical outcome of the reaction when using ligand **L1** (entries 12–14). In particular, when the reaction was carried out in diethyl ether the regioselectivity of the addition reaction remained practically the same but the

enantioselectivity increased to 93 % (entry 14). Finally, increasing the LA amount to 3 equivalents led to higher reaction rates and higher selectivities, namely a regioselectivity of 1,6/1,4 = 96:4, 81 % yield upon isolation, and an excellent enantioselectivity of 95 % for **2a** (entry 15).

With the optimized set of reaction conditions in hand, we investigated the generality of this methodology and the results of this scope study are shown in Schemes 2 and 3. Generally speaking, this catalytic and highly regio- and enantioselective reaction reaches nearly full conversion in 10–16 hours when using 5 mol % of Cu/**L1**, with regioselectivities above 90 %, and in some cases even reaching 100 %. A broad substrate and organomagnesium reagent scope is tolerated, and we observed an interesting correlation between substrate substituents and regioselectivity as detailed below.

Evaluation of the addition reaction using EtMgBr and various dienyl amides, differing by the substituent at the δ -position, revealed a strong influence of the substitution pattern on the regioselectivity (Scheme 2). Addition reactions with amide substrates featuring linear, as well as functionalized aliphatic substituents, at the δ -position led predominantly to (more than 90 %) 1,6-adducts (**2a–e**) with high yields and enantioselectivities (80–99 %). In contrast, highly regioselective 1,4-addition (more than 92 %) was observed with amide substrates featuring electron-rich and electron-poor aromatics, heteroaromatics, and branched aliphatic substituents at the δ -position. The corresponding 1,4-adducts **3k–3p** were obtained with high yields and excellent 94 to 99 % enantioselectivities.

Next, we studied substrates with various substituents on N, using dienyl amides with a linear aliphatic substituent at the δ -position (Scheme 2). We found that incorporation of various substituents at N is well tolerated and excellent selectivities and yields were obtained for N-dialkyl-, N-phenyl-N-methyl-, N-diallyl-substituted compounds (**2a**, **2j**, **2g**, and **2h**). Importantly, the addition to morpholine-substituted enamide leads to the 1,6-addition product **2f** with a 78 % yield upon isolation and 91 % ee, and it is amenable to further synthetic transformations. Remarkably, even the addition of EtMgBr to a secondary amide bearing an acidic proton was possible. Also in this case the corresponding 1,6-addition product **2i** was obtained with high regio- and enantioselectivity.

Having established the substrate scope, we moved to assess the scope with respect to the organomagnesium reagents. For this purpose we selected two substrates, the aliphatic dienyl amide **1a** and aromatic dienyl amide **1k**, as substrates to study both 1,6- and 1,4-additions, respectively (Scheme 3). Our catalytic system enables the introduction of organomagnesium reagents of various chain lengths, for example, Et, *n*Bu, *n*Hex, and *i*Pent, affording the corresponding products **4a–6a** with high regio- and enantioselectivities as well as yields. When using β -branched organomagnesium reagent, the increase in steric hindrance caused by the branching led to diminished enantioselectivity (76 %) for the product **7a**. No reaction was observed with PhMgBr under various reaction conditions.

Methylations have always been challenging because of the diminished reactivity of the corresponding organometallics compared to those with a higher number of carbon atoms.^[10]

Scheme 2. Scope of the reaction with respect to dienyl amides. Reaction conditions: BF₃·Et₂O (3 equiv) and EtMgBr (2 equiv), L1 (6 mol %), CuBr·SMe₂ (5 mol %), and dienyl amide (0.2 mmol) in diethyl ether at -78 °C overnight. Yields are those for the isolated products. The ee values were determined using chiral-phase HPLC. The 1,6/1,4 ratios were determined by ¹H NMR spectroscopy. [a] The absolute configuration was determined by conversion into a known compound (see the Supporting Information). [b] CH₂Cl₂ (2 mL) and TMSOTf (2 equiv) were employed instead of Et₂O and BF₃·Et₂O, respectively, to enhance the substrate conversion.

We were pleased to observe smooth addition of MeMgBr to the natural product piperine, providing the addition product **4p** with excellent 1,4-regioselectivity and a remarkable enantioselectivity of more than 99% (Scheme 3).

Next we extended our methodology to nucleophilic additions to dicarboxylic acid derivatives, namely to the carboxamide derivative of muconic acid **1q** (Scheme 4a). This substrate represents some challenges with respect to the control of both reactivity and selectivity. Therefore we were pleased to find that by using our catalytic system, addition of various organomagnesium reagents to this demanding substrate affords predominantly the 1,6-addition products **2q–4q** (more than 95%) with enantioselectivities above 95% and high yields.

Scheme 3. Scope of the reaction with respect to organomagnesium reagents. Reaction conditions: BF₃·Et₂O (3 equiv), EtMgBr (2 equiv), L1 (6 mol %), CuBr·SMe₂ (5 mol %), and dienyl amide **1** (0.2 mmol) in 2 mL diethyl ether at -78 °C overnight. Yields are those for the isolated products. The ee values were determined using chiral-phase HPLC. The 1,4/1,6 ratios were determined by ¹H NMR spectroscopy. [a] CH₂Cl₂ (2 mL) and TMSOTf (2 equiv) were employed instead of Et₂O and BF₃·Et₂O, respectively, to enhance the substrate conversion.

Scheme 4. Application of the methodology: a) to conjugate addition of organomagnesium reagents to carboxamide derivative of (2E,4E)-muconic acid **1q** and b) towards the synthesis of the natural product penicillenol A.

Finally, we applied our methodology to the synthesis of an important precursor (**8**) for the synthesis of the natural product Penicillenol A (Scheme 4b).^[11] The compound **8** was obtained in two steps, namely catalytic asymmetric 1,6-addition to **1a**, followed by the oxidation of the double-bond product **5a**.^[12]

In summary, we developed the first catalytic asymmetric addition of organometallics to various dienyl carboxamides

leading to α -, β -, or δ -substituted chiral functionalized amides with excellent 1,6- or 1,4-regioselectivities. The combination of Lewis acid activation and the high reactivity of reagents lies at the basis of this feat, as it overcomes the low reactivity of the amide substrates. Although the substrate structure can strongly affect the regioselectivity outcome we have shown that under our catalytic conditions almost exclusively one regioisomer is formed with excellent enantioselectivity.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · conjugation · copper · Lewis acids · regioselectivity

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