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Enantioselective 1,6-Conjugate Addition to Cyclic Dienones Catalyzed by the Cu−DiPPAM Complex

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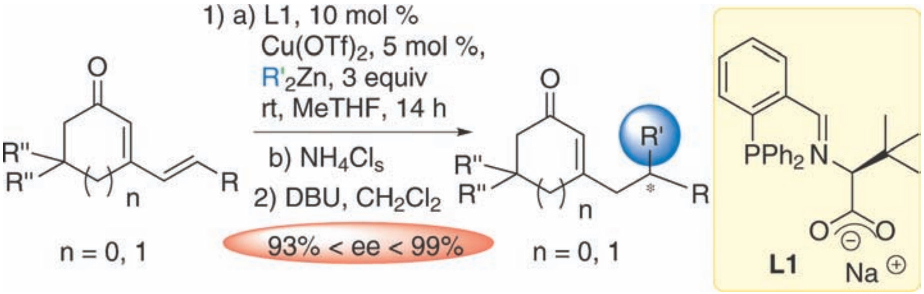
ABSTRACT



In the presence of a Cu/DiPPAM catalytic system, various diorganozinc reagents realize 1,6-asymmetric conjugate addition on various cyclic five- and six-membered cyclic dienones, with complete regioselectivity and high ee's (93−99%).

Due to increasing economic and ecological pressure, the design of readily available and efficient chiral ligands has become a new challenge of modern asymmetric organometallic catalysis. In this context, our group has recently developed original, "one-step and quantitatively available" ligands—the diphenylphosphinoazomethinylate salts (DiPPAMs).[1] Structurally related to "small peptide ligands",[2,3] the DiPPAMs have already proved their efficiency for two C−C bond-forming reactions: copper-catalyzed 1,4-asymmetric conjugate addition (ACA)[1] and palladium-catalyzed allylic alkylation.[4] High enantioselectivities combined with unusual behavior encouraged us to focus on a much less explored reaction—copper-catalyzed 1,6-ACA. In fact, the challenge of this reaction is due to the presence of an additional electrophilic site and the possibility of forming regioisomers.[5] The first example of the asymmetric version of this reaction was disclosed in 2005 by

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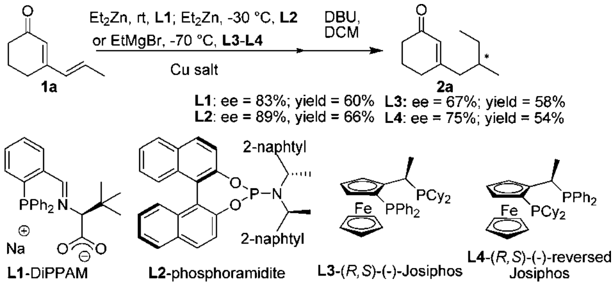
Hayashi using the Rh−BINAP complex.[6] The same group reported in 2010 an Ir−tbf catalytic system for the 1,6-addition of arylboroxines to linear dienones.[7] Moreover, several reports have appeared on copper-catalyzed 1,6-ACA to both cyclic and linear substrates.[8] Those publications, as well as previous studies on an achiral version of copper-catalyzed 1,6-CA,[5] suggest that nucleophilic attack usually leads to the 1,6-adducts. However, recent results reported by Alexakis seem to contradict this observation.[9] Alexakis observed that the regioselectivity of the ACA to $\alpha,\beta,\gamma,\delta$-unsaturated six-membered cyclic dienone **1a** depends on the nature of the nucleophile and the chiral ligand; 1,6 regioselectivity was observed if Et_2Zn or Et_3Al was used in the presence of a Cu−phosphoramidite complex, whereas the 1,4-adduct was isolated when Grignard reagents were employed in the presence of a Cu−NHC catalyst. Hoveyda reported, as well, one example of the 1,4-selectivity for the addition of Me_2Zn to dienone catalyzed by an iminopeptide−Cu complex.[10] Those studies show that copper-catalyzed 1,6-ACA to cyclic substrates, and in particular five-membered cyclic dienones, never reported in the literature, is still underdeveloped. Moreover, the resulting products, original Michael acceptors, could have great potential in synthesis. Thus, we explored the potential of DiPPAM in 1,6-ACA, and we report herein the regio- and enantioselective addition of diorganozinc to five- and six-membered functionalized cyclic dienones.

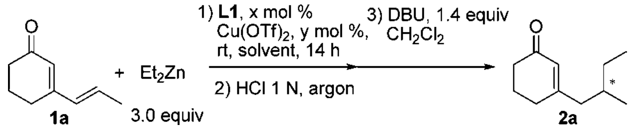
The first test reaction with Cu−**L1** led to the formation of the desired product **2a** (after reconjugation in the presence of DBU) with total regioselectivity, as expected, and 83% ee (Scheme 1). This nonoptimized result was slightly worse than the unique reported example, −89% ee, obtained with the Cu−**L2** catalyst.[9] The Josiphos-type ligands (**L3** and **L4**), particularly efficient in 1,6-ACA to linear dienoates,[8c] for this selected reaction were totally regioselective but seemed to be less enantioselective (**L3**, 67% ee; **L4**:, 75% ee; Scheme 1). Thus, **L1** could be considered as a highly promising ligand for this transformation.

Scheme 1. Cu-Catalyzed 1,6-ACA on Cyclic Dienone **1**



Indeed, the optimization of the experimental conditions enabled us to increase the enantiocontrol of this reaction. The choice of the cosolvent (33% of the solvent is hexanes from the commercial Et_2Zn solution) was crucial for an efficient enantiocontrol. The reactions, carried out in both Et_2O and *t*-BuOMe, afforded **2a** with moderate ee's (Table 1, entries 2 and 3), whereas the use of toluene or AcOEt gave **2a** with ee > 80% (Table 1, entries 4 and 5). The best result, 87% ee, was obtained in MeTHF (Table 1, entry 6). The Cu/DiPPAM ratio also has a very important influence on the enantioselectivity of the reaction. The excess of Cu toward the ligand led to a drastic decrease of the ee (Table 1, entry 7). On the contrary, when the Cu/DiPPAM ratio was inferior to 1, an improvement of the enantioselectivity was observed (Table 1, entries 8−10). Nevertheless, the reaction performed in the absence of $Cu(OTf)_2$ did not afford any product, thus the necessity of the presence of the metal was demonstrated (Table 1, entry 11).

Table 1. Optimization of Experimental Conditions



entry	*x* %	*y* %	solvent	convn (%)[a]	ee (%)[b]
1	5	5	THF	>99	83
2	5	5	Et_2O	98	63
3	5	5	*t*-BuOMe	83	56
4	5	5	toluene	98	80
5	5	5	AcOEt	>99	84
6	5	5	MeTHF	>99	87
7	5	10	MeTHF	>99	56
8	6	5	MeTHF	>99	91
9	7.5	5	MeTHF	>99	93
10	10	5	MeTHF	>99	94
11	10	-	MeTHF	-	-
12[c]	10	5	MeTHF	>99	96
13[c,d,e]	10	5	MeTHF	>99	97

[a] Determined by GC-MS analysis. [b] Determined by GC analysis. [c] Reaction performed at 0 °C. [d] Addition of a Et_2Zn solution in MeTHF.[11] [e] Reaction treatment: NH_4Cl_s, argon.

The additional improvement of the enantioselectivity was reached through a decrease of the reaction temperature to 0 °C and the use of a Et_2Zn solution in MeTHF (Table 1, entries 12 and 13).[11] Unsurprisingly, the desired reaction was accompanied by the formation of a small amount of the oxidative byproduct.[9,12] To prevent this, a slight modification

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(11) For experimental procedure, see Supporting Information.

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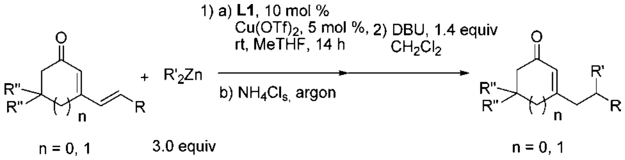
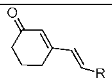
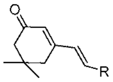
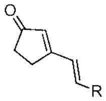
of the treatment procedure was incorporated.[9] The reaction was quenched by the addition of solid NH_4Cl followed by the direct addition of the solution of DBU in CH_2Cl_2 to the reaction mixture.

With the optimized conditions in hand, we turned our attention to the scope of this reaction. Thereby, a panel of five- and six-membered cyclic substrates was prepared by modifying the hindrance at the δ position, introducing substitution on the ring or introducing a supplementary functional group. Additionally, different organozinc reagents were used, including the noncommercial functionalized $Zn((CH_2)_3OAc)_2$.[13] The results are summarized in Table 2.

Table 2. Cu/DiPPAM-Catalyzed 1,6-ACA on Various Dienones

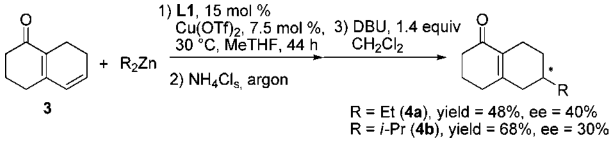


ent	substrate	R	R'	yield (%)	ee (%)
1^{a,d}		Me (**1a**)	Et	75 (**2a**)	97
2^{d}		Me (**1a**)	*n*-Bu	79 (**2b**)	97
3^{b,d}		Me (**1a**)	*i*-Pr^{g}	71 (**2c**)	97
4^{c,d}		*n*-Bu (**1b**)	Et	63 (**2d**)	95
5^{d}		Me (**1c**)	*n*-Bu^{g}	66 (**2e**)	> 95
6^{d}		Me (**1d**)	Et	70 (**2f**)	99
7^{d}		Me (**1d**)	*n*-Bu	75 (**2g**)	99
8^{b,d}		Me (**1d**)	*i*-Pr	84 (**2h**)	99
9^{b,d}		Me (**1d**)	AcO-$(CH_2)_4$	28^{f} (**2i**)	97
10^{b,d}		*n*-Bu (**1e**)	Et	57 (**2j**)	97.5
11^{b,e}		$(CH_2)_2CH(Me)_2$ (**1f**)	Et	63 (**2k**)	95
12^{c,e}		$(CH_2)_2OTBDMS$ (**1g**)	Et	61 (**2l**)	93

[a] Reaction performed at 0 °C. [b] Reaction time = 40 h. [c] Reaction time = 60 h. [d] ee determined by GC. [e] ee determined by HPLC. [f] Formation of byproduct **2a** was observed, due to the presence of Et_2Zn in the crude $Zn((CH_2)_3OAc)_2$. [g] Two treatments with DBU were required.

As expected, the regiocontrol of the reaction was complete in all cases. The isolated yields were moderate to good, which could be explained by the partial volatility of the products and the moderate stability of the substrates. High enantiocontrol was observed with all six-membered cyclic substrates ($95\% < ee \leq 97\%$) (Table 2, entries 1−5). Neither the structure of the dienone nor the type of diorganozinc reagent had an important influence on the ee's. Furthermore, unprecedented results were observed for the five-membered ring substrates (Table 2, entries 6−12). Seven products were isolated with $93\% < ee \leq 99\%$. Cu−DiPPAM catalyst tolerated the silyl ether protecting group of the substrate and the acetoxy group of the diorganozinc reagent (Table 2, entries 9 and 12). The hindrance at the δ position made the reaction more sluggish; nonetheless, a longer reaction time enabled total conversions of starting materials to products (Table 2, entries 4 and 10−12). To explore the tolerance of Cu−DiPPAM catalyst for challenging bicyclic compounds, substrate **3** was prepared.[14] Unfortunately, the results were quite disappointing. Although the regioselectivity of the reaction was complete, the enantiocontrol was moderate for the addition of both Et_2Zn (ee = 40%) and *i*-Pr_2Zn (ee = 30%) (Scheme 2).

Scheme 2. Cu/DiPPAM-Catalyzed 1,6-ACA on Bicyclic Dienone **3**



These results are similar to those reported by Alexakis with **L2** and confirm that bicyclic compounds are very demanding substrates for 1,6-ACA.[9] In summary, we have developed a very efficient catalytic system for copper-catalyzed 1,6-ACA to $\alpha,\beta,\gamma,\delta$-unsaturated five- and six-membered cyclic dienones. Due to the strong tolerance of the Cu/DiPPAM catalyst to numerous, even functionalized, substrates and mild experimental conditions, this method should prove to be of use in the total synthesis of complex molecules. Nevertheless, the design of new ligands should be carried out to develop more efficient catalysts for copper-catalyzed 1,6-ACA on bicyclic compounds.

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

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(14) For the synthesis of **3**, see Supporting Information.