Asymmetric Conjugate Addition Reactions of Meldrum's Acid Derived Acceptors Employing Chiral Phosphoramidite Ligands
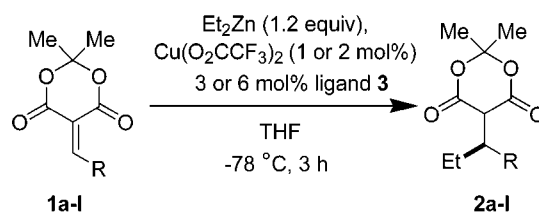
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ABSTRACT

The enantioselective conjugate addition reaction of Et₂Zn to Meldrum's acid derived acceptors, mediated by a catalyst formed from Cu(O₂CCF₃)₂ and a phosphoramidite ligand, is reported. Adducts are obtained in useful yields and up to 94% ee.

The conjugate addition reaction of organometallic reagents to acceptor substrates provides access to a number of useful building blocks for the synthesis of complex molecules. There have been recent exciting advances in this area of synthetic methodology,[1] including both cyclic as well as acyclic acceptors.[2−5] We have initiated a program focused on acceptors derived from the condensation reaction of aldehydes and Meldrum's acid,[6] because these are expected to be reactive acceptors[7] and the subsequent product hydrolysis to the acid is anticipated to be easy. Herein we report preliminary studies involving the addition of Et₂Zn to a wide range of Meldrum's acid derived acceptors in up to 94% ee.

Based on the impressive results reported by Feringa, we decided to focus on the use of BINOL-derived phosphoramidite ligands in Cu-catalyzed additions of Et₂Zn to Meldrum's acid derived acceptors. The work of Alexakis on conjugate additions suggested that a screening of Cu-salts could also be of significance.[2m] In initial experiments involving Et₂Zn additions to **1a** with ligand **5** and a variety of Cu salts, we observed the following selectivities for **2a**

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(3) For early reports on the Cu-catalyzed additions of organozinc reagents, see: (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368−3370. (b) Lipshutz, B. H.; Wood, M. R.; Tirado, R. *J. Am. Chem. Soc.* **1995**, *117*, 6126−6127.
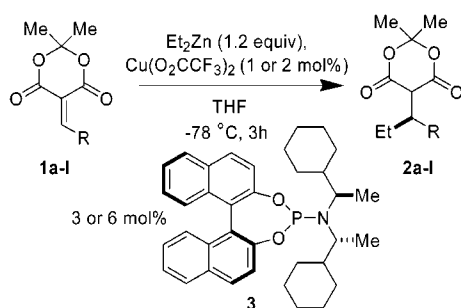
Scheme 1
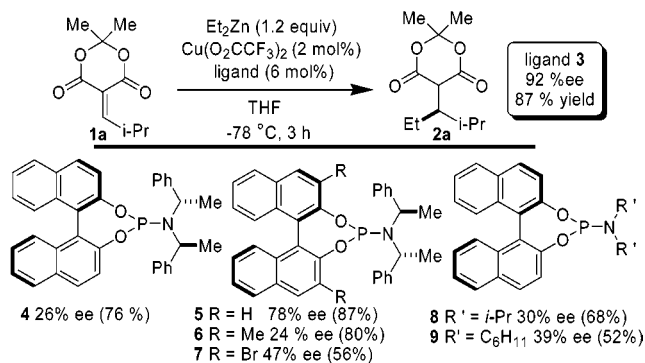
Scheme 1

(Scheme 1): Cu(OTf)$_2$, 71% ee; Cu(OAc)$_2$·H$_2$O, 76% ee; Cu(O$_2$CCF$_3$)$_2$, 78% ee; CuTC, 81% ee (TC: 2-thiophene carboxylate). Although the best Cu salt proved to be CuTC, the convenience of using the trifluoroacetate salt as well as the fact that in other test cases the difference in selectivity compared to CuTC was minimal led us to employ Cu(O$_2$CCF$_3$)$_2$ in subsequent studies.

A particularly attractive feature of the phosphoramidite ligands is the convenience with which its structure can be varied. We thus screened a number of phosphoramidites with the aim of identifying a ligand that gave highest enantioselectivity. It is interesting to note that in the addition of Et$_2$Zn to **1a** the use of the phenethylamine ligand **4** that has been most commonly employed was not optimal; instead, the use of the (*R*,*R*)-bis-(1-cyclohexylethyl)amine analogue **3** furnished optimal enantioselectivity (Scheme 2). To the

Scheme 2

Scheme 2

best of our knowledge, ligand **3** has not been previously reported in conjugate addition reactions.

As shown in Table 1 and Scheme 2, the conjugate addition reaction can be carried out with a wide range of Meldrum's

Table 1. Et$_2$Zn Additions to Meldrum's Acid Derived Acceptors[a]

entry	substrates (R)		yield (%)	ee (%)	major isomer
1	*i*-Pr	**1a**	87	92	*R*-(−)
2	C$_6$H$_{11}$	**1b**	84	94	*R*-(−)
3	Ph	**1c**	94	40	*R*-(+)
4	C$_6$H$_4$-*p*-OMe	**1d**	71	87	*R*-(+)
5[b]	C$_6$H$_4$-*p*-NMe$_2$	**1e**	89	88	(−)
6	C$_6$H$_4$-*p*-Cl	**1f**	66	44	(+)
7	C$_6$H$_4$-*p*-Br	**1g**	61	45	(+)
8	C$_6$H$_4$-*p*-Me	**1h**	78	47	(+)
9[b]	C$_6$H$_4$-*p*-CF$_3$	**1i**	72	62	(+)
10	2-naphthyl	**1j**	83	67	(+)
11	2-furanyl	**1k**	64	80	(+)
12	2-thiophenyl	**1l**	89	82	(+)

[a] The reactions were conducted at −78 °C in THF with 2 mol % Cu(O$_2$CCF$_3$)$_2$ and 6 mol % **3** with 0.16 mmol of **1a**−**l** and 1.2 equiv of Et$_2$Zn (Scheme 2). [b] 1 mol % Cu(O$_2$CCF$_3$)$_2$ and 3 mol % **3** was used. [c] Enantioselectivity was assayed by chiral HPLC of the anilides derived from **2a**−**l**; see the Supporting Information. [d] For entries 1−4, the configuration of the adducts was correlated to known compounds, for entries 5−12, it was correlated by analogy.

acid acceptors including those bearing aliphatic and aromatic substituents in yields ranging from 61 to 94%. The aliphatic substrates elicit the highest selectivity (92 and 94% ee), while the aromatic substituted acceptors show an interesting trend. Electron-rich aryl groups as substituents on the acceptor afforded the highest enantioselectivity 80−88% ee, with the *p*-dimethylamino substituted arene proving optimal. It is thus interesting that it is not the best acceptor that affords the highest selectivities or yields. These observations are consistent with a transition-state structure in which association of the metal with the carbonyl of the acceptor is critical.

In conclusion, we have expanded the scope of Cu-catalyzed enantioselective conjugate addition reactions of diethylzinc to include Meldrum's acid derived acceptors, which are conveniently accessed through simple condensation reactions. We have found that the previously unreported ligand **3** in combination with Cu(O$_2$CCF$_3$)$_2$ is optimal for selectivity in the conjugate addition, proceeding in up to 94% ee. The study opens up the possibility of using Meldrum's acid derived acceptors in other useful catalytic processes, which are the subject of ongoing investigations at present.

Supporting Information Available: Characterization data for compounds **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) For reference to recent conjugate additions with enolates, see: Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582−2590.

(5) For the addition of arylboronic acids to enones, see: (a) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591−11592. (b) Boiteau, J.-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 681−684.

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