DOI: 10.1002/chem.200801343

Copper-Catalyzed Enantioselective Conjugate Addition of Dialkylzinc Reagents to α' -Oxy Enones

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The Cu-catalyzed asymmetric conjugate addition (ACA) of organozinc reagents to α , β -unsaturated carbonyl groups constitutes a $C-C$ bond forming reaction of great synthetic value because of its mildness and broad functional group tolerance.^[1,2] When using cyclic α , β -unsaturated carbonyls as acceptors, the stereocontrol of the reaction is often remarkable.^[3] However, the acyclic counterparts generally give poor results,[4] likely because of the s-cis/s-trans conformational flexibility inherent to open chain enoyl systems.[2b] In the case of unsaturated aldehydes and esters, the competing 1,2-addition reaction^[5,6] and the reduced reactivity,^[7] respectively, are two additional problems. Another common limitation within this methodology is the high substrate specificity of most catalytic systems; each family of acceptors, or even each set of enone substrates within the enone family, commonly requiring a different optimized catalyst ligand. While the finding of more universal ligands remains a formidable task and much work has been directed towards this goal, $[1, 2]$ the identification of achiral templates that fulfil the criteria of selectivity, generality, and versatility constitutes an alternative approach. To date only a few of such templates are known, namely α , β -unsaturated imides,^[8] N-enoyl oxazolidinones.^[9] and Knoevenagel adducts of malonate^[10] and Meldrum's acid,^[11] and in each case important limitations with regard substrate and alkylzinc generality and/or enantioselectivity prevail.^[12] Here we report α' -oxy enones as a dis-

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- Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801343.

tinct and well suited class of acceptors for the Cu-catalyzed ACA of dialkylzincs that help to solve these problems.

It was reasoned that templates featuring enough reactivity as Michael acceptor and well biased enoyl conformation could best fulfil the chemical and stereochemical requirements, and that acyclic α' -oxy enones^[13] might be suitable candidates in this endeavor. Firstly, the reactivity of enones towards the Cu-catalyzed addition of organozinc reagents appears to be optimal,^[2] secondly, allylic $A^{1,3}$ strain predicted in the s-trans conformation,^[14] specially in quaternary α' silyloxy enones (Scheme 1b), can eventually cancel undesired conformational flexibility (Scheme 1a), and, finally, the ketol moiety in the resulting adducts is a quite versatile group for post-reaction transformations.[15]

Scheme 1. Controlling enoyl conformation.

For initial evaluation, the reaction of $Et₂Zn$ with several α' -oxy enones 4–7 was studied in the presence of complexes formed from Cu(OTf)₂ and chiral ligands 1 ,^[16], 2 ,^[9] and 3 ,^[4d] three representative ligands (see below) with distinct coordination capacity. Except for ligand 1, which led to moderate ee values in the examples tested, results in Table 1 clearly show the decisive role played by groups \mathbb{R}^2 and \mathbb{R}^3 of enone template. Contrary to what was previously observed, $[15]$ the strongly chelating α' -hydroxy enone **5a** $(R^3=H)$ gave low very poor results (entries 4, 6), while the O-silyl protected 4a (entries 3, 5, 7, 8) gave the best ee. Similarly, enone $7g$

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lacking the quaternary carbon center $(R^2=H)$ led to diminished ee values (compare entries 7 and 9) even at lower temperatures. These results indicate the prevalence of steric effects on reaction stereocontrol.

Table 1. Finding the best α' -oxy enone template and conditions.^[a]

	R^3O R^2 R^2	R ¹ $4 - 7$	$+ Et2Zn$ 3 equiv	Cu(OTf) ₂ /L [*] (cat) R^3O solvent, 0 °C R^2		R^2	R^1 $8 - 11$	
Entry	L^*	\mathbf{R}^1	\mathbb{R}^2	R^3	Enone	Product	ee [%][b]	
1	1	PhCH ₂ CH ₂	Me	Et ₃ Si	4a	8a	$45^{[c]}$	
2				H	5a	9a	$64^{[c]}$	
3	2	PhCH ₂ CH ₂	Me	Et ₃ Si	4a	8a	$80^{[d]}$	
4				H	5a	9 _a	$< 5^{[d]}$	
5	3	PhCH ₂ CH ₂	Me	Et ₃ Si	4a	8a	78 (94) ^[d]	
6			Me	H	5a	9 a	12	
7		Ph	Me	Et ₃ Si	4g	8g	94 (94) ^[d]	
8				t BuMe ₂ Si	6g	10 a	90	
9		Ph	Н	Et ₃ Si	7ջ	11 g	72 (84)[d]	

[a] mol% Cu(OTf)₂/L^{*}: (1) 5:10; (2) 5:12; (3) 3:3.6. CH₂Cl₂ as solvent unless otherwise stated; >99% conversion in all cases. [b] Determined by HPLC. $[c]$ Et₂O as solvent. $[d]$ Toluene as solvent.

Given the generally superior behavior of ligand 3 with respect to 2, the former was adopted for exploration of the scope (Table 2). Gratifyingly, yields (typically over 80%) and enantioselectivities (90->95%) were uniformly high for α '-silyloxy enones 4 bearing aliphatic either cyclic, open chain acyclic, or branched chain, being 4f $(R^1=tert$ -butyl) an exception. On the other hand, the $Et₂Zn$ addition to aryl enones $4h$ –n proceeded nicely, in both toluene and CH₂Cl₂, irrespective of the electronic character and bound position of the substituent on the aromatic ring. Of significance, the method is also applicable to substrates bearing functional groups sensitive to more reactive alkylmetals, that is, Grignard reagents.^[17] For instance, the acetoxy $(41,$ entry 12), methoxycarbonyl $(4m,$ entry 13), and acetyl $(4n,$ entry 14) derivatives led to the respective ACA adducts with complete chemoselectivity.

It was subsequently observed that not only $Et₂Zn$, but also the less reactive Me₂Zn, the hindered iPr_2Zn , and longer chain dialkylzinc reagents, such as $Bu₂Zn$, added efficiently to give products 12–14 with ee values in the range 93–98% (Table 3). In addition, the reaction of enones $40/4p$ with $Me₂Zn$ to afford 16/17 documents the suitability of the

Table 2. Reaction of Et₂Zn with β -substituted enones 4 to give 8.^[a]

Entry	Compound	\mathbb{R}^1	Yield $8 [%]^{[b]}$	ee [%] ^[c]
1	a	$PhCH_2CH_2$	84 (86)	94 (78)
\overline{c}	b	$CH3(CH2)3$	90	92
3	c	CH ₃	86	80
$\overline{4}$	d	c -C ₆ H ₁₁	83	96
5	e	(CH_3) , CHCH,	83	96
6	f	$(CH_3)_3C$	$\lfloor d \rfloor$	
		Ph	91 (88)	94 (94)
		4 -CH ₃ C ₆ H ₄	79 (76)	88 (97)
9		2 -CH ₃ C ₆ H ₄	91 (89)	94 (94)
10		4 -CH ₃ OC ₆ H ₄	(89)	(96)
11	k	$4-CIC6H4$	(92)	(97)
12	ı	$4-MeCO2C6H4$	(91)	(94)
13	m	$4-MeO2CC6H4$	(88)	(92)
14	n	3-MeCOC ₆ H ₄	(90)	(90)

[a] Mol ratio of $4/Et_2Zn/Cu/3$ 1:3:0.03:0.036, 0°C, 6–14 h in either toluene or CH₂Cl₂. [b] Yields after chromatography. Data in parentheses for reactions run in CH₂Cl₂. [c] Determined by HPLC. [d] No reaction.

method for an iterative approach to deoxypropionates, which are motifs holding biological relevance.^[18] Both the high level of enantioselectivity uniformly achieved and the scope with respect to the enone substrate and dialkylzinc reagent clearly surpass previous realisations. $[4, 12]$ It is worth noting once again the key importance of the flanking quaternary carbon center for effective chirality transfer as indicated by the comparatively poor result attained in the reaction of enone $7g$ with Bu₂Z_n to give 15g.

The potential of this catalytic model may be further demonstrated by the smooth transformation of adducts into either carboxylic acids such as 18 and 19 or aldehydes such as 20 , in high yields and preserved ee values (Scheme 2).^[19] In these transformations acetone is the only organic byproduct formed, which constitutes an additional aspect of practical interest. It is worth to stress that the catalytic ACA of dialkylzinc reagents to simple aliphatic unsaturated esters, that is, methyl cinnamate and methyl crotonate, hardly proceed, while parallel reactions with simple enals are essentially lacking.^[5,20]

Table 3. ACA of other dialkylzinc reagents to α' -silyloxy enones.^[a]

Enone \mathbb{R}^1		\mathbb{R}^2	R ₂ Zn	Product R Et ₃ SiO. R ¹ R^2 R^2	Yield $[%]^{[b]}$	ee $[%]^{[c]}$
4a	PhCH ₂ CH ₂		Me $Me2Zn$	12a	82	95
		Me	$iPr_{2}Zn$	13a	80	94
4d	c -C ₆ H ₁₁	Me	Me ₂ Zn	12d	88	> 98
4e	(CH_3) , CHCH ₂	Me	$iPr_{2}Zn$	13 _e	88	94
4g	Ph	Me	$Bu, Zn^{[d]}$	14g	85	93
7g	Ph	H	$Bu_2Zn^{[d]}$	15g	85	72
40	H ₂ C		Me Me ₂ Zn	16	95	$96^{[e]}$
4 p	H_2C	Me	Me ₂ Zn	17	90	$80^{[e,f]}$

[a] Conditions: ratio of enone: $R_2Zn/Cu/3$ 1:3:0.03:0.036, CH₂Cl₂, 0 °C, 14 h. [b] Yields after chromatography. [c] Determined by HPLC. [d] Toluene as solvent. [e] de determined by 13 C NMR. [f] Starting from enone 4p of 84% ee. For details see Supporting Information.

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Scheme 2. Elaboration of adducts.

In conclusion, α' -oxy enones are disclosed as a distinct class of carboxylic acid and aldehyde surrogates for the Cucatalyzed ACA of dialkylzinc reagents, featuring broader substrate and dialkylzinc reagent scope than previously established templates.

Experimental Section

General procedure for the ACA of dialkylzinc reagents: In a flame-dried Schlenk tube were placed $Cu(OTT)_2$ (5.5 mg, 0.015 mmol), ligand 3 (9.3 mg, 0.018 mmol) and toluene or CH_2Cl_2 (2 mL). The resulting mixture was stirred at room temperature for 1h, and then cooled in an ice bath followed by the addition of a solution of α' -triethylsilyloxy enone 4 (0.5 mmol) in the same solvent (1.5 mL). After 15 min of stirring, $Et₂Zn$, Me₂Zn, or iPr_2Zn (1.5 mmol, solutions in toluene), or net Bu₂Zn, was added dropwise over 3 min. The mixture was stirred until TLC analysis indicated completion of the reaction (6–14 h). Then, the reaction was quenched with sat. NH₄Cl (15 mL) and the resulting mixture was extracted with $Et₂O$ (15 mL) three times. The combined organic layer was dried over $MgSO₄$ and concentrated under reduced pressure. Adducts were purified by silica gel column chromatography (hexane/EtOAc 100:1).

Conversion of adducts into carboxylic acids: To a solution of the conjugate addition adduct (0.5 mmol) in acetonitrile (6 mL) at 0° C was added dropwise a solution of cerium(IV) ammonium nitrate (CAN) (0.82 g, 1.5 mmol) in water (3 mL) and the mixture was stirred at room temperature for 2–3 h. Then water (15 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 15 mL). The combined organic extracts were washed with water (20 mL), dried over MgSO₄, filtered and the solvent evaporated. The carboxylic acid products were purified by flash chromatography (silica gel, hexane/EtOAc 10:1).

Acknowledgements

This work was financially supported by The University of the Basque Country (UPV/EHU), Ministerio de Educación y Ciencia (MEC, Spain), and Gobierno de Navarra.

Keywords: asymmetric catalysis · asymmetric synthesis · dialkylzinc derivatives · Michael addition · oxy enones

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Received: July 3, 2008 Published online: August 20, 2008