

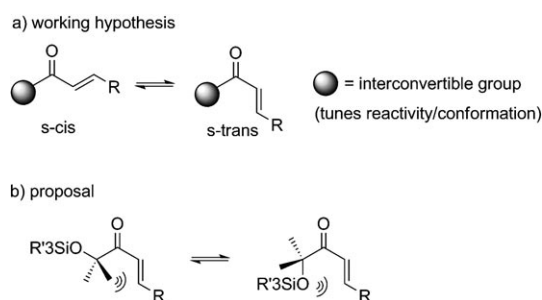
Copper-Catalyzed Enantioselective Conjugate Addition of Dialkylzinc Reagents to α' -Oxy Enones

Jesús M. García,^[b] Alberto González,^[b] Bharat G. Kardak,^[a] José M. Odriozola,^[b] Mikel Oiarbide,^[a] Jesús Razkin,^[b] and Claudio Palomo*^[a]

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 oxazolidiones,^[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-

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]



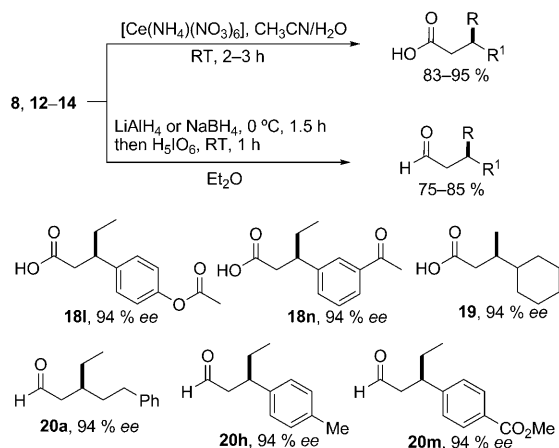
Scheme 1. Controlling enoyl conformation.

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 R² and R³ of enone template. Contrary to what was previously observed,^[15] the strongly chelating α' -hydroxy enone **5a** (R³=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**

[a] Dr. B. G. Kardak, Prof. Dr. M. Oiarbide, Prof. Dr. C. Palomo
Departamento de Química Orgánica I, Facultad de Química
Universidad del País Vasco, Apdo. 1072
20080 San Sebastián (Spain)
Fax: (+34)943-015-270
E-mail: claudio.palomo@ehu.es

[b] Dr. J. M. García, Prof. Dr. A. González, Dr. J. M. Odriozola,
Dr. J. Razkin
Departamento de Química Aplicada
Universidad Pública de Navarra, Campus de Arrosadía
31006 Pamplona (Spain)

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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 Cu-catalyzed 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 $\text{Cu}(\text{OTf})_2$ (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 1 h, 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, Et_2Zn , Me_2Zn , or $i\text{Pr}_2\text{Zn}$ (1.5 mmol, solutions in toluene), or net Bu_2Zn , 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. NH_4Cl (15 mL) and the resulting mixture was extracted with Et_2O (15 mL) three times. The combined organic layer was dried over MgSO_4 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 \times 15 mL). The combined organic extracts were washed with water (20 mL), dried over MgSO_4 , filtered and the solvent evaporated. The carboxylic acid products were purified by flash chromatography (silica gel, hexane/ EtOAc 10:1).

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

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