

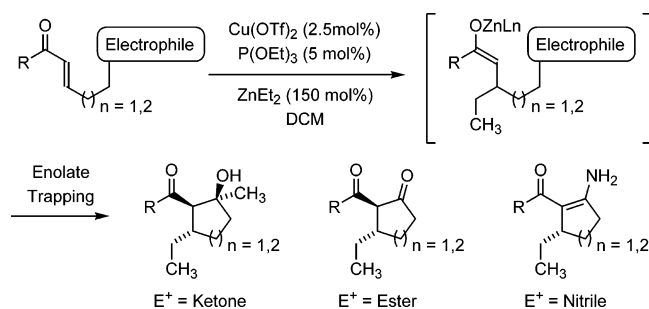
Copper-Catalyzed Tandem Conjugate Addition–Electrophilic Trapping: Ketones, Esters, and Nitriles as Terminal Electrophiles

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Tandem C–C bond formations are attractive methodological targets, as they enable rapid increases in molecular complexity.^{1,2} Recently, we have explored conjugate addition–electrophilic trapping as a modular platform for catalytic reaction development.^{3–7} Through variation of the nucleophilic initiator and electrophilic trap, a variety of catalytic conjugate addition–cyclizations are enabled: Co- and Rh-catalyzed conjugate reduction–aldol cyclizations,^{3,4} related Co- and phosphine-catalyzed Michael cyclizations,^{3,5} a two-component catalyst system for enone cycloallylation,⁶ and finally, a diastereo- and enantioselective Rh-catalyzed conjugate addition–aldol cyclization have been developed.⁷ To extend the latter reaction type, a study of Cu-catalyzed conjugate addition–electrophilic trapping was undertaken. Here, we report that exposure of enone substrates **1a–18a**, which possess appendant ketone, ester, and nitrile moieties, to organozinc reagents in the presence of catalytic Cu(OTf)₂/P(OEt)₃ provides the cyclized products in good to excellent yields and diastereoselectivities. *These results represent the first use of ketones, esters and nitriles as terminal electrophiles in Cu-catalyzed conjugate addition–electrophilic trapping.*



Cu-catalyzed addition of organozinc reagents to α,β -unsaturated carbonyl compounds has been the subject of intensive investigation.⁸ Enantioselective variants of the parent transformation now encompass diverse α,β -unsaturated substrates.⁹ Moreover, trapping of the intermediate Zn-enolate has been achieved using aldehydes,¹⁰ Pd- π -allyls,^{10a,11} halides and tosylates,¹² and oxocarbenium ions¹³ (by way of acetal decomposition). While ketone aldols are observed as homocondensation side products in Cu-catalyzed conjugate addition,^{10d} the deliberate use of ketones as electrophilic traps is reported to fail in the absence of strong Lewis acidic additives.¹³ To our knowledge, the use of esters and nitriles as terminal electrophiles in Cu-catalyzed conjugate addition remains unexplored.

It was recognized that the limitations inherent to the use of such recalcitrant electrophiles *vis-à-vis* intermolecular condensation might be overcome in the case of the analogous intramolecular processes, because of a reduced entropy of activation. To assess the veracity of this analysis, keto-enone **2a** was subjected to conditions for Cu-catalyzed conjugate addition.

Gratifyingly, it was found that exposure of keto-enone **2a** to Et₂Zn in the presence of Cu(OTf)₂ and triethyl phosphite gave the

Table 1. Cu-Catalyzed Tandem Conjugate Addition–Aldol Cyclization^a

Entry	Substrate	Product ^b	Yield (%)	(d.r.) ^d
1			83%	(>95:1)
			81%	(>95:1)
			76% ^c	(>95:1)
			91%	(>95:1)
2			98%	(>95:1)
3			77%	(3:1)
4			96%	(2.2:1)
5			99%	(>95:1)
6			99%	(10:1) ^e
7			96%	(2:1)
8			84%	(8:1)
9			94%	(>95:1)
10			78%	(3:1)

^a See Supporting Information for detailed experimental procedures. ^b The structural assignment of **6b**, **8b–10b** is based on X-ray diffraction analysis. ^c Compound **1d** was prepared via Cu-catalyzed addition of the Grignard reagent as described in the Supporting Information. ^d Reflects ratio of *syn*-aldol to *anti*-aldol product. ^e Reflects ratio of *cis*-fused to *trans*-fused hydrindane.

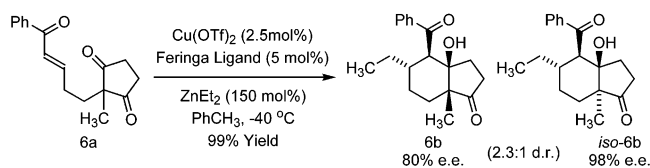
Table 2. Cu-Catalyzed Tandem Conjugate Addition–Dieckmann and Blaise Condensation^a

Entry	Substrate	Product ^b	Yield (%)
1			93%
			88%
			88%
2			87%
3			90%
4			93%
5			84%
			91%
			87%
6			73% ^c
7			98%
8			85%

^a See Supporting Information for detailed experimental procedures. ^b The structural assignment of **15b** is based on X-ray diffraction analysis. ^c The vinylogous amide **16b** spontaneously hydrolyzes in situ to afford β -diketone **12b**.

desired cyclization product **2b** in nearly quantitative yield and as a single diastereomer. Under these optimized conditions, Cu-catalyzed tandem conjugate addition–aldolization of keto-enone substrates **1a–10a** was demonstrated (Table 1). Inspired by these results and the established ability of zinc-enolates to condense with recalcitrant electrophiles such as nitriles,¹⁴ related catalytic tandem conjugate addition–Dieckmann and Blaise cyclizations were explored. Upon application of standard reaction conditions to mono-enone mono-esters **11a–14a** and mono-enone mono-nitriles **15a–18a**, the corresponding cyclized products were obtained in excellent yield (Table 2). Finally, to demonstrate the feasibility of developing enantioselective variants of these tandem C–C bond formations, enone-dione **6a** was subjected to standard reaction conditions using Feringa's phosphoramidite ligand.^{8c} While diastereoselectivity suffered, high levels of asymmetric induction were observed.

In summation, the use of ketones, esters, and nitriles as terminal electrophiles in Cu-catalyzed tandem conjugate addition–electro-



philic trapping has been demonstrated. Future studies will focus on the development of related catalytic tandem C–C bond forming transformations with attendant applications toward the total synthesis of complex natural products.

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Supporting Information Available: Spectral data for all new compounds (¹H NMR, ¹³C NMR, IR, HRMS) (CIF and PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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