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Stereoselective Multicomponent Reactions Using Zincate Nucleophiles: β -Dicarbonyl Synthesis and Functionalization

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Abstract

A general strategy for conjugate addition–*C*-acylation that enables the synthesis of enantioenriched β -dicarbonyl compounds is described. A novel method for derivatizing these adducts by stereo- and site-selective zinc-catalyzed addition of alkyl lithium reagents is also reported. These reactions can be performed in tandem to achieve an enantio- and diastereoselective four-component coupling. The in situ generation of weakly basic lithium zincate species is central to the success of all three transformations.

Graphical Abstract

Multicomponent reactions rapidly increase molecular complexity, allowing improvements in synthetic efficiency.¹ The conjugate addition of an organometallic reagent to an enone followed by trapping of the resulting enolate with an aldehyde (the Noyori three-component coupling, Figure 1A, top) exemplifies the power of such transformations to affect strategic fragment couplings.² The ability to access ketone enolates with regiocontrol is a noteworthy element of this strategy. However, the related sequence involving 1,4-addition and enolate *C*-acylation is conspicuously underdeveloped (Figure 1A, bottom).^{2b,3} As noted in a review, "...conjugate addition–enolate acylation reactions are very substrate dependent. With certain substrates, *O*-acylation competes or even predominates despite the use of conditions conducive to reaction at carbon."^{2b} Competitive proton transfer from the β -dicarbonyl product to the enolate can also occur, which leads to *C,O*-diacylated and nonacylated

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Supporting Information

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Experimental procedures and characterization data (PDF)

The authors declare no competing financial interest.

products.^{2b,3c} Consequently, reliable methods for β -diketone synthesis by a three-component coupling strategy have been elusive, and enantioselective variants are unknown.⁴

Herein, we report the first general strategy for affecting enantio- and diastereoselective 1,4-addition-*C*-acylation reactions (Figure 1B). Key to its success is the use of in situ generated zincate enolates that are highly nucleophilic at carbon but weakly basic.⁵ This reaction yields *C*-acylated products irrespective of the nucleophile, enone, or acylating reagent employed. Furthermore, we have leveraged the power of this sequence to develop a four-component coupling that sets three contiguous stereocenters with absolute and relative stereocontrol (Figure 1C). This transformation combines 1,4-addition-*C*-acylation with a novel 1,2-addition of zincates to β -diketones. As shown, the latter transformation can also be performed independently using zinc catalysis.

To control the absolute stereochemistry of 1,4-addition, we employed Feringa's phosphoramidite-based method, which is among the most general and reliable for stereoselective 1,4-addition of organozinc reagents to enones.^{4a,6} As shown in Scheme 1, direct trapping of the resulting methylzinc enolate with acetyl chloride was inefficient and provided the *C*-, *O*-, and diacylated products **2a–4a** in 11–36% yields.^{7,8} We hypothesized that this methylzinc enolate could be activated by the addition of a second nucleophile to form an ate complex in situ. Noyori's finding that the lithium enolate of cyclohexanone undergoes *C*-acylation after activation with dimethylzinc provided an important precedent.^{5a} Indeed, a dramatic increase in reactivity and regioselectivity was observed when methyllithium (1.05 equiv) was added immediately before the acylating reagent.⁹ The resulting lithium dimethylzincate enolate was rapidly *C*-acylated at –78 °C to provide the 1,3-dicarbonyl **2a** in 80% isolated yield. The *O*-acylated and diacylated products **3a** and **4a** were not detected by ¹H NMR or GC–MS analysis.

This three-component coupling is general and provides access to an array of stereochemically defined 1,3-diketones (Scheme 2). In all cases examined, exclusive *C*-acylation was observed irrespective of the organozinc reagent, enone, or acid chloride employed. Furthermore, all products were generated in >90% ee, and only the *trans* diastereomers were formed, although the products **2a–g,n,o** exist partially as their enol tautomers. In agreement with Feringa's report on the 1,4-addition of organozinc reagents to enones,^{4a} the absolute configuration of **2j** was established to be 2*S*,3*S* on the basis of single-crystal X-ray analysis.¹⁰ Unhindered or electron-deficient aliphatic acid chlorides underwent acylation rapidly at –78 °C (**2a–d**), while warming to 0 °C was necessary when more hindered electrophiles, such as isobutyryl chloride (**2g**), were employed. Sterically and electronically diverse aroyl chlorides were excellent substrates for this reaction. Although certain aroyl chlorides displayed reactivity in the absence of methyllithium, the yields and selectivities were diminished in those instances.¹¹ Esters (**2q**), anisoles (**2p**), benzyl ethers (**2d**), aryl chlorides (**2o**), *ortho*-substitution (**2n** and **2o**), and proximal quaternary centers (**2m**) were all compatible with this sequence. Furthermore, the method is applicable to medium-sized enones such as 2-cyclohepten-1-one and 2-cycloocten-1-one (products **2k** and **2l**). In contrast to analogous reactions with organocopper reagents,³ >20:1 *C*-selectivity was maintained with a variety of β -substituents (**2a–c,h–j**).

The scope of this reaction includes a range of carbonyl electrophiles (Table 1). Chloroformates, cyanoformates,¹³ anhydrides, and benzoyl fluorides provided the corresponding addition-acylation products in 48–73% yields (entries 1–4). It is noteworthy that chloroformates and anhydrides typically provide *O*-acylated products when reacted with a variety of metalloenolates,^{2b,14,15} and in the absence of activation, monoalkylzinc enolates were completely unreactive toward chloroformates and cyanoformates (entries 1 and 2). The reaction was readily performed on a 21 mmol scale using Mander's reagent as the electrophile (entry 2).

The β -dicarbonyl compounds accessed in this study can be converted to other stereochemically complex products. For example, ketoester **2s** undergoes diastereoselective *C*-alkylation on treatment with iodomethane and sodium *tert*-butoxide (Scheme 3, eq 1). Based on our finding that zincate enolates are nonbasic nucleophiles useful in β -dicarbonyl synthesis, we considered that trialkylzincates might be ideal nucleophiles for 1,2-addition to enolizable β -dicarbonyls. Existing methods for the 1,2-addition of organometallic reagents to β -diketones employ stoichiometric amounts of cerium trichloride or excess Grignard reagents with heating.¹⁶ By comparison, we found that the addition could be carried out efficiently using substoichiometric amounts of ZnCl₂ (10 mol %) and 1.25 equiv of methyllithium (Scheme 3, eq 2). We believe that methyllithium reacts rapidly with the zinc salt leading to in situ formation of the triorganozincate.¹⁷ In the absence of zinc chloride, 1,2-addition products are formed in only 25% yield as mixtures of regioisomers and diastereomers. Treating **2h** with preformed LiZn(CH₃)₃ led to the β -hydroxy ketone **6a** in 98% yield as a single isomer, supporting the intermediacy of a triorganozincate in the zinc-catalyzed process.

This zinc-catalyzed 1,2-addition is applicable to a variety of enolizable cyclic and acyclic β -diketones (Scheme 4). Using the products derived from conjugate addition–*C*-acylation, the cyclic dialkyl ketone substituent undergoes addition in preference to the aryl ketone (>20:1 regioselectivity). The high stereo- and regioselectivity are maintained for substrates with varying steric bulk at the β -position (**6a–c**). While yields were excellent for electron-neutral and electron-rich β -diketones (**6a–d**), substrates with electron-withdrawing substituents provided low yields of product (30%, **6e**), potentially due to competitive proton transfer. Distinct regioselectivity was observed when acyclic β -diketones were employed. In these instances, the zincate underwent selective addition to the aryl ketone in preference to the dialkyl ketone and the selectivity improved when bulkier substrates were employed (**6f–h**).

Stereochemical models for the 1,2-addition of zincates to diketones are depicted in Scheme 5. Given the high levels of stereoselectivity obtained when either cyclic or acyclic substrates are used, we suggest that the β -diketones chelate to a lithium cation leading to a rigid transition state.¹⁸ In the case of acyclic substrates, *syn*-pentane interactions force the alkyl backbone of the molecule into an extended conformation that increases the steric demand around the dialkyl ketone. Thus, addition occurs to the aryl ketone from the face opposite the α -substituent. The regioselectivity is reversed for cyclic substrates. In these instances, the substituents on the dialkyl ketone are constrained by the ring, rendering that carbonyl more accessible. Furthermore, nucleophilic addition to the aryl ketone would generate *syn*-pentane interactions between the β -alkyl substituent and either the aryl group or incoming

nucleophile. Accordingly, equatorial attack of the zincate on the cyclohexanone occurs to produce the observed stereoisomer.

Finally, we discovered that this method can be modified to affect a one-flask asymmetric four-component coupling (Scheme 6). By increasing the amount of methyllithium used to activate the zinc enolate from 1.05 to 2.05 equiv, the β -hydroxy ketone **6a** was obtained in 54% yield as a single detectable diastereomer and in 96% ee. The yield was improved to 61% when methylmagnesium bromide was used as the activator and products **6i,j** were synthesized using alternative acid chlorides and organolithium reagents. This four-component coupling forges three C–C bonds and sets three contiguous stereocenters.

In summary, we have developed a general method for the stereoselective addition of organozinc reagents to α,β -unsaturated ketones followed by high-yielding acylation of the resulting enolates. This fundamental sequence provides stereo- and regiocontrolled access to 1,3-dicarbonyl products and closes a long-standing gap in the methodological literature. The products are useful precursors to other complex products via site- and stereoselective C-alkylation or zinc-catalyzed alkylation. Key to the success of these strategies was the use of zincate nucleophiles which undergo chemo-, regio-, and diastereoselective addition reactions while avoiding competitive proton transfers from acidic 1,3-dicarbonyl functional groups. This strategy is applicable to a wide range of enones, organozinc reagents, and carboxylic acid derivatives, and the use of these methods in multistep synthesis is currently ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A. Multi-component reactions involving 1,4-addition and enolate trapping

B. Organozincate enolates for conjugate addition–C-acylation

C. Asymmetric four-component coupling

Figure 1.

(A) Tandem conjugate addition–acylation is highly substrate dependent. (B) Strategy for tandem conjugate addition–acylation exploiting the activation of zinc enolates with organolithium reagents. (C) Four-component coupling to establish three contiguous stereocenters in a single flask.

Scheme 1.

Reactivity of Alkylzinc Enolates and Lithium Dialkylzinc Enolates

conditions	yield (%)	dr	rr
CH ₃ Li (1.25 equiv), ZnCl ₂ (10 mol %)	95	>20:1	>20:1
CH ₃ Li (1.05 equiv)	25	1:1.3	1:2
CH ₃ MgBr (1.05 equiv)	20	>20:1	1:2.5
Li ⁺ Zn(CH ₃) ₃ ⁻ (1.05 equiv)	98	>20:1	>20:1

Scheme 3. C-Alkylation and Nucleophilic Addition

^aYield over two steps (conjugate addition–acylation and C-alkylation).

Scheme 4. Scope of ZnCl₂-Catalyzed Addition of Methyl lithium to β -Diketones

Scheme 5.

Stereochemical Models for 1,2-Additions to Ketones with Zincate Nucleophiles

Scheme 6. Four-Component Coupling Reactions

^aMethylmagnesium bromide used instead of methyllithium.

Table 1. Scope of the Carbonyl Electrophile in the Asymmetric Conjugate Addition–Acylation^{a,b}

no.	electrophile	with CH_3Li		without CH_3Li	
		yield (%)	C:O	yield (%)	C:O
1	2r $\text{R}'\text{OCOC}\text{Cl}^c$	48	>20:1	<1 ^d	
2	2s $(\text{CH}_3\text{O})\text{COCN}$	72 ^e	>20:1	<1 ^d	
3	2h $(\text{C}_6\text{H}_5\text{CO})_2\text{O}$	73	7.3:1	25 ^f	1:1.7
4	2h $\text{C}_6\text{H}_5\text{COF}$	65	11:1	30 ^f	11:1

^a Acylations performed in the absence of CH_3Li were conducted at 22 °C for 2 h.^b Each product is formed in 96% ee.^c $\text{R}' = (R)\text{-menthyl}$.^d Determined by GC–MS analysis.^e 21 mmol scale. Isolated after *C*-methylation.^f NMR yields.