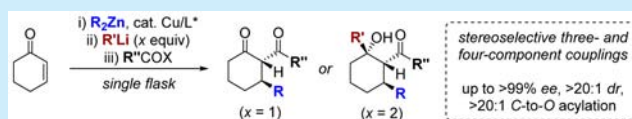


Stereoselective Multicomponent Reactions Using Zincate Nucleophiles: β -Dicarbonyl Synthesis and FunctionalizationStephen K. Murphy,[†] Mingshuo Zeng,[†] and Seth B. Herzon^{*,†,‡}[†]Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States[‡]Department of Pharmacology, Yale School of Medicine, New Haven, Connecticut 06520, United States

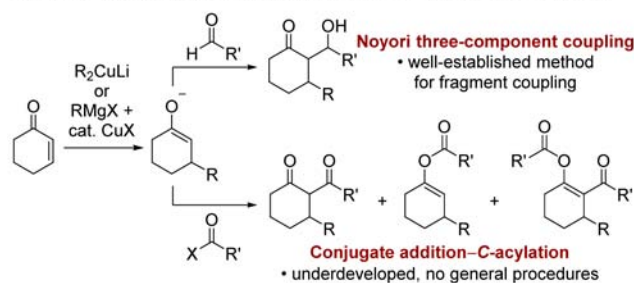
S Supporting Information

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.



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

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



B. Organozincate enolates for conjugate addition–C-acylation



C. Asymmetric four-component coupling

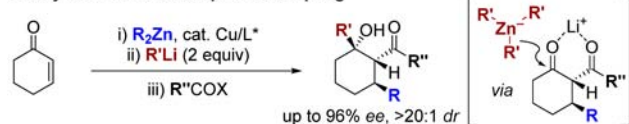


Figure 1. (A) Tandem conjugate addition–acylation is highly substrate dependent. (B) Strategy for tandem conjugate addition–acylation exploiting the activation of zinc enolates with organolithium reagents. (C) Four-component coupling to establish three contiguous stereocenters in a single flask.

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 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

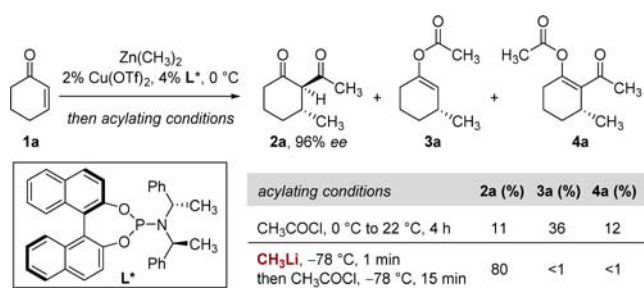
Herein, we report the first general strategy for affecting enantio- and diastereoselective 1,4-addition–C-acylation reactions (Figure 1B). Key to its success is the use of in situ generated zincate enolates that are highly nucleophilic at carbon but weakly basic.⁵ This reaction yields C-acylated products 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

Received: August 8, 2016

Published: September 27, 2016

Scheme 1. Reactivity of Alkylzinc Enolates and Lithium Dialkylzinc Enolates

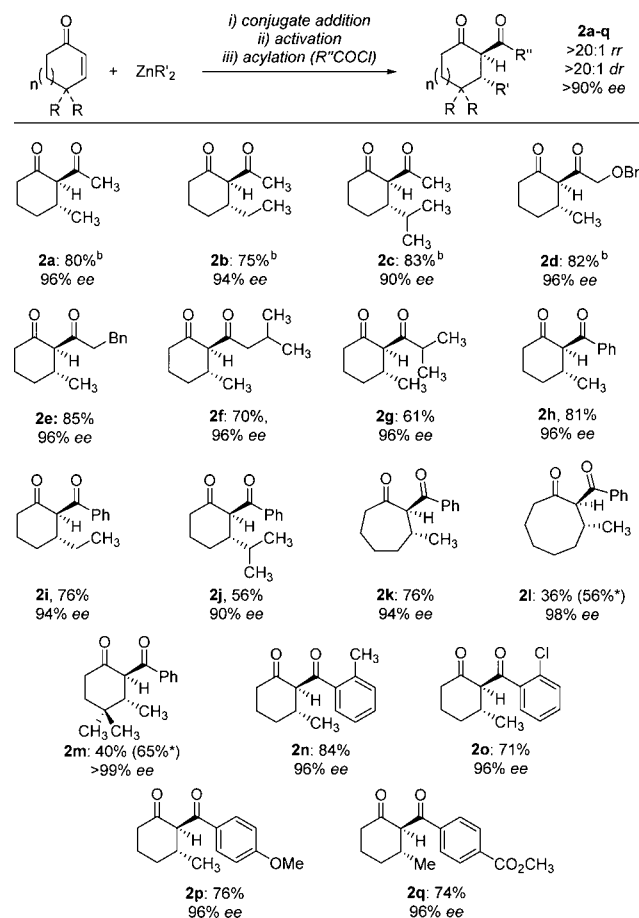


addition of a second nucleophile to form an ate complex in situ. Noyori's finding that the lithium enolate of cyclohexanone undergoes C-acylation after activation with dimethylzinc provided an important precedent.^{5a} Indeed, a dramatic increase in reactivity and regioselectivity was observed when methyl-lithium (1.05 equiv) was added immediately before the acylating reagent.⁹ The resulting lithium dimethylzinc 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 methyl-lithium, 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

Scheme 2. Scope of the 1,4-Addition–Acylation Sequence^a

^aGeneral conditions: R₂Zn (1.05 equiv), Cu(OTf)₂ (2 mol %), L* (4 mol %), Et₂O, -30 to 0 °C, 0.5–5 h, then CH₃Li (1.05 equiv), -78 °C, 1–5 min, then acid chloride (1.2 equiv), -78 to 0 °C, 15 min–3 h. In general, isolated yields were 5–15% lower than NMR yields due to decomposition of diketones on silica gel. This phenomenon has been noted by others.¹² Instances where the isolated yields and NMR yields differed by >20% are denoted with an asterisk. ^bAverage of two runs.

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

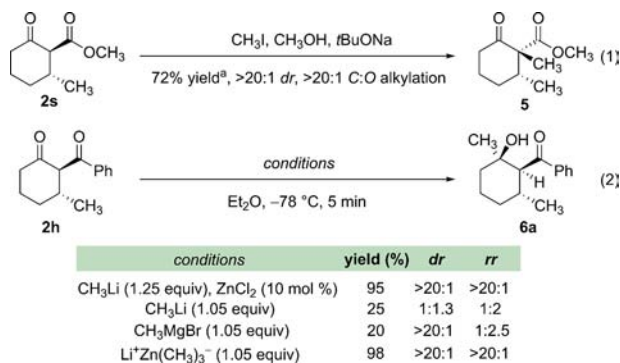
Reaction scheme showing the conversion of cyclohex-2-en-1-one (**1a**) to cyclohex-2-en-1-one derivatives (**2h, 2r, 2s**) using $\text{Zn}(\text{CH}_3)_2$, 2% $\text{Cu}(\text{OTf})_2$, 4% L^* , 0 °C, then CH_3Li , -78 °C, 1 min, then electrophile, -78 °C to 0 °C.

		electrophile	with CH_3Li		without CH_3Li	
no.			yield (%)	C:O	yield (%)	C:O
1	2r	$\text{R}'\text{OCOCl}^c$	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

^aAcylation performed in the absence of CH₃Li were conducted at 22 °C for 2 h. ^bEach product is formed in 96% ee. 'R' = (R)-menthyl. ^dDetermined by GC-MS analysis. ^e21 mmol scale. Isolated after C-methylation. ^fNMR yields.

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

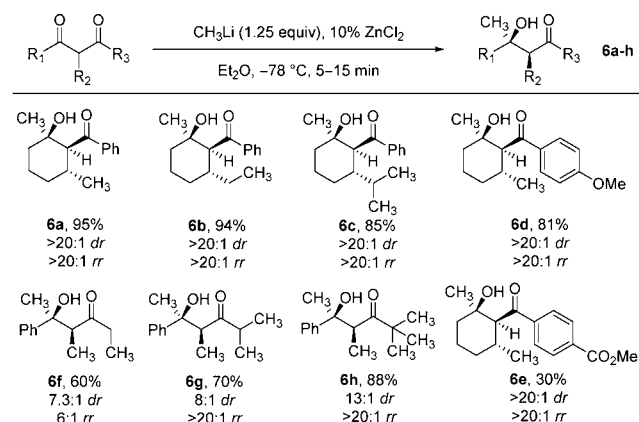
Scheme 3. C-Alkylation and Nucleophilic Addition



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

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

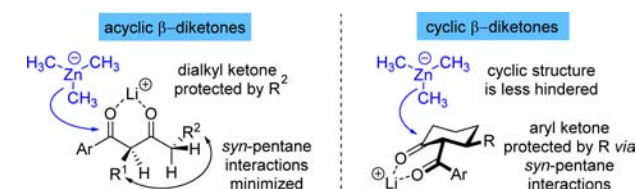
Scheme 4. Scope of ZnCl₂-Catalyzed Addition of Methyllithium to β -Diketones

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

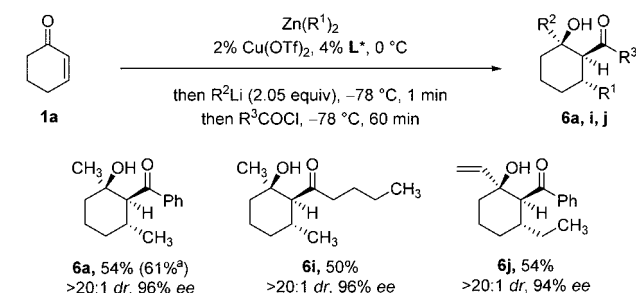
Scheme 5. Stereochemical Models for 1,2-Additions to Ketones with Zincate Nucleophiles



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

Scheme 6. Four-Component Coupling Reactions



^aMethylmagnesium bromide used instead of methyllithium.

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.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b02320](https://doi.org/10.1021/acs.orglett.6b02320).

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from Yale University, the National Institute of General Medical Sciences (R01GM090000), and the National Sciences and Engineering Research Council of Canada (postdoctoral fellowship to S.K.M.) is gratefully acknowledged. We thank Dr. Brandon Mercado for X-ray crystallographic analysis.

■ REFERENCES

- (1) For a review, see: Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439.
- (2) (a) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847. For general reviews on conjugate addition–enolate functionalization reactions, see: (b) Taylor, R. J. K. *Synthesis* **1985**, 364. (c) Kim, J. H.; Ko, Y. O.; Bouffard, J.; Lee, S.-g. *Chem. Soc. Rev.* **2015**, *44*, 2489.
- (3) For selected examples of 1,4-addition of organocopper reagents, followed by acylation, see: (a) Tanaka, T.; Kurozumi, S.; Torn, T.; Kobayashi, M.; Miura, S.; Ishimoto, S. *Tetrahedron Lett.* **1975**, *16*, 1535. (b) Tanaka, T.; Kurozumi, S.; Toru, T.; Kobayashi, M.; Miura, S.; Ishimoto, S. *Tetrahedron* **1977**, *33*, 1105. (c) Bernasconi, S.; Gariboldi, P.; Jommi, G.; Sisti, M. *Tetrahedron Lett.* **1980**, *21*, 2337.
- (4) Related strategies for accessing enantioenriched 1,3-dicarbonyl compounds have been reported. For the tandem conjugate addition–aldol reaction followed by PCC oxidation of the resulting β -hydroxy ketones, see: (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620. For the enantioselective conjugate addition of organozinc reagents to α -acyl enones, see: (b) Tang, X.; Blake, A. J.; Lewis, W.; Woodward, S. *Tetrahedron: Asymmetry* **2009**, *20*, 1881.
- (5) For selected examples of applications of zincate enolates, see: (a) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785. (b) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934. (c) Dudley, G. B.; Engel, D. A.; Ghiviriga, I.; Lam, H.; Poon, K. W. C.; Singletary, J. A. *Org. Lett.* **2007**, *9*, 2839. (d) Tomita, Y.; Ichikawa, Y.; Itoh, Y.; Kawada, K.; Mikami, K. *Tetrahedron Lett.* **2007**, *48*, 8922.
- (6) For a complementary approach to enantioselective addition of organozinc reagents to enones, see: Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755.
- (7) Related alkylzinc enolates have been trapped intermolecularly by aldehydes, oxycarbenium ions, allylic electrophiles, and silylating agents, see: (a) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104. (b) Alexakis, A.; Trevitt, G. P.; Bernardinelli, G. *J. Am. Chem. Soc.* **2001**, *123*, 4358. (c) Knopff, O.; Alexakis, A. *Org. Lett.* **2002**, *4*, 3835. (d) Dijk, E. W.; Panella, L.; Pinho, P.; Naasz, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2004**, *60*, 9687. For intramolecular reactions, see: (e) Agapiou, K.; Cauble, D. F.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4528.
- (8) Acylation of the zinc enolate derived from ethyl *tert*-butyl ketone with benzoyl chloride has been reported to occur in 65% yield, see: Hansen, M. M.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069. The rhodium-catalyzed acylation of zinc enolates with aroyl chlorides has also been reported, see: Sato, K.; Yamazoe, S.; Yamamoto, R.; Ohata, S.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Org. Lett.* **2008**, *10*, 2405.
- (9) Other organometallic reagents, such as methylmagnesium bromide, *n*-butyllithium, phenyllithium, and vinylolithium, can be used to promote C-acylation.
- (10) The data for **2j** has been deposited to the CCDC (ref no. CCDC 1503495).
- (11) See the Supporting Information for comparisons.
- (12) Bartlett, S. L.; Beaudry, C. M. *J. Org. Chem.* **2011**, *76*, 9852.
- (13) During the preparation of this manuscript, a related procedure for the conjugate addition of dimethylzinc to 2-cyclohexen-1-one and acylation with Mander's reagent was employed in the asymmetric total synthesis of amphilectane and serrulatane natural products, see: Yu, X.; Su, F.; Liu, C.; Yuan, H.; Zhao, S.; Zhou, Z.; Quan, T.; Luo, T. *J. Am. Chem. Soc.* **2016**, *138*, 6261.
- (14) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736.
- (15) Vuagnoux-d'Augustin, M. V.; Alexakis, A. *Tetrahedron Lett.* **2007**, *48*, 7408.
- (16) (a) Bartoli, G.; Marcantoni, E.; Petrini, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1061. (b) Yuan, R.; Zhao, D.; Zhang, L.-Y.; Pan, X.; Yang, Y.; Wang, P.; Li, H.-F.; Da, C.-S. *Org. Biomol. Chem.* **2016**, *14*, 724. (c) Leighton and co-workers developed a method for the enantioselective allylation of diketones using a chiral allylsilane reagent, see: Chalifoux, W.; Reznik, S. K.; Leighton, J. L. *Nature* **2012**, *487*, 86.
- (17) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998.
- (18) Lower yields were obtained when the reaction was conducted in tetrahydrofuran, perhaps due to interfere with the formation of chelated intermediates.