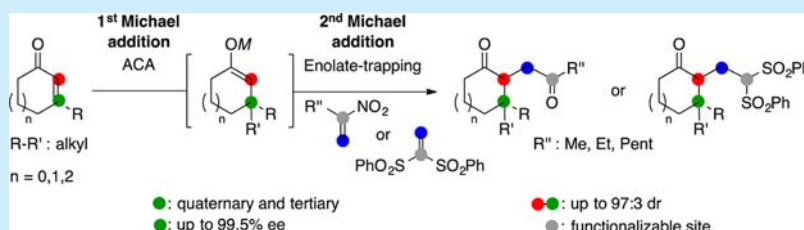


Domino Asymmetric Conjugate Addition—Conjugate Addition

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S Supporting Information



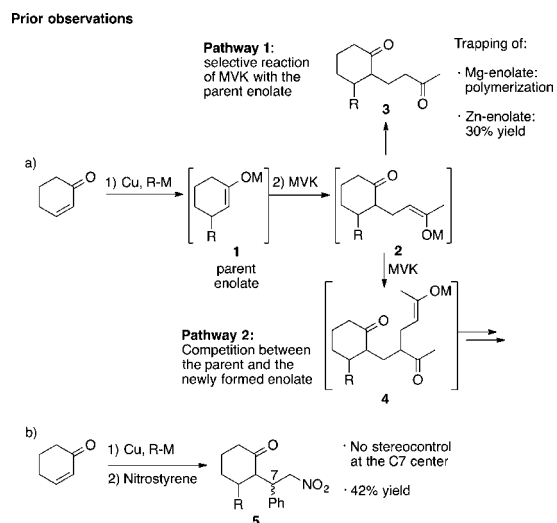
ABSTRACT: Enantioenriched Al-, Mg-, and Zn-enolates undergo electrophilic trapping by nitroolefins and vinylsulfones to afford 1,4-diketones and 2-(bis(phenylsulfonyl)ethyl)ketones in good yield and excellent diastereoselectivity. A one-pot preparation of indenenes and enantiopure syntheses of tetrahydrobenzofurans, tetrahydrobenzopyrroles, and azulenes are disclosed. A site-selective two-step sequence of three conjugate additions is also demonstrated.

Access to enantiopure small molecules is a continuous challenge for organic chemists. Asymmetric conjugate addition (ACA) offers a selective tool for the preparation of molecules bearing one or multiple stereogenic centers.¹ Many transition metals have been reported to catalyze this reaction, but copper salts are now accepted to be the most versatile of them.² Copper not only is among the cheapest transition metals used in asymmetric catalysis but also is easily transmetalated from organoaluminum, -magnesium, and -zinc. As a result, methodologies involving these organometallic reagents complement each other, and their association with various optimized catalytic complexes brings an accurate tool to the organic chemistry community.³ Noteworthy is the synthetic potential of metal-enolates resulting from the conjugate addition of organocuprates to enones: in the presence of an additional electrophile, a second stereocenter can be created.^{4,5}

Due to the aggregation state of metal-enolates, and the Lewis acidity of the metal, Al-, Mg-, and Zn-enolates have a different reactivity toward a given electrophile. While Mg-enolates are the most reactive, Al-counterparts are often more problematic except when coordination with the entering electrophile is possible like aldehydes or imines.⁶ Another way to increase the reactivity of Al-enolates is to form in situ an Alanate by addition of 1 equiv of MeLi.⁷ Zn-enolates can be successfully reacted in situ to form aldol, Mannich, Blaise, or Dieckmann adducts, but in these examples, at least two diastereomers are isolated.^{4g,8,9} Furthermore, despite numerous examples of alkylation of metal-enolates, the electrophilic trapping by Michael acceptors could broaden the scope of ACA. The synthetic challenge associated with this cascade reaction¹⁰ combined with the constant need for straightforward syntheses of functionalized small molecules prompted us to consider this topic.

We initiated our work by optimizing the Cu-catalyzed conjugate addition of organometallic reagents to cyclohexenone followed by addition of MVK (Scheme 1a).^{11,12} In the case of

Scheme 1. Functionalization of Enolates Using MVK (Methyl Vinyl Ketone) and Nitrostyrene



Mg-enolate, the desired product could not be isolated; an inseparable mixture of products was obtained instead, probably resulting from a polymerization process through 4, while the Zn-enolate led to a mixture of products from which the desired 1,5-diketone could be isolated in 30% yield. These results can be rationalized by looking at the reaction pathway: after the first conjugate addition, a parent metal-enolate 1 is trapped by MVK, generating another enolate 2. Yet, 1 and 2 compete and MVK can be indifferently trapped by the two enolates to give 3 or 4. To circumvent this selectivity issue, a different Michael acceptor is needed with charge-stabilizing functionality. Unlike the enolate

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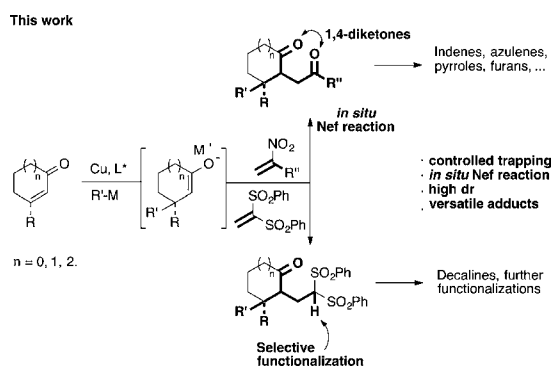
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derived from the conjugate addition to enones, 1,4-additions to nitroolefin and vinyl sulfone should result in less reactive species, lowering potential over-reactions.

To test this concept, a first reaction was run with commercially available nitro-styrene. The desired ketone **5** was obtained in 42% yield, but no diastereocontrol at C-7 was observed (Scheme 1b).^{13,14} Hence, Michael acceptors should not be β -substituted and must be compatible with Al-, Mg-, and Zn-enolates. Ideal electrophiles for the domino ACA-Conjugate Addition would also lead to easily derivatizable adducts in high enantiomeric excess (ee) and diastereoselective ratio (dr).

Herein, we propose 1-alkyl-1-nitroolefin and bis-(phenylsulfonyl) ethylene as valuable substitutes to our early attempts (Scheme 2). This choice was also inspired by the work of Mayr et al. who recently stated that nitroolefins and vinyl disulfones have comparable electrophilicity.¹⁵

Scheme 2. Reactivity of Enolates towards Michael Acceptors



Since the present study was motivated by the need for enantioenriched complex molecules, our methodology was designed to allow for the preparation of relevant bicyclic scaffolds. The core structures of the three sesquiterpenes (Valeric acid,¹⁶ Ambrosin,¹⁷ Halipanacine¹⁸) and meroterpenoid Liphagal¹⁹ are potential targets of this work (Figure 1).

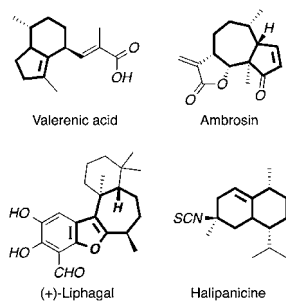


Figure 1. Potential target of this work.

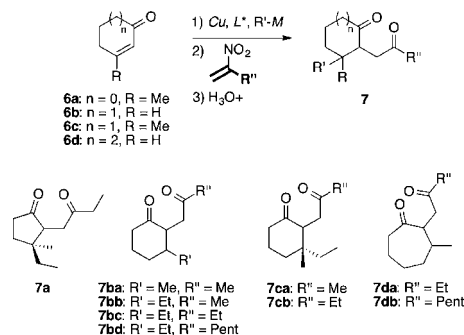
Nitroolefins have been used in two-step processes involving silyl enol ether in Sakurai-type reactions mediated by tin tetrachloride or aluminum trichloride.²⁰ Yet, the reactivity of nitroolefins with Al-, Mg-, and Zn-enolates remains underexplored. Li-enolates have been reacted with nitroolefins, but two steps are needed and regioselectivity issues cannot be avoided.^{5,21}

The reactivity of the various enantioenriched metal enolates was then explored.²² We assumed that the catalytic Cu/chiral ligand complexes did not influence the outcome of the trapping step.

In all the cases, and with Mg, Al, and Zn, the straightforward ACA-trapping proceeded smoothly via *in situ* Nef reaction^{23,24}—no nitro-ketones were detected—and 1,4-diketones were isolated in good to excellent yields and dr. Experimentally, 2-nitropropene and -butene showed comparable reactivity.

Indeed, starting from the same Mg-enolate, **7bb** and **7bc** needed both 2 h at 0 °C to reach full conversion (Table 1, entries

Table 1. Synthesis of Chiral 1,4-Diketones via Domino Conjugate Additions



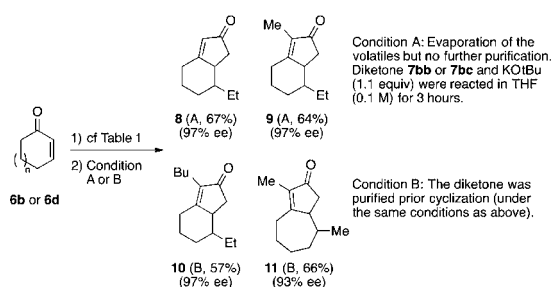
entry	product	R	yield (%) ^a	dr ^b	ee (%) ^c
1	7a	EtMgBr	64	66:34	87
2 ^d	7ba	Me ₃ Al	84	82:18	95
3	7bb	EtMgBr	63	86:14	97
4	7bc	EtMgBr	66	90:10	97
5	7bd	Et ₂ Zn	82	88:12	>99.5
6	7ca	EtMgBr	68	57:43	90
7	7cb	EtMgBr	71	66:34	90
8 ^d	7da	Me ₃ Al	81	97:3	93
9	7db	Me ₂ Zn	72	92:8	>99.5

^a¹H NMR spectroscopy and GC showed full conversion for all examples. ^bTrans/cis ratio. ^cMeasured before trapping and compared to reported data. No erosion has been noted. ^dReaction scaled up to 5 mmol. Equimolar addition of methyllithium was used prior to the addition of nitroolefin.

3 and 4). In contrast, Al-enolates react sluggishly. To enhance the reactivity, 1 equiv of MeLi was added to form the corresponding more nucleophilic Alanate. The reaction rate was then comparable to Mg-enolate (entry 2 vs 3). To our delight, Zn-enolate resulting from the ACA of diethylzinc to **6b** gave diketone **7bd** in only 1.5 h at 0 °C in 82% yield and 88:12 dr (entry 5). We can conclude that, under optimized conditions, our three enolates have comparable reactivity profiles toward 1-alkylnitroolefins. The concept was further extended to seven-membered rings with even higher dr's up to 97:3 (entries 8 and 9). The isolation of **7a** in 64% yield demonstrated that five-membered rings were also tolerated (entry 1). Gratifyingly, the reaction was compatible with sterically demanding vicinal quaternary centers: diketones **7ca** and **7cb** were obtained in up to 71% isolated yield. As expected, better diastereocontrol was obtained for ketones bearing contiguous tertiary centers (entry 4 vs 7). Our methodology was eventually amenable to 5 mmol in 81% yield (entry 8).

With our optimized conditions in hand, we set different experimental procedures in order to demonstrate the synthetic versatility of 1,4-diketones (Scheme 3). After transformations of our enantioenriched adducts, not only can the precursors of molecules depicted in Figure 1 be targeted but also other natural compounds featuring common molecular scaffolds can be prepared. The regioselective aldol reaction is one possible

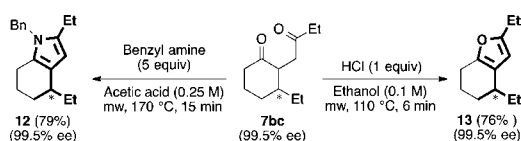
Scheme 3. One-Pot and Two-Pot Syntheses of Enantioenriched Indenones and Azulene Derivatives



reaction.⁴⁰ For condition A, no purification is needed and the construction of functionalized indenones **8** and **9** proceeded smoothly, while for condition B, the intermediate 1,4-diketones was isolated prior to the cyclization step to yield indene **10** and azulene-type **11**, a useful guaiane skeleton.²⁵

In addition, 1,4-diketones are also pyrrole and furan precursors (Scheme 4).²⁶ Microwaves-assisted Paal–Knorr synthesis using

Scheme 4. Syntheses of Enantiopure Tetrabenzopyrrole and Tetrabenzofuran Derivatives



benzyl amine in acetic acid yielded one enantiomer of *N*-benzylpyrrole derivative **12** in 79% yield.²⁷ Analogously, acid-catalyzed Paal–Knorr furan synthesis gave tetrahydrobenzofuran **13** in 76% yield.²⁸ The preparations of enantioenriched 4,5,6,7-tetrahydropyrrole and -furan have been scarcely disclosed.²⁹

As a significant class of small synthetic fragments, sulfones have found a broad scope of applications.³⁰ Also called chemical chameleons, they are versatile derivatizable functions.³¹ As a consequence, they have been extensively used in organic synthesis and notably in organocatalyzed reactions.³²

To the best of our knowledge, metal-enolates have never been trapped by vinyl disulfones. We then decided to test the same chiral enolates derived from ketones **6a–d** (Table 2).

Zn-enolates were converted to ketones **14ba** and **14bb** in 3 h at $-30\text{ }^{\circ}\text{C}$ in up to 75% yield (entries 2 and 4). The reaction was fast and produced the desired product in 83:17 and 85:15 dr respectively. The trapping has been also successfully applied to Al-enolates, affording adducts **14ba** in 82%, 95:5 dr, 96% ee and **14bb** in 71%, 81:19 dr, 95% ee (entries 3 and 5). However, 15 h at $-30\text{ }^{\circ}\text{C}$ and activation by methyllithium were required to achieve full conversion. Without methyllithium, the reaction proceeded at a much lower rate and the concomitant formation of undesired products was observed. Here also, the same results were obtained when scaling up to 5 mmol for the synthesis of **14ba**. Analogously to the preceding table, the excellent behavior of Mg-enolates allowed us to validate the method with five-membered rings and in the presence of bulky quaternary centers. Hence, functionalized ketones were obtained in 85% yield in 2 h at $0\text{ }^{\circ}\text{C}$ (entries 1 and 5). Also, no erosion of the enantioselectivity was noticed. From a practical point of view, adducts **14** are easily isolated as white solids and can be further purified by recrystallization in ethyl acetate.

Table 2. Domino Michael Reactions with Vinyl *gem*-Disulfones

entry	product	R'	yield (%) ^a	dr ^b	ee (%) ^c
1	14a	EtMgBr	85	53:17	86
2	14ba	Me ₂ Zn	67	83:17	93
3 ^d	14ba	Me ₃ Al	82	95:5	96
4	14bb	Et ₂ Zn	75	85:15	>99.5
5	14bb	Et ₃ Al	71	81:19	95
6	14c	EtMgBr	85	53:47	90

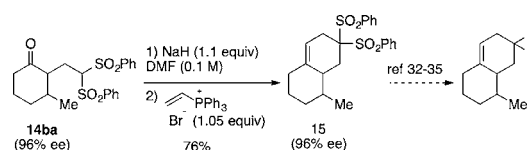
6a: n = 0, R = Me
6b: n = 1, R = H
6c: n = 1, R = Me
14a: n = 0, R = Me, R' = Et
14ba: n = 1, R = H, R' = Me
14bb: n = 1, R = H, R' = Et
14c: n = 1, R = Me, R' = Et

^a¹H NMR and GC showed full conversion for all examples. ^b*Trans/cis* ratio. ^cMeasured on 1,4-adduct before trapping and compared to reported data. ^dReaction scaled up to 5 mmol. Equimolar addition of methyllithium was used prior to the addition of disulfone.

As stated above, sulfones derivatives are tunable synthetic entities.³³ The homolytic cleavage of disulfone has been introduced many years ago, and methodologies using lithium naphthalenide or samarium iodide are well-established procedures for the synthesis of various compounds.³⁴

Mechanistically, the trapping step leads to an anion stabilized by the *gem*-disulfone. A second trapping would be theoretically possible, but only moderate yields were obtained. **14a–c** feature three potential acidic positions, but the selective deprotonation of the most acidic of those was possible using sodium hydride.³⁵

Treatment of **14ab** under basic conditions followed by the addition of vinyl triphenylphosphonium bromide yielded a transient phosphonium ylide, which readily reacted with the ketone to afford the Wittig adduct **15** in 76% yield (Scheme 5).³⁶ This transformation was the result of three conjugate additions in a row. By following the same procedure, allyl iodide was trapped in a modest 33% yield.³⁷

Scheme 5. Derivatization of Ketone **14ba** by Conjugate Addition–Wittig-like Condensation Sequence To Form Indene **15**

The sequence of Michael additions involving ACA and enolate trapping with nitroolefin and vinyl sulfone has been demonstrated to be a reliable transformation for enantioenriched Al-, Mg-, and Zn-enolates. The domino ACA–enolate trapping by Michael acceptors afforded 1,4-diketones and γ -sulfonylated ketones in high yield and diastereoselectivity. These Michael adducts were then derivatized toward notable bicyclic structures. This work emphasizes the versatility of metal-enolates and shows that investigations are still needed in this field. Extension of the methodology and its application toward the rapid synthesis of natural products are currently underway in our laboratory and will be reported in due time.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures and complete characterizations (NMR spectra, GC traces, and HRMS) are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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