# Broad Spectrum Enolate Equivalent for Catalytic Chemo-, Diastereo-, and Enantioselective Addition to *N*-Boc Imines

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S *Supporting Information*

ABSTRACT: Alkynyl ketones are attractive but challenging nucleophiles in enolate chemistry. Their susceptibility to other reactions such as Michael additions and the difficulty of controlling the enolate geometry make them difficult substrates. Mannich-type reactions, which previously have not been reported using *N*-carbamoyl-imines with simple ketone enolates, became our objective. In this report, we describe the first direct catalytic Mannich-type reaction between various ynones and *N*-Boc imines, whose stereocontrol presumably derives from catalyst control of enolate geometry. This method produces α-substituted β-amino ynones with excellent chemo-, diastereo-, and enantioselectivity. The products can be readily transformed into a broad range of molecular scaffolds upon further one-step transformations, demonstrating the utility of ynones as masked synthetic equivalents for a variety of unsymmetrically substituted acyclic ketones. In particular, alkynyl alkyl ketones resolve the long-standing problem of the inability to use the enolates of unsymmetrical dialkyl ketones lacking α-branching for regio- and stereoselective reactions.
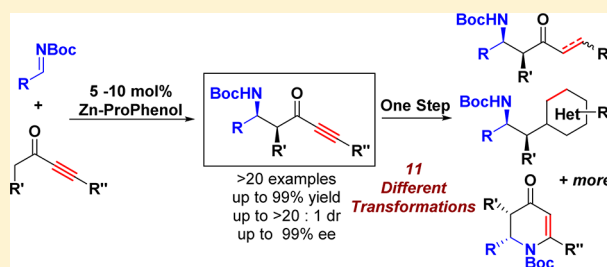
INTRODUCTION

C−C bond formation through enolate chemistry is one of the most fundamental and broadly utilized transformations in modern synthetic organic chemistry. Over the past few decades, significant progress in this field has been made not only in achieving high levels of control in additions to diverse electrophiles but also with processes that no longer require stoichiometric generation of the enolate intermediates.[1] Alkynyl ketones are valuable yet underexplored nucleophiles in this active area of research. Their propensity to act as Michael acceptors and the difficulty of controlling the enolate geometry due to lack of steric bulk on the acetylene moiety render them challenging substrates.[2] Nonetheless, ynones are versatile building blocks for structural proliferation into various synthetic targets.[3] The high metallophilicity of the acetylene moiety can be employed in chemoselective C−C bond formations such as [2 + 2 + 2] cycloadditions,[4] alkyne−alkyne or alkene−alkyne coupling,[5] and reductive coupling reactions.[6] The adjacent carbonyl group also allows rapid construction of various heterocycles.[7] The valuable ability of ynone enolates to act as a broad spectrum enolate equivalent is significant, especially in a lead generation program in drug discovery, where rapid access to a broad diversity of skeletal classes is required.

Our initial motivation derived from the fact that unsymmetrical acyclic ketones lacking functionality in proximity of the carbonyl group, such as 3-hexanone, do not participate in reactions proceeding through enol or enolates with high chemo-, regio-, diastereo-, and enantioselectivity. As shown in eq 1 (Scheme 1), the source of these difficulties lies in the inability to control the regio- and geometric selectivity of the enolization process. Thus, in attempting to develop the

Scheme 1. Problems and Known Strategy To Selectively Functionalize Unsymmetrical Dialkyl Ketones
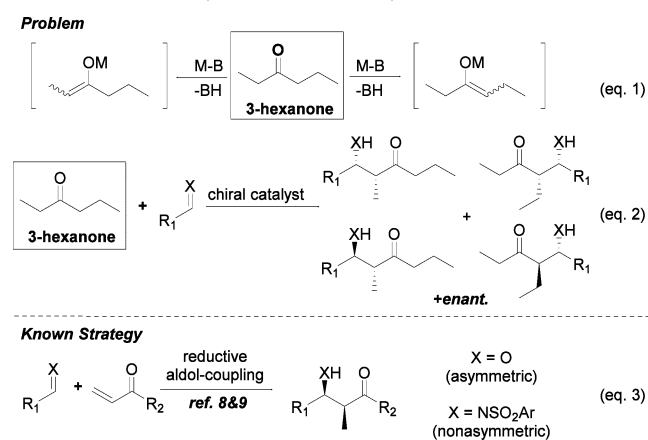
addition of such a ketone with an electrophile under catalytic conditions, up to eight total isomers are possible (eq 2).

One way to generate regiodefined acyclic dialkyl ketone enolates involves the metal-catalyzed reductive coupling of α,β-unsaturated ketones via hydrogenation (eq 3).[8] In such processes, the selected enone first undergoes 1,4-addition by hydride to generate the reactive enolate intermediate, which then is trapped by the desired electrophile.[9,10] Although effective, this strategy is generally applied to ketones bearing a simple vinyl group. Since an alkyne can function as a masked

alkane, the use of ynones also provides a potential route to direct regio-, diastereo-, and enantioselective modification on nonsymmetrical dialkyl ketones (Scheme 2). This particular

Scheme 2. Ynones as Advantageous Acyclic Donors in Enolate Chemistry
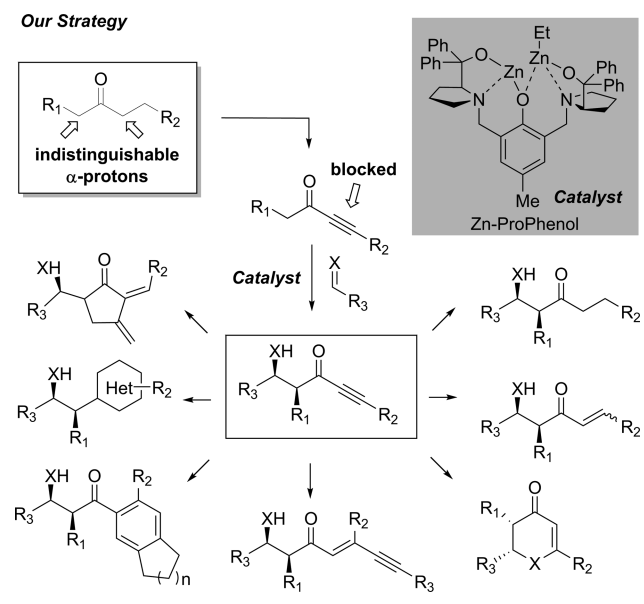

strategy relies on an acetylene moiety on one side of the ketone, preventing enolization on that side. After performing the enolate chemistry, the acetylene moiety can be transformed into a variety of compounds, including fully saturated unsymmetrical ketones via hydrogenation.

Reports of direct catalytic enolization of ynones for enantioselective additions are rare.[11] Previous examples in the literature mainly focus on aldol reactions between aldehydes and methyl ynones, and good diastereocontrol was only observed in the presence of an α-hydroxy group. More importantly, the use of ynones in Mannich-type reactions is unknown. The lack of methods for diastereo- and enantioselective Mannich-type reactions of ynones and the valuable α-substituted β-amino ynone products provided a fitting challenge and opportunity for further development of our metal−ProPhenol system.[12] The commercially available ProPhenol ligand is a member of the aza-crown family that was mainly inspired by the work of Cram on chiral crown compounds.[13] When treated with an alkyl metal reagent such as Et$_2$Zn or Bu$_2$Mg, this proline-derived ligand spontaneously assembles into a chiral dinuclear metal complex via deprotonation of the three hydroxyl groups. The resulting complex contains a Lewis acidic site to activate an electrophile and a Brønsted basic site to deprotonate a pronucleophile.

Despite previous success in an array of direct asymmetric aldol and Mannich-type reactions using zinc−ProPhenol catalysis, the scope of donors has been restricted to methyl ketones (acetophenones,[12a] acetone,[12e] methyl vinyl ketone,[12f] methyl ynones[11a]) or unsubstituted α-hydroxy carbonyl compounds.[12f,g] To demonstrate the difficulty of using higher alkyl ketones, a control experiment using 3-hexanone and imine A was conducted. As shown in eq 4 (Scheme 3), no desired Mannich product was observed using the Zn−ProPhenol catalyst. We therefore anticipated the possibility of ynones to overcome this observed limitation due to the unique steric and

Scheme 3. Control Experiments
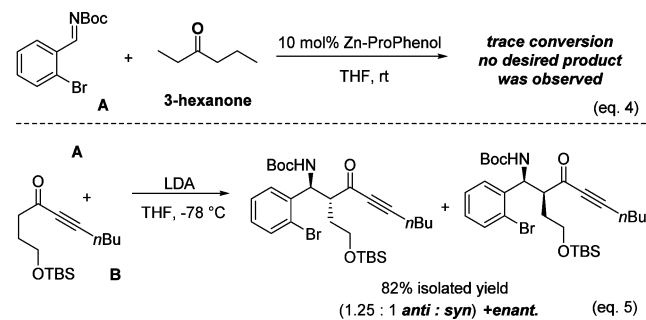
electronic properties of the alkyne group. The excellent properties of Boc as a nitrogen protecting group make the use of N-Boc imines preferentially attractive. However, curiously, according to a recent review, there are no examples of simple ketone enolates serving as suitable donors for such imines.[14] To illustrate the difficulty of controlling the enolate geometry via traditional approaches even in the case of alkynyl ketones, a control experiment using imine A and ynone B was conducted under standard enolate conditions (eq 5). As expected, poor diastereoselectivity of 1.25:1 was obtained, suggesting the lack of steric differentiation between the oxygen and the acetylene moiety. In this respect, the catalyst must exercise control of the enolate geometry.

■ RESULTS AND DISCUSSION

We initiated our studies with silyl-protected ynone **2a** as the model substrate since it is less likely to undergo undesired Michael addition due to steric bulk (Table 1). The benzyldimethylsilyl group was chosen due to the potential subsequent functionalization via Hiyama cross-coupling.[15] Moreover, Boc-protected aldimine **1a** was selected for the initial optimization process due to its stability and ease of handling. Astonishingly, the first experiment using 2 equiv of **2a** and aldimine **1a** in the presence of 20 mol % of Zn−ProPhenol catalyst produced a near perfect result (entry 1), in which the desired Mannich adduct **3a** was obtained as a single diastereomer in 99% yield and 97% ee. This result suggested that our catalyst system did generate one enolate isomer preferentially over the other. Decreasing the catalyst loading to 10 mol % did not show any detrimental effect. Although excellent selectivity was retained by further decreasing the catalyst loading to 5 mol %, the reaction never proceeded to full conversion even at room temperature (entry 3). Subsequent optimization showed that ynone **2a** can be reduced to 1.2 equiv to give **3a** in 99% yield and excellent diastereo- and enantioselectivity (entry 5). To our delight, reactions with alkyl-substituted ynone **2g**, which is more prone to undergo undesired Michael additions, gave comparable results despite minor erosion of the diastereoselectivity (entry 7), and further adjustment of the reaction temperature did not give significant improvement (entries 8 and 9). Eventually, by reducing the catalyst loading to 5 mol %, **3h** was obtained as a single diastereomer in 91% yield with excellent ee (entry 10). The high conversion of **2g** with only 5 mol % of catalyst in contrast to **2a** might potentially be due to the absence of the bulky silyl-protecting group directly attached to the acetylene moiety. Finally, it should be noted that the ligand can be easily recovered and recycled via chromatography (80% recovery), hence enhancing the effective turnover number.

Table 1. Optimization of the Reaction Conditions[a]
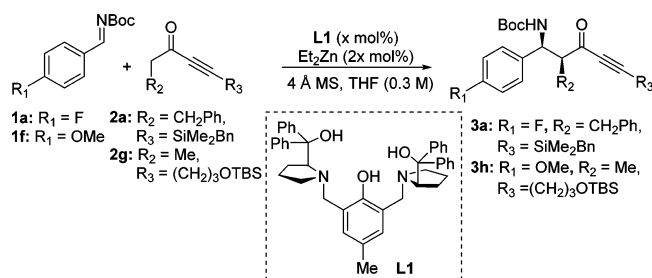
entry	3	x	equiv. of 2, T (°C)	yield[b]	dr[c]	ee[d]
1	3a	20	2, 4	99%	>20 : 1	97%
2	3a	10	2, 4	95%	>20 : 1	99%
3[e]	3a	5	2, rt	78%	>20 : 1	98%
4	3a	10	1.5, 4	96%	>20 : 1	97%
5	3a	10	1.2, 4	99%	>20 : 1	99%
6	3a	10	1.0, 4	85%	>20 : 1	99%
7	3h	10	1.2, 4	93%	15 : 1	99%
8	3h	10	1.2, -10	70%	16 : 1	99%
9	3h	10	1.2, rt	95%	15 : 1	95%
10[e]	3h	5	1.2, 4	91%	>20 : 1	99%

[a]Reaction conditions: 0.24 mmol of **1**, x mol % of **L1**, $2x$ mol % of Et$_2$Zn (1.0 M in hexanes), 4 Å molecular sieves (10 mg), in THF (0.3 M) at the indicated temperature and concentration. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC on a chiral stationary phase. [e]Reaction was done in 0.6 M THF.

With the optimized conditions in hand, we then evaluated the generality of this catalytic process (Table 2). On the acceptor side, a variety of aromatic N-Boc aldimines was successfully reacted with ynone donors. Both electron-withdrawing and electron-donating groups were tolerated in ortho, meta, and para positions. Heteroaromatic imines also gave the product in high yields and selectivities without poisoning the Zn catalyst. On the donor side, a variety of functional groups including alkenes, unprotected terminal acetylenes, esters, protected alcohols, arenes, and bulky alkyl chains were tolerated without significant perturbation of the reactivity and selectivities, demonstrating the high chemoselectivity of this catalytic process. Moreover, as described in the optimization table, reactions with alkyl-substituted ynones were performed using 5 mol % loading of catalyst (**3h−k**).

This reaction can also be performed using simple methyl ynones as donors (**3l−o**) to give high yields and excellent selectivity at −10 °C. To show the scalability and practicality of the method, several examples (**3h**, **3k**, **3m**) were performed at 2.4 mmol scale, giving comparable results to the small-scale reactions. In contrast to the result from the control experiment (Scheme 3), our new approach can allow the formation of ynone **3j** in 85% yield with excellent ee and dr. In addition, N-Dpp-protected imines were also examined. However, low conversions and selectivities were observed (see SI Table S5).

The catalytic process was also applicable to nonaromatic imines. Using the standard conditions with **L1**, α,β-unsaturated imine **1j** gave high product yields and diastereoselectivity (entry 1, Table 3). To enhance the enantioselectivity of this process,

Table 2. Scope of the Reaction with Aromatic Imines[a]

entry	3	Structure	yield[b]	dr/ee
1	a		99%	>20 : 1, 99%
2	b		95%	>20 : 1, 91%
3	c		88%	>20 : 1, 99%
4	d		86%	>20 : 1, 98%
5	e		75%	>20 : 1, 99%
6	f		95%	>20 : 1, 92%
7	g		89%	9.5 : 1, 99%
8[b]	h	2.4 mmol scale	91%	>20 : 1, 99%
9[b]	i		81%	13 : 1, 92%
10[b]	j		85%	17 : 1, 96%
11[b]	k	2.4 mmol scale	91%	16 : 1, 99%
12[c]	l		85%	NA, 97%
13[c]	m	2.4 mmol scale	85%	NA, 94%
14[c]	n		83%	NA, 92%
15[c]	o		80%	NA, 95%

[a]Reaction conditions: 0.24 mmol **1**, 0.29 mmol **2**, 10 mol % **L1**, 20 mol % Et2Zn, 4 Å molecular sieves (10 mg), in THF (0.3 M) at 4 °C for 16 h. [b]Reaction run with 5 mol % catalyst in THF (0.6 M). [c]Reaction run at −10 °C for 48 h.

Table 3. Optimization with α,β-Unsaturated Imine 1j[a]

entry	L	x	T (°C)	yield[b]	dr[c]	ee[d]
1	L1	10	4	88%	9 : 1	75%
2	L1	10	-10	68%	9 : 1	77%
3	L1	5	4	60%	10 : 1	74%
4	L2	10	4	96%	9 : 1	88%
5	L3	10	4	75%	7 : 1	77%
6	L4	10	4	85%	8 : 1	82%
7	L5	10	4	63%	8 : 1	65%
8	L6	10	4	80%	9 : 1	70%

[a]Reaction conditions: 0.24 mmol of 1, x mol % of L, 2x mol % of Et$_2$Zn (1.0 M in hexanes), 4 Å molecular sieves (10 mg), in THF (0.3 M) at the indicated temperature for 8 h. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC on a chiral stationary phase.

Table 4. Optimization with Aliphatic Imine 1k[a]

| entry	L	equiv. of 1k	slow add. (h)	yield[c]	dr[d]	ee[e]
1[b]	L1	1.0	0	n.p.	NA	NA
2	L1	2.0	3	32%	>20 : 1	82%
3	L1	2.0	6	55%	>20 : 1	80%
4	L1	2.0	12	88%	>20 : 1	85%
5	L1	1.5	12	84%	>20 : 1	85%
6	L2	1.5	12	89%	>20 : 1	95%
7	L3	1.5	12	75%	>20 : 1	80%
8	L4	1.5	12	86%	>20 : 1	88%

[a]Reaction conditions: 0.24 mmol of 2a, x mol % of L, 2x mol % of Et$_2$Zn (1.0 M in hexanes), 4 Å molecular sieves (10 mg), in THF (0.3 M) at rt and stirred for 12 h after imine addition. [b]No desired product. [c]Isolated yield. [d]Determined by ^{1}H NMR analysis. [e]Determined by HPLC on a chiral stationary phase.

Table 5. Reaction with Nonaromatic Imines

entry	3	Structure	yield[b]	dr/ee
1[a]	p	(BocHN, EtO$_2$C, O, OTBS)	86%	9 : 1, 88%
2[a]	q	(BocHN, EtO$_2$C, O, TBSO)	90%	9 : 1, 91%
3[a]	r	(BocHN, EtO$_2$C, O, SiMe$_2$Bn, Ph)	86%	>20 : 1, 99%
4[b]	s	(BocHN, O, SiMe$_2$Bn, Ph)	89%	>20 : 1, 95%
5[b]	t	(BocHN, O, SiEt$_3$)	85%	>20 : 1, 94%
6[b]	u	(BocHN, O, SiMe$_2$Bn, Ph)	95%	>20 : 1, 98%
7[b]	v	(BocHN, O, SiMe$_2$Bn, Ph)	95%	>20 : 1, 97%

[a]Reaction conditions: 0.24 mmol of 1, 0.29 mmol of 2, 10 mol % of L2, 20 mol % of Et$_2$Zn (1.0 M in hexanes), 4 Å molecular sieves (10 mg), in THF (0.3 M) at 4 °C for 8 h. [b]Reaction run with dropwise addition of imines (1.5 equiv) over 12 h at rt.

several ligands were examined, especially the recently developed non-C_2-symmetric ProPhenol ligands, which have been shown to improve the enantioselectivity substantially in the vinylation reaction previously described.[12h] To our delight, the combination of p-trifluoromethylphenyl and phenyl in the prolinol backbone L2 was found to be optimal without perturbing the conversion and diastereoselectivity (entry 4). Interestingly, when switching to the more electron-rich ligand L3 (entry 5), the enantioselectivity was similar to the parent ProPhenol ligand L1. The differential enantioinduction of L2 was further demonstrated by performing the reaction with the C_2-symmetric analogous L5, in which significant decreases in yield and enantioselectivity were observed (entry 7). Curiously, using a donor−acceptor substituted as in L4 also showed a decrease in ee as well as yield (entry 6). ProPhenol L6, which has been shown to improve the enantioselectivity of the aldol reaction of glycinate benzophenone imines, did not result in any beneficial effect.[12i]

Initial examination using aliphatic imine 1k, on the other hand, led to complete isomerization to the corresponding enecarbamate under typical reaction conditions (entry 1, Table 4). This observation suggested the α-proton of imine 2k is comparably or even more acidic than the α-protons of ynone 2a under the reaction conditions. Fortunately, we were able to overcome this undesirable process via slow addition of the imine. Subsequent adjustments of the addition rate as well as the equivalence of imine gave 84% yield and 85% ee as a single diastereomer (entry 5). Finally, further ligand optimization showed that the same non-C_2-symmetric ligand L2 was optimal for the enantioselectivity (entry 6).

With the optimized conditions, different nonaromatic N-Boc imines were examined (Table 5). In general, good to excellent selectivities were observed. More importantly, imines bearing

two enolizable α-protons were also compatible substrates in this process (entries 6 and 7), giving the corresponding ynones in excellent yields and selectivities. The incorporation of these

**Scheme 4. Exemplified One-Step Structural Diversification of β-Amino Ynones**
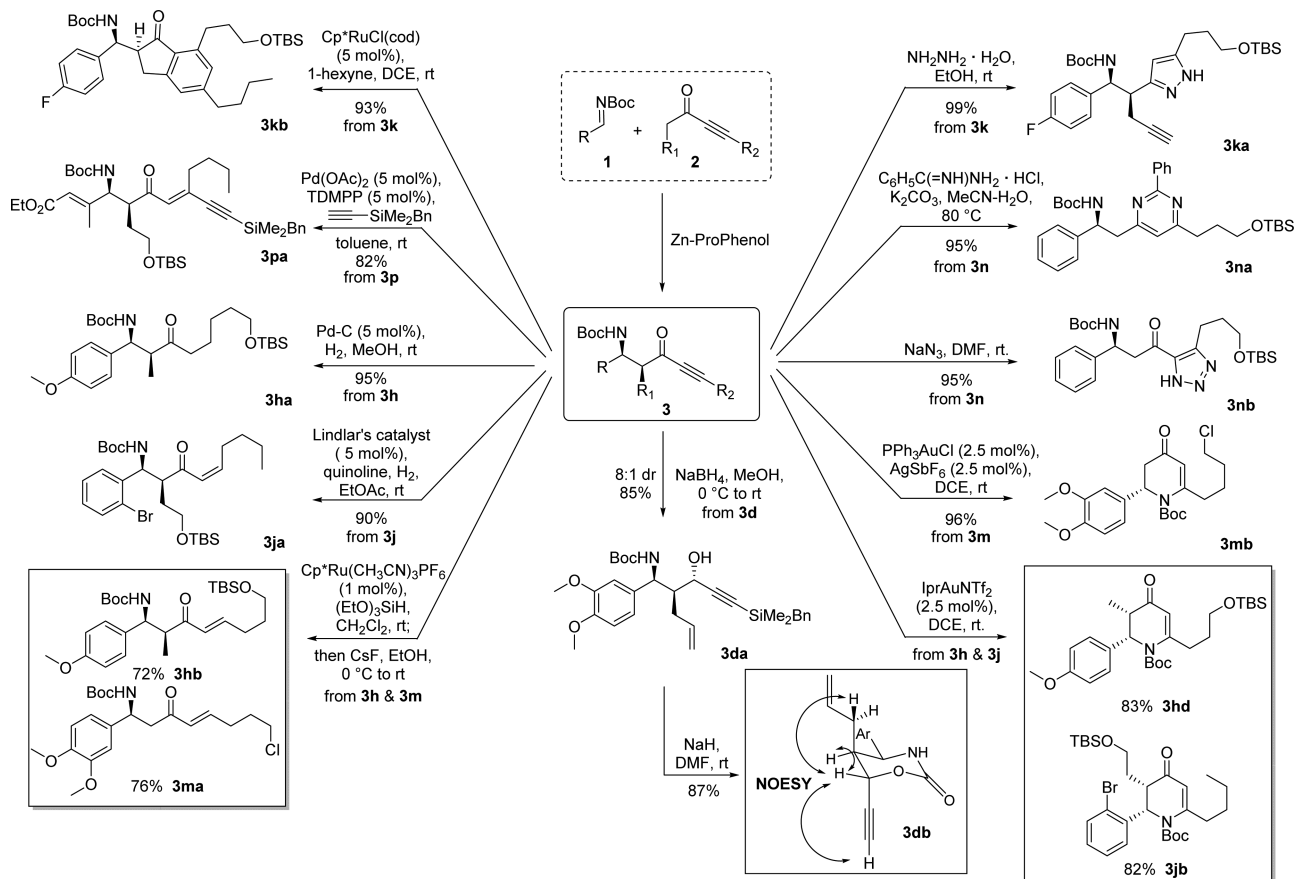
highly enolizable imines not only considerably enhances the scope of this reaction but also serves as a rare occasion where simple ketones are used as successful donors.[14]

We then further elaborated the obtained products **3** to demonstrate their synthetic utility, especially with respect to library design in which each Mannich adduct can be converted into a wide diversity of scaffolds via a single step (Scheme 4). These transformations also validate the utility of ynones as a masked synthetic equivalent for a variety of unsymmetrically substituted acyclic ketones. Ketones with different degrees of unsaturation can be readily prepared. Pd−C-catalyzed hydrogenation gave the fully saturated ketone **3ha** in 95% yield, demonstrating an efficient route to products equivalent to direct functionalization of unsymmetrical dialkyl ketones via two effective atom-economic catalytic addition processes. Our previously developed Ru-catalyzed hydrosilylation and subsequent same-pot desilylation with CsF gave (*E*)-enones **3hb** and **3ma** in good yields,[16] whereas (*Z*)-enone **3ja** was generated upon partial hydrogenation using Lindlar's catalyst with quinoline. Heterocycles, including pyrazole **3ka**, pyrimidine **3na**, and triazole **3hc**, were obtained in excellent yields using literature single-step processes.[7a−c] Upon $NaBH_4$ reduction, chiral propargyl alcohol **3da** was prepared in high yield with 8:1 dr, and the relative configuration was determined by NOESY after cyclization to the cyclic carbamate **3db** using NaH. The benzyldimethylsilyl group was removed during the reaction as well due to in-situ-generated *tert*-butoxide.

A 6-*endo-dig* cyclization catalyzed by in-situ-generated PPh_3AuSbF_6 gave pyridinone **3mb** in 96% yield,[17] which is an important intermediate for a later total synthesis (Scheme

5). α-Substituted ynones, which have never been employed in this type of transformation, reacted sluggishly with significant epimerization at the α-position using the same catalyst, but changing to a more σ-donating NHC ligand gave **3hd** and **3jb** in high yields without any side reaction. The relative configurations of the α-substituted β-amino ynones were

Scheme 5. Total Synthesis of (−)-Lasubine II
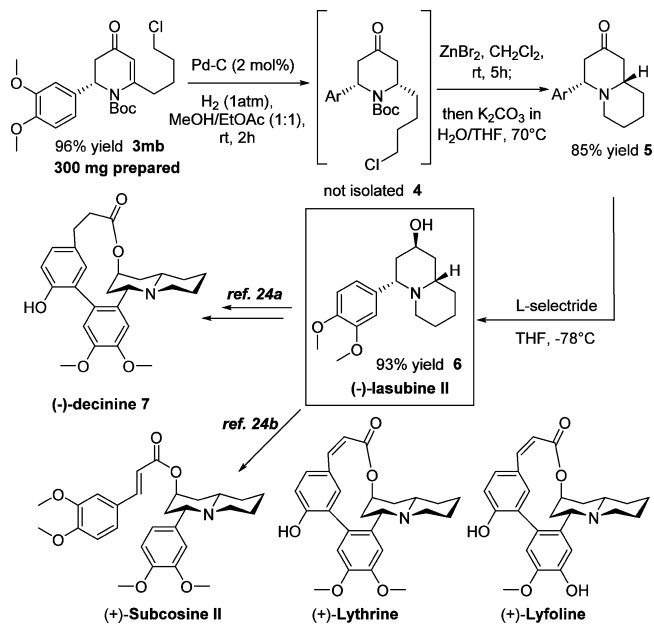
unambiguously determined by comparing the vicinal homo-nuclear $^1H-^1H$ coupling constants upon Au-catalyzed 6-*endo-dig* cyclizations, which are consistent with other results reported in the literature.[18] Using our reported Pd-catalyzed alkyne–alkyne coupling conditions, heavily functionalized enyne **3pa** was obtained in 82% yield with excellent stereo- and chemoselectivity.[5c] Finally, Ru-catalyzed [2 + 2 + 2] cyclo-addition[19] with 1-hexyne gave β-amino indanone **3kb**, a member of a class of molecule that can modify muscarinic receptor activity for treating or alleviating diseases,[20] in 93% yield as a single regioisomer.

Pyridinone **3mb** was readily converted into (−)-lasubine II **6** (Scheme 5), which was originally isolated from the leaves of *Lagerstroemia subcostata koehne* by Fuji et al.[21] The quinolizidine moiety is widely encountered in drug-like compounds and natural products of potential biological activities.[22] After Pd–C-catalyzed hydrogenation, $ZnBr_2$-mediated Boc deprotection followed by a same-pot intramolecular S_N2 displacement under basic condition furnished quinolizidine **5** in 85% yield. Other typical Boc removal conditions, including TFA, TMSOTf, HCl in organic solvents, thermolysis, and other metallic Lewis acids, generally resulted in ring opening via elimination of the C–N bond due to the adjacent electron-rich aromatic group. Subsequent reduction using L-selectride gave (−)-lasubine II **6** in 93% yield as a single diastereomer.[23] Alkaloid **6** is also an essential fragment in many bioactive compounds from the Lythraceae alkaloid family,[24] one noticeable example being (−)-decinine **7**, which can be readily synthesized from **6**.[25] The total synthesis of **6** further demonstrated the exceptional synthetic utility of our methodology incorporating ynones, in which cyclic tertiary alkaloids can be readily constructed from the common backbone **3**.

The absolute configuration of the C–N bond of **3** was further confirmed using *O*-methylmandelic amides[26] **9** and **9′** derived from **3da** after Boc removal using TFA and the subsequent same-pot EDC coupling (Scheme 6). Substantial anisotropic magnetic effects were observed on H1 and H2 of **9** due to the proximal phenyl ring on the *O*-methylmandelic acid moiety in the most stable conformation. A similar shielding effect was also observed on the 3,4-dimethoxyphenyl group of **9′** when the opposite enantiomer of *O*-methylmandelic acid was applied.

The proposed catalytic cycle is depicted in Scheme 7. After the formation of the dinuclear Zn–ProPhenol complex **10**, deprotonation of ynone **2** occurs and places the nucleophile in a chiral environment (**11** and **11′**), in which the enolate can adopt either the (*E*)- or the (*Z*)-geometry with reversible interconversion. N-Boc imine **1** then enters the reaction cycle and binds preferentially to the catalyst system bearing the (*Z*)-enolate via a bidentate coordination to both zinc atoms (**12**). This explains the high diastereoselectivity of the reaction even when the electrophiles were introduced in slow addition as shown in the case of aliphatic imines. The particular arrangement of **12** minimizes the steric interactions of notably R and R1 of both substrates and the corresponding prolinol diphenyl ligand substituents. The enolate then attacks the electrophile to give intermediate **13** with the observed stereochemistry. Finally, deprotonation of ynone **2** liberates the Mannich-adduct **3** and turnovers the catalytic cycle.
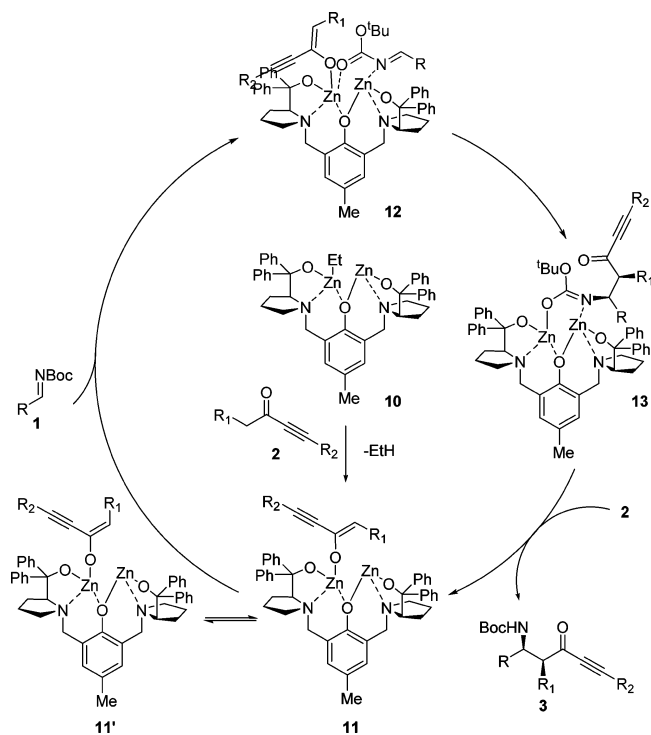
◼ CONCLUSION

The present study provides a highly chemo-, diastereo-, and enantioselective Mannich-type reaction using ynones as the

Scheme 6. Determination of Absolute Stereochemistry Using *O*-Methylmandelic Acid
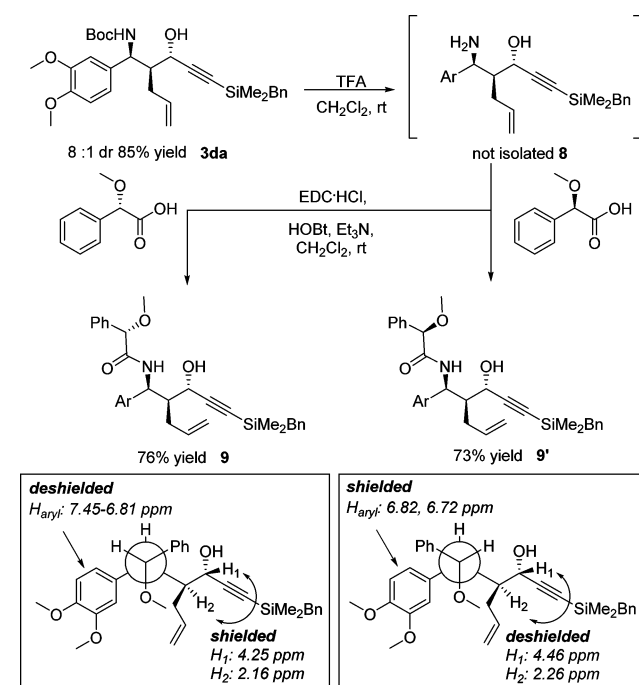
Scheme 7. Proposed Catalytic Cycle

donors catalyzed by the Zn–ProPhenol complex. This method tolerates a variety of functional groups on the donors and acceptors, allowing rapid construction of chiral and heavily functionalized α-substituted β-amino ynones. This process provides the broadest spectrum of Mannich products in a catalytic fully selective manner. More importantly, the products offer rapid access to a broad spectrum of chiral-amine-containing skeletal types utilizing the synthetic versatility of the ynone moiety and also provide an effective route to

selectively functionalize unsymmetrical dialkyl ketones. This Mannich–ynone approach can facilitate lead discovery in medicinal chemistry and the preparation of pharmaceutical analogues and complex natural products. Considering the broad scope and functional group compatibility of this methodology along with the high diastereo- and enantioselectivity, we anticipate that this process can be expanded to other electrophiles, such as aldehydes, ketones, or ketimines, offering new classes of chiral ynones ready for structural diversification.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11248.

> Experimental procedures and compound characterization description (PDF)
> Compound spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(2) A control experiment was conducted by exposing ynone **2g** to catalytic potassium *tert*-butoxide (5 mol%) in anhydrous THF. The resulting complicated mixture due to decomposition suggested the intrinsic instability of ynones under basic conditions.

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