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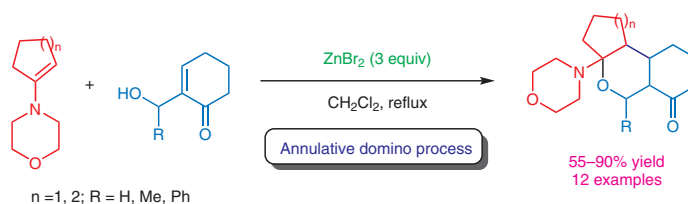
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First Zinc Bromide Promoted Annulative Domino Reactions between Enamines and Cyclic Morita–Baylis–Hillman Alcohols: Synthesis of *N,O*-Ketals

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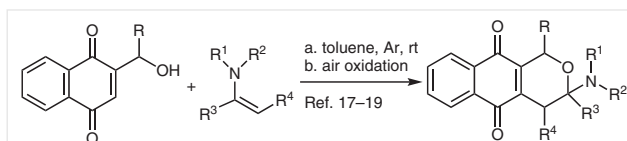
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Abstract A new efficient $ZnBr_2$ -mediated annulative domino reaction between enamines and cyclic Morita–Baylis–Hillman (MBH) alcohols is disclosed. The process involves a tandem sequence (intermolecular conjugate addition of enamines to MBH alcohols and intramolecular nucleophilic addition of the hydroxyl moiety to the transiently generated iminium ion), affording the corresponding *N,O*-ketals diastereoselectively in good yields.

Key words MBH alcohol, conjugate addition, enamines, domino reactions, zinc bromide, *N,O*-ketals

alcohol moiety. The reaction involves an intermolecular 1,4-addition of the enamine to the enone moiety, followed by a spontaneous intramolecular addition of the hydroxyl group to the transiently generated iminium ion. Following exposure to air, the resulting adducts were oxidized to the corresponding aminonaphthopyran diones (Scheme 1).



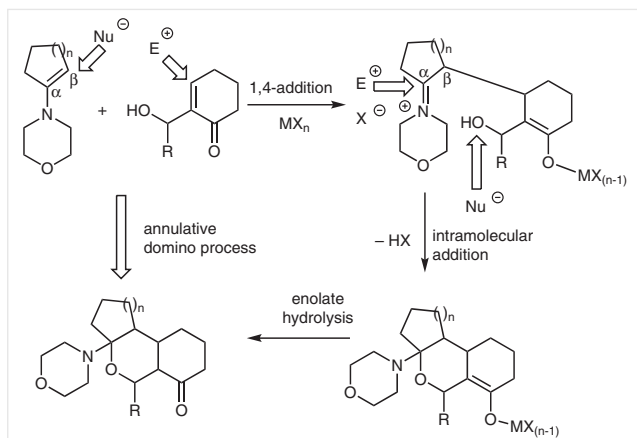
Scheme 1 Reactions of enamines with naphthoquinone derivatives

Enamines are versatile synthetic intermediates^{1,2} that are commonly involved in the chemistry of natural products such as terpenes, steroids, alkaloids and pharmaceuticals.³ After the pioneering work of Stork⁴ in the fifties, the nucleophilic behavior of this functional group has been successfully exploited in a number of conjugate additions to electron-poor alkenes such as α,β -unsaturated enones,^{5,6} allyl ketones and esters,⁷ as well as methyl acrylate,⁸ 2-formylcyclohexenones,⁹ and 2-acetyl-1,4-naphthoquinones.¹⁰

Moreover, enamines are capable of undergoing palladium- as well as iridium-catalyzed S_N2 and/or S_N2' C-allylations in the presence of allylic acetates,^{11,12} phenyl ethers,¹³ benzotriazoles,¹⁴ carbonates,¹⁵ and even allylic alcohols.¹⁶

In particular, Kobayashi and co-workers^{17–19} have studied the coupling reaction between enamines and α -(1-hydroxyalkyl)-1,4-naphthoquinones, as bifunctional substrates bearing an enone function juxtaposed to an allylic

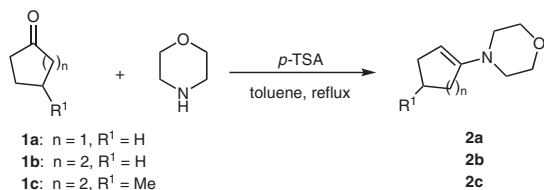
Recently, our group²⁰ reported a $ZnBr_2$ promoted^{21–23} palladium-catalyzed allylation of ketoenamines with MBH adducts bearing good leaving groups such as acetates and ethers. We now report a new reactivity, taking place between these ketoenamines and unprotected Morita–Baylis–Hillman (MBH) alcohols carrying a poor leaving group (OH). On the one hand, an enamine bears a nucleophilic site at the β -carbon, while an electrophilic site at the α -carbon is generated in the initial product of its C-allylation. On the other hand, an MBH adduct bears an electrophilic site at the β -position to the carbonyl group as well as a nucleophilic hydroxyl moiety. We thus reasoned that if the first interaction between these reaction components involved the conjugate addition of the enamine to the MBH alcohol, under appropriate reactions conditions, we might be able to accomplish an annulative domino reaction, as shown in Scheme 2.



Scheme 2 Annulative domino reactions of enamines and MBH alcohols

The enamines **2a–c** were prepared by the reaction between the corresponding ketones **1a–c** and morpholine under conventional reaction conditions^{20,24} (Table 1).

Table 1 Synthesis of Enamines **2a–c** from the Reaction of Ketones **1a–c** with Morpholine^a



Entry	Enamine 2	Reaction time (days)	Yield 2 (%) ^b
1		3	60
2		4	70
3		1	65

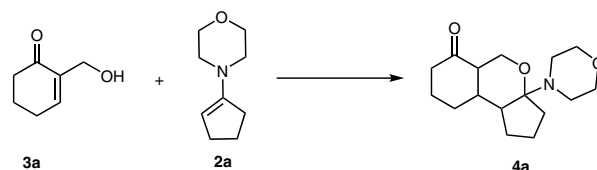
^a Reaction conditions: ketone **1a–c** (1.0 equiv), morpholine (1.5 equiv), *p*-toluenesulfonic acid (2 equiv), toluene.

^b Isolated yield.

We then explored the reaction between MBH alcohol **3a** (1 equiv) and enamine **2a** (1 to 5 equiv) as the model reaction. At room temperature, or at 40 °C, under solvent-free conditions, and without any additive, the starting materials were always recovered (Table 2, entry 1). The same result was obtained using CH₂Cl₂ as the solvent at room temperature or at reflux for 24 h (entries 2 and 3). Extensive further experimentation allowed us to establish the optimized con-

ditions as ZnBr₂ (3 equiv), CH₂Cl₂, reflux. Under these conditions, the reaction between MBH alcohol **3a** (1 equiv) and enamine **2a** (5 equiv) afforded the desired annulated *N,O*-ketal **4a** within 3 h (entry 4) in 90% yield as a single diastereoisomer (Scheme 3, see below).

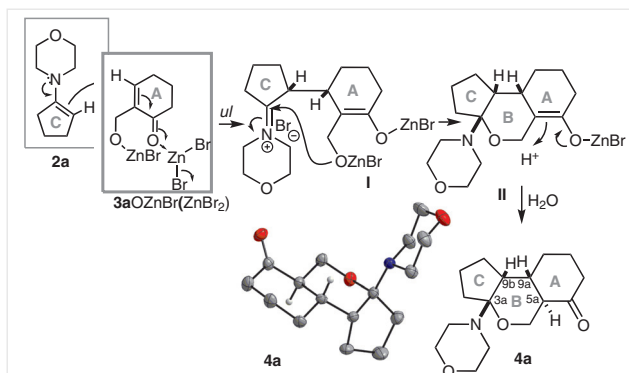
Table 2 Optimization of the Reaction Conditions for the Synthesis of **4a**^a



Entry	Additive	Solvent	<i>T</i> (°C)	Time (h)	Yield 4a (%) ^b
1	none	none	r.t. → 40	24	none
2	none	CH ₂ Cl ₂	r.t.	24	none
3	none	CH ₂ Cl ₂	reflux	24	none
4	ZnBr ₂ (3 equiv)	CH ₂ Cl ₂	reflux	3	90

^a Reagents and condition for optimized conditions: cyclic MBH alcohol **3a** (1.5 mmol, 1 equiv), enamine **2b** (5 equiv) ZnBr₂ (3 equiv), CH₂Cl₂, reflux.
^b Isolated yield.

We believe that the mechanism of this reaction involves the initial conjugate addition of enamine **2a** to the ZnBr₂-activated MBH adduct **3a** to afford the corresponding iminium intermediate **I**, followed by intramolecular addition^{25,26} of the zinc alkoxide function to the transiently formed iminium ion to give the *N,O*-ketal zinc enolate **II**. Final hydrolytic quench affords the *N,O*-ketal **4a**^{18,27} (Scheme 3, Table 2, entry 4). From a mechanistic viewpoint, it is worth noting that the role of ZnBr₂ in the present reaction is different from that of our previous study.²⁰ Indeed, while in our previous study ZnBr₂ triggered the generation of a η³-allyl palladium complex, in this study it is expected to be involved in the conjugate addition step as well as the subsequent cyclization onto the iminium ion.



Scheme 3 Proposed mechanism for the domino reaction **2a** + **3a** to give **4a** and X-ray crystal structure of **4a**. Thermal ellipsoids are shown at 30% probability.

The structure of the *N,O*-ketal **4a** as well as the nature of the A/B and B/C ring junctions were elucidated on the basis of X-ray diffraction analysis. Notably, the domino reaction generates, in a single operation, four contiguous stereogenic centers (3aR*,5aR*,9aS*,9bR*) with complete diastereoselection. Such a selectivity is determined in the course of three separate steps. Indeed, the relative stereochemistry at C9a/C9b is determined during the 1,4-addition, which takes place with *ul* topicity, while center C3a is determined in the subsequent alkoxy addition to the iminium ion. Finally, the stereochemistry at C5a is decided during the hydrolytic enolate quench. The A/B *trans* junction for compound **4a** is consistent with the work of Alexakis²⁸ on conjugate additions to α -substituted cyclic enones. The observed selectivity for the *cis*-fusion of the B/C rings is not surprising, being the result of a 6-*exo-trig*-nucleophilic addition on a five-membered electrophilic substrate. This is also in line with the work of Kobayashi and co-workers,¹⁸ who showed that the treatment of 2-hydroxymethyl-1,4-naphthoquinone with morpholine enamines afforded exclusively *cis*-3-morpholino-3,4-dihydro-1*H*-naphthopyran-5,10-diones.

To examine the scope of this reaction, a variety of differently substituted ($R^2 = \text{H, Me, Ph}$) six- and five-membered cyclic MBH alcohols **3a-d** were selected and their behavior towards enamines **2a-c** was investigated, under the previously optimized conditions (ZnBr_2 (3 equiv), dichloromethane, reflux) (Table 3, entries 2–12). Thus, the addition of enamines **2b** and **2c** was also successfully performed with six-membered cyclic alcohol **3a** ($n = 2$, $R^2 = \text{H}$), providing **4b** and **4c** in 87 and 80% yields, respectively (entries 2 and 3). Moreover, the reaction of enamines **2a-c** with five-membered cyclic alcohol **3b** ($n = 1$, $R^2 = \text{H}$) worked well, furnishing, within 4–5 h, the *N,O*-ketals **4d-f** in 55–58% yields (entries 4–6).

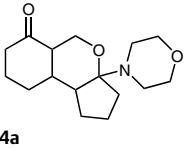
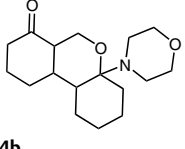
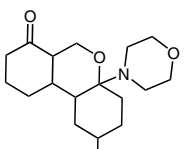
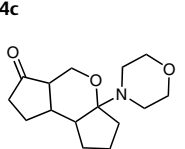
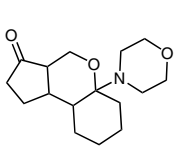
These interesting results prompted us to also investigate the behavior of β -substituted cyclic MBH alcohols **3c,d** ($n = 2$, $R^2 = \text{Me, Ph}$) towards enamines **2a-c** to elucidate the possible effect of steric hindrance at the β' -carbon on the course of the reaction. Under the optimized conditions, we observed that the optimized protocol still works well, leading to the *N,O*-ketals **4g-l** in 60–75% yields (entries 7–12).

It is notable that the isolated yields of adducts **4g-l** (60–75%), using β' -substituted alcohols **3c** and **3d** ($n = 2$, $R^2 = \text{Me, Ph}$) (Table 3, entries 7–12) are lower than those of **4a-c** (80–90%), starting from the alcohol **3a** ($n = 2$, $R^2 = \text{H}$) (entries 1–3). We believe that the presence of a substituent at the β' -position of alcohols **3c** and **3d** may introduce a moderate steric hindrance responsible for the yield decrease in **4g-l**.

In conclusion, we have described an efficient synthetic route toward polycyclic functionalized *N,O*-ketals **4a-l**²⁹ via a ZnBr_2 -promoted annulation between morpholine enamines and cyclic MBH alcohols. The mechanism of this transformation is proposed to involve an initial conjugate addition of the enamine to the α,β -unsaturated ketone followed

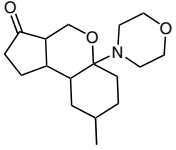
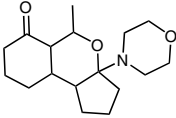
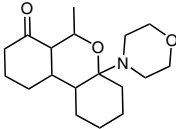
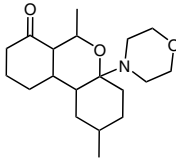
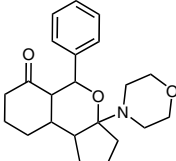
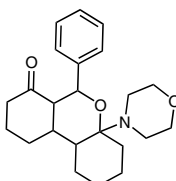
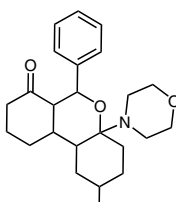
by an intramolecular addition of the zinc alkoxide to the iminium ion. Since *N,O*-ketals are known for their interesting biological activities as well as their use as precursors for complex molecules,³⁰ in vitro biological activity tests for the derivatives **4a-l** are in progress in our laboratory. Moreover, compounds **4a-l** can be regarded as masked 1,5-diketones, the deketalization of which would generate the corresponding open 1,4-addition adducts.²⁷ In future work, we plan to expand the scope of this protocol to include noncyclic MBH adducts³¹ and a variety of enamines using various catalysts.^{20,32–34}

Table 3 Annulative Domino Reactions of Enamines **2a-c** and Cyclic MBH Alcohols **3a-d**^a

Entry	Alcohol 3	Enamine 2	Time (h)	<i>N,O</i> -Ketal 4	Yield 4 (%) ^b
1	3a	2a	3		90
2	3a	2b	5		87
3	3a	2c	4		80
4	3b	2a	5		55
5	3b	2b	5		57

$n = 1, 2$; $R^2 = \text{H, Me, Ph}$; $R^1 = \text{H, Me}$

Table 3 (continued)

Entry	Alcohol 3	Enamine 2	Time (h)	<i>N,O</i> -Ketal 4	Yield 4 (%) ^b
6	3b	2c	4		58
				4f	
7	3c	2a	4		67
				4g	
8	3c	2b	6		60
				4h	
9	3c	2c	6		65
				4i	
10	3d	2a	7		70
				4j	
11	3d	2b	6		73
				4k	
12	3d	2c	7		75
				4l	

^a Reaction performed using cyclic MBH alcohols **3** (1 equiv), ketoenamine **2** (5equiv), and ZnBr₂ (3 equiv), CH₂Cl₂, reflux.

^b Isolated yield.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0040-1707467>.

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- (29) **Synthesis of *N,O*-Ketals **4a–l**; General Procedure:** Under nitrogen, a mixture of cyclic MBH alcohols **3** (1.5 mmol), and ZnBr₂ (4.5 mmol, 1.013 g) was heated to reflux in CH₂Cl₂ (10 mL) for 15 min. Then a solution of enamine **2a–c** (7.5 mmol) in CH₂Cl₂ (5 mL) was added, and the reaction mixture was heated to reflux for 3–6 h. After the evaporation of CH₂Cl₂, water (10 mL) and aq NaOH (1 M, 30 mL) were added, and the mixture was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layers were washed with a saturated solution of ammonium chloride (10 mL) and dried over magnesium sulfate. After filtration and removal of solvent, the residue was subjected to column chromatography, eluting with petroleum ether/ether/acetone = 40:40:20, to produce the pure *N,O*-ketals **4a–l**.
3a-Morpholinodecahydrocyclopenta[c]isochromen-6(2H)-one (4a): Yield: 90%; white solid; mp 146–148 °C. ¹H NMR (CDCl₃, 300 MHz): δ = 4.03 (t, *J* = 12 Hz, 1 H), 3.69 (t, *J* = 4.5 Hz, 4 H), 3.62 (dd, *J* = 6, 3 Hz, 1 H), 2.67–2.55 (m, 2 H), 2.42–2.27 (m, 5 H), 2.16–2.08 (m, 3 H), 1.81–1.69 (m, 4 H), 1.64–1.47 (m, 5 H).
¹³C NMR (CDCl₃, 75 MHz): δ = 212.1, 97.1, 67.3, 58.7, 46.8, 45.8, 41.8, 40.9, 39.0, 29.7, 28.3, 26.5, 22.6, 19.8. HRMS: *m/z* [M + H]⁺ calcd for C₁₆H₂₅NO₃⁺: 280.1913; found: 280.1913.
4a-Morpholino-6-phenyldecahydro-1H-benzo[c]chromen-7(10bH)-one (4k): Yield: 73%; white solid; mp 153–155 °C. ¹H NMR (CDCl₃, 300 MHz): δ = 7.84–7.82 (m, 2 H), 7.55–7.37 (m, 3 H), 4.26 (d, *J* = 12 Hz, 1 H), 3.64 (t, *J* = 4.5 Hz, 4 H), 3.16 (tt, *J* = 3, 6 Hz, 1 H), 2.54–2.35 (m, 4 H), 2.30–2.10 (m, 4 H), 1.88–1.43 (m, 7 H), 1.30–0.86 (m, 5 H). ¹³C NMR (CDCl₃, 75 MHz): δ = 209.3, 198.7, 137.9, 132.9, 128.6, 128.1, 67.8, 64.8, 61.9, 42.1, 40.7, 40.4, 26.2, 25.8, 25.5, 25.5, 23.9, 23.8. HRMS: *m/z* [M + H]⁺ calcd for C₂₃H₃₁NO₃⁺: 370.2382; found: 370.2381.
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