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N-Benzyloxyacrylamides as Bisnucleophiles in an Organocatalyzed Domino aza-Michael/Morita-Baylis-Hillman Sequence

Ismail Alahyen, Catherine Taillier, Jérôme Lhoste, Vincent Dalla,* and Sébastien Comesse*



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ABSTRACT: We herein describe a stereoselective organocatalyzed aza-Michael/Morita-Baylis-Hillman reaction between readily accessible acrylamides and α,β -unsaturated carbonyls. This novel, PPh_3 -promoted atom economic one-pot process features medium to good yields and good stereoselectivity leading to variously substituted piperidin-2-ones bearing an exocyclic olefinic bond, which was shown to be an excellent anchor for further chemical diversification.



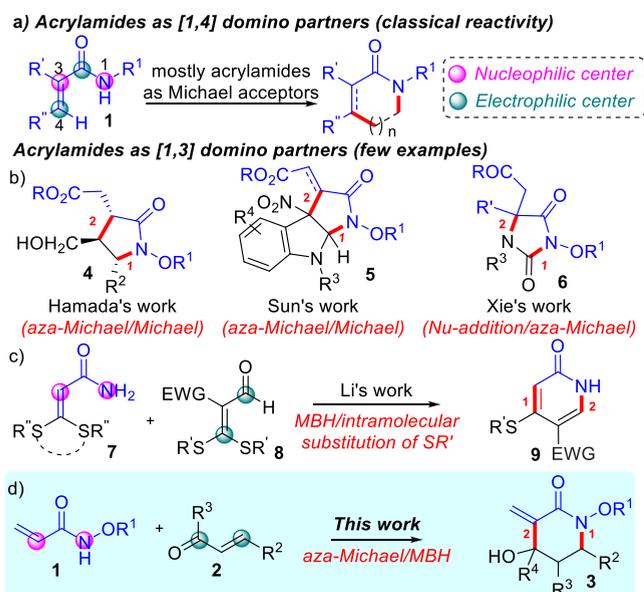
Acrylamides **1** are adaptative building blocks embedding multiple reactive sites: (i) a nucleophilic nitrogen atom, (ii) an electrophilic carbonyl carbon, (iii) an underlying nucleophilic α -carbon, and (iv) an electrophilic β -carbon (see [Scheme 1](#)). Thus, the modular nature of acrylamides **1** potentially offers a myriad of possibilities in domino chemistry for heterocyclic syntheses,¹ through the implementation of controlled and well-orchestrated sequences involving two (or more) of the reactivity centers mentioned above. The synthetic value of these interesting domino reactive platforms has already been nicely illustrated through either metal-catalyzed

or organocatalyzed methods;² nevertheless, their huge potential is still largely untapped. Indeed, most of the nonmetal strategies published so far rely on acrylamides **1** as [1,4]-dipoles typically forming δ -lactams through sequences using an acrylamide as a Michael acceptor first and then an aza-nucleophile (see [Scheme 1a](#)). Only a handful of inverse sequences, starting with an aza-Michael addition, have been reported.³ Likewise, examples of domino transformations of acrylamides based on 1,3-reactive centers targeting γ -lactams have barely been described.

Hamada and co-workers published in 2012 a well-designed iminium-based enantioselective aza-Michael/Michael sequence starting from *N*-alkoxyacrylamides ([Scheme 1b](#)).⁴ This organocatalytic reaction implied equipping the acrylamides **1** with an *N*-alkoxy moiety ($\text{R}^1 = \text{OR}^1$)⁵ to increase aza-nucleophilicity and a β -ester ($\text{R}'' = \text{CO}_2\text{R}$) to cause umpolung of the α -center into an electrophilic site. On reaction with cinnamaldehyde derivatives or cyclic enones, these custom [1,3]-*N*, α -dipolar acrylamides gave, after subsequent NaBH_4 reduction in MeOH of the aldehyde function, the desired densely functionalized γ -lactams **4**. In line with Hamada's work, Sun's⁶ team and Xie et al.⁷ have developed two related organocatalytic variants for the synthesis of γ -lactams **5** and **6**, respectively.

To the best of our knowledge, a single example of acrylamides engaged as [1,3]-bis-nucleophilic domino partners is known and was published by Li et al. for the synthesis of substituted 2-pyridones **9** ([Scheme 1c](#)).⁸ This peculiar Morita-

Scheme 1. Reactivity of Acrylamides in Nonmetal Catalyzed Domino Reactions and This Work



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Baylis-Hillman (MBH)/intramolecular substitution of an SR' sequence triggered by acidic conditions was based on the use of rather exotic ketene S,S-acetals **7** and **8**.

The above overview shows to which extent the modular nature of acrylamides is underexploited, and in particular, their potential as 1,3-bis-nucleophiles in domino reactions is virtually blank. Besides novelty, the motivations to develop this specific axis of the domino chemistry of acrylamides is supported by several assets, including the great simplicity and accessibility of potential reactive partners, rapid access to polysubstituted and postfunctionalizable N-heterocycles, under conditions respecting the economy of atoms and steps. Our team has been interested for a long time in the development of such domino reactions starting from simple substrates for the synthesis of functionalized lactams.⁹ In the present study, an organocatalyzed aza-Michael/MBH domino reaction between N-alkoxyacrylamides **1** and Michael acceptors **2** has been designed (Scheme 1d)¹⁰ as a new methodology allowing one-pot efficient access to polysubstituted piperidin-2-ones (δ -lactams) **3** bearing an exocyclic alkene easily modulable.

N-Benzyloxyacrylamide **1b** and crotonaldehyde **2b** were chosen as model substrates to optimize the reaction conditions (Table 1). Isopropanol (*i*-PrOH) was first selected as a solvent,

Table 1. Optimization of the Reaction Conditions^a

entry	Cat. (%)	solvent	T (°C), time	yield ^b (%)	dr ^c (%)
1	none	<i>i</i> -PrOH	rt, 24 h	0	0
2	DABCO (50)	<i>i</i> -PrOH	rt, 35 h	26	80:20
3	DMAP (50)	<i>i</i> -PrOH	rt, 35 h	36	82:18
4	PPh ₃ (50)	<i>i</i> -PrOH	rt, 20 h	81	89:11
5	P(Bu) ₃ (50)	<i>i</i> -PrOH	rt, 20 h	dec ^d	-
6	PPh ₃ (50)	EtOH	rt, 24 h	74	92:8
7	PPh ₃ (50)	DCM	rt, 48 h	64	88:12
8	PPh ₃ (50)	CHCl ₃	rt, 72 h	53	89:11
9	PPh ₃ (50)	MeCN	rt, 48 h	71	83:17
10	PPh ₃ (50)	DMF	rt, 70 h	24	89:11
11	PPh ₃ (20)	<i>i</i> -PrOH	rt, 20 h	56	89:11
12	PPh ₃ (20)	<i>i</i> -PrOH	50, 20 h	69	89:11
13	PPh ₃ (50)	<i>i</i> -PrOH	50, 7 h	86	89:11

^aReactions were carried out with acrylamide **1b** (0.28 mmol, 1 equiv), crotonaldehyde **2b** (0.56 mmol, 2 equiv), and catalyst (usually 0.14 mmol, 0.5 equiv) in 1.4 mL of solvent. ^bIsolated yield of **3a**. ^cdr: diastereomeric ratio determined on the crude mixture. ^ddec: decomposition. DABCO: 1,4-diazabicyclo[2.2.2]octane. DMAP: 4-(dimethylamino)pyridine.

since it is commonly used in MBH transformations and is compatible with the initial aza-Michael step. No reaction occurred in the absence of any promoter at room temperature (Table 1, entry 1, see SI). Because Lewis bases are common catalysts for the two individual transformations involved in the domino process, we envisioned a procedure catalyzed by a single organic compound.

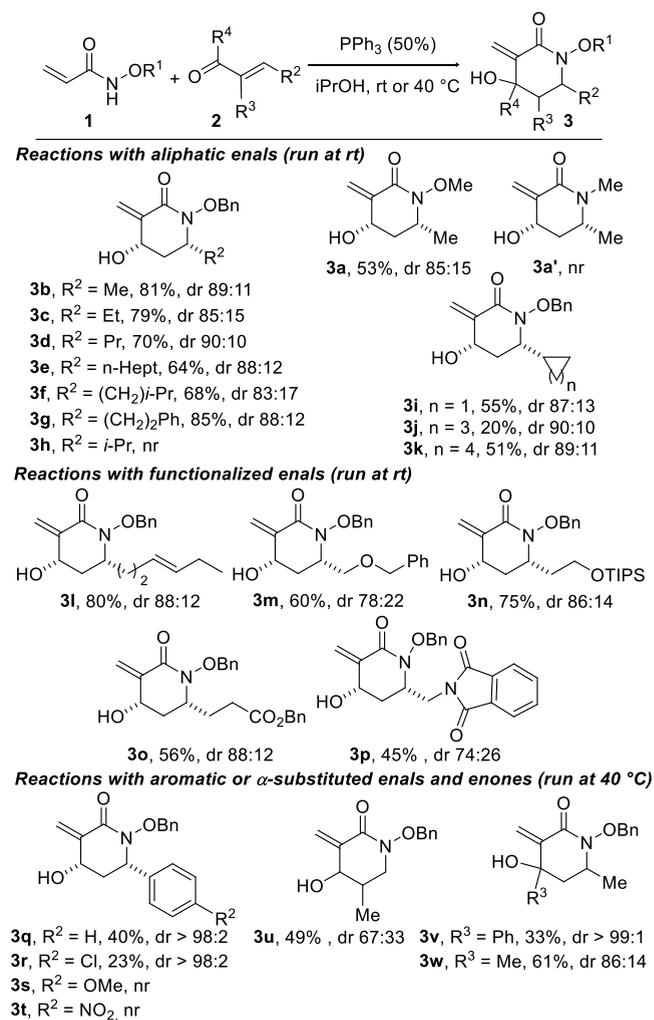
When DABCO and DMAP were used as typical nitrogen-based organocatalysts, low yields (26 and 36% yields, respectively) of the desired cyclic product were obtained (Table 1, entries 2 and 3). The best results in terms of reaction time, yield, and stereoselectivity were by far observed with

PPh₃¹¹ when the more nucleophilic PBu₃ proved to be detrimental, leading to the decomposition of the starting materials (Table 1, entries 4 and 5). Lower yields were observed with other solvents, notably aprotic ones, (Table 1, entries 6–10) while decreasing the amount of the PPh₃ catalyst to 20 mol % led to decreased yields even at 50 °C (Table 1, entries 11 and 12). At this temperature, with our optimal load of 50 mol % of PPh₃, the reaction time could be reduced from 20 to 7 h for similar results (Table 1, compare entries 4 and 13). However, for the rest of the study, we selected the mildest conditions at room temperature, leading to the desired product with a good 81% yield and a correct diastereoisomeric ratio of 89:11 (Table 1, entry 4). The relative *syn* stereochemistry of the major stereoisomer was ascertained by single X-ray structure analysis (see the X-ray structure of **3b** in Scheme 3 and SI).

With these optimized conditions in hand, we then explored the effect of the substituent on the nitrogen atom. Shifting from *N*-benzyloxy- to *N*-methoxyacrylamide in reaction with crotonaldehyde led to a similar selectivity but a clear loss of reactivity (Scheme 2, compared **3a** and **3b**).

The use of *N*-methylacrylamide led to no conversion, confirming the need for the alkoxy moiety onto the nitrogen atom.⁵ We then turned our attention toward enals and enones **2** in reaction with acrylamide **1b** as depicted in Scheme 2, and

Scheme 2. Scope of the Domino aza-Michael/MBH



aliphatic enals were first tested. A variety of β -substituted enals ($R^2 \neq \text{Me}$) were then subjected to the domino aza-Michael/MBH reaction to give **3a–3g** in 53–85% yield with consistently good drs (85:15–90:10). Overall, good yields were obtained except for $R^2 = i\text{-Pr}$, probably due to steric hindrance retarding the aza-Michael addition (Scheme 2, **3h**). The impact of steric effects was confirmed when enals carrying cycloalkyl substituents on the β position were engaged, only with moderate to acceptable yields ranging from 20 to 55% being obtained depending on the size of the ring.¹² Functionalized enals bearing alkene or protected heteroatoms were also nicely tolerated forming **3l–3n** in 60–80% yield. An ester or imide function can also be used without apparent interference with the created hydroxyl function, giving the corresponding products **3o** and **3p** in 56 and 45% yields, respectively.

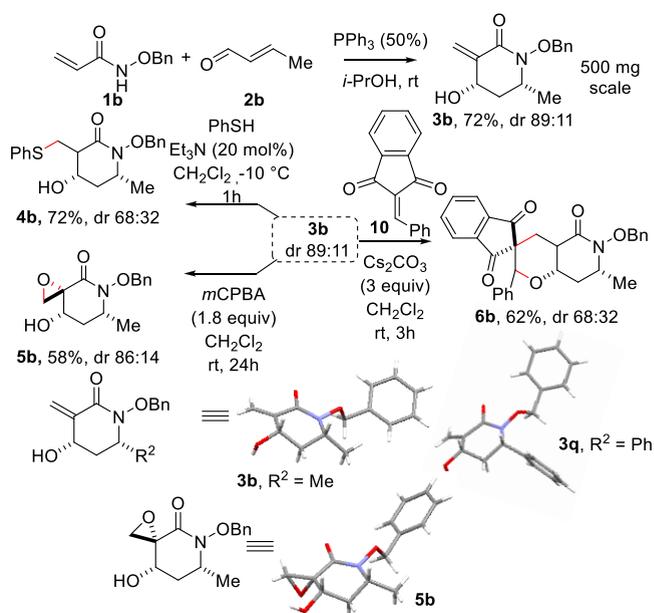
The domino transformation of aryl substrates proved to be much more challenging than expected due probably to reversibility of the aza-Michael addition favoring the highly conjugated aromatic enals. Indeed, with the standard conditions, no reaction occurred, and the temperature needed to be increased up to 40 °C to permit reactivity. Nevertheless, cinnamaldehyde-derived adduct **3q** was isolated in a moderate 40% yield and the *para*-chloro product **3r** in an even lower 23% yield, even though high dr was attained.¹³ This poor reactivity was further accentuated when aryl substrates bearing strong electron-donating or electron-withdrawing groups were employed, for which no reaction occurred. Next, one α -substituted enal, *i.e.*, methacrolein, and enones were tested for the reaction, and again, the temperature had to be increased up to 40 °C. In these conditions, the desired lactams **3u–3w** were obtained in 33–61% yields and a dr up to 99:1 for the (*E*)-1-phenylbut-2-en-1-one derivative **3v**.

To showcase the synthetic value of this new methodology, additional experiments were next conducted (Scheme 3). First, a 500 mg scale was performed, and the product **3b** was isolated in 72% yield and the same 89:11 diastereoisomeric ratio, demonstrating that there is almost no loss of efficiency. The resulting mixture **3b** could be transformed by taking advantage of the exocyclic double bond reactivity.

Despite its conjugation with the weakly electron-withdrawing carboxamide function, this alkene is still nucleophilic enough to react with an electrophilic reagent such as *m*-CPBA. Epoxidation in CH_2Cl_2 at rt¹⁴ indeed led to the spiro-lactam **5b** in 58% yield and a 86:14 diastereomeric ratio. The stereoselective outcome for the major product, a *syn* relationship between the oxygen of the epoxide and the alcohol function (see X-ray structure of **5b** in Scheme 3), can be explained by the well-described allylic alcohol hydrogen bonding with *m*-CPBA.¹⁵ The soft electrophilic carbon of the double bond also reacted with thiophenol (PhSH) in the presence of Et_3N ¹⁶ forming the thio-Michael product **4b** in 72% yield as a 68:32 diastereomeric mixture.¹⁷ These two first elaborations emphasize the interesting ambivalent nature of the exocyclic alkene bond carried by the domino products. Going one step further, a domino oxa-Michael/Michael was next studied by reaction with 1,3-indanedione derivative **10** employing conditions described in the literature for allylic alcohols.¹⁸ Rewardingly, the targeted original tetracyclic spiro-product **6b** bearing four stereogenic centers was isolated in 60% yield with a 68:32 dr.

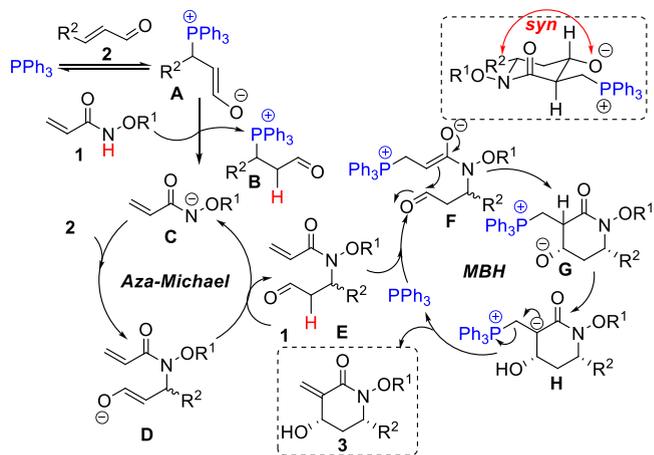
Our mechanistic proposal is the manifestation of a rare autotandem catalysis manifold¹⁹ implicating an aza-Michael

Scheme 3. 500 mg Scale Reaction and Postfunctionalizations of **3b** and X-ray Structures of Domino Products **3b** and **3q** and Epoxide Derivative **5b**



addition and an MBH cyclization (Scheme 4).²⁰ A first 1,4-addition of PPh_3 onto the α,β -unsaturated carbonyl **2**

Scheme 4. Proposed Mechanism



generates the zwitterionic intermediate **A**, which deprotonates *N*-alkoxyacrylamide **1** ($\text{p}K_a \approx 8\text{--}9$),²¹ thus generating the more nucleophilic amide intermediate **C**.²² Conjugate addition to enal **2** leads to the formation of enolate **D**. The last step of this first catalytic cycle is the deprotonation of another equivalent of *N*-alkoxyacrylamides **1** by **D** to regenerate **C** and form aza-Michael adduct **E**. Then, the second catalytic cycle is triggered by the addition of PPh_3 onto **E** to give zwitterionic enolate **F**, which, by an intramolecular aldolization, provides a second, distal zwitterion **G**. The stereoselective outcome of the process could be explained at this stage, the major intermediate **G** being probably the one with all the substituents in pseudoequatorial positions, explaining the *syn* relationship observed between the R group and the OH in final products **3** (see X-ray structures of **3b** and **3q** in Scheme 3).

Finally, a proton transfer, possibly assisted by the protic solvent, generates a last, proximal zwitterion **H** leading to product **3** after the elimination and regeneration of PPh₃. It is worth noting that no product resulting from a Rauhut-Currier dimerization of enals was observed and that changing the sequence of addition of the reactants did not impact the process.

In summary, we have developed an original aza-Michael/MBH domino reaction catalyzed by PPh₃ that efficiently led to various new aza-heterocyclic skeletons. These functionalized piperidin-2-ones were diastereoselectively obtained with *syn*-relative stereochemistry, confirmed by single X-ray analyses. These domino products feature an ambivalent exocyclic alkene bond that can be fashioned by either electrophilic or nucleophilic reagents and therefore provide a useful versatile platform toward structurally diversified molecules, as briefly demonstrated in this study. Work is currently underway to further expand the versatility of this new one-pot process.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its [Supporting Information](#).

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.4c00295>.

Detailed experimental procedures, full spectroscopic data for all new compounds, copies of NMR spectra and X-ray data ([PDF](#))

Accession Codes

CCDC 2165244–2165246 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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