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Zn(II)-Catalyzed One-Pot Synthesis of Coumarins from Ynamides and Salicylaldehydes

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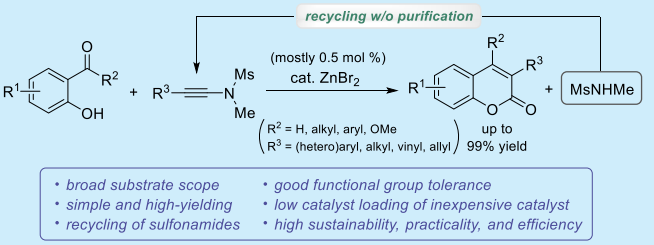
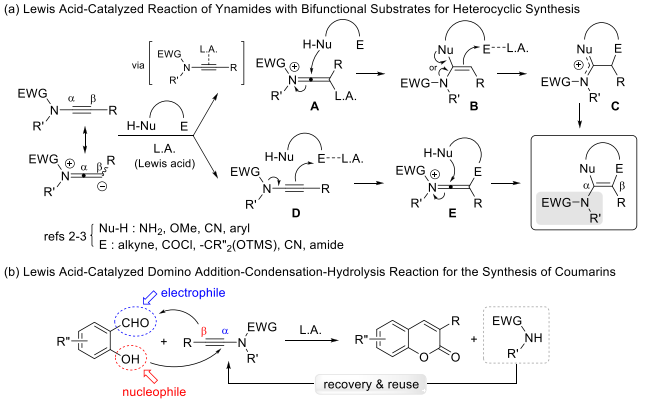
Supporting Information

ABSTRACT: A highly efficient and straightforward synthesis of diversely substituted coumarins from ynamides and salicylaldehydes in the presence of Zn(II) catalyst has been developed. The sulfonamide moiety of ynamides was successfully recycled in this process, serving as an effective traceless directing group for high regioselectivity in the bond-forming event. The advantages of this protocol are good functional group tolerance, broad substrate scope, simple and high-yielding reaction, recovery/reuse of the sulfonamides, low catalyst loading of inexpensive catalyst, and, by these merits, a more cost-effective and greener process.



Ynamides exhibit unique reactivity, intrinsic dual electrophilic (α-position) and nucleophilic (β-position) properties, due to possible delocalization of the nitrogen lone-pair electrons and thus have been widely utilized as versatile building blocks in organic synthesis.[1] In recent years, various bifunctional substrates bearing both nucleophilic and electrophilic moieties, which can consecutively and regioselectively react with ynamides in the presence of Brønsted/Lewis acid, have been developed to access a wide range of heterocycles. Two mechanistic modes can be conceived for this process (Scheme 1a): (1) Initial intermolecular nucleophilic attack at the α-position of a keteniminium species **A**, *in situ* generated from an ynamide under acid catalyst, followed by intramolecular enamine addition to the electrophilic moiety (**B** → **C**) and deprotonation[2] or (2) intermolecular nucleophilic attack of an ynamide to a Lewis acid-activated electrophilic moiety (**D** → **E**), followed by nucleophilic cyclization to the keteniminium moiety.[3] In general, the resulting heterocyclic products retain the amide substituent derived from ynamide starting materials.

Scheme 1. Annulation Reaction between Ynamides and Bifunctional Compounds



On the other hand, there are a handful of reports in the literature on the Brønsted-/Lewis acid-catalyzed reaction of either alcohols[4] or aldehydes[5] as nucleophile or electrophile, respectively, with ynamides. Moreover, an intriguing tandem reaction of ynamides, silanols, and aldehydes under acid catalysis has been demonstrated.[6] Considering these precedents and the regioselective reactivity of ynamides, we envisaged salicylaldehydes bearing both alcohol and aldehyde moieties in the molecule as interesting bifunctional substrates with regard to the possibility of a domino cyclization reaction, which could afford coumarins devoid of an amide substituent, along with amide byproducts through a spontaneous hydrolysis[7] (Scheme 1b). In this context, we were interested in exploring the possibility of the recovery and reuse of amides for future cycles, which is unprecedented to the best of our knowledge. Previously, Cao's group reported a base-mediated synthesis of iminocoumarins from *N*,*N*-disulfonyl ynamides and 3 equiv of salicylaldehydes, involving a ketenimine intermediate through desulfonylation of ynamides with salicylaldehydes in the presence of NEt_3.[8]

Herein, we report a highly efficient Zn-catalyzed one-pot reaction process between ynamides and salicylaldehydes for facile synthesis of diversely substituted coumarin derivatives, which are commonly found in numerous bioactive natural products, pharmaceuticals, and organic materials and thus are of great importance.[9] In sharp contrast to related prior works,[2,3,6,8] the *N*-alkylsulfonamide moiety of ynamides serves

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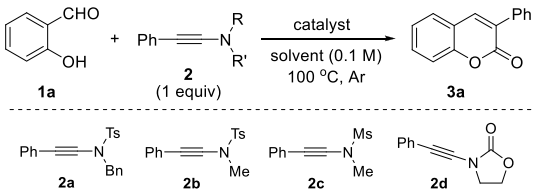
as an effective traceless directing group in this new protocol, providing not only high regioselectivity in the C−O/C−C bond formation sequence but also the ability to be spontaneously removed and recycled, leading to the formation of coumarins instead of iminocoumarins.

We began our investigations on a variety of Brønsted/Lewis acids and inorganic/organic bases using **1a** and **2a** as the test substrates (Table 1; for complete data, see the Supporting Information). Gratifyingly, as proposed, the desired coumarin **3a** was obtained along with an amide byproduct, alluding to involvement of spontaneous hydrolysis and dehydration (*vide infra*). Among a variety of catalysts examined, $ZnBr_2$ was the most effective for this transformation (entries 2−8). Various solvents were examined, and toluene appeared preferable (entries 9−11). Subsequently, we examined the effects of different *N*-substituents of ynamides (entries 12−15). *N*-Mesyl-*N*-methyl-substituted ynamide **2c** proved to be optimal with regard to reaction time and product yield (entry 14). Further optimization of reaction conditions secured a very high yield of **3a** after a short reaction time (99%, 3 h, entry 16).

With establishment of the optimized conditions as entry 16 in Table 1, we set out to explore the scope of this process. First, we examined the reaction of various ynamides (**2**) with salicylaldehyde **1a** (Scheme 2a). A wide range of aryl-substituted ynamides underwent this reaction smoothly irrespective of electronic property and the position of their substituents, producing the corresponding coumarins in good

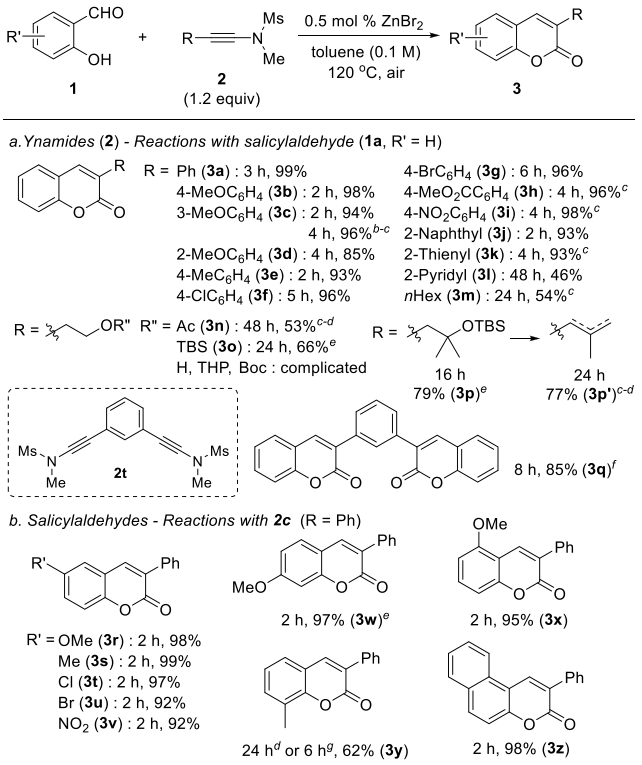
Table 1. Optimization Studies



entry	2	catalyst (mol %)	solvent	*t* (h)	yield (%)[a]
1	**2a**	-	toluene	24	13
2	**2a**	$ZnBr_2$ (10)	toluene	24	70 (68)
3	**2a**	$ZnCl_2$ (10)	toluene	24	67 (58)
4	**2a**	$Zn(OTf)_2$ (10)	toluene	24	12
5	**2a**	$InBr_3$ (10)	toluene	24	22
6	**2a**	$InCl_3$ (10)	toluene	24	37
7	**2a**	CuCl (10)	toluene	24	27
8	**2a**	others[b]	toluene	24	-
9	**2a**	$ZnBr_2$ (10)	$ClCH_2CH_2Cl$	24	51
10	**2a**	$ZnBr_2$ (10)	1,4-dioxane	24	39
11	**2a**	$ZnBr_2$ (10)	MeCN	24	-
12[c]	**2a**	$ZnBr_2$ (5)	toluene	3	(94)
13[c]	**2b**	$ZnBr_2$ (5)	toluene	1.5	(95)
14[c]	**2c**	$ZnBr_2$ (5)	toluene	1	(97)
15[c]	**2d**	$ZnBr_2$ (5)	toluene	24	(72)
16[d]	**2c**	$ZnBr_2$ (0.5)	toluene	3	(99)
17[d]	**2c**	$ZnBr_2$ (0.25)	toluene	12	(98)
18[d]	**2c**	$ZnBr_2$ (0.2)	toluene	24	(83)
19[d]	**2c**	$ZnBr_2$ (0.175)	toluene	48	(80)

[a]Determined by ^{1}H NMR. Values in parentheses indicate isolated yields. [b]10 mol % of MCl_3 (M = Al, Bi, Fe, Yb, Ru), MCl_2 (M = Mg, Fe, Cu, Pd), *p*TsOH, AcOH, TFA, M_2CO_3 (M = Na, K, Cs), NaOAc, K_3PO_4, NEt_3, DMAP, or DBU. [c]Using 1.5 equiv of **2** at 120 °C under air. [d]Using 1.2 equiv of **2c** at 120 °C under air.

Scheme 2. Substrate Scope[a]



[a]Isolated yields. [b]0.1 mol % of $ZnBr_2$. [c]At 140 °C. [d]Using 5 mol % of $ZnBr_2$. [e]Using 1 mol % of $ZnBr_2$. [f]Reaction of 2.1 equiv of **1a** and 1 equiv of **2t**. [g]Using 10 mol % of $ZnBr_2$.

to excellent yields (**3a−j**). It is noteworthy that the amount of $ZnBr_2$ could be reduced to 0.1 mol %, producing **3c** in 96% yield with a turnover number (TON) of 960. Heteroaryl- and alkyl-substituted ynamides proved to be suitable substrates (**3k−p**). While ynamides bearing a free hydroxyl and THP- or Boc-protected hydroxyl groups led to a complicated mixture, Ac- and TBS-protected hydroxyl groups were well tolerated (**3n−p**). Previously, Cao and Xu reported very intriguing Zn-mediated cyclization reactions of ynamides with benzyl or propargyl silyl ethers, wherein a carbocation is initially formed from silyl ethers with stoichiometric amounts of $ZnBr_2$.[3b,c] In sharp contrast, intact silyl ether groups in our protocol resulting from the use of a very small amount of $ZnBr_2$ catalyst (**3o−p**) are highly noteworthy. Meanwhile, **3p′** was obtained efficiently by slight increase of catalyst loading, allowing access to structurally diverse and synthetically useful coumarins from the same starting materials. In addition, reaction of bis-(ynamide) **2t** proceeded smoothly to afford bis(coumarin) **3q** in a good 85% yield.

Next, we proceeded to explore the scope of salicylaldehydes (**1**) (Scheme 2b). In general, a variety of substituted salicylaldehydes were well tolerated regardless of electronic property and the position of their substituents, leading to diversely substituted coumarins (**3r−z**). While the substituents *ortho* to the −CHO moiety had no significant effect on the reactivity (e.g., **3x**, **3z**, 95−98% yields with 0.5 mol % of $ZnBr_2$ for 2 h), the substituent *ortho* to the −OH group retarded the reaction considerably, requiring both higher catalyst loading (5−10 mol % $ZnBr_2$) and longer reaction time (6−24 h) to afford **3y** in 62% yield.

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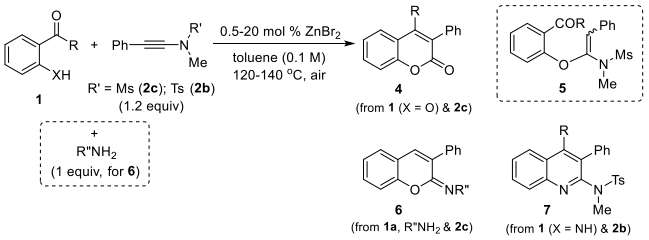
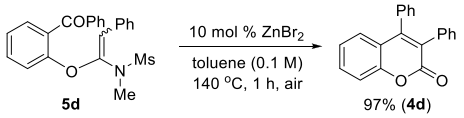
Table 2. Substrate Scope: 2-Hydroxy- or 2-Aminobenzoyl Groups[a]



entry	X	R	R″	[Zn] (mol %)/T (°C)/t (h)	yield (%)[b]
1	O	Me (**1k**)	-	5/120/2	99 (**4a**)
2	O	*c*Hex (**1l**)	-	5/120/3	100 (**5b**)
3	O	*c*Hex (**1l**)	-	10/140/24	82 (**4b**)
4	O	*t*Bu (**1m**)	-	20/140/48	7 (**4c**), 87 (**5c**)
5	O	Ph (**1n**)	-	5/120/2	18 (**4d**), 77 (**5d**)
6	O	Ph (**1n**)	-	10/140/1	88 (**4d**)
7	O	OMe (**1o**)	-	20/140/48	63 (**4e**)
8	O	H (**1a**)	PMP	0.5/140/2	89 (**6a**)
9	O	H (**1a**)	Bn	1/140/2	81 (**6b**)
10	NH	Me (**1p**)	-	20/140/2	95 (**7a**)
11	NH	Ph (**1q**)	-	15/140/2	84 (**7b**)

[a]For entries 1−7, reaction of **1** with **2c** to form **4**/**5**; for entries 8−9, reaction of **1a** with R″NH_2 and **2c** to form **6**; for entries 10−11, reaction of **1** with **2b** to form **7**. [b]Isolated yields.

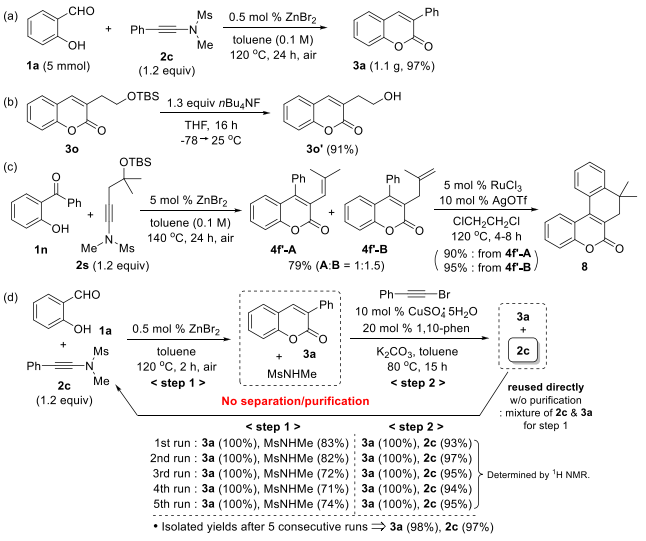


Encouraged by these results obtained with salicylaldehydes, we extended our investigation to *o*-hydroxyaryl ketones and methyl salicylate (Table 2). The steric property of the ketones strongly influenced the cyclization step in this reaction: while the reaction with 2′-hydroxyacetophenone (**1k**, X = O, R = Me) proceeded uneventfully to afford **4a** in 99% yield (entry 1), reaction of the substrates bearing a sterically bulkier substituent (**1l**-**n**, R = *c*Hex, *t*Bu, Ph) was drastically impeded, resulting in the formation of uncyclized product **5** as a sole or major product (entries 2 and 4−5). In the cases of **1l** and **1n**, increasing both catalyst loading and reaction temperature secured the formation of the desired coumarin products **4** in good yields (entries 3 and 6). Meanwhile, subjecting the uncyclized product **5d** to the reaction conditions for the formation of **4d** afforded **4d** in 97% yield. These findings suggest that this reaction proceeds through the initial additions of the phenol moiety of **1** to ynamide **2**, followed by intramolecular enamine addition to the aldehyde moiety (Scheme 1a, top, **A** → **C**) and hydrolysis/dehydration.

Methyl salicylate **1o** could also be used as a bifunctional substrate to give 4-methoxy-3-phenyl-substituted coumarin **4e** (entry 7). Much to our delight, the scope of this reaction could be further extended, resulting in the formation of iminocoumarins[8,10] **6a,b** through one-pot, three-component assembly of **1a**, amines, and **2c** (entries 8 and 9). In addition, the reaction of *o*-aminoaryl ketones (**1p**−**q**, X = NH) with ynamide **2b** gave 2-aminoquinolines **7** (entries 10 and 11), which are also very important structural motifs.[11]

To highlight the synthetic utility of this reaction, a large-scale synthesis of coumarins was carried out (Scheme 3a). The desired product **3a** was obtained in 97% yield (1.1 g) using 5 mmol of **1a**, demonstrating the scalability of this process. Moreover, further transformation of the coumarins obtained from this process was undertaken. Smooth removal of the TBS group led to free hydroxyl-containing coumarin **3o′** in high yield (Scheme 3b). As illustrated in Scheme 3c, Zn(II)-catalyzed reaction of 2-hydroxybenzophenone (**1n**) with silyl-ether-containing ynamide (**2s**) proceeded smoothly to afford 3-vinyl- (**4f′-A**) and 3-allyl-substituted (**4f′-B**) coumarins in a good combined yield. Subsequent Ru-catalyzed intramolecular hydroarylation[12] between 3-alkenyl and 4-phenyl moieties of the two isomers was readily accomplished to afford the fused polycyclic coumarin **8** in excellent yields. Coumarins obtained herein can also be easily converted to 3,4-dihydrocoumarins,

Scheme 3



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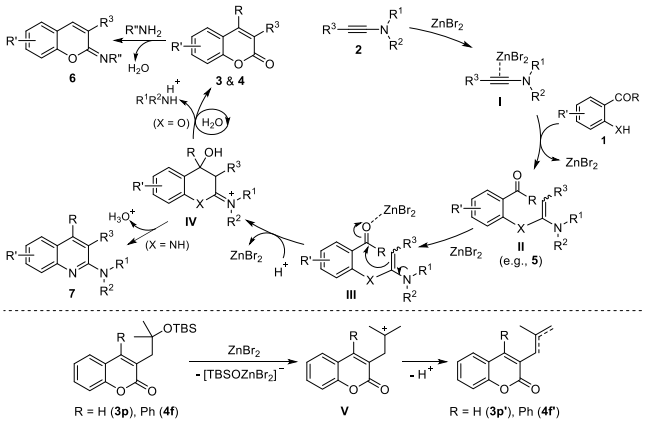
which constitute pervasive motifs in many natural products and bioactive molecules, by known methods.[13]

Given generation of sulfonamide byproducts during the reaction, we finally tested the recycling of amides and sequential synthesis of coumarin **3a** as well as ynamide **2c** directly without purification (Scheme 3d). After completion of the reaction between **1a** and **2c** (step 1), simple filtration and evaporation of the remaining solvents gave the crude mixture of MsNHMe and **3a**, which was directly used for the following Cu-catalyzed coupling[14] with 1-bromo-2-phenylacetylene (step 2). Step 2 proceeded uneventfully in the presence of **3a** formed in step 1 to afford **2c** in excellent yields without loss of **3a**, suggesting that the catalytic activity of the Cu complex was not affected by the remaining coumarin **3a**. Subsequently, the crude mixture of **2c** and **3a** was reused for step 1 with extra addition of **1a**, $ZnBr_2$, and toluene. Again, the presence of **3a** in the reaction vessel and the purity of ynamide **2c** did not influence the outcome of step 1. During five consecutive runs, the efficiency of both steps remained almost constant regardless of the presence of **3a** and the ynamide purity, providing comparably high yields of both **3a** and **2c**. Moreover, coumarin **3a** did not decompose during these repeated processes and was finally produced in 98% yield based on the total amount of **1a** overall used from the first to fifth runs, alluding to the tolerance of these reactions. These results demonstrate that successful recycling of sulfonamide avoids tedious and time-consuming step-by-step isolations and purifications, thus significantly improving the practicality and efficiency while reducing the cost and waste.

Based on our experimental findings and by analogy with mechanisms proposed for related processes,[2,3,6] a plausible mechanism for this reaction is proposed in Scheme 4.

Scheme 4. Proposed Mechanism



Activation of ynamide **2** by coordination to $ZnBr_2$ (**I**) is followed by intermolecular nucleophilic attack by the phenolic oxygen (X = O) of **1** to give enamine intermediate **II**. Then, the Zn-activated carbonyl moiety undergoes the intramolecular nucleophilic attack by the enamine moiety of **III**, leading to cyclized keteniminium intermediate **IV**. Subsequent hydrolysis and dehydration afford the coumarin products **3**/**4** along with a sulfonamide. On the other hand, deprotonation rather than hydrolysis takes place in the intermediate **IV** derived from *o*-aminoaryl ketones (X = NH) to produce 2-aminoquinolines **7** without loss of the sulfonamide moiety. In the presence of amines, coumarin **3** is further transformed to imminocoumarin **6**. In the case of coumarins bearing a silyl ether substituent (e.g., **3p**, **4f**), Zn-catalyzed silyl ether cleavage could further occur to deliver carbocation **V**.[15] Finally, deprotonation and olefin isomerization produce 3-allyl- and 3-vinyl-substituted coumarins **3p′** and **4f′**.

In summary, we developed a highly efficient and facile one-pot reaction for the synthesis of diversely substituted coumarins from ynamides and salicylaldehydes. In this process, the *N*-alkylsulfonamide moiety of ynamides serves as an effective traceless directing group not only providing high regioselectivity in the C−O/C−C bond formation sequence but also capable of being spontaneously removed and recycled. This protocol offers straightforward, robust, and sustainable access to a diverse array of valuable coumarins from readily available starting materials with good functional group tolerance, broad substrate scope, and high practicality and efficiency.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01181.

Full experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(15) With increasing catalyst loading, reaction temperature, and/or reaction time, the gradual conversion of **3p** and **4f** to **3p′** and **4f′**, respectively, was observed by TLC, suggesting that the formation of **3p′** and **4f′** is triggered by the initial generation of **3p** and **4f**. However, initial loss of the OTBS group in ynamide **2s** followed by the Zn-catalyzed reaction of **1a**/**1n** with the so-obtained ynamide cannot be completely excluded.

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