OL Organic Letters

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Catalytic Ynone–Amidine Formal [4 + 2]-Cycloaddition for the Regioselective Synthesis of Tricyclic Azepines

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03711 Read Online

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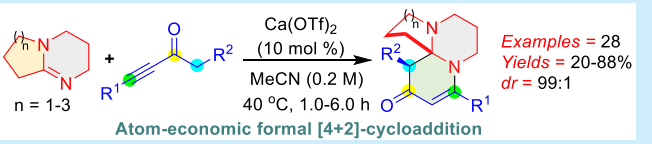
ABSTRACT: A $Ca(OTf)_2$- and self-promoted ynone–amidine atom-economic formal [4 + 2]-cycloaddition of various ynones with amidines is reported for the construction of highly functionalized tricyclic azepines. High reaction rate, ease of operation, and high product selectivity with wide substrate scope are the key advantages of the present annulation protocol.



Ynones have recently surfaced as Michael acceptors with versatile reactivity, giving way to the construction of varied hetero/carbocyclic systems.[1−3] In this field, pioneering work has been done by the Tomita and Fu groups exploiting ynones in trialkylphosphine-catalyzed intramolecular zipper cyclizations (Scheme 1a).[1] Influenced by their work, we developed a complementary triphenylphosphine-catalyzed intermolecular Tomita zipper cyclization of ynones with olefins (Scheme 1b).[2f] Meticulous analysis of the aforementioned reaction mechanisms brings to light some salient features of trialkylphosphine, which rationalizes their excellent catalytic activity in such reactions. Primarily, the free lone pair on phosphorus renders the nucleophilic attack on C-4 carbon of ynones, resulting in a zwitterion. Finally, in the absence of alternative neutralization pathways, stabilization of this zwitterion drives the detachment of the catalyst from the substrate through novel zipper cyclization, hence regenerating it. These catalytic features that make trialkylphosphine exceptional catalysts prevent them from becoming good substrates capable of permanently bonding to its reacting partner.

Such dual behavior, of a catalyst and a substrate, has been known to be displayed by amidine bases like DBU.[4] This is as a consequence of the fact that, following the nucleophilic attack by N-8 of DBU on ynones, the resultant zwitterion can be neutralized by proton loss from C-6 or by nucleophilic attack on the iminium ion carbon (Scheme 1c,d). These alternative stabilization routes impart unparalleled nucleophilic capabilities on amidine (DBU), leading to its incorporation into several acetylenic moieties like alkynoates[5a−d] and electron-deficient propargylic alcohols to give fused tricyclic derivatives (Scheme 1c).[5e−h]

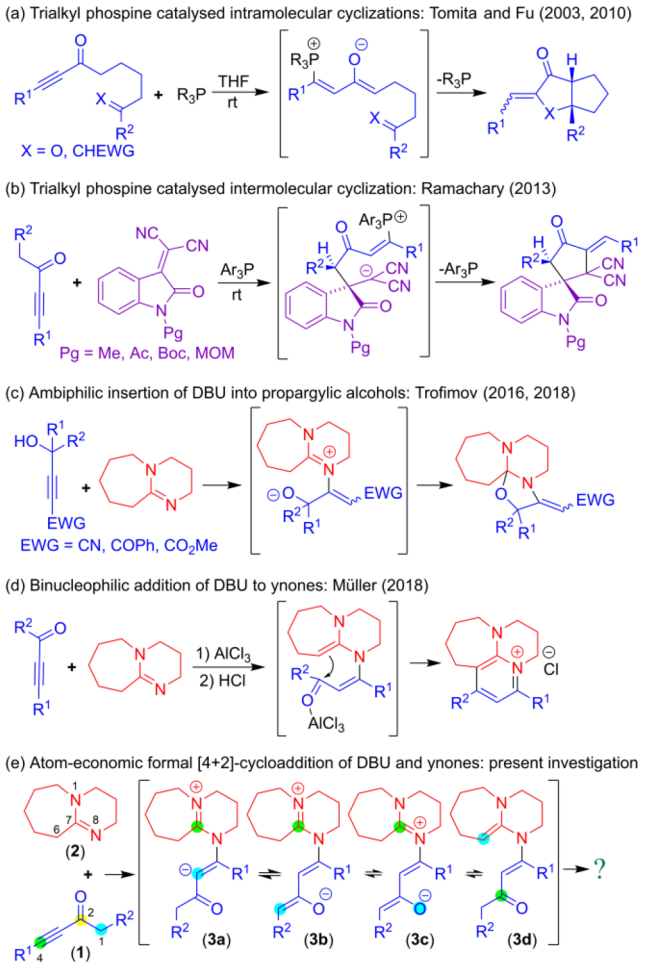
Even though such diverse modes of reactivity of DBU with triple bond exist, stoichiometric addition to ynones has seldom been explored. An attempt was made in this direction recently, by Müller's group,[6] where DBU's binucleophilic nature was exploited in annulation to ynones yielding tricyclic aminopyridinium salts (Scheme 1d). This protocol's major drawback lies in its use of ynones bearing only aromatic substituents. The absence of α-acidic hydrogens largely restricts the ynones to behave only as bielectrophiles (at C-2 and C-4). In contrast, nucleophilic capabilities of ynones with an enolizable methylene next to the carbonyl (C-1) have been demonstrated previously by our group.[2,3] Hence, our present experimental quest is focused on reacting α-enolizable ynones with an ambiphilic DBU as a substrate, in turn taping into the complete reactivity competence of ynones with DBU (Scheme 1e). Achieving exclusively a ynone–DBU addition poses a grave challenge since this addition is in direct competition with ynone self-addition.[2k] Such an insertion of DBU to ynones is further complicated by possibility of diverse cyclization modes from intermediates **3a**, **3b**, **3c**, and **3d** (Scheme 1e).

The preliminary reaction was tested under the self-catalysis between ynone **1a** and 1.3 equiv of DBU **2a** at 60 °C in DCE. To our astonishment, from a plethora of possible products (Scheme 1e) a single cyclized product **4aa** was obtained in 65% yield with 99:1 dr within 1.5 h (Table 1, entry 1). Product **4aa** turned out to be quite different from that obtained by Müller (Scheme 1d). To increase the product **4aa** yields, an extensive solvent screening was carried out (Table 1). To begin, nonpolar aprotic solvents like DCM, chloroform, and toluene furnished **4aa** in poor yields (Table 1, entries 2–4), and no reaction was observed in 1,1,2,2-terachloroethane (Table 1, entry 5). These disappointing results directed our investigation toward more polar solvents like EtOH (61% yield, entry 6) and other solvents like THF, DMF, and DMSO gave just above average yields of 38%, 65%, and 62%, respectively (Table 1, entries 7–9). Self-catalyzed cyclization

Received: November 8, 2020

https://dx.doi.org/10.1021/acs.orglett.0c03711
Org. Lett. XXXX, XXX, XXX−XXX

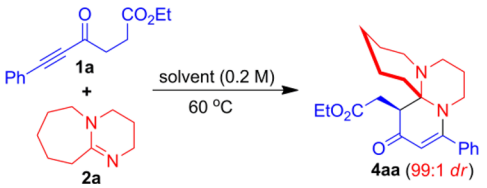
Scheme 1. Previous and Present Reaction Designs for the Annulation of Ynones with Olefins



reaction of **1a** and 1.3 equiv of **2a** in MeCN (0.2 M) at 60 °C in just 24 min furnished **4aa** in very good yield (78%, entry 10). Further, all attempts to improve the yield either by increasing the **2a** equiv to 1.5 or decreasing to 1.1, carrying out the reaction at a lower temperature (30 °C) or lower concentration (0.15 M) went in vain (Table 1, entries 11−14). Thus MeCN (0.2 M) at 60 °C was fixed as the best condition for the self-catalyzed cyclization of **1a** with **2a**.

Surprisingly, subjecting the methyl ester **1b** to the optimized self-catalyzed condition (MeCN at 60 °C) with **2a** resulted in a moderate yield of 45% of **4ba** (Table 2, entry 1). Even reversal of reactant equivalents by taking 1.3 equiv of **1b** with respect to **2a** in MeCN at 60 °C caused a further reduction in yield to 23% (Table 2, entry 2). Such dismal results compelled us to reanalyze the optimized condition with **1b** in the presence of various additives **5** at 40 °C (Table 2). Catalytic amount of Brønsted acids **5a−e** like CH_3CO_2H, *o*-$FC_6H_4CO_2H$, $PhCO_2H$, *p*-$MeOC_6H_4CO_2H$, and 2-naphthoic acid were initially employed with the aim of slightly activating the ynone carbonyl without deactivating DBU. However, all of the aforementioned additives **5a−e** had a detrimental effect on the product yields, furnishing just 19−64% of **4ba** (Table 2, entries 3−7). As a consequence, the reaction was again performed in the presence of a mild base like DMAP **5f** and (±)-BINOL **5g**, both of which gave poor yields of 32% and 41%, respectively (Table 2, entries 8 and 9). Such discouraging results shifted

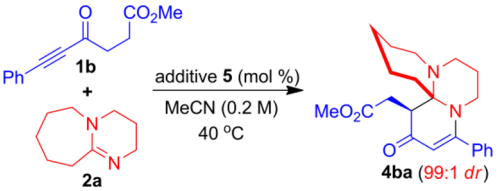
Table 1. Reaction Solvent Optimization[a]



entry	**2** (equiv)	solvent (0.2 M)	time (h)	yield **4aa**[b] (%)
1	1.3	DCE	1.5	65
2	1.3	DCM	1	35
3	1.3	$CHCl_3$	2.5	44
4	1.3	toluene	1	13
5	1.3	$Cl_2CHCHCl_2$	48	NR
6	1.3	EtOH	2.5	61
7	1.3	THF	1.5	38
8	1.3	DMF	0.7	65
9	1.3	DMSO	0.5	62
10	**1.3**	**MeCN**	**0.4**	**78**
11	1.5	MeCN	0.5	73
12	1.1	MeCN	0.6	61
13[c]	1.3	MeCN	0.5	65
14[d]	1.3	MeCN	2.5	73

[a]Reactions were carried out in solvent (0.2 M) with **2a** relative to **1a** (0.3 mmol). [b]Yield refers to the column purified product. [c]MeCN (0.15 M). [d]*T* = 30 °C. Note: Complete consumption of **1a** was observed in all reactions.

Table 2. Reaction Additive Optimization[a]



entry	additive **5** (mol %)	time (h)	yield **4ba**[b] (%)
1[c]		0.3	45
2[d]		0.25	23
3	**5a**: CH_3CO_2H (20 mol %)	2.5	19
4	**5b**: *o*-$FC_6H_4CO_2H$ (20 mol %)	21.0	50
5	**5c**: $PhCO_2H$ (20 mol %)	5.5	64
6	**5d**: *p*-$MeOC_6H_4CO_2H$ (20 mol %)	4.5	53
7	**5e**: 2-naphthoic acid (20 mol %)	4.5	51
8	**5f**: DMAP (20 mol %)	2.0	32
9	**5g**: (±)-BINOL (10 mol %)	3.0	41
10	**5h**: AgOTf (10 (10 mol %)	4.0	66
11	**5i**: $Cu(OTf)_2$ (10 mol %)	1.0	36
12	**5j**: $Zn(OTf)_2$ (10 mol %)	2.5	36
13	**5k**: $In(OTf)_3$ (10 mol %)	4.0	48
14	**5l**: $Sc(OTf)_3$ (10 mol %)	2.5	51
15	**5m**: $Mg(OTf)_2$ (10 mol %)	3.0	46
16	**5n: $Ca(OTf)_2$ (10 mol %)**	**3.0**	**70**

[a]Reactions were carried out in solvent (0.2 M) with 1.3 equiv of **2a** relative to **1b** (0.3 mmol) in the presence of additive **5**. [b]Yield refers to the column purified product. [c]*T* = 60 °C. [d]1.3 equiv of **1b** relative to **2a** (0.3 mmol) at the 60 °C. Note: Complete consumption of **1b** was observed in all reactions.

our focus toward testing Lewis acids like metal triflates **5h−n** for promoting the formation of **4ba** in higher yields. Out of all the metal triflates **5h−n** screened, AgOTf **5h** and $Ca(OTf)_2$ **5n**

https://dx.doi.org/10.1021/acs.orglett.0c03711
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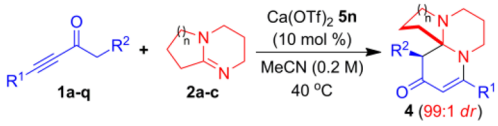
proved promising as additives by furnishing **4ba** in 66% and 70% yields, respectively (Table 2, entries 10−16). Hence, we narrowed down on 1.3 equiv of **2a** with **1b** in the presence of 10 mol % of $Ca(OTf)_2$ **5n** at 40 °C in MeCN (0.2 M) as the final optimized condition (Table 2, entry 16).

Having established the optimum conditions, a variety of α-enolizable ynones **1** and amidine bases **2** were tested under the catalytic protocol to explore the formal [4 + 2]-cycloaddition scope. Initially, just extending the aliphatic chain as an R^2 substituent from methyl to ethyl **1c−d** had a negligible effect on the reaction outcome with **2a** yielding the products **4ca−4da** in very good yields of 84 and 83%, respectively (Table 3, entries 1 and 2). Hence, our substrate variation was guided toward varying the R^1 group as differently substituted aromatics with R^2 fixed as Me. Phenyl groups bearing halogens F and Cl at the *para* positions (Table 3, entries 3 and 4) and electron-donating substituents like *p*-Me and *p*-OMe (Table 3, entries 5 and 6) delivered good yields of the desired products **4ea−4ha** (68−80% yields). Exceptionally, an electron-withdrawing group like a *p*-NO_2-substituted phenyl ring provided an inseparable mixture of compounds within a short span of 12 min (Table 3, entry 7).

Heteroaromatics like 3-thiophenyl were also well tolerated under the present catalytic protocol (Table 3, entry 8). However, the ynone **1k** containing both R^1 and R^2 as Ph groups gave complete decomposition of the starting material during the reaction (entry 9). This indicates that increased reactivity on account of the stabilization of the α-anion (Scheme 1e, **3b**) via electron-withdrawing or delocalizing groups both lead to occurrence of multiple side reactions. Surprisingly, reaction of 4-phenylbut-3-yn-2-one or but-3-yn-2-one with DBU **2a** gave an inseparable mixture of compounds (results not shown in Table 3). Therefore, a fine balance of ynone reactivity was found to be crucial for success of this strategy. On similar lines, due to the −I effect of the OCH_2Ph group as R^2 diminished the product **4la** yield to 38% (Table 3, entry 10). Subsequently, locking R^1 as a Ph or *p*-FC_6H_4 group in conjunction with substituting R^2 as methylene esters like ethyl, benzyl, and isopropyl generated the desired products **4aa−4oa** in good to excellent yields of 72−87% (Table 3, entries 11−14). Even complex chiral substituents like methylene ester of (−)-menthyl as R^2 also fared well under this reaction strategy, furnishing **4pa** and **4′pa** in excellent 88% yield with 1:1 dr (entry 15). Fully aliphatic ynone **1q** also produced the final product **4qa** in 42% yield (Table 3, entry 16). This protocol's scope was further broadened by utilizing other amidine bases like DBN **2b** in reaction with a handful of ynones **1a−o** delivering the respective products **4ab−4ob** in 40−70% yields (Table 3, entries 17−20).

Further, some unanticipated results were obtained with other amidine bases like **2c** where the reaction with **1b** gave a very poor yield (20%) of the product **4bc** (Table 3, entry 21). However, utilizing the same amidine **2c** in reaction with the ynone **1c** proceeded to give a unique open-ring product **7cc** via the intermediate **6cc** with incorporation of a molecule of water from the solvent during the course of reaction. This reaction path was confirmed by crude NMR analysis (Scheme 2, eq 1).

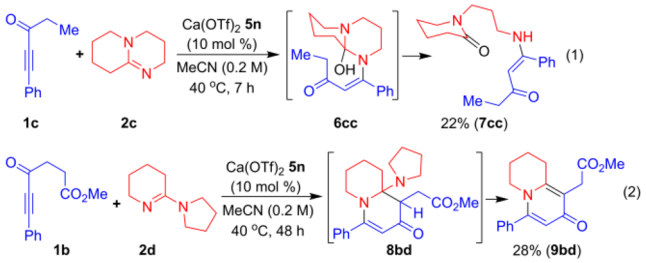
Table 3. Reaction Substrate Scope



entry	ynone (**1**)	amidine (*n*, **2**)	time (h)	yield **4** (%)[a]
1	**1c**: R^1, R^2 = Ph, Me	3, **2a**	5.0	84 (**4ca**)
2	**1d**: R^1, R^2 = Ph, CH_2Me	3, **2a**	5.0	83 (**4da**)
3	**1e**: R^1, R^2 = *p*-FC_6H_4, Me	3, **2a**	5.0	76 (**4ea**)
4	**1f**: R^1, R^2 = *p*-ClC_6H_4, Me	3, **2a**	5.0	80 (**4fa**)
5	**1g**: R^1, R^2 = *p*-MeC_6H_4, Me	3, **2a**	5.0	68 (**4ga**)
6	**1h**: R^1, R^2 = *p*-$MeOC_6H_4$, Me	3, **2a**	6.0	78 (**4ha**)
7[b]	**1i**: R^1, R^2 = *p*-$NO_2C_6H_4$, Me	3, **2a**	0.2	− (**4ia**)
8	**1j**: R^1, R^2 = 3-thiophenyl, Me	3, **2a**	5.0	75 (**4ja**)
9[b]	**1k**: R^1, R^2 = Ph, Ph	3, **2a**	0.5	− (**4ka**)
10	**1l**: R^1, R^2 = Ph, OCH_2Ph	3, **2a**	1.0	38 (**4la**)
11	**1a**: R^1, R^2 = Ph, CH_2CO_2Et	3, **2a**	3.0	87 (**4aa**)
12	**1m**: R^1, R^2 = Ph, $CH_2CO_2CH(Me)_2$	3, **2a**	3.0	74 (**4ma**)
13	**1n**: R^1, R^2 = Ph, $CH_2CO_2CH_2Ph$	3, **2a**	3.0	72 (**4na**)
14	**1o**: R^1, R^2 = *p*-FC_6H_4, CH_2CO_2Et	3, **2a**	3.0	81 (**4oa**)
15[c]	**1p**: R^1, R^2 = Ph, $CH_2CO_2R^3$	3, **2a**	1.5	88 (**4pa**)
16	**1q**: R^1, R^2 = $CH_2(CH_2)_2CH_3$, Me	3, **2a**	6.0	42 (**4qa**)
17	**1a**: R^1, R^2 = Ph, CH_2CO_2Et	1, **2b**	1.0	70 (**4ab**)
18	**1c**: R^1, R^2 = Ph, Me	1, **2b**	2.0	50 (**4cb**)
19	**1e**: R^1, R^2 = *p*-FC_6H_4, Me	1, **2b**	3.0	40 (**4eb**)
20	**1o**: R^1, R^2 = *p*-FC_6H_4, CH_2CO_2Et	1, **2b**	1.0	56 (**4ob**)
21	**1b**: R^1, R^2 = Ph, CH_2CO_2Me	2, **2c**	1.0	20 (**4bc**)

[a]Yield refers to the column purified product. [b]Compound **1** totally consumed with formation of multiple spots. [c]R^3 = (−)-menthyl and 1:1 dr (**4pa**:**4′pa**) obtained.

Scheme 2. Unexpected Reactivity of Ynones with Amidines



Another peculiar reactivity was observed in the interaction of amidine **2d** with the ynone **1b**, where a molecule of pyrrolidine was eliminated from the expected product **8bd** to yield the stable compound **9bd** in 28% yield (Scheme 2, eq 2). The structure and relative stereochemistry of the products **4** were assigned by NMR analysis and also finally confirmed by X-ray structure analysis on **4oa** as shown in Figure S1 (see the Supporting Information).

Taking cognizance of the crystal structure of **4oa** and activation of the carbonyl **1** by calcium salts,[7] a mechanism was hypothesized as elucidated in Scheme 3. In the present mechanism, oxophilicity of calcium drives the coordination of $Ca(OTf)_2$ **5n** to ynone carbonyl **1**, in turn activating the ynone toward Michael addition at C-4 by DBU's N-8. The zwitterion intermediate **3a** thus formed, undergoes a [1,3]-hydrogen shift to yield resonance hybrid intermediates **3b** and **3c**.[1,2] Such intermediates could be neutralized through a myriad of reaction pathways. Loss of an adjacent proton at DBU's C-6

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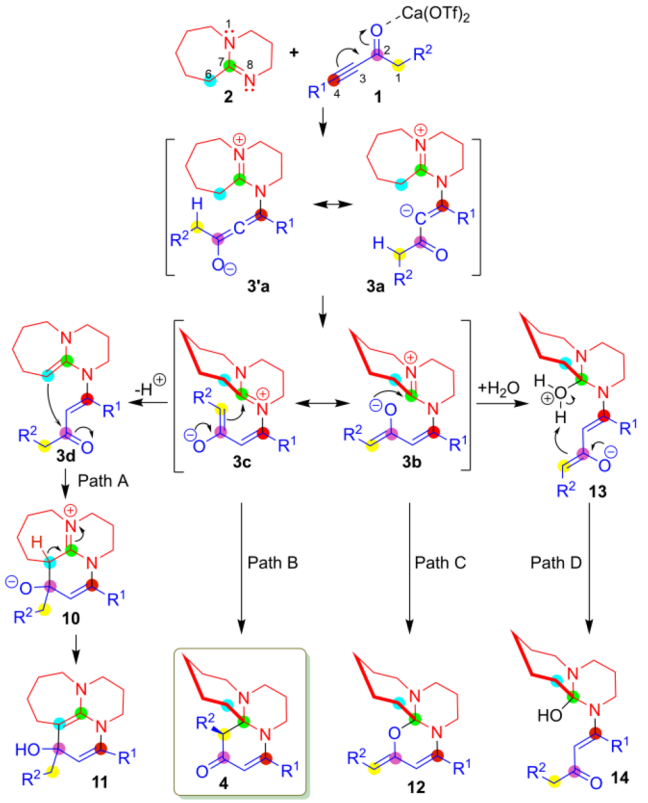
Scheme 3. Proposed Reaction Mechanism

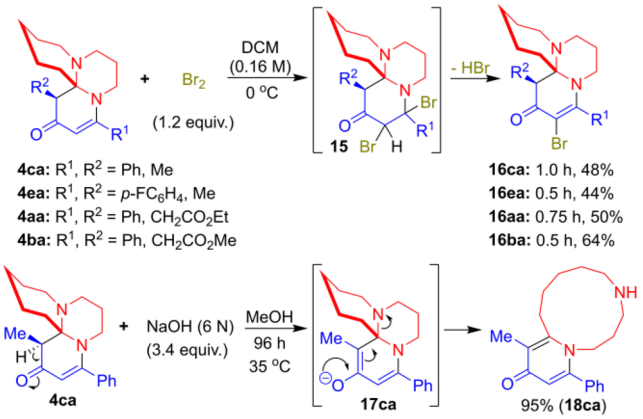


followed by a nucleophilic attack on ynone C-2 could lead to the addition product **11** similar to that obtained by Müller's group (Scheme 1d) via path A.

Path B dictates a selective nucleophilic enolate attack by the α to the carbonyl moiety on iminium C-7 furnishing the cyclized products **4**. The same intermediate **3b** could also yield the cyclized products **12** through path C. Finally, this reaction sequence could also be truncated intermolecularly with addition of water from solvent at C-7, giving entities like **14** through path D. Amidst such manifold reaction possibilities, the present reaction design yields singularly products **4** via path B. Reaction pathway D even elucidates the formation of product **7cc** via **6cc**. Isolation of **7cc**, additionally, is a testament to the existence of intermediates **3a**, **3b**, **3c**, and **3d** along with the initial regiochemistry of interaction between DBU **2a** and the ynone **1**. *In the zwitterionic intermediate* **3c** *for reaction with ester ynones, a larger "R" group of ester functionality sterically locks the ester carbonyl in a conformation favoring stabilizing interactions between the ester carbonyl's and the positively charged iminium nitrogen at the lower temperatures (40 °C), thus rationalizing the decrease in yield on moving from ethyl ynone ester* **1a** *to methyl ynone ester* **1b**.

The final cyclized products **4** were further scrutinized for their chemical reactivity, paving the way for their synthetic applications (Scheme 4). Hence, intentional libraries of compounds **4** were made to undergo facile bromination succeeded by bromination addition followed by dehydrohalogenation to yield the monobrominated products **16** in good yields. In addition, compound **4ca** underwent C−N bond cleavage on treatment with aqueous NaOH (6.0 N) in methanol via formation of the enolate **17ca** to generate an 11-membered fused heterocycle **18ca** in excellent yield. The structure and relative stereochemistry of the products **16** were

Scheme 4. Synthetic Applications



assigned by NMR analysis and also finally confirmed by X-ray structure analysis on **16ca** as shown in Figure S2 (see the Supporting Information).

In essence, an unprecedented ambiphilic addition of ynones across a carbon−nitrogen bond of amidines has been achieved in a formal [4 + 2]-cycloaddition fashion under self- and calcium catalysis. Furthermore, a single ynone−amidine adduct was obtained among many possibilities, highlighting the unique regioselectivity of the present reaction strategy. Our future efforts will be directed toward applying the profitable insights gained about the reactivity of amidines and ynones from the present study to new reactions and substrate designs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03711.

Details of experimental procedures for the catalytic reactions and spectroscopic data for the products (PDF)
NMR spectral data (PDF)

Accession Codes

CCDC 2024821−2024822 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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https://dx.doi.org/10.1021/acs.orglett.0c03711
Org. Lett. XXXX, XXX, XXX−XXX

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was made possible by a grant from the Department of Science and Technology (DST), SERB, New Delhi (Grant No.: CRG/2018/000775). T.P.R. thanks UGC-BSR (New Delhi) for his senior research fellowship. J.G. thanks CSIR (New Delhi) for his senior research fellowship. P.R. thanks UGC (New Delhi) for his senior research fellowship. We thank Dr. P. Raghavaiah, Central University of Karnataka, Gulbarga, for X-ray structural analysis.

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