Cyclotrimerization

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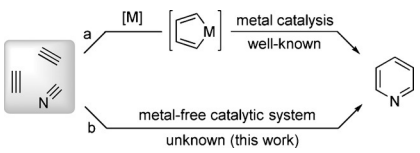
Metal-Free [2+2+2] Cycloaddition of Ynamides and Nitriles: Mild and Regioselective Synthesis of Fully Substituted Pyridines

Yong Wang, Li-Juan Song, Xinhao Zhang, and Jianwei Sun**

Abstract: *A metal-free trimolecular [2+2+2] cycloaddition of internal ynamides and nitriles for de novo synthesis of fully substituted pyridines is disclosed. With the versatile Brønsted acid catalyst $HNTf_2$, the mild intermolecular cyclotrimerization process proceeds with complementary chemoselectivity and excellent regioselectivity.*

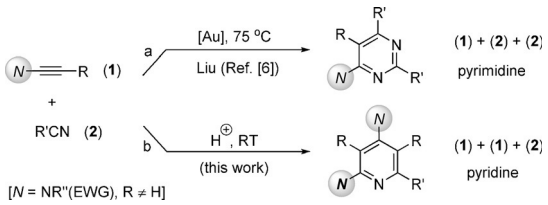
Pyridine is an important heterocycle present in numerous natural products and biologically active molecules.[1] Their de novo synthesis has thus attracted tremendous attention over the past few decades.[1–5] In particular, [2+2+2] cycloaddition of alkynes and nitriles represents one of the most convenient and straightforward strategies (Scheme 1).[2–4]



Scheme 1. [2+2+2] Cycloaddition of alkynes and nitriles for pyridine synthesis.

Consequently, numerous catalytic systems have been developed for these processes. However, almost all of them rely on metal catalysis and hypothetically proceed via a key metallocyclopentadiene intermediate (Scheme 1a). In contrast, metal-free catalytic systems remain essentially unknown.

In addition, there remain some limitations to the state of the art of these metal-catalyzed processes. For example, many of them are bimolecular or unimolecular (i.e., employing diynes, cyanoalkynes, cyanodiynes, etc.), which obviate potential challenges that are likely encountered for trimolecular processes, such as unfavorable entropy change, elusive regiocontrol, and chemoselectivity.[2] Indeed, truly trimolecular processes of this type with high regioselectivity are underdeveloped. Furthermore, most of these processes still require either high temperature or photoirradiation. In this context, here we describe the first metal-free trimolecular [2+2+2] cycloaddition between internal ynamides and unactivated nitriles, thus leading to mild and regioselective synthesis of fully substituted pyridines (Scheme 1b).



Scheme 2. Catalyst-controlled reactivity divergence. EWG = electron-withdrawing group.

Recently, Liu and co-workers reported an efficient synthesis of pyrimidines by gold-catalyzed [2+2+2] cyclotrimerization of internal ynamides and nitriles (Scheme 2a).[6] Inspired by this elegant work as well as our recent success in proton activation of electron-rich alkynes,[7] we hypothesized that initiation of this process by a proton might alter the reaction outcome and/or barrier. Remarkably, a suitable Brønsted acid could catalyze the reaction of essentially the same substrates not only at room temperature, but also leading to entirely different products, fully substituted pyridines, which represents a new example of catalyst-controlled reactivity divergence (Scheme 2b).

We started this study with the ynamide **1a** and acetonitrile (**2a**) as representative substrates.[8] Various Brønsted acids were evaluated (Table 1), but typical organic acids (e.g., TFA, MsOH, TsOH) were not capable of catalyzing the reaction. HCl also did not show appreciable catalytic ability in spite of its strong acidity. However, triflic acid (HOTf) exhibited dramatically higher catalytic activity leading to the pyridine **3aa** in 88% yield. Gratifyingly, triflimide ($HNTf_2$)[9] was found to be even more effective (entry 5).[10] Next, we evaluated other reaction parameters. A lower catalyst loading led to decreased reaction rate, but the selectivity remained excellent (entry 7), and was also observed with either a lower concentration or other solvents (entries 8 and 10–12). Either a higher concentration or neat conditions resulted in slightly diminished yields. The reaction run open air also gave comparable yield (entry 13).

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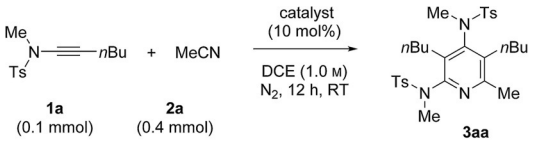
Table 1: Optimization of reaction conditions.



1a (0.1 mmol) **2a** (0.4 mmol) **3aa**

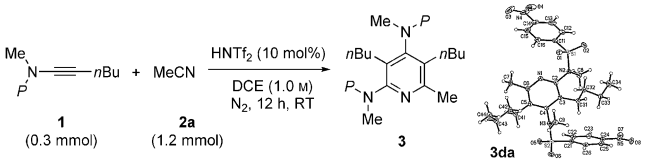
Entry	Reaction conditions	Conv. [%][a]	Yield [%][a]
	Catalyst evaluation		
1	CF_3CO_2H	10	<5
2	$MeSO_3H$	15	<5
3	$TsOH{\cdot}H_2O$	20	<5
4	HCl[b]	15	<5
5	HOTf	100	88
6	$HNTf_2$	100	95 (89)
	Variation from entry 6		
7	$HNTf_2$ (7.5 mol%)	95	89
8	$c = 0.5$ M	90	83
9	$c = 2.0$ M	100	86
10	solvent = DCM	88	82
11	solvent = EtOAc	65	48
12	solvent = toluene	80	72
13	under air (no N_2)	100	89

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. [b] Run with the commercial HCl solution in 1,4-dioxane. DCE = 1,2-dichloroethane, DCM = dichloromethane, Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

Under the established reaction conditions (Table 1, entry 6), ynamides with various N-sulfonyl groups all participated in the pyridine-formation reaction with good efficiency (Table 2). The structure of the pyridine **3da** was confirmed by X-ray crystallography. A wide range of N-Ts-substituted ynamides with various substituents also smoothly participated in the process with excellent regiocontrol (Table 3), although some of them required a higher temperature, presumably because of the increased steric hindrance (entries 8–12). A terminal ynamide was also found to be suitable, albeit in a moderate yield (entry 13). This outcome might be a result of the relatively unstable intermediates involved.

Moreover, this protocol is applicable to a range of unactivated nitriles, including sterically hindered and variously functionalized ones (Table 4). Notably, the strong acidic

Table 2: Evaluation of different electron-withdrawing groups.

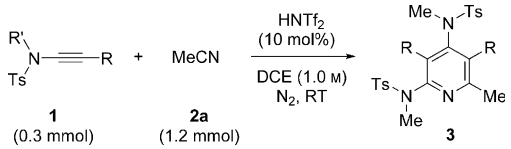


1 (0.3 mmol) **2a** (1.2 mmol) **3** **3da**

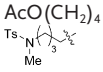
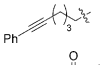
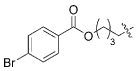
P	**3**	Yield [%]
p-Ts	**3aa**	89 (83)[a]
$PhSO_2$	**3ba**	88
(*p*-Br)$C_6H_4SO_2$	**3ca**	87
Ns	**3da**	78[b]
Ms	**3ea**	63[c]

[a] Yield at 2.0 mmol scale. [b] 24 h. X-ray structure of **3da** is shown.[13] Thermal ellipsoids are shown at 40% probability. [c] 60 °C for 24 h. Ns = *p*-nitrobenzenesulfonyl, Ms = methanesulfonyl.

Table 3: Scope with respect to ynamides.

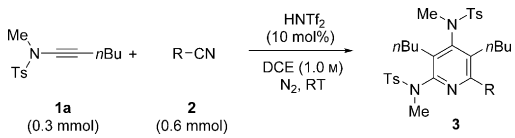


1 (0.3 mmol) **2a** (1.2 mmol) **3**

Entry	R	R′	**3**	*t* [h]	Yield [%][a]
1	$PhCH_2CH_2$	Me	**3fa**	12	71
2	$TBSO(CH_2)_4$	Me	**3ga**	24	64
3	$AcO(CH_2)_4$	Me	**3ha**	12	83
4		Me	**3ia**	24	73
5		Me	**3ja**	24	67
6		Me	**3ka**	12	81
7		Me	**3la**	24	74
8	Ph	Me	**3ma**	24	68[b]
9	*n*Bu	Et	**3na**	12	92[c]
10	*n*Bu	Bn	**3oa**	12	80[c]
11	*n*Bu	allyl	**3pa**	12	77[c]
12	*n*Bu	$MeO(CH_2)_2$	**3qa**	12	75[c]
13	H	Me	**3ra**	24	66[b]

[a] Yield of isolated product. [b] 60 °C. [c] 80 °C. TBS = *tert*-butyldimethylsilyl.

Table 4: Scope with respect to nitriles.



1a (0.3 mmol) **2** (0.6 mmol) **3**

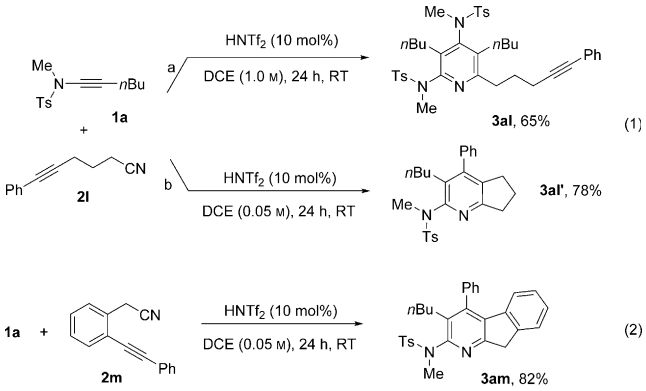
Entry	R-CN	**3**	*t* [h]	Yield [%][a]
1	*n*BuCN	**3ab**	12	88
2	BnCN	**3ac**	12	70
3	PhCN	**3ad**	12	64[b]
4	*t*BuCN	**3ae**	24	72
5		**3af**	12	82 (78)[c]
6		**3ag**	24	72
7		**3ah**	24	74
8		**3ai**	24	79
9		**3aj**	24	74
10		**3ak**	24	68

[a] Yield of isolated product. [b] Run with 1.5 equivalents of PhCN (0.45 mmol). [c] Yield for reaction run at 2.0 mmol scale.

conditions showed impressive functional-group compatibility (e.g., TBS-protected alcohols, ethers, esters, alkenes, alkynes, bromoalkynes). It is also worth noting that, instead of intramolecular cyclization, those nitriles tethered with an alkene or alkyne still proceeded intermolecularly to form the pyridines **3ag–aj** (entries 6–9). Finally, thiocyanate is also a suitable reaction partner leading to the 2-sulfenylpyridine **3ak**.

Although the initial attempt to disrupt the trimolecular process with an internal reactive tether was not fruitful [Table 4 and Eq. (1a)], we reasoned that such disruption

might be favored at a lower concentration. Indeed, the reaction with the cyanoalkyne **2l** showed dramatic sensitivity to concentration. Remarkably, at 0.05 M concentration and under otherwise identical reaction conditions, **2l** reacted by a bimolecular process to give the bicyclic pyridine **3al′** in 78% yield. Thus, it is a new example of concentration-controlled selectivity divergence. This bimolecular protocol could also be extended to the formation of the fused tricyclic pyridine **3am** [Eq. (2)].



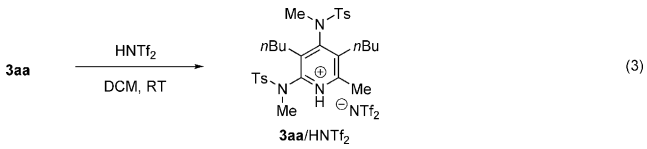
(1)

(2)

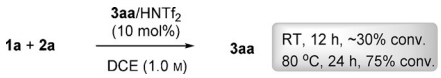
Mechanistically, it is noteworthy to observe smooth turnover of the strong acid catalyst in the presence of the basic pyridine product. Thus, we were curious about the catalytic activity of the pyridine/$HNTf_2$ adduct. We prepared and fully characterized the adduct **3aa**/$HNTf_2$ [Eq. (3)]. Indeed, this adduct could catalyze the reaction of **1a** and **2a** to form **3aa**, but at a significantly low rate [Eq. (4)]. Even at 80 °C, the reaction could not proceed to completion within 24 hours, and is in sharp contrast to the standard protocol (complete conversion, 12 h, RT). Such a dramatic rate decrease likely suggests that this adduct is not the actual catalyst in the standard protocol, even beyond 10% conversion. To rationalize the observed good reactivity for the standard protocol beyond 10% conversion, at which time sufficient base has been generated to potentially form the less active adduct **3aa**/$HNTf_2$, we pre-added **3aa** (0.15 equiv) to the standard reaction mixture to mimic the state at 15% conversion. Surprisingly, the reaction rate remains essentially the same as that of the standard reaction when set up side by side [Eq. (5)]. These results suggest that the ynamide outcompetes the product in reacting with $HNTf_2$, and is critically important to ensure smooth catalyst turnover.

Although **3aa**/$HNTf_2$ is not as active as the free $HNTf_2$, it is capable of catalyzing the reaction to achieve good efficiency at the expense of temperature and time [Eq. (6)]. In retrospect, the failure of those weak acids to catalyze this reaction (Table 1) might not necessarily be a result of their weak acidity. The low nucleophilicity of the counter anion ($^-NTf_2$) might be important to maintain the cationic nature and/or reactivity of certain intermediates involved.[11]

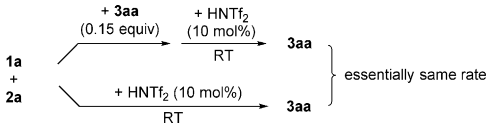
Possible catalytic cycles are proposed in Scheme 3. The reaction begins with ynamide protonation to form the keteniminium **A**, from which two paths are possible. In path a, nucleophilic attack on **A** by another ynamide molecule forms the vinyl keteniminium **B**. Subsequent nitrile addition forms the cyclic intermediate **D**, which might proceed either stepwise (via **C**) or in a concerted fashion. Finally, deprotonation of **D** delivers the pyridine product and regenerates the acid catalyst. Alternatively, **A** might undergo nitrile attack to form **E** (path b), which then reacts with another ynamide molecule to form the cyclic intermediate **G** via **F**. A similar deprotonation closes the catalytic cycle with concomitant product formation.



(3)



(4)



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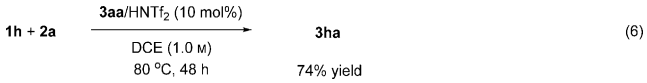
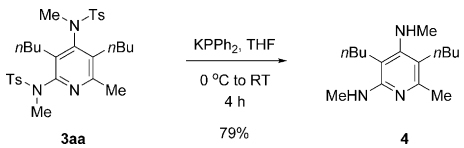


(6)

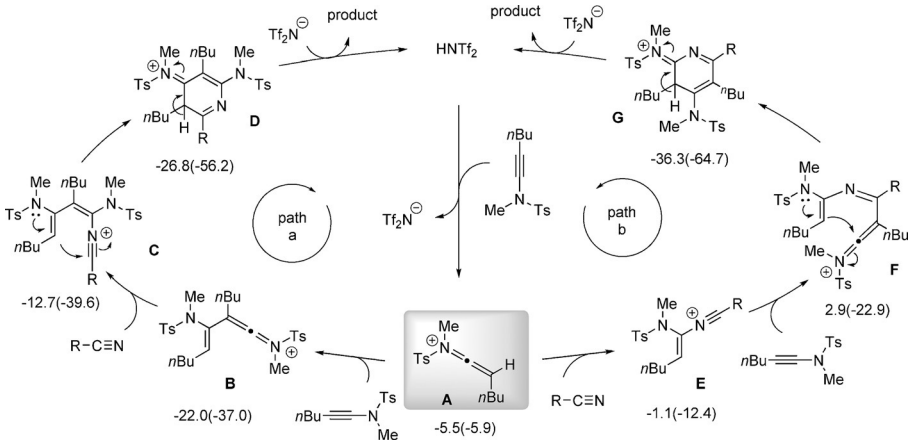
To gain mechanistic insights, DFT calculations of these two cycles were conducted. Relative free energies for the above-mentioned intermediates are included in Scheme 3. Path a is kinetically more favorable than path b (see Figure S1 in the Supporting Information for the overall free energy profile). Moreover, the significant energy difference between **B** and **E** led us to obtain more experimental data by monitoring the reaction with NMR spectroscopy, using a stoichiometric amount of $HNTf_2$ and stepwise addition of reaction partners. Indeed, the experimental results are consistent with the computational studies (see Scheme S2).

Finally, the Ts group in the products can be easily removed in the presence $KPPh_2$ under mild reaction conditions. It is important to note that 2,4-diaminopyridines are useful core structures of many bioactive molecules.[12]



(7)

In summary, we have developed the first metal-free trimolecular [2+2+2] cyclotrimerization of ynamides and nitriles for the efficient de novo synthesis of fully substituted pyridines. The mild protocol based on Brønsted acid catalysis overcomes the unfavorable trimolecular entropy change to



Scheme 3. Possible catalytic cycles and calculated energies of the key intermediates. The relative free energies and electronic energies (within parentheses) are given in kcal mol^{-1}.

proceed efficiently with complementary chemoselectivity (versus gold catalysis) and excellent regiocontrol. Of particular note is the smooth acid catalyst turnover in view of the basic pyridine product. DFT calculations and control experiments with the product/$HNTf_2$ adduct provided important insights into the mechanism. The outstanding performance of $HNTf_2$ is attributed to not only its high acidity, but also the low nucleophilicity of its counter anion ($^{-}NTf_2$).

Acknowledgments

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Keywords: Brønsted acid · cycloaddition · cyclotrimerization · heterocycles · reaction mechanisms

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[13] CCDC 1469439 (**3da**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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