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Acid-catalyzed [2 + 2 + 2] cycloaddition of two cyanamides and one ynamide: highly regioselective synthesis of 2,4,6-triaminopyrimidines†

Alexey Yu. Dubovtsev, *[a] Valeria V. Zvereva, [a] Nikolay V. Shcherbakov, [a] Dmitry V. Dar'in, [a] Alexander S. Novikov [a] and Vadim Yu. Kukushkin *[a,b]

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Triflic acid (10 mol%) catalyzes the highly regioselective [2 + 2 + 2] cycloaddition between two cyanamides and one ynamide to grant the 2,4,6-triaminopyrimidine core. The developed synthetic method is effective for the preparation of a family of the diversely substituted heterocyclic products (30 examples; yields up to 94%). The synthesis can be easily scaled up and conducted in gram quantities. As demonstrated by the post-functionalizations involving the amino-substituents, the obtained heterocycles represent a useful platform for the construction of miscellaneous pyrimidine-based frameworks. The performed density functional theory calculations verified a particular role of H^+, functioning as an electrophilic activator, in the regioselectivity of the cycloaddition.

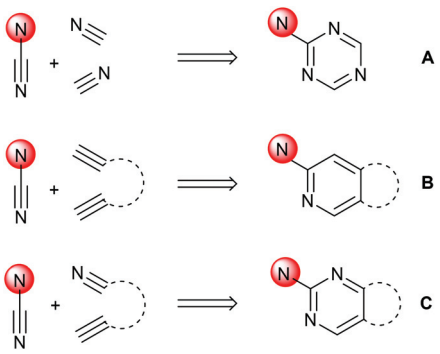
Introduction

[2 + 2 + 2] Cycloadditions leading to amino-functionalized N-heterocycles are among the most important applications of cyanamide[1,2] synthons. These cycloadditions can be divided into three groups (Scheme 1) according to the number and nature of the reactants. Group A comprises the reactions between one cyanamide and two nitriles; group B covers the cycloadditions between one cyanamide and two alkynes; and group C involves the interplay between one cyanamide, one nitrile and one alkyne.

The overwhelming majority of studies on the [2 + 2 + 2] cycloaddition of cyanamides is focused on the synthesis of 2-aminopyridines (Type B) under metal-catalyzed conditions (M = Fe,[3,4] Ir,[5] Co,[6,7] Ni,[8,9] Ru,[10–12] Rh[13]). Type A reactions—mainly include the trimerization of cyanamides to give amino-1,3,5-triazines—proceed under the action of Lewis acids (*e.g.*, $Y(OTf)_3$,[14] $[Al(NMe_2)_3]_2$ [15]) or other reactive species (LiHMDS,[16] Tf_2O,[17] Na,[18] PhLi[19]).

In contrast to the wealth of types A and B cycloadditions, only two examples of type C reactions are known. Both reported transformations accomplished the aminopyrimidine core, which is an important heterocyclic platform in natural product- and pharmaceutical chemistry.[20–24] Thus, Louie and coworkers proposed a method for the [2 + 2 + 2] cycloaddition between cyanamides and tethered cyanoalkynes in the presence of the catalytic system comprised of FeI_2 and $^{i\text{-Pr}}$PDAI.[25] The Maulide group reported the [2 + 2 + 2] cycloaddition of a limited scope (one example has been provided) that includes two *N*,*N*-dimethylcyanamides and one thio-substituted alkyne; this integration requires a stoichiometric amount of TfOH.[26]

In continuation of our project on cyanamide chemistry,[27–30] we recently reported on the reaction dichotomy of cyanamides with respect to β-arylynamides: under gold(I)-catalyzed conditions type C [2 + 2 + 2] cycloaddition and side-[4 + 2]-cycloaddition (the latter involves ynamide β-aryl-moiety) occur sim-



Scheme 1 Types of [2 + 2 + 2] cycloadditions involving cyanamides.

[a]*Saint Petersburg State University, Universitetskaya Nab. 7/9, 199034 Saint Petersburg, Russian Federation. E-mail: a.dubovtsev@spbu.ru, v.kukushkin@spbu.ru*

[b]*South Ural State University, 76, Lenin Av., 454080 Chelyabinsk, Russian Federation*

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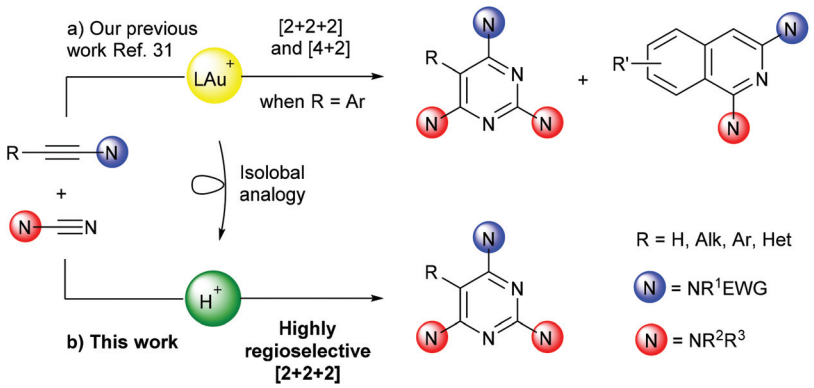


Scheme 2 Unselective gold-catalyzed (a, ref. 31) and highly regioselective acid-catalyzed (b, this work) cycloadditions of cyanamides and ynamides.

ultaneously (Scheme 2a).[31] By varying the Au-catalyzed reaction conditions, the regioselectivity of the [2 + 2 + 2] cycloaddition can be increased, however, the side-[4 + 2]-reaction leading to isoquinolines cannot be completely suppressed and the isolation/purification of the target pyrimidines therefore represent a separate task.

In our search for suitable catalysts providing the highly regioselective [2 + 2 + 2] cycloaddition of cyanamides and ynamides, we turned to Brønsted acids. These acids can be employed as an alternative to gold-based catalysts[32–39] in view of the isolobality of H^+ and LAu^+.[40–44] We now report on the facile triflic acid-catalyzed (10 mol%) integration of two cyanamides and one ynamide. In contrast to the previous nonspecific method leading simultaneously to pyrimidines and isoquinolines (Scheme 2a) and utilizing the gold-based catalysts,[31] the use of catalytic amounts of TfOH leads to the highly regioselective [2 + 2 + 2] cycloaddition (Scheme 2b) to give a variety of useful 2,4,6-triaminopyrimidines. All our experimental and theoretical results relevant to this novel synthetic method are detailed in the following sections.

Results and discussion

For this study, we addressed ynamides,[45–49] *i.e.* alkynes featuring an amide substituent at the C≡C bond. The ynamide conjugated system is highly nucleophilic and capable of activation by such isolobal electrophiles as Au^+ or H^+. The successful replacement of gold-based catalysts by H^+ in some reactions has been demonstrated,[50,51] although such examples are more an exception than the general rule. We also took into account that Brønsted acids catalyze some other cycloadditions of either cyanamides,[26] or ynamides;[40,41] however, acid-catalyzed cyanamide and ynamide integration has never been reported.

The scenario of this work is the following: we performed the screening of electrophilic activators for the [2 + 2 + 2] cycloaddition of cyanamides and ynamides (with particular focus on H^+) and also uncovered the synthetic potential of this highly regioselective reaction. For some of the synthesized compounds, post-functionalizations involving the amino-substituents were carried out. Appropriate theoretical calculations verified the role of H^+, functioning as an electrophilic activator, in the regioselectivity of the [2 + 2 + 2] cycloaddition.

Screening of electrophilic activators

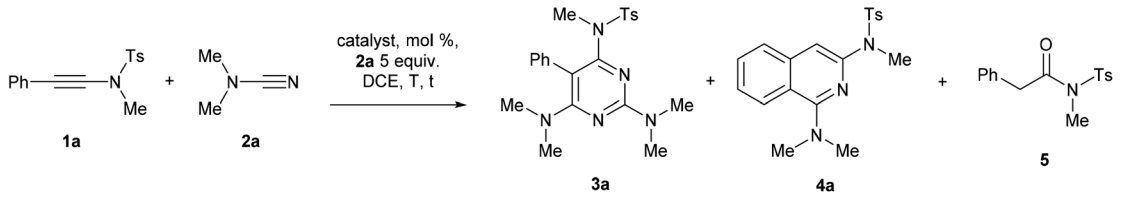
We began our studies by exploring the reactivity of ynamide **1a** toward *N*,*N*-dimethylcyanamide (**2a**) in the presence of various electrophilic activators (Table 1). Previously, when gold(I) complexes were used[31] (entries 1 and 2), in addition to the desired 2,4,6-triaminopyrimidine **3a**, derived from the [2 + 2 + 2] cycloaddition, we obtained 1,3-diaminoisoquinoline **4a** that originates from the formal [4 + 2] cycloaddition. The model reaction in the presence of TfOH (10 mol%), taken instead of the gold species, gave pyrimidine **3a** (65%) as the only heterocyclic product (entry 3). In this case, the significant formation of **5**, as a result of the hydration of **1a**, was observed but the side isoquinoline was not detected in the reaction mixture. Catalytic amounts of weaker Brønsted acids were ineffective (entries 4–6), but superacidic bistriflimide (Tf_2NH, entry 7) showed the result comparable to that observed for TfOH. The target pyrimidine was also obtained selectively when such Lewis acids as $BF_3{\cdot}Et_2O$ or TMSOTf were applied as the catalysts (entries 8 and 9); even traces of the [4 + 2] cycloaddition product were not detected (entries 3–9).

TfOH that showed the best result was chosen for further study. The experiments were carried out in dry DCE with freshly distilled TfOH under dry argon atmosphere to prevent the ynamide hydration. The optimizations of the reaction temperature/time and catalyst loading revealed that the best yield of **3a** was achieved at 80 °C for 24 h with only 3 equiv. of **2a** and 10 mol% of TfOH (entry 14).

TfOH-catalyzed synthesis of 2,4,6-triaminopyrimidines and its applications

With the optimal conditions at hand, the substrate scope and limitations for the synthesis of 2,4,6-triaminopyrimidines **3** were examined. Initially we explored different cyanamides with ynamide **1a**, taken as the alkyne component (Table 2). The

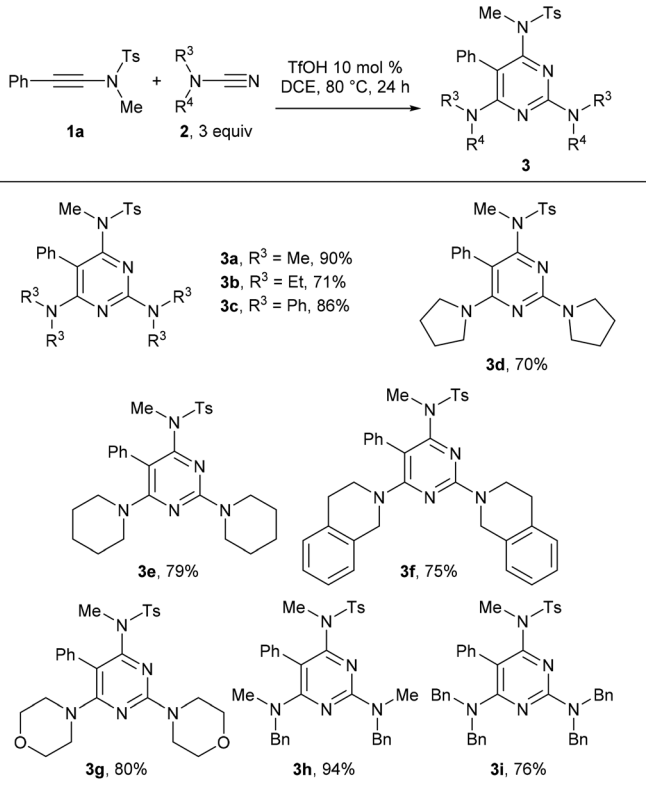
Table 1 Optimization of the synthesis of **3a**[a]



Entry	Catalyst, mol%	*t*, °C	Time, h	Conversion,[b] %	Yields,[b] %		
					3a	**4a**	**5**
1	$Ph_3PAuNTf_2$, 5	60	3	58	31	21	2
2	$IPrAuNTf_2$, 5	60	3	97	46	48	3
3	TfOH, 10	60	3	89	65	—	18
4	TFA, 10	60	3	17	—	—	15
5	TsOH, 10	60	3	23	—	—	20
6	MsOH, 10	60	3	15	—	—	13
7	Tf_2NH, 10	60	3	86	61	—	22
8	$BF_3{\cdot}Et_2O$, 10	60	3	71	50	—	20
9	TMSOTf, 10	60	3	80	58	—	16
10[c]	TfOH, 10	rt	24	45	14	—	28
11[c]	TfOH, 5	80	24	72	61	—	5
12[c]	TfOH, 10	80	24	99	86	—	6
13[c]	TfOH, 20	80	24	96	80	—	10
14[c,d]	**TfOH, 10**	**80**	**24**	**98**	**88**	—	6
15[e]	TfOH, 10	80	24	45	32	—	13

[a] All reactions were carried out on a 0.1 mmol scale (0.2 M). [b] Estimated by ^{1}H NMR spectroscopy using durene as an internal standard. [c] Under dry argon atmosphere. [d] 3 equiv. of **2a** was used. [e] 1 equiv. of **2a** was used.

Table 2 Reactivity screening for cyanamides **2**[a,b]

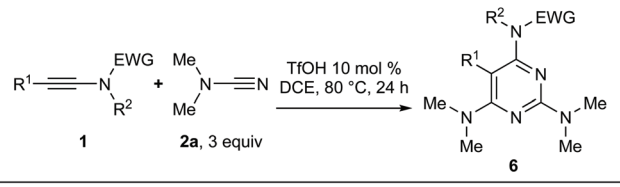


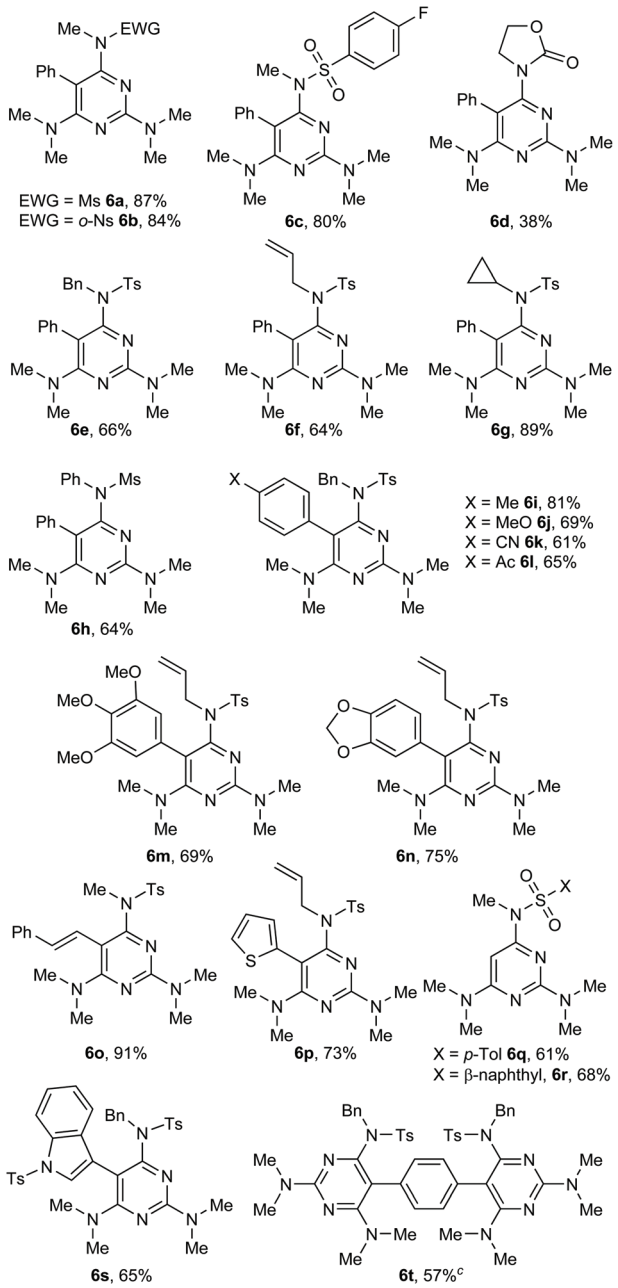
[a] All reactions were carried out on a 0.2 mmol scale (0.2 M). [b] Isolated yield.

application of all *N*,*N*-dimethyl-, *N*,*N*-diethyl- and bulky *N*,*N*-diphenyl-cyanamides led to good yields of corresponding pyrimidines **3a–c**. The reaction conditions were effective for introducing a diversity of cyclic amino-functionalities, such as pyrrolidine, piperidine, tetrahydroisoquinoline, and morpholine fragments, into the both 2nd and 6th positions of the pyrimidine core (**3d–g**). Notably, complex reaction mixtures were obtained when we attempted the preparation of pyrimidines from cyanamides containing the free NH-fragments (NH_2CN, PhNHCN, *n*-BuNHCN). This reactivity pattern is probably related to the competing ynamide hydroamination.[52] Nevertheless, pyrimidines **3h,i**, bearing easily cleavable benzyl *N*-protective groups, were obtained in excellent yields.

Next, we tested various ynamides **1** in their reactions with *N*,*N*-dimethylcyanamide (Table 3). The cycloadditions proceed smoothly with the reactants featuring various electron-withdrawing *N*-sulfonyl substituents (**6a–c**). On the contrary, pyrimidine **6d** bearing a cyclic carbamate substituent was obtained in a rather poor yield. Ynamides featuring *N*-alkyl and *N*-phenyl groups delivered the corresponding pyrimidines in good to excellent yields (**6e–h**). In contrast to our previous method,[31] the reaction conditions were applicable to the [2 + 2 + 2] cycloaddition of ynamides with diverse R^1-substituents (**6i–t**). Thus various functionalities can be introduced into the 5th position of pyrimidine ring, including alkenyl (**6o**), high electron-donor aryl (**6j,m,n**), and heteroaryl (**6p,s**) moieties. In the case of activation by gold complexes,[31] the [4 + 2] cycloaddition is the main reactive route for such electron-rich ynamides. Terminal ynamides **1q,r** were successfully converted

Table 3 Reactivity screening for ynamides **1**[a,b]





[a] All reactions were carried out on a 0.2 mmol scale (0.2 M). [b] Isolated yield. [c] 20 mol% of TfOH was used.

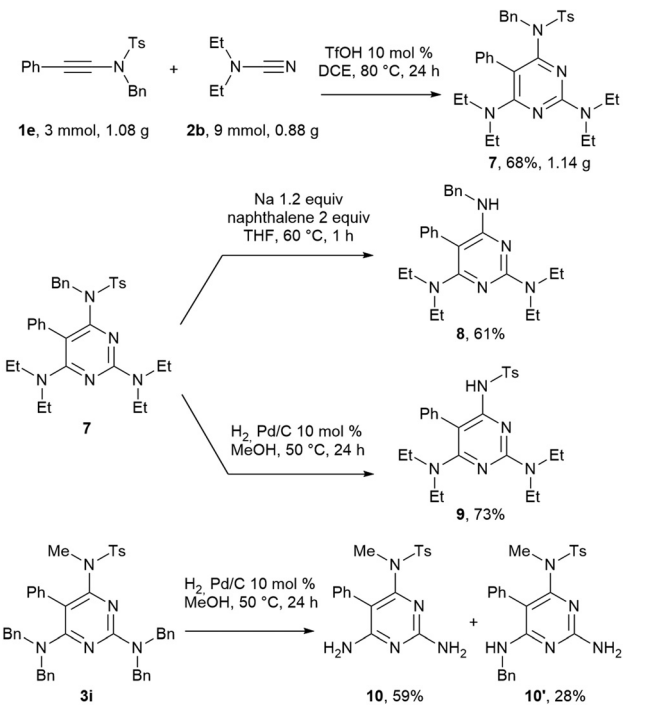
into corresponding 5-unsubstituted pyrimidines **6q,r**. The cycloaddition was carried out in a bidirectional manner giving bispyrimidine **6t**.

Given the value of 2,4,6-triaminopyrimidines for medicinal chemistry, we were eager to demonstrate the further utility of our synthetic approach (Scheme 3). The preparation of **7** can be conducted on a gram scale, while post-functionalizations of compounds **3i** and **7** were illustrated by the detosylation and debenzylations of the amino-substituents at the 2nd, 4th, and 6th positions of the pyrimidine rings.

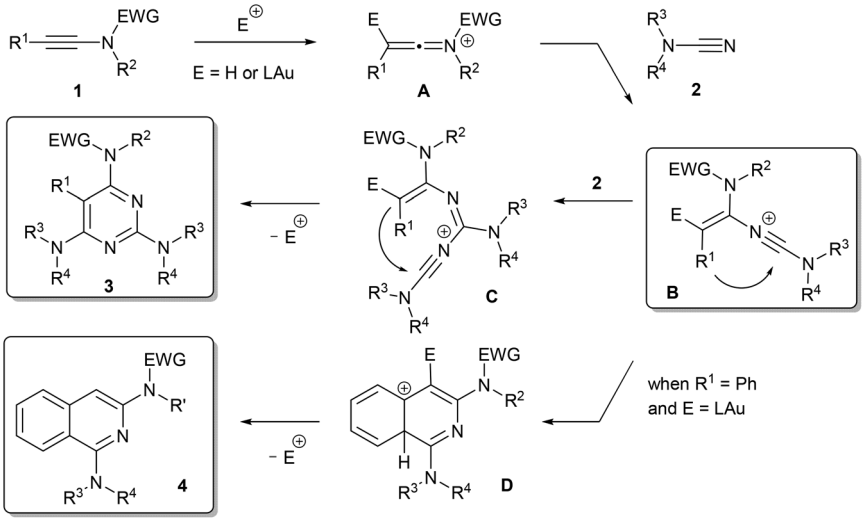
Reaction mechanism and DFT calculations

Plausible mechanisms of both [2 + 2 + 2] and [4 + 2] ynamide-cyanamide integrations are given in Scheme 4. Highly reactive ketiminium intermediate **A** is generated by the action of an electrophile (H^+ or LAu^+) on ynamide **1**. Further attack of **A** by cyanamide **2** leads to nitrilium ion **B**. In turn, two reaction pathways for intermediate **B** could be assumed: (i) the interaction of **B** with another molecule of **2** leads to the closure of the pyrimidine ring of **3**; (ii) when R^1 is an aryl (in particular, phenyl), an intramolecular Friedel–Crafts reaction could lead to isoquinolines **4**. The second pathway is realized exclusively when the gold-based catalysts are used as activators (E = LAu).

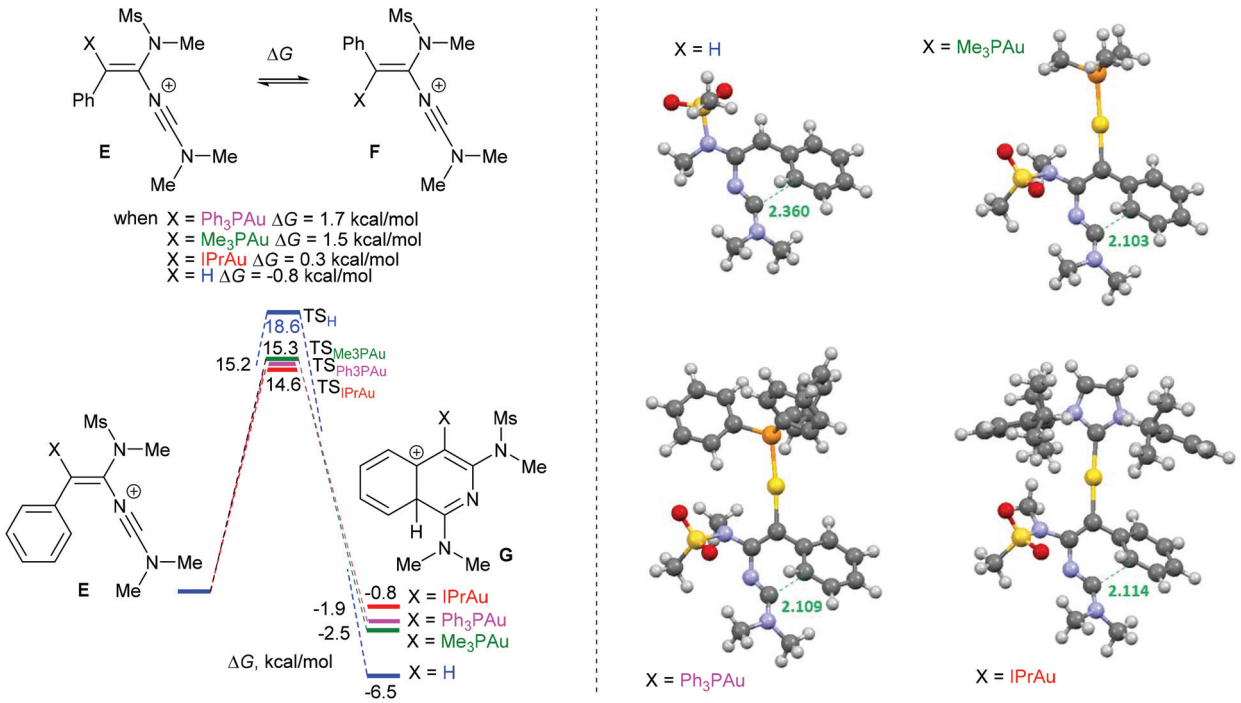
Intrigued by this mechanistic dichotomy illustrated on Scheme 2, we were interested in obtaining theoretical data shedding the light on the crucial role of Brønsted acids in the highly regioselective [2 + 2 + 2] cycloaddition of ynamides and cyanamides. We carried out DFT calculations (B3LYP/MWB60 (Au) and 6-31G*(other atoms) level of theory) for the intramolecular cyclization of the adduct of PhC≡CN(Me)Ms and dimethylcyanamide, when either a gold entity (Ph_3PAu, IPrAu,



Scheme 3 Gram-scale synthesis of **7** and post-functionalizations of **3i** and **7**.



Scheme 4 A plausible mechanism for generation of **3** and **4**.



Scheme 5 The DFT calculations results.

Me_3PAu), or H^+ are used as the electrophilic activators (Scheme 5).

We compared the energy of both possible geometrically isomeric nitrilium intermediate **E** and **F**. In the case of acid (X = H), isomer **F** (for which undesirable intramolecular cyclization is not possible) turned out to be more energetically favorable compared to the corresponding gold species. Next we compared the energies of transition states for cyclization of **E** to **G**. The calculations indicate that the transition state for the activation by Ph_3PAu^+ is more energetically beneficial than that for H^+ (by 3.4 kcal mol^{-1}). In the case of the strong electron-donating and bulky IPr ligand, the energy barrier to the cyclization is further reduced (by 4.0 kcal mol^{-1}). The calculated energies for hypothetical product, reagent, and transition state when X = Me_3PAu only slightly differ from the value for X = Ph_3PAu.

The right half of Scheme 5 shows the transition states for cyclization **E** to **G**, when X = H, Me_3PAu, Ph_3PAu, and IPrAu. In the case of activation by a proton, the distance between the phenyl *ortho*-carbon and the cyanamide carbon is much

higher (2.360 Å) than in the cases of activation by gold; the latter distances change insignificantly for various LAu (2.103–2.114 Å).

Finally, we calculated the activation barrier for the addition of dimethylcyanamide to adduct **E**, which leads to the [2 + 2 + 2] product. When X = H, this barrier was 8.1 kcal mol^{-1}, which is significantly lower than that for the cyclization of **E** to **G** (18.6 kcal mol^{-1}). When X = IPrAu, the activation energy for the addition of dimethylcyanamide to **E** increases to 18.9 kcal mol^{-1}.

These calculations are fully consistent with our experimental data demonstrating the growing trend of isoquinoline formation in a row of the electrophilic activators TfOH ≪ $Ph_3PAuNTf_2$ < $IPrAuNTf_2$ (Table 1). When the cycloaddition is catalyzed by triflic acid (X = H), only the energetically beneficial [2 + 2 + 2] pathway is observed even for ynamides bearing electron-rich aryl fragments at the β-position. On the contrary, an increase of the donor properties of the substituents X (H < Ph_3PAu < IPrAu) favors the intramolecular Friedel–Crafts reaction of nitrilium ions **E** because the presence of a more donating substituent increases the electron density at the *ortho*-positions of the phenyl ring thus making it more sensitive to the electrophilic attacks. Very likely, the steric factors also affect the selectivity of cycloadditions: the presence of the bulky gold-containing substituents X brings the phenyl ring and the cyanamide carbon in adduct **E** closer together, favoring the formation of the isoquinoline.

Conclusions

The previously studied [2 + 2 + 2] cycloadditions between cyanamides and alkynes were mainly focused on the construction of amino-substituted pyridines and triazines. Herein we developed a facile, atom-economic, and high-yielding route toward the pharmaceutically significant 2,4,6-triaminopyrimidines. Our method is based on the highly regioselective TfOH-catalyzed (10 mol%) integration of two cyanamides and one ynamide, which operates under mild conditions, utilize easily available substrates, and can be performed on a gram scale. The versatility of the obtained pyrimidine platform was demonstrated by useful post-functionalizations of the amino-substituents at the 2^{nd}, 4^{th}, and 6^{th} positions of the pyrimidine rings.

In contrast to our previous method[31] for the cyanamide–ynamide integration, which utilizes Au-based catalysts and leads to the mixtures of isoquinolines and pyrimidines, Brønsted acids (in particular TfOH) highly regioselectively promotes the [2 + 2 + 2] cycloaddition to give the pyrimidine core. The DFT calculation data are in line with our experimental observations and both approaches reveal that the side-[4 + 2]-cycloaddition to give isoquinolines is totally suppressed by the switch from the gold-based activators to H^+. The probable cause of the observed selectivity is the combined action of electronic and steric factors. The yields of triaminopyrimidines obtained by the method reported here are comparable to those for the gold catalytic reaction. At the same time this method, in contrast to the gold-catalyzed approach, provides good yields of the products derived from β-aryl ynamides containing electron-donor substituents. Thus, the employment of triflic acid in the cycloaddition represents an attractive alternative to the gold catalyzed route. We believe that our results would be of particular importance for the search of an appropriate catalytic system for cycloadditions involving both cyanamides and ynamides.

Author contributions

A.Yu.D. conceptualized the research project. A.Yu.D., V.V.Z., and N.V.S. conducted the experiments and prepared the ESI.† A.S.N. performed the DFT calculations. A.Yu.D., D.V.D., and V. Y.K. designed the experiments and wrote the paper. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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