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A Copper-Catalyzed Ficini [2 + 2] Cycloaddition of Ynamides

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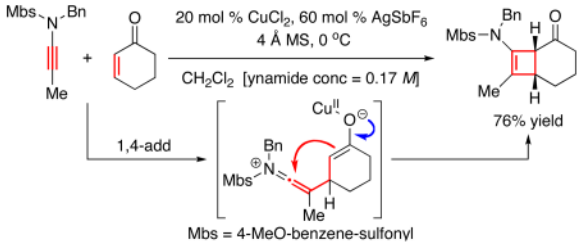
Abstract



The Ficini [2 + 2] cycloaddition using *N*-sulfonyl substituted ynamides is described, featuring the utility of $CuCl_2$ and $AgSbF_6$ as catalysts. This work represents the first success example of ynamides participating in a thermal [2 + 2] cycloaddition with enones.

More than 40 years ago, Ficini[1] disclosed perhaps the most useful carbon-carbon bond forming reaction involving ynamines[2]: a thermally driven stepwise [2 + 2] cycloaddition[3] of ynamine [**1**] with cyclic enones, leading to the formation of cyclobutenamine **3** [Scheme 1].[4-6] In the last 15 years, ynamides have emerged as a superior synthetic equivalent of ynamines.[7,8] Beautiful chemistry in the area of [2 + 2] cycloadditions has followed by way of Tam's Ru-catalyzed ynamide-[2 + 2] cycloaddition of norbornene,[9] Danhesier's thermal cycloaddition of ketenes,[10] and formal [2 + 2] processes through enyne cycloisomerizations using platinum or gold catalysts developed by Malacria[11] and Cossy.[12] However, a thermally driven stepwise [2 + 2] cycloaddition in a Ficini manner using ynamides remained elusive.[13] Our own efforts in trying to develop this cycloaddition reaction lasted for 13 years. We report here our first success in a Ficini [2 + 2] cycloaddition of ynamides.

Over the last 15 years, we failed numerous attempts at succeeding Ficini [2 + 2] cycloaddition of ynamides using lactam or oxazolidinone substituted ynamides under thermal and/or Lewis-acidic consitions.[14] In the current pursuit of this cycloaddition, we chose to employ *N*-sulfonyl substituted ynamides because the nitrogen pair of the sulfonamido group is more delocalized toward the alkyne.[15] Therefore, *N*-sulfonyl substituted ynamides possess enhanced nucleophilicity over simple amide or urethane substituted ynamides, and they are also less stable than amide or urethane substituted ynamides.

However, to our disappointment, *N*-sulfonyl substituted ynamides such as **7** and **10** did not undergo any desired thermal cycloaddition [Scheme 2]. Even when we used quinone and adopt the more electron-rich para-methoxy benzensulfonyl group [Mbs] as shown in ynamide **10**, no

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Supporting Information **Available:** Experimental procedures as well as NMR spectra, and characterizations are available for all new compounds and free of charge via Internet http://pubs.acs.org.

appreciable amount of the desired cycloadduct **9b** was observed, thereby further underscoring the superior stability of ynamides over ynamines.

Our next best option would appear to again involve Lewis acids, which had not been successful over the years when using lactam or oxazolidinone substituted ynamides.[14] More specifically, our efforts were derailed when using Lewis acids because hydro-halogenations of ynamides, leading to alpha-halogenated enamides, was a serious competing pathway.[14,16,17] In addition, when hydro-halogenation is not competing, possible hydrolysis under these suitable Lewis acids represents another challenge associated with ynamides. Consequently, much of ynamide chemistry[7a] has been limited to halo-substituted Lewis acids that do not involve metals such as Mg, Ti, Sn, Si, B, Al, or In [i.e., CuX_2 or ZnX_2 is feasible], or Lewis acids with OTf serving as the counter anion. As a result, we screened a small sample of Lewis acids as summarized in Table 1.

Initial failure is quite evident in entries 1-6 when using ynamide **10**. However, after observing trace amount of the possible product **11** when using $CuCl_2$ and $AgSbF_4$ [entry 6], we speculated that **10** was polymerizing under these reactions conditions. Therefore, we turned to ynamide **12** with a Me group as the terminal-substitution. Gratifyingly, we found that cycloadduct **13**[18] could be attained in good yields at three different low temperatures within an hour [entries 7-9]. This result represents the first successful Ficini [2 + 2] cycloaddition using ynamides. Cycloadduct **13** was unambiguously assigned using X-ray [Figure 1]. It is noteworthy that the amido-cyclobutene motif is quite robust. The pericyclic ring-opening does not occur readily since the allowed thermal conrotatory ring-opening would lead to a *trans*-cycloalkenone.[19]

The generality of this cycloaddition could be established from examples shown in Figure 2. Several features are: (a) The *N*-sulfonyl group does not need to be Mbs [entries 1, 2, and 10]; (b) acyclic enones are also suitable [entries 5 and 6];[20] (c) the alkyne substitutions [entries 7, 8, 14, and 15] and substitutions on the nitrogen atom [entries 11-15] can be varied, which should significantly enhance the potential applications of these cycloadducts.

Moreover, the [2 + 2] cycloadducts such as **13** could be subjected to hydrolytic conditions and further undergo retro-Claisen via the intermediacy of diketone **29** [Scheme 3], leading to keto-ester **30**.[21] Intriguingly, while anhydrous conditions led to **30** in 76% yield, when using MeOH-H_2O as solvent, keto-imide **31**[22] was found in addition to **30**. Ficini also observed ketoamide formation but only under neutral or basic hydrolytic conditions, and its formation likely proceeded through an aminal intermediate.[1,4,23] The modest *syn*-selectivity was also reported in Ficini's related work,[4,23] and the saponified **30**-*syn* was used by Ficini in their synthesis of (±)-juvabione.[24]

Lastly, a simple and straightforward mechanistic consideration would be that this is step-wise cycloaddition with a nucleophilic 1,4-addition by the ynamide onto the enone activated via the cationic Cu(II) catalyst [see Possibility A in Figure 3]. However, there may be another possibility. That is, the cationic Cu(II) species is activating the alkyne [Possibility B], leading to an intermediate that could participate in a cuprate-like 1,4-addition. While we are not sure of the oxidation state of such copper species, this proposed possibility resonates with our earlier proposal of the intermediacy of **C** to explain the exclusive *syn* addition of "H-X" [hydro-halogenation] to ynamides that was observed when using catalysts such as MgX_2,[14] $TiCl_4$,[16] or $Rh(I)Cl(Ph_3P)_3$.[17] We are currently exploring such a mechanistic possibility.

We have uncovered here the Ficini [2 + 2] cycloaddition using ynamides. These reactions could be catalyzed using $CuCl_2$ and $AgSbF_6$. Efforts are underway to develop synthetic applications of this cycloaddition reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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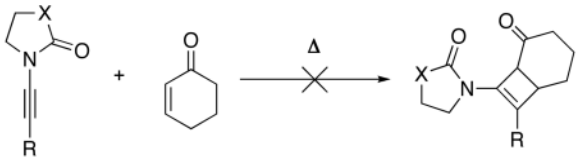

15. While sulfonamides [$R^1(SO_2)$-N(H)R^2 are more acidic than amides $R^1CO_2N(H)R^2$ in general because of the overall stability different between the respective conjugate bases [as one referee kindly pointed out], sulfonyl substituted ynamides [or enamides] are more reactive and less stable than simple amide or urethane substituted ynamides [or enamide]. The nitrogen lone pair in the former is more delocalized into the alkyne [or alkene motif], and more into the carbonyl group in the latter. Likewise but in a reverse sense, for iminium ion chemistry, sulfonyl substituted iminium species are more stable and less reactive than straight N-Acyl iminium ions because the nitrogen lone pair in the former is more involved in the pi-donation to the carbocation. See: Royer J, Bonin M, Micouin L. Chem Rev 2004;104:2311. [PubMed: 15137793]
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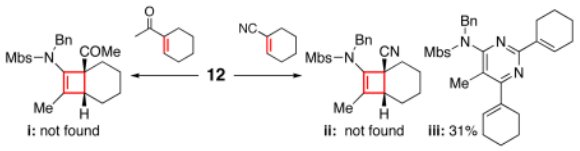
20. Conjugation appears to be a key, as cyclohexenyl methyl ketone did not give **i** when reacted with ynamide **12**. On the other hand, cyclohexenyl nitrile gave a completely different product pyrimidine **iii**, thereby suggesting a cyclotrimerization process. Regiochemistry of **iii** was assigned using nOe [see SI].



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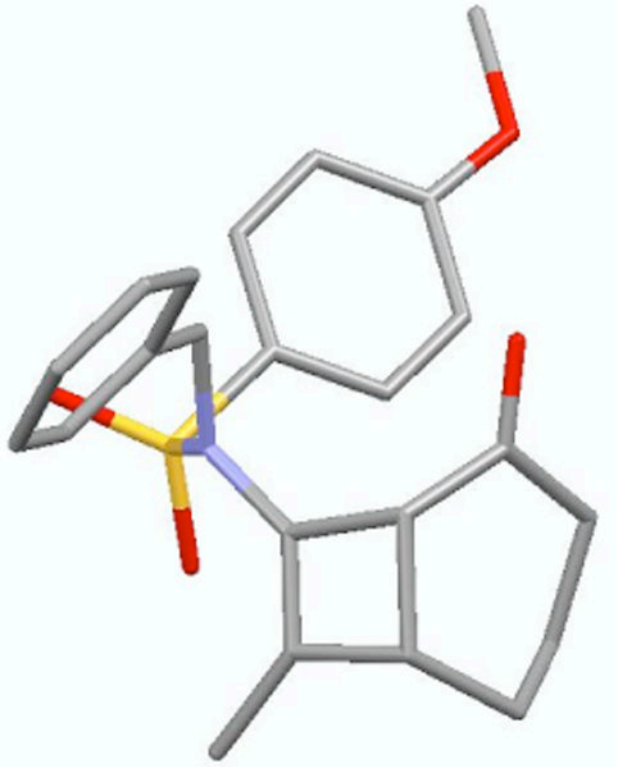


Figure 1.
X-Ray Structure of the [2 + 2] Cycloadduct **13**.

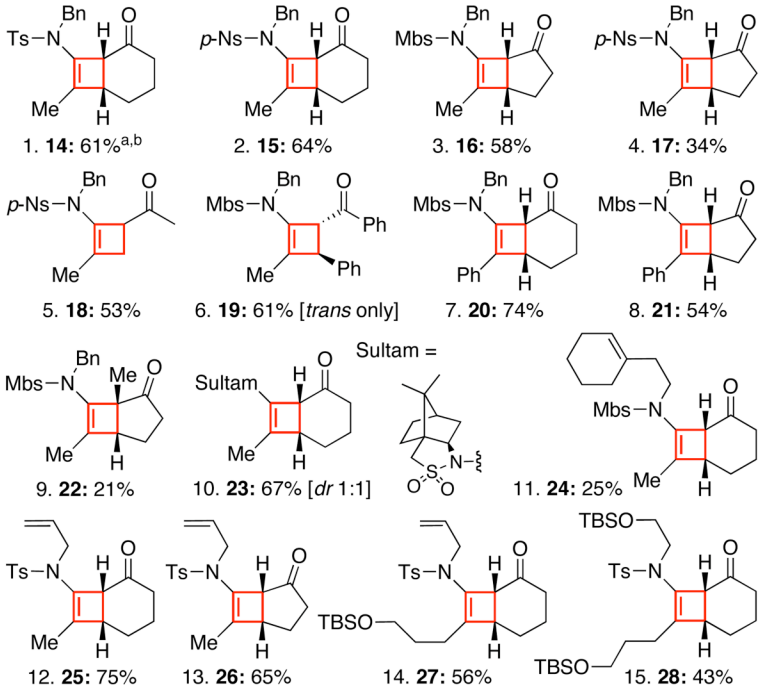
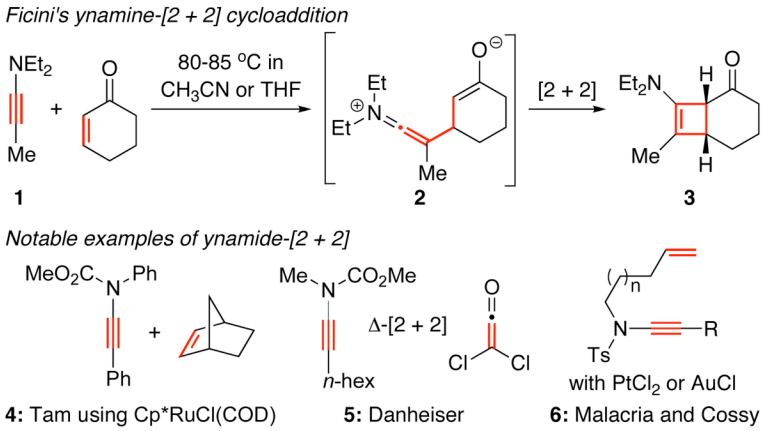


Figure 2.

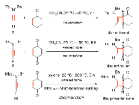
Scope of the Ynamide-[2 + 2] Cycloaddition.

a. All reactions were carried out in anhyd CH_2Cl_2 [ynamide conc = 0.17 *M*] using 4 Å MS, 20 mol % of $CuCl_2$, and 60 mol % of $AgSbF_6$; $CuCl_2$ and $AgSbF_6$were premixed at RT for 1 h prior to the addition of a respective ynamide and enone [1.20 equiv] as a combined solution via a syringe pump over 1 h at 0 °C; the reaction was stirred for an additional 30 min to 1 h before isolation. **b.** Isolated yields.

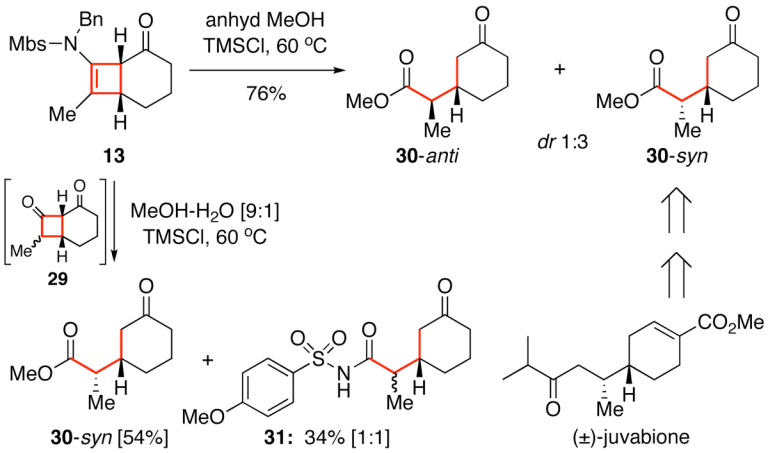
Figure 3.
Mechanistic Considerations.



Scheme 1.
Ficini's Ynamine-[2 + 2] Cycloadditions.



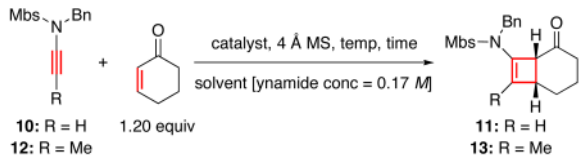
Scheme 2.
Thermal Ficini [2 + 2] Cycloadditions of Ynamide.



Scheme 3.
Stereoselective Hydrolysis of the Cycloadduct **13**.

Table 1

A Cu(II)-Catalyzed Ynamide-[2 + 2] Cycloaddition.



10: R = H
12: R = Me

1.20 equiv

11: R = H
13: R = Me

entry	R =	solvent	catalyst [mol %]	temp [°C]	time [h][a]	yield [%][b]
1	**10:** H	CH_3CN	$In(OTf)_2$ [30]	- 15	1	--[c]
2	**10:** H	CH_3CN	$Sc(OTf)_3$ [30]	- 15	1	--[c]
3	**10:** H	CH_3CN	$Cu(OTf)_2$ [10]	25 – 80	4	--[d]
4	**10:** H	CH_3CN	$AgSbF_6$ [10]	0 – 80	5	--[d]
5	**10:** H	CH_3CN	$AgSbF_6$ [10]	50 – 120	2	--[d]
6	**10:** H	CH_2Cl_2	$CuCl_2/AgSbF_6$ [20/42]	- 78 – 25	10	≤ 5[d,e]
7	**12:** Me	CH_2Cl_2	$CuCl_2/AgSbF_6$ [20/60]	- 40	1	72
8	**12:** Me	CH_2Cl_2	$CuCl_2/AgSbF_6$ [20/60]	- 15	1	77
9	**12:** Me	CH_2Cl_2	$CuCl_2/AgSbF_6$ [20/60]	0	1	76

[a] Time for syringe pump addition of a solution of **10** [or **12**] and enone.

[b] Isolated yields.

[c] Hydrolysis of **10** was the major outcome.

[d] No reaction – recovered starting material **10**.

[e] Polymerization was the major outcome in addition to hydrolysis.