ORGANIC LETTERS

2010
Vol. 12, No. 17
3780−3783

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

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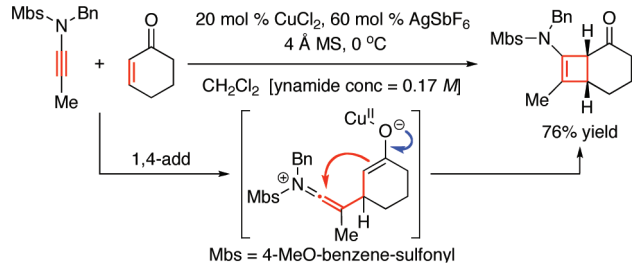
Received June 18, 2010

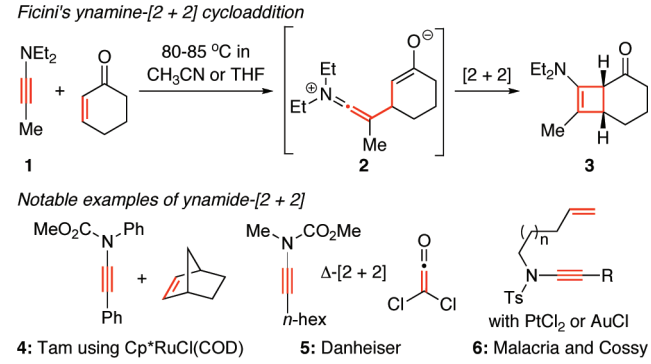
ABSTRACT



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 successful 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

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



(1) For a seminal review on Ficini [2 + 2] cycloaddition using ynamines, see: Ficini, J. *Tetrahedron* **1976**, *32*, 1448.

(2) For two other comprehensive reviews on ynamine chemistry, see: (a) Himbert, G. *Methoden Der Organischen Chemie (Houben-Weyl)*; Kropf, H.,; Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1993; pp 3267−3443. (b) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575.

(3) For a review on thermal [2 + 2] cycloaddition reactions, see: Baldwin, J. E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: New York, 1991; Vol. 5, p 63.

(4) (a) Ficini, J.; Krief, A. *Tetrahedron Lett.* **1969**, *10*, 1431. (b) Ficini, J.; Touzin, A.-M. *Tetrahedron Lett.* **1972**, *13*, 2093. (c) Ficini, J.; Touzin, A.-M. *Tetrahedron Lett.* **1972**, *13*, 2097. (d) Ficini, J.; Touzin, A.-M. *Tetrahedron Lett.* **1974**, *15*, 1447. (e) Ficini, J.; Falou, S.; d'Angelo, J. *Tetrahedron Lett.* **1977**, *18*, 1931. For cycloadditions to quinone, see: (f) Ficini, J.; Krief, A. *Tetrahedron Lett.* **1967**, *8*, 2497.

(5) For related examples that were contemporary, see: (a) Franck-Neuman, M. *Tetrahedron Lett.* **1966**, *7*, 341. (b) Grubbs, R. H. *Ph.D. Dissertation*, Columbia University, 1968. (c) Kuehne, M. E.; Linde, H. *J. Org. Chem.* **1972**, *37*, 4031.

(6) For Ficini's later work, see: (a) Ficini, J.; Guingant, A.; d'Angelo, J.; Stork, G. *Tetrahedron Lett.* **1983**, *24*, 907. (b) Ficini, J.; Krief, A.; Guingant, A.; Desmaele, D. *Tetrahedron Lett.* **1981**, *22*, 725.

(7) For comprehensive reviews on chemistry of ynamides, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Shi, Z.; Zhang, Y.; HsungR. P. *Chem. Rev.* **2010**, *110*, ASAP. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840.

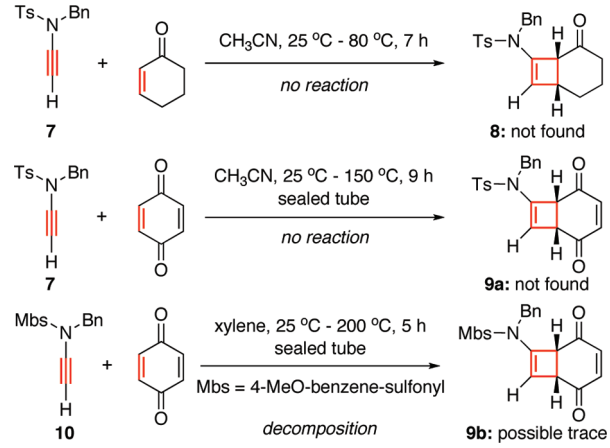
10.1021/ol101418d
Published on Web 08/06/2010

[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 a successful Ficini [2 + 2] cycloaddition of ynamides using lactam- or oxazolidinone-substituted ynamides under thermal and/or Lewis-acidic conditions.[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.

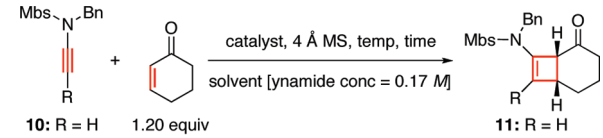
However, to our disappointment, *N*-sulfonyl-substituted ynamides such as **7** and **10** did not undergo any desired thermal cycloaddition (Scheme 2). Even when we used quinone and adopt the more electron-rich *para*-methoxy benzensulfonyl group [Mbs] as shown in ynamide **10**, no appreciable amount of the desired cycloadduct **9b** was observed, thereby further underscoring the superior stability of ynamides over ynamines.

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



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 α-halogenated enamides, were 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 counteranion. As a result, we screened a small sample of Lewis acids as summarized in Table 1.

Table 1. Cu(II)-Catalyzed Ynamide-[2 + 2] Cycloaddition



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.

Initial failure is quite evident in entries 1−6 when using ynamide **10**. However, after observing a trace amount of the

(8) For recent examples, see: (a) Li, H.; Antoline, J. E.; Yang, J.-H.; Al-Rashid, Z. F.; Hsung, R. P. *New J. Chem.* **2010**, *34*, 1309. (b) Kramer, S.; Madsen, J. L. H.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2010**, *12*, 2758. (c) Banerjee, B.; Litvinov, D. N.; Kang, J.; Bettale, J. D.; Castle, S. L. *Org. Lett.* **2010**, *12*, 2650. (d) Gourdet, B.; Rudkin, M. E.; Lam, H. W. *Org. Lett.* **2010**, *12*, 2554. (e) Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000. (f) DeKorver, K. A.; Hsung, R. P.; Lohse, A. G.; Zhang, Y. *Org. Lett.* **2010**, *12*, 1840. (g) Burley, G. A.; Davies, D. L.; Griffith, G. A.; Lee, M.; Singh, K. *J. Org. Chem.* **2010**, *75*, 980. (h) Yamasaki, R.; Terashima, N.; Sotome, I.; Komagawa, S.; Saito, S. *J. Org. Chem.* **2010**, *75*, 480.

(9) (a) Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681. (b) Cockburn, N.; Karimi, E.; Tam, W. *J. Org. Chem.* **2009**, *74*, 5762.

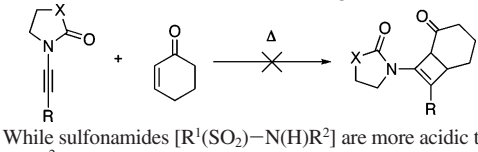
(10) Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* **2006**, *62*, 3815.

(11) (a) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509. (b) Marion, F.; Coulomb, J.; Servais, A.; Courillon, C.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2006**, *62*, 3856. Also see: (c) Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2005**, *70*, 9345.

(12) (a) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6726. (b) Couty, S.; Meyer, C.; Cossy, J. *Tetrahedron* **2009**, *65*, 1809.

(13) For a beautiful equivalent of this reaction using ynol-ethers and $AgNTf_2$, see: Sweis, R. F.; Schramm, M. P.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 7442.

(14) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H. A.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547.



(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 difference 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 π-donation to the carbocation. See: Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311.

possible product **11** when using $CuCl_2$ and $AgSbF_6$ [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

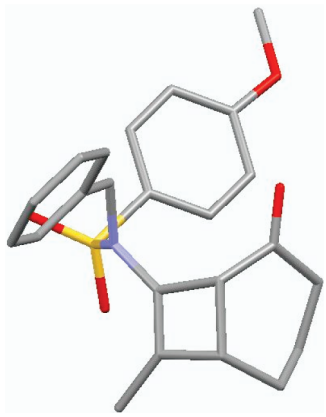


Figure 1. X-ray structure of the [2 + 2] cycloadduct **13**.

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.

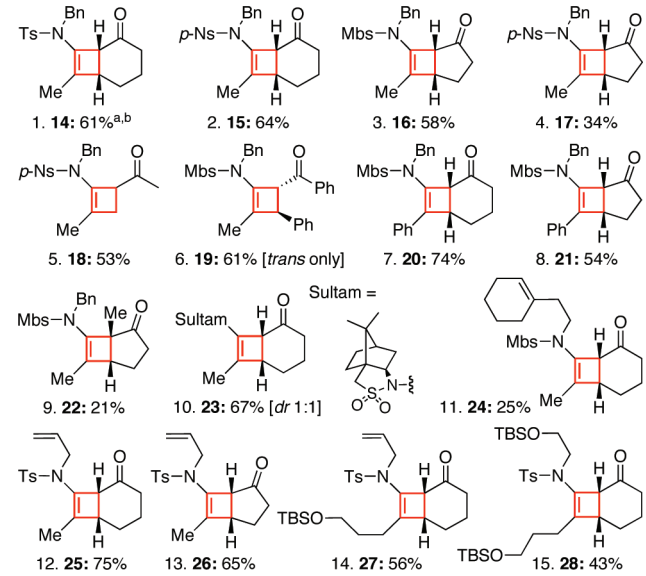
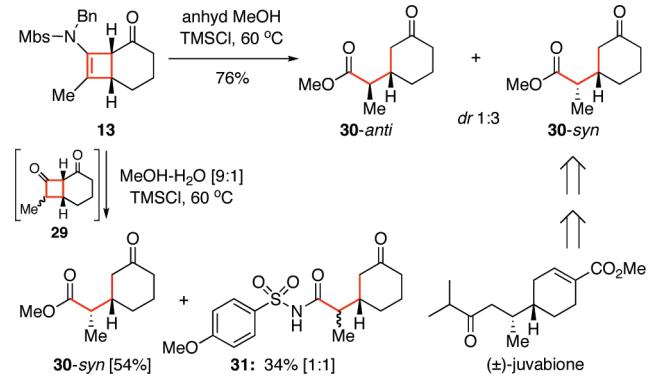


Figure 2. Scope of the ynamide-[2 + 2] cycloaddition. (a) All reactions were carried out in anhyd CH_2Cl_2 [ynamide conc = 0.17 M] using 4 Å MS, 20 mol % of $CuCl_2$, and 60 mol % of $AgSbF_6$; $CuCl_2$ and $AgSbF_6$ were premixed at rt for 1 h prior to the addition of a respective ynamide and enone [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.

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),

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



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

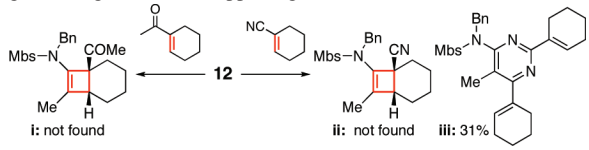
(16) Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. *Org. Lett.* **2006**, *8*, 231.

(17) For α-halogenations of ynamides observed using Pd(0) and Rh(I), see: (a) Tracey, M. R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. *Org. Lett.* **2004**, *6*, 2209. (b) Oppenheimer, J.; Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361.

(18) See Supporting Information.

(19) (a) Ficini, J.; Dureault, A. *Tetrahedron Lett.* **1977**, *18*, 809. Also see (b) Büchi, G.; Burgess, E. M. *J. Am. Chem. Soc.* **1960**, *82*, 4333. (c) Corey, E. J.; Bass, J. D.; Le Mahisu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

(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 Supporting Information].



(21) Mikami, K.; Terada, M.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 5456.

(22) Keto-imide **31** could be further hydrolyzed to **30**-*syn* and **30**-*anti* in 1:1 ratio using the same conditions.

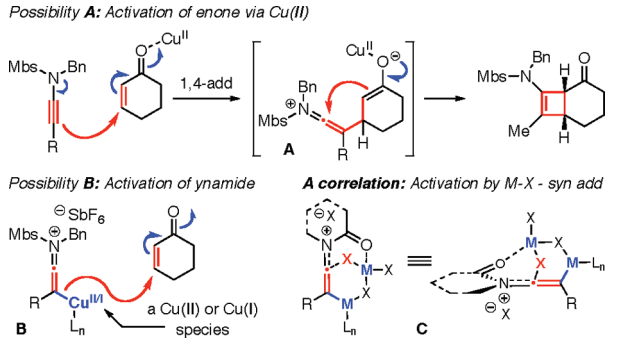


Figure 3. Mechanistic considerations.

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 stepwise 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.

Acknowledgment. We thank the NIH [GM066055] for funding. We thank Dr. Vic Young of the University of Minnesota for providing X-ray structural analysis. We also thank Professor Steve Burke of the University of Wisconsin for valuable discussions.

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

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(23) (a) Ficini, J.; Guingant, A. *Nouv. J. Chim.* **1980**, *4*, 421. (b) Ficini, J.; Desmaele, D.; Touzin, A.-M. *Tetrahedron Lett.* **1983**, *24*, 1025. (c) Ficini, J.; Eman, A.; Touzin, A.-M. *Tetrahedron Lett.* **1976**, *17*, 679.

(24) Ficini, J.; d'Angelo, J.; Noiré, J. *J. Am. Chem. Soc.* **1974**, *96*, 1213.