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Organic &
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Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 7483

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COMMUNICATION

Highly selective synthesis of tetra-substituted furans and cyclopropenes: copper(I)-catalyzed formal cycloadditions of internal aryl alkynes and diazoacetates†

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Received 6th July 2012, Accepted 9th August 2012
DOI: 10.1039/c2ob26295a

A convenient Cu(I)-catalyzed cycloaddition of electron rich internal aryl alkynes and diazoacetates was discovered for the chemoselective and regioselective synthesis of tetra-substituted furans and cyclopropenes in moderate isolated yields (18–67%), and alkyne conversion (29–73%).

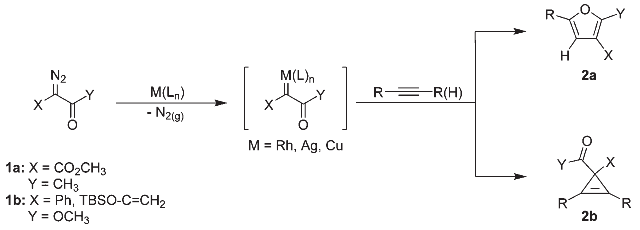
Introduction

Alkynes are a valuable class of hydrocarbons for transition metal-catalyzed carbenoid cycloadditions due to their synthetic versatility to undergo highly selective transformations into furans,[1–3] indenes,[4] dihydroazulenes,[5] cyclopentadienes,[6,7] and cyclopropene compounds.[5,8–11] The diversity of these cycloadducts contain structural features that are found in a wide range of natural products, and therefore, are useful synthetic building blocks in agricultural, pharmaceutical, and material science applications.[12,13] Despite the fact that many metal carbenoid cycloaddition methods are known for terminal alkynes, the lack of synthetic procedures developed for internal alkynes still remains a significant limitation.

Several decades of transition-metal carbenoid research suggest that the judicious choice of reactant partners is crucial for developing selective and efficient two-component cycloaddition reactions.[14] One major finding is that the divergence in chemoselectivity of the cycloaddition of acetylenic compounds depends largely on the electronic nature of the carbenoid structure. As a result, metal carbenoids are classified as (1) acceptor–acceptor diazoacetates that contain two electron withdrawing groups; (2) acceptor-only diazoacetates that contain a single electron-withdrawing group; and (3) donor–acceptor diazoacetates that contain an electron-donating and electron-withdrawing group.[15] It can be generalized, with some notable exceptions,[4,9,16] that alkynes in the presence of highly electrophilic diazoacetate compounds **1a** undergo [3 + 2] cycloadditions to yield tri-substituted furans **2a**.[1,2] On the other hand, alkynes and highly selective donor–acceptor diazoacetate compounds **1b** exclusively undergo [2 + 1] cycloaddition reactions to afford 1,3,3-trisubstituted cyclopropene compounds **2b** (Scheme 1).[6,10,17]

Unlike terminal alkynes, reports of internal alkynes indicate that they are less reactive partners. Experimental and computational evidence suggests that internal alkynes are ineffective substrates for rhodium-catalyzed cyclopropenation due to their sterically hindered approach to the carbenoid center.[6,10] The pioneering work of Davies and co-workers discovered that silver carbenoids, which are more reactive than traditional rhodium carbenoids, efficiently catalyzed the cyclopropenation of internal alkynes in the presence of aryldiazoacetates **1b** to form tetra-substituted cyclopropene compounds **3** in excellent overall yields (64–98%) (Scheme 2).[8] This was the first research report where internal alkyne substrates underwent a carbenoid cycloaddition reaction. Furthermore, unlike $Rh_2(OAc)_4$, the $AgSbF_6$-catalyzed cyclopropanation of *trans*-substituted alkenes afford highly diastereoselective cyclopropane **4** in high diastereoselectivity (Scheme 2).[18] Very recently, it was reported that chiral cationic gold complexes, activated by silver metal, catalyzed the asymmetric cyclopropenation of internal alkynes in high yields and enantioselectivities.[19]

Still, steric and electronic influences on the metal carbenoid are not the only consideration. The coupling partner also plays a



Scheme 1

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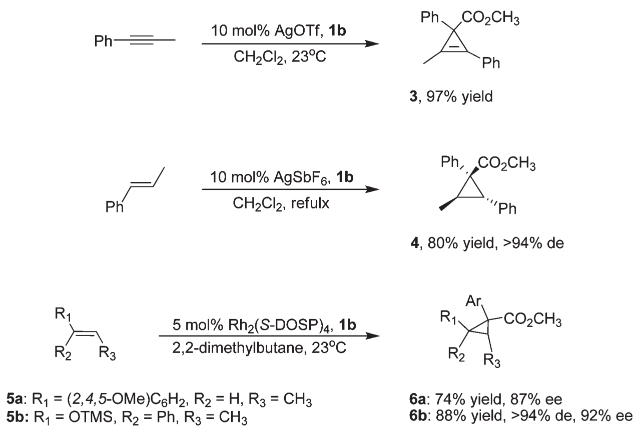
† Electronic supplementary information (ESI) available. CCDC 889654–889658. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26295a



Scheme 2

significant role on the overall reactivity and selectivity of the carbenoid cycloaddition. Electron-rich *trans*-1,2-disubstituted **5a**, and even tri-substituted alkenes **5b**, in the presence of aryldiazoacetates **1b** afforded highly chemo- and stereoselective cyclopropane compounds **6a** and **6b** when catalyzed by the sterically demanding $Rh_2(S\text{-DOSP})_4$ catalyst (Scheme 2).[20]

Similar findings were observed for the $Rh_2(OAc)_4$-catalyzed [3 + 2] cycloaddition of terminal alkynes, where increasing the electron density of the alkyne, was credited for improving the chemoselectivity from the formation of cyclopropene products to exclusively tri-substituted furans.[1] Chang and co-workers discovered that electron-donating groups on phenyl acetylenes react more readily with **1b**, than the electron-deficient alkynes.[4] In this communication, we wish to report the copper(I)-catalyzed cycloaddition of electron-rich internal alkynes for the chemo- and regioselective construction of tetra-substituted furans and cyclopropene compounds.

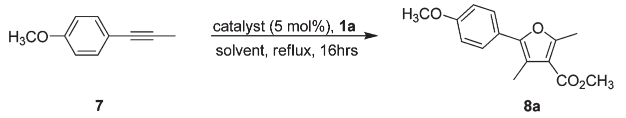
Results and discussion

To the best of our knowledge, there are no known reports illustrating the transition-metal catalyzed [3 + 2] cycloaddition of internal alkynes and diazoacetate compounds for the formation of tetra-substituted furans. We considered this to be an excellent starting point to begin our investigation of electron-rich 1-(*p*-CH_3O)phenylprop-1-yne **7** and acceptor–acceptor diazoacetate **1a** in the presence of various transition metals (Table 1).

We determined that palladium(II) and various copper(I) salts were ineffective and **8a** was not observed by ^1H NMR (entries 1–5). However, copper iodide indicated more effectiveness by increasing the temperatures, equivalents of **1a**, and reaction time to afford **8a** in low to modest yields (1.9%–47%, entries 6–8). X-ray crystallographic analysis of **8a** unambiguously confirmed the structure (see ESI†) (Fig. 1).

Overall, the reaction is highly selective with no cyclopropene or regioisomers observed by crude ^1H NMR. In all instances, the acetyl group of the diazoacetate **1a** is responsible for ring closure. Conducting the reaction neat reduced the equivalents of diazoacetate needed without sacrificing the yield or selectivity (entry 9). Equivalent findings were observed when the copper(I) *N*-heterocyclic carbene chloride catalyst was used (48% yield, entry 10). Dirhodium(II) acetate, a benchmark catalyst in metal carbenoid chemistry, was found to be less effective (17% yield, entry 11). In the absence of catalyst, a thermally induced background reaction was determined to be relatively low (5.9% yield, entry 12).

Table 1 Screen of transition-metal salts for the [3 + 2] metal carbenoid cycloaddition[a]



Entry	Catalyst	Solvent	Yield[b] (%)	Conversion[c] (%)
1	$Pd(OAc)_2$	CH_2Cl_2	0	—
2	CuTHC	CH_2Cl_2	0	—
3	CuBr	CH_2Cl_2	0	—
4	$Cu(CH_3CN)_4BF_4$	CH_2Cl_2	0	—
5	$Cu(CH_3CN)OTf$	CH_2Cl_2	0	—
6	CuI	CH_2Cl_2	1.9	6.4
7[d]	CuI	CH_3CN	5.4	8.9
8[d]	CuI	$PhCH_3$	47	50
9[e]	CuI	Neat	50	61
10	CuNHC	Neat	48	61
11	$Rh_2(OAc)_2$	Neat	17	22
12	—	Neat	5.9	13

[a] Reaction conditions: 2.1 mmol (0.41 M) of **7** and 6.2 mmol (1.2 M) of **1a** used in 5 mL of solvent. [b] Isolated yield. [c] Based on recovered **7**. [d] 16 mmol (3.1 M) of **1a**, 48 h. [e] 13 mmol of **1a**, 110 °C CuTHC: Cu(I)-thiophene-2-carboxylate. CuNHC: chloro[1,3-bis(2,6-di-i-propylphenyl)-imidazol-2-ylidene]Cu(I).

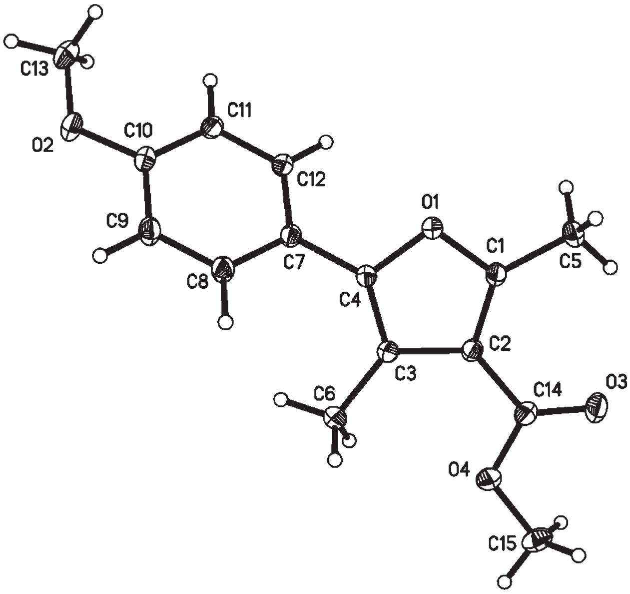
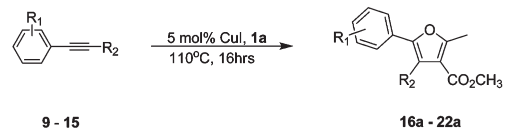


Fig. 1 Crystal structure of **8a**.

With the best reaction conditions in hand, we then tested the functional group tolerance of the newly developed Cu(I)-catalyzed [3 + 2] cycloaddition of internal alkynes (Table 2).

First, electron neutral alkyne **9** was found to yield furan product **16a** as a 5 : 1 regioisomeric mixture in poor yield (8.5%,

Table 2 Cu(I)-catalyzed [3 + 2] cycloaddition of internal alkynes[a]



Entry	Alkyne	R$_1$	R$_2$	Product	Yield[b] (%)	Conversion[c] (%)
1[d]	**9**	H	CH_3	**16a**	9	n.d.
2	**10**	2-OCH_3	CH_3	**17a**	19	35
3	**11**	4-OCH_3	$CH_2OSi(CH_3)_2$-(*t*-Bu)	**18a**	38	59
4	**12**	4-OCH_3	$CH_2OCO_2CH_3$	**19a**	24	35
5	**13**	4-OCH_3	$CH_2O_2CCH_3$	**20a**	19	29
6	**14**	4-OCH_3	$Si(CH_3)_3$	**21a**	19	32
7	**15**	4-OPh	CH_3	**22a**	39	58

[a] Reaction conditions: 2.1 mmol of **7** and 13 mmol of **1a**. [b] Isolated yield. [c] Based on recovered alkyne. [d] 5 : 1 mixture of regioisomers determined by ^{1}H NMR. n.d = not determined.

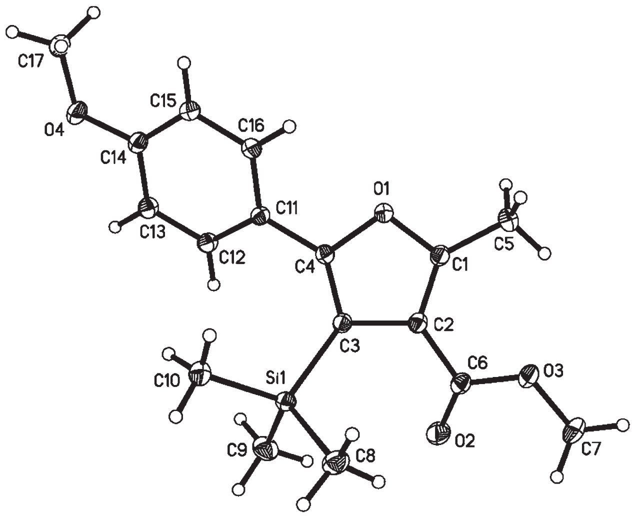
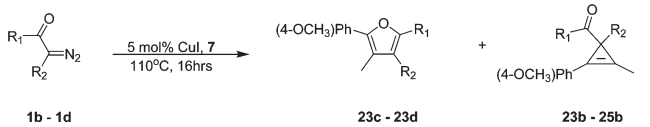


Fig. 2 X-ray structure of **21a**.

entry 1). The crude reaction mixture was complex and no alkyne was recovered. It is thought that the presence of the *para*-methoxy group stabilizes the dipolar transition states. Reaction with sterically demanding *ortho*-substituted alkyne **10** was also an effective substrate albeit in low yield (19%, entry 2). The scope of the Cu(I)-catalyzed [3 + 2] cycloaddition was further explored with alkynes containing methylene site capable of C–H insertion. In all cases, the internal alkynes **11–13** were converted to the corresponding tetra-substituted furans (entries 3–5). Internal alkyne containing a trimethylsilyl group **14** was also effective for the synthesis of silyl-substituted furan product **21a** (19% yield, entry 6, Fig. 2). The former result is particularly useful building block for organic synthesis due to the important role of silicon in the substitution of furans.[12] Diphenyl ether methyl acetylene **15** was also an effective substrate for this chemistry (39% yield, entry 7).

Table 3 Role of the diazoacetate on the chemoselectivity of metal carbenoid cycloadditions



Entry	Diazo	R$_1$	R$_2$	Product	Yield[a] (%)	Conversion[b] (%)
1	**1b**	CH_3	Ph	**23b**	59	65
2	**1c**	OCH_3	CO_2CH_3	**23c**	23	23
3	**1d**	OCH_3	CF_3	**23d**	23	23
4[c]	**1b**	CH_3	Ph	**24b**	67	73
5[d]	**1b**	CH_3	Ph	**24b**	46	49

[a] Isolated yield. [b] Based on recovered alkyne. [c] Alkyne **10** was used. [d] Alkyne **14** was used.

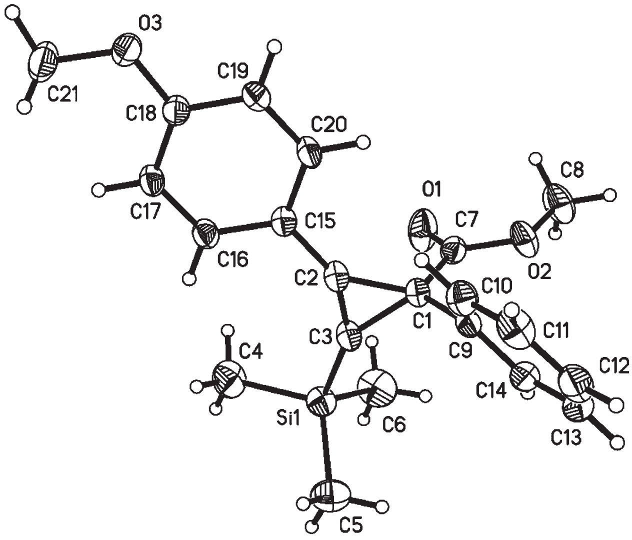


Fig. 3 Crystal structure of **25b**.

In order to test the role of the diazoacetate on the chemoselectivity of the metal carbenoid cycloaddition, **7** was subjected to various diazoacetate compounds (Table 3).

The copper(I)-catalyzed cyclopropenation of donor–acceptor substituted diazoacetate **1b** and internal alkyne **7** afforded cyclopropene **23b** in good yield (59%). It well established that donor–acceptor diazoacetates are highly chemoselective for cyclopropenation and no furan products were observed. The reaction of acceptor–acceptor substituted diazomalonate **1c** and **7** afforded tetra-substituted furan **23c** in 23% yield. Trifluoromethyl diazoacetate **1d** was equally effective yielding exclusively furan product **23d** as a single regioisomer (23%, entries 3). Moreover, the copper(I)-catalyzed [2 + 1] cycloaddition of **1b** in the presence of alkyne **10** gave the corresponding cyclopropene **24b** in 67% yield, while alkyne **14** was converted to the 1-silylcyclopropene product **25b** (46% yield, Fig. 3) (see ESI†).

1-Silylcyclopropene product **25b** is an attractive building block for organic synthesis.[21] The analogous Ag(OTf)-catalyzed cyclopropenation of 1-TMS-2-phenylethyne and **1b** is ineffective due to the formation of insoluble silver acetylide salts.[8]

In conclusion, we have demonstrated the first examples of Cu(I)-catalyzed [3 + 2] cycloaddition reactions of internal alkynes and acceptor–acceptor diazoacetates to afford highly chemo- and regioselective tetra-substituted furan products. It was also discovered that copper(I) iodide is an efficient catalyst for the cyclopropenation of internal alkynes and donor–acceptor diazoacetates. Although the overall conversion of the internal alkynes to the corresponding cycloadduct products was relatively modest (29–73%), it is thought that the simple recovery of internal alkyne starting material, reduced reaction times, and ease of purification suggests that this approach is promising. Aims to increase the overall yields and expand the scope of electron-rich internal alkyne substrates are currently underway.

Acknowledgements

We would like to thank the Rochester Institute of Technology Office of the Vice President of Research, College of Science, and School of Chemistry and Materials Sciences for their generous financial support.

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