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Cyclopropenation of Internal Alkynylsilanes and Diazoacetates Catalyzed by Copper(I) *N*-Heterocyclic Carbene Complexes

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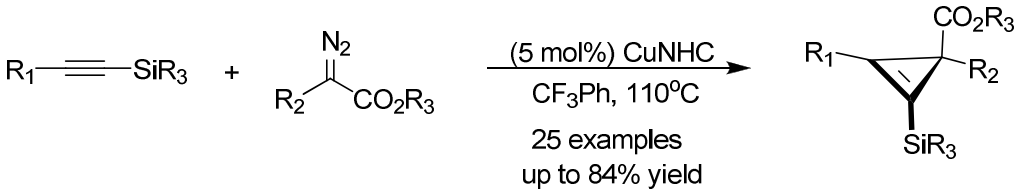
Abstract

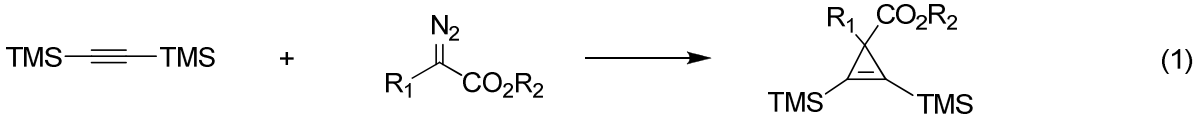
Copper(I) *N*-heterocyclic carbene (CuNHC) complexes are more catalytically active than traditional transition metal salts for the cyclopropenation of internal alkynylsilanes and diazoacetate compounds. A series of 1,2,3-trisubstituted and 1,2,3,3-tetrasubstituted cyclopropenylsilane compounds were isolated in good overall yields. An interesting regioselective and chemodivergent reaction pathway was also observed to furnish a tetra-substituted furan for an electron-rich donor/acceptor diazoacetate. Finally, a practical synthesis of a cyclopropenyl-containing starting material that is useful for bioorthogonal chemistry is also described.



Introduction

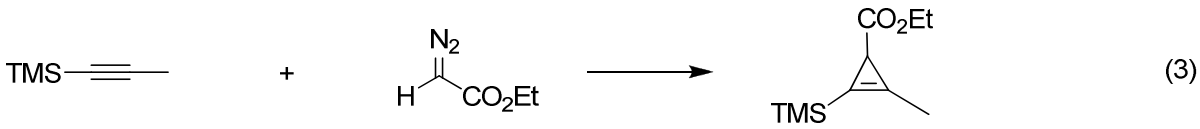
Cyclopropene compounds are a valuable class of highly strained (54.5 kcal/mol)[1] three-membered carbocyclic molecules which possess a uniquely reactive π bond. Many useful synthetic activation modes are known for the conversion of cyclopropene compounds into a diverse array of complex cyclic and acyclic molecular building blocks.[2] However, the synthesis of cyclopropene compounds has received less attention. One promising approach is the transition metal-catalyzed cyclopropenation of alkynes and diazoacetates, which has several distinct synthetic advantages over traditional 1,2-elimination strategies.[3] However, only a few transition metal catalysts (e.g. Rh(II),[4] Cu(I),[5] Co(II),[6] and Ir(II)[7]) are reported for the cyclopropenation of *terminal alkynes* and diazoacetates; while, an entirely different set of catalysts (e.g. Cu(I),[8] Ag(I),[9] and chiral Ag(I)/Au(I),[10]) are reportedly known to be most effective for the cyclopropenation of *internal alkynes* with the exception of the copper(I)–homoscorpionate catalysts.[11] And yet, to a much lesser extent, a series of miscellaneous reactions have been reported for the cyclopropenation of *internal alkynylsilanes* with rather ineffective catalysts (e.g Rh(II)-,[4b, 12] Cu(0)-,[13] Cu(I)-,[14] and Cu(II)-[8, 15]). This is despite the fact that 1-silylcyclopropenes are useful starting materials for platinum-catalyzed rearrangements,[16] Sila Morita-Baylis-Hillman reactions,[17] indium-catalyzed cycloisomerizations,[18] Pauson-Khand transformations,[12a, 19] gold-catalyzed isomerizations,[20] and rearrangements into complex Vaska-type iridium complexes.[13a] Furthermore, 1-silylcyclopropene compounds also serve as building blocks for the synthesis of a new class of bioorthogonal chemical reporters that are used in cellular metabolic labeling experiments.[21]

There are two widely used methods for the synthesis of 1- and 2-silylcyclopropenes.[22] In the first method, cyclopropene starting materials are treated to strongly basic/nucleophilic reaction conditions that are incompatible with base-sensitive functional groups and are more susceptible to destructive ring-opening reactions.[22a] To circumvent this, an inverse-addition protocol,[22b] carboxylate dianion approach,[22c] and a more mild, Cu(I)-catalyzed silylation have been reported.[22d] Still, the transition metal-catalyzed [2+1] cycloaddition of alkynylsilanes and diazoacetates is the most direct and general approach for the synthesis of 1-silylcyclopropenes, but these strategies are often fraught with consistently low yields (< 41%) and use an excess of alkynylsilane (2.5 – 10 fold) (Scheme 1).



Maier (ref 14): R_1 = H, R_2 = Et *catalytic* CuBr, 18% yield
Kohn and Chen (ref 12b): R_1 = H, R_2 = Et (8.2 : 1 equivs) 2.5 mol% $Rh_2(OC_7H_{15})_4$, 60°C, 84h, 34% yield
Wheeler (ref 15e): R_1 = CO_2Me , R_2 = Me (5.1 : 1 equivs) 10^3 mol% $Cu(acac)_2$, 145°C, 36h, 33% yield

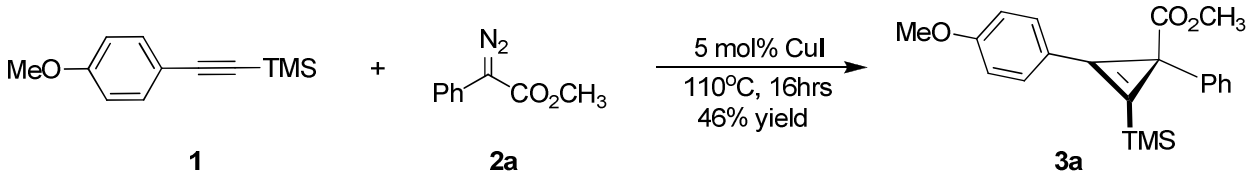
Wu (ref 13a): (2.83 : 1 equivs) 2 mol% Cu powder, 130°C, 16h, 30% yield
Neunhoeffer (ref 13b): (1 : 1 equivs) 23 mol% Cu powder, 135 - 145°C, 22% yield
Mueller and Granicher (ref 12c): (4.9 : 1 equivs) 1.7 mol% $Rh_2(OAc)_4$, 23°C, 11% yield



Shapiro (refs 15b-d): (3.0 : 1 equivs) *catalytic* $CuSO_4$, 110 - 120°C, 37% yield
Fox (ref 19): (2.0 : 1 equivs) 2 mol% $Rh_2(OAc)_4$ 25°C, 2.5h, 41% yield

Scheme 1. Collection of metal-catalyzed cyclopropenation of internal alkynylsilanes and diazoacetates

Recently, we reported a CuI-catalyzed cyclopropenation of 1-TMS-2-(4-methoxyphenyl)acetylene **1** (1.00 mmol) in the presence of a donor-acceptor diazoacetate **2a** (3.00 mmol) that afforded the corresponding 1,2,3,3-tetrasubstituted cyclopropenylsilane **3a** in modest yield (Scheme 2).[23]



1 **2a** **3a**

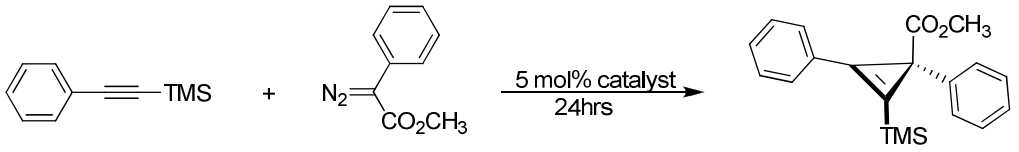
Scheme 2. Cu(I)-catalyzed synthesis of a tetra-substituted cyclopropene

Given that this new finding gave slightly higher yields than all other previous examples, in addition to the commercial availability of highly active copper(I) *N*-heterocyclic carbene complexes for catalytic carbene transfer reactions,[24] we set out to examine their overall effectiveness for this transformation.

Results and Discussion

Our study commenced by measuring the catalytic activities of various Cu(I)- and Rh(II)-salts for the cyclopropenation of 1-phenyl-2-trimethylsilylacetylene **4** and diazoacetate **2a** towards the synthesis of 1,2,3,3-tetrasubstituted cyclopropenylsilane **5a** (Table 1).

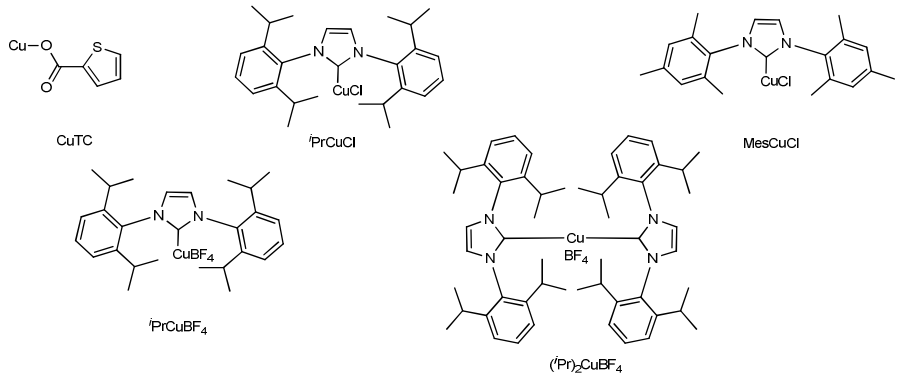
Table 1. Optimization of reaction conditions



4 **2a** **5a**

entry	catalyst	solvent	temperature (°C)	isolated yield (%)
1	CuI	CH_2Cl_2	23	-
2	CuI	CH_3Ph	23	-
3	CuI	CH_3Ph	110	26
4	CuI	CF_3Ph	110	34
5[a]	CuI	CF_3Ph	110	8
6	CuTC	CF_3Ph	110	15
7	^{i}PrCuCl	CF_3Ph	110	84
8	^{i}PrCuCl	CF_3Ph	23	-
9	MesCuCl	CF_3Ph	110	74
10	^{i}PrCuBF$_4$	CF_3Ph	110	65
11	$(^{i}Pr)_2$CuBF$_4$	CF_3Ph	110	64
12	$Rh_2(OAc)_4$	CF_3Ph	110	24
13	none	CF_3Ph	110	24

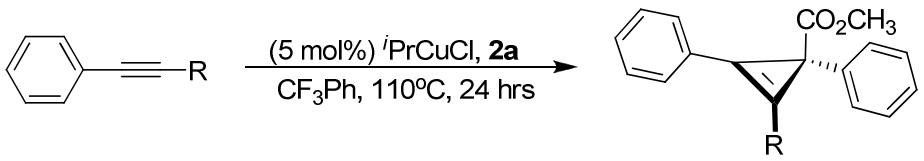
Reaction Conditions: A solution of **4** and catalyst in CF_3Ph (2mL) was added a solution of **2a** in CF_3Ph (20mL) at 1.00 mL/min at 110°C. The reaction was concentrated and purified by flash chromatography



Although no product was observed at room temperature (Table 1, entries 1 – 2, 8), higher reaction temperatures (110^{o}C) resulted in modest isolated yields of the cyclopropenylsilane product **5a** (Table 1, entries 3 – 6) with cuprous salts. Comparatively, trifluorotoluene proved to be a more inert solvent than toluene and we did not observe cyclopropanation byproducts (Table 1, entry 4). (1,3-bis-(diisopropyl-phenyl)imidazole-2-ylidene) copper(I) chloride, (^{i}PrCuCl), afforded **5a** in high isolated yield (84%, Table 1, entry 7). ^{i}PrCuCl is a *N*-heterocyclic carbene (NHC) copper (I) metal salt that is useful for the cyclopropanation and aziridination reactions of olefins.[24] Other Cu(I)-NHC salts were screened, but no significant improvement in the isolated yield was observed (Table 1, entries 9 – 11). Dirhodium(II) acetate, a benchmark catalyst for carbene transfer reactions, afforded cyclopropene **5a** in significantly lower isolated yield (24%, Table 1, entry 12). Finally, the thermally-induced cyclopropenation of **4** and **2a** afforded **5a** in comparable yield (24%).

With the optimized ^{i}PrCuCl-catalyzed reaction conditions in hand, we investigated the role of the silyl group's steric size on the reactivity of the cyclopropenation reaction (Table 2).

Table 2. Silane steric effects on the ^{i}PrCuCl-catalyzed cyclopropenation

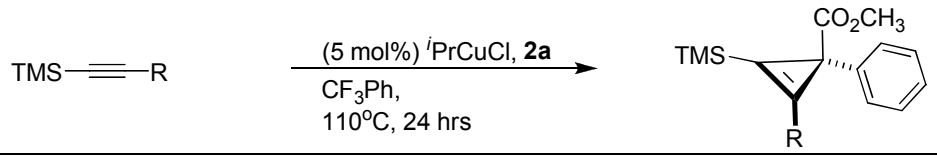


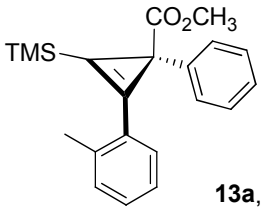
entry	alkyne	R	product	isolated yield (%)
1	**6**	$(CH_3)_2{}^{t}BuSi$	**11a**	81
2	**7**	$(^{n}Pr)_3Si$	**12a**	8
3	**8**	$(^{i}Pr)_3Si$		-
4	**9**	$(Ph)_2{}^{t}BuSi$		-
5	**10**	$(Ph)_3Si$		-

1-TBS-2-phenylacetylene **6** was easily converted to the corresponding cyclopropene **11a** in good yield (81%), while phenyl tripropylsilylacetylene **7** afforded cyclopropene **12a** in poor yield (8%). Increasing the steric bulk of the silane group any further had a detrimental effect on the reactivity and alkynylsilanes **8 – 10** were recovered without significant decomposition. This feature may be especially useful when one or more acetylenic sites are reactive.[19]

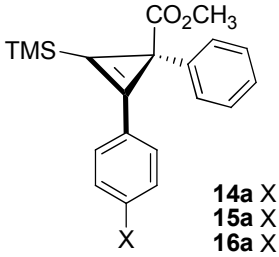
With the optimum reaction conditions in hand, we surveyed various aliphatic and aromatic alkynylsilanes to measure the activity of ^{i}PrCuCl-catalyzed cyclopropenation in the presence of **2a** (Table 3).

Table 3. Cyclopropenation of electronically and structurally diverse alkynylsilanes

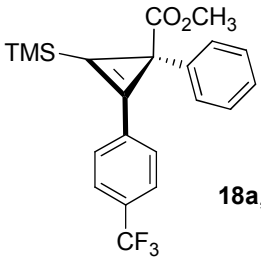




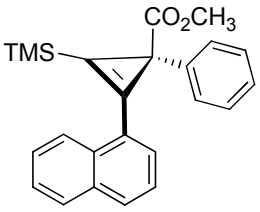
13a, 71%



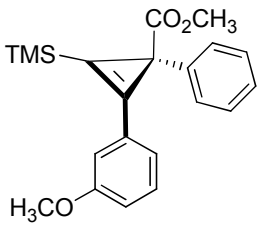
14a X = F, 35%
15a X = Cl, 45%
16a X = Br, 25%
17a X = I, 3.8%



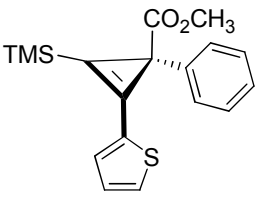
18a, 49%



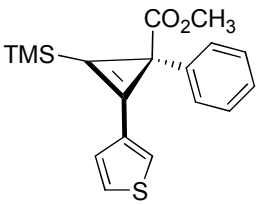
19a, 58%



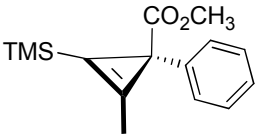
20a, 57%



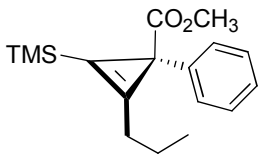
21a, 49%



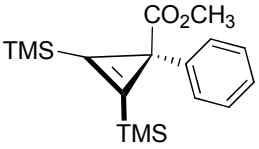
22a, 46%



23a, 61%



24a, 64%



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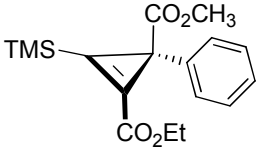


0%

The relatively electron-rich and sterically-hindered *ortho*-tolyl(trimethylsilyl)acetylene was converted into the corresponding cyclopropene **13a** in good yield (71%). Electron-deficient *para*-halophenyl(trimethylsilyl)acetylenes furnished the corresponding cyclopropenes **14a** – **17a** in moderate overall yields, while 2-(4-iodophenyl)cyclopropene **17a** was isolated in low

yield (3.8%). In a straightforward manner, trifluorotolyl, 1-naphthyl, and *meta*-methoxyphenyl alkynylsilanes furnished cyclopropenyl esters **18a** – **20a** in useful overall yields (> 49%, Table 3). Interestingly, both 2- and 3-thiophene substituted alkynylsilanes were converted into cyclopropenes **21a** and **22a** in modest isolated yields. 2-alkyl-1-trimethylsilylacetylenes were smoothly converted into 3-alkylcyclopropenylsilanes **23a** and **24a** in good isolated yields (61% and 64%, respectively, Table 3). Unfortunately, both bistrimethylsilylacetylene and ethyl 3-(trimethylsilyl)propiolate were unreactive and no cyclopropene product was observed presumably due to the relatively higher electron deficient nature of the internal alkyne (Table 3). Compound **15a**, serving as a representative example of the 1,2,3,3-tetrasubstituted cyclopropenes synthesized in this study, was recrystallized from refluxing hexane to yield suitable crystals for X-ray crystallography (Figure 1).

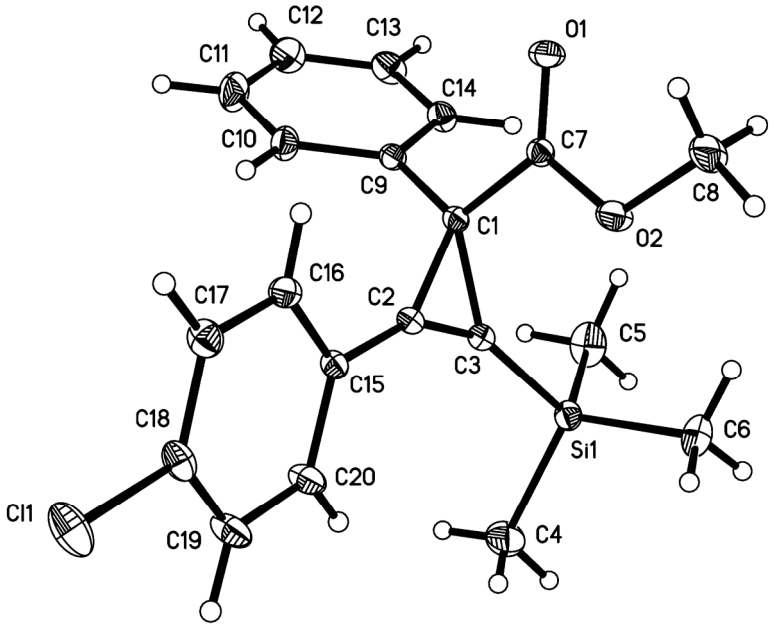


Figure 1. OTREP diagram of **15a**

Several decades of transition metal carbenoid research suggests that the selectivity for carbene transfer reactions is largely dependent on the electronic nature of the diazoacetate.[25] As a result, three classes of diazoacetate compounds have been classified based primarily on their differing reactivity and/or selectivity observed for carbene transfer reactions (Figure 2).

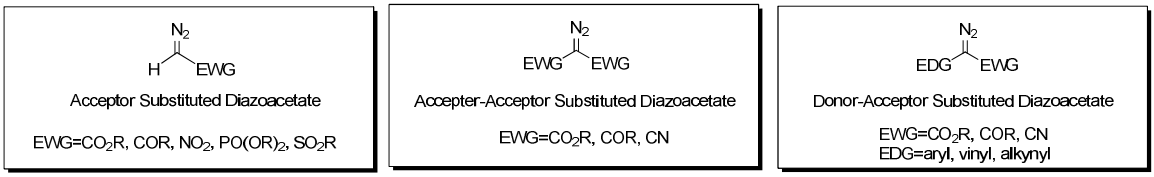
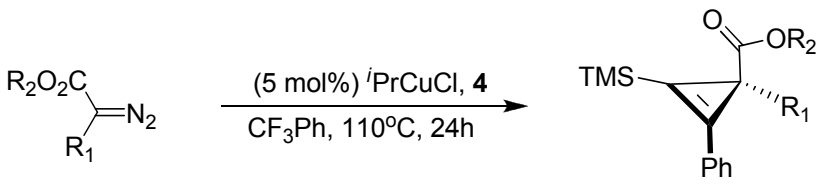
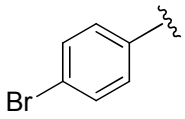
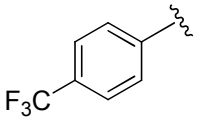
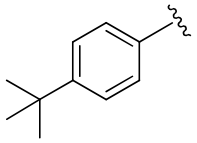
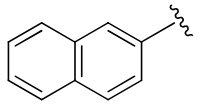
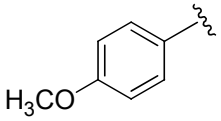


Figure 2. Three classes of diazoacetate compounds used in carbene transfer reactions

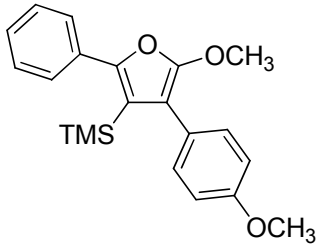
With this in mind, we tested the reactivity and selectivity of various diazoacetate compounds for the ^{i}PrCuCl-catalyzed cyclopropenation of internal alkynylsilane compounds (Table 4).

Table 4. Survey of the reactivity of various diazoacetate compounds



entry	diazoacetate	R_1	R_2	product	isolated yield (%)
1[a]	**25b**	H	CH_2CH_3	**32b**	41
2	**25b**	H	CH_2CH_3	**32b**	77
3[b]	**26c**	CO_2CH_3	CH_3	-	n.d.
4	**27d**		CH_3	**33d**	63
5	**28e**		CH_3	**34e**	54
6	**29f**		CH_3	**35f**	69
7	**30g**		CH_3	**36g**	61
8[c]	**31h**		CH_3	**37h**	69

[a] 5 mol% CuI; [b] n.d. = not determined. [c] tetra-substituted furan **38h** was also isolated.

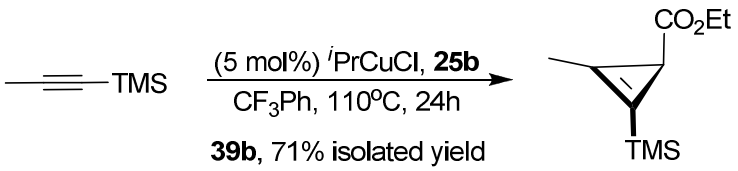


38h, 21% isolated yield

Both the CuI- and ^{i}PrCuCl-catalyzed cyclopropenation of alkynylsilane **4** in the presence of acceptor-substituted diazoacetate **25b** cleanly furnished cyclopropene **32b** in substantially higher overall isolated yields than previous reports (Table 4, entries 1 and 2).[12c, 13] The acceptor-acceptor substituted diazomalonate compound **26c** was completely unreactive in the presence of alkynylsilane **4** (Table 4, entry 3). Electron-deficient donor-acceptor diazoacetates **27d** and **28e** afforded cyclopropene compounds **33d** and **34e** in satisfactory isolated yields (63% and 54%, respectively) (Table 4, entries 4 and 5). Cyclopropenes **35f** and **36g** were also isolated in good yields from donor-acceptor diazoacetates **29f** and **30g** (69% and 61%, respectively) (Table 4, entries 6 and 7). Interestingly, electron-rich donor-acceptor diazoacetate **31h** afforded a chemodivergent mixture of a tetra-substituted cyclopropene **37h** and a tetra-substituted substituted furan **38h** as a separable mixture by flash chromatography in good overall yields (Table 4, entry 9). To the best of our knowledge, this is the first example of a donor-acceptor diazoacetate undergoing a formal [3+2] cycloaddition of acetylenic compounds to form a tetra-substituted furan. A two-dimensional [^{1}H, ^{1}H]-NOESY spectrum was recorded to corroborate the structure of **38h**. NOE crosspeaks were observed between the TMS group and both the (i) phenyl group and (ii) para-methoxy-substituted phenyl group (*see Supporting Information*). It is plausible that the β-silicon hyperconjugation in close proximity to the site of C-O bond formation is responsible for the high regioselectivity observed.

The real-time labelling of a biomolecule containing a reactive non-natural functional group with a molecular imaging agent – often referred to as bioorthogonal chemistry – is among the most essential tools used for imaging cellular processes under physiological conditions.[26] In recent years, cyclopropenyl-containing compounds have emerged as an

important class of bioorthogonal moieties that are effectively incorporated in biomolecules and subsequently labeled via an inverse-demand Diels-Alder cycloaddition reaction with a tetrazine fluorescent tag.[21] We applied our methodology towards the synthesis of a frequently utilized cyclopropene starting material **39b** and observed the highest isolated yield (71%) reported to date from 1-TMS-propyne and ethyl diazoacetate (Scheme 3).



Scheme 3. Synthesis of a bioorthogonal chemical reporter precursor

In comparison to other previously reported transition metal-catalyzed processes (Scheme 1, equation 3),[15b-d, 19] this strategy is a more sustainable alternative for the synthesis cyclopropenyl-containing bioorthogonal ligands.

Conclusions

Cu(I)-NHC salts are efficient catalysts for the direct transition metal-catalyzed cyclopropenation of a wide range of internal alkynylsilanes and diazoacetate towards the synthesis of poly-substituted 1-silylcyclopropene compounds in good overall yields. In particular, diazoacetate compounds displayed a wide range of reactivity ranging from unreactive to facilitating an unexpected regioselective tetra-substituted furan product in a chemodivergent pathway. Finally, the ^{i}PrCuCl-catalyzed cyclopropenation of 1-TMS-2-propyne and ethyl diazoacetate is a highly effective method for the synthesis of a bioorthogonal chemical reporter that is useful for imaging cellular processes.

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