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Palladium-Catalyzed Trimethylenemethane Cycloaddition of Olefins Activated by the σ-Electron-Withdrawing Trifluoromethyl Group

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Supporting Information

ABSTRACT: α-Trifluoromethyl-styrenes, trifluoromethyl-enynes, and dienes undergo palladium-catalyzed trimethylenemethane cycloadditions under mild reaction conditions. The trifluoromethyl group serves as a unique σ-electron-withdrawing group for the activation of the olefin toward the cycloaddition. This method allows for the formation of exomethylene cyclopentanes bearing a quaternary center substituted by the trifluoromethyl group, compounds of interest for the pharmaceutical, agrochemical, and materials industries. In the diene series, the cycloaddition operates in a [3 + 4] and/or [3 + 2] manner to give rise to seven- and/or five-membered rings. This transformation greatly improves the scope of the TMM cycloaddition technology and provides invaluable insights into the reaction mechanism.

Organofluorine compounds are of significant importance for a variety of applications in the pharmaceutical, agrochemical, and materials industry.[1] It is indeed well-established that the strategic introduction of fluorine-containing functional groups can enhance the physicochemical properties of organic molecules.[2] For example, the inclusion of the electron-withdrawing CF_3 group in drug candidates has appeared as a general strategy to increase robustness against metabolic oxidation in the "hit to lead" approach.[3] In this context, new methods allowing for the selective introduction of the CF_3 group at positions susceptible to undergo metabolic oxidation will have a significant synthetic utility.

Cyclopentanes bearing a quaternary center substituted by the CF_3 group have been found to impart benefits in many bioactive molecules (Figure 1).[4] However, despite these interesting properties, existing methods for their preparation are extremely limited.[5] Cycloadditions with trifluoromethyl alkenes are particularly attractive in view of the construction of cyclic compounds bearing CF_3-quaternary centers. Nevertheless, examples of such cycloadditions where the CF_3 group serves as the activating group are rare and of limited scope. Preliminary work has shown that trifluoropropene can serve as a poorly reactive dienophile.[6] Bégué et al. have also demonstrated one example of a [3 + 2]-cycloaddition with an azomethine ylide[7] or a nitrone[8a] and one example of a thermal [4 + 2]-Diels–Alder reaction with the activated Danishefsky diene.[8] In contradistinction, to the best of our knowledge, a metal-catalyzed Michael-type cycloaddition exploiting the σ-electron-withdrawing character of the CF_3 group has never been reported.

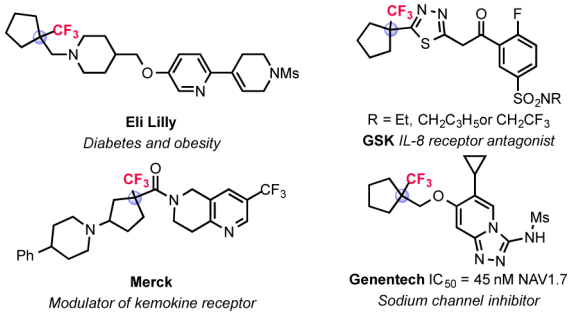

Figure 1. Trifluoromethylated cyclopentanes with biological activity.

As part as our long-standing interest in the palladium-catalyzed [3 + 2]-cycloaddition of trimethylenemethane (TMM) with electron-deficient olefins,[9] we questioned whether the σ-electron-withdrawing properties of the CF_3 group would be sufficient to activate a trifluoromethyl olefin toward the cycloaddition process. In contrast to previous studies on TMM-cycloadditions, the absence of a strong electron-withdrawing π-acceptor (ketone, ester, nitro, sulfone, etc.) capable of decreasing the olefin's LUMO energy level was expected to dramatically challenge the reactivity limits of the TMM-donor. Nevertheless, we recognized that, if reactive, trifluoromethyl alkenes would represent unique mechanistic probes into TMM-cycloadditions. In fact, the mechanism of the TMM-cycloaddition with respect to its concerted nature is still debatable and may strongly depend on the olefinic partner.[10] At the outset of our study, it was thus unclear whether the cycloaddition with trifluoromethyl olefins would give rise to the desired cycloadduct or be interrupted by a fluoride elimination. Indeed, nucleophilic additions to trifluoromethyl alkenes concomitant with fluoride eliminations are well-established processes.[11] Herein we report this unprecedented type of transformation in Pd-catalyzed TMM-cycloadditions and strong evidence for a nonconcerted pathway.

We began our investigations by examining the reaction of TMM-donor **2a** with α-trifluoromethylstyrene **1a**. Ligands that proved successful in the TMM-cycloadditions such as triisopropylphosphite or dppe led to poor conversion and no desired product (Table 1, entries 1 and 2). To the extent that the reactivity involves the TMM-complex functioning as a donor interacting with a typical Michael-type alkene acceptor, enhancing the donor properties of the TMM-PdL_2 complex should increase reactivity. While the use of phosphorus triamide did not deliver any of the desired cycloadduct (Table 1, entry 3), phosphoramidite

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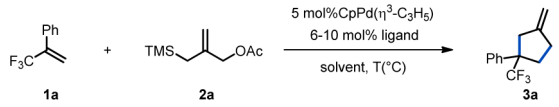
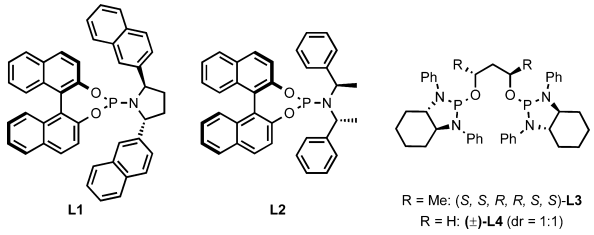
Table 1. Selected Optimization Studies[a]



entry	ligand	solvent	T (°C)	% conv.[b]	% yield[b]
1	$P(O^iPr)_3$	dioxane	60	13	0
2	dppe	dioxane	60	18	2
3	$P(NMe_2)_3$	dioxane	60	14	0
4	**L1**	dioxane	60	27	6
5	**L2**	dioxane	60	98	66
6	**L3**	dioxane	60	100	100 (75)[c]
7	**L2**	dioxane	23	85	46
8	**L3**	dioxane	23	100	100 (79)[c]
9	**L3**	THF	23	100	69[c]
10	**L3**	toluene	23	100	91
11	**L4**	dioxane	23	100	100 (80)[c]

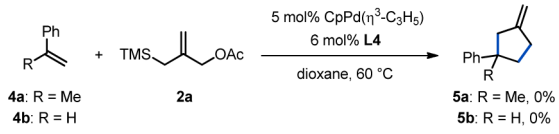
[a]All reactions were conducted on a 0.10 mmol scale at 0.33 M for 12 h in the indicated solvent with 1.55 equiv of **2a**, 5 mol % of $PdCp(\eta^3\text{-}C_3H_5)$ and 10 mol % of ligand **L1**/**L2** or 6 mol % of ligand **L3**/**L4**. [b]Conversions and yields were determined by GC analysis using dodecane as an internal standard. [c]Isolated yield.



ligands **L1** and **L2** gave much more encouraging results (Table 1, entries 4 and 5).[12] Gratifyingly, bidentate diaminophosphite ligand **L3**, recently developed in our laboratory,[13] delivered the targeted cycloadduct **3a** in quantitative GC yield and 75% isolated yield (Table 1, entry 6). The obtention of the cycloadduct **3a** unaccompanied by fluoride elimination may be suggestive of a concerted mechanism.

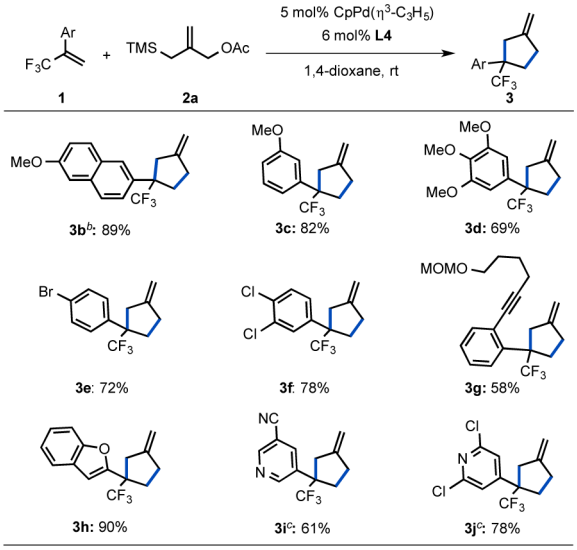
Efforts turned to optimizing the reaction variables. Decreasing the reaction temperature showed that diaminophosphite ligand **L3** is best-suited for this system (Table 1, entries 7 and 8). In addition, dioxane was found to be the optimum solvent (Table 1, entries 8, 9 and 10). Finally ligand **L4** was shown to be as effective as the parent enantioenriched ligand **L3** (Table 1, entries 8 and 11). The singular activating role of the CF_3 group is nicely underlined by the fact that α-methylstyrene **4a** and styrene **4b** are completely inert under the reaction conditions, even when run at 60 °C (Scheme 1).

Scheme 1. Evidence of the Activation by the CF_3-Group



We investigated the scope of the new cycloaddition. A variety of arenes with different steric and electronic constraints were evaluated (Chart 1). Aromatic rings are well tolerated regardless of the position of substitution around the arene ring (**3b**–**g**). Noteworthy, electron-deficient (**3c**,**e**,**f**,**i**,**j**), electron-neutral (**3a**,**b**), and electron-rich (**3d**,**g**,**h**) styrenes are all competent

Chart 1. Palladium-Catalyzed [3 + 2] Reaction with Trifluomethylstyrenes[a]

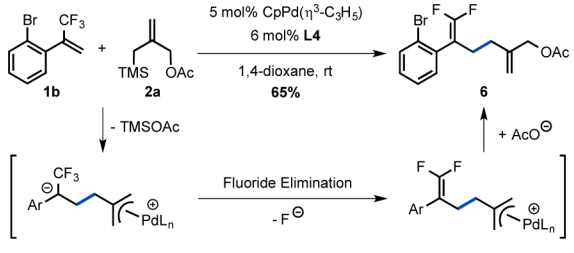


[a]All reactions were perfomed at 0.33 M concentration with 0.10 mmol of substrate. [b]Reaction was performed on 1 mmol scale. [c]Reaction was performed at 60 °C using 2 equiv of donor **2a**.

substrates in this transformation; a feature that further demonstrates the unique role of the CF_3 group. Interestingly, aryl bromides (**3e**) and chlorides (**3f**,**j**) are also compatible with the mild reaction conditions. Likewise, heteroaromatic structures of importance in medicinal chemistry such as benzofurans (**3h**) and pyridines (**3i** and **3j**) are well-tolerated. In addition, the reaction allows for the introduction of a variety of useful functional groups such as alkynes (**3g**), acetals (**3g**), and nitriles (**3i**).

The moderate yield obtained in the case of cycloadduct **3g** may be due to the formation of significant amounts of vinyldifluoride arising from the undesired elimination of a fluoride anion mentioned earlier as determined by NMR spectroscopy analysis of the crude reaction mixture.[14] Notably, the introduction of a bromide substituent at the ortho-position of the starting styrene **1b** resulted in the exclusive formation of the eliminated product **6** (Scheme 2). In striking contrast to the earlier comment on concertedness, the generation of such an adduct strongly supports the hypothesis of a stepwise mechanism.

Scheme 2. Competitive Fluoride Elimination



The generality of the cycloaddition between the standard donor **2a** and α-trifluoromethylstyrenes **1** led us to explore even more challenging substrates. Thus, reaction of styrene **1a** with the less reactive TMM-donor **2b** bearing an alkyne substituent stabilizing the negative charge in the palladium–TMM complex[15] gave rise to the corresponding cyclopentene **7** in 91% isolated yield (Scheme 3). Gratifyingly, trisubstituted alkene (*Z*)-**8a** delivered cyclo-

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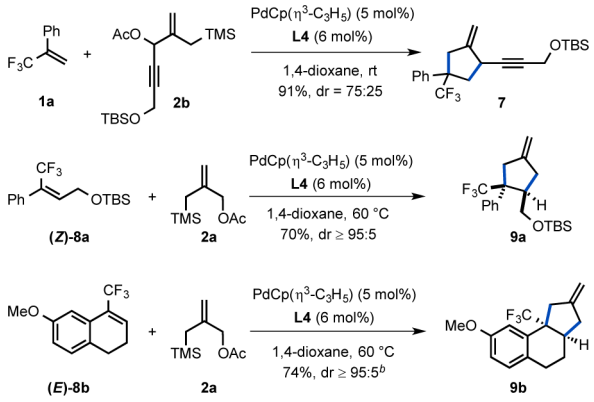
Scheme 3. Extension of the Scope of the Cycloaddition[a]

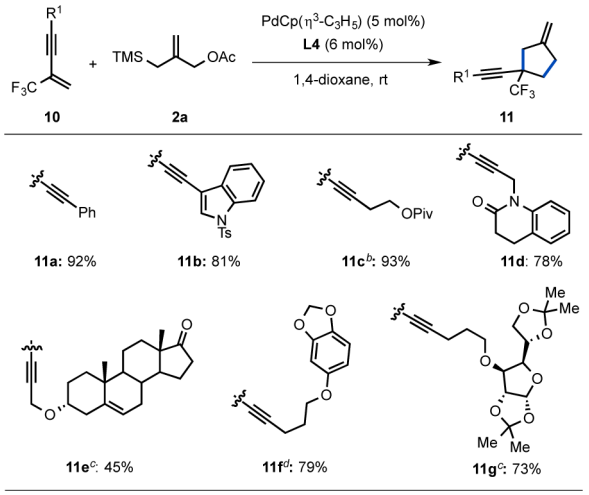


[a]All reactions were performed at 0.33 M concentration with 0.1 mmol of substrate. [b]The reaction was performed at 0.4 M with 0.3 mmol of substrate.

adduct **9a** in good yield and as a single diastereoisomer. This transformation constitutes the first example of a cycloaddition involving a trisubtituted trifluoromethylstyrene where activation occurs through the CF_3 group. Indeed, the utility of these substrates was previously limited to the hydrogenation of the trisubstituted alkene.[16] In addition, (*E*)-styrenes are also competent substrates in this transformation as illustrated by the high-yielding formation of tricycle **9b** starting from dihydronaphthalene (*E*)-**8b**.

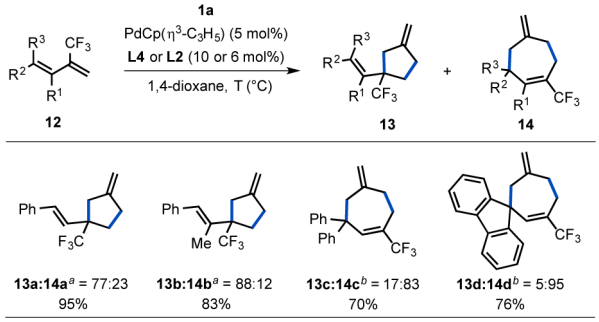
The susceptibility of alkynes to transition-metal-catalyzed processes raises the interesting question of chemoselectivity in the use of trifluoromethylenynes. To our delight, 1,3-enynes **10** were found to be particularly effective substrates and the [3 + 2]-cycloaddition smoothly proceeded (Chart 2).[17] This novel reactivity is exciting since alkynes are very useful building blocks in numerous reactions and especially in metal-catalyzed processes.[18] Aromatic (**11a**), heteroaromatic (**11b**), and even aliphatic R^1 substituents (**11c**–**g**) on the alkyne were perfectly tolerated, and cyclopentenes **11** were obtained in high yields. Noteworthy, the reaction is compatible with esters (**11c**), amides (**11d**), ketones (**11e**), and masked alcohols (**11g**). In addition, as illustrated by example **11c**, the cycloaddition is efficient on gram scale employing a lower catalyst and ligand loading (Chart 2).

Chart 2. Cycloaddition with 1,3-Enynes[a]



[a]All reactions were perfomed at 0.33 M concentration with 0.10 mmol of substrate **4**. [b]The reaction was performed on 6 mmol scale using 2.5 mol % of PdCp(η^3-C_3H_5) and 3 mol % of ligand **L4**. [c]The reaction was performed at 45 °C using 2 equiv of **2**. [d]The reaction was performed on a 1 mmol scale.

Chart 3. [3 + 2]- vs [3 + 4]-Cycloadditions with 1,3-Dienes



[a]Reaction was performed with **L4** at 23 °C. [b]Reaction was performed with **L2** at 60 °C.

Dienes **12** also successfully reacted. Most interestingly, both [3 + 2]- and [3 + 4]-products were obtained in this case (Chart 3). The involvement of both unsaturations in the cycloaddition is noteworthy. In contrast, despite the fact that alkynes are well-known to react in transition-metal-catalyzed cycloadditions, enynes only reacted in a [3 + 2]-fashion. Formation of the [3 + 2]-cycloadduct is favored by the use of bidentate ligand **L4** (**13a,b**), while Feringa ligand **L2** favors the formation of the [3 + 4]-cycloadduct (**14c,d**).[19] We previously noted that some dienes may react in both [3 + 2]- and [3 + 4]-mode.[9b] Such competitive behavior seems more consistent with a stepwise mechanism. Indeed, the evidence herein would seem to be best compatible with a short-lived intramolecular ion pair and is working in the same direction as our earlier observation of fluoride elimination (example **3g**, Chart 1 and example **6**, Scheme 2).

The new reaction allows an easy access to cycloadducts with a unique juxtaposition of functionality. Thus, selective modification of the exocyclic double bond is straightforward. In particular, osmium-catalyzed oxidative cleavage readily delivers the corresponding cyclopentanones **15** (Scheme 4a). A complementary two-step protocol consists in epoxidizing the exomethylene followed by oxidative cleavage by periodic acid (example **15d**, Scheme 4b). Interestingly, these seemingly simple ketones are formal products of 1,4-addition of a CF_3 anion onto cyclopentenones and were not previously accessible. Additionally, selective functionalization of the alkyne in cycloadduct **11c** was achieved exploiting our intramolecular ruthemium-catalyzed trans-hydrosilylation (example **17**, Scheme 4c). This strategy furnishes cyclic siloxanes, which we previously demonstrated to be useful building blocks for Tamao–Fleming oxidation and Hiyama cross-coupling chemistry.[20]

In summary, we have demonstrated the first example of the cycloaddtion of TMM with olefins activated by a σ-electron withdrawing substituent: the CF_3 group. Diaminophosphite ligand **L4** was instrumental in the development of this method. The reaction proceeds well with α-styrenes, 1,3-enynes and 1,3-dienes. The availability of the cycloadducts derived from enynes and dienes allow entry to alkyl substituents too. Further investigations into the full scope of this new transformation and toward the development of an enantioselective cyloaddition are ongoing and will be reported in due course. The current results

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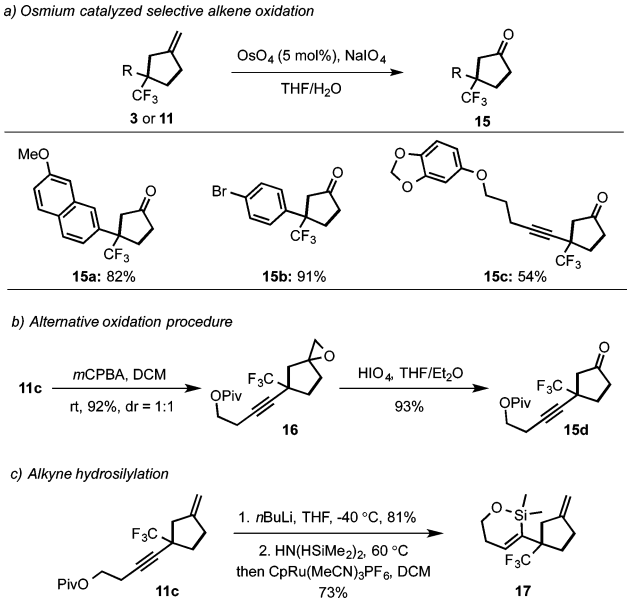
Scheme 4. Functionalization of the Cycloadducts



provide good evidence for a stepwise mechanism albeit with an especially short-lived zwitterion intermediate. The successful development of these transformations allows envisioning the use of new classes of olefins in the TMM cycloaddition beyond the typical Michael-type acceptors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07573.

Experimental procedures and characterization spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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