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Chemospecific Alkynylation of Organic Iodides[1]

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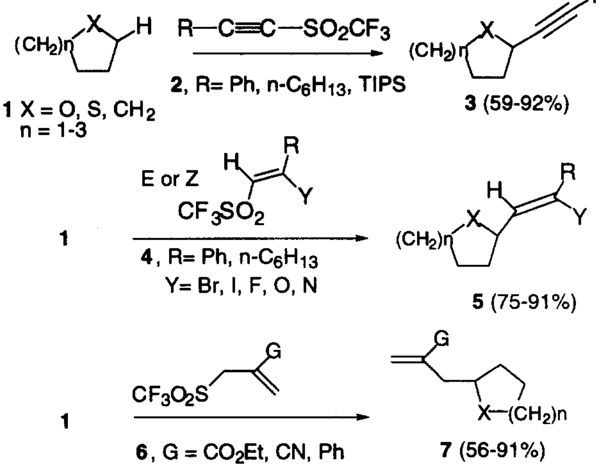
Abstract: Organic iodides undergo chemospecific alkynylation with triisopropylsilylacetylenic triflone under photochemical irradiation. Examples include primary, secondary, and tertiary iodides. The reaction is compatible with many functional groups, such as alcohol, ester, amide, thiazole, and a potential β-elimination substrate.

We recently reported that reaction of ethers, sulfides, and hydrocarbons with acetylenic and β-heteroatom substituted vinyl triflones such as **2** and **4** provides facile access to substituted alkynes **3** and alkenes **5** (Scheme 1).[2] The reaction proceeds via radical C-H abstraction by the highly electrophilic trifluoromethyl radical[3] in a process involving subsequent addition of the substrate radical to the α-carbon of the acetylenic (or vinyl) triflone. Elimination of trifluoromethyl-sulfonyl radical, followed by fragmentation to sulfur dioxide and trifluoromethyl radical, propagates the chain. The power of this method lies in the fact that the chain transfer reaction (fragmentation) is rapid and unimolecular.[4] To further extend the scope of C-H bond functionalization, we recently prepared functionalized allylic triflones **6**.[5] These allyl triflones also provide excellent yields of C-H functionalization products **7**.

Scheme 1



After exploring the scope and limitations of unsaturated triflones as reagents for C-H functionalization, we wished to develop complementary methodology whereby we could selectively functionalize other positions of substrates that bear competing activated C-H bonds, such as the α-H in ethers and sulfides. The goal is stated graphically in Scheme 2. Chemoselective generation of a free radical at the 4-position of a tetrahydropyran by using the labile C-X bond, followed by alkynylation should lead to the 4-substituted product. One typical procedure to generate similar free radicals involves irradiation of a mixture of hexabutyldistannane and an organic halide.[6,7]

Our initial investigations employed the inexpensive cyclohexyl bromide. After testing a few conditions, we concluded that C-Br bonds were not labile enough to carry the chain reaction. We next turned to substrates bearing the C-I bond, which proved successful. We anticipate that the differential reactivity of the two halogens will prove advantageous, since bromides may provide an additional site for later (conventional) functionalization.

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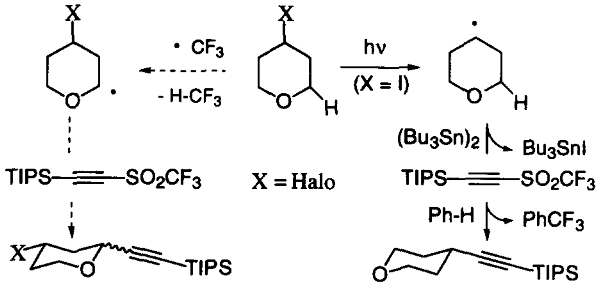
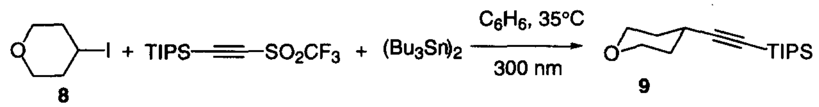
Scheme 2



In the event, we were delighted to find that photolysis of a benzene solution of 4-iodotetrahydropyran and hexabutyldistannane in the presence of TIPS-substituted acetylenic triflone generates the desired alkynylated products and tributylstannyl iodide (from the photochemical initiation reaction[7]). It is likely that the trifluoromethyl radical is scavenged by its known reaction with benzene,[8] although no attempt was made to isolate this volatile co-product. While use of a "catalytic" amount (25%) of hexabutyldistannane is able to carry the reaction to completion, the optimal conditions employ 0.5 eq. $(Bu_3Sn)_2$ and provide the best yield and shortest reaction times. More importantly, only 1.2 eq. of acceptor acetylenic triflone is necessary (Scheme 3). This contrasts to other work where large excess of acceptor (allyl stannane, allyl sulfide, or allyl sulfone) is usually needed.[9]

Scheme 3

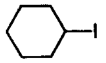
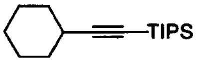
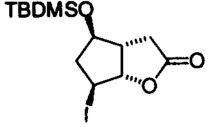
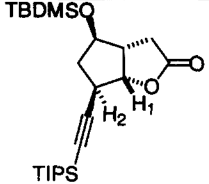
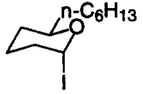
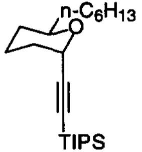
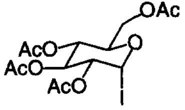
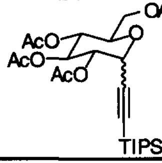
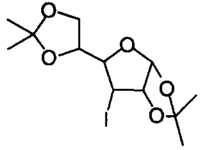
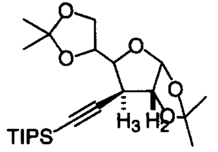
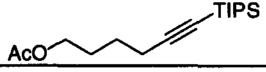
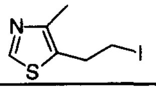
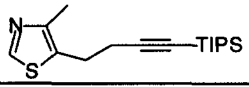
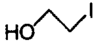
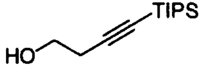
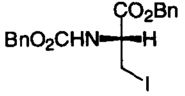
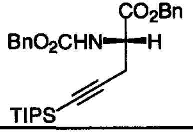
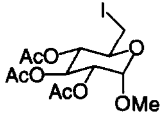
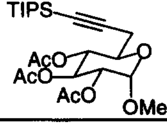
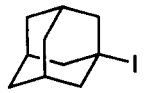
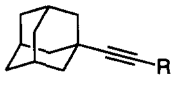


1 eq.	2 eq.	0.5 eq.	7h	82%
1 eq.	1.2 eq.	0.5 eq.	8h	83%
1 eq.	2 eq.	0.25 eq.	20h	73%

Based on the success with 4-iodotetrahydropyran, we examined the scope of this chemospecific alkynylation. It is found that not only secondary iodides (Table 1, entries 1-5), but also primary and tertiary iodides (Table 1, entries 6-7) work well. Consistent with mild conditions typically associated with free radical bond formation, this reaction is compatible with many functional groups, such as a free hydroxyl group, ester, amide, thiazole, and a potential β-elimination substrate. It is necessary to point out that the low yields in entries 3 and 5 (Table 1) are due to partial decomposition of starting materials based on control experiments. For C-glycosylation of α-iodo pyrans (Table 1, entries 3 and 4), the stereochemistry at the anomeric center was determined by analysis of the ^1H NMR spectrum. The formation of the sterically unfavored α-anomers indicates that either an anomeric effect is at work in the radical C-C bond formation or that σ-radicals are formed which are trapped by triflone before their inversion.[10] The stereochemistries of entries 2,5 (Table 1) are *exo* based on the analysis of ^1H NMR spectrum.[11]

Efforts to extend the chemistry to vinyl triflones is not successful because the desired reaction was very slow while isomerization of starting material became dominant (Scheme 4). Allylic triflones are reasonably reactive acceptors, affording the desired products in moderate yields.

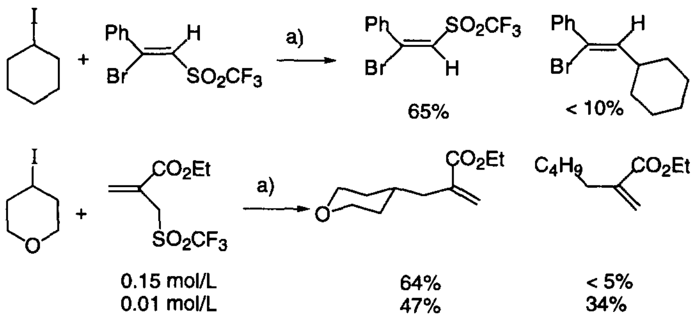
Table 1 Chemospecific alkynylation of organic iodides[a]

Entry	S.M.	#	Product	#	Time, Yield
1		10		21	7h, 80%
2		11		22	10h, 78% (J_{12}=2.1Hz)
3		12		23	5h, 35% (J_{12}=3.7Hz)
4		13	 12:1 α/β	24	8h, 65% (J_{12}=5.4Hz)
5		14		25	11h, 45% (J_{23}=0.5Hz)
6		15		26	16h, 77%
7		16		27	16h, 84%
8		17		28	18h, 62%
9		18		29	17h, 72%
10		19		30	14h, 71%
11		20		31	R=Ph, 6h, 61% R=TIPS, 20h, 82%

a) Iodide concentration 0.15 mol/L, ratio of iodide : triflone : tin = 1:1.2:0.5, irradiation with 300 nm light under argon.

The reactions are run at 0.15 mol/L, since allyl triflones often polymerize at higher concentrations.[5] Attempts to avoid the polymerization by lowering the reaction concentration were unsuccessful since large amounts (34%) of another side product began to appear. It was isolated and characterized as the simple butyl addition product.

Scheme 4



a) 0.5 eq. $(Bu_3Sn)_2$, C_6H_6, 300 nm, 35°C, 5-10h

Starting material iodides are either commercially available or are prepared based on literature procedures.[12,13,14]

In conclusion, we have developed a new free radical mediated C-I bond alkynylation. Radical coupling of highly functionalized entities with for acetylenic and allyl triflones should provide a useful methodology for carbon-carbon bond formation.

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