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Photochemically induced radical alkynylation of C(sp^3)–H bonds†

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A general strategy for photochemical alkynylation of unreactive C(sp^3)–H bonds has been developed. After C–H abstraction by the photo-excited benzophenone, a two-carbon unit was efficiently transferred to the generated radical from 1-tosyl-2-(trimethylsilyl)acetylene to afford the alkynylated product. The present reaction enables construction of various tri- and tetra-substituted carbons from heteroatom-substituted methylenes, methines and alkanes in a highly chemoselective fashion, and would serve as a new synthetic strategy for rapid construction of complex structures.

Introduction

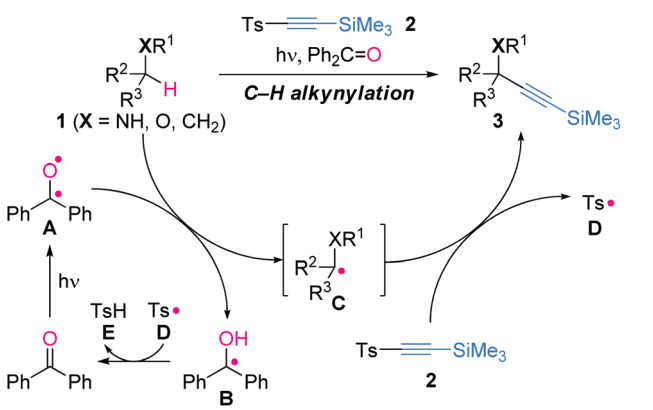
Carbon–carbon (C–C) bond formation plays a central role in chemical syntheses, and innovations in these types of reactions profoundly improve the overall synthetic efficiency. Among the various C–C forming strategies, the direct transformation of C(sp^3)–H bonds into C(sp^3)–C bonds has attracted much interest in recent years, since it eliminates prior functional group manipulations for substrate activation, resulting in simpler and shorter synthetic schemes.[1,2]

Typically, such a direct transformation is a challenge, because the reagents are required to cleave the requisite strong C(sp^3)–H bond selectively without affecting other C–H bonds in the organic molecules. Recently, we employed photochemically-generated highly reactive oxyl radicals to induce C(sp^3)–H functionalizations,[3] and developed chemoselective acylation,[4a] carbamoylation,[4b] and cyanation strategies.[4c] These studies prompted us to apply the photochemical reaction system for attachment of an alkyne, a more versatile building block.

The carbon–carbon triple bond is one of the most important functional groups in organic chemistry due to its unique physicochemical properties, as well as the wide range of available methods for its functionalization.[5] Therefore, direct transfer strategies of acetylene to organic molecules are highly desirable in the syntheses of functional materials, pharmaceuticals and natural products. Here we report direct alkynylation of C(sp^3)–H bonds under photo-irradiation conditions (Scheme 1).[6–8] The present reaction enables the construction of various tri- and tetra-substituted carbons from heteroatom-substituted methylenes, methines and alkanes, and provides a new synthetic strategy for rapid construction of architecturally complex molecules.

Results and discussion

Our plan for the direct C(sp^3)–H alkynylation is illustrated in Scheme 1. We employed benzophenone ($Ph_2C{=}O$) as an oxyl radical precursor and 1-tosyl-2-(trimethylsilyl)acetylene **2** as an alkynylating agent (Scheme 1).[9,10] The photochemically formed **A** is an electrophilic oxyl radical, and thus would chemoselectively abstract the hydrogen of an electron-rich C–H bond of **1** to furnish carbon radical **C**.[11] Upon reaction with the electron-deficient alkyne **2**, **C** is expected to preferentially add at the α-position than the β-position of the sulfonyl group, due to the unfavorable steric interaction with the bulky



Scheme 1 Direct alkynylation of C(sp^3)–H bonds and proposed reaction mechanism.

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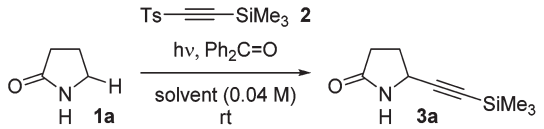
Table 1 Optimization of alkynylation conditions[a]



Entry	1, equiv.	2, equiv.	Solvent	*T* (h)	Yield[b] (%)	Recovery[b] (%)
1	3	1	MeCN	4	53	31
2	3	1	Benzene	4	52	9
3	3	1	*t*-BuOH	1	57	13
4	8	1	*t*-BuOH	1	83[c]	0

[a] Reaction conditions: **1a**, **2**, $Ph_2C{=}O$ (1 equiv.), solvent (0.04 M), rt, photo-irradiation using a Riko 100 W medium pressure mercury lamp. [b] Yield was determined by NMR analysis. [c] Isolated yield.

trimethylsilyl group. Subsequent release of the tosyl radical **D** from the produced vinyl radical intermediate would result in formation of the alkynylated product **3**, while **D** abstracts a hydrogen from the ketyl radical **B** to regenerate $Ph_2C{=}O$. Importantly, high-yielding transformation from **1** to **3** is realized only when all the radical species properly follows the series of reactions depicted in Scheme 1.

We first established the optimum photochemical conditions for an efficient C–H alkynylation (Table 1). Pyrrolidinone **1a** was selected as a substrate based on the expectation that the nitrogen functionality would secure the selective functionalization of its electron-rich nitrogen-substituted methylene. In fact, irradiation of **1a** (3 equiv.), **2** (1 equiv.) and $Ph_2C{=}O$ (1 equiv.) in MeCN with a medium-pressure mercury lamp successfully provided the adduct **3a** in 53% yield (entry 1). While the reaction proceeded in benzene and *t*-BuOH in similar yields (entries 2 and 3), conversion in *t*-BuOH was apparently faster in comparison to other solvents. The modest yields in entries 1–3 appeared to originate from the undesired reaction involving the reactive propargylic tertiary C–H bond of **3a**, since disappearance of **3a** was observed upon irradiation of **3a** just in the presence of $Ph_2C{=}O$.[12] Consequently, a significant improvement in the yield of **3a** was attained by applying 8 equiv. of **1a** in *t*-BuOH (83%, entry 4).[13]

The established conditions were next applied to a variety of electron-rich secondary C–H bonds adjacent to nitrogen-based functional groups (Table 2). Similar to alkynylation of the five-membered lactam **1a** (entry 1), both the six- and seven-membered lactams **1b** and **1c** were chemoselectively functionalized to afford the corresponding adducts **3b** and **3c**, respectively, in high yields (entries 2 and 3). The reactions of the protected piperidines, bearing Boc **1d**, Ac **1e**, and Troc **1f**, all efficiently provided the corresponding products **3d–3f** (entries 4–6). The Boc-substituted alkylamine **1g** and the Ph-substituted diethylamine **1h** were also converted to the non-cyclic products **3g** and **3h**, respectively (entries 7 and 8). In the case of *N*-Boc morpholine **1i**, C–H functionalization chemoselectively occurred at the methylene proximal to the *N*-Boc group to generate **3i** (entry 9), clearly indicating that the C–H bond attached to the nitrogen atom is more reactive than that attached to the oxygen atom. When the substrates with preexisting stereocenters were used, high diastereoselectivity was observed (entries 10 and 11). C–H alkynylations of the cyclic carbamate **1j** and the proline derivative **1k** stereoselectively produced the 1,2-*trans*-disubstituted **3j** and the 1,3-*trans*-disubstituted **3k**, respectively, in a completely chemo- and stereoselective fashion.

The present protocol realized high-yielding functionalizations of oxygen-substituted methylenes (Table 2, entries 12–15). Dioxane **1l** (entry 12) and 15-crown-5 ether **1m** (entry 13) underwent mono-alkynylation to produce the adducts **3l** and **3m**, respectively, while (−)-ambroxide **1n** was chemoselectively alkynylated at the ethereal C–H bond among other potentially reactive C–H bonds to provide **3n** (entry 14). Moreover, two carbon-elongation of the non-protected primary alcohol **1o** was possible, leading to the propargylic alcohol **3o** (entry 15). The order of the favorable reactive sites is clarified from Table 2, and determined to be nitrogen- > oxygen- > non-heteroatom-substituted carbons.

Despite their more sterically hindered nature, tertiary C–H bonds adjacent to nitrogen- and oxygen-based functional groups were efficiently transformed (Table 3). Alkynylation of 5-methylpyrrolidin-2-one **1p** under the optimized conditions in Table 1 (conditions A: **1p**/**2**/$Ph_2C{=}O$ = 8 : 1 : 1) resulted in formation of the alkyne-attached tetrasubstituted carbon of **3p** in quantitative yield within 1 h (entry 1). Because the product **3p** does not have a reactive propargylic C–H bond, increasing the irradiation time did not cause over-reactions of **3p**, and thus reducing the reagent amount was possible without decreasing the yield. Namely, **3p** was obtained in 75% yield even upon irradiating a limited amount of **1p** (1 equiv.) with 1.5 equiv. of **2** and 0.5 equiv. of $Ph_2C{=}O$ (conditions B: **1p**/**2**/$Ph_2C{=}O$ = 1 : 1.5 : 0.5) for 10 h (entry 2). Significantly, conditions B were applicable for construction of nitrogen- and oxygen-substituted tetrasubstituted carbons in high yields (entries 3–6). The bicyclic lactam **1q**[14] was chemoselectively alkynylated at the methine position in the presence of the less hindered oxygen-substituted methylene, providing **3q** in 81% yield (entry 3).[15,16] Mono-functionalization of both the *cis*- and *trans*-diaminocyclohexane derivatives **1r** and **1s**[17] took place stereoselectively, providing the same *cis*-fused bicyclic compound **3r** as a sole product (entries 4 and 5). The configurational change of the bicyclic system between **1s** and **3r** supported the intermediacy of an α-amino carbon radical.[4,18] Alkynylation of the ethereal tertiary C–H bond in the cyclohexanediol derivative **1t** stereoselectively furnished the *cis*-fused ring system **3t** in 70% yield (entry 6).[15,19] Since the secondary alcohol **1u** exhibited lower reactivity, conditions A were again adopted to generate the propargylic alcohol **3u** in 57% yield (entry 7).

The protocol was then utilized for the direct alkynylation of C–H bonds of alkanes, which are known to be less reactive than those of heteroatom-substituted compounds (Table 4). Cyclooctane **1v** was converted to the alkyne-branched

Table 2 Alkynylation of C–H bonds of heteroatom-substituted methylenes[a]

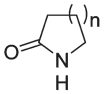
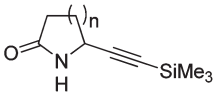
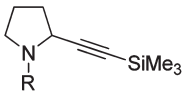
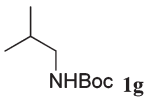
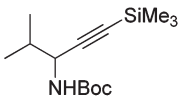
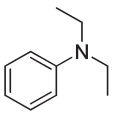
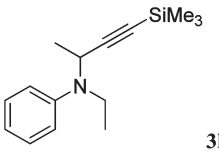
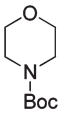
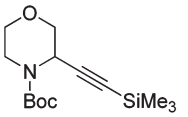
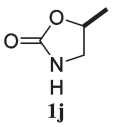
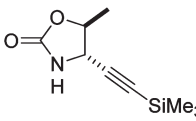
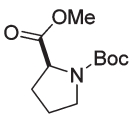
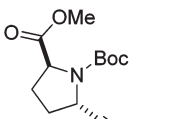
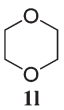
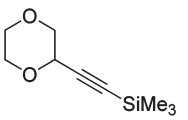
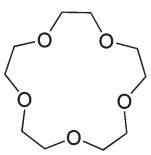
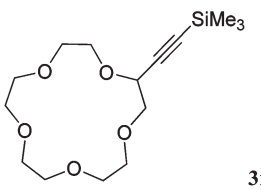
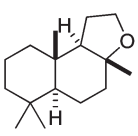
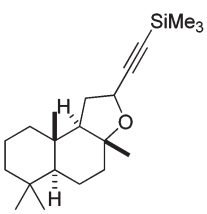
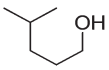
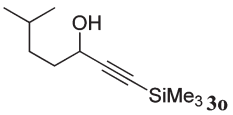
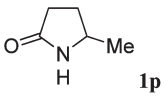
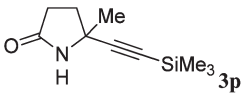
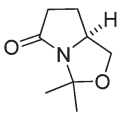
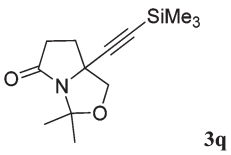
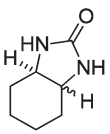
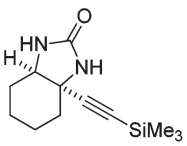
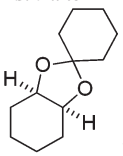
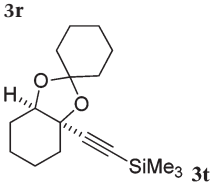
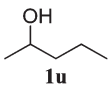
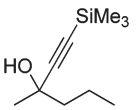
Entry	Starting material	*t* (h)	Product	Yield[b] (%)
				
1	**1a:** n = 1	1	**3a**	83
2	**1b:** n = 2	1.5	**3b**	81
3	**1c:** n = 3 	2	**3c** 	73
4	**1d:** R = Boc	1	**3d**	82
5	**1e:** R = Ac	1.5	**3e**	89
6	**1f:** R = Troc	1.5	**3f**	87
7	 **1g**	2.5	 **3g**	62
8	 **1h**	1.5	 **3h**	78
9	 **1i**	1	 **3i**	92
10	 **1j**	3	 **3j**	77
11	 **1k**	2	 **3k**	94
12[c]	 **1l**	2	 **3l**	75
13	 **1m**	1	 **3m**	82
14	 **1n**	1	 **3n**	74[d]

Table 2 *(Contd.)*

Entry	Starting material	*t* (h)	Product	Yield[b] (%)
15	 **1o**	2	 **3o**	73

[a] Reaction conditions: **1**/**2**/$Ph_2C{=}O$ = 8 : 1 : 1, *t*-BuOH (0.04 M), rt, photo-irradiation. [b] Isolated yield. [c] **1l** (16 equiv.) was used. [d] Mixture of diastereomers (dr = 3 : 4).

Table 3 Alkynylation of C–H bonds of heteroatom-substituted methines[a]

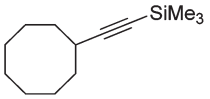
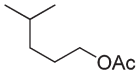
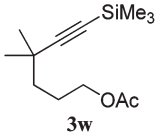
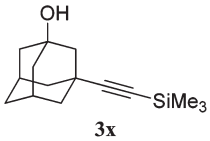
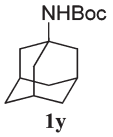
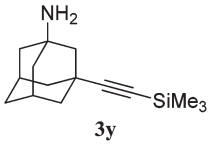
Entry	Starting material	Cond., *t* (h)	Product	Yield[b] (%)
1	 **1p**	A, 1	 **3p**	99
2	 **1q**	B, 10	 **3q**	75
3[c]		B, 7		81
4	**1r**: *cis*	B, 10	**3r**	80
5	**1s**: *trans*	B, 20	**3r**	52[d]
6[c,d]	 **1t**	B, 12	 **3t**	70[e]
7	 **1u**	A, 4	 **3u**	57

[a] Conditions A: **1**/**2**/$Ph_2C{=}O$ = 8 : 1 : 1, *t*-BuOH (0.04 M), rt, photo-irradiation; conditions B: **1**–**2**–$Ph_2C{=}O$ = 1 : 1.5 : 0.5, *t*-BuOH (0.04 M), rt, photo-irradiation. [b] Isolated yield. [c] Reaction was conducted in the presence of 2,6-di(*t*-butyl)pyridine (1 equiv.). [d] Recovery of **1** was observed in 10% yield. [e] $Ph_2C{=}O$ (1 equiv.) was used.

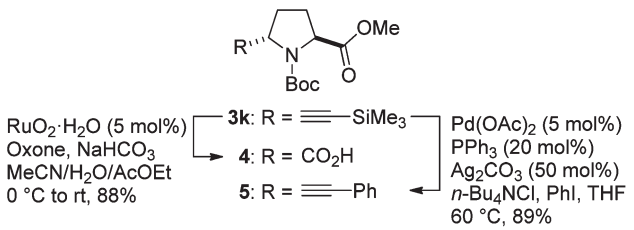
carbocycle **3v** in 70% yield (entry 1). When the alcohol was capped with an electron-withdrawing Ac group, alkynylation did not occur at the α-oxy carbon, but the most electron-rich and hindered tertiary C–H bond was selectively functionalized in the presence of less electron-rich primary and secondary C–H bonds, giving rise to **3w** in 54% yield (entry 2). In the case of the adamantane structures **1x** and **1y**, the reaction also proceeded exclusively at the methine positions to install the quaternary carbons. Consequently, compound **3x** was obtained in 86% yield (entry 3), and **3y**, which is a two carbon homolog of the antiviral drug, amantadine, was isolated in 73% yield after removal of the Boc group (entry 4). In particular, constructions of the hindered tetrasubstituted centers from a variety of structures (Tables 3 and 4, entries 2–4) demonstrated the power and generality of the present methodology.

The synthetic utility of the introduced C–C triple bond was exemplified by the two functional group transformations from the proline derivative **3k** (Scheme 2). Treatment of **3k** with RuO_2 and Oxone[20] transformed the alkyne moiety to the carboxylic acid *via* oxidative C–C bond cleavage, giving rise to the differentially protected C_2-symmetric pyrrolidine **4** in 88% yield.[21] On the other hand, the Sonogashira-type reaction[22] using the combination of Pd^0 and Ag^I catalysts directly coupled TMS-protected acetylene **3k** and phenyl iodide to provide phenylacetylene **5** in 89% yield.

Table 4 Alkynylation of alkanes[a]

Entry	Starting material	t (h)	Product	Yield[b] (%)
1	 **1v**	2	 **3v**	70
2	 **1w**	24	 **3w**	54
3	 **1x**	4	 **3x**	86
4	 **1y**	6	 **3y**	73[c]

[a] Reaction conditions: **1**/2/$Ph_2C{=}O$ = 8 : 1 : 1, *t*-BuOH (0.04 M), rt, photo-irradiation. [b] Isolated yield. [c] Boc group was removed using TFA (5 equiv.).



Scheme 2 Transformations of the TMS-protected acetylene.

Conclusions

In conclusion, we developed a direct photochemical alkynylation of unreactive C(sp^3)–H bonds using $Ph_2C{=}O$ as the precursor reagent of the C–H bond abstraction and 1-tosyl-2-(trimethylsilyl)acetylene as the alkynylating agent. The present transformation proceeds at ambient temperature with wide applicability of starting substrates, including amine derivatives, ethers, alcohols, and alkanes, and enables one-step construction of tetrasubstituted carbon centers. The sequence of the preferred reaction sites was established to be nitrogen- > oxygen-substituted carbons > non-substituted methines > non-substituted methylenes. The simple procedure, mild conditions, and predictable chemoselectivity make this protocol a unique and powerful tool for carbon–carbon bond formation. Since transformations of the introduced C–C triple bonds allow further attachments of a variety of carbon units at the alkyne terminus as well as the conversion to carboxylic acids, the newly developed C–H alkynylation strategy should be highly suitable for streamlined construction of pharmaceuticals and natural products.

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Notes and references

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12 Compound **3a** was recovered only in 24% yield after photoirradiation of only **3a** for 2 h at rt in the presence of $Ph_2C{=}O$ (1 equiv.) in *t*-BuOH (0.04 M).

13 No product was obtained in the absence of $Ph_2C{=}O$. Use of other oxyl radical precursors instead of $Ph_2C{=}O$ (*e.g.* 4,4′-dimethoxybenzophenone, acetophenone and xanthone) gave alkynylated product **3a** in lower yields (<25%).

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18 The steric hindrance around the reaction sites as well as the stereoelectronic effect of the abstracting C–H bonds is responsible for the difference in yields between **1r** and **1s**.

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