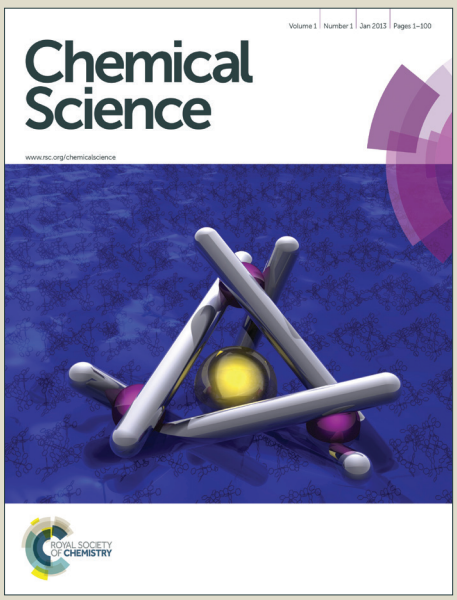
Chemical Science

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemicalscience

Journal Name

RSCPublishing

View Article Online
DOI: 10.1039/C4SC01631A

ARTICLE

Photochemically Induced Radical Alkenylation of C(sp^3)–H Bonds

ite this: DOI: 10.1039/x0xx00000x

Yuuki Amaoka,[a] Masanori Nagatomo,[a] Mizuki Watanabe,[b] Keisuke Tao,[b] Shin Kamijo,*[b] and Masayuki Inoue*[a]

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

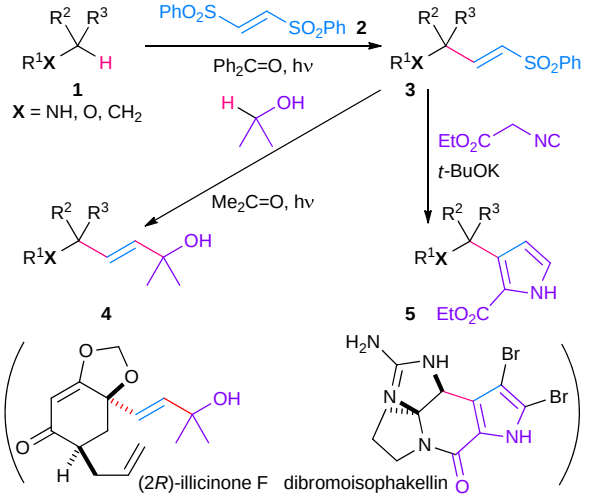
www.rsc.org/

Direct alkenylation of C(sp^3)–H bonds was achieved by employing benzophenone and 1,2-bis(phenylsulfonyl)ethylene under photo-irradiation conditions. This simple metal-free reaction enables the substitution of heteroatom-substituted methine, methylene and aliphatic C(sp^3)–H bonds by the (*E*)-sulfonylalkene units in a highly chemoselective manner. The derived sulfonylalkenes were further converted in a single step to the prenyl derivatives via a second photo-induced radical substitution and to the pyrrole derivatives via cyclization and aromatization. The present protocol thus serves as an efficient method for the direct extension of carbon skeletons for the synthesis of structurally complex natural products and pharmaceuticals.

Introduction

The direct transformation of C(sp^3)–H bonds to C(sp^3)–C bonds is one of the most ideal methodologies for constructing the complex carboskeletons of pharmaceutically important molecules,[1,2] which often contain a high proportion of sp^3-hybridized carbon centers.[3] Such reactions generally eliminate the need for preactivation steps and thus dramatically simplify the synthetic scheme. Accordingly, many transition-metal catalyzed activation methods have been developed to realize such C(sp^3)–H transformations. On the other hand, there are fewer reports of metal-free C–H transformations, mainly because chemoselective functionalization of the requisite strong C(sp^3)–H bond is generally a challenge especially when using organic molecules. Recently, we employed photochemically-generated highly reactive oxyl radicals as a key species for the homolytic cleavage of C(sp^3)–H bonds, and demonstrated chemoselective acylation, carbamoylation, cyanation, alkynylation and pyridination.[4] These studies prompted us to apply the metal-free photochemical reaction to the direct attachment of an alkene unit.

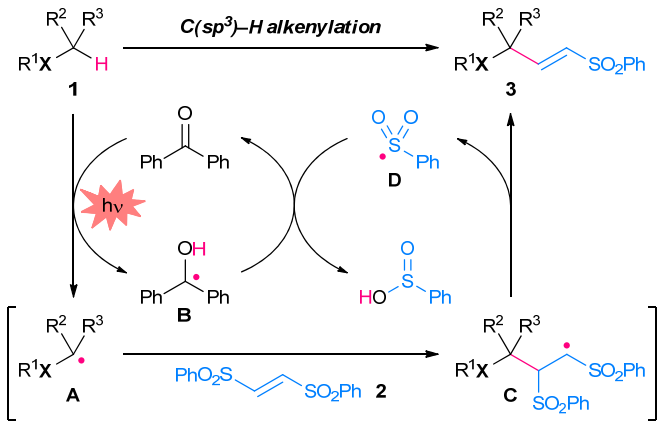
Alkenes are not only incorporated as important functional groups in natural products and pharmaceuticals, but are also used as a handle for further carbon elongations and synthetic manipulations. Therefore, there has been much interest in approaches allowing the direct introduction of alkene units to C(sp^3)–H bonds.[5,6] Herein we report a simple and versatile method for the alkenylation of C(sp^3)–H bonds using a new reagent system consisting of commercially available benzophenone (Ph_2C=O) and *trans*-1,2-bis(phenylsulfonyl)ethylene **2** under photo-irradiation conditions (Scheme 1).[7,8] The present transformation is widely applicable to the heteroatom-substituted methine, methylene and even aliphatic C(sp^3)–H bonds of starting materials **1**, and generates the corresponding (*E*)-sulfonylalkenes **3** in a highly chemoselective fashion. The synthetic utility of the resultant (*E*)-sulfonylalkenes **3** is further demonstrated by its single-step transformations into prenyl derivatives **4** and pyrrole derivatives **5**, both of which are substructures of various natural products and pharmaceuticals (e.g. (2*R*)-illicinone F[9] and dibromoisophakellin[10]).



Scheme 1. Photochemically induced C(sp^3)–H alkenylation using benzophenone and 1,2-bis(phenylsulfonyl)ethylene

Results and discussion

Our reaction design for C(sp^3)–H alkenylation using *trans*-1,2-bis(phenylsulfonyl)ethylene **2** is illustrated in Scheme 2. First, photo-excited Ph_2C=O, a highly reactive oxyl radical species, cleaves an C(sp^3)–H bond of **1** to provide carbon radical intermediate **A** and ketyl radical **B**. Then, the electrophilic oxyl radical irreversibly abstracts a hydrogen from the most electron-rich C(sp^3)–H bond in **1**. The chemoselectivity of the reaction is kinetically determined by this C(sp^3)–H homolysis. Since a proximal heteroatom (X = N or O) generally activates the C(sp^3)–H bond through hyperconjugation from its lone pair, the C(sp^3)–H bonds of the heteroatom-substituted carbons are expected to be selectively abstracted in the presence of the aliphatic counterparts.[11] After H-abstraction, the electron-rich carbon radical **A** in turn reacts with the electrophilic radical acceptor **2** to form another carbon radical, **C**. Subsequent release of phenylsulfonyl radical **D** from **C** affords the desired alkenylated product **3**, and Ph_2C=O is regenerated if the hydrogen atom is transferred from **B** to **D**.

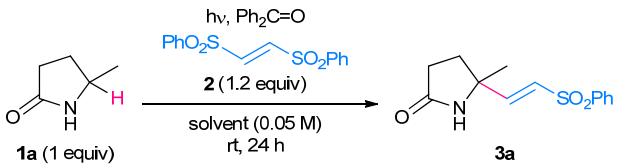


Scheme 2. Reaction design of C(sp^3)–H alkenylation

Based on the design in Scheme 2, we screened reaction conditions using 5-methyl-2-pyrrolidone **1a** as a starting material (Table 1). First, a 0.05 M MeCN solution of **1a** (1 equiv), **2** (1.2 equiv) and Ph_2C=O (1 equiv) was photo-irradiated with a Riko 100 W medium-pressure mercury lamp for 24 h (entry 1), resulting in the formation of (*E*)-sulfonylalkene **3a** in 57% yield. The most electron-rich C(sp^3)–H bond proximal to the nitrogen of **1a** was thus chemoselectively alkenylated to generate the new tetra-substituted carbon of **3a**. The yield of desired product **3a** was increased to 94% and the reaction time was shortened to 5h, when 5 equiv of **1a** was employed with **2** (1 equiv) and Ph_2C=O (1 equiv) (entry 2).[12] Alternatively, changing the solvent from MeCN to *t*-BuOAc improved the efficiency even when using **1a** as the limiting reagent (77% yield, entry 3). Other solvents were found to be less effective than *t*-BuOAc (entries 4-6). Although a decrease in the amount of Ph_2C=O from 1 equiv (entry 3) to 0.5 equiv (entry 7) did not significantly affect the outcome, the desired reaction did not proceed in the absence of Ph_2C=O (entry 8).[13] These results corroborated the essential role of Ph_2C=O as a hydrogen-abstracting agent.

Next, the scope of the applicable starting materials was expanded using the two optimized conditions shown in Table 1: conditions A (entry 3, **1**/**2**/Ph_2C=O, 1:1.2:1, *t*-BuOAc solvent) and conditions B (entry 2, **1**/**2**/Ph_2C=O, 5:1:1, MeCN solvent). Under both conditions, alkenylation occurred at the most electron-rich methine C(sp^3)–H bonds adjacent to the heteroatoms, despite their steric hindrances (Table 2). Bicyclic lactam **1b** was alkenylated selectively at the methine C(sp^3)–H bond adjacent to the nitrogen in the presence of the methylene C(sp^3)–H bond proximal to the oxygen, providing **3b** as the sole product (entries 1 and 2).[14] The alkenylation of bicyclic urea **1c** gave *cis*-fused sulfonylalkene **3c** in a highly diastereoselective fashion (entries 3 and 4).[15] As shown in entries 5-8, the C(sp^3)–H bonds adjacent to the oxygen functionalities were successfully alkenylated when the non-nitrogen substituted compounds were applied to either conditions A or B. Specifically, bicyclic acetal **1d** and cyclohexanol **1e** were functionalized at the ethereal and alcoholic methine C(sp^3)–H bonds to afford **3d** (entries 5 and 6) and **3e** (entries 7 and 8), respectively.[16] Furthermore, the versatility of the present method was demonstrated using the more complex steroidal structure. The reaction of methyl deoxycholate **1f**, which has two oxygen-substituted and six aliphatic methine C(sp^3)–H bonds, selectively proceeded at the O-substituted methine at C3 in the presence of more hindered C12-methine to provide sulfonylalkene **3f** (entries 9 and 10). It was particularly remarkable that the single-step constructions of the tetra-substituted carbons of the various molecules were achieved using only approximately equimolar amounts of **1**, **2** and Ph_2C=O (conditions A).

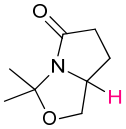
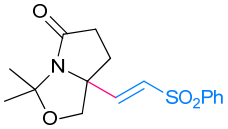
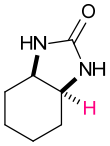
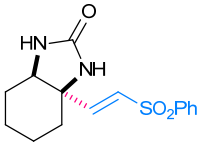
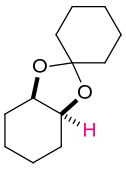
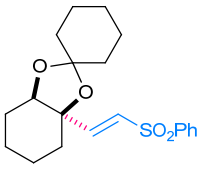
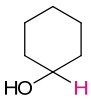
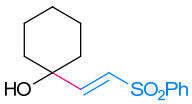
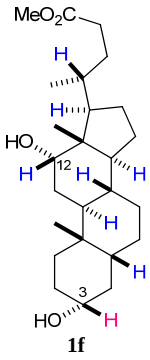
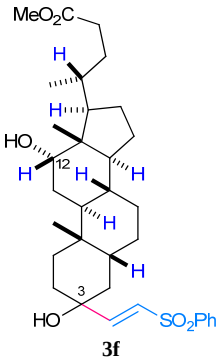
Table 1. Optimization of the reaction conditions[a]



Entry	Ph_2C=O, equiv	Solvent	Yield **3a**, %
1	1	MeCN	57
2[b]	**1**	**MeCN**	**94**
3	**1**	***t*-BuOAc**	**77**
4	1	*t*-BuOH	74
5	1	benzene	61[c]
6	1	$ClCH_2CH_2Cl$	48[c]
7	0.5	*t*-BuOAc	68
8	0	*t*-BuOAc	0[c]

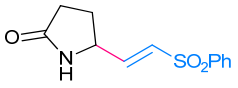
[a] Conditions: **1a** (1 equiv), **2** (1.2 equiv), Ph_2C=O, solvent (0.05 M), rt, photo-irradiation using a Riko 100 W medium-pressure mercury lamp (hν). [b] **1a** (5 equiv) and **2** (1 equiv) were irradiated for 5 h; yield was calculated with respect to **2**. [c] Yield was determined by ^{1}H NMR analysis.

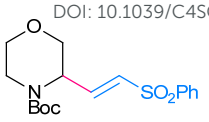
Table 2. Alkenylation of heteroatom-substituted methine C(sp^3)–H bonds[a]

Entry	Starting material	Cond., time, h	Product	Yield **3**, %
1[b]		A, 24		49
2[b]		B, 5		88
	1b		**3b**	
3[c]		A, 24		57
4		B, 4		81
	1c		**3c**	
5[b]		A, 24		50
6[b]		B, 7		83
	1d		**3d**	
7[c]		A, 24		45
6		B, 14		95
	1e		**3e**	
9[c]		A, 24		27[d]
10		B, 11		75[e]
	1f		**3f**	

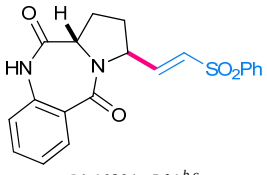
[a] Conditions A: **1**/**2**/Ph_2C=O, 1:1.2:1, *t*-BuOAc (0.05 M), rt, hν; conditions B: **1**/**2**/Ph_2C=O, 5:1:1, MeCN (0.05 M), rt, hν, yield was calculated with respect to **2**. [b] Reaction was conducted with 2,6-di(*t*-butyl)pyridine (1-1.2 equiv). [c] MeCN was employed instead of *t*-BuOAc. [d] Mixture of diastereomers (dr = 1.5:1). [e] Mixture of diastereomers (dr = 1.7:1).

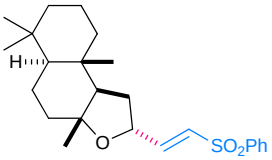
Table 3. Alkenylation of heteroatom-substituted methylene C(sp^3)–H bonds and aliphatic C(sp^3)–H bonds[a]

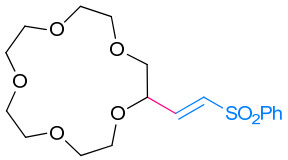

3g (81%, 10 h)

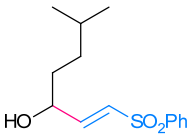

3h (90%, 6 h)

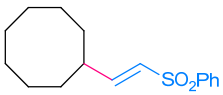

3i[b] (99%, 5 h)

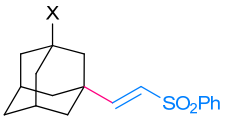

3j (68%, 5 h)[b,c]

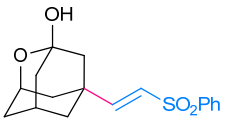

3k (77%, 5 h)[d]

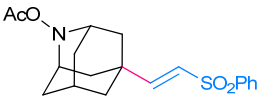

3l (71%, 5 h)

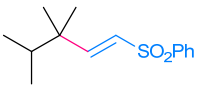

3m (74%, 5 h)[e]

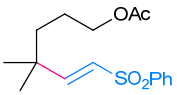

3n (86%, 9 h)


3o: **X** = OH (91%, 5 h)
3o: **X** = OH (43%, 24 h)[f]
3p: **X** = NHAc (90%, 19 h)
3q: **X** = COMe (75%, 10 h)


3r (90%, 8 h)


3s (72%, 5 h)


3t (65%, 24 h)[g]

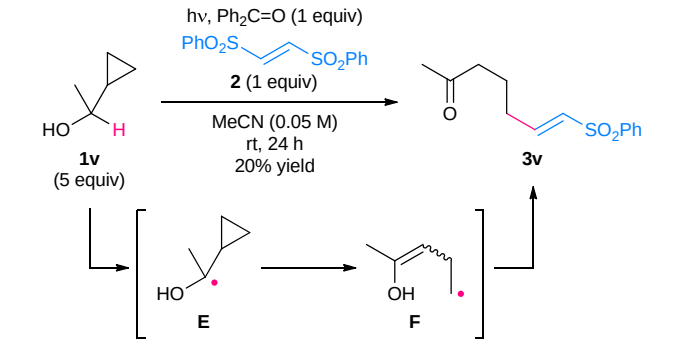

3u (65%, 24 h)[g]

[a] Conditions: **1**/**2**/Ph_2C=O, 5:1:1, MeCN (0.05 M), rt, hν, yield was calculated with respect to **2**. [b] single diastereomer. [c] 0.01 M. [d] Mixture of diastereomers (dr = 3.8:1). [e] **1m** (10 equiv) was employed. [f] **1o** (1 equiv), **2** (1.2 equiv) and Ph_2C=O (1 equiv) in *t*-BuOAc solvent (0.05 M) were irradiated for 24 h. [g] **1t** or **1u** (20 equiv) was employed.

The alkenylation of the methylene C(sp^3)–H bonds adjacent to heteroatoms (**1g-m**) and aliphatic C(sp^3)–H bonds (**1n-u**) was realized next (Table 3). Because these bonds are generally less reactive than the N/O-substituted methine C–H bonds, conditions B (**1**/**2**/Ph_2C=O, 5:1:1, MeCN solvent) was applied to these substrates. The reaction of 2-pyrrolidone **1g** gave the corresponding sulfonylalkene **3g**, and *N*-Boc morpholine **1h** was alkenylated to provide **3h**. The latter result clearly

indicated that the C–H bond of the N-substituted methylene is more reactive than that of the O-substituted methylene. The alkenylation of L-proline derivative **1i**, benzodiazepine derivative **1j** and (−)-ambroxide **1k** proceeded from the less hindered faces to furnish the corresponding adducts **3i**, **3j** and **3k** in a highly diastereoselective fashion. The ethereal methylene C(sp^3)–H bond of 15-crown-5 ether **1l** underwent mono-alkenylation to provide **3l** as a sole product, while non-protected primary alcohol **1m** was alkenylated at the alcoholic methylene position to give allyl alcohol derivative **3m**.

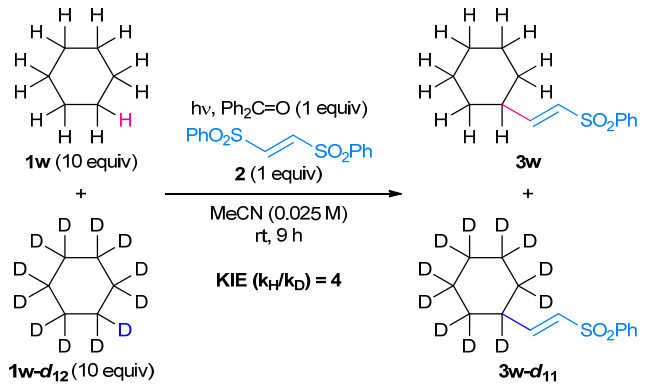
Conditions B permitted direct functionalization of the inert aliphatic C(sp^3)–H bond to install the tertiary (**3n**, Table 3) or quaternary carbon (**3o-u**). The methylene C(sp^3)–H bond of cyclooctane **1n** was alkenylated to provide the adduct **3n**. The adamantane derivatives **1o**, **1p** and **1q** with various polar functional groups were smoothly converted to the corresponding sulfonylalkenes **3o**, **3p** and **3q** at their electron-rich methine C(sp^3)–H bonds. [17] The alkenylation of 2-oxaadamantane-1-ol **1r** and *N*-acetoxy-2-azaadamantane **1s** proceeded at the non-heteroatom substituted positions to provide **3r** and **3s**, respectively. These seemingly inconsistent chemoselective outcomes from **1r** and **1s** can be rationalized by the non-hyperconjugation between the heteroatom-substituted methine C(sp^3)–H bond and the lone-pair of the heteroatom, because these are fixed within the rigid adamantane structure. [18] Finally, the reactions of 2,3-dimethylbutane **1t** and 4-methyl-1-pentyl acetate **1u** took place at the most electron-rich aliphatic methine positions in the presence of the methylene and methyl positions to afford **3t** and **3u**. The relative reactivity of the aliphatic methine of **1u** turned out to be higher than that of the O-substituted methylene, presumably due to the deactivating nature of the electron-withdrawing acetate.



Scheme 3. Ring-opening reaction of cyclopropane derivative **1v**

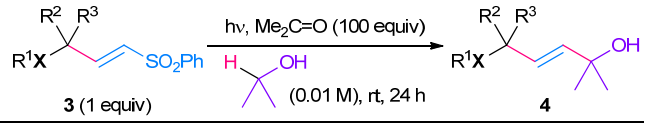
Intermediacy of the carbon radical was confirmed by a radical-clock experiment (Scheme 3). [19] The reaction of 1-cyclopropyl-1-ethanol **1v** under the alkenylation conditions afforded the ring-opened sulfonylalkene **3v** as the only isolable compound. Thus, after the homolytic cleavage of the C(sp^3)–H bond (**1v**), the cyclopropane ring of **E** opened to generate the primary carbon radical **F**, which was trapped with the radical acceptor **2** to produce the observed product **3v**.

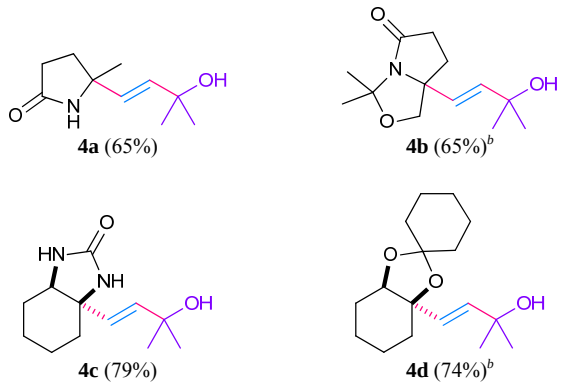
Moreover, the product-determining step of the alkenylation was determined to be homolysis of the C–H cleavage step, as envisioned in Scheme 2 (Scheme 4). Treatment of **2** (1 equiv) with cyclohexane **1w** (10 equiv) and its deuterated analogue **1w-d_{12}** (10 equiv) under the optimized conditions provided the corresponding sulfonylalkenes **3w** and **3w-d_{11}**. By analysing the ^{1}H NMR spectra of the product mixture, the kinetic isotope effect (KIE) value was calculated to be 4, clarifying the kinetic significance of cleavage of C(sp^3)–H bonds. [20] Hence, this mechanistic study further indicates that the chemoselectivity is established at the H-abstraction step and thus is predictable by considering the electron-richness of the C(sp^3)–H bonds of the molecule.



Scheme 4. Kinetic isotope effect of the C(sp^3)–H alkenylation

Table 4. One-step conversion of sulfonylalkenes to prenyl derivatives[a]





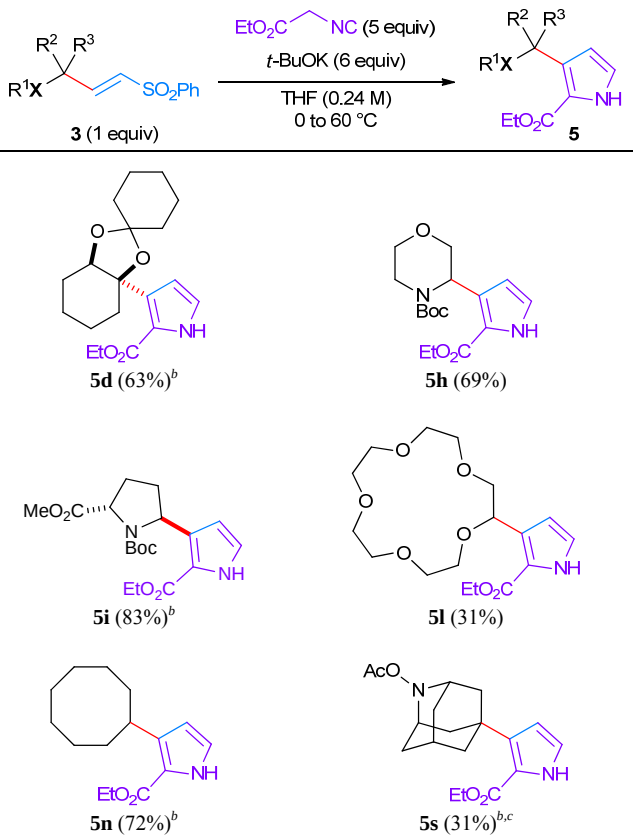
[a] Conditions: **3** (1 equiv), acetone (100 equiv), *i*-PrOH (0.01 M), rt, hν. [b] Reaction was conducted with 2,6-di(*t*-butyl)pyridine (1 equiv).

The synthetic utility of the introduced (*E*)-sulfonylalkene structures of the obtained **3** was exemplified by two single-step transformations. First, the photochemical substitution reactions were demonstrated to construct the oxidized prenyl structures (Table 4). [21] Photo-irradiation of an isopropanol solution of **3a** in the presence of acetone realized the carbon-chain extension to generate **4a**. The more complex bicyclic compounds **3b**, **3c** and **3d** were also converted to the corresponding prenyl

derivatives **4b**, **4c** and **4d**, respectively. The reaction was considered to proceed via a radical substitution mechanism similar to the one in Scheme 2. The carbon radical, formed via H-abstraction of the methine C(sp^3)–H of isopropanol by photo-activated acetone, added to the less hindered α-carbon of sulfonylalkene **3**, leading to **4** after expulsion of the sulfonyl radical.[22]

Second, we examined the conversion of the sulfonylalkenes **3** to pyrrole derivatives **5** by treating with ethyl isocyanoacetate under basic conditions (Table 5).[23] Pyrroles containing acetal (**5d**), morpholine (**5h**), proline (**5i**), crown ether (**5l**), cyclooctane (**5n**) and azaadamantane units (**5s**) were readily synthesized in a single operation via cyclization and aromatization. Carbonyl functionalities, such as the ester groups in **5i** and **5s** as well as the carbamate groups in **5h** and **5i**, were tolerant under these reaction conditions. In addition, the pyrrole derivatives **5d** and **5s**, substituted with a bulky group containing a tetra-substituted carbon center, were successfully prepared. Consequently, the present protocol offers the two-step preparation of 2,3-disubsituted pyrroles **5** starting from readily available materials **1**.

Table 5. One-step conversion of the sulfonylalkenes to pyrrole derivatives[a]



[a] Conditions: **4** (1 equiv), ethyl isocyanoacetate (5 equiv), *t*-BuOK (6 equiv), THF (0.24 M), 0 to 60 °C. [b] Reaction was conducted with ethyl isocyanoacetate (5.5 equiv) and *t*-BuOK (5 equiv). [c] Recovery of **3s** was observed in ca. 37% yield.

Conclusions

In conclusion, we developed a mild and metal-free alkenylation of C(sp^3)–H bonds using Ph_2C=O and *trans*-1,2-bis(phenylsulfonyl)ethylene under photo-irradiation conditions. The notable features of the present carbon chain extension reaction are: (1) simplicity of the synthetic technique; (2) wide applicability to various starting materials (ethers, alcohols, amine derivatives, and alkanes); (3) predictable chemoselectivity toward the most electron-rich C(sp^3)–H bond within a starting material (nitrogen- > oxygen-substituted carbons > aliphatic carbons); and (4) high efficiency in constructing N/O-containing tetrasubstituted carbons and quaternary carbons in hindered settings. Furthermore, the introduced (*E*)-sulfonylalkene unit was converted in a single step to the prenyl and pyrrole derivatives, which are substructures of numerous bioactive molecules. Because of these advantages, the present C(sp^3)–H alkenylation protocol, together with the subsequent two transformations, should serve as powerful tools for constructing the diverse carbon skeletons of complex natural products and pharmaceuticals.

Acknowledgements

This research was financially supported by the Funding Program for Next Generation World-Leading Researchers (JSPS) to M.I., and by The Naito Foundation, The Iwatani Naoji Foundation's Research Grant, and a Program to Disseminate Tenure Tracking System (MEXT) to S.K. A fellowship from JSPS to Y.A. is gratefully acknowledged.

Notes and references

[a] Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.
E-mail: inoue@mol.f.u-tokyo.ac.jp; Fax: (+81) 3-5841-0568
[b] Graduate School of Science and Engineering, Yamaguchi University, Yamaguchi 753-8512, Japan.
E-mail: kamijo@yamaguchi-u.ac.jp; Fax: (+81) 83-933-5733

† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/b000000x/

1 For recent reviews on C–H transformations, see: (a) *Handbook of C–H Transformations*; ed. G. Dyker, Wiley-VCH, Weinheim, 2005, vol. 1 and 2; (b) *Handbook of Reagents for Organic Synthesis: Reagents for Direct Functionalization of C–H Bonds*, ed. L. A. Paquette and P. L. Fuchs, Wiley, Chichester, 2007; (c) *Chem. Soc. Rev.*, 2011, **40**, (4), special issue on *C–H Functionalizations in Organic Synthesis*; (d) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960.

2 For recent reviews on direct C(sp^3)–H transformation to form C–C bonds, see: (a) Y. Ishii, S. Sakaguchi and T. Iwahama, *Adv. Synth. Catal.*, 2001, **343**, 393; (b) A. A. Fokin and P. R. Schreiner, *Adv. Synth. Catal.*, 2003, **345**, 1035; (c) R. Knorr, *Chem. Rev.*, 2004, **104**, 3795; (d) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (e) F. Kakiuchi and T. Kochi, *Synthesis*, 2008, 3013; (f) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (g) T. Akindele, K. Yamada and K. Tomioka, *Acc. Chem. Res.*, 2009, **42**, 345; (h) O. Daugulis, H.-Q. Do and D. Shabashov,

Acc. Chem. Res., 2009, **42**, 1074; (i) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (j) M. Klussmann and D. Sureshkumar, *Synthesis*, 2011, 353; (k) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293. (l) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726; (m) R. Rohlmann and O. G. Mancheño, *Synlett*, 2013, **24**, 6; (n) J. Xie, H. Jin, P. Xu and C. Zhu, *Tetrahedron Lett.*, 2014, **55**, 36; (o) Y. Qin, J. Lv and S. Luo, *Tetrahedron Lett.*, 2014, **55**, 551; (p) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74.

3 (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752; (b) F. Lovering, *Med. Chem. Commun.*, 2013, **4**, 515.

4 For our publications employing benzophenone as an oxyl radical precursor, see: (a) S. Kamijo, T. Hoshikawa and M. Inoue, *Tetrahedron Lett.*, 2011, **52**, 2885; (b) S. Kamijo, T. Hoshikawa and M. Inoue, *Org. Lett.*, 2011, **13**, 5928; (c) T. Hoshikawa, S. Kamijo and M. Inoue, *Org. Biomol. Chem.*, 2013, **11**, 164; (d) T. Hoshikawa, S, Yoshioka, S. Kamijo and M. Inoue, *Synthesis*, 2013, **45**, 874; (e) T. Hoshikawa and M. Inoue, *Chem. Sci.*, 2013, **4**, 3118.

5 Fuchs and co-workers developed a pioneering C(sp^3)–H alkenylation using vinyl triflones, see: (a) J. Xiang and P. L. Fuchs, *J. Am. Chem. Soc.*, 1996, **118**, 11986; (b) J. Xiang, W. Jiang, J. Gong and P. L. Fuchs, *J. Am. Chem. Soc.*, 1997, **119**, 4123.

6 For recent examples on direct C(sp^3)–H alkenylation, see: (a) Y.-J. Jang, Y.-K. Shih, J.-Y. Liu, W.-Y. Kuo and C.-F. Yao, *Chem. Eur. J.*, 2003, **9**, 2123; (b) Y. Zhang and C.-J. Li, *Tetrahedron Lett.*, 2004, **45**, 7581; (c) R. A. Doohan, J. J. Hannan and N. W. A. Geraghty, *Org. Biomol. Chem.*, 2006, **4**, 942; (d) T. Kagayama, M. Nakayama, R. Oka, S. Sakaguchi and Y. Ishii, *Tetrahedron Lett.*, 2006, **47**, 5459; (e) A. V. Messorosh, A. V. Trukhin and E. V. Eliseenkov, *Tetrahedron*, 2008, **64**, 10849; (f) C.-X. Song, G.-X. Cai, T. R. Farrell, Z.-P. Jiang, H. Li, L.-B. Gan and Z.-J. Shi, *Chem. Commun.*, 2009, 6002; (g) M. Wasa, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3680; (i) H. Mo and W. Bao, *J. Org. Chem.*, 2010, **75**, 4856; (h) Y. Nakao, E. Morita, H. Idei and T. Hiyama, *J. Am. Chem. Soc.*, 2011, **133**, 3264; (i) K. J. Stowers, K. C. Fortner and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 6541; (j) W. R. Gutekunst, R. Gianatassio and P. S. Baran, *Angew. Chem., Int. Ed.*, 2012, **51**, 7507; (k) H. Yang, P. Sun, Y. Zhu, H. Yan, L. Lu, X. Qu, T. Li and J. Mao, *Chem. Commun.*, 2012, **48**, 7847; (l) G. Zhang, Y. Ma, S. Wang, Y. Zhang and R. Wang, *J. Am. Chem. Soc.*, 2012, **134**, 12334.

7 For recent reviews on photochemical reactions, see: (a) M. Fagnoni, D. Dondi, D. Ravelli and A. Albini, *Chem. Rev.*, 2007, **107**, 2725; (b) N. Hoffmann, *Chem. Rev.*, 2008, **108**, 1052; (c) D. Ravelli, M. Fagnoni and A. Albini, *Chem. Soc. Rev.*, 2013, **42**, 97.

8 For examples of using bissulfonylethylenes as a radical acceptor, see: (a) S. Kim and C. J. Lim, *Angew. Chem., Int, Ed.*, 2002, **41**, 3265; (b) S. Lee, C. J. Lim and S. Kim, *Bull. Korean Chem. Soc.*, 2004, **25**, 1611; (c) A.-P. Schaffner, V. Darmency and P. Renaud, *Angew. Chem., Int. Ed.*, 2006, **45**, 5847; (d) S. Kim and S. Kim, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 809; (e) M. Lüthy, V. Darmency and P. Renaud, *Eur. J. Org. Chem.*, 2011, 547; (f) V. Liautard, F. Robert and Y. Landais, *Org. Lett.*, 2011, **13**, 2658; (g) C. Poittevin, V. Liautard, R. Beniazza, F. Robert and Y. Landais, *Org. Lett.*, 2013, **15**, 2814.

9 (a) Y. Fukuyama, N. Shida, Y. Hata and M. Kodama, *Phytochemistry*, 1994, **36**, 1497. For other representative examples, see: (b) S. Yamamura, L. R. Simpol, K. Ozawa, K. Ohtani, H. Otsuka, R. Kasai, K. Yamasaki and W. G. Padolina, *Phytochemistry*, 1995, **39**, 105; (c) M. Matsuhisa, Y. Shikishima, Y. Takaishi, G. Honda, M. Ito, Y. Takeda, H. Shibata, T. Higuti, O. K. Kodzhimatov and O. Ashurmetov, *J. Nat. Prod.*, 2002, **65**, 290; (d) R. Sekizawa, S. Ikeno, H. Nakamura, H. Naganawa, S. Matsui, H. Iinuma and T. Takeuchi, *J. Nat. Prod.*, 2002, **65**, 1491; (e) H. Bai, S. Li, F. Yin and L. Hu, *J. Nat. Prod.*, 2005, **68**, 1159; (f) I. I. Rodríguez, A. D. Rodríguez, Y. Wang and S. G. Franzblau, *Tetrahedron Lett.*, 2006, **47**, 3229.

10 (a) S. A. Fedoreyev, N. K. Utkina, S. G. Ilyin, M. V. Reshetnyak and O. B. Maximov, *Tetrahedron Lett.*, 1986, **27**, 3177; (b) T. Kato, Y. Shizuri, H. Izumida, A. Yokoyama and M. Endo, *Tetrahedron Lett.*, **1995**, *36*, 2133. For recent reviews, see: (c) S. M. Weinreb, *Nat. Prod. Rep.* 2007, **24**, 931; (d) A. Al-Mourabit, M. A. Zancanella, S. Tilvi and D. Romo, *Nat. Prod. Rep.*, 2011, **28**, 1229.

11 (a) J. M. Tedder, *Tetrahedron*, 1982, **38**, 313; (b) A. A. Fokin and P. R. Schreiner, *Chem. Rev.*, 2002, **102**, 1551; (c) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.*, 2011, **50**, 3362. See also reference 4.

12 Under these conditions, product **3a** was obtained in 92% yield on a gram scale. See Supporting Information for details.

13 The used $Ph_2C=O$ was partly converted to benzopinacol (1,1,2,2-tetraphenylethane-1,2-diol) via the homo-coupling of ketyl radical **B**.

14 Because of the acid sensitivity of starting materials, 2,6-di(*t*-butyl)pyridine was added for neutralization of generated acids (e.g., sulfinic acid) during the reaction, see ref. 4b.

15 Acetonitrile was employed instead of *t*-butyl acetate (Table 2, entry 5), because of the low solubility of **1c** in the *t*-butyl acetate solvent.

16 Cyclohexanone was obtained as a major byproduct from **1e**, when *t*-butyl acetate was employed as a reaction solvent (Table 2, entry 9).

17 In the absence of $Ph_2C=O$, the degradation of compound **1q** was observed via Norrish type 1 fragmentation of the carbonyl group.

18 (a) V. Malatesta and K. U. Ingold, *J. Am. Chem. Soc.* 1981, **103**, 609; (b) P. R. Schreiner, O. Lauenstein, I. V. Kolomitsyn, S. Nadi and A. A. Fokin, *Angew. Chem., Int. Ed.*, 1998, **37**, 1895.

19 D. Griller and K. U. Ingold, *Acc. Chem. Res.*, 1980, **13**, 317.

20 E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066.

21 For reviews on the chemistry of sulfonyl compounds, see: (a) P. L. Fuchs and T. F. Braish, *Chem. Rev.*, 1986, **86**, 903; (b) N. S. Simpkins, *Tetrahedron*, 1990, **46**, 6951; (c) C. Nájera and M. Yus, *Tetrahedron*, 1999, **55**, 10547; (d) A. El-Awa, M. N. Noshi, X. M. Du Jourdin and P. L. Fuchs, *Chem. Rev.*, 2009, **109**, 2315.

22 The steric hindrance around the β-carbon would be important factor for the regiocontrol of the radical addition to compound **3**, see: K. Ogura, A. Kayano and M. Akazome, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 3091.

23 (a) D. H. R. Barton and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1985, 1098; (b) P. Carter, S. Fitzjohn, S. Halazy and P. Magnus, *J. Am. Chem. Soc.*, 1987, **109**, 2711; (c) H. Uno, M. Tanaka, T. Inoue and N. Ono, *Synthesis*, 1999, 471; (d) R. Bhattacharya, A. K. Atta, D. Dey and T.

Pathak, *J. Org. Chem.* 2009, **74**, 669. For a review, see: N. Ono, *Heterocycles*, 2008, **75**, 243.

View Article Online
DOI: 10.1039/C4SC01631A