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Revealing the Metal-like Behavior of Iodine: An Iodide-Catalysed Radical Oxidative Alkenylation†

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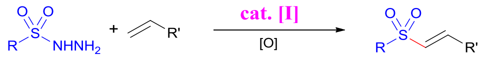
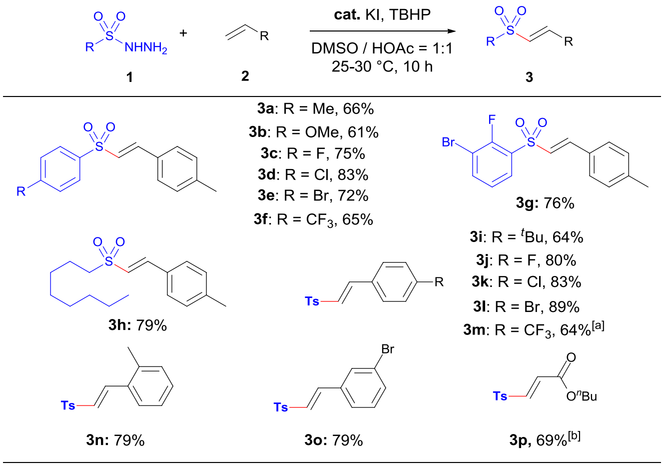
In this work, we described an alternative alkenylation approach to illustrate the metal-like behaviour of iodine in cross-coupling reactions. Alkenylation could proceed through iodide catalysed radical initiation, radical addition and iodine promoted alkenyl functionality recovery. Catalytic HI elimination similar to the β-hydride elimination of transition metals was realized for the radical alkenylation of sulfonyl hydrozides. Operando IR and cyclic voltammetry experiments were carried out to confirm the crucial role of iodine in the radical alkenylation process.

Over the past few decades, transition-metal-catalysed cross-coupling reaction has been proved to be a powerful tool for the construction of natural, biological, pharmaceutical, and material molecules.[1] The remarkable capability in electron transfer processes is the major reason why transition metals are the most widely exploited catalysts. Transition metals usually have moderate redox potentials, which makes them easy to obtain and lose electrons in cross-coupling reactions.[2] As a nonmetallic element, iodine has diverse valence states as well as moderate redox potentials.[2b, 3] These features make it possible for serving as an alternative catalyst for transition metals. Over the past few years, iodine-catalysed reactions have been increasingly explored.[4] Importantly, iodine has been reported to catalyze many reactions in which transition metals were used as catalysts.[5] Initiated by Ishihara and Wan, iodine catalysis has been applied as efficient alternative catalysts for transition metals in CDC reactions for C-O,[6] C-N[7] and C-C[8] bond formations. Interestingly, Li and co-workers have demonstrated an I$_2$-catalysed indole formation via oxidative cyclization of N-aryl enamines, which was known to have been catalysed by transition metals before.[9] What's more, iodine catalysis has also been proved to be successful for replacing transition-metals in direct oxidative aminations of azoles with same efficiency.[10] From all these promising results in oxidative coupling reactions[11], we could say that iodine catalysis might serve as a promising replacement for transition metal catalysis. However, little attention has been paid to investigate the metal-like behavior of iodine. Thus, the study on discovering metal-like iodine catalysed cross coupling reactions as well as understanding the behavior of iodine during catalytic reactions would be of highly importance for synthetic organic chemistry. Herein, we report our progress in the iodide-catalysed radical alkenylation of sulfonyl hydrazides with simple alkenes (eqn. (1)).



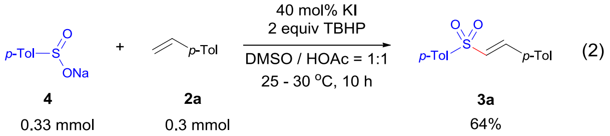
(1)

Heck reaction was known to go through transition metal involved alkene insertion and β–hydride elimination of aryl or vinyl halides (or sulfonates).[12] Recently, radical involved Heck-type reaction has been gradually developed, which offers alkenylation reactions with more alternatives.[13] Nevertheless, only limited examples have been reported to be successful in radical alkenylation processes. In most cases, radical addition to alkenes would end up with hydrogenation or alkene difunctionalization since there is a lack of elimination protocols.[14] Thus, developing elimination strategies is the key to achieve radical alkenylation. In this work, we describe that HI elimination[13e, 15] can be realized in a catalytic version for successful radical alkenylation, which is similar to the β-hydride elimination of transition metals in tradition Heck reaction.

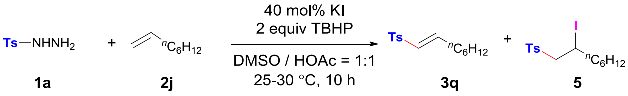


Scheme 1. Iodide catalysed oxidative radical alkenylation for the synthesis of alkenyl sulfones. Reaction condition: The reactions were carried out with **1a** (0.33 mmol), **2** (0.30 mmol), KI (40 mol%), TBHP (0.60 mmol, 70% in aqueous solution), DMSO (0.15 mL), HOAc (0.15 mL), 25-30 °C, 10 h. [a] DMSO (0.5 mL) and HOAc (0.5 mL) were used to ensure solubility. [b] 80 °C

As stable solids, sulfonyl hydrazides are readily accessible. By breaking the C-S, C-N and S-N bonds in the structure, they have demonstrated versatile reactive characteristics.[16] Among these transformations, iodine has been shown to be a good catalyst for initiating the sulfonyl radical.[16b, 16h 16i] As a continuous interest in radical alkenylation,[13f, 13g, 13j, 13k] we found that the combination of KI and TBHP with DMSO/HOAc as co-solvent gave a good result for the oxidative alkenylation for *p*-toluenesulfonohydrazide (**1a**) with *p*-methyl styrene (**2a**) under mild condition. Under these conditions, a 66% isolated yield of alkenyl sulfone (Scheme 1, **3a**) was obtained at room temperature. Effects of reaction parameters were shown in supporting information Table S1. Encouraged by the preliminary results, we tried to explore the functional group tolerance for the synthesis of various alkenyl sulfones under the standard condition. First of all, various substituted sulfonyl hydrazides were tried in this radical alkenylation process (Scheme 1, **3a-3h**). Strong electron donating methoxyl group, strong electron withdrawing trifluoromethyl group and halide groups at the *para* position were all tolerated and afforded good yields. When two halide atoms were introduced to the *meta* and *ortho* position, the reaction proceeded smoothly as well (Scheme 1, **3g**). To our pleasure, aliphatic sulfonyl hydrazides were proved to be good substrates for this reaction (Scheme 1, **3h**). Regarding another widely existing sulfonyl source, sodium sulfinates were applied in this system. Sodium *p*-tolylsulfinate (**4**) was tested with *p*-methyl styrene under the standard condition. Delightfully, the alkenylation product was obtained in 64% yield (eqn. (2)). Next, various olefins were employed to synthesize alkenyl sulfones. *para*-*tert*-Butyl styrene afforded the coupling product in 64% yield (Scheme 1, **3i**). ortho-Methyl substituent showed a positive effect on the generation of the product with 79% isolated yield (Scheme 1, **3n**). Halide substituents were well tolerated in this transformation and the reaction proceeded chemoselectively to afford the desired alkenylation products (Scheme 1, **3j-3l, 3o**). Trifluoromethyl group at the *para* position of styrene gave the alkenylation product in good yields (Scheme 1, **3m**). Furthermore, we tried to apply more electron-deficient olefins as the substrates. We found that even butyl acrylate could give the desired product in good selectivity under an increased temperature (Scheme 1, **3p**).



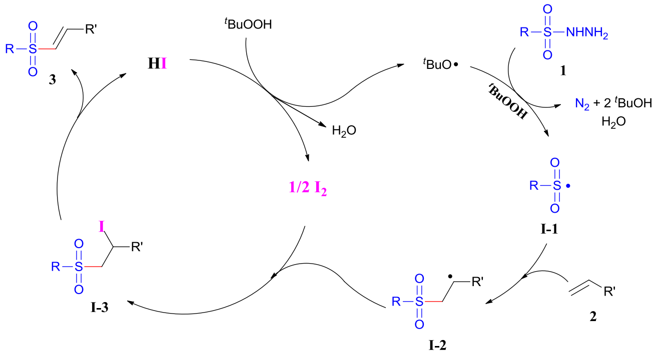
When 1-octene (**2j**) was applied as the substrate, iodosulfonylation product (**5**) was obtained instead of the desired alkenylation product (**3q**). This result showed the possibility for C-I bond formation in this iodide catalysed system. As expected, **3q** turned to be the only product when the reaction was heated up to 110 °C, which indicated that HI elimination might be the key to alkenylation (Scheme 2).[17]



0.33 mmol	0.30 mmol	Temperature	Yield of 3q	Yield of 5
		30 °C	trace	38%
		110 °C	44%	trace

Scheme 2. Effect of temperature on the reactivity for aliphatic olefin towards alkenylation.

For understanding the role of iodine, we first outlined a radical involved reaction pathway for this alkenylation process (Scheme 3). Initially, iodide is oxidized by TBHP under acidic condition to generate iodine and *tert*-butoxyl radical.[6b, 6d] Subsequently, *tert*-butoxyl radical abstracts hydrogen atom from sulfonyl hydrazide 1, which initiates the generation of sulfonyl radicals (**I-1**) with the release of molecular nitrogen.[16b, 16h] Afterwards, the radical addition of I-1 to olefin **2** generates carbon radical **I-2**.[14g, 16a, 16g] The key step for alkenylation is that radical **I-2** reacts with in-situ generated iodine to generate β-iodosulfone **I-3**.[18] At last, HI elimination from **I-3** affords the final alkenylation product [3.15]



Scheme 3. Proposed mechanism.

Since iodine was believed to be the key for alkenylation, experiments were done to confirm the role of iodine in the reaction system. Firstly, we attempted to use in situ IR to monitor the reaction between **1a** and **2a**. The profile of relative absorbance (ConcIRT) versus time for individual species is shown in Figure 1. Before the addition of KI, signals of the starting materials kept steady except for changes from dilustration when one material was added. This phenomenon indicates that it is hard for sulfunyl hydrazide to undergo dehydrogenation spontaneously under mild temperature. When KI was added into the reaction, the absorbance of **1a** and **2b** immediately decreased immediately. At the same time, the reaction color turned to purple rapidly, which might suggest the formation of I_2. Furthermore, cyclic voltammetry (CV) experiments were carried out to study the redox potential of sulfonyl hydrazide. In the presence of toluenesulfonohydrazide (**1a**) in DMSO, no obvious oxidation peak was observed below 1.0 V [Figure 2, (c)]. It means that direct one-electron oxidation of sulfonyl hydrazide is not that easy at room temperature. These results were consistent with our assumption that the iodide oxidation was the key for initiating the sulfonyl radical from sulfonyl hydrazide under mild temperature.

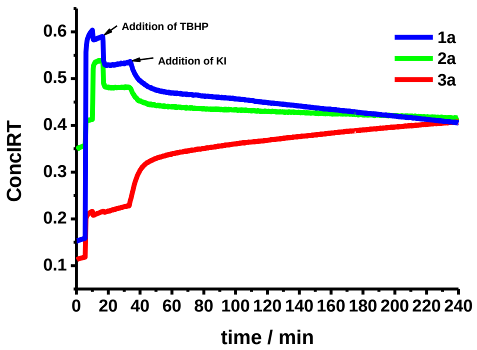


Figure 1. 2D kinetic profile of the reaction of **1a** (3.3 mmol), **2a** (3.0 mmol), TBHP (6.0 mmol) and KI (1.2 mmol) added to DMSO (2.0 mL) and (2.0 mL) at 30 °C in succession; the reaction was monitored by in situ IR spectroscopy.

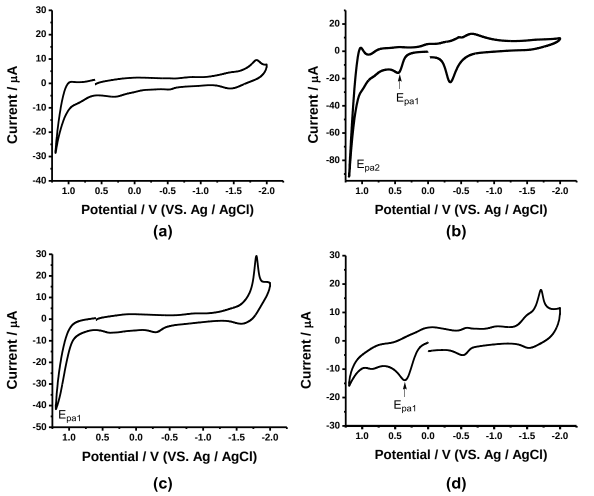
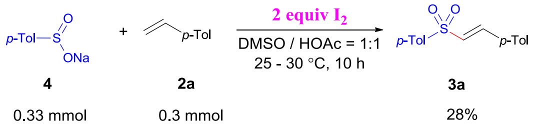


Figure 2. Cyclic voltammetry in DMSO with nBu_4NBF_4 (0.1 M) under N_2 at room temperature. The scan rate is v=0.5 V/s at a steady gold disk electrode. (a) none; (b) nBu_4NI; (c) toluenesulfonohydrazide; (d) sodium *p*-tolylsulfinate

Since I_2 was proposed to be generated in the reaction, experiments were done to confirm the role of I_2 in the reaction system. I_2 was used directly as the oxidant in the absence of peroxides. Little product was observed for the oxidative alkenylation of *p*-methyl styrene (**2a**) with *p*-toluenesulfonohydrazide (**1a**) (eqn. (3)). This result might be explained by the assumption that sulfonyl radical from sulfonyl hydrazide needed to be initiated by *tert*-butoxyl radical according to the proposed mechanism. On the other hand, the alkenylation did proceed in the case of sodium *p*-toluenesulfonate (**4**) with a 28% yield (eqn. (4)). CV experiments were also carried out for **4** and iodide. In the presence of sodium *p*-tolylsulfinate (**4**) in DMSO, an obvious oxidative peak was detected at 0.40 V [Figure 2, (d), Epa1]. At the same time, the oxidative peak of I^- was also observed at 0.43 V [Figure 2, (b), Epa2], suggesting single-electron-transfer could happen between I_2 and sodium *p*-tolylsulfinate to generate sulfonyl radical. Since the alkenyaltion of sodium sulfionate could be realized just in the presence of I_2, we could see that I_2 served as a reactive intermediate for the radical elimination of carbon radical to generate alkenyl sulfone.

(3)



(4)

Conclusions

We have demonstrated that iodine behave as a metal in the alkenyl functionality recovery of carbon radicals. This system provides both a mild and easy-to-handle method for the synthesis of biologically useful alkenyl sulfones.[19] During the reaction, iodide was oxidized under acidic condition, which is crucial for initiating the dehydrogenation of sulfonyl hydrazides to generate sulfonyl radical. Subsequently, catalytic HI elimination similar to the β-hydride elimination of transition metals was realized for the alkenylation for sulfonyl radical from various sulfonyl hydrazides. Importantly, this work provides an example for applying iodine as a promising alternative catalyst for transition metals in cross coupling reactions. Detailed mechanistic investigations as well as employing the HI elimination protocol to achieve alkenylation for other radicals are underway in our laboratory and will be reported in due course.

Acknowledgement

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Notes and references

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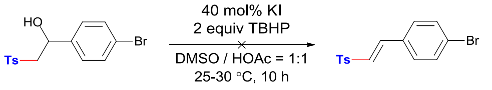
† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1. (a) E.-i. Negishi, *Angew. Chem. Int. Ed.*, 2011, **50**, 6738-6764; (b) A. d. Meijere and F. Diederich, *Metal-catalyzed cross-coupling reactions*, 2nd, completely rev. and enl. edn., Wiley-VCH, Weinheim, 2004.
2. (a) D. Astruc, *Electron transfer and radical processes in transition-metal chemistry*, VCH, New York, N.Y., 1995; (b) G. Milazzo, S. Caroli, V. K. Sharma and International Union of Pure and Applied Chemistry. Electrochemistry Commission., *Tables of standard electrode potentials*, Wiley, New York, 1978.
3. F. C. Küpper, M. C. Feiters, B. Olofsson, T. Kaiho, S. Yanagida, M. B. Zimmermann, L. J. Carpenter, G. W. Luther, Z. Lu, M. Jonsson and L. Kloo, *Angew. Chem. Int. Ed.*, 2011, **50**, 11598-11620.
4. (a) R. D. Richardson and T. Wirth, *Angew. Chem. Int. Ed.*, 2006, **45**, 4402-4404; (b) T. Dohi and Y. Kita, *Chem. Commun.*, 2009, 2073-2085.
5. P. Finkbeiner and B. J. Nachtsheim, *Synthesis*, 2013, **45**, 979-999.
6. (a) M. Uyanik, D. Suzuki, T. Yasui and K. Ishihara, *Angew. Chem. Int. Ed.*, 2011, **50**, 5331-5334; (b) L. Chen, E. Shi, Z. Liu, S. Chen, W. Wei, H. Li, K. Xu and X. Wan, *Chem. Eur. J.*, 2011, **17**, 4085-4089; (c) J. Feng, S. Liang, S.-Y. Chen, J. Zhang, S.-S. Fu and X.-Q. Yu, *Adv. Synth. Catal.*, 2012, **354**, 1287-1292; (d) E. Shi, Y. Shao, S. Chen, H. Hu, Z. Liu, J. Zhang and X. Wan, *Org. Lett.*, 2012, **14**, 3384-3387; (e) G. Majji, S. Guin, A. Gogoi, S. K. Rout and B. K. Patel, *Chem. Commun.*, 2013, **49**, 3031-3033; (f) M. Uyanik, H. Okamoto, T. Yasui and K. Ishihara, *Science*, 2010, **328**, 1376-1379.
7. (a) Z.-Q. Lao, W.-H. Zhong, Q.-H. Lou, Z.-J. Li and X.-B. Meng, *Org. Biomol. Chem.*, 2012, **10**, 7869-7871; (b) Y. Yan, Y. Zhang, C. Feng, Z. Zha and Z. Wang, *Angew. Chem. Int. Ed.*, 2012, **51**, 8077-8081; (c) Q. Xue, J. Xie, H. Li, Y. Cheng and C. Zhu, *Chem. Commun.*, 2013, **49**, 3700-3702.
8. (a) T. Nobuta, N. Tada, A. Fujiya, A. Kariya, T. Miura and A. Itoh, *Org. Lett.*, 2013, **15**, 574-577; (b) T. Nobuta, A. Fujiya, T. Yamaguchi, N. Tada, T. Miura and A. Itoh, *RSC Advances*, 2013, **3**, 10189-10192.
9. Z. He, W. Liu and Z. Li, *Chem. Asian. J*, 2011, **6**, 1340-1343.

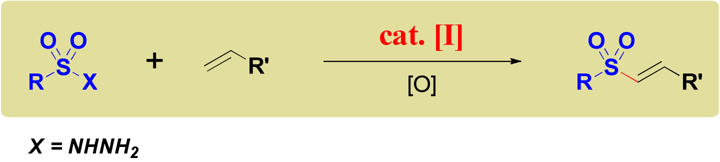
10. T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner and B. J. Nachtsheim, *Org. Lett.*, 2011, **13**, 3754-3757.
11. (a) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780-1824; (b) C. Liu, L. Jin and A. Lei, *Synlett*, 2010, 2527-2536.
12. (a) M. Oestreich, *The Mizoroki-Heck reaction*, Wiley, Hoboken, N.J., 2009; (b) X. L. L. Jin, A. Lei, *Acta Chim. Sinica*, 2012, **70**, 1538-1542.
13. (a) Y. Ikeda, T. Nakamura, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2002, **124**, 6514-6515; (b) W. Affo, H. Ohmiya, T. Fujioka, Y. Ikeda, T. Nakamura, H. Yorimitsu, K. Oshima, Y. Imamura, T. Mizuta and K. Miyoshi, *J. Am. Chem. Soc.*, 2006, **128**, 8068-8077; (c) K. S. Bloome, R. L. McMahen and E. J. Alexanian, *J. Am. Chem. Soc.*, 2011, **133**, 20146-20148; (d) N. Taniguchi, *Synlett*, 2011, 1308-1312; (e) N. Iqbal, S. Choi, E. Kim and E. J. Cho, *J. Org. Chem.*, 2012, **77**, 11383-11387; (f) C. Liu, S. Tang, D. Liu, J. Yuan, L. Zheng, L. Meng and A. Lei, *Angew. Chem. Int. Ed.*, 2012, **51**, 3638-3641; (g) J. Wang, C. Liu, J. Yuan and A. Lei, *Angew. Chem. Int. Ed.*, 2013, **52**, 2256-2259; (h) T. Naveen, S. Maity, U. Sharma and D. Maiti, *J. Org. Chem.*, 2013, **78**, 5949-5954; (i) S. Maity, S. Manna, S. Rana, T. Naveen, A. Mallick and D. Maiti, *J. Am. Chem. Soc.*, 2013, **135**, 3355-3358; (j) Q. Liu, H. Yi, J. Liu, Y. Yang, X. Zhang, Z. Zeng and A. Lei, *Chem. Eur. J.*, 2013, **19**, 5120-5126; (k) S. Tang, C. Liu and A. Lei, *Chem. Commun.*, 2013, **49**, 2442-2444.
14. (a) H. Togo, *Advanced free radical reactions for organic synthesis*, 1st edn., Elsevier, Amsterdam Boston, 2004; (b) K. Cheng, L. Huang and Y. Zhang, *Org. Lett.*, 2009, **11**, 2908-2911; (c) W. Wei and J.-X. Ji, *Angew. Chem. Int. Ed.*, 2011, **50**, 9097-9099; (d) W. Liu, Y. Li, K. Liu and Z. Li, *J. Am. Chem. Soc.*, 2011, **133**, 10756-10759; (e) Y. Li and A. Studer, *Angew. Chem. Int. Ed.*, 2012, **51**, 8221-8224; (f) M. Hartmann, Y. Li and A. Studer, *J. Am. Chem. Soc.*, 2012, **134**, 16516-16519; (g) Q. Lu, J. Zhang, F. Wei, Y. Qi, H. Wang, Z. Liu and A. Lei, *Angew. Chem. Int. Ed.*, 2013, **52**, 7156-7159; (h) Y. Su, X. Sun, G. Wu and N. Jiao, *Angew. Chem Int. Ed.*, 2013, **52**, 9808-9812; (i) A. Deb, S. Manna, A. Modak, T. Patra, S. Maity and D. Maiti, *Angew. Chem. Int. Ed.*, 2013, **52**, 9747-9750; (j) B. Zhang and A. Studer, *Org. Lett.*, 2013, **15**, 4548-4551; (k) C. Zhang, Z. Li, L. Zhu, L. Yu, Z. Wang and C. Li, *J. Am. Chem. Soc.*, 2013, **135**, 14082-14085; (l) J. D. Nguyen, J. W. Tucker, M. D. Konieczynska and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2011, **133**, 4160-4163; (m) C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2012, **134**, 8875-8884; (n) Y. Yasu, T. Koike and M. Akita, *Angew. Chem. Int. Ed.*, 2012, **51**, 9567-9571.
15. P. Katrun, S. Chiampanichayakul, K. Korworapan, M. Pohmakotr, V. Reutrakul, T. Jaipetch and C. Kuhakarn, *Eur. J. Org. Chem.*, 2010, 5633-5641.
16. (a) T. Taniguchi, A. Idota and H. Ishibashi, *Org. Biomol. Chem.*, 2011, **9**, 3151-3153; (b) X. Li, X. Xu and C. Zhou, *Chem. Commun.*, 2012, **48**, 12240-12242; (c) F.-L. Yang, X.-T. Ma and S.-K. Tian, *Chem. Eur. J.*, 2012, **18**, 1582-1585; (d) R. Singh, D. S. Raghuvanshi and K. N. Singh, *Org. Lett.*, 2013, **15**, 4202-4205; (e) F.-L. Yang and S.-K. Tian, *Angew. Chem. Int. Ed.*, 2013, **52**, 4929-4932; (f) N. Singh, R. Singh, D. S. Raghuvanshi and K. N. Singh, *Org. Lett.*, 2013, **15**, 5874-5877; (g) W. Wei, C. Liu, D. Yang, J. Wen, J. You, Y. Suo and H. Wang, *Chem. Commun.*, 2013, **49**, 10239-10241; (h) X. Li, X. Xu, P. Hu, X. Xiao and C. Zhou, *J. Org. Chem.*, 2013, **78**, 7343-7348; (i) X. Li, X. Xu and Y. Tang, *Org. Biomol. Chem.*, 2013, **11**, 1739-1742.
17. During our investigation, we also noticed that β-hydroxysulfones could be generated for some electron-neutral styrenes (**3i-k**) at slightly lower temperature of 20 ºC. We wonder whether the alkenylation products were generated through the direct elimination of hydroxy group. So we prepared 1-(4-bromophenyl)-2-tosylethanol (**6**) and applied it as a substrate under the standard condition directly. However, no reaction could be observed, suggesting β-hydroxysulfones was not the intermediate for generating the alkenylation product [Eq. (5)].



(5)

6 **3e**

18. (a) K. Inomata, S.-i. Sasaoka, T. Kobayashi, Y. Tanaka, S. Igarashi, T. Ohtani, H. Kinoshita and H. Kotake, *B. Chem. Soc. Jpn.*, 1987, **60**, 1767-1779; (b) C. M. M. da Silva Correa, M. D. C. M. Fleming, M. A. B. C. S. Oliveira and E. M. J. Garrido, *J. Chem. Soc. Perkin Trans. 2*, 1994, 1993-2000.
19. (a) J. T. Palmer, D. Rasnick, J. L. Klaus and D. Bromme, *J. Med. Chem.*, 1995, **38**, 3193-3196; (b) R. Ettari, E. Nizi, M. E. Di Francesco, M.-A. Dude, G. Pradel, R. Vičík, T. Schirmeister, N. Micale, S. Grasso and M. Zappalà, *J. Med. Chem.*, 2008, **51**, 988-996.



Catalytic HI elimination similar to the β-hydride elimination of transition metals was realized for the radical alkenylation of sulfonyl hydrozides.