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SO₂F₂ mediated cascade dehydrogenative Morita–Baylis–Hillman reaction of the C(sp³)–H of primary alcohols with the C(sp²)–H of electron-deficient olefins for the assembly of allylic alcohols†

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A cascade dehydrogenative Morita–Baylis–Hillman reaction of the C(sp³)–H of primary alcohols with the C(sp²)–H of electron-deficient olefins for forming allylic alcohols mediated by SO₂F₂ was developed. This method provides a mild process for the preparation of allylic alcohol moieties without the requirement of transition metals.

Allylic alcohols are valuable scaffolds that are used in the construction of multifunctional building blocks and complex natural products.¹ The versatility of these molecules has been demonstrated in the preparation of a series of biologically active compounds.² A representative protocol for the synthesis of allylic alcohols is the well-known Morita–Baylis–Hillman reaction, one of the most widely applied methods for C–C bond formation.³

In fact, C–C bond formation is among the most significant processes in chemistry and plays a central role in the construction of new organic molecules,⁴ in which transition metal catalysed C–C bond formation has particularly attracted great interest in recent years.⁵ For instance, a reaction for the direct formation of C–C bonds using two different unfunctionalized C–H bond partners was reported (Scheme 1a).⁶ Despite the great advantages of these dehydrogenative reactions for the formation of C–C bonds⁷ there are still certain limitations, such as that precious metal catalysts are still required (metal catalysts are sometimes undesirable).⁸ To overcome the limitations, we developed a new protocol for the formation of allylic alcohol motifs using abundant and inexpensive reagents.

Alcohols, as a class of cheap and abundant industrial chemicals, have great advantages in green chemistry and organic synthesis.⁹ Sulfuryl fluoride (SO₂F₂), is also another inexpensive (about \$1 per kg) and abundant chemical, which has attracted significant attention for chemical transformation.¹⁰ As part of our continuous efforts on the use of SO₂F₂ in exploring new synthetic methods to access important chemicals,^{10c–l} herein, we report

a one-pot process for the construction of valuable allylic alcohols through a dehydrogenative Morita–Baylis–Hillman reaction of the C(sp³)–H of primary alcohols with the C(sp²)–H of electron-deficient olefins (Scheme 1b).

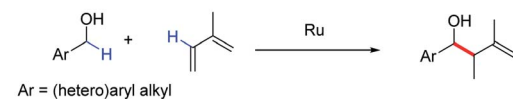
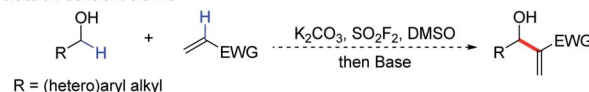
Initially, we examined the feasibility of this transformation using (4-nitrophenyl)methanol **1a** as a model substrate to react with methyl methacrylate **2a** to generate the corresponding allylic alcohol **3a**. It has been widely established that tertiary amines such as trimethylamine (Me₃N), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) are effective for the Baylis–Hillman reaction,¹¹ which inspired us to carry out our preliminary experiments using these bases. The use of Me₃N and DBU provided the desired product **3a** in only 5% and 41% yields, respectively (Table 1, entries 1 and 2). Excitingly, when 3.0 equivalents of DABCO was used, the yield of product **3a** increased to 74% (Table 1, entry 3), indicating that DABCO is a suitable base for the desired transformation. In order to maximize the yield of allylic alcohol, the temperature was elevated to 40 °C and an obvious increase in the yield was achieved (Table 1, entry 4, 83% yield). Further elevating the temperature to 50 °C resulted in a slightly lower yield of **3a** (Table 1, entry 5). The loading of DABCO was subsequently examined (Table 1, entry 6 and 7), which revealed that a 3.0-fold excess was an appropriate amount. Decreasing the amount of methyl acrylate **2a** to 1.0 equivalent resulted in a significant decrease in the formation of **3a** (Table 1, 52% vs. 83%; entry 8 vs. entry 4). When 5.0 equivalents of methyl acrylate **2a** was used, the yield of product **3a** was not obviously increased compared with the use of 3.0 equivalents of acrylate **2a** (Table 1, 84% vs. 83%; entry 9 vs. entry 4). Therefore, the parameters in entry 4 of Table 1 were selected as the standard conditions for further substrate scope examination.

We subsequently investigated the substrate scope of benzyl alcohols **1** under the optimized conditions, and the results are summarized in Table 2. Not surprisingly, a variety of substituted

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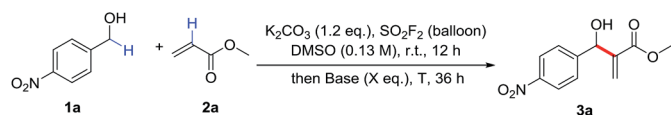
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(a) dehydrogenative C-C bond formation of C(sp³)-H of alcohols and C(sp²)-H of acyclic dienes(b) Proposed dehydrogenative Morita-Baylis-Hillman reaction of C(sp³)-H of alcohols with C(sp²)-H of electron-deficient olefins

Scheme 1 Dehydrogenative reactions for the formation of C-C bonds.

benzyl alcohols **1** smoothly reacted with methyl acrylate **2a** to provide their corresponding allylic alcohols (**3a–3n**) in moderate to excellent yields. Both electron-withdrawing (**1a–1j**) and electron-donating (**1l** and **1m**) groups on the aryl rings were all well tolerated under the standard reaction conditions, even though the reactivity of electron-deficient substrates was somewhat superior to those of electron-rich ones. Notably, the positions of substituents on the aryl rings did seem to have much influence on the efficiency. Sterically hindered *ortho*-position substituted benzylic alcohols were used to furnish the desired products in slightly lower yields than the *para*-position functionalized substrates (e.g. **3a** vs. **3b**). It was noteworthy to find that a broad range of heterocyclic benzylic alcohols bearing sulfur or nitrogen atoms on the aryl rings (**1o–1u**) were smoothly converted to their corresponding allylic alcohols in moderate yields. Remarkably, this method is compatible with various electron-deficient terminal alkenes (**2v**, **2w** and **2x**) for the formation of their corresponding allylic alcohol products (**3v**, **3w** and **3x**).

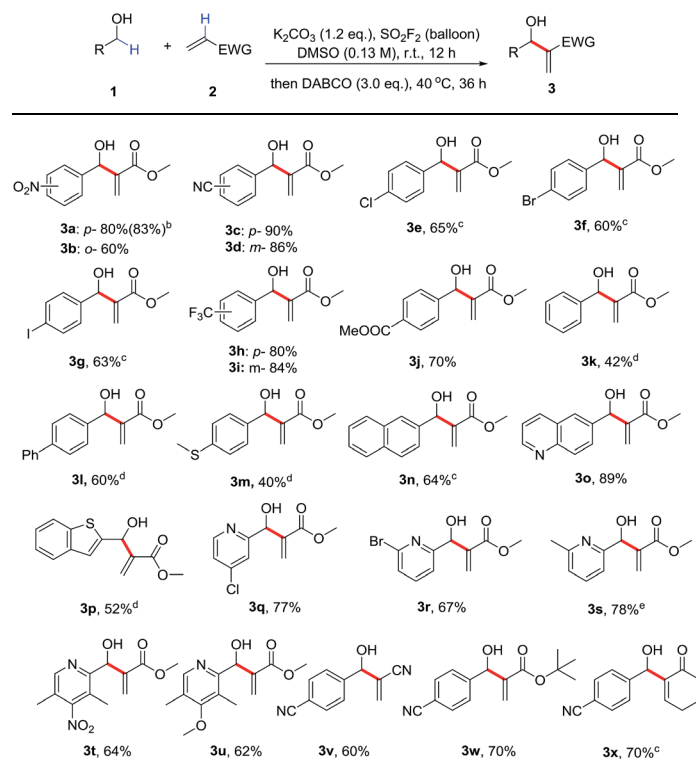
Table 1 Optimization of the reaction conditions^a

Entry	Base (X eq.)	2a (Y eq.)	Temperature (°C)	Yield ^b (3a, %)
1	Me ₃ N (3.0)	3.0	rt	5
2	DBU (3.0)	3.0	rt	41
3	DABCO (3.0)	3.0	rt	74
4	DABCO (3.0)	3.0	40	83
5	DABCO (3.0)	3.0	50	77
6	DABCO (1.0)	3.0	40	42
7	DABCO (5.0)	3.0	40	85
8	DABCO (3.0)	1.0	40	52
9	DABCO (3.0)	5.0	40	84

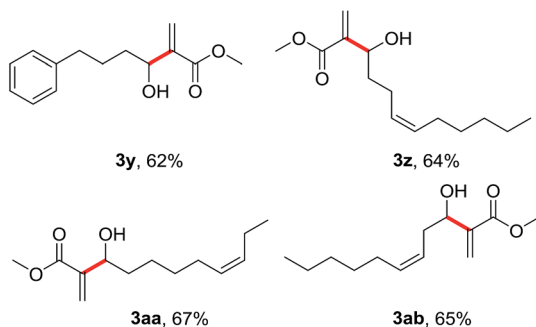
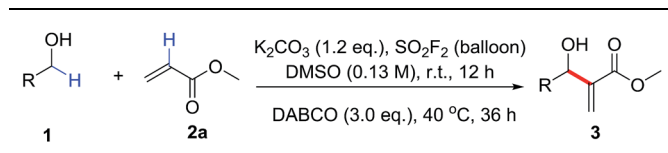
^a General reaction conditions: a mixture of (4-nitrophenyl)methanol (**1a**, 0.2 mmol), K₂CO₃ (0.24 mmol, 1.2 eq.) and DMSO (1.5 mL, 0.13 M) under an atmosphere of SO₂F₂ (balloon) was stirred at room temperature for 12 h before base (X eq.) and methyl acrylate **2a** (Y eq.) were added. The resulting mixture was stirred at the corresponding temperature for an additional 36 h. ^b HPLC yields using the pure methyl 2-(hydroxy(4-nitrophenyl)methyl)acrylate (**3a**, 0.2 mmol) as the external standard (*t*_R = 3.021 min, λ_{max} = 272.5 nm, MeOH/H₂O = 70 : 30 (v/v)).

To further demonstrate the generality and substrate scopes of the process, we also examined some long-chain aliphatic alcohols under the standard conditions for the coupling with methyl acrylate **2a** (Table 3). Not surprisingly, these aliphatic alcohols (**1y–1ab**) were also smoothly converted to their corresponding allylic alcohols (**3y–3ab**) in moderate yields.

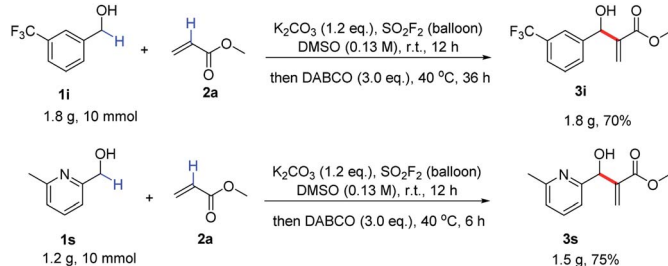
In order to demonstrate the practicality of the process, a couple of gram-scale reactions were performed under the standard conditions (Scheme 2). Despite a slight decline in the yield, **1i** was successfully converted to its corresponding allylic alcohol **3i** in 70% yield. Pyridine-containing benzylic alcohol **1s**

Table 2 Substrate scope examination of the dehydrogenative Morita-Baylis-Hillman reaction^a

^a General reaction conditions: benzyl alcohols (**1**, 1.0 mmol), K₂CO₃ (1.2 mmol, 1.2 eq.), DMSO (7.5 mL, 0.13 M), SO₂F₂ (balloon), rt, 12 h. Then DABCO (3.0 mmol, 3.0 eq.) and methyl acrylate **2a** (3.0 mmol, 3.0 eq.), 40 °C, 36 h. Isolated yield. ^b HPLC yield. ^c 40 °C, 72 h. ^d 40 °C, 5 days. ^e 40 °C, 6 h.

Table 3 Dehydrogenative Morita–Baylis–Hillman reaction of long-chain aliphatic alcohols with methyl acrylate **2a**^a

^a General reaction conditions: long-chain aliphatic alcohols (**1**, 1.0 mmol), K₂CO₃ (1.2 mmol, 1.2 eq.), DMSO (7.5 mL, 0.13 M), SO₂F₂ balloon, rt, 12 h. Then DABCO (3.0 mmol, 3.0 eq.) and methyl acrylate **2a** (3.0 mmol, 3.0 eq.), 40 °C, 36 h. Isolated yield.

**Scheme 2** Gram-scale reactions.

was also smoothly transformed into the corresponding allylic alcohol **3s** in 75% yield without any deterioration in efficiency.

In conclusion, we have developed a cascade dehydrogenative Morita–Baylis–Hillman reaction of the C(sp³)-H of primary alcohols with the C(sp²)-H of electron-deficient olefins to form allylic alcohols mediated by SO₂F₂. This new protocol has the features of a wide scope and great functional group compatibility. Using this method, inexpensive, easily accessible, and abundant alcohols can be directly transformed to highly valuable allylic alcohols under mild conditions without the use of precious transition metals.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- For the application in total synthesis, see: (a) A. Patra, S. Batra, A. P. Bhaduri, A. Khanna, R. Chander and M. Dikshit, *Bioorg. Med. Chem.*, 2003, **11**, 2269; (b) M. J. Lee, K. Y. Lee, J. Y. Lee and J. N. Kim, *Org. Lett.*, 2004, **6**, 3313; (c) L. R. Reddy, P. Saravanam and E. J. Corey, *J. Am. Chem. Soc.*, 2004, **126**, 6230; (d) A. Ho, K. Cyrus and K.-B. Kim, *Eur. J. Org. Chem.*, 2005, **22**, 4829; (e) L. J. Reddy, L. F. Fournier, B. V. S. Reddy and E. J. Corey, *Org. Lett.*, 2005, **7**, 2699; (f) X. Lei and J. A. Porco, *J. Am. Chem. Soc.*, 2006, **128**, 14790; (g) V. Singh and S. Batra, *Tetrahedron*, 2008, **64**, 4511; (h) X.-Y. Guan, Y. Wei and M. Shi, *Chem.-Eur. J.*, 2010, **16**, 13617; (i) H.-P. Deng, Y. Wei and M. Shi, *Adv. Synth. Catal.*, 2012, **354**, 783; (j) F. Le Hu, Y. Wei and M. Shi, *Chem. Commun.*, 2014, **50**, 8912.
- (a) L. K. Kohn, C. H. Pavam, D. Veronese, F. Coelho, J. E. de Carvalho and W. P. Almeida, *Eur. J. Med. Chem.*, 2006, **41**, 738; (b) C. R. Yu, L. H. Xu, S. Tu, Z. N. Li and B. Li, *J. Fluorine Chem.*, 2006, **127**, 1540; (c) R. O. M. A. de Souza, V. L. P. Pereira, M. F. Muzitano, C. A. B. Falcao, B. Rossi-Bergmann, E. B. A. Filho and M. L. A. A. Vasconcellos, *Eur. J. Med. Chem.*, 2007, **42**, 99.
- (a) D. Basavaiah, J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811; (b) G.-N. Ma, J.-J. Jiang, M. Shi and Y. Wei, *Chem. Commun.*, 2009, 5496.
- (a) Z. Li and C.-J. Li, *Org. Lett.*, 2004, **6**, 4997; (b) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 11810; (c) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 3672; (d) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 6968; (e) Y. Zhang and C.-J. Li, *J. Am. Chem. Soc.*, 2006, **128**, 4242; (f) Z. Li, L. Cao and C.-J. Li, *Angew. Chem., Int. Ed.*, 2007, **46**, 6505; (g) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74.
- (a) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731; (b) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (c) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (d) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (e) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900.
- (a) J. F. Bower, I. S. Kim, R. L. Patman and M. J. Krische, *Angew. Chem., Int. Ed.*, 2009, **48**, 34; (b) J. R. Zbieg, J. Moran and M. J. Krische, *J. Am. Chem. Soc.*, 2011, **133**, 10582; (c) E. L. McInturff, E. Yamaguchi and M. J. Krische, *J. Am. Chem. Soc.*, 2012, **134**, 20628; (d) J. R. Zbieg, E. Yamaguchi, E. L. McInturff and M. J. Krische, *Science*, 2012, **336**, 324.
- (a) C.-H. Jun, *Chem. Soc. Rev.*, 2004, **3**, 610; (b) S. R. Dubbaka and P. Vogel, *Angew. Chem., Int. Ed.*, 2005, **44**, 7674; (c) F. Chen, T. Wang and N. Jiao, *Chem. Rev.*, 2014, **114**, 8613.



- 8 (a) C. J. Scheuermann, *Chem.-Asian J.*, 2010, **5**, 436; (b) X. Han, Y. Zhang and J. Wu, *J. Am. Chem. Soc.*, 2010, **132**, 4104.
- 9 (a) The Merck Index, *An Encyclopedia of Chemicals, Drugs, and Biologicals*, Merck, Rahway, NJ, 11th edn, 1989, p. 1138, ISBN 091191028X; (b) A. Rahimi, A. Azarpira, H. Kim, J. Ralph and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 6415; (c) T. P. Vispute, H. Zhang, A. Sanna, R. Xiao and G. W. Huber, *Science*, 2010, **330**, 1222; (d) K. Barta and P. C. Ford, *Acc. Chem. Res.*, 2014, **47**, 1503; (e) C. O. Tuck, E. Perez, I. T. Horvath, R. A. Sheldon and M. Poliakoff, *Science*, 2012, **337**, 695.
- 10 Sulfuryl fluoride (**2**) has been produced annually at more than 3 million kilograms per year since 2000, with a price as low as \$1 per kg. See: (a) M. P. Sulbaek Andersen, D. R. Blake, F. S. Rowland, M. D. Hurley and T. J. Wallington, *Environ. Sci. Technol.*, 2009, **43**, 1067; for reviews of SO₂F₂ utilization, see: (b) L. Revathi, L. Ravindar, J. Leng, K. P. Rakesh and H.-L. Qin, *Asian J. Org. Chem.*, 2018, **7**, 662. For some selected examples of using **2** in chemical transformations, see: (c) P. S. Hanley, T. P. Clark, A. L. Krasovskiy, M. S. Ober, J. P. O'Brien and T. S. Staton, *ACS Catal.*, 2016, **6**, 3515; (d) X.-Y. Wang, J. Leng, S.-M. Wang, A. M. Asiri, H. M. Marwani and H.-L. Qin, *Tetrahedron Lett.*, 2017, **58**, 2340; (e) W.-Y. Fang, Y.-M. Huang, J. Leng and H.-L. Qin, *Asian J. Org. Chem.*, 2018, **7**, 751; (f) G.-F. Zha, W.-Y. Fang, Y.-G. Li, J. Leng, X. Chen and H.-L. Qin, *J. Am. Chem. Soc.*, 2018, **140**, 17666; (g) G.-F. Zha, W.-Y. Fang, J. Leng and H.-L. Qin, *Adv. Synth. Catal.*, 2019, **361**, 2262; (h) W.-Y. Fang and H.-L. Qin, *J. Org. Chem.*, 2019, **84**, 5803; (i) S.-M. Wang, C. Zhao, X. Zhang and H.-L. Qin, *Org. Biomol. Chem.*, 2019, **17**, 4087; (j) Y. Jiang, B. Sun, W.-Y. Fang and H.-L. Qin, *Eur. J. Org. Chem.*, 2019, 3190; (k) J. Leng and H.-L. Qin, *Org. Biomol. Chem.*, 2019, **17**, 5001; (l) W.-Y. Fang, G.-F. Zha, C. Zhao and H.-L. Qin, *Chem. Commun.*, 2019, **55**, 6273.
- 11 (a) V. K. Aggarwal and A. Mereu, *Chem. Commun.*, 1999, 2311; (b) P. Caumul and H. C. Hailes, *Tetrahedron Lett.*, 2005, **46**, 8125; (c) D. Basavaiah, B. S. Reddy and S. S. Badsara, *Chem. Rev.*, 2010, **110**, 5447.

