Organic LETTERS

Letter

pubs.acs.org/OrgLett

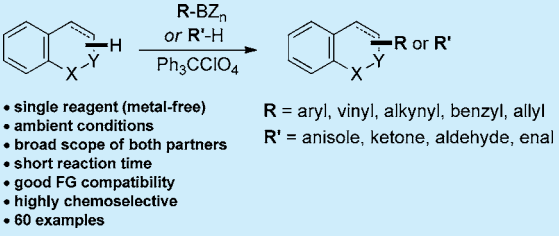
Structurally Diverse α-Substituted Benzopyran Synthesis through a Practical Metal-Free C(sp^3)−H Functionalization

Wenfang Chen,‡ Zhiyu Xie,‡ Hongbo Zheng,‡ Hongxiang Lou,* and Lei Liu*

Key Laboratory of Chemical Biology of Ministry of Education, School of Pharmaceutical Sciences, Shandong University, Jinan 250012, PR China

Supporting Information

ABSTRACT: A trityl ion-mediated practical C−H functionalization of a variety of benzopyrans with a wide range of nucleophiles (organoboranes and C−H molecules) at ambient temperature has been disclosed. The metal-free reaction has an excellent functional group tolerance and high chemoselectivity and displays a broad scope with respect to both benzopyran and nucleophile partners, efficiently affording a collection of benzopyrans bearing diverse skeletons and α-functionalities in one step.



Benzopyrans are one of the most common structural motifs spread across biologically active natural products and synthetic pharmaceuticals.[1] For example, benzopyrans comprising (iso)chromans and (iso)chromenes bearing diverse α-functionalities (aryl, vinyl, and alkyl) have been extensively used as antioxidants (e.g., vitamin E) and pharmaceuticals possessing antipsychotic, antibacterial, antifungal, antiviral, and anticancer activities (Figure 1).[1] Besides that, α-functionalized benzopyrans have also found a wide range of applications in other high-tech applications like photochromic lenses and sensitizers in solar cells.[2]

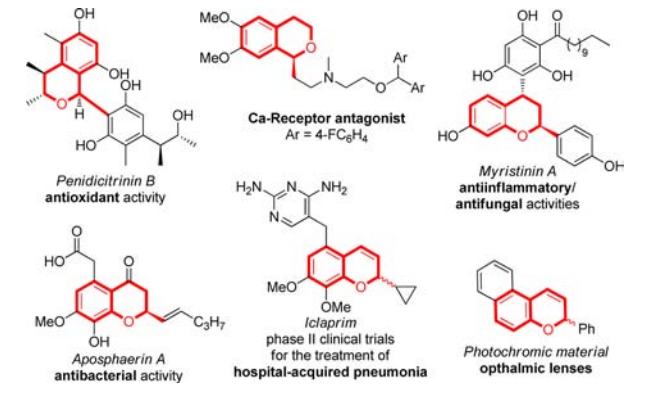


Figure 1. Representative α-substituted benzopyrans in human technology.

Inspired by the significance of these compounds in modern pharmacology, extensive efforts have been devoted to their synthesis. While the traditional strategies relying on reactive functional group transformations have found wide utility in chemical synthesis, the installation of the functionalities usually requires multiple and unproductive steps.[3] On the other hand, precise and direct C−H functionalization of ethers with carbon components presents an atom- and step-economic strategy without prior incorporation of activating groups.[4] Since Li's pioneering study in 2006, the synthesis of α-substituted benzopyran derivatives through direct sp^3 C−H functionalization has attracted considerable attention.[5,6] In the presence of suitable metals, oxidants including 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), organic peroxides, *N*-hydroxyphthalimide (NHPI), 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate ($T^+BF_4^-$), and $Na_2S_2O_8$ were reported to promote the cross-dehydrogenative coupling (CDC) of isochromans with several types of C−H nucleophiles including reactive carbonyl compounds, arylacetylene, and electron-rich aryl rings including indole and anisole. Despite great innovation, each method only focused on a single class of the nucleophile, and the scope with respect to benzopyran is largely restricted to xanthene and isochroman moieties. Moreover, known methods rely heavily on the employment of a metal additive, usually requiring high temperature, neat conditions, and long reaction time, all of which are generally disadvantageous for developing asymmetric variants. With respect to the synthetic utility, the specific structures of employed C−H nucleophiles restrict the integrated pattern of functionalities in the α-position of benzopyrans. Therefore, the majority of structures exhibited in Figure 1 could not be concisely achieved through these methods. Recently, Muramatsu and Li disclosed a one-pot oxidative coupling of isochroman with Grignard reagents, affording diverse α-substituted derivatives in high efficiency.[7] However, the employment of Grignard reagents might bring about unfavorable regioselectivity and functional group intolerance during the manipulation of highly functionalized substrates. Highly functionalized organometallic reagents might also not be readily accessible. Therefore, the development of a practical and mild metal-free method for direct C−H functionalization of a variety

Received: October 13, 2014
Published: November 11, 2014

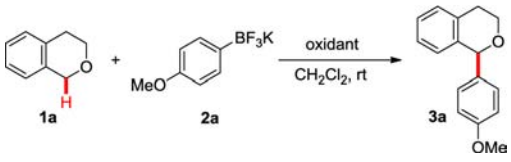
dx.doi.org/10.1021/ol503004a | Org. Lett. 2014, 16, 5988−5991

of benzopyrans with a wide range of carbon nucleophiles is highly desired.

We focused our attention on trityl ions as the oxidant for benzopyran oxidation for the following reasons: trityl ions are stable, nontoxic, easily handled, and readily prepared from trityl chloride and the corresponding acid (e.g., $HClO_4$ or HBF_4) in a single step.[8a] Moreover, trityl ions were reported to mediate benzyl ether cleavage and the C−H functionalization of 1,3-dioxolane.[8b−d] Very recently, we disclosed that the combination of Ph_3CCl and 1 equiv of $GaCl_3$ can promote C−H functionalization of a variety of ethers with potassium phenylethynyltrifluoroborate.[9] Although isochroman was a suitable substrate for the specific nucleophile, the oxidation system proved to be ineffective for alkylethynylboranes and other types of organoboranes, such as aryl-, vinyl-, benzyl-, and allylboranes, as well as typical C−H nucleophiles like reactive carbonyls and aryl rings.[10] While the origin of the limited scope was not clear, the different counterion effect of the trityl ion on the coupling efficiency observed in the previous study encouraged us to explore the suitable oxidation system for the C−H functionalization of benzopyrans with a wide range of nucleophiles.[8d]

Given the paramount importance of α-arylated benzopyrans, the arylation of isochroman **1a** with potassium (4-methoxyphenyl)trifluoroborate **2a** was initially selected as a model reaction for the optimization (Table 1). A variety of trityl

Table 1. Screen for the Oxidant[a]



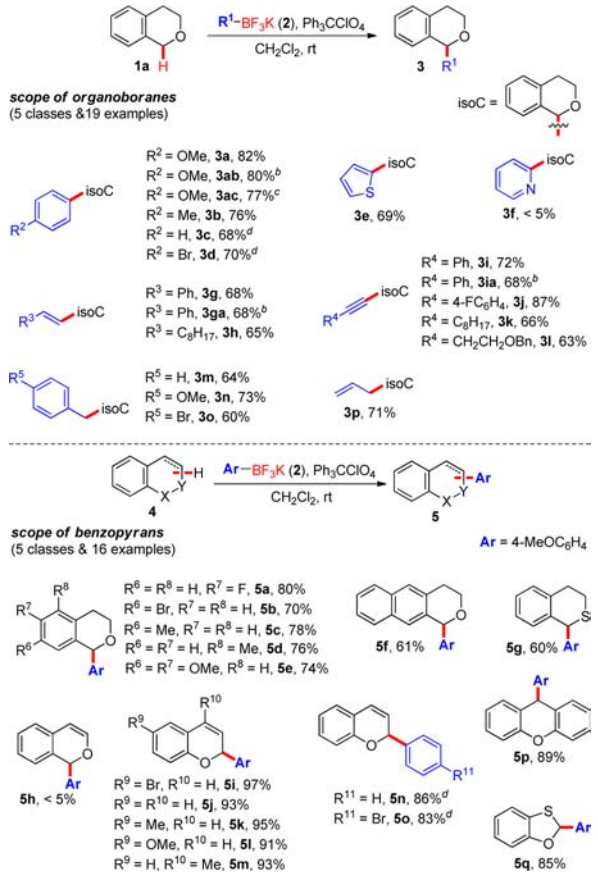
entry	trityl ion	time (h)	yield[b] (%)
1	$Ph_3CCl/GaCl_3$	2	10
2	Ph_3CSbCl_6	2	33
3	Ph_3COTf	2	49
4	Ph_3CPF_6	2	46
5	Ph_3CClO_4	2	82
6	Ph_3CBF_4	2	80
7	$C_7H_7BF_4$	24	0
8[c]	Oxidant	24	<5

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), and oxidant (0.2 mmol) in CH_2Cl_2 (2.0 mL) at rt. [b]Isolated yield. [c]Oxidants including DDQ, $PhI(OAc)_2$, $K_2S_2O_8$, CAN, MnO_2 and TBHP/$CuBr_2$. Tf = trifluoromethanesulfonyl.

salts bearing different counterions were examined, and reaction optimization experiments identified Ph_3CClO_4 in CH_2Cl_2 at room temperature in 2 h as ideal conditions (entries 1−6, Table 1). Other common oxidants including tropylium cation ($C_7H_7BF_4$), DDQ, $PhI(OAc)_2$, $Na_2S_2O_8$, CAN (cerium ammonium nitrate), MnO_2, and TBHP (*tert*-butyl hydroperoxide)/$CuBr_2$ failed to effect the coupling (entries 7 and 8 and Table S1 in the Supporting Information).

The reaction proved general for a broad range of organoboranes, allowing for efficient coupling with potassium aryl-, vinyl-, alkynyl-, benzyl-, and allyltrifluoroborates (Table 2). Boronic acids (**3ab**, **3ga**, and **3ia**) and boronate ester (**3ac**) are also competent components, providing results comparable to those of the potassium trifluoroborate (**3a**, **3g** and **3i**). The employment of organoboranes as nucleophiles is classically confined to π-rich aryl moieties or relies on transition metals or

Table 2. Coupling of Benzopyrans with Organoboranes[a]



[a]The reaction was carried out with **1a** or **4** (0.2 mmol), **2** (0.4 mmol), and Ph_3CClO_4 (0.2 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C or rt in 2 h. [b]Boronic acid as nucleophile. [c]Diethyl (*p*-methoxyphenyl)boronate as nucleophile. [d]Reaction at 40 °C.

Lewis acids.[11] As shown in Table 2, the metal-free reaction is efficient not only for the π-rich aryl (**3a,b**) and heteroaryl borates (**3e**) but also for π-neutral (**3c**) and π-deficient (**3d**) arylboranes, though electron-poor 2-pyridinyl borate (**3f**) failed to give the desired product. The C−H functionalization strategy does not require any additive and thus alleviates potential chemoselectivity problems that usually arise from the conventional Lewis acid initiated methods for electrophile formation through acetal collapse. Consequently, the functional group compatibility is excellent, with halogens (**3d**, **3j**, and **3o**), benzyl ether (**3l**), olefins (**3g**, **3h**, and **3p**), and alkynes (**3i−l**) well-tolerated for further manipulations.

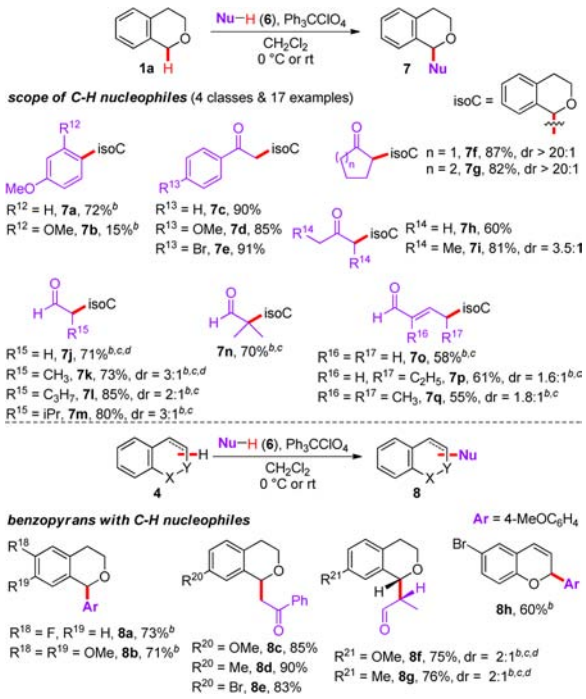
Next, we examined the scope of benzopyrans (Table 2). Structurally and electronically varied isochromans **4a−f** reacted smoothly with potassium aryltrifluoroborate **2a**. Electron-rich isochromans, which were expected to be much less reactive than isochroman **1a**, also afforded products in good yields (**5c−e**).[5b,7] Isothiochroman (**4g**) reacted well under the standard conditions. 1*H*-Isochromene (**4h**) was subjected to decomposition under the oxidation conditions, which could be ascribed to an incompatibility of the enol ether moiety toward the Lewis acidity of the trityl ion.[12] 2*H*-Chromenes also proved to be competent substrates, with electronically varied substrates **5i−m** well tolerated. The reaction is highly regioselective, delivering predominantly C_2-addition products, and no double functionalization was observed. High efficiency was also achieved when π-neutral (**2c**) and π-deficient (**2d**) arylboranes were applied (**5n**

dx.doi.org/10.1021/ol503004a | *Org. Lett.* 2014, 16, 5988−5991

and **5o**). In consideration of a variety of known protocols utilizing the unsaturation in 2*H*-chromene as a reactive handle for further functionalization, the direct access to α-substituted chromenes provides excellent opportunities to develop a structurally and stereochemically diverse library of chroman-like compounds through diversity-oriented synthesis.[13] Xanthene (**5p**) and benzoxathiole (**5q**) also worked well under the standard conditions.

The CDC of isochromans with C−H nucleophiles typically required the employment of metal additives under harsh conditions for reaction completion,[5] and each condition is only suitable for a single class of the nucleophile. The mild metal-free oxidation system encouraged us to explore the scope of CDC reactions by using the trityl ion as the sole agent (Table 3). The

Table 3. Scope of Trityl Ion-Mediated CDC Reactions[a]



[a]The reaction was carried out with **1a** or **4** (0.2 mmol), **6** (0.4 mmol), and Ph_3CClO_4 (0.2 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C or rt in 2 h. [b]**6** was added once the oxidation process was complete. [c]Na_2HPO_4 (0.4 mmol) was added. [d]1.0 mmol of aldehyde used.

arylation of **1a** with anisole proceeded smoothly at 0 °C in 2 h to deliver **7a** in a yield comparable to that reported by Todd through DDQ/$CuCl_2$-mediated coupling at 100 °C after 36 h.[5b] 3-Methoxyanisole, a challenging substrate for the DDQ system, afforded the desired **7b** in 15% yield.[5b] Trityl ion mediated mild conditions allowed a variety of ketones (**7c**−**i**) including volatile acetone (**7h**) to participate in the coupling efficiently. The aldehyde component was next studied. However, when propanal **6k** was subjected to the standard conditions, no desired **7k** was detected, with aldehyde self-condensation identified as the major pathway probably because of the Lewis acidity of the trityl ion.[12] After extensive investigation of a variety of basic additives, Na_2HPO_4 was finally found to be essential to suppress the undesired pathway, affording **7k** in 73% yield (see Table S2, Supporting Information). Under the optimized conditions, both linear aldehydes like acetaldehyde (**7j**) and pentanal (**7l**) and sterically hindered branched ones like **7m** and **7n** joined in the coupling efficiency.[14] Additionally, the modified condition adapted to α,β-unsaturated aldehydes, yielding predominantly γ-alkylated products in good efficiency (**7o**−**q**). Electronically varied isochromans and 2*H*-chromenes were competent substrates for CDC reactions with representative C−H nucleophiles like anisole, acetophenone, and propanal (**8a**−**h**).

The trityl ion mediated C−H oxidation is typically believed to undergo direct hydride abstraction or formal hydride transfer involving an initial single electron transfer (SET) (Figure 2).[15]

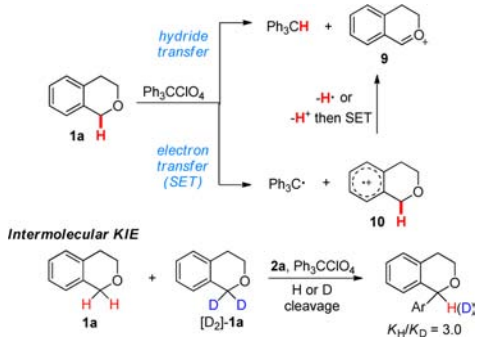


Figure 2. Mechanistic analysis for Ph_3CClO_4-mediated benzopyran oxidation.

The reaction efficiency was not influenced when the C−H oxidation was conducted prior to the addition of **2a**, suggesting that the organoborane might not participate in the oxidation process. Substrates displayed a kinetic isotope effect, indicating the C−H cleavage involved in the rate-determining step. Radical trapping experiments were performed, in which the coupling of **1a** with **2a** was not affected by 1 equiv of 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT). The observation suggested that a radical intermediate might not be involved in the reaction. While we cannot conclude which of the two possibilities might be viable at this time, we would like to reemphasize that DDQ-mediated C−H oxidation, typically involving a formal hydride transfer initiated by a SET,[16] could be dramatically suppressed in the similar radical trapping experiments.[5b,17]

In conclusion, a metal-free C−H functionalization of benzopyrans using a readily available trityl ion as the sole oxidizing agent has been developed. The reaction proceeds smoothly under ambient temperature with excellent chemoselectivity, and it exhibits a broad scope with respect to both benzopyran ((iso)chroman and chromene) and nucleophile (organoborane and C−H component) partners with high functional group tolerance. The integrated pattern of functionalities in the α-position of benzopyrans is broad, including aryl, vinyl, alkynyl, benzyl, allyl, and alkyl moieties, which have potential for further functional handles. We envision that this avenue will not only allow a facile and rapid access to series of multiple benzopyrans through "structural core diversification" strategy to discover biologically significant small molecules but also provide a valuable platform for further efforts toward inventing catalytic asymmetric C−H functionalization of benzopyrans.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/ol503004a | *Org. Lett.* 2014, 16, 5988−5991

AUTHOR INFORMATION

Corresponding Authors

*E-mail: louhongxiang@sdu.edu.cn.
*E-mail: leiliu@sdu.edu.cn.

Author Contributions

‡W.C., Z.X., and H.Z. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge the National Science Foundation of China (21202093, 21472112), the Program for New Century Excellent Talents in University (NCET-13-0346), Young Scientist Foundation Grant of Shandong Province (BS2013YY001), and the Fundamental Research Funds of Shandong University (2014JC005) for financial support. We are also grateful to the Program for Changjiang Scholars and Innovative Research Team in University (IRT13028).

REFERENCES

(1) (a) Lu, Z.; Lin, Z.; Wang, W.; Du, L.; Zhu, T.; Fang, Y.; Gu, Q.; Zhu, W. *J. Nat. Prod.* **2008**, *71*, 543. (b) TenBrink, R. E.; Bergh, C. L.; Duncan, J. N.; Harris, D. W.; Huff, R. M.; Lahti, R. A.; Lawson, C. F.; Lutzke, B. S.; Martin, I. J.; Rees, S. A.; Schlachter, S. K.; Sih, J. C.; Smith, M. W. *J. Med. Chem.* **1996**, *39*, 2435. (c) Clarke, R. L.; Harris, L. S. *J. Med. Chem.* **1962**, *5*, 77. (d) Albrecht, U.; Lalk, M.; Langer, P. *Bioorg. Med. Chem.* **2005**, *13*, 1531. (e) Sawadjoon, S.; Kittakoop, P.; Kirtikara, K.; Vichai, V.; Tanticharoen, M.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67*, 5470. (f) Bauer, D. J.; Selway, J. W. T.; Batchelor, J. F.; Tisdale, M.; Caldwell, I. C.; Young, D. A. B. *Nature* **1981**, *292*, 369. (g) Gauthier, S.; Caron, B.; Cloutier, J.; Dory, Y. L.; Favre, A.; Larouche, D.; Mailhot, J.; Ouellet, C.; Schwerdtfeger, A.; Leblanc, G.; Martel, C.; Simard, J.; Mérand, Y.; Bélanger, A.; Labrie, C.; Labrie, F. *J. Med. Chem.* **1997**, *40*, 2117.

(2) (a) Pina, F.; Melo, M. J.; Laia, C. A. T.; Parola, A. J.; Lima, J. C. *Chem. Soc. Rev.* **2012**, *41*, 869. (b) Nigel, C. S.; Partington, S. M.; Towns, A. D. *Color. Technol.* **2009**, *125*, 249.

(3) (a) Larghi, E. L.; Kaufman, T. S. *Synthesis* **2006**, 187. (b) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. (c) Moquist, P. N.; Kodama, T.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 7096. (d) Maity, P.; Srinivas, H. D.; Watson, M. P. J. *Am. Chem. Soc.* **2011**, *133*, 17142. (e) Graham, T. J. A.; Doyle, A. G. *Org. Lett.* **2012**, *14*, 1616 and references cited therein.

(4) (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (b) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (d) Li, C. J. *Acc. Chem. Res.* **2009**, *42*, 335. (e) Girard, S. A.; Knauber, T.; Li, C. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (f) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (g) Zhang, S. Y.; Zhang, F. M.; Tu, Y. Q. *Chem. Soc. Rev.* **2011**, *40*, 1937. (h) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Rev.* **2011**, *111*, 1293. (i) Giri, R.; Shi, B. F.; Engle, K. M.; Maugel, N.; Yu, J. Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (j) Yoo, W. J.; Li, C. J. *Top. Curr. Chem.* **2010**, *292*, 281. (k) Scheuermann, C. J. *Chem.—Asian J.* **2010**, *5*, 436. (l) Klussmann, M.; Sureshkumar, D. *Synthesis* **2011**, 353.

(5) For examples of C−H functionalization of benzopyrans, see: (a) Zhang, Y.; Li, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 4242. (b) Park, S. J.; Price, J. R.; Todd, M. H. *J. Org. Chem.* **2012**, *77*, 949. (c) Qvortrup, K.; Rankic, D. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 626. (d) Zhang, Y.; Li, C. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949. (e) Correia, C. A.; Li, C. J. *Heterocycles* **2010**, *82*, 555. (f) Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnürch, M. *Chem. Commun.* **2010**, *46*, 8836. (g) Richter, H.; Rohlmann, R.; García Mancheño, O. *Chem.—Eur. J.* **2011**, *17*, 11622. (h) Zhang, B.; Cui, Y.; Jiao, N. *Chem. Commun.* **2012**, *48*, 4498. (i) Pintér, Á.; Sud, A.; Sureshkumar, D.; Klussmann, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5004. (j) Schweitzer-Chaput, B.; Sud, A.; Pintér, Á.; Dehn, S.; Schulze, P.; Klussmann, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 13228. (k) Li, Z.; Li, H.; Guo, X.; Cao, L.; Yu, R.; Li, H.; Pan, S. *Org. Lett.* **2008**, *10*, 803. (l) Clausen, D. J.; Floreancig, P. E. *J. Org. Chem.* **2012**, *77*, 6574. (m) Xu, Y.; Kohlman, D. T.; Liang, S. X.; Erikkson, C. *Org. Lett.* **1999**, *1*, 1599. (n) Liu, X.; Sun, B.; Xie, Z.; Qin, X.; Liu, L.; Lou, H. *J. Org. Chem.* **2013**, *78*, 3104. (o) Pan, X.; Hu, Q.; Chen, W.; Liu, X.; Sun, B.; Huang, Z.; Zeng, Z.; Wang, L.; Zhao, D.; Ji, M.; Liu, L.; Lou, H. *Tetrahedron* **2014**, *70*, 3447. (p) Meng, Z.; Sun, S.; Yuan, H.; Lou, H.; Liu, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 543. (q) Richter, H.; García Mancheño, O. *Eur. J. Org. Chem.* **2010**, 4460.

(6) For examples of C−H functionalization of saturated ethers, see: (a) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem.—Eur. J.* **2011**, *17*, 4085. (b) Kumar, G. S.; Pieber, B.; Reddy, K. R.; Kappe, C. O. *Chem.—Eur. J.* **2012**, *18*, 6124. (c) Pan, S.; Liu, J.; Li, H.; Wang, Z.; Guo, X.; Li, Z. *Org. Lett.* **2010**, *12*, 1932. (d) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497. (e) Liu, D.; Liu, C.; Li, H.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 4453. (f) Liu, D.; Liu, C.; Li, H.; Lei, A. *Chem. Commun.* **2014**, *50*, 3623. (g) He, T.; Yu, L.; Zhang, L.; Wang, L.; Wang, M. *Org. Lett.* **2011**, *13*, 5016. (h) Huang, X. F.; Zhu, Z. Q.; Huang, Z. Z. *Tetrahedron* **2013**, *69*, 8579. (i) Guo, X.; Pan, S.; Liu, J.; Li, Z. *J. Org. Chem.* **2009**, *74*, 8848. (j) Singh, P. P.; Gudup, S.; Aruri, H.; Singh, U.; Ambala, S.; Yadav, M.; Sawant, S. D.; Vishwakarma, R. A. *Org. Biomol. Chem.* **2012**, *10*, 1587. (k) Kamijo, S.; Hoshikawa, T.; Inoue, M. *Org. Lett.* **2011**, *13*, 5928. (l) Hoshikawa, T.; Kamijo, S.; Inoue, M. *Org. Biomol. Chem.* **2013**, *11*, 164.

(7) (a) Muramatsu, W.; Nakano, K.; Li, C. J. *Org. Lett.* **2013**, *15*, 3650. (b) Muramatsu, W.; Nakano, K. *Org. Lett.* **2014**, *16*, 2042.

(8) (a) Lambert, J. B.; Schulz, W. J.; McConnell, J. A.; Schilf, W. *J. Am. Chem. Soc.* **1988**, *110*, 2201. (b) Yadav, V. K.; Agrawal, D. *Chem. Commun.* **2007**, 5232. (c) Hashimoto, Y.; Mukaiyama, T. *Chem. Lett.* **1986**, 1623. (d) Xie, Z.; Liu, L.; Chen, W.; Zheng, H.; Xu, Q.; Yuan, H.; Lou, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3904.

(9) Wan, M.; Meng, Z.; Lou, H.; Liu, L. *Angew. Chem., Int. Ed.* **2014**, DOI: 10.1002/anie.201407083.

(10) (a) Nielsen, D. K.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 6056. (b) Vo, C.-V. T.; Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 14082. (c) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194.

(11) (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169.

(12) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, 1759.

(13) (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.

(14) Relative configurations of products of the coupling of aldehydes and isochromans were assigned according to ref 5p.

(15) (a) Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877. (b) Fukuzumi, S.; Kitano, T.; Ishikawa, M. *J. Am. Chem. Soc.* **1990**, *112*, 5631. (c) Mayr, H.; Basso, N.; Hagen, G. *J. Am. Chem. Soc.* **1992**, *114*, 3060. (d) Horn, M.; Schappele, L. H.; Lang-Wittkowski, G.; Mayr, H.; Ofial, A. R. *Chem.—Eur. J.* **2013**, *19*, 249.

(16) (a) Sundberg, R. J.; Hunt, P. J.; Desos, P.; Gadamasetti, K. G. *J. Org. Chem.* **1991**, *56*, 1689. (b) Buckley, D.; Dunstan, S.; Henbest, H. B. *J. Chem. Soc.* **1957**, 4880. (c) Jung, H. H.; Floreancig, P. E. *Tetrahedron* **2009**, *65*, 10830.

(17) (a) Yi, H.; Liu, Q.; Liu, J.; Zeng, Z.; Yang, Y.; Lei, A. *ChemSusChem* **2012**, *5*, 2143. (b) Zhang, G.; Ma, Y.; Wang, S.; Kong, W.; Wang, R. *Chem. Sci.* **2013**, *4*, 2645. (c) Zhang, G.; Zhang, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 10429.