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DOI: 10.1039/D0CC02832K

COMMUNICATION

Direct Enantioselective Allylic Substitution of 4-Hydroxycoumarin Derivatives with Branched Allylic Alcohols via Iridium Catalysis

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A highly efficient direct asymmetric allylic substitution (AAS) reaction of 4-hydroxycoumarin derivatives with branched allylic alcohols was realized by combining a chiral iridium complex catalyst with Lewis acid under mild reaction conditions, delivering various chiral allylation products in remarkably high yields and excellent enantioselectivities. The salient features of this transformation include mild reaction conditions, general substrate scope, good functional-group tolerance, high yields, excellent selectivities and easy scale-up. Furthermore, the obtained products can be readily transformed into several kinds of bioactive compounds.

Coumarin derivatives are important chemicals in the perfume, cosmetic, agricultural and pharmaceutical industries, and have been well recognized as the key structural scaffolds in many bioactive compounds.[1] They have always fascinated synthetic and medicinal chemists because of their comprehensive pharmacological profiles such as analgesic,[2] anti-arthritis,[3] anti-inflammatory,[4] anti-platelet,[5] anti-bacterial,[6] anti-viral,[7] and anti-cancer[8] properties. (Figure 1) For example, Phenprocoumon, a coumarin derived long-acting oral anticoagulant drug, is a well-known vitamin K antagonist that inhibits coagulation by blocking synthesis of coagulation factors II, VII, IX and X.[9] Warfarin and acenocoumarol, medications that are used as anticoagulants, are commonly used to treat blood clots such as deep vein thrombosis and pulmonary embolism and to prevent stroke in people who have atrial fibrillation, valvular heart disease or artificial heart valves.[10] Therefore, much attention has been paid towards the syntheses and structural modifications of coumarins and their analogues.

In spite of a wide range of literature reports towards the synthesis of coumarin derivatives,[11] it is still highly desirable to explore enantioselective approaches to the synthesis of optically pure coumarin derivatives. The use of 4-hydroxycoumarin as the starting material has been demonstrated as an important strategy ascribed to its bifunctional character. The organocatalytic or transition-metal catalyzed direct asymmetric Michael addition of 4-hydroxycoumarin to electron-deficient C=C double bonds has proved to be one of the most convenient approaches to furnish coumarin derived chiral compounds (Scheme 1, a).[12] However, to the best of our knowledge, the utilization of 4-hydroxycoumarin in the catalytic asymmetric allylic substitution (AAS) reactions with the direct use of allylic alcohol derivatives remains an unexplored challenge.

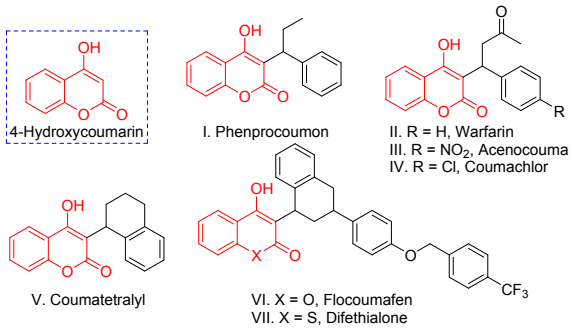
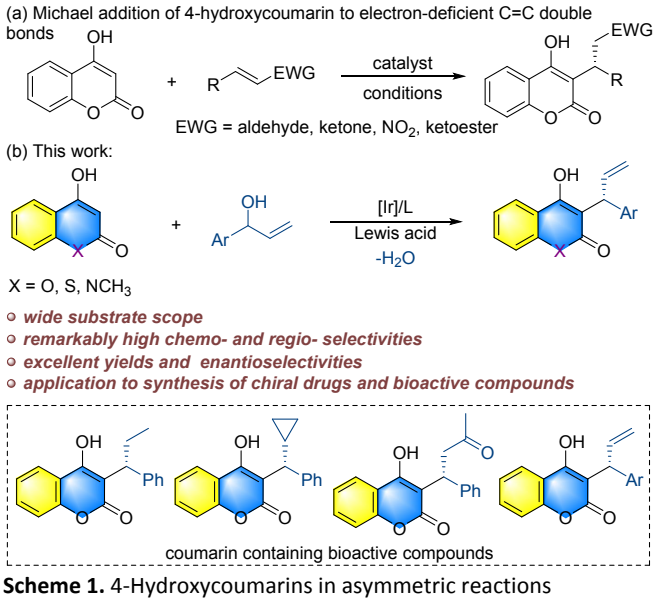


Figure 1. Drugs and Bioactive Molecules Containing (Thio)Coumarin



Scheme 1. 4-Hydroxycoumarins in asymmetric reactions

Iridium-catalyzed enantioselective allylic substitution has been established as a powerful synthesis strategy for the formation of carbon-carbon and carbon-heteroatom bonds, with both excellent regio- and stereoselectivities. Largely due to the pioneering work of Takeuchi,[13] Helmchen,[14] Hartwig,[15] Carreira,[16] Krische,[17] You,[18] Zhang[19] and other research groups,[20] a wide variety of nucleophiles have been successfully employed in iridium-

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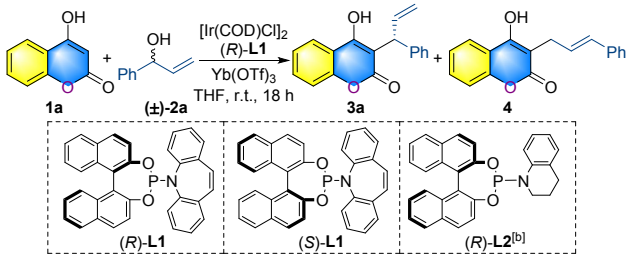
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

catalyzed AAS reactions. We thus envisioned that the use of 4-hydroxycoumarin as the nucleophile in iridium-catalyzed AAS reaction would provide a highly efficient method to enantiomeric enriched coumarin containing allylation products, which could act as the key synthetic intermediate for further conversion to several kinds of bioactive privileged scaffolds. The major challenges in achieving this goal are threefold. First, a mode of activation must be identified that could avoid the *O*-allylation reaction. Second, an optimal reaction condition must be found to control the branched/linear (b:l) selectivity of the allylation reaction. Third, a powerful asymmetric catalytic system must be established to ensure the substitution in a highly stereoselective manner. Thus, it is a formidable task to develop a highly efficient direct catalytic AAS reaction of 4-hydroxycoumarins.

In line with our recent research[21] on the selectivity controllable allylic substitution reactions with allylic alcohols,[22] we considered whether the catalytic strategy pioneered by Carreira and co-workers would be suitable for this catalytic asymmetric allylic transformation, which involves iridium/chiral ligand as the catalyst together with an acid as the promotor in the reaction.[23] Herein, we report a cooperative iridium/Lewis acid catalyzed AAS reaction of 4-hydroxycoumarin with racemic branched allylic alcohols in good yields and excellent enantioselectivities (Scheme 1, b). In addition, the corresponding allylation products could be easily transformed to useful pharmaceutical molecules.

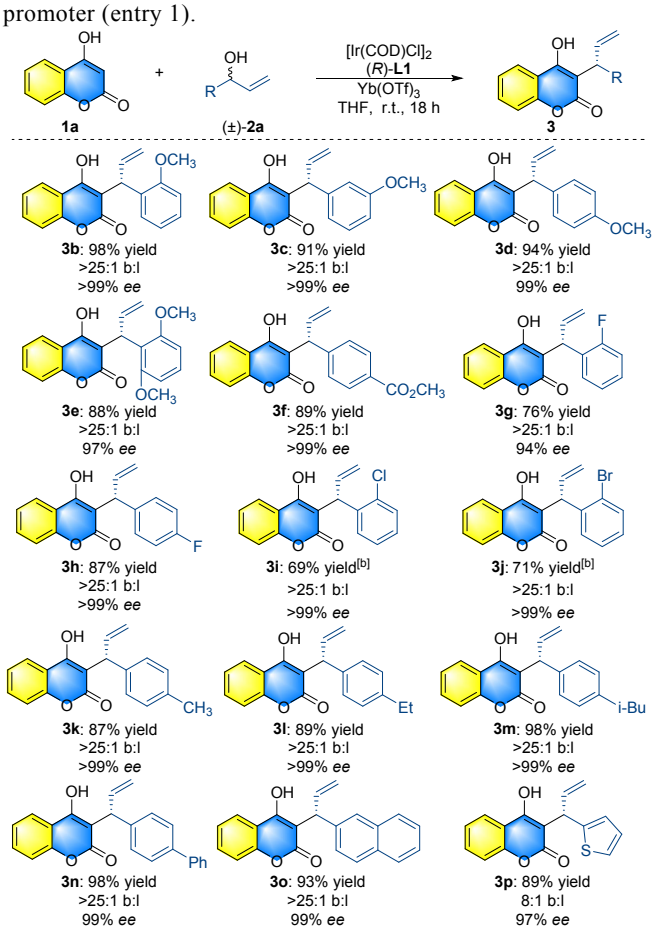
Table 1. Reaction conditions optimization[a]



Entr	Change in condition	Yield(%)	3a/4[c]	*ee*[%]
1	**none**	**93**	**>25/**	**>99**
2	without $[Ir(COD)Cl]_2$ catalyst	n.r.	-	-
3	without Ligand	n.r.	-	-
4	(*R*)-**L2** instead of (*R*)-**L1**	<5	n.d.	n.d.
5	(*S*)-**L1** instead of (*R*)-**L1**	92	>25/	<-99
6	DPP instead of $Yb(OTf)_3$	78	>25/	>99
7	$Sc(OTf)_3$ instead of $Yb(OTf)_3$	53	>25/	98
8	no acid promoter was added	n.r.	-	-
9	DCM instead of THF	66	>25/	96
10	dioxane instead of THF	26	>25/	97
11	water instead of THF	74	>25/	84
12	5 mol% of $Yb(OTf)_3$ was used	83	>25/	>99

[a] General conditions: **1a** (0.2 mmol), (±)-**2a** (0.4 mmol), $[Ir(COD)Cl]_2$ (2 mol%), chiral ligand (8 mol%), and acid promoter (10 mol%) in 1.3 mL solvent under the argon protection, 18 h. [b] Yields of isolated product. [c] Measured by ^{1}H NMR of the crude reaction mixture. [d] Determined by chiral HPLC using chiralpak AD-H column. [f]Reaction time: 36 h. DPP = diphenyl phosphate.

To verify our hypothesis, we initiated our studies by using commercially available 4-hydroxycoumarin (**1a**) and racemic branched allylic alcohol (±)-**2a** as model substrates. We were engaged in examining an array of reaction parameters and exploring a range of iridium/phosphoramidite complex as extrinsic chiral catalysts to provide a possible mode of stereocontrol (Table 1). It was found that the desired product **3a** was obtained in 93% yield with >99% ee when the reaction was carried out in THF at room temperature for 18 hours in the presence of 2 mol% of $[Ir(COD)Cl]_2$, 8 mol% of (*R*)-**L1** and 10 mol% of $Yb(OTf)_3$ as acid promoter (entry 1).

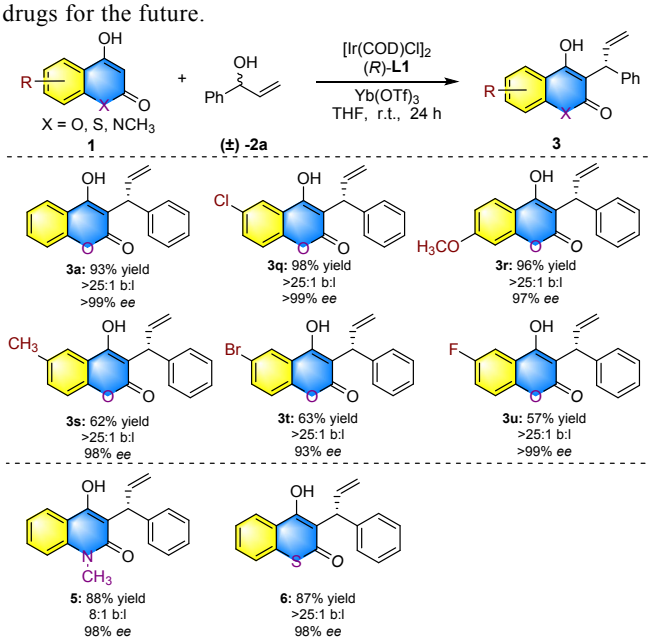


Scheme 2. Substrate scope of allylic alcohols.[a]

The reaction could not proceed in the absence of any of iridium catalyst, chiral ligand or acid promoter (entries 2, 3 and 8). The use of other chiral ligands (*R*)-**L2** instead of (*R*)-**L1** could not promote the reaction at all (entry 4). It is noteworthy that the alkylated product with inversed absolute configuration could be afforded in almost the same yield and *ee* value when (*S*)-**L1** was employed (entry 5). Other acid promoters, such as $(PhO)_2PO_2H$ and $Sc(OTf)_3$ were also investigated (entries 6 and 7), the stereoselectivities were maintained in excellent levels, however, the yields were decreased. A massive number of documents evidenced that the reaction solvents could significantly impact the stereoselectivity and yield of many reactions. Hence, different reaction solvents, such as DCM and dioxane (entries 9 and 10), were screened and all resulted in lower *ee* values and yields. In addition, water, a general and green solvent, was also tested in the reaction, and the desired **3a** was still isolated in high yield (entry 11), which demonstrated the potential of aqueous mediated AAS reaction. Additionally, slightly lowering the load of $Yb(OTf)_3$ or allylic alcohol resulted in reduction of the yield (entry 12).

With the optimized reaction conditions in hand, the scope of the reaction was explored with a range of allylic alcohols. The results are summarized in Scheme 2. From Scheme 2, it could be seen that allylic alcohols bearing either electron-donating or withdrawing groups at the *ortho*-, *meta*-, or *para*-position of the phenyl group participated in this reaction to give the desired products (**3b**–**3n**) in remarkably high yields with excellent stereoselectivities (94–>99% ee's). Notice that the reaction was slightly affected by

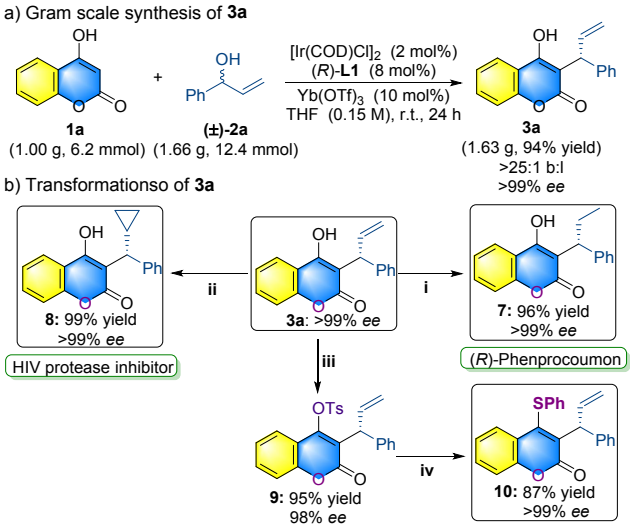
the electronic effects of substituents in the aromatic ring of allylic alcohols. The substrates bearing stronger electron-donating groups (OCH_3 group, **3b**, **3c**, **3d** and **3e**) in the aromatic ring provided the expected products in higher yields than those bearing electroneutral or electron-deficient groups. The absolute stereochemistry of **3a** was determined to be *R* by comparison of its optical rotation with the known compound reported in the literature (see the Supporting Information).[26] Furthermore, the reactions of naphthyl and heteroaryl substituted allyl alcohols were successfully carried out to give their respective products in good yields with excellent enantioselectivities (**3o-3p**), which opened up the possibility of diverse synthesis of coumarin-based drugs for the future.



Scheme 3. Substrate scope of 4-hydroxycoumarins[a]

Encouraged by the excellent results achieved with different allylic alcohols, the scope of a series of 4-hydroxycoumarin derivatives was next investigated. As can be seen from Scheme 3, variation of the coumarin derivatives was suitable for the reaction and corresponding compounds **3q-3u** were afforded in good to excellent yields with excellent regio- and stereoselectivities. During the past several decades, quinoline-2,4-diones and thiocoumarins played important role in natural and synthetic chemistry due to their biological and pharmacological activities.[27] Subsequently, 4-hydroxy-1-methyl-2(1*H*)-quinolone and thiocoumarin were employed as substrates in this reaction. We are very pleased to find that both types of compounds were suitable for the reaction, providing the allylation products **5** and **6** in excellent results.

To verify the practicality and synthetic potential of the newly developed synthetic methodology, a scale-up synthesis of product **3a** was conducted. Under the standard conditions, the reaction of **1a** with **2a** on a 6.2 mmol scale delivered 1.63 g of **3a** (94% yield) without any erosion of *ee* value, which demonstrated the efficacy of this protocol (Scheme 4, a). Moreover, the long-acting oral anticoagulant drug, (*R*)-Phenprocoumon (**7**),[24] could be easily afforded by reduction of (*R*)-**3a** under $TsNHNH_2$, excellent yield and enantioselectivity were obtained (Scheme 4, b). Furthermore, the HIV protease inhibitor **8**[25] could also be synthesized efficiently from the cyclopropanation of the terminal alkene of **3a** with CH_2I_2 (*Simmons-Smith Reaction*), delivering the corresponding cyclopropanation product in excellent results without any loss of *ee* value. In addition, the 4-hydroxyl group of **3a** could be easily converted to different functionalities, which greatly facilitated the construction of coumarin derived optically active small molecular libraries. For example, the 4-hydroxy group was firstly treated with TsCl, and then functionalized by thiophenol to give enantiomeric enriched compound **10**.



Scheme 4. Gram scale synthesis and transformation of **3a**. (i) $TsNHNH_2$, NaOAc, EtOH, reflux, 6 h; (ii) CH_2I_2, Et_2Zn, TFA, 0 °C to rt., 4-6 h; (iii) TsCl, Et_3N, DCM, 0 °C to rt., 4-6 h; (iv) PhSH, Et_3N, DCM, rt., 6-8 h.

In summary, we have disclosed a highly efficient direct iridium-catalyzed AAS reaction between 4-hydroxycoumarins/ thiocoumarins/quinolones and allylic alcohols for the first time, to the best of our knowledge. A variety of allylic alcohols as well as substituted coumarin derivatives were utilized to access biologically interesting coumarin-based chiral allylated compounds with remarkably high yields (up to 98%) and excellent regio- and enantioselectivities (>25:1 b:l, >99% *ee* for most cases) under mild reaction conditions. Notably, the biologically important quinoline-2,4-dione derivatives and thiocoumarin were both suitable substrates in the reaction. Furthermore, the reaction could be enlarged to gram-scale and this crafted synthetic approach greatly facilitates the synthesis of different chiral pharmaceuticals and precursors in comparison to the traditional method.

We gratefully acknowledge the Natural Science Foundation of China (No. 21672048), the Natural Science Foundation of Zhejiang Province (LY18B020015), and Hangzhou Normal University for financial support. X. Z. acknowledges a Xihu Scholar award from Hangzhou City, and G. Z. acknowledges a Qianjiang Scholar from Zhejiang Province in China.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For selected reviews on coumarins, see: (*a*) P. Anand, B. Singh and N. Singh, *Bioorg. Med. Chem.* 2012, **20**, 1175. (*b*) R. Pratap and V. J. Ram, *Chem. Rev.* 2014, **114**, 10476. (*c*) J. Grover and S. M. Jachak, *RSC Adv.* 2015, **5**, 38892. (*d*) H. Wei, J.-L. Ruan and X.-J. Zhang, *RSC Adv.* 2016, **6**, 10846.

2 (*a*) P. Kamnaing, S. N. Y. F. Free, Z. T. Fomun, M.-T. Martin and B. M. Bodo, *Phytochem.* 1994, **36**, 1561. (*b*) E. Okuyama, Y. Okamoto, M. Yamazaki and M. Satake, *Chem. Pharm. Bull.* 1996, **44**, 333.

3 H. Achenbach, R. Waibel and M. Zwanzger, *J. Nat. Prod.* 1992, **55**, 918.

4 (*a*) M. Balasubramanian and J. G. Keay, *In Comprehensive Heterocyclic Chemistry II*; A. R. Katritzky, C. Rees and W. E. F. V. Scriven, Eds. *Pergamon Press: Oxford, New York*, 1996, **5**, 245. (*b*) P. K. Mahata, C. Venkatesh, U. K. Syam Kumar, H. lla and H. Junjappa, *J. Org. Chem.* 2003, **68**, 3966.

5 (*a*) O. Bruno, S. Schenone, A. Ranise, F. Bondavalli, W. Filippelli, G. Falcone, G. Motola and F. Mazzeo, *II Farmaco* 1999, **54**, 95. (*b*) O. Bruno, C. Brullo, S. Schenone, A. Ranise, F. Bondavalli, E. Barocelli, M. Tognolini, F. Magnanini and V. Ballabeni, *II Farmaco* 2002, **57**, 753. (*c*) O. Bruno, C. Brullo, S. Schenone, F. Bondavalli, A. Ranise, M. Tognolini, M. Impicciatore, V. Ballabeni and E. Barocelli, *Bioorg. Med. Chem.* 2006, **14**, 121.

6 (*a*) G. M. Gingolani, F. Gaultrieri, Pigini. Notes. *J. Med. Chem.* 1969, **12**, 531. (*b*) A. M. El-Naggar, F. S. Ahmed, A. M. Abd El-Salam, M. A. Rady, M. S. A. *J. Heterocycl. Chem.* 1981, **18**, 1203. (*c*) A. Goel, V. J. Ram, *Tetrahedron* 2009, **65**, 7865.

7 H.-P. Hsieh, T.-A. Hsu, J.-Y. Yeh, J.-T. Horng, S.-R. Shih, S.-T. Chang, and Y.-S. Chao, U.S. Pat. Appl. US 20090312406 A1 2009127, 2009.

8 (*a*) S. J. Mohr, M. A. Chirigos, F. S. Fuhrman and J. W. Pryor, *Cancer Res.* 1975, **35**, 3750. (*b*) J. Dai, Y. Liu, H. Jia, Y.-D. Zhou and D. G. Nagle, *J. Nat. Prod.* 2007, **70**, 1462. (*c*) Y. Dong, K. Nakagawa-Goto, C.-Y. Lai, S. L. Morris-Natschke, K. F. Bastow and K.-H. Lee, *Bioorg. Med. Chem. Lett.* 2010, **20**, 4085. (*d*) Y. Dong, K. Nakagawa-Goto, C.-Y. Lai, S. L. Morris-Natschke, K. F. Bastow and K.-H. Lee, *Bioorg. Med. Chem. Lett.* 2011, **21**, 2341.

9 L. R. Pohl, R. Haddock, W. A. Garland and W. F. Trager, *J. Med. Chem.* 1975, **18**, 513.

10 (*a*) A. K. Daly, *Arch. Toxicol.* 2013, **87**, 407. (*b*) E. Milatova and V. Milata, *Ceska Slov. Farm.* 2013, **62**, 111.

11 For selected documents: (*a*) R. Jana, J. J. Partridge and J. A. Tunge, *Angew. Chem., Int. Ed.* 2011, **50**, 5157. (*b*) J. B. Metternich and R. Gilmour, *J. Am. Chem. Soc.* 2016, **138**, 1040. (*c*) S.-M. Yang, C.-Y. Wang, C.-K. Lin and P. Karanam, *Angew. Chem., Int. Ed.* 2018, **57**, 1668.

12 For selected documents: (*a*) F. F. Wolf, H. Klare and B. Goldfuss, *J. Org. Chem.* 2016, **81**, 1762. (*b*) A. S. Kucherenko, A. A. Kostenko, G. M. Zhdankina, O. Yu. Kuznetsova and S. G. Zlotin, *Green Chem.* 2018, **20**, 754. (*c*) V. Modrocká, E. Veverková, M. Mečiarová and R. Šebesta, *J. Org. Chem.* 2018, **83**, 13111. (*d*) I. G. Sonsona, E. Marques-Lopez, M. C. Gimeno and R. P. Herrera, *New J. Chem.* 2019, **43**, 12233.

13 For reviews: (*a*) R. Takeuchi and S. Kezuka, *Synthesis* 2006, 3349. For selected examples: (*b*) R. Takeuchi, N. Ue, K. Tanabe, K. Yamashita and N. Shiga, *J. Am. Chem. Soc.* 2001, **123**, 9525. (*c*) G. Onodera, K. Watabe, M. Matsubara, K. Oda, S. Kezuka and R. Takeuchi, *Adv. Synth. Catal.* 2008, **350**, 2725.

14 For reviews: (*a*) J. Qu and G. Helmchen, *Acc. Chem. Res.* 2017, **50**, 2539. (*b*) G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies and R. Weihofen, *Chem. Commun.* 2007, 675.

15 For reviews: (*a*) J. F. Hartwig and L. M. Stanley, *Acc. Chem. Res.* 2010, **43**, 1461. (*b*) J. F. Hartwig and M. J. Pouy, *Top. Organomet. Chem.* 2011, **34**, 169.

16 (*a*) Roggen, M. Carreira, E. M. *J. Am. Chem. Soc.* 2010, **132**, 11917. (*b*) Lafrance, M. Roggen, M. Carreira, E. M. *Angew. Chem., Int. Ed.* 2012, **51**, 3470. (*c*) Rossler, S. L. Krautwald, S. Carreira, E. M. *J. Am. Chem. Soc.* 2017, **139**, 3603.

17 For a review: S. W. Kim, W. Zhang and M. J. Krische, *Acc. Chem. Res.* 2017, **50**, 2371.

18 For reviews: (*a*) W.-B. Liu, J.-B. Xia and S.-L. You, *Top. Organomet. Chem.* 2011, **38**, 155. (*b*) Q. Cheng, H.-F. Tu, C. Zheng, J.-P. Qu, G. Helmchen and S.-L. You, *Chem. Rev.* 2019, **119**, 1855.

19 For reviews: (*a*) J.-K. Fu, X.-H. Huo, B.-W. Li and W.-B. Zhang, *Org. Biomol. Chem.* 2017, **15**, 9747. (*b*) N. Butt and W.-B. Zhang, *Chem. Soc. Rev.* 2015, **44**, 7929.

20 (*a*) S. Rieckhoff, J. Meisner, J. Kästner, W. Frey and R. Peters, *Angew. Chem., Int. Ed.* 2018, **57**, 1404. (*b*) Y. S. Lee, J. Y. Park and S. H. Cho, *Angew. Chem., Int. Ed.* 2018, **57**, 12930. (*c*) S. Ghorai, S. S. Chirke, W.-B. Xu, J.-F. Chen and C.-K. Li, *J. Am. Chem. Soc.* 2019, **141**, 11430. (*d*) X. Zhang and D.-W. Niu, *J. Am. Chem. Soc.* 2016, **138**, 13103. (*e*) H.-H. Zhang, J.-J. Zhao and S.-Y. Yu, *J. Am. Chem. Soc.* 2018, **140**, 16914. (*f*) L. Chen, M.-J. Luo, F. Zhu, W. Wen and Q.-X. Guo, *J. Am. Chem. Soc.* 2019, **141**, 5159. (*g*) S.-Q. Qiu, T. Ahmad, Y.-H. Xu and T.-P. Loh, *J. Org. Chem.* 2019, **84**, 6729.

21 (*a*) D. Shen, Q.-L. Chen, P.-P. Yan, X.-F. Zeng, G.-F and Zhong, *Angew. Chem., Int. Ed.* 2017, **56**, 3242. (*b*) S.-L. Pan, B.-Q. Wu, J.-J. Hu. R.-G. Xu, M. Jiang, X.-F. Zeng and G.-F. Zhong, *J. Org. Chem.* 2019, **84**, 10111. (*c*) P.-P. Yan, S.-L. Pan, J.-J. Hu, J.-M. Lu, X.-F. Zeng and G.-F. Zhong, *Adv. Synth. Catal.* 2019, **361**, 1322.

22 For reviews of allylic alcohols, see: (*a*) M. Bandini, *Angew. Chem., Int. Ed.* 2011, **50**, 994. (*b*) B. Sundararaju, M. Achard and C. Bruneau, *Chem. Soc. Rev.* 2012, **41**, 4467.

23 S. Krautwald, D. Sarlah, M. A. Schafroth and E. M. Carreira, *Science* 2013, **340**, 1065.

24 (*a*) J.-J. Zhu and J.-G. Jiang. *Mol. Nutr. Food Res.* 2018, **62**, 1701073. (*b*) J. C. Menezes and M. Diederich, *Future Med. Chem.* 2019, **119**, 1057.

25 S. Thaisrivongs, K. D. Watenpaugh, W. J. Howe, P. K. Tomich, L. A. Dolak, K.-T. Chong, C.-S. C. Tomich, A. G. Tomasselli, S. R. Turner, J. W. Strohbach, A. M. Mulichak, M. N. Janakiraman, J. B. Moon, J. C. Lynn, M.-M. Homg, R. R. K. A. Hinshaw, Curry and D. J. Rothrock, *J. Med. Chem.* 1995, **38**, 3624-3637.

26 W. R. Porter, K. Kunze, E. J. Valente and W. F. Trager, *J. Labelled Compds. Radiopharm. XII* 1976, 763.

27 A. Detsi, V. Bardakaos and J. Markopoulos, *J. Chem. Soc. Perkin Trans 1* 1996, **24**, 2909.