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Branch-Selective Allylic C–H Carboxylation of Terminal Alkenes by Pd/sox Catalyst

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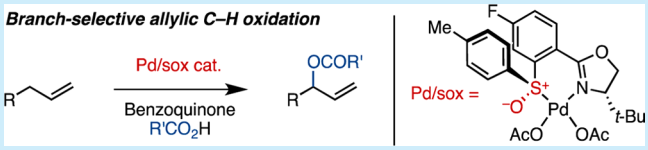
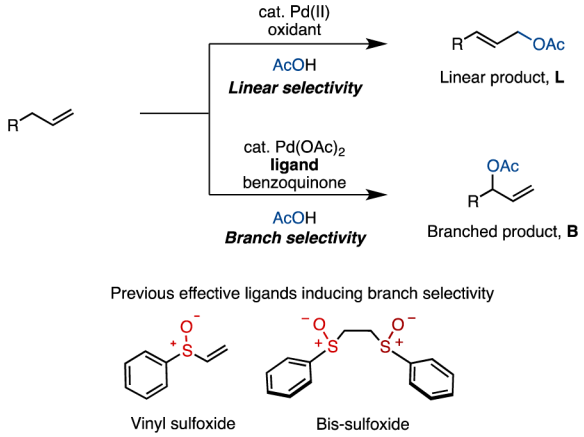
Supporting Information

ABSTRACT: A ligand-controlled branch-selective allylic C–H carboxylation through Pd catalysis is described. The developed catalytic system, which consists of $Pd(OAc)_2$, sulfoxide–oxazoline (sox) as a ligand and benzoquinone as an oxidant, couples terminal alkenes and carboxylic acids to furnish the corresponding branched allylic esters with high regioselectivity.



Allylic C–H oxidation of alkenes has received much attention from the organic chemistry community because it can form allylic alcohol and amine derivatives that are useful in the synthesis of pharmaceuticals and complex natural products.[1] Palladium catalysis has proven particularly effective for such alkene C–H oxidations, and various procedures for cyclic alkene substrates have been developed.[2] Recently, regioselective C–H oxidation of terminal alkenes using Pd catalysts has been reported (Scheme 1). Efforts to control the regioselectivity of C–H oxidation of terminal alkenes have mostly resulted in a preferential reaction at the less hindered position to give linear products (**L**).[3] Only a few catalytic systems are known to be effective in producing branched products (**B**) as exemplified by the pioneering works reported by the group of White.[4,5] Most of these reactions use sulfoxide ligands such as dimethyl sulfoxide (DMSO) and benzoquinone as an oxidant.[6] Additionally, it has been reported that the use of vinyl sulfoxide or bis-sulfoxide ligands is essential to give branched products (Scheme 1). It should also be emphasized that a ligand-controlled, enantioselective, allylic C–H oxidation has not been developed; White's chiral Lewis acid cocatalyst strategy is the sole example inducing enantioselectivity.[4c] Thus, the development of a new class of ligand system potentially inducing enantioselectivity is of great importance in the field.

Scheme 1. Pd-Catalyzed Regioselective C–H Oxidation of Terminal Alkenes



In 2013, as a part of our campaign exploring ligand-enabled catalysis for C–H coupling,[7] we discovered a C–H/C–B coupling of sterically hindered heteroarenes employing arylboronic acids and using catalytic amounts of $Pd(OAc)_2$, sulfoxide–oxazoline (sox) as the ligand, and iron phthalocyanine (FePc) as the cocatalyst under air (Scheme 2, eq 1).[8] For example, 2,3-dimethylthiophene can be coupled with (2-methylnaphthalen-1-yl)boronic acid in the presence of a Pd catalyst to give the corresponding coupling product in 92% yield using sulfoxide–oxazoline (sox) **L1** as the ligand, whereas DMSO and White's bis-sulfoxide resulted in low yields. We hypothesized that the Pd/sox catalyst might also be effective for allylic C–H oxidation. Moreover, due to the stronger bonding of the nitrogen than that of sulfur,[8] the *trans*-effect and the bulky steric hindrance of oxazoline substituent R provide a chance to tune the regioselectivity to afford the branch product (Scheme 2, eq 2). Thus, we set out to investigate the effect of sox ligands for allylic C–H oxidation, and herein we report a highly regioselective allylic C–H carboxylation of terminal alkenes by the Pd/sox catalyst.

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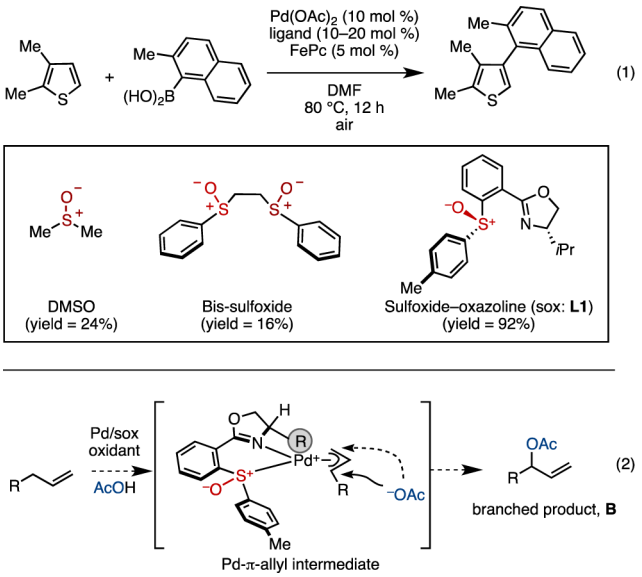
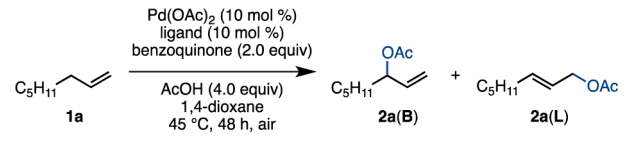
Scheme 2. C−H/C−B Coupling of Heteroarenes with Hindered Arylboronic Acids Using a Pd/sox Catalyst (eq 1) and Our Hypothesis for a Branch-Selective Allylic C−H Carboxylation Using the Pd/sox Catalyst (eq 2)



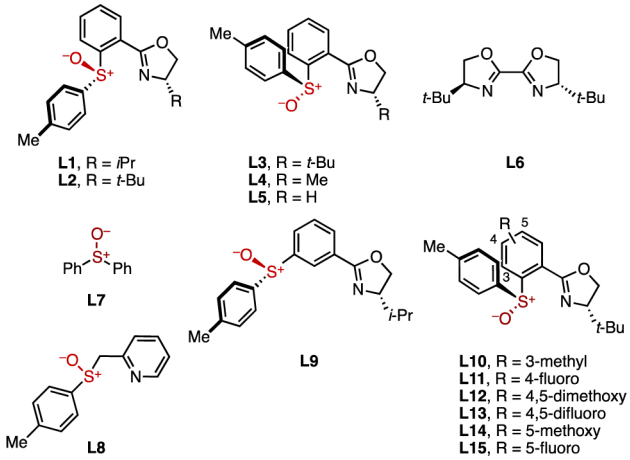
Using oct-1-ene (**1a**) as a model substrate for terminal alkenes, allylic C−H carboxylation was conducted using various sox ligands, following the standard procedure of White and co-workers: 10 mol % $Pd(OAc)_2$,[4b] 10 mol % ligand, 2.0 equiv of benzoquinone, and 4.0 equiv of AcOH in 1,4-dioxane for 48 h at 45 °C under air (Table 1).[9] When *i*Pr-sox **L1** was used as the ligand, allylic C−H acetoxylation of **1a** proceeded to give the corresponding product **2a**(**B**) (**B**: branch) and **2a**(**L**) (**L**: linear) in a combined 58% yield with 85:15 (**B**/**L**)-selectivity (Table 1, entry 1). Ligand *t*-Bu-sox **L2** gave a better branch-selectivity ratio of 99:1 (Table 1, entry 2). Surprisingly, *t*-Bu-sox **L3**, a diastereomer of *t*-Bu-sox **L2**, gave a slightly better yield (60% yield) whereas the **B**/**L** ratio was slightly decreased (96:4, Table 1, entry 3). When the *t*-Bu-sox **L3** was changed to Me-sox **L4** and H-sox **L5**, the branch selectivity became gradually worse (Table 1, entries 4 and 5). These results indicate that the substituent on the oxazoline might be more important in controlling the branch selectivity. Compared to the sox ligand, the bis-oxazoline ligands such as **L6** are ineffective for this transformation (Table 1, entry 6), which clearly indicate the importance of a sulfoxide moiety in ligand structure. Phenyl sulfoxide ligand **L7** and **L8** without the oxazoline moiety were not effective (Table 1, entries 7 and 8). A sox ligand **L9** with an oxazoline at the *meta*-position was also ineffective (Table 1, entry 9). Interestingly, when the loading of *t*-Bu-sox **L3** was lowered to 5 mol %, the yield and regioselectivity of **2a** were maintained (Table 1, entry 10).[10] Next, based on the *t*-Bu-sox **L3**, some modified ligands (**L10**−**L15**) bearing both electron-deficient and -donating substituents on the phenyl group were investigated (Table 1, entries 13−16). As a result, **L11** (4-fluoro) and **L13** (4,5-difluoro) were found to be the best ligands and afforded the branched product **2a**(**B**) in 86% and 84% yields, respectively with 98% branch selectivity (Table 1, entries 12 and 14).[11,12] It should be noted that, unfortunately, the enantiomeric excess of the branched product **2a**(**B**) was less than 5%. These results clearly show that the chiral environment created by the current sox system needs to be significantly modified to achieve an enantioselective allylic C−H oxidation process.

Table 1. Ligand Screening for the Pd-Catalyzed Allylic C−H Carboxylation[a]



entry	ligand	yield of **2a**/%[b]	(**B**)/(**L**)[c]
1	**L1**	58	85:15
2	**L2**	56	99:1
3	**L3**	60	96:4
4	**L4**	57	90:10
5	**L5**	47	84:16
6	**L6**	–	–
7	**L7**	7	87:13
8	**L8**	14	95:5
9	**L9**	3	99:1
10[d]	**L3**	66	97:3
11[d]	**L10**	74	97:3
12[d]	**L11**	86	98:2
13[d]	**L12**	74	96:4
14[d]	**L13**	84	98:2
15[d]	**L14**	74	>99:1
16[d]	**L15**	74	97:3

[a]Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand (0.02 mmol), benzoquinone (0.4 mmol), AcOH (0.8 mmol) in 1,4-dioxane (1.2 mL), 45 °C, 48 h, under air. [b]The yield of **2a** was determined by GC analysis. [c]The ratio of **2a**(**B**) and **2a**(**L**) was determined by GC analysis. [d]5 mol % ligand and 10 mol % $Pd(OAc)_2$ were employed.



Previously we have shown in the C−H/C−B biaryl coupling chemistry that a chiral sox ligand **L1** coordinates to palladium(II) in a bidentate fashion.[7] Since the optimal ligand structure in the present C−H oxidation turned out to be the diastereomer (**L3**, **L11**, and **L13**, for example), we questioned whether these new ligands also coordinate to palladium(II) in a S−N bidentate fashion. Thus, **L3** was treated with $PdCl_2$ in CH_2Cl_2 at room temperature to give the $PdCl_2$(**L3**) complex (**3**) (see the Supporting Information for details). The X-ray crystal structure analysis of **3** revealed that the S atom of the sulfoxide coordinates to the Pd center as well as the N atom of the oxazoline unit (Figure 1).

Next, we examined the scope of this reaction using several carboxylic acids and terminal alkenes using the $Pd(OAc)_2$/**L11**

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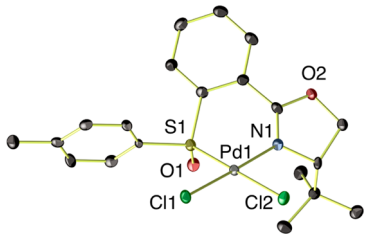

Figure 1. X-ray crystal structure of $PdCl_2$(**L3**) complex **3**. Selected bond lengths (Å): Pd1−N1 = 2.039(2), Pd1−S1 = 2.2402(8), Pd1−Cl1 = 2.2905(8), Pd1−Cl2 = 2.3048(8).

catalyst (Figure 2). When acetic acid was changed to other carboxylic acids such as cinnamic acid and their derivatives, the

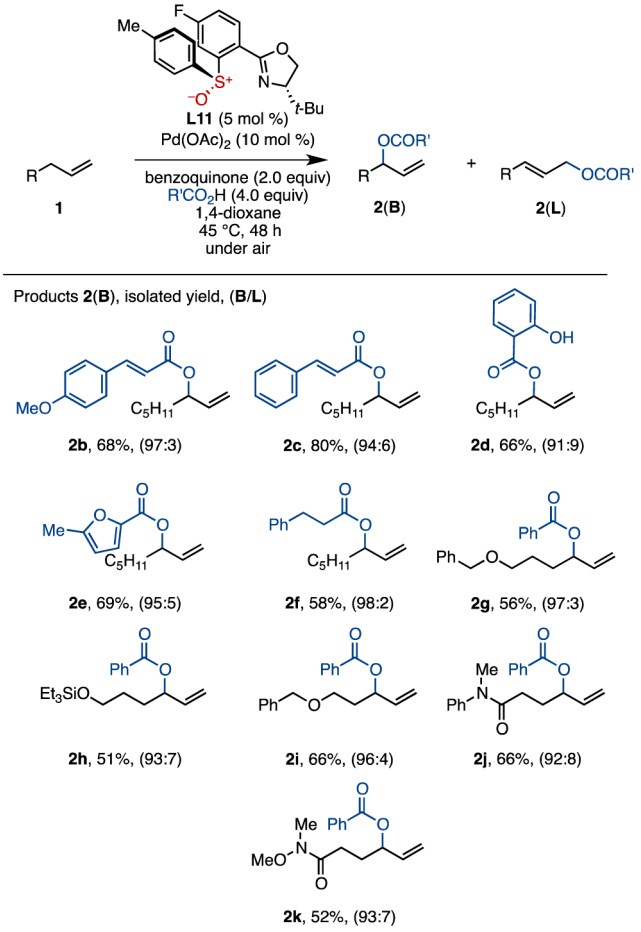

Figure 2. Scope of C−H carboxylation catalyzed by $Pd(OAc)_2$/**L11**. Reaction conditions: alkene **1** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), **L11** (0.01 mmol), benzoquinone (0.4 mmol), $R'CO_2H$ (0.8 mmol) in 1,4-dioxane (1.2 mL), 45 °C, 48−72 h, under air. The ratio of **2**(**B**) and **2**(**L**), which is described in parentheses (**B**/**L**), was determined by ^{1}H NMR.

reactions gave the corresponding products **2b** and **2c** in good yields with high branch selectivity. The reaction tolerated phenolic alcohols as well as furans, which are generally unstable toward oxidative conditions, to afford the products (**2d** and **2e**) in good yields. 3-Phenylpropionic acids can be used for this reaction as well (**2f**). Terminal alkenes bearing benzyloxy (**2g** and **2i**), triethylsiloxy (**2h**), and amide (**2j** and **2k**) groups also proceeded well.

In summary, we have developed a highly branch-selective allylic C−H carboxylation of terminal alkenes using a Pd catalyst with a sulfoxide−oxazoline (sox) ligand. The developed Pd/sox catalyst is responsible for the increase in both yield and regioselectivity. The development of related dual-functionalized catalysts and the application to other C−H functionalization reactions are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all new compounds, and details of computational study. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Selected examples: (a) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976. (b) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137. (c) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510. (d) Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547.
(2) Examples of Pd-catalyzed C−H oxidation of internal alkenes: (a) Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975. (b) Åkermark, B.; Larsson, E. M.; Oslob, J. D. *J. Org. Chem.* **1994**, *59*, 5729.
(3) Review: (a) Liu, G.; Wu, Y. *Top. Curr. Chem.* **2010**, *292*, 195. Recent representative examples: (b) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (c) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481. (d) Lin, B.-L.; Labinger, J. A.; Bercaw, J. E. *Can. J. Chem.* **2009**, *87*, 264. (e) Thiery, E.; Aouf, C.; Belloy, J.; Harakat, D.; Bras, J. L.; Muzart, J. *J. Org. Chem.* **2010**, *75*, 1771. (f) Henderson, W. H.; Check, C. T.; Proust, N.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 824. (g) Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116. (h) Pilarski, L. T.; Selander, N.; Böse, D.; Szabó, K. J. *Org. Lett.* **2009**, *11*, 5518. (i) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733. (j) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978.
(4) (a) Reference 3b. (b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (c) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448. (d) Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 12584. (e) Strambeanu, I. I.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 12032.

(5) Very recently, Zhou and coworkers demonstrated a branch-selective C−H oxidation of terminal alkenes by using a Cu catalyst. Zhang, B.; Zhu, S. F.; Zhou, Q.-L. *Tetrahedron Lett.* **2013**, *54*, 2665.
(6) For early works on the use of combined BQ-sulfoxide ligands, see: (a) Grennberg, H.; Gogoll, A.; Bäckvall, J.-E. *J. Org. Chem.* **1991**, *56*, 5808. (b) Grennberg, H.; Bäckvall, J.-E. *Chem.—Eur. J.* **1998**, *4*, 1083.
(7) Our representative recent achievements in this field: (a) Ueda, K.; Yanagisawa, S. J.; Yamaguchi, K.; Itami. *Angew. Chem., Int. Ed.* **2010**, *49*, 8946. (b) Yamaguchi, A. D.; Mandal, D.; Yamaguchi, J.; Itami, K. *Chem. Lett.* **2011**, *40*, 555. (c) Mochida, K.; Kawasumi, K.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 10716. (d) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387. (e) Mandal, D.; Yamaguchi, A. D.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 19660. (f) Hattori, K.; Yamaguchi, K.; Yamaguchi, J.; Itami, K. *Tetrahedron* **2012**, *68*, 7605. (g) Yamaguchi, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Chem. Sci.* **2012**, *3*, 2165. (h) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169. (i) Zhang, Q.; Kawasumi, K.; Segawa, Y.; Itami, K.; Scott, L. T. *J. Am. Chem. Soc.* **2012**, *134*, 15664. (j) Meng, L.; Kamada, Y.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10048. (k) Kawasumi, K.; Zhang, Q.; Segawa, Y.; Scott, L. T.; Itami, K. *Nat. Chem.* **2013**, *5*, 739. (l) Muto, K.; Yamaguchi, J.; Lei, A.; Itami, K. *J. Am. Chem. Soc.* **2013**, *135*, 16384. (m) Uehara, T. N.; Yamaguchi, J.; Itami, K. *Asian J. Org. Chem.* **2013**, *2*, 938. (n) Tani, S.; Uehara, T. N.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2014**, *5*, 123.
(8) Yamaguchi, K.; Kondo, H.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2013**, *4*, 3753.
(9) Initially, we conducted the allylic C−H oxidation of **1a** using 5 mol % FePc instead of benzoquinone in the presence of 10 mol % Pd/**L1** catalyst, which is exactly the same procedure as that in ref 8. However, the reaction gave **2a** only in 2% yield.
(10) 5 mol % Pd(II) source is enough for efficient promotion of this reaction. The excess amount of ligand might stabilize the active species within the catalytic cycle.
(11) The product yields (**B**/**L** ratio) after 12 and 24 h under the optimized conditions using **L11** are as follows: 29% yield (**B**/**L** = 99:1) after 12 h; 53% yield (**B**/**L** = 99:1) after 24 h.
(12) When White's Pd/bis-sulfoxide catalyst was used for the reaction of **1a**, **2a** was formed in 83% yield with 98% branch selectivity.

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