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A palladium-catalyzed approach to allenic aromatic ethers and first total synthesis of terricollene A†

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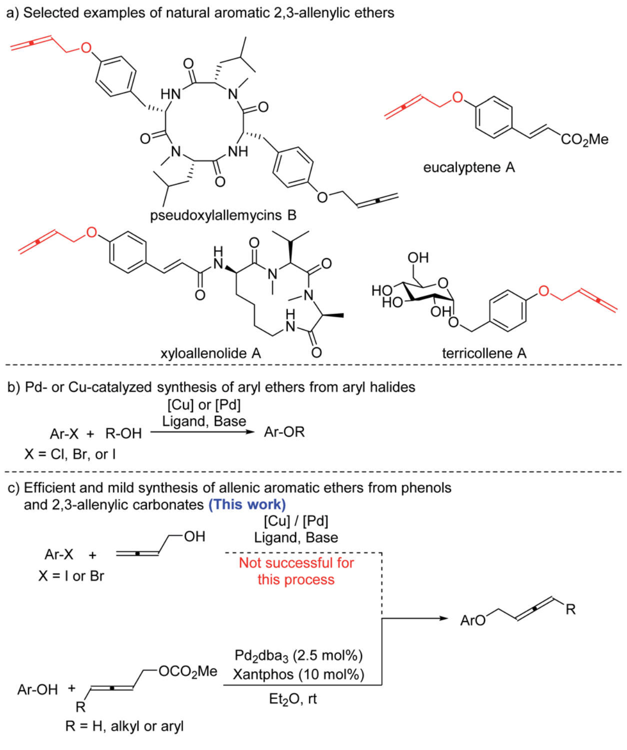
A palladium-catalyzed C–O bond formation reaction between phenols and allenylic carbonates to give 2,3-allenic aromatic ethers with decent to excellent yields under mild reaction conditions has been described. A variety of synthetically useful functional groups are tolerated and the synthetic utility of this method has been demonstrated through a series of transformations of the allene moiety. By applying this reaction as the key step, the total syntheses of naturally occurring allenic aromatic ethers, eucalyptene and terricollene A (first synthesis; 4.5 g gram scale), have been accomplished.

Introduction

Aromatic ethers are prevalent and prominent in a variety of natural products, pharmaceuticals, and agrochemicals.[1] Traditional methods for the preparation of aromatic ethers include the Williamson ether synthesis,[2] direct nucleophilic substitution reactions,[3] Mitsunobu reaction,[4] Ullman-type couplings of alkoxides with aryl halides,[5] *etc.* On the other hand, due to their unique chemical properties as well as the substituent-loading capability derived from the distinctive structure, allenes have been demonstrated as powerful platform molecules for the efficient syntheses of other functional organic compounds.[6,7] Interestingly, many aromatic 2,3-allenylic ethers are also found in the nature (Scheme 1a).[8] Reports on the syntheses of such aromatic ethers are very limited. Thus, development of new methods for the efficient synthesis of aromatic 2,3-allenylic ethers is of high interest currently. Herein, we disclose the development of palladium-catalyzed C–O bond formation between aryl phenols and allenylic carbonates to give allenic aromatic ethers in 70–99% yields under mild reaction conditions (Scheme 1c).

Results and discussion

In contrast to the well-established metal-catalyzed coupling reactions between aryl halides and phenols or aliphatic alcohols (Scheme 1b),[9] metal-catalyzed coupling reactions of aryl halides



Scheme 1 Naturally occurring aromatic 2,3-butadienyl ethers and the metal-catalyzed C–O bond formation for the synthesis of aromatic ethers.

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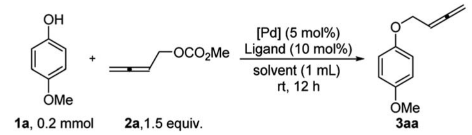
Table 1 Optimization of the reaction conditions for Pd-catalyzed reaction of *p*-methoxyphenol **1a** with 2,3-butadienyl carbonate **2a**[a]



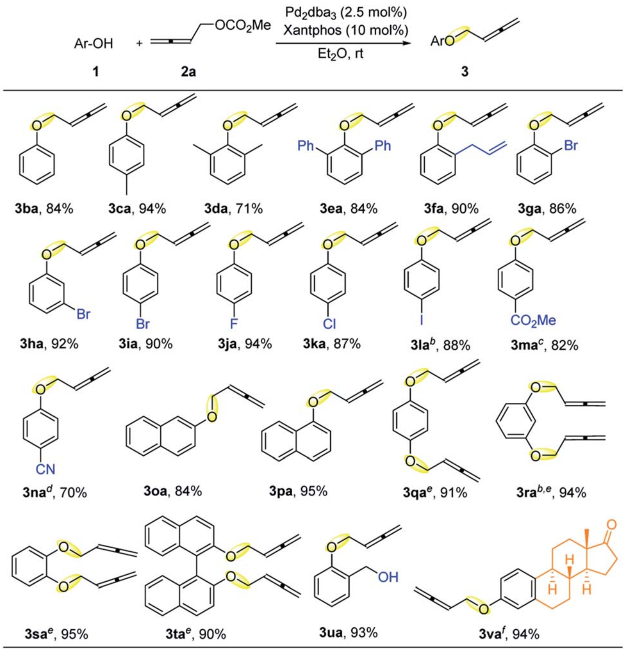
Entry	[Pd]	Ligand	Solvent	NMR yield of **3aa** (%)	Recovery of **1a** (%)
1	$[PdCl(\pi\text{-allyl})]_2$	BINAP	Toluene	39	48
2	Pd_2dba_3	BINAP	Toluene	68	26
3	$Pd(PPh_3)_4$	BINAP	Toluene	43	49
4	Pd_2dba_3	Xantphos	Toluene	80	10
5	Pd_2dba_3	DPEPhos	Toluene	28	70
6	Pd_2dba_3	BIPHEP	Toluene	10	89
7	Pd_2dba_3	SPhos	Toluene	68	13
8	Pd_2dba_3	Xantphos	MTBE	96	—
9	Pd_2dba_3	Xantphos	Et_2O	99 (95[b])	—
10	Pd_2dba_3	Xantphos	Dioxane	67	28
11	Pd_2dba_3	Xantphos	THF	49	47

[a] Yield and recovery were determined by ^1H NMR analysis using CH_3NO_2 as the internal standard. [b] The reaction was carried out with 1 mmol of **1a** and the isolated yield is shown in parentheses.

and allenols have not been developed (Scheme 1c). In a preliminary survey, the palladium-[10] and copper-catalyzed[11] coupling reactions between 4-iodoanisole and allenols were studied; however, only a trace amount of the desired allenyl aryl ether product was obtained (Scheme 1c, for details, see the ESI‡). Then 4-methoxyphenol **1a** was treated with 1.5 equiv. of 2,3-butadienyl carbonate **2a** in the presence of 2.5 mol% $[PdCl(\pi\text{-allyl})]_2$ and 10 mol% BINAP with toluene as the solvent at room temperature for 12 h. Interestingly, 39% yield of the expected allenol ether product **3aa** was formed with 48% recovery of 4-methoxyphenol **1a**. Various palladium catalysts and ligands were then screened (Table 1, entries 1–7). The combination of Pd_2dba_3 and Xantphos as the catalyst delivered the best result, affording 80% yield of **3aa** with 10% recovery of **1a** (Table 1, entry 4). Subsequent solvent screening (Table 1, entries 8–11) showed that Et_2O or MTBE was the best solvent, affording the product **3aa** in 99% or 96% yield, respectively (entries 8 and 9).

With the optimized conditions in hand, the scope of phenols was evaluated (Table 2). To our delight, parent phenol **1b** and electron-rich *p*-cresol **1c** gave high yields of **3ba** and **3ca**; even the reaction of highly sterically hindered 2,6-dimethyl or 2,6-diphenyl substituted phenols proceeded smoothly to afford **3da** or **3ea** in 71% or 84% yield, respectively. The *ortho*-allyl substituent also survived, allowing further modification based on the reactivity of the C–C double bond. Bromo-substituents at the *ortho*- (**3ga**), *meta*- (**3ha**), and *para*-positions (**3ia**) were all well tolerated without much difference, indicating that the steric effect is negligible and the relatively reactive C–Br bonds were tolerated. In addition, other synthetically useful halogen substituents such as F, Cl, and even I were all compatible, delivering the corresponding products **3ja**, **3ka**, and **3la** in 94%, 87%, and 88% yields, respectively. It is worth noting that the highly reactive C–I bond is generally less compatible in palladium-catalyzed reactions.[12] We reasoned that the relatively strong coordination effect of the allene unit brought the palladium catalyst to the carbonate, so that the oxidative addition of

Table 2 The substrate scope: phenols or naphthols[a]



[a] Reaction conditions: **1** (1.0 mmol), **2a** (1.5 mmol), Pd_2dba_3 (2.5 mol%), and Xantphos (10 mol%) in Et_2O (5 mL) at rt; isolated yields are shown. [b] In MTBE at 35 °C. [c] With 5 mol% $Pd(PPh_3)_4$ in dioxane at 35 °C. [d] With 5 mol% $Pd(PPh_3)_4$ in MTBE at 40 °C. [e] With 2.5 mmol of **2a**. [f] In MTBE at 60 °C in a sealed tube.

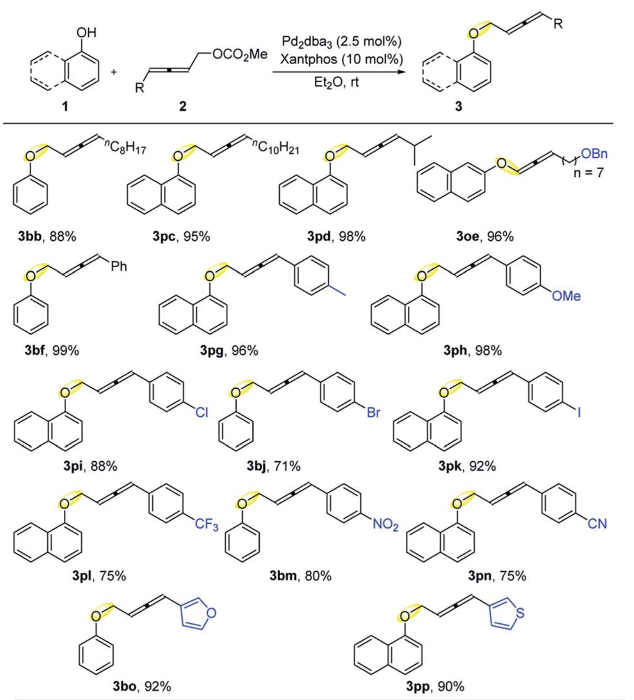
the palladium catalyst occurred exclusively to the carbonate unit, leaving the C–Br/I bond intact.[13] Furthermore, phenols with electron-withdrawing and synthetically versatile substituents such as CO_2Me and CN could also deliver the corresponding products **3ma** and **3na** in good to excellent yields upon changing the catalyst to $Pd(PPh_3)_4$. Moreover, 1- or 2-naphthols could also afford the corresponding products **3oa** or **3pa** in 84% and 95% yield, respectively. With 2.5 equiv. of allene **2a**, the coupling reactions of hydroquinone, resorcinol, catechol, and 1,1′-binaphthol gave the double-coupling products **3qa–3ta** in excellent yields. Interestingly, only the phenol hydroxy group was exclusively coupled leaving the benzylic hydroxyl group untouched to afford **3ua**. Such a coupling reaction of the hydroxyl group in estrone was also realized by changing the solvent to MTBE for a reaction at 60 °C to afford **3va** in an excellent yield.

We then evaluated the scope of 2,3-allenylic carbonates (Table 3): carbonates with 4-alkyl and isopropyl substituents delivered the coupling products **3bb**, **3pc**, and **3pd** in decent to excellent yields. Benzyl ether, which is a common and practical protecting group for the hydroxyl group, was also viable in this transformation affording **3oe** in 96% yield. 4-Phenyl-2,3-butadienyl carbonate **1f** reacted with phenol to afford **3bf** in an almost quantitative yield. Moreover, electron-donating groups such as *p*-methyl and *p*-methoxy and electron withdrawing yet potentially useful *p*-Cl, *p*-Br,[13] *p*-I,[13] *p*-CF_3, *p*-NO_2, and *p*-CN were all accommodated yielding the corresponding products **3pg–3pn** in decent yields. Last but not the least, 4-heteroaryl substituents such as a furyl and a thienyl group in allenylic carbonates **2** were also successfully tolerated affording corresponding products **3bo** and **3pp** in excellent yields.

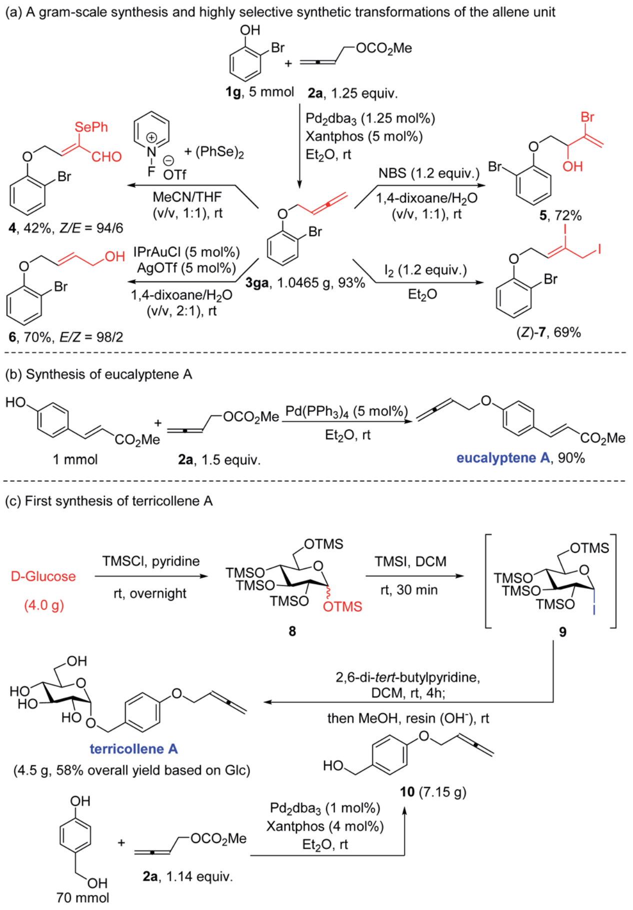
A gram-scale reaction between **1g** and **2a** delivered 1.0465 g of **3ga** in 93% yield with a reduced loading of both the catalyst and ligand (Scheme 2a). As a class of synthetically useful chemicals, the versatile allenyl unit could be transferred into different structure units: selenohydroxylation and oxidation of **3ga** with 1-fluoropyridinium/1,2-diphenyldiselane could deliver 2-selenoenal **4** with a *Z*/*E* selectivity of 94/6;[14] bromohydroxylation of this allenyl group in aqueous dioxane afforded terminal 2-bromoallylic alcohol **5** as the sole product in 72% yield;[15] the allenyl group may also be selectively transformed into the corresponding primary allylic alcohol **6** with an *E*/*Z* selectivity of 98/2 by a gold-catalyzed hydration reaction;[16] iodination of the allenyl group exclusively gave diiodide product (*Z*)-**7** in 69% yield.[17] It should be noted that these products are difficult to synthesize through traditional transition-metal catalyzed coupling reactions.[10,18]

Finally this method has been applied to the efficient syntheses of two naturally occurring allenes: eucalyptene A has been successfully synthesized under the catalysis of 5 mol% $Pd(PPh_3)_4$ in 90% yield from methyl 4-hydroxycinnamate and 2,3-butadienyl methyl carbonate (Scheme 2b); 70 mmol scale

Table 3 The substrate scope: 2,3-allenylic carbonates[a]



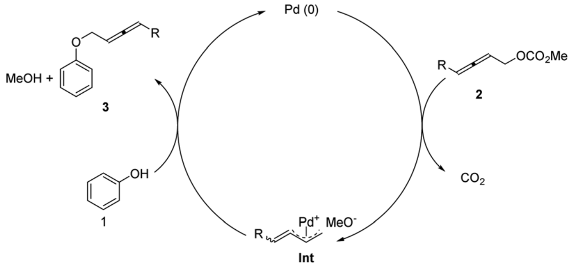
[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), Pd_2dba_3 (2.5 mol%), and Xantphos (10 mol%) in Et_2O (5 mL) at rt; isolated yield.


(a) A gram-scale synthesis and highly selective synthetic transformations of the allene unit

(b) Synthesis of eucalyptene A

(c) First synthesis of terricollene A

Scheme 2 Synthetic applications.



Scheme 3 Proposed mechanism.

reaction of *p*-hydroxymethylphenol with 1.14 equiv. of 2,3-butadienyl methyl carbonate **2a** afforded the corresponding *p*-hydroxymethylphenyl 2,3-butadienyl ether **10**. D-Glucose (4.0 g) was etherified with chlorotrimethylsilane in pyridine to give penta-*O*-trimethylsilyl-D-glucopyranose **8**, which was then reacted with iodotrimethylsilane to generate the glucosyl iodide **9** within 30 min at room temperature. The reaction of allene **10** (7.15 g) with **9** in the presence of 2,6-di-*tert*-butylpyridine in dry dichloromethane at room temperature for 4 h followed by treatment with methanol and resin(OH$^-$) to remove the silyl protecting groups afforded 4.5 g of terricollene A in 58% overall yield as the sole anomer, which is the first total synthesis of this natural product (Scheme 2c).[19]

A plausible mechanism is proposed (Scheme 3): the oxidative addition of Pd(0) with 2,3-allenylic carbonate would yield, after releasing CO$_2$, an α-methylene-π-allylic Pd intermediate **Int**,[20,13c,d] which would subsequently undergo a nucleophilic allenylation reaction with phenol to deliver the allenic aromatic ether **3** with regeneration of the catalytically active Pd(0) to finish the catalytic cycle.

Conclusions

In conclusion, we have described a general method of palladium-catalyzed C–O bond formation reaction between phenols and allenylic carbonates. This first example of such a C–O bond formation reaction exhibits a broad scope of both phenols and carbonates under very mild conditions, providing an attractive complement to traditional C–O bond formation reactions. The attractive reactivities of the allene unit in the products have been demonstrated. Moreover, the present catalytic system offers a convenient route for the efficient synthesis of naturally occurring aromatic 2,3-allenylic ethers, eucalyptene A and terricollene A, which exhibited cytotoxic activity against KB/KBv200 cells and HeLa/MCF-7 cells, respectively.[8b,d] Further studies are currently under way in our laboratories.

Data availability

The electronic supplementary information include experimental detail, NMR data, MS data, IR data, elemental analysis data, and all the spectra.

Author contributions

C. H. and S. M. conceived the idea. C. H. conducted the most of experiments. B. Y. supervised the total synthesis of terricollene A. C. H. and F. S. co-synthesized the terricollene A. Y. C., C. L., J. L., Q. L., A. Q., H. W., G. W., P. W., J. X., H. X., Y. Y., Y. Z., W. Z., and Y. Z. co-synthesized part of substrates and they contribute equally to this paper. C. H. and S. M. co-wrote the paper. All the authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) D. A. Evans and K. M. DeVries, in *Glycopeptide Antibiotics, Drugs and the Pharmaceutical Sciences*, ed. R. Nagarajan, Marcel Decker, Inc., New York, 1994, vol. 63, pp. 63–104; (*b*) A. V. R. Rao, M. K. Gurjar, K. L. Reddy and A. S. Rao, *Chem. Rev.*, 1995, **95**, 2135; (*c*) J. Zhu, *Synlett*, 1997, 133; (*d*) K. C. Nicolaou, C. N. C. Boddy, S. Bräse and N. Winssinger, *Angew. Chem., Int. Ed.*, 1999, **38**, 2096; (*e*) J. Blankenstein and J. Zhu, *Eur. J. Org. Chem.*, 2005, 1949; (*f*) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451; (*g*) X. Wang, A. Liu, L. Cao, M. Lei, Y. Ren, B. Zhou, L. Huang, D. Gao, H. Chen and L. Cheng, CN105985246A, 2016.

2 For selected examples, see: (*a*) B. Juršić, *Tetrahedron*, 1988, **44**, 6677; (*b*) E. Fuhrmann and J. Talbiersky, *Org. Process Res. Dev.*, 2005, **9**, 206; (*c*) A. R. Massah, M. Mosharafian, A. R. Momeni, H. Aliyan and H. J. Naghash, *Synth. Commun.*, 2007, **37**, 1807.

3 For selected examples, see: (*a*) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273; (*b*) J. Lindley, *Tetrahedron*, 1984, **40**, 1433; (*c*) A. J. Pearson and A. M. Gelormini, *J. Org. Chem.*, 1994, **59**, 4561; (*d*) T. F. Woiwode, C. Rose and T. J. Wandless, *J. Org. Chem.*, 1998, **63**, 9594; (*e*) J. Zilberman, *Org. Process Res. Dev.*, 2003, **7**, 303.

4 For selected examples, see: (*a*) R. G. Gentles, D. Wodka, D. C. Park and A. Vasudevan, *J. Comb. Chem.*, 2002, **4**, 442; (*b*) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman and K. V. P. P. Kumar, *Chem. Rev.*, 2009, **109**, 2551.

5 For selected examples, see: (*a*) F. Ullmann, *Chem. Ber.*, 1904, **37**, 853; (*b*) I. Beletskaya and A. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337.

6 N. Krause and A. S. K. Hashimi, *Modern Allene Chemistry*, Wiley-VCH, Weinheim, Germany, 2004.

7 For selected reviews, see: (*a*) A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3590; (*b*) S. Ma, *Acc. Chem. Res.*, 2003, **36**, 701; (*c*) S. Ma, *Chem. Rev.*, 2005, **105**, 2829; (*d*)

M. Jeganmohan and C. Cheng, *Chem. Commun.*, 2008, 3101; (*e*) S. Ma, *Acc. Chem. Res.*, 2009, **42**, 1679; (*f*) N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994; (*g*) S. Yu and S. Ma, *Angew. Chem., Int. Ed.*, 2012, **51**, 3074; (*h*) M. P. Muñoz, *Org. Biomol. Chem.*, 2012, **10**, 3584; (*i*) R. Zimmer and H.-U. Reissig, *Chem. Soc. Rev.*, 2014, **43**, 2888; (*j*) F. López and J. L. Mascareñas, *Chem. Soc. Rev.*, 2014, **43**, 2904; (*k*) T. Cañeque, F. M. Truscott, R. Rodriguez, G. Maestri and M. Malacria, *Chem. Soc. Rev.*, 2014, **43**, 2916; (*l*) Z. Wang, X. Xu and O. Kwon, *Chem. Soc. Rev.*, 2014, **43**, 2927; (*m*) W. Yang and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2014, **43**, 2941; (*n*) S. Kitagaki, F. Inagaki and C. Mukai, *Chem. Soc. Rev.*, 2014, **43**, 2956; (*o*) M. A. Tius, *Chem. Soc. Rev.*, 2014, **43**, 2979; (*p*) J. Le Bras and J. Muzart, *Chem. Soc. Rev.*, 2014, **43**, 3003; (*q*) E. Soriano and I. Fernández, *Chem. Soc. Rev.*, 2014, **43**, 3041; (*r*) B. Alcaide, P. Almendros and C. Aragoncillo, *Chem. Soc. Rev.*, 2014, **43**, 3106; (*s*) C. S. Adams, C. D. Weatherly, E. G. Burke and J. M. Schomaker, *Chem. Soc. Rev.*, 2014, **43**, 3136; (*t*) M. P. Muñoz, *Chem. Soc. Rev.*, 2014, **43**, 3164; (*u*) P. Koschker and B. Breit, *Acc. Chem. Res.*, 2016, **49**, 1524; (*v*) A. P. Pulis, K. Yeung and D. J. Procter, *Chem. Sci.*, 2017, **8**, 5240; (*w*) Y. Wei and M. Shi, *Org. Chem. Front.*, 2017, **4**, 1876; (*x*) B. Yang, Y. Qiu and J. Bäckvall, *Acc. Chem. Res.*, 2018, **51**, 1520; (*y*) J. Mascareñas, I. Varela and F. López, *Acc. Chem. Res.*, 2019, **52**, 465.

8 (*a*) A. Hoffmann-Röder and N. Krause, *Angew. Chem., Int. Ed.*, 2004, **43**, 1196; (*b*) S.-Y. Wang, W.-W. Mao, Z.-G. She, C.-R. Li, D.-Q. Yang, Y.-C. Lin and L.-W. Fu, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2785; (*c*) V. M. Dembitsky and T. Maoka, *Prog. Lipid Res.*, 2007, **46**, 328; (*d*) F. Zhang, S. Liu, X. Lu, L. Guo, H. Zhang and Y. Che, *J. Nat. Prod.*, 2009, **72**, 1782; (*e*) X.-L. Lu, Z.-L. Xu, X.-L. Yao, F.-J. Su, C.-H. Ye, J. Li, Y.-C. Lin, G.-L. Wang, J.-S. Zeng, R.-X. Huang, J.-S. Ou, H.-S. Sun, L.-P. Wang, J.-Y. Pang and Z. Pei, *Mar. Drugs*, 2012, **10**, 1307; (*f*) H. Guo, N.-B. Kreuzenbeck, S. Otani, M. Garciaaltares, H.-M. Dahse, C. Weigel, D.-K. Aanen, C. Hertweck, M. Poulsen and C. Beemelmanns, *Org. Lett.*, 2016, **18**, 3338; (*g*) A. J. Cameron, C. J. Squire, A. Gérenton, L. A. Stubbing, P. W. R. Harris and M. A. Brimble, *Org. Biomol. Chem.*, 2019, **17**, 3902.

9 For reviews of palladium-mediated ether synthesis, see: (*a*) J. F. Hartwig, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E.-i. Negishi, J. Wiley& Sons Inc., New York, 2002, pp. 1097–1106; (*b*) A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131–209; (*c*) S. Enthaler and A. Company, *Chem. Soc. Rev.*, 2011, **40**, 4912. For reviews of copper-mediated ether synthesis, see: (*d*) S. Bhunia, G. G. Pawar, S. V. Kumar, Y. Jiang and D. Ma, *Angew. Chem., Int. Ed.*, 2017, **56**, 16136. For reviews of other metal-mediated ether synthesis, see: (*e*) R. I. Khusnutdinov and A. R. Bayguzina, *Russ. J. Org. Chem.*, 2019, **55**, 903; (*f*) J. Zhang, S. Wang, Y. Zhang and Z. Feng, *Asian J. Org. Chem.*, 2020, **9**, 1519.

10 A. V. Vorogushin, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 8146.

11 (*a*) M. Wolter, G. Nordmann, G. E. Job and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 973; (*b*) D. Ma and Q. Cai, *Org. Lett.*, 2003, **5**, 3799.

12 (*a*) K. Okuro and H. Alper, *J. Org. Chem.*, 1997, **62**, 1566; (*b*) S. Husinec, M. Jadranin, R. Markovic, M. Petkovic, V. Savic and N. Todorovic, *Tetrahedron Lett.*, 2010, **51**, 4066; (*c*) A. Kumbhar, *J. Organomet. Chem.*, 2017, **848**, 22.

13 For the coordination effect of allenes with transition metal catalysts, see: (*a*) X. Pu, X. Qi and J. M. Ready, *J. Am. Chem. Soc.*, 2009, **131**, 10364; (*b*) F. Cai, X. Pu, X. Qi, V. Lynch, A. Radha and J. M. Ready, *J. Am. Chem. Soc.*, 2011, **133**, 18066; (*c*) S. Song, J. Zhou, C. Fu and S. Ma, *Nat. Commun.*, 2019, **10**, 507; (*d*) S. Song and S. Ma, *Chin. J. Chem.*, 2020, **38**, 1233; (*e*) H. K. Maliszewska, D. L. Hughes and M. P. Muñoz, *Dalton Trans.*, 2020, **49**, 4034.

14 B. Alcaide, P. Almendros, T. Martínez del Campo, L. Martín, G. Palop and M. Toledano-Pinedo, *Org. Chem. Front.*, 2019, **6**, 2447.

15 W. Kong, B. Guo, C. Fu and S. Ma, *Eur. J. Org. Chem.*, 2011, 2278.

16 Z. Zhang, S. Du Lee, A. S. Fisher and R. A. Widenhoefer, *Tetrahedron*, 2009, **65**, 1794.

17 M. J. Campbell, P. D. Pohlhaus, G. Min, K. Ohmatsu and J. S. Johnson, *J. Am. Chem. Soc.*, 2008, **130**, 9180.

18 (*a*) P. A. Evans and D. K. Leahy, *J. Am. Chem. Soc.*, 2000, **122**, 5012; (*b*) D. F. Taber, M. I. Sikkander, J. F. Berry and K. J. Frankowski, *J. Org. Chem.*, 2008, **73**, 1605; (*c*) A. Arfaoui, F. Saâdi, A. Nefzi and H. Amri, *Synth. Commun.*, 2015, **45**, 2627.

19 (*a*) W. Fan, Y. Wu, X.-K. Li, N. Yao, X. Li, Y.-G. Yu and L. Hai, *Eur. J. Med. Chem.*, 2011, **46**, 3651; (*b*) M. Furukawa, S. Kamo, M. Makino, M. Kurita, K. Tabata, K. Matsuzaki, T. Suzuki and T. Uchiyama, *Phytochemistry*, 2017, **136**, 147.

20 For selected examples of Pd-catalyzed reactions involving the α-methylene-π-allylic Pd intermediate with malonates and amides, see: (*a*) D. Djahanbini, B. Cazes and J. Gore, *Tetrahedron Lett.*, 1984, **25**, 203; (*b*) B. M. Trost and J. M. Tour, *J. Org. Chem.*, 1989, **54**, 484; (*c*) J. Nokami, A. Maihara and J. Tsuji, *Tetrahedron Lett.*, 1990, **31**, 5629; (*d*) M. E. Piotti and H. Alper, *J. Org. Chem.*, 1994, **59**, 1956; (*e*) Y. Imada, K. Ueno, K. Kutsuwa and S. Murahashi, *Chem. Lett.*, 2002, 140; (*f*) M. Rubin, J. Markov, S. Chuprakov, D. J. Wink and V. Gevorgyan, *J. Org. Chem.*, 2003, **68**, 6251; (*g*) M. Ogasawara, A. Okada, S. Watanabe, L. Fan, K. Uetake, K. Nakajima and T. Takahashi, *Organometallics*, 2007, **26**, 5025; (*h*) S. Song, J. Zhou, C. Fu and S. Ma, *Nat. Commun.*, 2019, **10**, 507.