ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Lin, T. Zhu, M. Jia and S. Ma, *Chem. Commun.*, 2019, DOI: 10.1039/C9CC00979E.

Volume 52 | Number 1 | 4 January 2016 | Pages 1–216

ChemComm

Chemical Communications

www.rsc.org/chemcomm

ISSN 1359-7345

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

Marilyn M. Olmstead, Alan L. Balch, Josep M. Poblet, Luis Echegoyen et al.

Reactivity differences of $Sc_3N@C_{2n}$ (2n = 68 and 80). Synthesis of the first methanofullerene derivatives of $Sc_3N@D_{5h}$-C_{80}

175 YEARS

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C9CC00979E

Journal Name

COMMUNICATION

Pd-catalyzed Ring Opening Coupling Reaction of 2,3-Allenylic Carbonates with Cyclopropanols

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

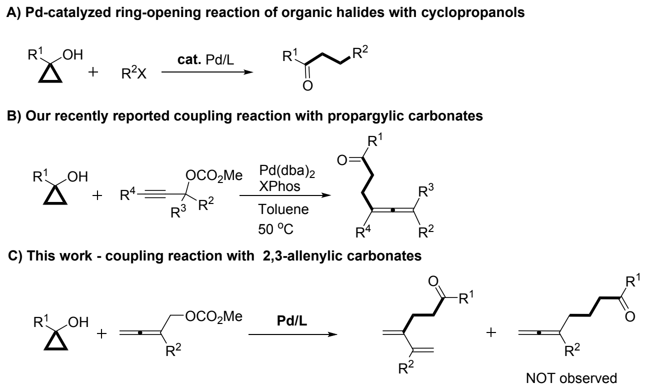
DOI: 10.1039/x0xx00000x

www.rsc.org/

Jie Lin,[a] Tonghao Zhu,[a] Minqiang Jia,[a] and Shengming Ma*[a,b]

Palladium-catalyzed coupling reaction of 2,3-allenylic carbonates with cyclopropanols was developed, affording valuable 1,3-diene products with different functional groups efficiently under mild reaction conditions. Gram scale synthesis was easily conducted with synthetic transformations demonstrated.

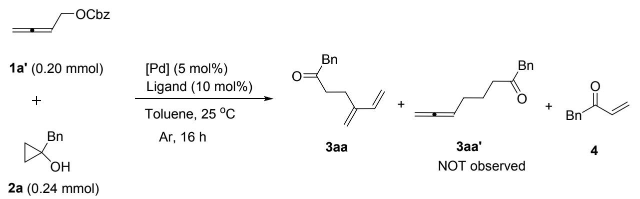
Cyclopropanols are important building blocks in organic synthesis, which may serve as the metal homoenolate surrogates.[1] Transitional metal catalyzed ring-opening coupling reaction of cyclopropanol with organic halide, such as aryl and benzyl halide,[2b-2d] has been reported (Scheme 1A).[2] With our longstanding interest in functional allene synthesis, we recently reported the matched coupling reaction of cyclopropanols with propargylic carbonates delivering the multi-substituted allene products in good yields (Scheme 1B).[3] Herein we wish to report the coupling reaction of cyclopropanols with 2,3-allenylic carbonates providing conjugated 1,3-diene products efficiently (Scheme 1C).[4]



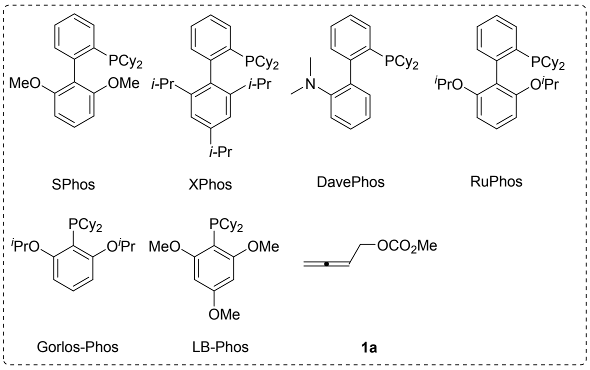
Scheme 1 Different coupling reaction types of cyclopropanols.

2,3-Allenylic benzyl carbonate **1a'** and cyclopropanol **2a** were selected as the model substrates. Firstly, different ligands were screened with $Pd(dba)_2$ as the palladium source for the reaction in toluene at 25 °C. When bidentate phosphorous ligand such as DPPF and BINAP were used, the unexpected product **3aa** was obtained in 8% and 11% yields, the ring-opening-β-H elimination product **4** was also captured in 12% and 19% yields, and the formation of allene product, 1-phenylocta-6,7-dien-2-one **3aa'**, was not detected (Table 1, entries 1 and 2). Other ligands such as PPh_3, PCy_3, SPhos, XPhos, DavePhos, RuPhos, *t*-BuXPhos, Gorlos-Phos, and LB-Phos were also screened, generating the product **3aa** in 6-58% yields (Table 1, entries 3-11): XPhos was found to be the optimal ligand, providing the corresponding conjugated 1,3-diene product **3aa** in 58% yield (Table 1, entry 6). PPh_3 and RuPhos also provided the product **3aa** in 40% and 47% yields, respectively (Table 1, entries 3 & 8). Different palladium sources, such as $Pd(OAc)_2$, $Pd(TFA)_2$, $Pd_2(dba)_3 \bullet CHCl_3$, $PdCl_2$, $Pd(PPh_3)_4$, and $[Pd(allyl)Cl]_2$ were also screened and $Pd(dba)_2$ was still the optimal (Table 1, entries 12-17). Different bases such as $K_3PO_4 \bullet 3H_2O$ or Et_3N were also investigated, however, the effect was NOT obvious (Table 1, entries 18 and 19). Finally, methyl carbonate was used instead to afford the final product **3aa** in 64% yield (Table 1, entry 20) and the β-H elimination product **4** was disappeared. It should be highlighted that **3aa** was selectively generated in this reaction, and **3aa'** was NOT observed in all the cases during our optimization of the reaction conditions.[4]

Table 1 Optimization of the reaction conditions[a]

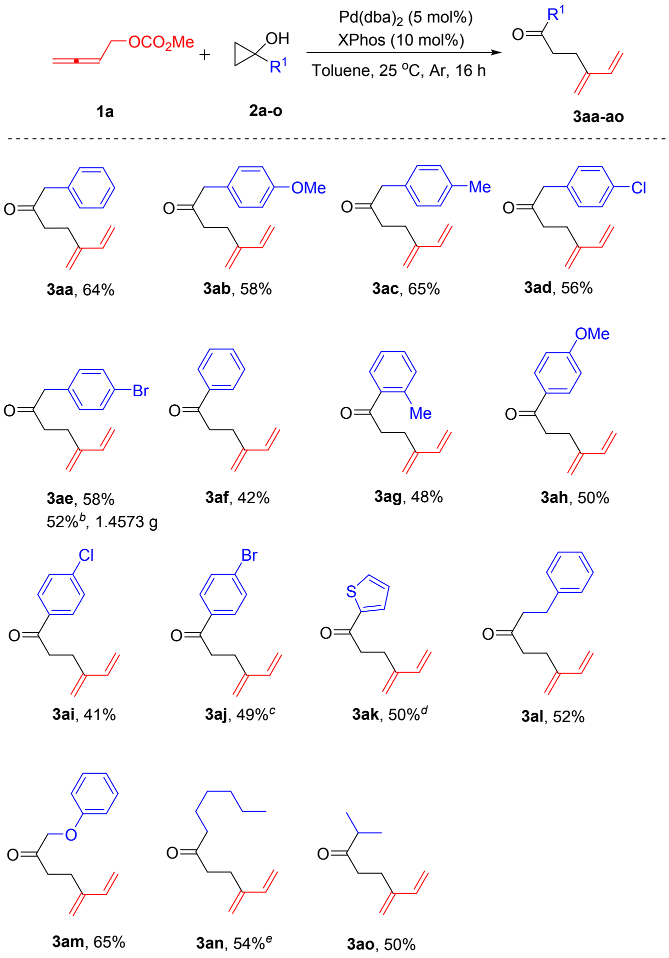


Entry	Ligand	[Pd]	(NMR, **3aa/4/1a'**, %)[b]
1	DPPF	$Pd(dba)_2$	8/12/7
2	BINAP	$Pd(dba)_2$	11/19/0
3	PPh_3	$Pd(dba)_2$	40/31/0
4	PCy_3	$Pd(dba)_2$	28/0/31
5	SPhos	$Pd(dba)_2$	36/36/0
6	XPhos	$Pd(dba)_2$	58/27/0
7	DavePhos	$Pd(dba)_2$	24/45/0
8	RuPhos	$Pd(dba)_2$	47/55/0
9	*t*-BuXPhos	$Pd(dba)_2$	6/6/0
10[c]	Gorlos-Phos	$Pd(dba)_2$	10/46/0
11[c]	LB-Phos	$Pd(dba)_2$	12/24/0
12	XPhos	$Pd(OAc)_2$	29/37/0
13	XPhos	$Pd(TFA)_2$	19/20/21
14	XPhos	$Pd_2(dba)_3•CHCl_3$	50/21/0
15	XPhos	$PdCl_2$	0/0/82
16	XPhos	$Pd(PPh_3)_4$	38/26/0
17	XPhos	$[Pd(allyl)Cl]_2$	0/0/93
18[d]	XPhos	$Pd(dba)_2$	61/20/0
19[e]	XPhos	$Pd(dba)_2$	61/24/0
20[f]	**XPhos**	**$Pd(dba)_2$**	**64 (64)/0/0**



[a] Reaction conditions: **1a'** (0.20 mmol), **2a** (0.24 mmol), [Pd] (5 mol%), and Ligand (10 mol%) in toluene (1.0 mL).[b] NMR yield with CH_2Br_2 as the internal standard. [c] K_2CO_3 (10 mol%) was added by using Gorlos-Phos•HBF_4 (10 mol%) or LB-Phos•HBF_4 (10 mol%) as the ligand. [d] K_3PO_4•$3H_2O$ (1.0 equiv) was added. [e] Et_3N (1.0 equiv) was added. [f] **1a** (0.20 mmol) was used; NMR yield with mesitylene as the internal standard; Isolated yield is in the parentheses.

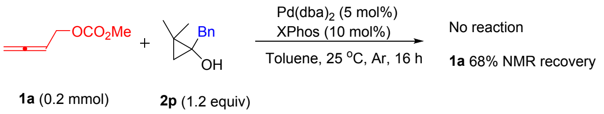
Under the optimized reaction conditions (Table 1, entry 20), different cyclopropanols were investigated to show the generality of this reaction. Different functional groups such as methoxy, methyl, chloro, and bromo may all be tolerated on the benzyl group providing the desired 1,3-diene products **3ab-3ae** in 56%-65% yields; the reaction of **1a** with **2e** was also carried out on 10 mmol scale providing the final product **3ae** in 1.4573 g (52% yield), demonstrating the practicability of this reaction. With phenylcylopropanols, different substituents on the phenyl groups, such as H, 2-methyl, 4-methoxy, 4-chloro, 4-bromo, may also be introduced providing the corresponding products **3af-3aj** in moderate yields (41%-50%). Thienyl substituted product **3ak** can also be synthesized successfully in 50% yield. Finally, different alkyl groups, such as phenylethyl, phenoxymethyl, *n*-hexyl and *i*-isopropyl also worked well in this reaction (**3al-3ao**, 52%-65% yields).



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), $Pd(dba)_2$ (5 mol%), and XPhos (10 mol%) in toluene (1.0 mL) at 25 ºC. [b] **1a** (10 mmol), **2e** (12 mmol), $Pd(dba)_2$ (5 mol%), and XPhos (10 mol%) in toluene (50 mL) at 25 ºC for 17 h. [c] **3aj** was obtained as a mixture with ring opening protonolysis product. [d] 25 h. [e] **1a** (1.0 mmol), **2n** (1.2 mmol), and toluene (5.0 mL) was used.

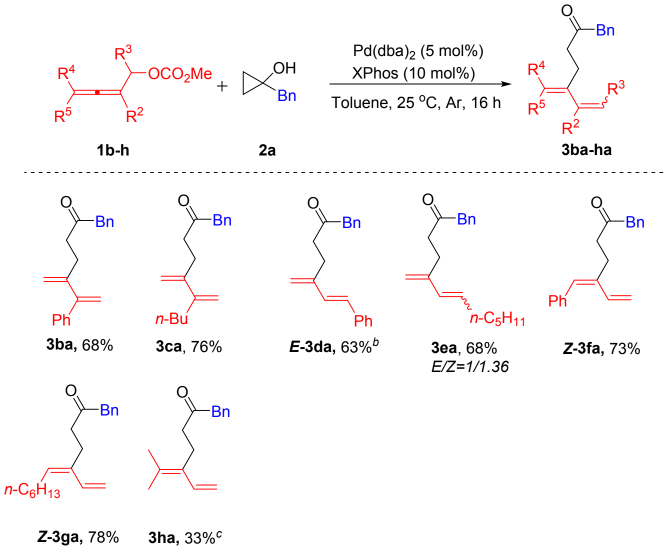
Scheme 2. Substrate scope referred to cyclopropanols.[a]

However, the reaction of sterically crowded substrate **2p** failed (eq 1).



(1)

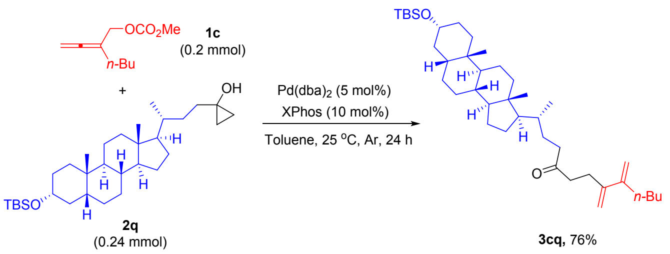
The scope of 2,3-allenyl methyl carbonates was also investigated with cyclopropanol **2a** (Scheme 3). R^2 could be either phenyl or *n*-butyl group providing the corresponding 2,3-disubstituted dienes **3ba** and **3ca** in 68% and 76% yield. R^3 could also be either phenyl or *n*-pentyl group providing the corresponding 1,3-disubstituted dienes ***E*-3da** and **3ea** in 63% and 68% yield. In the generated ***E*-3da**, a *E*/*Z* ratio of 7.2/1 was observed by ^{1}H NMR analysis using mesitylene as the internal standard, however, *Z*-isomer was converted to *E*-isomer exclusively after purification by column chromatography on silica gel. R^5 could also be phenyl or *n*-hexyl group providing the corresponding 3,4-disubstituted dienes ***Z*-3fa** and ***Z*-3ga** highly stereoselectively in 73% and 78% yield. When R^4 and R^5 were both methyl groups, the desired product **3ha** was obtained in 33% yield.



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), $Pd(dba)_2$ (5 mol%), and XPhos (10 mol%) in toluene (1.0 mL) at 25 °C. [b] **1** (0.26 mmol) and **2a** (0.2 mmol) were used. [c] **1** (0.4 mmol) and **2a** (0.2 mmol) were used.

Scheme 3 Substrate scope of 2,3-allenylic carbonates.[a]

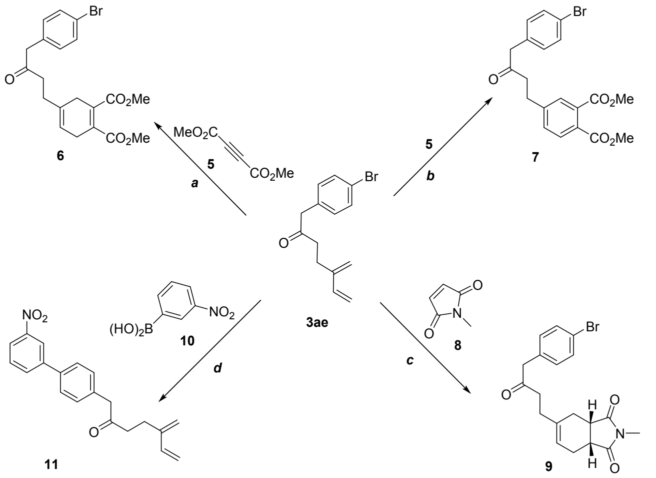
To our great delight, the steroid containing 2,3-disubstituted diene **3cq** could also be synthesized successfully in 76% yield, further proving the wide scope of this reaction(Scheme 4).



Scheme 4 Synthesis of conjugated diene containing a steroidal skeleton.

View Article Online
DOI: 10.1039/C9CC00879E

The final diene product **3ae** may undergo different transformations to show the utility of this reaction (scheme 5). Intermolecular Diels-Alder reaction of **3ae** with dimethyl but-2-ynedioate **5** provided the cyclohexadiene product **6** in 88% yield.[4g] The intermolecular Diels-Alder reaction with **5** followed by oxidation with DDQ delivered the aromatization product **7** (83% yield).[4g,5] The intermolecular Diels-Alder reaction with another acceptor *N*-Methylmaleimide **8** gave the cyclohexene product **9** in as high as 93% yield.[4g] Finally, the Suzuki coupling reaction of **3ae** with (3-nitrophenyl) boronic acid **10** generated the coupling product **11** efficiently in 71% yield.[6]

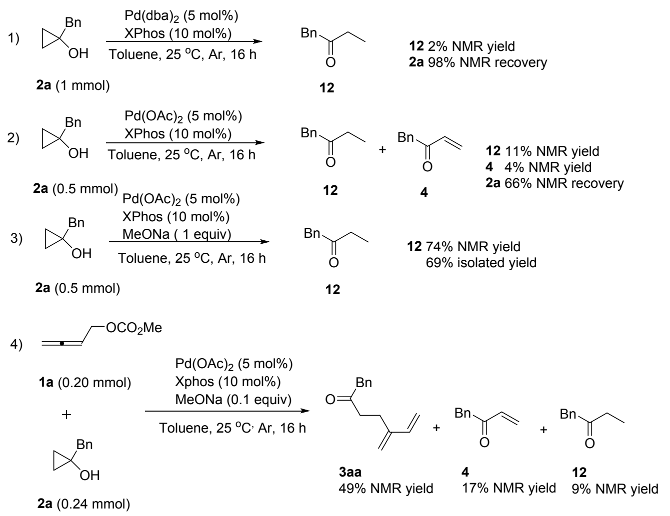


[a] **3ae** (0.5 mmol), **5** (2.5 equiv), DCM, dark, reflux, 77 h, 88%; [b] **3ae** (0.5 mmol), **5** (3.0 equiv), DCM, dark, reflux, 77 h; then DDQ (1.1 equiv), toluene, rt, 41 h, 83%; [c] **3ae** (0.5 mmol), **8** (1.5 equiv), DCM, reflux, 24 h, 93%; [d] **3ae** (0.2 mmol), **10** (3.0 equiv), $Pd(PPh_3)_4$ (5 mol%), K_3PO_4 (2.0 equiv), DMF, 50 °C, 65 h, 71%.

Scheme 5 Synthetic applications.

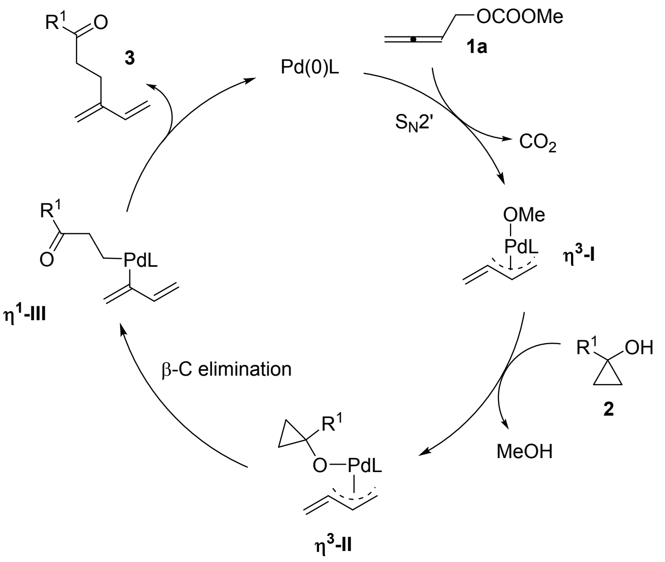
Several control experiments were carried out in order to unveil the reaction mechanism (Scheme 6). Firstly, when cyclopropanol **2a** reacted under the standard conditions, 98% yield of the starting material **2a** was recovered, and 2% of the ring opening-protonolysis product **12** was observed (eq 1). When $Pd(OAc)_2$ was used instead of $Pd(dba)_2$, the yield of ring opening-protonolysis product **12** was improved to 11%, and the ring opening/β-H elimination product **4** was also observed in 4% NMR yield (eq 2). Additionally, when MeONa was added, the ring opening-protonolysis product **12** was formed in 74% with no **2a** recovered (eq 3). The reaction in the presence of $Pd(OAc)_2$ (5 mol%) and NaOMe (10 mol%) afforded the diene product **3aa** in only 49% NMR yield together with 9% NMR yield of protonolysis product **12** and 17% of ring opening/β-H elimination enone product **4** being yield (eq. 4). These experiments revealed that Pd(II) and MeONa were facilitating the ring opening protonolysis of cyclopropanol **2a**.

View Article Online
DOI: 10.1039/C9CC00979E



Scheme 6 Mechanistic studies.

Based on these results, a possible mechanism was proposed (Scheme 7). Firstly, oxidative addition of **1a** with Pd(0) would form the methylene (π-allyl) palladium methoxide **η^3-I** by releasing one molecule of CO_2. Ligand exchange of cyclopropanol **2** with intermediate **η^3-I** with the help of MeO^- gave the intermediate **η^3-II**. Subsequent β-C elimination generated the branched intermediate **η^1-III** highly selectively.[4] Finally reductive elimination would form the desired product **3** and regenerate Pd(0).



Scheme 7 A proposed mechanism.

In conclusion, the palladium catalyzed coupling reaction of 2,3-allenylic carbonates with cyclopropanols was developed providing the synthetically useful 1,3-diene products efficiently. The reaction worked under very mild reaction conditions (at rt) with various different functional groups being tolerated. Several useful transformations, such as Diels-Alder reaction and Suzuki coupling reaction of the final diene products were also demonstrated.

Financial support from the National Basic Research Program (2015CB856600) and the National Natural Science Foundation of China (21502020) is greatly appreciated. We also thank Yang Tang in this group for reproducing the results of **3af**, **3ca**, and **3aj**.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For reaction of cyclopropanols, see reviews: (a) N. Nithiy, D. Rosa and A. Orellana, *Synthesis*, 2013, **45**, 3199; (b) D. Rosa, A. Nikolaev, N. Nithiy and A. Orellana, *Synlett,* 2015, **26**, 441; (c) A. Nikolaev and A. Orellana, *Synthesis*, 2016, **48**, 1741.

2 Selected recent examples, see: (a) P. P. Das, K. Belmore and J. K. Cha, *Angew. Chem. Int. Ed.,* 2012, **51**, 9517; (b) K. Cheng and P. J. Walsh, *Org. Lett.,* 2013, **15**, 2298; (c) D. Rosa and A. Orellana, *Chem. Commun.,* 2013, **49**, 5420; (d) N. Nithiy and A. Orellana, *Org. Lett.,* 2014, **16**, 5854; (e) Y. Li, Z. Ye, T. M. Bellman, T. Chi and M. Dai, *Org. Lett.,* 2015, **17**, 2186; (f) Z. Ye and M. Dai, *Org. Lett.,* 2015, **17**, 2190; (g) S. Wang, L. Guo, H. Wang and X.-H. Duan, *Org. Lett.,* 2015, **17**, 4798; (h) Z. Ye, K. E. Gettys, X. Shen and M. Dai, *Org. Lett.,* 2015, **17**, 6074; (i) H. Zhao, X. Fan, J. Yu and C. Zhu, *J. Am. Chem. Soc.,* 2015, **137**, 3490; (j) X. Zhou, S. Yu, L. Kong and X. Li, *ACS Catal.,* 2016, **6**, 647; (k) K. Jia, F. Zhang, H. Huang and Y. Chen, *J. Am. Chem. Soc.,* 2016, **138**, 1514; (l) H. Zhang, G. Wu, H. Yi, T. Sun, B. Wang, Y. Zhang, G. Dong and J. Wang, *Angew. Chem. Int. Ed.,* 2017, **56**, 3945; (m) A. Nikolaev, C. Y. Legault, M. Zhang and A. Orellana, *Org. Lett.,* 2018, **20**, 796.

3 P. Wu, M. Jia, W. Lin and S. Ma, *Org. Lett.,* 2018, **20**, 554.

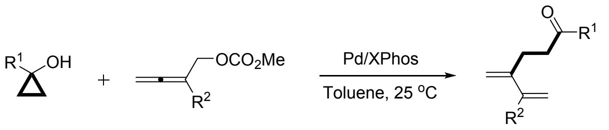
4 For selective generation of 1,3-diene products, see: (a) D. Djahanbini, B. Cazes and J. Gore, *Tetrahedron Lett.,* 1984, **25**, 203; (b) D. Djahanbini, B. Cazes and J. Gore, *Tetrahedron,* 1984, **40**, 3645; (c) D. Djahanbini, B. Cazes, J. Gore and F. Gobert, *Tetrahedron,* 1985, **41**, 867; (d) J. Nokami, A. Maiham and J. Tsuji, *Tetrahedron Lett.,* 1990, **31**, 5629; (e) T. Moriya, T. Furuuchi, N. Miyaura and A. Suzuki, *Tetrahedron*, 1994, **50**, 7961; (f) J. S. Schneekloth Jr., M. Pucheault and C. M. Crews, *Eur. J. Org. Chem.,* 2007, 40-43; (g) H. Wang, B. Beiring, D. Yu, K. D. Collins and F. Glorius, *Angew. Chem. Int. Ed*. 2013, **52**, 12430.

5 G. Hilt and M. Danz, *Synthesis*, 2008, **14**, 2257.

6 T. Watanabe, N. Miyaura and A. Suzuki, *Synlett*, 1992, 207.

View Article Online
DOI: 10.1039/C9CC00979E

Table of contents



23 examples, up to 78% yield

- √ **Room temperature reaction**
- √ **Without base**
- √ **Wide substrate scope**
- √ **Gram scale reaction and steroid skeleton tolerated**