ACS Catalysis

Letter

Cite This: ACS Catal. 2019, 9, 11669−11675

pubs.acs.org/acscatalysis

Highly Regioselective C−H Alkylation of Alkenes Through an Aryl to Vinyl 1,4-Palladium Migration/C−C Cleavage Cascade

Quannan Wang,[†,‡,¶] Rongjun Chen,[†,‡,⊥,¶] Jiang Lou,[†,‡,¶] Dong H. Zhang,[†,⊥] Yong-Gui Zhou,[*,†] and Zhengkun Yu[*,†,§]

[†]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, P. R. China

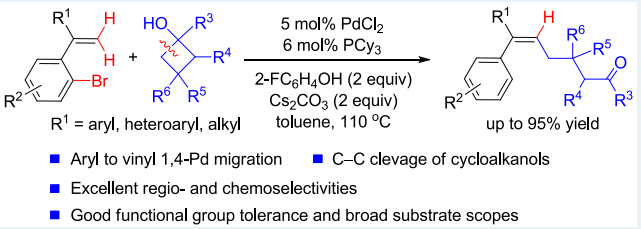
[‡]University of Chinese Academy of Sciences, Beijing 100049, P. R. China

[⊥]State Key Laboratory of Molecular Reaction Dynamics and Center for Theoretical and Computational Chemistry, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China

[§]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China

Supporting Information

ABSTRACT: Palladium-catalyzed C−H alkylation of *gem*-disubstituted ethylenes has been efficiently achieved with cyclobutanols as the coupling partners through an aryl to vinyl 1,4-palladium migration/ring-opening C−C cleavage cascade, giving trisubstituted alkenes in high yields. The protocol features good regioselectivity, high yields, broad substrate scopes, and good functional group tolerance. The mechanistic studies implicate that the cross-coupling reaction occurs via oxidative addition, 1,4-palladium migration, ring-opening C−C cleavage, and reductive elimination. DFT calculations have revealed that the high efficiency of the protocol is attributed to the thermodynamically favored 1,4-palladium migration assisted by 2-fluorophenol.



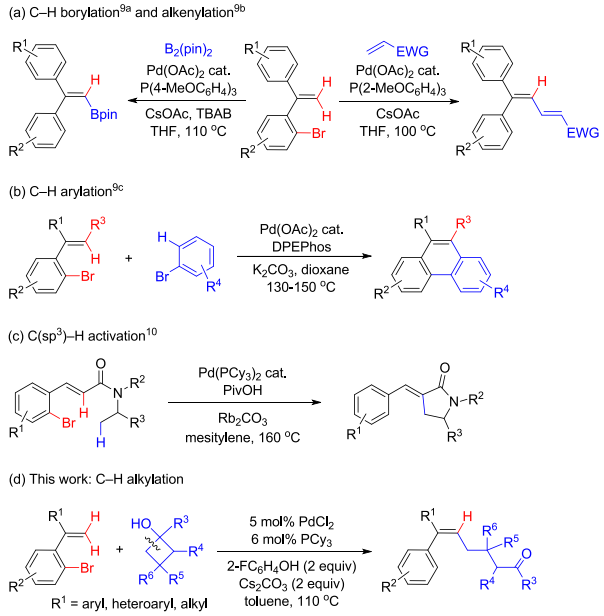
KEYWORDS: *palladium migration, C−H alkylation, alkenes, cyclobutanols, C−C bond cleavage*

Transition-metal-catalyzed site-selective C−H functionalization has been used as a promising concise route for the direct construction of carbon−carbon and carbon−heteroatom bonds in organic synthesis.[1] The directing strategy through introduction of coordinating moieties,[1c] or traceless directing groups such as halides[2] has been documented to achieve this goal. However, the former approach employing coordinating moieties as the directing groups often requires two redundant steps, that is, installation and removal of the directing groups. On the contrary, the latter one by means of traceless directing groups requires no removal of the directing groups and has recently been paid much attention as a useful synthetic tool to enable remote C−H functionalization.[2a,c,d,f] In this regard, 1,4-migration of a transition metal has been considered as an alternative method to introduce a metal moiety to a remote site, which can not be readily accessed through the conventional methods, to achieve the desired transformation.[3] The palladium migrations have been well explored, including those from aryl to aryl,[4] aryl to alkyl,[5] aryl to benzyl,[6] and alkyl to aryl.[7] A few examples have also been reported on vinyl to aryl or aryl to vinyl migration for a transition-metal. For example, Larock et al. developed a Pd-catalyzed cross-coupling of aryl iodides with alkynes for the synthesis of 9-alkylidene-9*H*-fluorenes via vinyl to aryl palladium migration.[8a] Suffert and co-workers reported a Pd-catalyzed cyclization and C−H activation/Stille cross-coupling tandem reaction involving vinyl to aryl 1,5-palladium shift.[8b,c] Palladium-catalyzed cross-coupling of alkynes and appropriately substituted aryl iodides was also achieved for the synthesis of substituted carbazoles, indoles, and dibenzofurans by heteroatom-directed vinyl to aryl palladium migration.[8d] In comparison to the relatively well-established vinyl to aryl 1,4-palladium migration, aryl to vinyl 1,4-palladium migration still remains a challenge presumably because of the relatively weak acidity of the vinylic C−H bond which renders the reaction to directly occur on the aryl ring rather than at the vinylic carbon site newly palladated by the palladium migration.[4b] Recently, Lin, Feng, and Zhang et al. realized the C−H borylation,[9a] alkenylation,[9b] and arylation/annulation[9c] of *gem*-diaryl alkenes through aryl to vinyl 1,4-palladium migration (Scheme 1a,b). A step-economical method to construct arylidene γ-lactams and indanones through a palladium-catalyzed domino reaction involving 1,4-palladium shift and C(sp^3)−H activation (Scheme 1c)[10] and asymmetric rhodium-catalyzed alkenylation of enones and imines with arylboronic acids by highly efficient aryl to vinyl 1,4-rhodium migration[11] were also reported. Although considerable advance has recently been made in aryl

Received: September 27, 2019
Revised: November 11, 2019
Published: November 13, 2019

DOI: 10.1021/acscatal.9b04161
ACS Catal. 2019, 9, 11669−11675

Scheme 1. Aryl to Vinyl 1,4-Palladium Migrations

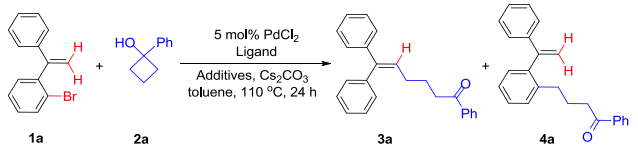


to vinyl 1,4-palladium and -rhodium migrations, C−H alkylation using this strategy has not yet been achieved.

Cyclobutanols[12] have been successfully employed as the building blocks for the synthesis of γ-substituted ketones by cleavage of the strained cyclic C−C bonds through transition-metal-catalyzed ring-opening reaction involving β-carbon elimination[13] or radical ring-opening.[14] During our ongoing investigation of C−C cleavage of cycloketone oxime esters[15] and C−H functionalization of internal alkenes,[16] we reasonably envisioned the C−H alkylation of *gem*-diaryl alkenes with cyclobutanols as the alkylating reagents through aryl to vinyl 1,4-palladium migration. Herein, we disclose palladium-catalyzed C−H alkylation of such terminal alkenes with cyclobutanols for the highly regioselective synthesis of trisubstituted alkenes (Scheme 1d).

Initially, the reaction of 1-bromo-2-(1-phenylvinyl)benzene (**1a**) with 1-phenylcyclobutanol (**2a**) was conducted to screen the reaction conditions (Table 1). In the presence of 5 mol % $PdCl_2$ as the catalyst, 10 mol % PCy_3 as the ligand, and Cs_2CO_3 (2 equiv) as the base in refluxing toluene, the reaction of **1a** and **2a** in a 1:2 molar ratio gave the direct cross-coupling product, that is, compound **4a** (92%), as the only detectable product, and no reaction occurred at the terminus of the alkenyl functionality (Table 1, entry 1). With water as the additive, **4a** was also obtained in a high yield (76%) (Table 1, entry 2). Surprisingly, addition of 2.0 equiv of phenol as the additive obviously inhibited the formation of **4a** and switched the reaction pathway to generate the target aryl to vinyl 1,4-palladium migration product **3a** (61%) with a 4.7:1 molar ratio of **3a**:**4a** (Table 1, entry 3). Use of 2-FC_6H_4OH further enhanced both the reaction efficiency and regioselectivity, leading to **3a** in 87% yield with minor formation of **4a** (**3a**:**4a** > 20:1) (Table 1, entries 4−9). Variation of the ligand loading from 10 mol % to 6 mol % did not affect the reaction, giving **3a**

Table 1. Screening of the Reaction Conditions[a]



entry	**1a**:**2a** (molar ratio)	PCy_3 (mol %)	additive (2 equiv)	yield of **3a** (%)	**3a**:**4a**[b] (molar ratio)
1	1:2	10		-/92[c]	<1:20
2	1:2	10	H_2O	-/76[c]	<1:20
3	1:2	10	C_6H_5OH	61	4.7:1
4	1:2	10	4-MeC_6H_4OH	80	10:1
5	1:2	10	2-MeC_6H_4OH	56	7:1
6	1:2	10	4-FC_6H_4OH	77	17.1:1
7	1:2	10	3-FC_6H_4OH	82	>20:1
8	1:2	10	2-FC_6H_4OH	87	>20:1
9	1:2	10	2-ClC_6H_4OH	85	>20:1
10	1:2	8	2-FC_6H_4OH	86	>20:1
11	1:2	7	2-FC_6H_4OH	87	>20:1
12	1:2	6	2-FC_6H_4OH	87	>20:1
13	1:2	5	2-FC_6H_4OH	84	17.5:1
14	**1:1.5**	**6**	**2-FC_6H_4OH**	**88**	>20:1
15	1:1	6	2-FC_6H_4OH	82	>20:1
16[d]	1:1.5	6	2-FC_6H_4OH	61	>20:1
17[e]	1:1.5	6	2-FC_6H_4OH	68	>20:1
18[f]	**1:1.5**	**6**	**2-FC_6H_4OH**	**87 (90)**[g]	>20:1
19[h]	1:1.5	6	2-FC_6H_4OH	0	
20	1:1.5		2-FC_6H_4OH	0	
21[i]	1:1.5	6	2-FC_6H_4OH	0	

[a]Conditions: **1a** (0.2 mmol), $PdCl_2$ (5 mol %), Cs_2CO_3 (2 equiv), 2 mL of toluene, 110 °C, 0.1 MPa N_2, 24 h. [b]Determined by ^1H NMR spectroscopy using dimethyl terephthalate as an internal standard. [c]Isolated yield of **4a**. [d]$Pd(OAc)_2$ as the catalyst. [e]$Pd(MeCN)_2Cl_2$ as the catalyst. [f]**1a** (0.3 mmol), 3 mL of toluene. [g]Isolated yield given in parentheses. [h]Without $PdCl_2$. [i]Without Cs_2CO_3.

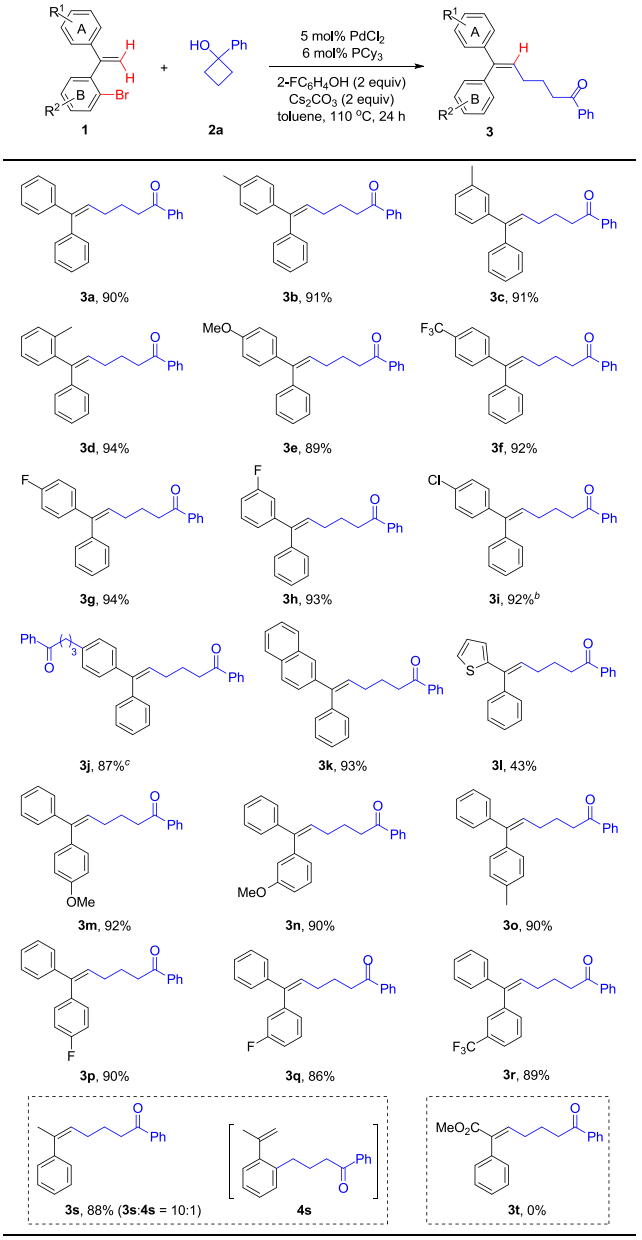
DOI: 10.1021/acscatal.9b04161
ACS Catal. 2019, 9, 11669−11675

in almost the same yield (Table 1, entries 10−13). Use of 1.5 equiv of **2a** was suitable for the reaction to form **3a** in a decent yield (Table 1, entries 14 and 15). Among the screened palladium sources $PdCl_2$, $Pd(OAc)_2$, and $Pd(MeCN)_2Cl_2$, the latter two were inferior to $PdCl_2$ (Table 1, entries 16 and 17). Performing the reaction on a 0.3 mmol scale of **1a** led to **3a** in 90% isolated yield (Table 1, entry 18). In the absence of the $PdCl_2$ catalyst, the PCy_3 ligand, or the Cs_2CO_3 base, the reaction did not occur at all (Table 1, entries 19−21). It is noteworthy that other phosphines such as XPhos, SPhos, PPh_3, Ph_2PCy, and PCy_3HBF_4 were evaluated to be less effective than PCy_3 (see the Supporting Information for details).

Next, the scope of terminal alkenes **1** was investigated under the optimized conditions (Table 2). Introduction of electron-donating groups such as methyl and methoxy and an electron-withdrawing group CF_3 or halogen atoms (F or Cl) onto the phenyl ring A did not obviously affect the reaction efficiency, and the reaction proceeded very efficiently to give the target products **3b−3i** in 89−94% yields, showing no obvious electronic and steric effects. It was noted that the 4-Cl group on the phenyl ring A could undergo further coupling with the cyclobutanol substrate under the stated conditions. In the case of synthesizing compound **3i** (92%), only one equivalent of **2a** was used to tolerate the 4-Cl functionality, while use of an excessive amount of **2a** (2 equiv) led to the double alkylation product **3j** (87%), revealing that the coupling reaction occurred at both the terminal vinylic C−H and aromatic C−Cl bonds. The 2-naphthyl-based *gem*-diarylated alkene substrate also reacted well with **2a** to give the target product **3k** (93%). However, replacement of phenyl ring A with 2-thienyl functionality gave product **3l** in a moderate yield (43%), presumably because of the poisoning interaction of the heteroaryl sulfur atom with the catalytically active palladium center during the reaction. In a similar fashion, the reaction of the terminal alkene substrates bearing various substituents such as 4-MeO, 3-MeO, 4-Me, 4-F, 3-F, and 3-CF_3 on phenyl ring B also efficiently proceeded to afford the target products **3m-3r** in 86−92% yields. It is noteworthy that the reaction of 2′-*α*-methylstyrene also reacted well with **2a** to form the target product **3s** in 88% yield with a slightly diminished regioselectivity (**3s**:**4s** = 10:1). This result reveals that the bulky aryl rings are essential for the high regioselectivity of the desired reaction. However, replacement of phenyl ring A with an ester group (CO_2Me) completely inhibited the reaction to form the target product **3t**, suggesting that introduction of an electron-withdrawing ester group to the C=C backbone reduced the electron density on the alkenyl moiety, which may be detrimental to the key 1,4-palladium migration process for the desired reaction. The molecular structure of compound **3b** was further confirmed by the X-ray single-crystal crystallographic determination (see the Supporting Information for details).

Then, the scope of cyclobutanols **2** was explored (Table 3). A variety of 1-aryl-cyclobutanols efficiently reacted with *gem*-diarylated alkene **1d**, forming the target products **5**. All the cyclobutanols bearing a 1-phenyl moiety substituted by MeO, Me, CF_3, CO_2Me, F, or Cl reacted well to give **5a−5h** (85−95%), exhibiting no steric effect but only a slight negative impact from the electron-withdrawing groups. 1-(2-Naphthyl), 2-thienyl, and benzyl-based cyclobutanols also reacted efficiently to afford the target products **5i−5k** (85−89%). (*E*)-1-Styrylcyclobutanol (**2m**) exhibited an excellent reactivity to produce **5l** (94%), while the sterically hindered (1-

Table 2. Scope of Alkenes (1)[a]

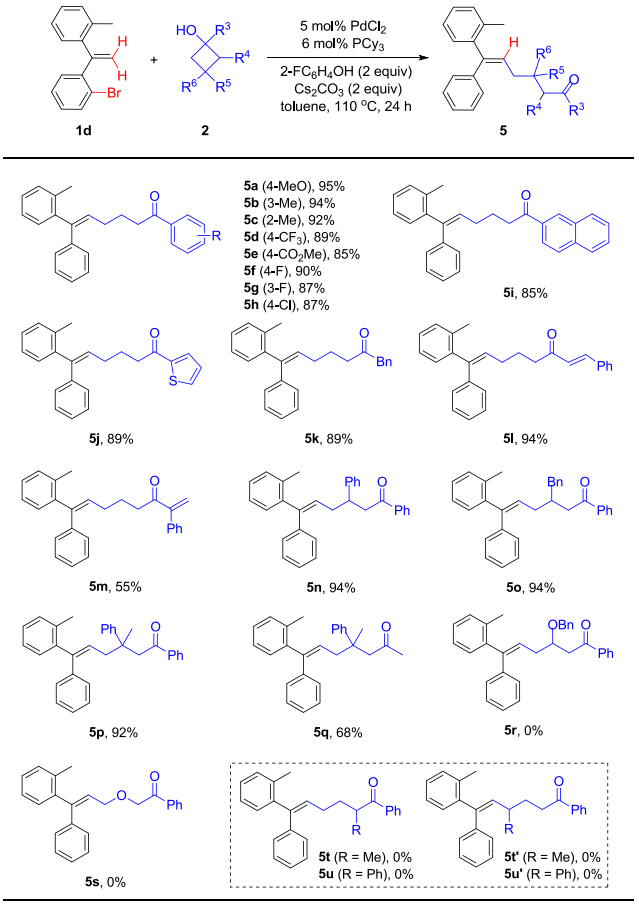


[a]Conditions: **1** (0.3 mmol), **2a** (0.45 mmol), $PdCl_2$ (0.015 mmol), PCy_3 (0.018 mmol), 2-FC_6H_4OH (0.6 mmol), Cs_2CO_3 (0.6 mmol), 3 mL of toluene, 110 °C, 0.1 MPa N_2, 24 h. [b]**2a** (0.3 mmol). [c]**2a** (0.6 mmol).

phenylvinyl)-cyclobutanol (**2n**) reacted less efficiently with **1d** to form compound **5m** in a moderate yield (55%). When 3-phenyl, benzyl, and phenyl/methyl substituted 1-phenyl-cyclobutanols were reacted with **1d**, the target products **5n−5p** were obtained in excellent yields (92−94%), while 3-phenyl-1,3-dimethyl-cyclobutanol (**2r**) only gave the product **5q** in 68% yield, revealing a negative electronic impact from the 1-methyl functionality on the cyclobutyl ring. Unexpectedly, 3-benzyloxycyclobutanol (**2s**) and 3-phenyloxetan-3-ol (**2t**) did not exhibit any reactivity to **1d** under the stated conditions, and 2-methyl and 2-phenyl-substituted cyclobutanols **2u** and **2v** could not react with **1d** either to execute the two possible ring-opening C−C cleavages to form compounds **5t**/**5t′** or **5u**/**5u′**, presumably because of the

DOI: 10.1021/acscatal.9b04161
ACS Catal. 2019, 9, 11669−11675

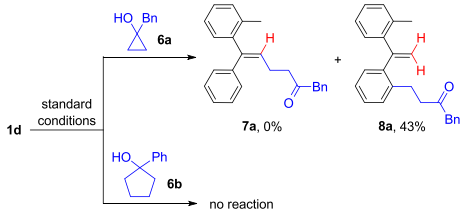
Table 3. Scope of Cyclobutanols (2)[a]



[a]Conditions: **1d** (0.3 mmol), **2** (0.45 mmol), $PdCl_2$ (0.015 mmol), PCy_3 (0.018 mmol), 2-FC_6H_4OH (0.6 mmol), Cs_2CO_3 (0.6 mmol), 3 mL of toluene, 110 °C, 0.1 MPa N_2, 24 h.

steric hindrance of the 2-substituents. The three- and five-membered cycloalkanols **6a** and **6b** were also reacted with **1d** under the standard conditions (Scheme 2). The former reacted

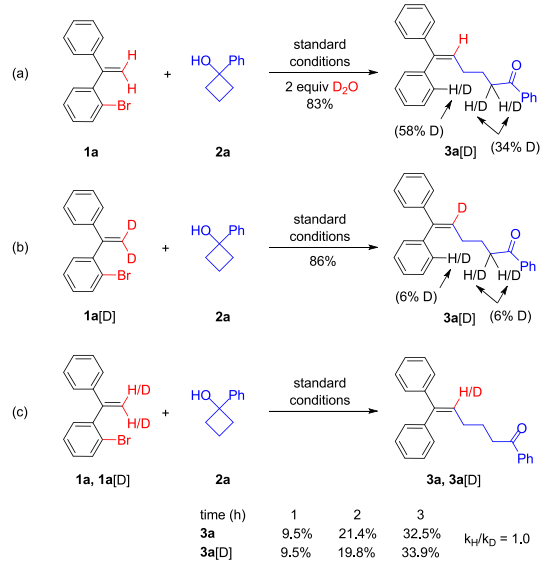
Scheme 2. Reaction of 3- and 5-Membered Cycloalkanols 6 with 1d



to give the direct alkylation product **8a** (43%) through the ring-opening C−C cleavage, but the desired 1,4-palladium migration product **7a** was not obtained, and the latter (**6b**) did not react at all. These results have suggested that suitable ring strain of the cycloalkanols is crucial to execute the aryl to vinyl 1,4-palladium migration/ring-opening C−C cleavage cascade.

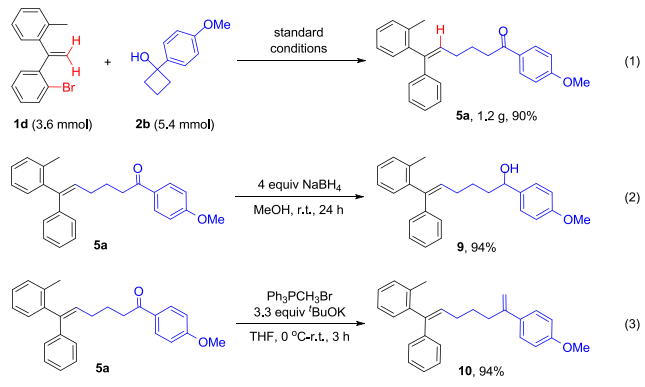
Control experiments were conducted to probe into the reaction mechanism. When alkene **1a** was reacted with cyclobutanol **2a** in the presence of 2 equiv of D_2O under the standard conditions, remarkable deuterium incorporation was observed at the *ortho*-position of phenyl ring B and the acidic C−H site α to the carbonyl (Scheme 3a). Use of the doubly deuterated alkene **1a**[D] as the substrate led to the target

Scheme 3. Deuterium-Labelling Experiments



product **3a**[D] in 86% yield with only 6% deuterium incorporation into the *ortho*-position of phenyl ring B (Scheme 3b). These deuterium-labeling results have implicated that the hydrogen atom at the *ortho*-position of phenyl ring B in **3a**[D] came from the reaction medium, cyclobutanol **2a**, or 2-FC_6H_4OH, rather than from the terminal alkenyl C−H of **1a** and the alkenyl hydrogen atom released in the form of $CsHCO_3$ (Figure 1, vide infra). The kinetic isotope effect (KIE) was measured from the parallel experiments using **1a** and its deuterated form **1a**[D] to react with **2a** (Scheme 3c). A primary isotope effect was observed with k_H/k_D = 1.0, suggesting that the alkenyl C−H bond activation/cleavage is not involved in the rate-determining step in the overall catalytic cycle (see the Supporting Information for details).

To demonstrate the utility of the synthetic protocol, a gram-scale preparation of compound **5a** was performed from **1d** and **2b**, achieving a 90% yield (eq 1). Chemoselective reduction of



ketone **5a** was readily conducted with $NaBH_4$ to give the corresponding alcohol **9** (94%) (eq 2). In addition, ketone **5a** could also undergo Wittig reaction to generate 1,6-diene **10** in 94% yield (eq 3).

DFT calculations were conducted with the Gaussian16 package to gain mechanistic insights into the 1,4-palladium

DOI: 10.1021/acscatal.9b04161
ACS Catal. 2019, 9, 11669−11675

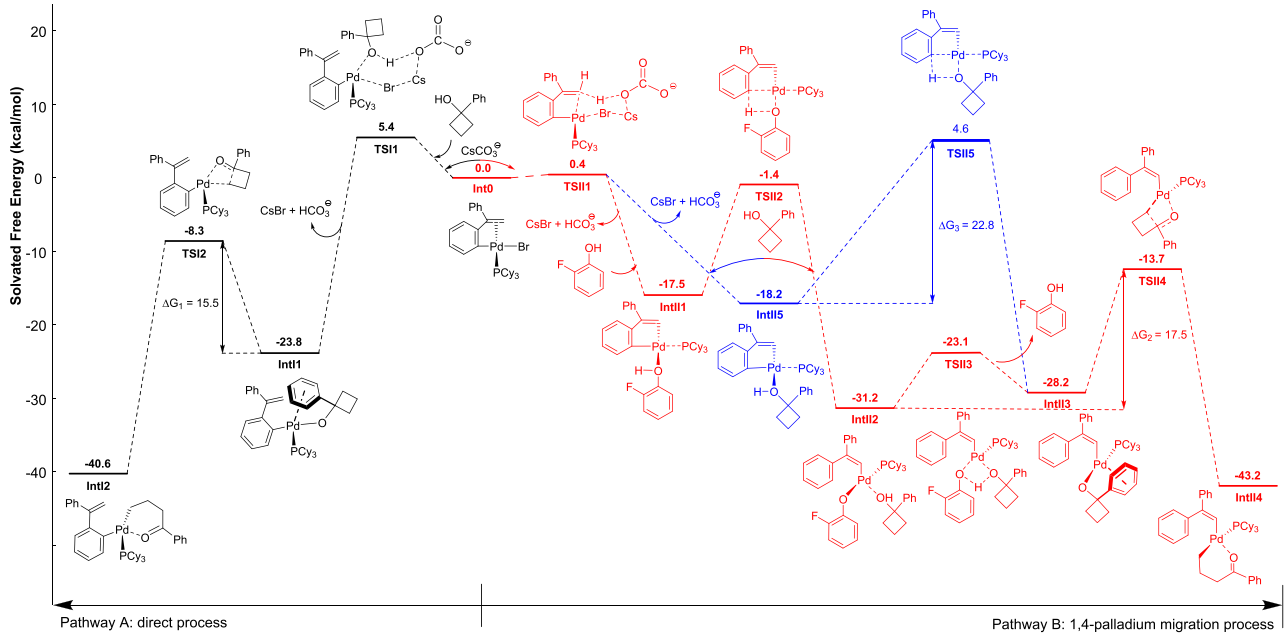


Figure 1. Computed free energy profiles for the three tentative reaction pathways at the B3LYP/6-311++G(2df,2p)//SMD (toluene)-M052x/6-31G(d)-SDD//B3LYP/6-31+G(d)-SDD level. The relative free energies are given in kcal/mol. The preferred pathway is shown in red.

migration pathway.[17] Molecular geometries were optimized without symmetry restraints, followed by frequency calculations to ascertain the nature of the stationary point (minimum vs saddle point) after probing conformational space. Calculations were performed by using the B3LYP-D3(BJ)/6-31+G(d)-SDD[11,18] and provided thermal corrections to the Gibbs free energies at 383.15 K based on the actual reaction conditions. The solvation energy corrections were taken into account at the M052*x*/6-31G(d)-SDD level with the SMD solvation model for toluene.[19] The single-point energies were computed with B3LYP/6-311++G(2df,2p) augmented with the D3(BJ) version to provide highly accurate energy information.[20] As shown in Figure 1, the four-coordinate intermediate of palladium(II) **Int0**, generated from the oxidative addition of 1-bromo-2-(1-phenylvinyl)-benzene (**1a**) to palladium(0),[21] generated in situ by reacting with PCy_3, is set as the zero energy point in the free energy profiles and could readily proceed in two different pathways to form the direct alkylation intermediate **IntI2** (pathway A) and 1,4-palladium migration intermediate **IntII4** (pathway B). Following pathway A, 1-phenylcyclobutanol (**2a**) weakly coordinates to the palladium center at the axial position to yield intermediate **IntI1** through a "boat-like" transition state **TSI1** assisted by anionic $CsCO_3^-$ which was dissociated from Cs_2CO_3.[22] As can be seen from this pathway, the process irreversibly occurs with concomitant release of HCO_3^- and CsBr. Finally, the four-member ring is opened, which is the rate-limiting step with an energy barrier of 15.5 kcal/mol for pathway A, leading to the irreversible formation of **IntI2**. Reductive elimination from **IntI2** gives the direct alkylation product **4a**. While in pathway B, the free energy barrier of the rate-limiting step is 17.5 kcal/mol from **IntII2** to **IntII4**, slightly higher than the direct alkylation process (pathway A). Initially, a similar process proceeds from **Int0** to **IntII1** with a lower energy barrier (0.4 kcal/mol vs 5.4 kcal/mol). Subsequent 1,4-palladium migration process occurs via an intermolecular hydrogen atom transfer from 2-FC_6H_4OH (**IntII1**) to the *ortho*-position of phenyl B (**IntII2**). Coordination of **2a** to the palladium center renders its hydroxyl hydrogen to migrate to 2-F-phenoxy functionality, readily removing 2-FC_6H_4OH from the metal center and giving rise to the thermally stable intermediate **IntII4** through a ring-opening process of **2a**. Reductive elimination from **IntII4** generates the 1,4-palladium migration product **3a**. The resulting energy difference 2.60 kcal/mol between the two lowest energy conformers (**IntII4** and **IntI2**) was employed to calculate their relative population according to the Boltzmann distribution. At 383.15 K, the molar ratio of **IntII4**:**IntI2** is 1:0.033 (ca. 96% for **IntII4**), which is in agreement with the observed experimental results of **3a**:**4a** > 20:1 (Table 1). At the same time, an alternative reaction pathway involving a coordination step of **2a** can also be proposed in the absence of the phenol (Figure 1, blue lines). Although **IntII5** is energetically more stable than **IntII1** by 0.7 kcal/mol, it should proceed with a relatively high energy barrier of 22.8 kcal/mol. Thus, such a 1,4-palladium migration process without 2-FC_6H_4OH is energetically unfavorable in comparison to pathway B. Taken together, these results have indicated that 2-FC_6H_4OH plays a crucial role in the current transformation, and the 1,4-palladium migration process is predominantly thermodynamically controlled, almost certainly because of the decreased steric effect, which is consistent with previous observations.[10]

The reaction results of the three- and five-membered cycloalkanols **6a** and **6b** with **1d** (Scheme 2) were also investigated by DFT calculations, which reveals a compromise of the energy barrier between the ring-opening and migration processes (see the Supporting Information for details). For the three-membered cycloalkanol, a higher free energy barrier (15.8 vs 3.3 kcal/mol) exists in the migration process, leading to the kinetically favored direct alkylation product. For the four-membered cycloalkanol substrate **2a**, the free energy barrier between the two processes are close (15.8 vs 12.3 kcal/mol) so that the thermally stable intermediate IntII4 was

DOI: 10.1021/acscatal.9b04161
ACS Catal. 2019, 9, 11669−11675

formed to give the major migration product. However, it is difficult to open the five-membered ring (>20 kcal/mol) that the reaction could not occur under the standard conditions.

In conclusion, efficient palladium-catalyzed C−H alkylation of *gem*-disubstituted ethylenes with cyclobutanols has been realized to access trisubstituted alkenes through an aryl to vinyl 1,4-palladium migration/ring-opening C−C cleavage cascade, reaching excellent reaction efficiency and regioselectivity with broad substrate scopes. DFT calculations have revealed that the excellent reaction efficiency is attributed to a thermodynamically favored 1,4-palladium migration process assisted by 2-FC_6H_4OH.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.9b04161.

Experimental materials and procedures, analytical data and NMR spectra of compounds, X-ray crystallographic analysis for **3b** (PDF)

B3LYP/6-31+G(d)-SDD geometries for all the optimized compounds and transition states (PDF)

X-ray crystallographic information for **3b** (CIF)

Check CIF/PLATON report (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zkyu@dicp.ac.cn (Z.K.Y.).

*E-mail: ygzhou@dicp.ac.cn (Y.G.Z.).

ORCID

Quannan Wang: 0000-0002-4136-0016

Jiang Lou: 0000-0002-5653-1359

Yong-Gui Zhou: 0000-0002-3321-5521

Zhengkun Yu: 0000-0002-9908-0017

Author Contributions

¶These authors contributed equally (Q.N.W., R.J.C., and J. L.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (21672209 and 21871253) and the National Basic Research Program of China (2015CB856600) for support of this research.

■ REFERENCES

(1) (a) Zhang, F. Z.; Spring, D. R. Arene C-H Functionalisation Using a Removable/Modifiable or a Traceless Directing Group Strategy. *Chem. Soc. Rev.* **2014**, *43*, 6906−6919. (b) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. Beyond Directing Groups: Transition-Metal-Catalyzed C-H Activation of Simple Arenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236−10254. (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C-H Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 788−802.

(2) (a) Tan, B. J.; Bai, L.; Ding, P.; Liu, J. J.; Wang, Y. Y.; Luan, X. J. Palladium-Catalyzed Intermolecular [4 + 1] Spiroannulation by C(sp^3)−H Activation and Naphthol Dearomatization. *Angew. Chem., Int. Ed.* **2019**, *58*, 1474−1478. (b) Cao, J.; Chen, L.; Sun, F.-N.; Sun, Y.-L.; Jiang, K.-Z.; Yang, K.-F.; Xu, Z.; Xu, L.-W. Pd-Catalyzed Enantioselective Ring Opening/Cross-Coupling and Cyclopropanation of Cyclobutanones. *Angew. Chem., Int. Ed.* **2019**, *58*, 897−901. (c) Lu, A. L.; Ji, X. M.; Zhou, B.; Wu, Z.; Zhang, Y. H. Palladium-Catalyzed C−H Silylation through Palladacycles Generated from Aryl Halides. *Angew. Chem., Int. Ed.* **2018**, *57*, 3233−3237. (d) Wu, Z.; Ma, D.; Zhou, B.; Ji, X. M.; Ma, X. T.; Wang, X. L.; Zhang, Y. H. Palladium-Catalyzed Alkylation with Alkyl Halides by C(sp^3)−H Activation. *Angew. Chem., Int. Ed.* **2017**, *56*, 12288−12291. (e) Liu, R.-R.; Wang, Y.-G.; Li, Y.-L.; Huang, B.-B.; Liang, R.-X.; Jia, Y.-X. Enantioselective Dearomative Difunctionalization of Indoles by Palladium-Catalyzed Heck/Sonogashira Sequence. *Angew. Chem., Int. Ed.* **2017**, *56*, 7475−7478. (f) Gutiérrez-Bonet, Á.; Juliá-Hernández, F.; de Luis, B.; Martin, R. Pd-Catalyzed C(sp^3)−H Functionalization/Carbenoid Insertion: All-Carbon Quaternary Centers *via* Multiple C−C Bond Formation. *J. Am. Chem. Soc.* **2016**, *138*, 6384−6387.

(3) Rahim, A.; Feng, J.; Gu, Z. H. 1,4-Migration of Transition Metals in Organic Synthesis. *Chin. J. Chem.* **2019**, *37*, 929−945. (b) Shi, F.; Larock, R. C. Remote C−H Activation *via* Through-Space Palladium and Rhodium Migrations. *Top. Curr. Chem.* **2009**, *292*, 123−164. (c) Ma, S. M.; Gu, Z. H. 1,4-Migration of Rhodium and Palladium in Catalytic Organometallic Reactions. *Angew. Chem., Int. Ed.* **2005**, *44*, 7512−7517.

(4) (a) Zhou, J.; He, J. J.; Wang, B. J.; Yang, W. J.; Ren, H. J. 1,7-Palladium Migration *via* C−H Activation, Followed by Intramolecular Amination: Regioselective Synthesis of Benzotriazoles. *J. Am. Chem. Soc.* **2011**, *133*, 6868−6870. (b) Campo, M. A.; Zhang, H. M.; Yao, T. L.; Ibdah, A.; McCulla, R. D.; Huang, Q. H.; Zhao, J.; Jenks, W. S.; Larock, R. C. Aryl to Aryl Palladium Migration in the Heck and Suzuki Coupling of *o*-Halobiaryls. *J. Am. Chem. Soc.* **2007**, *129*, 6298−6307. (c) Singh, A.; Sharp, P. R. Pt and Pd 1,4-Shifts at the Edge of Dibenz[*a*,*c*]anthracene. *J. Am. Chem. Soc.* **2006**, *128*, 5998−5999. (d) Campo, M. A.; Huang, Q. H.; Yao, T. L.; Tian, Q. P.; Larock, R. C. 1,4-Palladium Migration *via* C−H Activation, Followed by Arylation: Synthesis of Fused Polycycles. *J. Am. Chem. Soc.* **2003**, *125*, 11506−11507.

(5) (a) Rocaboy, R.; Anastasiou, I.; Baudoin, O. Redox-Neutral Coupling between Two C(sp^3)−H Bonds Enabled by 1,4-Palladium Shift for the Synthesis of Fused Heterocycles. *Angew. Chem., Int. Ed.* **2019**, *58*, 14625−14628. (b) Hitce, J.; Retailleau, P.; Baudoin, O. Palladium-Catalyzed Intramolecular C(sp^3)−H Functionalization: Catalyst Development and Synthetic Applications. *Chem. - Eur. J.* **2007**, *13*, 792−799. (c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. Catalysts for Suzuki-Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696. (d) Baudoin, O.; Herrbach, A.; Guéritte, F. The Palladium-Catalyzed C−H Activation of Benzylic *gem*-Dialkyl Groups. *Angew. Chem., Int. Ed.* **2003**, *42*, 5736−5740.

(6) Kesharwani, T.; Larock, R. C. Benzylic C−H Activation and C−O Bond Formation *via* Aryl to Benzylic 1,4-Palladium Migrations. *Tetrahedron* **2008**, *64*, 6090−6102.

(7) (a) Piou, T.; Bunescu, A.; Wang, Q.; Neuville, L.; Zhu, J. P. Palladium-Catalyzed Through-Space C(sp^3)−H and C(sp^2)−H Bond Activation by 1,4-Palladium Migration: Efficient Synthesis of [3,4]-Fused Oxindoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 12385−12389. (b) Lu, Z. Y.; Hu, C. M.; Guo, J. J.; Li, J.; Cui, Y. X.; Jia, Y. X. Water-Controlled Regioselectivity of Pd-Catalyzed Domino Reaction Involving a C−H Activation Process: Rapid Synthesis of Diverse Carbo- and Heterocyclic Skeletons. *Org. Lett.* **2010**, *12*, 480−483.

(8) (a) Tian, Q. P.; Larock, R. C. Synthesis of 9-Alkylidene-9*H*-Fluorenes by a Novel Palladium-Catalyzed Rearrangement. *Org. Lett.* **2000**, *2*, 3329−3332. (b) Bour, C.; Suffert, J. Cyclocarbopalladation: Sequential Cyclization and C−H Activation/Stille Cross-Coupling in the Pd-5-*Exo-Dig* Reaction. *Org. Lett.* **2005**, *7*, 653−656. (c) Mota, A. J.; Dedieu, A.; Bour, C.; Suffert, J. Cyclocarbopalladation Involving an Unusual 1,5-Palladium Vinyl to Aryl Shift as Rermination Step: Theoretical Study of the Mechanism. *J. Am. Chem. Soc.* **2005**, *127*, 7171−7182. (d) Zhao, J.; Larock, R. C. Synthesis of Substituted Carbazoles, Indoles, and Dibenzofurans by Vinylic to Aryl Palladium Migration. *J. Org. Chem.* **2006**, *71*, 5340−5348.

DOI: 10.1021/acscatal.9b04161
ACS Catal. 2019, 9, 11669−11675

(9) (a) Hu, T.-J.; Zhang, G.; Chen, Y.-H.; Feng, C.-G.; Lin, G.-Q. Borylation of Olefin C−H Bond *via* Aryl to Vinyl Palladium 1,4-Migration. *J. Am. Chem. Soc.* **2016**, *138*, 2897−2900. (b) Hu, T.-J.; Li, M.-Y.; Zhao, Q.; Feng, C.-G.; Lin, G.-Q. Highly Stereoselective Synthesis of 1,3-Dienes through an Aryl to Vinyl 1,4-Palladium Migration/Heck Sequence. *Angew. Chem., Int. Ed.* **2018**, *57*, 5871−5875. (c) Wei, D.; Li, M.-Y.; Zhu, B.-B.; Yang, X.-D.; Zhang, F.; Feng, C.-G.; Lin, G.-Q. Sequential Cross-Coupling/Annulation of *ortho*-Vinyl Bromobenzenes with Aromatic Bromides for the Synthesis of Polycyclic Aromatic Compounds. *Angew. Chem., Int. Ed.* **2019**, *58*, 16543−16547.

(10) Rocaboy, R.; Baudoin, O. 1,4-Palladium Shift/C(sp^3)−H Activation Strategy for the Remote Construction of Five-Membered Rings. *Org. Lett.* **2019**, *21*, 1434−1437.

(11) Zhang, S.-S.; Hu, T.-J.; Li, M.-Y.; Song, Y.-K.; Yang, X.-D.; Feng, C.-G.; Lin, G.-Q. Asymmetric Alkenylation of Enones and Imines Enabled by A Highly Efficient Aryl to Vinyl 1,4-Rhodium Migration. *Angew. Chem., Int. Ed.* **2019**, *58*, 3387−3391.

(12) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. Cyclobutanes in Catalysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740−7752.

(13) (a) Wu, P. L.; Jia, M. Q.; Ma, S. M. Pd-Catalyzed Coupling Reaction of Cyclobutanols with Propargylic Carbonates. *Org. Chem. Front.* **2019**, *6*, 1757−1761. (b) Ziadi, A.; Correa, A.; Martin, R. Formal γ-Alkynylation of Ketones *via* Pd-Catalyzed C−C Cleavage. *Chem. Commun.* **2013**, *49*, 4286−4288. (c) Ziadi, A.; Martin, R. Ligand-Accelerated Pd-Catalyzed Ketone γ-Arylation *via* C−C Cleavage with Aryl Chlorides. *Org. Lett.* **2012**, *14*, 1266−1269. (d) Ethirajan, M.; Oh, H. S.; Cha, J. K. Formation of Five-Membered Carbocycles by Intramolecular Palladium-Catalyzed Ring Opening of *tert*-Cyclobutanols. *Org. Lett.* **2007**, *9*, 2693−2696. (e) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. Palladium-Catalyzed Asymmetric Arylation, Vinylation, and Allenylation of *tert*-Cyclobutanois *via* Enantioselective C−C Bond Cleavage. *J. Am. Chem. Soc.* **2003**, *125*, 8862−8869.

(14) (a) Zhao, R.; Yao, Y.; Zhu, D.; Chang, D. H.; Liu, Y.; Shi, L. Visible-Light-Enhanced Ring Opening of Cycloalkanols Enabled by Brønsted Base-Tethered Acyloxy Radical Induced Hydrogen Atom Transfer-Electron Transfer. *Org. Lett.* **2018**, *20*, 1228−1231. (b) Che, C.; Qian, Z. S.; Wu, M. C.; Zhao, Y.; Zhu, G. G. Intermolecular Oxidative Radical Addition to Aromatic Aldehydes: Direct Access to 1,4-and 1,5-Diketones *via* Silver-Catalyzed Ring-Opening Acylation of Cyclopropanols and Cyclobutanols. *J. Org. Chem.* **2018**, *83*, 5665−5673. (c) Xu, B.; Wang, D. C.; Hu, Y. H.; Shen, Q. L. Silver-Catalyzed Ring-Opening Difluoromethylthiolation/Trifluoromethyl-thiolation of Cycloalkanols with $PhSO_2SCF_2H$ or $PhSO_2SCF_3$. *Org. Chem. Front.* **2018**, *5*, 1462−1465. (d) Ren, R. G.; Wu, Z.; Xu, Y.; Zhu, C. C−C Bond-Forming Strategy by Manganese-Catalyzed Oxidative Ring-Opening Cyanation and Ethynylation of Cyclobutanol Derivatives. *Angew. Chem., Int. Ed.* **2016**, *55*, 2866−2869. (e) Zhao, H. J.; Fan, X. F.; Yu, J. J.; Zhu, C. Silver-Catalyzed Ring-Opening Strategy for the Synthesis of β- and γ-Fluorinated Ketones. *J. Am. Chem. Soc.* **2015**, *137*, 3490−3493. (f) Ren, R. G.; Zhao, H. J.; Huan, L. T.; Zhu, C. Manganese-Catalyzed Oxidative Azidation of Cyclobutanols: Regiospecific Synthesis of Alkyl Azides by C−C Bond Cleavage. *Angew. Chem., Int. Ed.* **2015**, *54*, 12692−12696.

(15) (a) Lou, J.; He, Y.; Li, Y. L.; Yu, Z. K. Transition-Metal-Promoted Direct C−H Cyanoalkylation and Cyanoalkoxylation of Internal Alkenes *via* Radical C−C Bond Cleavage of Cycloketone Oxime Esters. *Adv. Synth. Catal.* **2019**, *361*, 3787−3799. (b) He, Y.; Lou, J.; Wu, K. K.; Wang, H. M.; Yu, Z. K. Copper-Catalyzed Radical C−C Bond Cleavage and [4 + 1] Annulation Cascade of Cycloketone Oxime Esters with Enaminothiones. *J. Org. Chem.* **2019**, *84*, 2178−2190.

(16) (a) Wang, Q. N.; Yang, X. G.; Wu, P.; Yu, Z. K. Photoredox-Catalyzed C−H Arylation of Internal Alkenes to Tetrasubstituted Alkenes: Synthesis of Tamoxifen. *Org. Lett.* **2017**, *19*, 6248−6251. (b) Wang, Q. N.; Lou, J.; Wu, P.; Wu, K. K.; Yu, Z. K. Iron-Mediated Oxidative C−H Alkylation of *S*,*S*-Functionalized Internal Olefins *via* C(sp^2)−H/C(sp^3)−H Cross-Coupling. *Adv. Synth. Catal.* **2017**, *359*, 2981−2998. (c) Yang, X. G.; Liu, Z. Q.; Sun, C. L.; Chen, J. P.; Yu, Z. K. Palladium-Catalyzed Oxidative Cross-Coupling of α-Cyanoketene Dithioacetals with Olefins. *Chem. - Eur. J.* **2015**, *21*, 14085−14094. (d) Yu, H. F.; Jin, W. W.; Sun, C. L.; Chen, J. P.; Du, W. M.; He, S. B.; Yu, Z. K. Palladium-Catalyzed Cross-Coupling of Internal Alkenes with Terminal Alkenes to Functionalized 1,3-Butadienes Using C−H Bond Activation: Efficient Synthesis of Bicyclic Pyridones. *Angew. Chem., Int. Ed.* **2010**, *49*, 5792−5797.

(17) See the Supporting Information for Computational Details.

(18) (a) Zhang, H.; Wang, H.-Y.; Luo, Y. X.; Chen, C. H.; Cao, Y. M.; Chen, P. H.; Guo, Y. L.; Lan, Y.; Liu, G. S. Regioselective Palladium-Catalyzed C−H Bond Trifluoroethylation of Indoles: Exploration and Mechanistic Insight. *ACS Catal.* **2018**, *8*, 2173−2180. (b) Abas, H.; Mas-Roselló, J.; Amer, M. M.; Durand, D. J.; Groleau, R. R.; Fey, N.; Clayden, J. Asymmetric and Geometry-Selective α-Alkenylation of α-Amino Acids. *Angew. Chem., Int. Ed.* **2019**, *58*, 2418−2422. (c) Donnelly, B. L.; Elliott, L. D.; Willis, C. L.; Booker-Milburn, K. I. Sequential Photochemical and Prins Reactions for the Diastereoselective Synthesis of Tricyclic Scaffolds. *Angew. Chem., Int. Ed.* **2019**, *58*, 9095−9098. (d) Chen, H. H.; Zhang, T.; Shan, C. H.; Liu, S.; Song, Q. L.; Bai, R. P.; Lan, Y. Mechanism of Brønsted-Base-Mediated Borylation of Propynols: A DFT Study. *Org. Lett.* **2019**, *21*, 4924−4928.

(19) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.

(20) Grimme, S.; Ehrlich, S.; Goerigk, L. Effect of the Damping Function in Dispersion Corrected Density Functional Theory. *J. Comput. Chem.* **2011**, *32*, 1456−1465.

(21) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Palladium(II)-Catalyzed C−H Activation/C−C Cross-coupling Reactions: Versatility and Practicality. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115.

(22) Guo, Z. W.; Li, M.; Mou, X.-Q.; He, G.; Xue, X.-S.; Chen, G. Radical C−H Arylation of Oxazoles with Aryl Iodides: dppf as an Electron-Transfer Mediator for Cs_2CO_3. *Org. Lett.* **2018**, *20*, 1684−1687.

DOI: 10.1021/acscatal.9b04161
ACS Catal. 2019, 9, 11669−11675