Palladium-Catalyzed Reaction of Olefins with PhI(OAc)$_2$–TBAB System: An Efficient and Highly Selective Bisfunctionalization Strategy

Lei Yu,* Lingfeng Ren, Rong Yi, Yulan Wu, Tian Chen, Rong Guo

School of Chemistry and Chemical Engineering, Yangzhou University, Shouxihu Campus, Yangzhou 225002, P. R. of China
Fax +86(514)87975244; E-mail: yulei@yzu.edu.cn

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Abstract: The palladium-catalyzed reaction of olefins with PhI(OAc)$_2$–TBAB system provides a novel, efficient, and highly selective bisfunctionalization strategy to introduce bromo and oxygen groups simultaneously. The substituents on the C=C bond control the regioselectivity of this reaction, which could be an effective supplement of bromohydroxylation in organic synthesis.

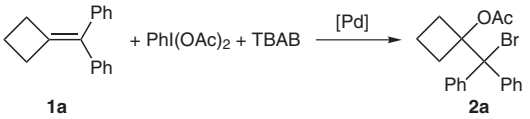
Key words: bisfunctionalization reactions, olefins, palladium-catalyzed reactions, selective

During the last decade, highly activated olefins have attracted the interest of chemists, and their novel reactions have been widely investigated. These include methylenecyclopropanes (MCP),[1] vinylidenecyclopropanes (VCP),[2] allenes,[3] cyclopropyl allenes (CPA),[4] and recently methylenecyclobutanes (MCB).[5] Due to their high ring strain or cumulated C=C bonding character, these olefins have high reactivity and can undergo a series of interesting reactions under mild conditions, providing convenient methods for the construction of many useful organic structures. Therefore, they are useful building blocks in organic synthesis.

Being able to introduce two different functional groups simultaneously, bisfunctionalization reactions are highly effective in organic synthesis. Halohydroxylation of olefins is one of those bisfunctional strategies. Since the two functional groups, that is, X and OH, could be introduced into the substrate at the same time, halohydroxylations of olefins provide a direct access to β-halogen-substituted alcohols, which are useful intermediates in medicinal chemistry.[6] In recent years, halo-hydroxylation reactions of highly activated olefins (e.g., allenes,[7] MCP,[8] CPA,[9] MCB[10]) have been investigated systemically. Rearrangements in the reaction routes may provide some unexpected particular products with high selectivity when highly activated olefins were employed.

Encouraged by these works, we are interested in the bisfunctionalization reactions of olefins. Herein, we wish to report that palladium complex could catalyze the reaction of olefins with PhI(OAc)$_2$–TBAB (tetrabutylammonium bromide) system[11] and introduced halogen and oxygen groups simultaneously.

Table 1 Reaction of MCB **1a** with PhI(OAc)$_2$–TBAB System[a]



1a **2a**

Entry	Solvent	Catalyst	Time (°C)	Time (h)	Yield of **2a** (%)[b]
1	MeCN	none	r.t.	3	0
2	MeCN	Pd_2dba_3	r.t.	5	trace
3	MeCN	Pd_2dba_3	40	3	34
4	MeCN	Pd_2dba_3	60	2	53
5	MeCN	$Pd(PPh_3)_4$	60	4	62
6	MeCN	$PdCl_2$	60	5	60
7	MeCN	$Pd(OAc)_2$	60	1.5	74
8	MeCN	none	60	10	0[c]
9	THF	$Pd(OAc)_2$	60	2	47
10	toluene	$Pd(OAc)_2$	60	4	40
11	DCE	$Pd(OAc)_2$	60	6	63

[a] Reaction conditions: **1a** (0.3 mol), PhI(OAc)$_2$ (0.6 mol), TBAB (0.3 mol), and solvent (2 mL) were employed. The catalyst dosage was 10 mol% based on **1a**.
[b] Isolated yields based on **1a**.
[c] Traces of unidentified complexes were observed.

We initially examined the reaction of MCB, and MCB **1a** was chosen as the model substrate. When **1a**, PhI(OAc)$_2$, and TBAB were stirred in MeCN at room temperature, no desired product was observed (Table 1, entry 1). Further investigations demonstrated that when the reaction could take place in the presence of palladium catalyst, and a bifunctional product **2a** was obtained. The yield of **2a** could be enhanced to 74% at a higher temperature in MeCN and in the presence of Pd(OAc)$_2$ (Table 1, entry 7). To confirm that catalyst palladium is necessary in this reaction, we examined the blank reaction, and only traces of unidentified complexes were observed (Table 1, entry 8). When other solvents, such as THF, toluene and DCE were employed, the yields of **2a** decreased (Table 1, entries 9–11).

With the optimized conditions, a series of MCB was employed to examine the reaction's application scope. Both

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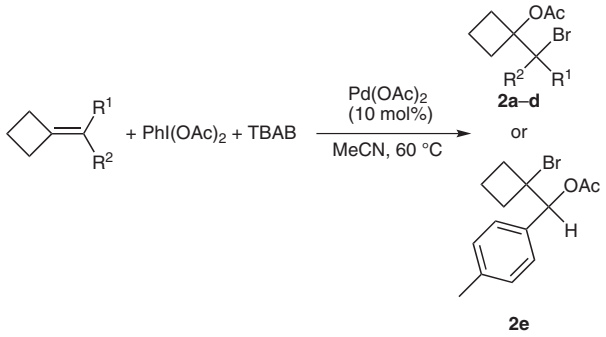
disubstituted and monosubstituted MCB led to the bifunctional products **2** smoothly (Table 2).[12] It is interesting that, when monosubstituted MCB **1e** was employed, the regioselectivity was reversed (Table 2, entry 5).

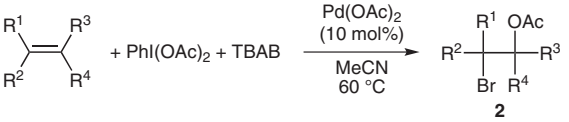
Table 2 Difunctional Reactions of a Series of MCBs



Entry	R^1, R^2	Time (h)	Yield of **2** (%)[a]
1	**1a** Ph, Ph	1.5	**2a** 74
2	**1b** 4-ClC_6H_4, 4-ClC_6H_4	2.5	**2b** 63
3	**1c** 4-FC_6H_4, 4-FC_6H_4	3	**2c** 68
4	**1d** 4-MeC_6H_4, Me	3	**2d** 55
5	**1e** 4-MeC_6H_4, H	1	**2e** 70

[a] Isolated yields.

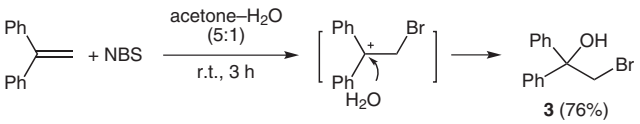
Table 3 Difunctional Reactions of a Series of Simple Olefins



Entry	R^1, R^2, R^3, R^4	Time (h)	Yield of **2** (%)[a]
1	**1f** Ph, Ph, H, H	7	**2f** 63
2	**1g** Ph, 4-MeC_6H_4, H, H	9	**2g** 67
3	**1h** Ph, 2-MeC_6H_4, H, H	10	**2h** 62
4	**1i** Ph, 1-$C_{10}H_7$, H, H	12	**2i** 51
5	**1j** Ph, 4-ClC_6H_4, H, H	14	**2j** 56
6	**1k** Ph, H, H, Ph	9	**2k** 50
7	**1l** C_7H_{15}, H, H, Ph	7	**2l** 58
8	**1m** H, H, H, Ph	10	**2m** 52
9	**1n** Ph, Ph, Ph, H	12	trace[b]
10	**1o** Bn, H, H, Pr	6	0[b]
11	**1p** R^1–R^2 = -($CH_2CH_2CHPhCH_2CH_2$)-, R^3 = H, R^4 = Pr	7	0[b]

[a] Isolated yields.
[b] A series of unidentified compounds were observed.

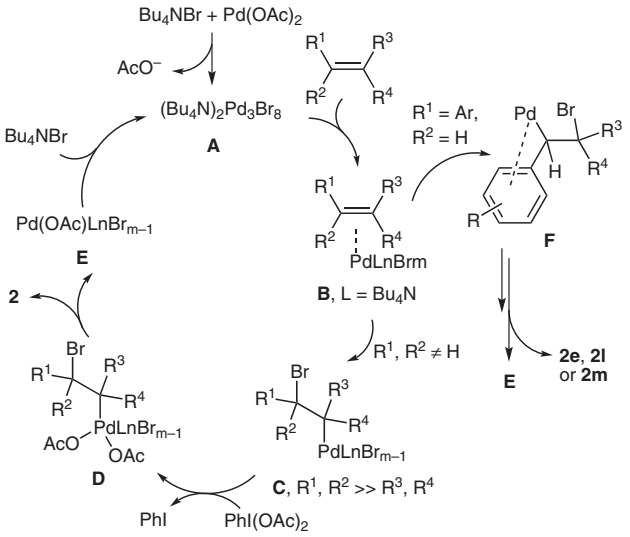
In order to gain more hints in mechanism studies, we examined the similar reactions on simple olefins. The experimental results showed that the reaction could also happen when simple olefins were employed. The reaction had high selectivity, and in the cases of the bisaryl substituted olefins, the oxygen group tended to add to the less steric hindrance site while the bromide added at the more hindered position (Table 3, entries 1–5). This is very different from traditional bromohydroxylations, which proceeded under Markovnikov rules (Scheme 1).[13] When monoaryl-substituted olefins were employed the regioselectivity changed, and acetyoxy group tended to add to the more sterically hindered carbon atom (Table 3, entries 7 and 8). Triphenylethene **1n** gave only trace of the desired product, probably due to the its steric hindrance (Table 3, entry 9). It was also found that the substrate should have at least one aryl group on the C=C bond. Otherwise, no desired product could be obtained (Table 3, entries 10 and 11).



Scheme 1

Based on the above experimental results as well as literature references, we supposed a possible mechanism. Reaction of $Pd(OAc)_2$ with TBAB would generate the palladium species **A**.[1h] Coordination of **A** with olefins then gave the palladium intermediate **B**. Further transformation of which led to the intermediate **C**. To reduce the steric hinderance, the larger palladium atom tended to add to the less sterically hindered position when bisaryl-substituted olefins were employed. This also determined the reaction regioselectivity. Oxidation of **C** with $PhI(OAc)_2$ generated intermediate **D**,[1h] and reductive elimination of which led to the final product **2** in an anti-Markovnikov fashion and generated palladium species **E**. Reaction of **E** with TBAB regenerate the palladium species **A** (Scheme 2). However, when monoaryl-substituted olefins were employed, the regioselectivity changed (Table 2, entry 5; Table 3, entries 7 and 8). Although the aryl-substituted carbon might have larger (in **1m**) or similar (in **1e** and **1l**) steric hindrance, the acetoxy group tended to add to the aryl carbon and gave **2e**, **2l**, and **2m** in high regioselectivity. For the monoaryl-substituted substrates, the steric hindrance of the aryl-substituted carbon decreased considerably and could accommodate the larger palladium group. Hence, steric hindrance was no longer an important factor in the regioselectivity-deciding step. Therefore, the palladium groups tended to add to the aryl-substituted carbon to generate the intermediate **F**, which led to the Markovnikov adducts (Scheme 2).

In conclusion, we have developed a novel bisfunctionalization reaction of olefins. In this reaction, oxygen and bromide groups could be introduced simultaneously. The regioselectivity of this reaction was controllable, depend-



Scheme 2

ing on the substituted groups on the C=C bond. Therefore, this strategy could be an effective supplement of bromohydroxylations in organic synthesis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **Typical Procedure for the Preparation of 2**
In the presence of $Pd(OAc)_2$ (0.03 mmol, 6.7 mg), olefins (0.3 mmol), $PhI(OAc)_2$ (0.6 mmol), and TBAB (0.3 mmol) were heated in MeCN (2 mL) at 60 °C. The reaction was monitored by TLC. When the reaction terminated, H_2O (5 mL) was added, and the liquid was extracted by EtOAc (3 × 5 mL). The combined organic layer was dried by anhyd $MgSO_4$, and the solvent was evaporated under vacuum. The residue was subjected to preparative TLC (eluent: PE–EtOAc = 8:1) to give the corresponding product **2**.
Data for Compound 2a
Oil. IR (film): 2952, 1751, 1639, 1494, 1446, 1366, 1218, 1084, 1013, 986, 961, 904, 750, 706 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.52–7.53 (m, 4 H), 7.30–7.32 (m, 6 H), 3.28–3.30 (m, 2 H), 2.40–2.43 (m, 1 H), 2.25–2.28 (m, 2 H), 2.12 (s, 3 H), 1.83–1.85 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.8, 22.3, 37.3, 74.4, 88.7, 127.0, 127.8, 129.7, 137.7, 168.0 ppm. MS (EI, 70 eV): *m/z* (%) = 278 (3) [M^+ – Br], 183 (100). Anal. Calcd for $C_{19}H_{19}BrO_2$: C, 63.52; H, 5.33. Found: C, 63.20; H, 5.14.

(13) **Procedure for the Bromohydroxylation of Compound 1f**
Compound **1f** (0.3 mmol) and NBS (0.3 mmol) were stirred in acetone–H_2O (2 mL; 5:1) at r.t. The reaction was monitored by TLC (eluent: PE). When the reaction terminated, the liquid was subjected to preparative TLC (eluent: PE–EtOAc = 7:1) to give the adduct **3** in 76% yield.
Data for 3
Oil. IR (film): 3060, 3029, 2971, 1493, 1448, 1425, 1332, 1279, 1226, 1163, 1062, 1032, 993, 913, 843, 750, 699 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.25–7.43 (m, 10 H), 4.09 (s, 2 H), 3.14 (s, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 44.0, 76.9, 126.4, 127.7, 128.4, 143.5. MS (EI, 70 eV): *m/z* (%) = 276 (3) [M^+], 105 (100). Anal. Calcd for $C_{14}H_{13}BrO$: C, 60.67; H, 4.73. Found: C, 60.95; H, 4.88.