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Palladium catalysed β-selective oxidative Heck reaction of an electron-rich olefin†

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A palladium catalysed oxidative β-arylation of an electron-rich olefin is described. The reaction was under mild conditions; meanwhile, additives and directing groups are not needed. Various arylboronic acids worked well under the standard conditions.

The Heck reaction has become one of the most important tools for constructing aryl substituted alkenes since the 1960s.[1] Electron-deficient olefins applied in the Heck reaction generally generate highly regioselective linear β-arylated products, while for electron-rich olefins a mixture of both α,β-arylated regio-isomeric products is generally obtained.[2] Recently, much effort has been applied to solve this problem, for instance, diphosphine ligands, ionic liquids and alcohol additives have shown high efficiency in the formation of α-regioselective products for electron rich olefins.[2d,3] Oxidative Heck reactions using arylboronic acids as nucleophiles have also shown high efficiency in obtaining highly regioselective α-arylated electron rich olefins.[2b,c]

Although directing-group-assisted β-selective Heck reactions of electron rich olefins have been achieved in the past years, few reports have focused on establishing an efficient catalytic system for the β-arylation of electron rich olefins without a directing group.[3a,4] The major reason is the electrical properties of the two olefin carbons, which highly influence the olefin insertion step of a Heck reaction (Fig. 1). Therefore, it is a big challenge to establish an α-selective Heck reaction system with an electron-deficient olefin and a β-selective Heck reaction system with a simple electron-rich olefin. Herein, we report an oxidative β-selective Heck reaction for the electron rich olefin vinyl acetate (Scheme 1).

β-Arylated vinyl esters, with their hydrolysates, are important building blocks. Although β-arylated vinyl esters can be easily generated from α-arylated aldehydes, α-arylated aldehydes are not easy to obtain.[5] Thus, it is highly desirable to establish a catalytic system for β-arylated vinyl esters synthesis from commercially available simple olefins under mild conditions.

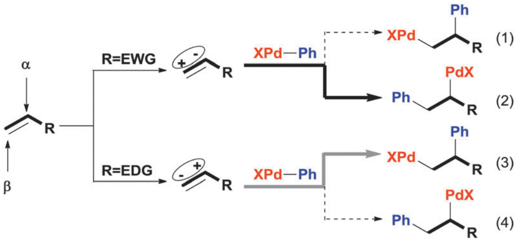
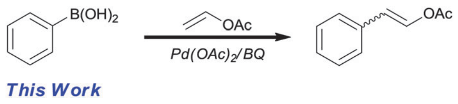


Fig. 1 Alternative olefin insertion pathways.



Scheme 1 Formation of β-arylated vinyl acetate.

This work was started by testing various electron-rich olefins to react with arylboronic acids (see details in ESI†). HOAc was initially chosen as solvent to inhibit homocoupling of arylboronic acids **1**.[6] Fortunately, after testing several electron-rich olefins, vinyl acetate was found to be able to convert to the β-arylation product in 23% yield. This promising result encouraged us to further investigate this β-selective oxidative Heck reaction.

After screening multiple conditions, only the co-solvent was found to highly influence the yield of the β-arylation product. When DMSO was applied as co-solvent, the yield increased to 51% (Table 1, entry 1), while other co-solvents had an adverse effect on the β-arylation reaction with only a small amount of β-arylation product obtained (Table 1, entries 2–6). Subsequently, other acids were also tested. When HOAc was replaced by TFA, no β-arylation product could be obtained; this might be due to hydration of vinyl acetate in the strongly acidic environment or the decomposition of arylboronic acid (Table 1, entry 7). The amount of HOAc also had an effect on the yield of the desired product. A lower loading of HOAc led to a decreased yield whereas no desired product was

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc47045h

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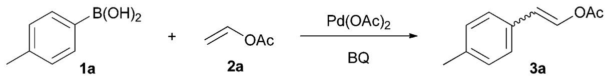
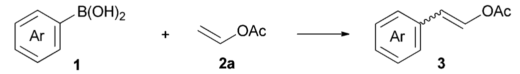
Table 1 Solvent effect on the β-selective oxidative Heck reaction[a]

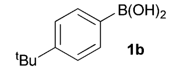
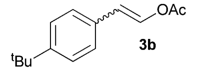
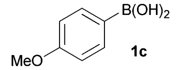
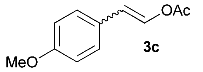
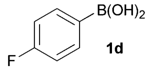
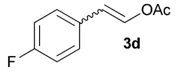
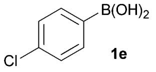
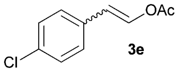
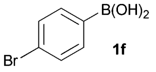
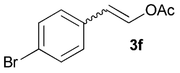
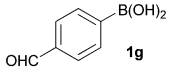
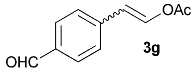
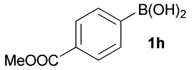
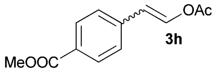
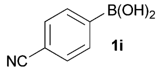
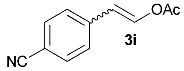
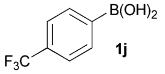
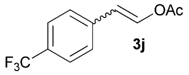
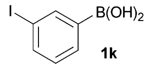
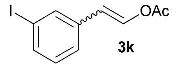
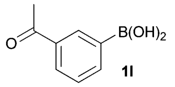
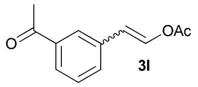
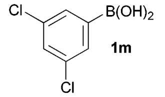
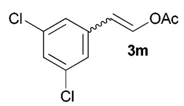


Entry	Sol. 1	Sol. 2	1/2a	Yield[b] (%)
1	HOAc	DMSO	1/20	51
2	HOAc	DMF	1/20	12
3	HOAc	1,4-Dioxane	1/20	12
4	HOAc	MeCN	1/20	9
5	HOAc	THF	1/20	2
6	HOAc	Toluene	1/20	6
7	TFA	DMSO	1/20	n.d.
8	—	DMSO	1/20	n.d.
9[c]	HOAc	DMSO	1/20	54
10[d]	**HOAc**	**DMSO**	**1/20**	**61**[e]
11	HOAc	DMSO	1/5	47
12	HOAc	DMSO	1/1	36

[a] The reaction was carried out with **1** (1 eq., 68 mg, 0.5 mmol), **2a**, $Pd(OAc)_2$ (5 mol%, 5.6 mg, 0.025 mmol), BQ (1,4-benzoquinone, 1.2 eq., 64.8 mg, 0.6 mmol), in sol. 1/sol. 2 (1 mL/1 mL), at 50 °C, for 12 h. [b] GC yield. [c] Sol. 1/sol. 2 (1.5 mL/0.5 mL). [d] 60 °C. [e] Isolated yield.

Table 2 Scope of arylboronic acids for β-selective oxidative Heck reaction with vinyl acetate[a]



Entry	Substrate	Yield[b] (%)	Product
1	 1b	63	 3b
2	 1c	24	 3c
3	 1d	49	 3d
4	 1e	64	 3e
5	 1f	64	 3f
6	 1g	76	 3g
7	 1h	77	 3h
8	 1i	86	 3i
9	 1j	76	 3j
10	 1k	45	 3k
11	 1l	67	 3l
12	 1m	75	 3m

[a] The reaction was carried out with **1** (1 eq., 0.5 mmol), **2a** (20 eq., 10 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg, 0.025 mmol), BQ (1.2 eq., 64.8 mg, 0.6 mmol), in 1 mL HOAc and 1 mL DMSO, at 60 °C, for 12 h. [b] Isolated yield.

observed in the absence of HOAc, along with high yields of biaryl by-products (Table 1, entry 8). Lowering the amount of DMSO seemed to have little effect on the yield of β-arylation product (Table 1, entry 9), while lowering the amount of vinyl acetate decreased the yield of β-arylation product (Table 1, entries 11 and 12). Higher temperature was found to increase the yield of β-arylation product. When the reaction was carried out at 60 °C, the best result of β-arylation product was obtained respectively (Table 1, entry 10).

With the optimized condition established, the scope of the arylboronic acids for this palladium catalysed β-arylation reaction was examined for a number of arylboronic acids (Table 2). Moderate to good yields were obtained. Halogens (F, Cl, Br and I) were all well tolerated, thus allowing additional transformation of the initial β-arylation products (**3d–f**, **3k**). In addition, both electron-rich and electron-deficient arylboronic acids were compatible under the current conditions (**3b**, **3h–j**, **3l–m**). It is noteworthy that higher yields of the corresponding product could be generated with electron-poor arylboronic acids (**3g–j**, **3l**). Furthermore, aldehyde, ketone, ester and cyan groups also went smoothly and gave the corresponding products in good yields (**3g–i**, **3l**).

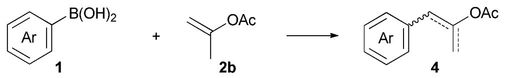
Next, the substrate scope of arylboronic acids with regard to the vinyl acetate moiety was examined. Prop-1-en-2-yl acetate **2b** also coupled with arylboronic acids (Table 3). When (4-chlorophenyl)-boronic acid was applied to couple with **2b** the β-arylation product could be obtained in up to 92% yield (Table 3, entry 1). Aryl groups bearing an electron-donating substituent were also well tolerated under the current reaction conditions; when (4-(*tert*-butyl)phenyl)-boronic acid was applied a 74% yield of β-arylation product could be isolated (Table 3, entry 2).

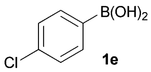
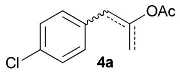
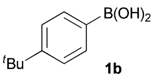
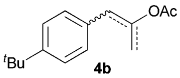
The coupling product of arylboronic acids with prop-1-en-2-yl acetate was the acetate protected 1-arylpropan-2-one. This indicated that this β-arylation reaction could be a precursor for 1-arylpropan-2-one synthesis. Arylboronic acid **1h** was tested for the corresponding 1-arylpropan-2-one synthesis and 1-arylpropan-2-one was found to be generated in 63% in two steps (Scheme 2).

Furthermore, kinetic experiments were conducted by using *operando* IR. Firstly, the relations of reaction rate *vs.* the concentration of oxidant were studied. Kinetic data showed that the concentration of oxidant had little influence on the reaction rate; this indicated that oxidation of Pd(0) to Pd(II) was not the rate limiting step for this reaction (see ESI†). Then the relationships of reaction rate with the concentration of arylboronic acid and palladium catalyst were also studied (Fig. 2 and 3). These results showed that the concentrations of arylboronic acid and palladium catalyst all have an influence on the reaction rate of this β-arylation process. Therefore we may come to the conclusion that the transmetalation step might be the rate limiting step for this reaction (see ESI†).

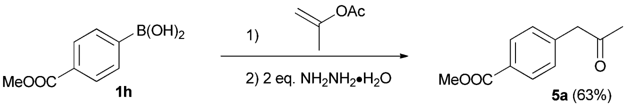
This oxidative Heck reaction proceeds under acidic conditions, which usually makes the corresponding Pd catalyst more

Table 3 Scope of arylboronic acids for β-selective oxidative Heck reaction with prop-1-en-2-yl acetate[a]



Entry	Substrate	Yield[b] (%)	Product
1	 1e	92	 4a
2	 1b	74	 4b

[a] The reaction was carried out with **1** (1 eq., 0.5 mmol), **2b** (20 eq., 10 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg, 0.025 mmol), BQ (1.2 eq., 64.8 mg, 0.6 mmol), in 1 mL HOAc and 1 mL DMSO, at 60 °C, for 12 h. [b] Isolated yield.



Scheme 2 Synthesis of 1-arylpropan-2-one through β-arylation reaction of vinyl acetate.

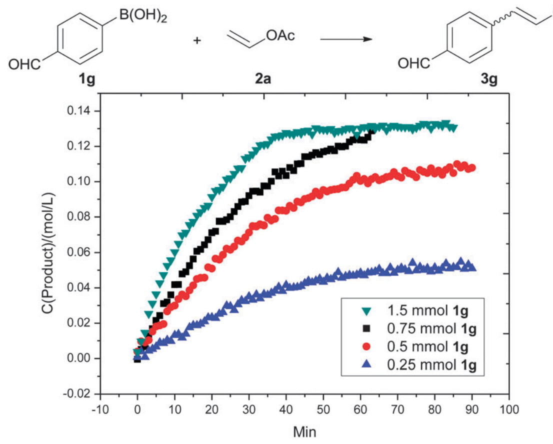


Fig. 2 The effect of concentration of arylboronic acid.

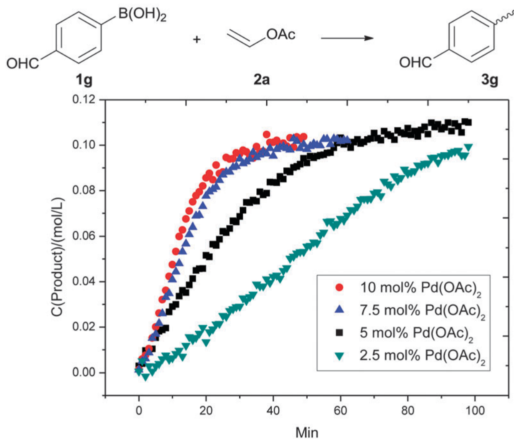


Fig. 3 The effect of concentration of catalyst.

electron-deficient. In the proposed catalytic cycle, Pd species **I** is the key intermediate for generating the selectivity (see ESI†). Usually, for α-selectivity, the phenyl migration to the α-position dominates. However, in this case, as the Pd center is electron-deficient, migration of the electron-rich phenyl group from the Pd center is prohibited. Moreover, deprotonation at the β-position to generate intermediate **III** (path A) or reductive elimination at the β-position to generate intermediate **II** would also be possible (path B) (see ESI†).

In summary, we have demonstrated the first β-selective oxidative Heck reaction between arylboronic acid and vinyl acetate. Various substituted arylboronic acids were found to be suitable for the synthesis of important building block β-arylated vinyl acetates. In addition, the reaction conditions are mild, and no ligand or base were needed. *Operando* IR experiments showed that the transmetalation step might be the rate limiting step for this reaction.

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Notes and references

1 (*a*) R. F. Heck, *J. Am. Chem. Soc.*, 1968, **90**, 5535–5538; (*b*) T. Mizoroki, K. Mori and A. Ozaki, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 581; (*c*) I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009–3066; (*d*) A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945–2964.

2 (*a*) W. Cabri and I. Candiani, *Acc. Chem. Res.*, 1995, **28**, 2–7; (*b*) M. M. S. Andappan, P. Nilsson, H. von Schenck and M. Larhed, *J. Org. Chem.*, 2004, **69**, 5212–5218; (*c*) J. Ruan, X. Li, O. Saidi and J. Xiao, *J. Am. Chem. Soc.*, 2008, **130**, 2424–2425; (*d*) J. Ruan and J. Xiao, *Acc. Chem. Res.*, 2011, **44**, 614–626.

3 (*a*) M. Larhed, C.-M. Andersson and A. Hallberg, *Tetrahedron*, 1994, **50**, 285–304; (*b*) L. Xu, W. Chen, J. Ross and J. Xiao, *Org. Lett.*, 2001, **3**, 295–297; (*c*) J. Mo, L. Xu and J. Xiao, *J. Am. Chem. Soc.*, 2005, **127**, 751–760; (*d*) W. Pei, J. Mo and J. Xiao, *J. Organomet. Chem.*, 2005, **690**, 3546–3551; (*e*) Z. Hyder, J. Mo and J. Xiao, *Adv. Synth. Catal.*, 2006, **348**, 1699–1704; (*f*) J. Mo and J. Xiao, *Angew. Chem., Int. Ed.*, 2006, **45**, 4152–4157; (*g*) L. R. Odell, J. Lindh, T. Gustafsson and M. Larhed, *Eur. J. Org. Chem.*, 2010, 2270–2274.

4 (*a*) C. M. Andersson and A. Hallberg, *J. Org. Chem.*, 1988, **53**, 235–239; (*b*) P. Nilsson, M. Larhed and A. Hallberg, *J. Am. Chem. Soc.*, 2001, **123**, 8217–8225; (*c*) S. Chandrasekhar, C. Narsihmulu, S. S. Sultana and N. R. Reddy, *Org. Lett.*, 2002, **4**, 4399–4401; (*d*) Y. C. Jung, R. K. Mishra, C. H. Yoon and K. W. Jung, *Org. Lett.*, 2003, **5**, 2231–2234; (*e*) J. Tian and K. D. Moeller, *Org. Lett.*, 2005, **7**, 5381–5383; (*f*) G. K. Datta, H. von Schenck, A. Hallberg and M. Larhed, *J. Org. Chem.*, 2006, **71**, 3896–3903; (*g*) A. Trejos, A. Fardost, S. Yahiaoui and M. Larhed, *Chem. Commun.*, 2009, 7587–7589; (*h*) S. M. Bromidge, R. Arban, B. Bertani, M. Borriello, A.-M. Capelli, R. Di-Fabio, S. Faedo, M. Gianotti, L. J. Gordon, E. Granci, A. Pasquarello, S. K. Spada, A. Worby, L. Zonzini and V. Zucchelli, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7092–7096; (*i*) V. Chandrasekhar and R. S. Narayanan, *Tetrahedron Lett.*, 2011, **52**, 3527–3531.

5 (*a*) Y. Terao, Y. Fukuoka, T. Satoh, M. Miura and M. Nomura, *Tetrahedron Lett.*, 2002, **43**, 101–104; (*b*) R. Martín and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2007, **46**, 7236–7239; (*c*) R. Martín and S. L. Buchwald, *Org. Lett.*, 2008, **10**, 4561–4564; (*d*) G. D. Vo and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2008, **47**, 2127–2130; (*e*) N. Chernyak and S. L. Buchwald, *J. Am. Chem. Soc.*, 2012, **134**, 12466–12469.

6 M. Chen, J. Wang, Z. Chai, C. You and A. Lei, *Adv. Synth. Catal.*, 2012, **354**, 341–346.