Oxidative Olefin Arylation

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Oxidative Heck Arylation for the Stereoselective Synthesis of Tetrasubstituted Olefins Using Nitroxides as Oxidants**

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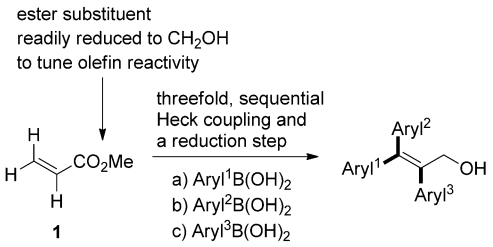
The Heck arylation belongs to the most important methods for C–C bond formation and has therefore found widespread application in organic synthesis.[1] Various halides or pseudo halides are readily cross-coupled with olefins under Pd catalysis. In contrast, the oxidative Heck reaction using aryl boronic acids in combination with an external oxidant and a Pd catalyst has been less intensively investigated.[2,3] Oxidative Heck-type coupling is strongly influenced by the olefin substituents and therefore lacks generality. In particular the synthesis of highly substituted olefins using this approach is not established. The regio- and stereoselective synthesis of highly substituted olefins is very challenging.[4] Herein we describe the mild and highly stereoselective sequential oxidative Pd-catalyzed C–H arylation of alkenes for the synthesis of alkyltriarylethenes.

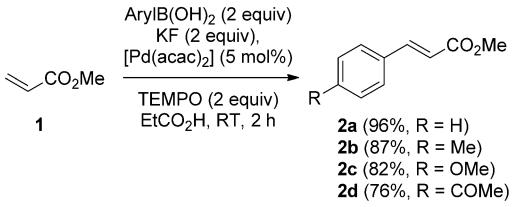
Our approach was based on the fact that substituents at the olefin strongly influence the regio- and stereoselectivity of the oxidative Heck coupling.[2] The goal was to develop an iterative threefold Heck sequence starting from methyl acrylate (**1**) [Eq. (1)]. The ester substituent is readily reduced



(1)

to the hydroxymethyl group to adjust the reactivity of the intermediate olefins. Moreover, the allylic OH group can be further chemically modified to vary the fourth substituent.

Methyl acrylate (**1**) is a well-established olefin for Heck coupling with aryl boronic acids. Various oxidants have been used to conduct that reaction.[2] After some experimentation we found that the 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO)[5,6] is a suitable oxidant for this reaction. When a solution of **1** with $PhB(OH)_2$, KF, $[Pd(acac)_2]$ (5 mol%), and TEMPO in propionic acid was stirred at room temperature, product **2a** was obtained with excellent diastereoselectivity (*E* only) in 96% yield [Eq. (2)]. Double phenylation, which is a problem when $Pd(OAc)_2$ is used as the catalyst, was not



(2)

observed.[7] Under these mild conditions, other aryl boronic acids bearing electron-rich and also electron-poor substituents reacted with complete diastereoselectivity (*E* only, **2b–d**).

The best yields for the introduction of the second aryl group were achieved upon reacting **2** with an arylboronic acid, KF, 4-HO-TEMPO, and $Pd(OAc)_2$ in propionic acid at room temperature (Table 1).[8a] With $[Pd(acac)_2]$ under otherwise identical conditions only moderate yields were obtained.

The nature of the arylboronic acid influenced the reactivity and selectivity. The highest selectivity was achieved with the electron-poor CF_3-substituted congener (> 98:2, see **3b**), whereas with 4-$MeC_6H_4B(OH)_2$ (27:1, **3a**) and 4-$MeOC_6H_4B(OH)_2$ (10:1, **3c**) lower selectivities resulted. Encouraged by these results we decided to test also non-acrylate-based disubstituted olefins and found that stilbene and its derivatives reacted efficiently. In these reactions we used pivalic acid/THF (5:1) as the solvent mixture.[8b] Excellent yields and good selectivities were obtained in the reaction of *trans*-stilbene with *meta*- and *para*-substituted aryl boronic acids (**3e–h**). However, the yield dropped significantly for the *ortho*-tolyl derivative, probably for steric reasons (**3i**). We unambiguously assigned the relative configuration of **3e** by X-ray analysis (Figure 1).[9] The stereochemical outcome of the reaction agreed with that expected for an oxidative Heck-type coupling.[2] Other compounds were assigned by analogy. The unsymmetrical *trans*-phenyl-*o*-tolylethene reacted with with $PhB(OH)_2$ in good regioselectivity for steric reasons (9:1, **3l**), and $PhCH{=}CHC_6F_5$ delivered only one regioisomer **3j**, probably for electronic reasons. As expected, when the electronic difference of the aryl substituents was not that pronounced (see, for example, 4-$CH_3OC_6H_4CH{=}CHC_6H_4$-4-CF_3), the regioselectivity was lower (3:1, **3k**). With respect to the yield, the reaction was generally more efficient for electron-rich olefins. Excellent

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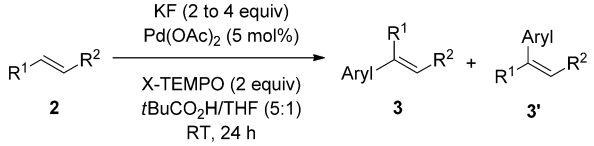
Table 1: Pd-catalyzed C–H bond arylation of *trans*-disubstituted olefins (X = H, OH).



R^1	R^2	Aryl	Yield [%]	Prod.	**3**/**3′**
Ph	CO_2Me	4-$CH_3C_6H_4$	82[a,b]	**3a**	27:1[c]
Ph	CO_2Me	4-$CF_3C_6H_4$	67[a,b]	**3b**	>98:2[c]
Ph	CO_2Me	4-$CH_3OC_6H_4$	41[a,b]	**3c**	10:1[c]
4-$CH_3C_6H_4$	CO_2Me	Ph	87[a,b]	**3d**	20:1[c]
Ph	Ph	4-$CH_3C_6H_4$	99[d]	**3e**	25:1[e]
Ph	Ph	4-$CH_3OC_6H_4$	91[d]	**3f**	24:1[e]
Ph	Ph	4-FC_6H_4	84[d]	**3g**	15:1[e]
Ph	Ph	3-$CH_3C_6H_4$	89[d]	**3h**	24:1[e]
Ph	Ph	2-$CH_3C_6H_4$	35[d]	**3i**	14:1[e]
Ph	C_6F_5	Ph	38[d]	**3j**	>99:1[f]
4-$CH_3OC_6H_4$	4-$CF_3C_6H_4$	4-$CH_3C_6H_4$	52[d]	**3k**	>98:2[c,g]
Ph	2-$CH_3C_6H_4$	Ph	68[d]	**3l**	9:1[f]
Me	Ph	Ph	69[d]	**3m**	>99:1[e,h]
Me	Ph	4-$CH_3OC_6H_4$	74[d]	**3n**	>99:1[e,h]
Me	Ph	4-ClC_6H_4	62[d]	**3o**	>99:1[e,h]

[a] Yield of isolated product; HO-TEMPO was used. [b] In propionic acid. [c] Selectivity was determined by ^{1}H NMR analysis. [d] Yield of isolated product; TEMPO was used. [e] Selectivity was determined by GC analysis. [f] Ratio of regioisomers. [g] Other regioisomer: 17% (*Z*/*E* > 98:2). [h] Other regioisomer not identified.

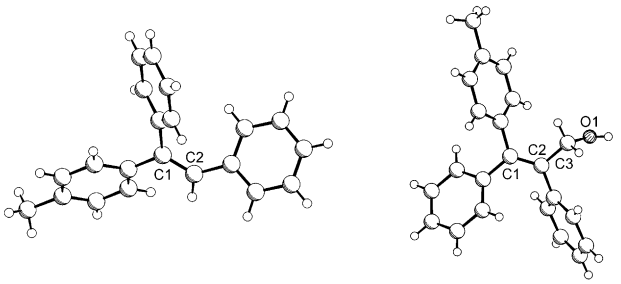


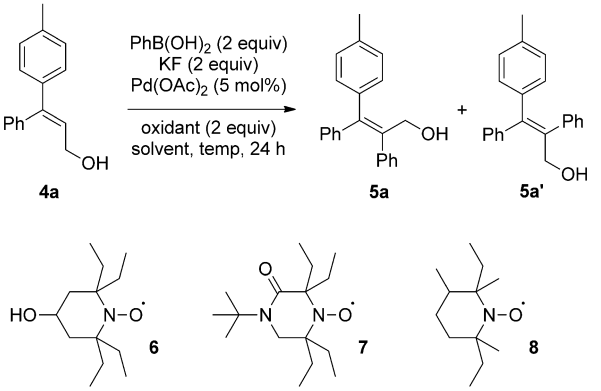
Figure 1. Molecular structures of **3e** (left) and **5a** (right).

regio and *trans*/*cis* selectivity were also obtained in the arylation of *trans*-methyl-β-styrene, which can be obtained from **2a** by reduction and deoxygenation (**3m–o**).

Oxidative arylation occurred stereospecifically, as documented by the transformation of *cis*-stilbene to the isomeric arylation products. Thus, reaction with 4-$MeC_6H_4B(OH)_2$ under our standard conditions afforded tolyl stilbene **3e′** in 72% yield as a 13:1 mixture of isomers (**3e′**/**3e**). By analogy, alkenes **3f′** (61%, ratio 12:1) and **3g′** (55%, ratio 8:1) were obtained as major isomers upon reaction of *cis*-stilbene with 4-$MeOC_6H_4B(OH)_2$ and 4-$FC_6H_4B(OH)_2$, respectively.

We then focused on the highly challenging arylation of the C–H group in trisubstituted olefins. Electron-poor β,β-diarylacrylates were not reactive enough to undergo oxidative Heck coupling. The ester moiety was reduced and arylation was optimized with allyl alcohol **4a** and $PhB(OH)_2$ to provide **5a** and **5a′** (Table 2). Oxidants and solvents were systematically varied. With 2 equiv of $PhB(OH)_2$ in propionic acid at room

Table 2: Oxidative phenylation of **4a**.

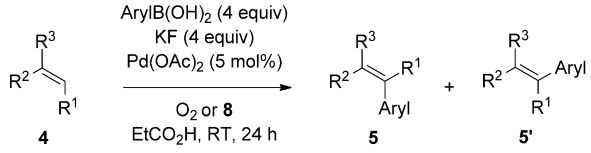


Entry	Oxidant	Solvent	*T* [°C]	Yield [%][a]	**5a**/**5a′**[b]
1	TEMPO	$EtCO_2H$	RT	47	9:1
2	TEMPO	$EtCO_2H$	50	54	6:1
3	TEMPO	$MeCO_2H$	50	28	2.4:1
4	4-HO-TEMPO	$EtCO_2H$	RT	37	2.7:1
5	4-AcNH-TEMPO	$EtCO_2H$	RT	31	2.3:1
6	**6**	$EtCO_2H$	RT	51	40:1
7	**7**	$EtCO_2H$	RT	46	35:1
8	**8**	$EtCO_2H$	RT	68	39:1
9	**8**	$EtCO_2H$	RT	77[c]	41:1
10	$Cu(OAc)_2$	$EtCO_2H$	RT	n.r.[d]	–
11	benzoquinone	$EtCO_2H$	RT	trace	–
12	$PhI(OAc)_2$	$EtCO_2H$	RT	trace	–
13	AgOAc	$EtCO_2H$	RT	5	33:1
14	O_2 (1 atm)	$EtCO_2H$	RT	79[e]	43:1

[a] Yield of isolated product. [b] Selectivity was determined by ^{1}H NMR analysis. [c] With 4 equiv $PhB(OH)_2$, 4 equiv KF, and 4 equiv **8**. [d] n.r. = no reaction. [e] With 4 equiv $PhB(OH)_2$ and 4 equiv KF.

temperature in the presence of KF and TEMPO, phenylation occurred in 47% yield with good stereoselectivity (9:1; Table 2, entry 1). Selectivity was determined by ^{1}H NMR analysis and the relative configuration was determined unambiguously by X-ray analysis of the major isomer **5a** (see Figure 1).[9] Yield was improved by increasing the temperature at the expense of lower selectivity (Table 2, entry 2). The reaction was less efficient in acetic acid (Table 2, entry 3). Replacing TEMPO with 4-HO-TEMPO or 4-AcNH-TEMPO led to lower yields (Table 2, entries 4 and 5). Surprisingly, the selectivity dropped, indicating that the reduced nitroxide formed during reoxidation of the Pd^0 species likely ligates the Pd metal which can influence the stereochemical outcome of the β-H elimination step. Along this line, the sterically highly hindered nitroxides **6**[10] and **7**[11] provided the arylation product with excellent selectivity (Table 2, entries 6 and 7). Interestingly, nitroxide **8**,[12] which is between TEMPO and **6** in size, afforded a better yield while the very high selectivity was maintained (Table 2, entries 8 and 9). Such subtle steric effects of the nitroxide on transition-metal-catalyzed oxidative couplings are unprecedented. Importantly, **8** was readily recovered in 76–82% (see the Supporting Information). Other oxidants such as $Cu(OAc)_2$, benzoquinone, $PhI(OAc)_2$, and AgOAc did not work well (Table 2, entries 10–13). Surprisingly, O_2 (balloon, 1 atm), which was not an efficient oxidant for the first two arylations,

Table 3: Scope of the third arylation.



R^1	R^2	R^3	Aryl	Prod.	Yield [%][a]	**5/5'**[b]
CH_2OH	Ph	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	**5b**	79[c]	20:1
CH_2OH	Ph	4-$CH_3C_6H_4$	4-$CF_3C_6H_4$	**5c**	54[c]	29:1
CH_2OH	Ph	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	**5d**	45[c]	24:1
CH_2OH	Ph	4-$CH_3C_6H_4$	3-$CH_3C_6H_4$	**5e**	77[c]	34:1
CH_2OH	Ph	4-$CH_3C_6H_4$	2-$CH_3C_6H_4$	**5f**	32[c]	27:1
CH_2OH	Ph	4-$CH_3C_6H_4$	3-FC_6H_4	**5g**	51[c]	34:1
CH_2OH	Ph	4-$CH_3C_6H_4$	4-PhC_6H_4	**5h**	57[c]	17:1
CH_2OH	4-$CH_3C_6H_4$	Ph	Ph	**5i**	45[c]	17:1
CH_2OH	4-$CH_3C_6H_4$	Ph	Ph	**5i**	67[d]	13:1
CH_2OH	4-$CF_3C_6H_4$	Ph	Ph	**5j**	71[c]	30:1
CH_2OH	4-$CF_3C_6H_4$	Ph	Ph	**5j**	57[d]	30:1
CH_2OH	Ph	4-$CH_3OC_6H_4$	Ph	**5k**	19[c]	>98:2
CH_2OH	Ph	4-$CH_3OC_6H_4$	Ph	**5k**	78[d]	>98:2
CH_2OH	Ph	4-$CF_3C_6H_4$	Ph	**5l**	57[c]	>98:2
CH_2OH	Ph	4-$CF_3C_6H_4$	Ph	**5l**	49[d]	>98:2
Me	Ph	Ph	Ph	**5m**	70[c]	–
Et	Ph	Ph	Ph	**5n**	64[c]	–
*i*Pr	Ph	Ph	Ph	**5o**	6[c]	–

[a] Yield of isolated product. [b] Selectivity was determined by ^{1}H NMR analysis. [c] With O_2 (balloon, 1 atm). [d] With nitroxide **8** (4 equiv).

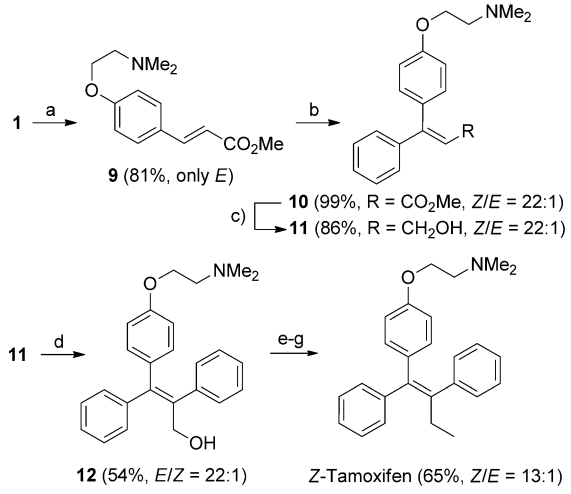
performed well and **5a** was isolated in 79% yield with excellent selectivity (43:1; Table 2, entry 14).

Under optimized conditions we tested the scope of the third arylation using either O_2 or **8** as oxidants (Table 3).[13] Under O_2 atmosphere the *para*- and *meta*-substituted phenylboronic acids reacted with good to very good yields and high selectivities to provide the corresponding tetrasubstituted olefins (see **5b–e,g,h**). A significantly reduced yield was obtained for the *o*-tolyl derivative (**5f**), for steric reasons. We found that the aryl group in *trans* position to the H atom influenced the reaction outcome. With the more electron-rich *p*-tolyl derivative, the yield decreased using the O_2 protocol and **5i** was isolated in 45%. Replacing O_2 with **8** led to an increase of the yield (67%). However, for the electron-poor *trans*-4-$CF_3C_6H_4$ congener, the O_2 setup provided a better result (**5j**). A similar and even more pronounced trend was observed when R^3 was varied. Oxidative phenylation of the electron-rich 4-$CH_3OC_6H_4$ derivative with O_2 provided **5k** in only 19% yield, whereas with **8**, **5k** was isolated in 78% yield with excellent selectivity. The electron-poor 4-$CF_3C_6H_4$ derivative afforded **5l** in 57% using O_2, and the nitroxide protocol delivered **5l** in 49% yield. Hence, for electron-rich olefins, the reaction was better using **8** as oxidant and the third arylation of electron-poorer olefins is better conducted with O_2.

We were pleased to find that the final arylation was not restricted to bisarylated allyl alcohols as substrates. The OH group was not necessary as shown by the successful preparation of **5m** (R^1 = Me) and **5n** (R^1 = Et). However, with the bulkier *i*Pr congener, the yield dropped to 6% (see **5o**).

Finally, we applied our oxidative Heck sequence to the synthesis of *Z*-Tamoxifen (Scheme 1).[4a–c,f,14] Oxidative arylation of methyl acrylate (**1**) with 4-(2-dimethylaminoethoxy)phenylboronic acid using [Pd(acac)$_2$] as the catalyst afforded **9** in high yield and complete *E* selectivity. Renewed Pd-catalyzed oxidative arylation with $PhB(OH)_2$ provided **10** in quantitative yield and high *Z* selectivity. DIBALH reduction gave allyl alcohol **11** (86%) ready for the third arylation. As expected based on our model studies, arylation of this electron-rich system **11** (*Z*/*E* = 22:1) could be conducted with nitroxide **8** as an oxidant, and **12** was obtained in 54% yield with excellent stereospecificity. It is important to note that O_2-mediated phenylation of **11** did not deliver product **12**, showing the importance of the nitroxide for this difficult arylation. Oxidation,[15] Wittig methenylation, and hydrogenation under slightly modified literature conditions[14a] eventually afforded *Z*-Tamoxifen.[16]

In summary, we have documented the potential of the nitroxide-mediated Pd-catalyzed oxidative Heck arylation for the stereoselective synthesis of tetrasubstituted triarylated olefins. The reactions presented mostly occurred in good yields and high stereoselectivities under mild conditions. Importantly, we have shown that the nature of the oxidant strongly influences the oxidative Heck reaction. Our results show that in future studies on nitroxide-mediated oxidative coupling reactions, nitroxides other than the typically used TEMPO should be included. Furthermore, we applied our arylation methodology to the synthesis of *Z*-Tamoxifen. Protecting groups were not necessary for the synthesis of this pharmacologically important olefin.



Scheme 1. Synthesis of *Z*-Tamoxifen: a) 4-(2-dimethylaminoethoxy)phenylboronic acid (2 equiv), TEMPO (2 equiv), KF (2 equiv), [Pd(acac)$_2$] (5 mol%), $EtCO_2H$, RT, 24 h; b) $PhB(OH)_2$ (4 equiv), HO-TEMPO (2 equiv), KF (4 equiv), $Pd(OAc)_2$ (5 mol%), $EtCO_2H$, RT, 24 h; c) DIBALH, THF; d) $PhB(OH)_2$ (4 equiv), **8** (4 equiv), KF (4 equiv), $Pd(OAc)_2$ (10 mol%), $EtCO_2H$, 40°C, 24 h; e) tetrapropylammonium perruthenate (5 mol%), NMO (2 equiv), RT, 0.5 h (80%, *E*/*Z* = 18:1); f) NaH, Ph_3PCH_3Br, THF, reflux, 4 h (85%, *Z*/*E* = 13:1); g) H_2, Pd/C, EtOAc, RT, 2 h (95%, *Z*/*E* = 13:1).

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[7] With O_2 as the oxidant instead of TEMPO, **2a** was formed in trace amounts. With $Pd(OAc)_2$ as the catalyst, a compound of type **3** resulting from double phenylation was observed.

[8] a) When O_2 was used instead of 4-HO-TEMPO a significantly lower yield resulted (32% for **3a**). With TEMPO, the yield for **3a** was lower (70%). b) Experiments with *trans*-stilbene revealed that *E*/*Z* selectivity is lower when the reaction is conducted in $MeCO_2H$, $EtCO_2H$, or $iPrCO_2H$.

[9] CCDC 853228 (**3e**) and CCDC 853229 (**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[12] Reagent **8** can be readily prepared in analogy to TEMPO by replacing acetone with ethyl methyl ketone as a starting material, see: H. Brunetti, J. Rody, N. Soma, T. Kurumada, DE-Patent, 2,621,841, **1976**. **8** was used as a mixture of its 4 diastereoisomers: 65:14:13:8.

[13] Some substrates were not isomerically pure (see the Supporting Information). In these cases, the stereospecificity is higher than the ratio given by **5**/**5′**.

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[16] Little isomerization occurred during oxidation and also during Wittig methenylation under the applied conditions.

