Mizoroki-Heck cross-coupling of acrylate derivatives with aryl halides catalyzed by palladate pre-catalysts

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Abstract: The Mizoroki-Heck (MH) reaction involving aryl halides with various acrylates and acrylamides has been studied using air and moisture-stable imidazolium-based palladate pre-catalysts. These pre-catalysts can be converted into Pd-NHC species (NHC = N-heterocyclic carbene) under catalytic conditions and are capable of facilitating the Mizoroki-Heck reaction of aryl halides with various acrylates. The effects of solvent, catalyst loading, temperature and bases on the reaction outcome have been investigated. Various coupling partners were tolerated under the optimal reaction conditions catalyzed by palladate **1**, [SIPr·H][Pd(η^3-2-Me-allyl)Cl_2]. The efficiency of the optimized synthetic methodology was tested on various aryl halides and substituted acrylates as well as acrylamides. The MH reaction yielded the coupled products in good to excellent isolated yields (up to 98%).

Introduction

Palladium-catalyzed cross-coupling reactions are one of the most effective synthetic approaches for the construction of carbon-carbon bonds, sparking an ever-growing demand for the development of new and more active catalysts, which can operate under mild conditions.[1,2] Among these couplings, the Mizoroki-Heck reaction has emerged as a highly useful synthetic tool,[3] widely used in the medicinal,[4] fine-chemical[5] and polymer chemistry sectors,[6] as well as in the synthesis of natural products.[7] An interesting use of this strategy can be found in a the report by Jiang and co-workers on the synthesis of a retinoid x receptor antagonist, diazepinylbenzoic acid, where the Mizoroki-Heck reaction was a determining step of the synthetic strategy.[8] The direct cross-coupling of an alkene/acrylate with an aryl/alkyl halide provides rapid access to functionalized building blocks that are of great importance as precursors in medicinal industry, as UV absorbers or as molecular devices.[7-9]

In this regard, the design and implementation of new palladium pre-catalysts have significantly improved the efficiency of various cross-coupling reactions.[3,10-11] Pd-NHC catalysts are among the most used nowadays for various cross-coupling reactions, including carbon-nitrogen,[11a] carbon-carbon,[11b] and carbon-sulfur[11c] bond formations as well as arylation of ketones.[11d] Using these NHC-based palladium complexes, several advances in the Mizoroki-Heck reactions have been reported albeit to a lesser extent than other cross-coupling reactions.[12]

Recently, palladate-NHC complexes, of the formula [NHC·H]Pd(η^3-R-allyl)Cl_2], have been described as bench-stable and highly efficient pre-catalysts for several cross-coupling reactions,[13] including a preliminary proof-of-concept in the Mizoroki-Heck (MH) reaction.[13a] Their ease of access (one step from commercially available materials) and ease of activation (no need for additives or any prior activation as long as the reactions are conducted under slightly basic conditions) make them highly useful tool for the synthetic community.

In this report, we describe the investigation/optimization of the Mizoroki-Heck reaction starting from various aryl halides and substituted acrylates as well as acrylamides, using NHC-based palladate complexes, [NHC·H]Pd(η^3-R-allyl)Cl_2], as pre-catalysts.

Results and Discussion

Based on our previous work,[13a] 1, 3-bis (2,6-diisopropylphenylimidazolidene (SIPr) was chosen as the optimal NHC ligand for the palladate precursors. In this manner, initial optimization was conducted using [SIPr·H][Pd(η^3-2-Me-allyl)Cl_2] (**Pd-1**) and [SIPr·H][Pd(η^3-cin)Cl_2] (**Pd-2**). These pre-catalysts were synthesized using our previously reported procedure that makes use of simply grinding the corresponding palladium precursors, [Pd(η^3-2-Me-allyl)(μ-Cl)]$_2$ or [Pd(η^3-cin)(μ-Cl)]$_2$, with the imidazolium salt (SIPr·HCl).[13b] These two palladates were initially tested in the Mizoroki-Heck reaction involving 4-bromoanisole **1a** and *n*-butyl acrylate **2a** as standard substrates (Scheme 1).

Initially, the coupling reaction was conducted with 0.5 mol% of palladate (**Pd-1** or **Pd-2**) in THF at 50 °C and at 100 °C with 1.5 equiv. of K_2CO_3 as base (Table 1, entries 1-3). A 47% NMR conversion was observed at 100 °C when **Pd-1** was used (Table 1, entry 2). The use of **Pd-2** gave lower conversions even after increasing the catalyst loading to 1 mol% (Table 1, entries 3-4). Increasing the temperature, catalyst loading and base did not lead to any improvement in the reaction outcome (Table 1,

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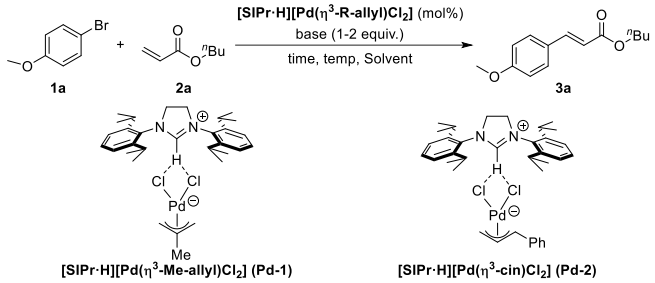
entries 5-6). Upon conducting the reaction in DMF using **Pd-1** as catalyst, a 76% NMR conversion to **3a** was obtained (Table 1, entry 7). Of note, 2.0 equiv. of K_2CO_3 was used for the remainder of the optimisation as it proved optimum.



Scheme 1. Selected palladate-catalyzed Mizoroki-Heck reaction using 4-bromoanisole **1a** and *n*-butyl acrylate **2a**.

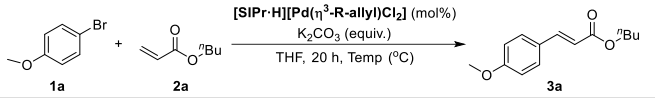


Table 1. Initial catalyst system screening.

Entries	Catalyst (mol%)	K_2CO_3 (equiv.)	Temp (°C)	Conversion (%)[b]
1[c]	**Pd-1** (0.5)	1.5	50	-
2	**Pd-1** (0.5)	1.5	100	47
3	**Pd-2** (0.5)	1.5	100	25
4	**Pd-2** (1.0)	1.5	110	32
5	**Pd-1** (0.5)	2.0	110	48
6	**Pd-1** (1.0)	2.0	110	40
7[d]	**Pd-1** (1.0)	2.0	110	76
8[d]	**Pd-2** (1.0)	2.0	110	10

[a] Reaction Conditions: [SIPr·H][Pd(η3-2-Me-allyl)Cl2] (**Pd-1**), K_2CO_3, THF (1 mL), **1a** (0.5 mmol), **2a** (0.5 mmol) at the indicated temperature for 20 h. [b] Conversion was determined by NMR based on 4-bromoanisole disappearance. Value calculated from an average of two reactions. [c] Reaction time was 16 h. [d] 1 mL of DMF was used.

Next, the catalyst loading and time were investigated at 100-110 °C. The catalyst loading was gradually increased from 0.5 mol% to 2.0 mol%, showing maximum NMR conversions (99%) at 100 °C and 110 °C with 1.4 mol% of **Pd-1** (Table 2, entries 1-7). It should be noted that 20 h were needed for full conversion; shorter reaction times led to a significant decrease in conversion (Table 2, entries 8-10). Lowering the temperature from 100 °C to 80 °C was also detrimental to the reaction outcome, affording no conversion to the desired product (Table 2, entry 11).

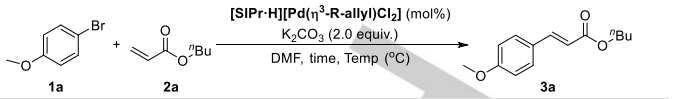


Table 2. Catalyst loading and time optimisation.

Entries	**Pd-1** (mol%)	Temp (°C)	Time (h)	Conv. (%)[b]
1[c]	0.5	100	20	36
2	1.0	100	20	76
3	1.3	110	20	88
4	1.4	110	20	99
5	1.4	100	20	99
6	1.5	110	20	96
7	2.0	110	20	90
8	1.4	110	08	51
9	1.4	110	16	73
10	1.4	110	24	98
11	1.4	80	20	-

[a] Reaction Conditions: [SIPr·H][Pd(η3-2-Me-allyl)Cl2] (**Pd-1**), K_2CO_3 (138 mg, 1 mmol), DMF (1 mL), **1a** (0.5 mmol), **2a** (0.5 mmol), at the indicated temperature for the indicated time. [b] Conversion was determined by NMR based on 4-bromoanisole disappearance. Value calculated from an average of two reactions.

Varying the solvent did not bring further improvement to the reaction conversion (Table 3). However, an interesting solvent choice, DMF/H_2O, arose as an alternative reaction media. Attempts to improve the conversion by varying the solvent ratio proved moderately successful; only an optimal 81% NMR conversion was achieved using a 2:1 DMF/H_2O mixture at 100 °C (Table 3, entry 11). Interestingly, when the reaction was performed in acetone, two MH products were formed with 96% total NMR conversion (74% mono-substituted and 22% di-substituted). The isolated yields of both products were 65% and 18% for the mon-substituted (**3a**) and the di-substituted (**3'a**) MH products, respectively.

Next, the MH reaction of 4-bromoanisol and n-butyl acrylate was explored using several inorganic and organic bases and the findings are presented in Table 4. Among the tested inorganic bases (Na_2CO_3, NaOH, Cs_2CO_3, Li_2CO_3, KOH and K_2CO_3), K_2CO_3 was found to be the most effective, yielding 99% conversion to the desired product **3a** (Table 4, entries 1-7). Organic bases such as NEt_3, $NHEt_2$ and DBU were also tested and found to be almost ineffective in this reaction (Table 4, entries 8-10). The use of 2.0 equiv. of K_2CO_3 was shown to be essential for achieving full conversion (Table 4, entries 11-12). In an attempt to reduce the reaction temperature, the MH coupling was conducted at 80 °C using LiCl and TBAI as additives (Table 4, entries 13-14). Even though, the addition of TBAI gave a high conversion at this temperature, the obtained NMR spectra of the crude clearly shower multiple products.

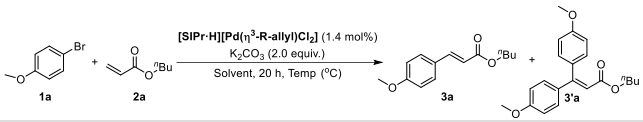


Table 3. Solvent and temperature screening.

Entries[a]	Solvent	Temp (°C)	Conversion (%)[b]
1	Acetone	100	74:22 (**3a**/**3'a**)
2	EtOH	100	-
3	H_2O	110	15
4	DMSO	110	02
5	DMF/H_2O (1:1)	80	not clean
6	DMF/H_2O (2:1)	80	not clean
7	DMF/H_2O (4:1)	80	not clean
8	DMF/H_2O (1:2)	80	not clean
9	DMF/H_2O (1:4)	80	08
10	DMF/H_2O (1:1)	100	59
11	DMF/H_2O (2:1)	100	81
12	DMF/H_2O (4:1)	100	>99 (multiple products)
13	DMF/H_2O (1:2)	100	59 (multiple products)
14	DMF/H_2O (1:4)	100	58 (multiple products)

[a] Reaction Conditions: [SIPr·H][Pd(η^3-2-Me-allyl)Cl_2] (**Pd-1**) (4.4 mg, 1.4 mol%), K_2CO_3 (138 mg, 1 mmol), solvent (1 mL), **1a** (0.5 mmol), **2a** (0.5 mmol), at the indicated temperature for 20 h. [b] Conversion was determined by NMR based on 4-bromoanisole disappearance. Value calculated from an average of two reactions.

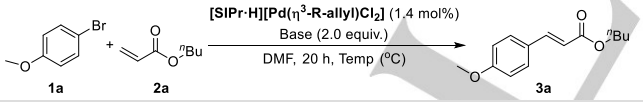


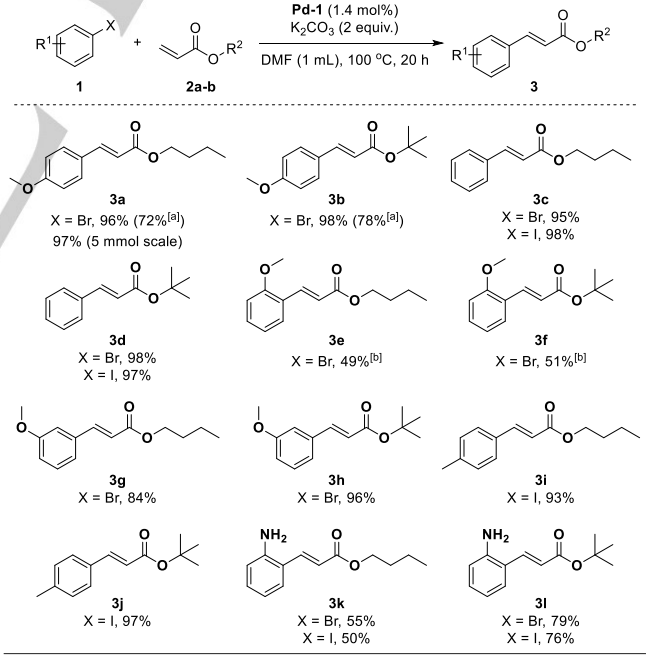
Table 4. Base screening.

Entries[a]	Base	Temp (°C)	Conv. (%)[b]
1	Na_2CO_3	110	42
2	NaOH	110	43
3	Cs_2CO_3	110	70
4	Li_2CO_3	110	10
5	KOH	110	05
6	K_2CO_3	110	99
7	K_2CO_3	100	>99
8	NEt_3	110	16
9	$NHEt_2$	110	07
10	DBU	110	03
11[c]	K_2CO_3	110	81
12[d]	K_2CO_3	110	92
13	K_2CO_3+LiCl (1 eq.)	80	10
14	K_2CO_3+TBAI (1 equiv.)	80	95 (Not clean)

[a] Reaction Conditions: [SIPr·H][Pd(η^3-2-Me-allyl)Cl_2] (**Pd-1**) (4.4 mg, 1.4 mol%), base (2.0 equiv.), DMF (1 mL), **1a** (0.5 mmol), **2a** (0.5 mmol), at the indicated temperature for 20 h. [b] Conversion was determined by NMR based on 4-bromoanisole disappearance. Value calculated from an average of two reactions. [c] 1.5 equivalents were used. [d] 1.75 equivalents were used.

During the initial investigation, the optimal amount of n-butyl acrylate was also investigated, demonstrating that using the acrylate in excess significantly reduces the conversion. Therefore, 1 equivalent of acrylate **2a** was selected as the optimal amount to be used (see Supporting Information).

Based on the above findings, the best conversion for the Mizoroki–Heck reaction of 4-bromoanisol and n-butyl acrylate was obtained at 100 °C in DMF using 1.4 mol% of **Pd-1** in the presence of 2.0 eq. K_2CO_3. These optimized conditions were then applied to various aryl halides (**1a-h**) and acrylates (**2a-e**) (Scheme 2).



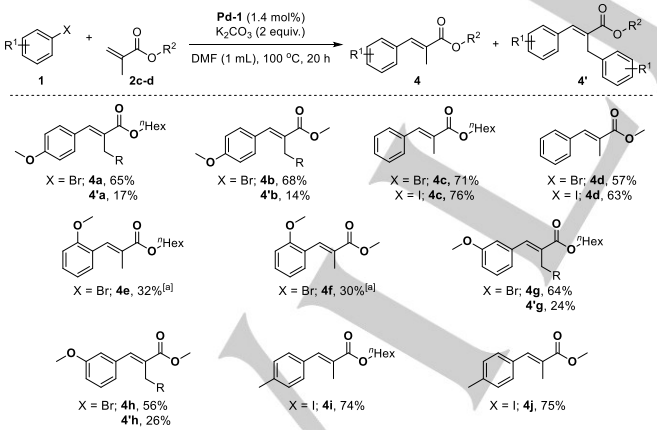
Reaction Conditions: [SIPr·H][Pd(η^3-2-Me-allyl)Cl_2] (**Pd-1**) (4.4 mg, 1.4 mol%), K_2CO_3 (138 mg, 1 mmol), DMF (1 mL), aryl halide (0.5 mmol), acrylate (0.5 mmol), 100 °C, 20 h. Isolated yields, average of two reactions. [a] Using 1.4 mol% of [Pd(SIPr)(μ^3-2-Me-allyl)Cl], [b] Reaction time 40 h

Scheme 2. Substrate scope for the MH reaction with acrylate **2a-b**.

The reactions proceeded smoothly with n-butyl acrylate (**2a**) and tert-butyl acrylate (**2b**), with the latter affording higher yields in

most cases (Scheme 2). Para- and meta-methoxy-substituted aryl halides were well tolerated under our reaction conditions, affording 96%, 98%, 84% and 96% isolated yields for **3a**, **3b**, **3g** and **3h**, respectively. In order to compare the palladate reactivity with its neutral Pd-NHC analogue, **3a** and **3b** were again synthesized using 1.4 mol% of [Pd(SIPr)(η^3-2-Me-allyl)Cl] instead of palladate **Pd-1**, affording 72% and 78%, respectively. This interesting result highlights the better efficiency of palladates compared to their neutral Pd-NHC counterparts, in accordance with our previous observations.[13] As for ortho-substituted bromoanisole, only moderate yields were obtained even after prolonged reaction times (40 h, 49% and 51% for **3e** and **3f**, respectively). 4-bromotoluene was also tolerated, affording excellent isolated yields with both acrylates (93% and 97% for **3i** and **3j**, respectively). Ortho-substituted bromo and iodo anilines were also successfully coupled with both acrylates, affording moderate to good yields of **3k** and **3l**. In this case, it should be noted that higher yields were obtained when tert-butyl acrylate was used. It should be noted that arylchlorides do not lead to substantial yields of product using this protocol. The issue of low reactivity in this MH reaction is something we are examining at present. In order to confirm the reliability and robustness of this MH procedure, the reaction was scaled up tenfold, i.e. 5 mmol of 4-bromoanisole and 5 mmol n-butyl acrylate, to afford **3a** in 97% isolated yield. It should be mentioned that in all cases where we did not obtain high yields of the desired product, unconsumed starting materials were observed.

Next, methacrylates **2c** and **2d** were used as coupling partners (Scheme 3). Similar to what was previously observed, aryl bromides and iodides were coupled with both methacrylates, although only moderate isolated yields were observed in this case.

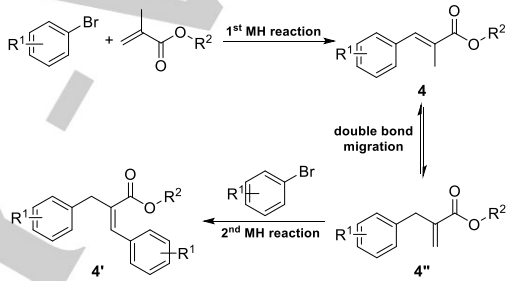


Reaction Conditions: [SIPr·H][Pd(η^3-2-Me-allyl)Cl_2] (**Pd-1**) (4.4 mg, 1.4 mol%), K_2CO_3 (138 mg, 1 mmol), DMF (1 mL), aryl halide (0.5 mmol), acrylate (0.5 mmol), 100 °C, 20 h. Isolated yields, average of two reactions. [a] Reaction time 40 h.

Scheme 3. Substrate scope for the MH reaction with methacrylate **2c-d**.

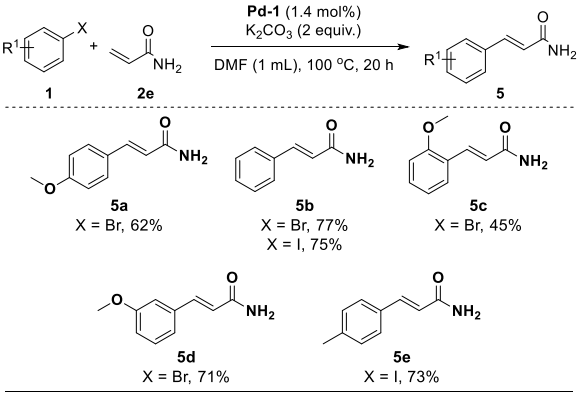
Interestingly, when the coupling was performed with para or meta-substituted bromoanisoles, two coupled products were observed (Scheme 3); mono-coupled MH product **4** (major) and bis-coupled product **4'** (minor) (with yield ratios: 65%:17% for **4a**/**4'a**; 68%:14% for **4b**/**4'b**; 64%:24% for **4g**/**4'g**; 56%:26% for **4h**/**4'h**). The mechanism for the formation of compound **4'** is shown in Scheme 4; after the 1st MH reaction affords product **4**, a double bond migration leads to intermediate **4''**, which is then subjected to a second MH coupling to afford the observed product **4'**. It should be noted that the addition of excess aryl halide and/or the increase in catalyst loading in an attempt to afford full conversion toward the bis-coupled product **4'**, did not lead to any significant improvement.

In the remaining cases (**4c-f** and **4i-j**), moderate to good yields were obtained of the desired mono-coupled products. As observed previously, the coupling of ortho-substituted bromoanisole with both methacrylates performed poorly, affording 32 and 30% isolated yields of **4e** and **4f**, respectively, even after prolonged reaction times (40 h).



Scheme 4. Proposed mechanism for the formation of the bis-coupled product **4'**.

Next, we turned our attention to acrylamides as potential coupling partners. Acrylamide scaffolds are typically present in various anticancer agents,[14] and therefore, selective and efficient access to this class of compounds would be highly interesting. In this context, our newly optimized method was applied for the coupling of aryl halides (**1a-f**) with acrylamide (**2e**) to afford moderate to good yields of the coupled product **5a-e** (Scheme 5).



Reaction Conditions: [SIPr·H][Pd(η^3-2-Me-allyl)Cl_2] (**Pd-1**) (4.4 mg, 1.4 mol%), K_2CO_3 (138 mg, 1 mmol), DMF (1 mL), aryl halide (0.5 mmol), acrylamide (0.5 mmol), 100 °C, 20 h. Isolated yields, average of two reactions.

Scheme 5. Substrate scope for the MH reaction with acrylamide **2e**.

Conclusions

In conclusion, the use of an easily accessible SIPr-based palladate as pre-catalyst in the Mizoroki-Heck coupling reaction was successfully demonstrated. Palladate pre-catalyst **Pd-1** successfully promoted the coupling of aryl halides with acrylate and methacrylate derivatives as well as acrylamide to afford the desired coupled products (**3**, **4** and **5**) in moderate to good yields, in the presence of an inexpensive and mild base (i.e. K_2CO_3). It should be noted that, contrarilyy to previous applications involving palladates, **Pd-1** no prior activation under the described conditions is required. In some cases, the bis-coupled products **4'** were observed, indicating that at some point an isomerization of the double bond in **4** occurs; this implies that three sequential reactions are occurring in the reaction mixture. Further investigation into this reaction is ongoing in our laboratories.

Experimental Section

General procedure for the Mizoroki-Heck reaction: In air, a vial was charged with [SIPr·H][Pd(η^3-2-Me-allyl)Cl_2] (**Pd-1**) (4.4 mg, 1.4 mol%), K_2CO_3 (2.0 equiv.), DMF (1 mL) and a magnetic stir bar. The corresponding aryl halide (0.5 mmol) was added followed by the corresponding acrylate (1.0 equiv.), and the vial was then sealed with a screw cap. The reaction was left to stir for 20 h at 100 °C. Afterwards, distilled water (2 mL) was added and the products were extracted with diethyl ether (3x3 mL). Finally, the products were isolated by flash column chromatography. The isolated yields are average of two runs. All the related supporting data are given in the Supporting Information.

Mizoroki-Heck reaction scale up: Following the general procedure, [SIPr·H][Pd(η^3-2-Me-allyl)Cl_2] (**Pd-1**) (44 mg, 1.4 mol%), K_2CO_3 (1.38 g, 2.0 equiv.), DMF (10 mL) were charged into oven dried 20 ml screwed cap vial. 4-bromoanisol (0.93 g, 5 mmol) and n-butyl acrylate (0.64 g, 5 mmol) were added subsequently and the vial was closed and heated to 100 ºC for 20 h. the reaction residue was purified by column chromatography 100-200 mesh silica gel and EtOAc/n-hexane (3:97) to afford **3a** in 1.13 g (97%) as a yellow liquid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) = 7.63 (d, *J* = 16.4 Hz, 1H, C**H**=CH), 7.47 (d, *J* = 8.8 Hz, 2H$_{Ar}$), 6.90 (d, *J* = 8.8 Hz, 2H$_{Ar}$), 6.31 (d, *J* = 16.4 Hz, 1H, CH=C**H**), 4.19 (t, *J* = 7.2 Hz, 2H, OC**H**$_2$), 3.84 (s, 3H, OC**H**$_3$), 1.64 – 1.70 (m, 2H, C**H**$_2$), 1.40 – 1.46 (m, 2H, C**H**$_2$), 0.96 (t, *J* = 7.6 Hz, 3H, C**H**$_3$). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):** δ (ppm) = 167.6 (**C**=O), 161.4 (O**C**$_{Ar}$), 144.3 (**C**H=CH), 129.8 (**C**$_{Ar}$), 127.3 (**C**$_{Ar}$), 115.9 (CH=**C**H), 114.5 (**C**$_{Ar}$), 64.4 (O**C**H$_2$), 55.5 (O**C**H$_3$), 30.9 (**C**H$_2$), 19.3 (**C**H$_2$), 13.9 (**C**H$_3$).

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Keywords: Mizoroki-Heck • Coupling • Palladate • aryl halide • acrylate

[1] a) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651-2710; b) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085; c) *New Trends in Cross-Coupling: Theory and Applications, RSC catalysis series No. 21* (Ed.: T. J. Colacot), RSC, Cambridge, **2015**; d) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489; e) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177-2250; f) S. Würtz, F. Glorius, *Acc. Chem. Res.* **2008**, *41*, 1523-1533; g) M. S. Viciu, R. A. Kelly, E. D. Stevens, F. Naud, M. Studer, S. P. Nolan, *Org. Lett.* **2003**, *5*, 1479-1482; h) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649

[2] *Science of Synthesis: N-Heterocyclic Carbenes in Catalytic Organic Synthesis*, vol 1 & 2 (Eds.: S. P. Nolan, C. S. J. Cazin) Thieme, Stuttgart, **2016**.

[3] a) R. N. Prabhu, R. Ramesh, *Tetrahedron Lett.* **2012**, *53*, 5961-5965; b) E. Peris, R. H. Crabtree, *Coord. Chem. Rev.* **2004**, *248*, 2239-2246; c) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009-3066; d) C. Frech, *Angew. Chem. Int. Ed.* **2009**, *48*, 6947-6947.

[4] a) Y. Zhang, Z. Lv, H. Zhong, M. Zhang, T. Zhang, W. Zhang, K. Li, *Tetrahedron* **2012**, *68*, 9777-9787; b) Y.-H. Ding, H.-X. Fan, J. Long, Q. Zhang, Y. Chen, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6087-6092.

[5] J. G. De Vries, *Can. J. Chem.* **2001**, *79*, 1086-1092.

[6] T. Sato, T. Takata, *Polym. J.* **2009**, *41*, 470.

[7] A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945-2964.

[8] X. Jiang, G. T. Lee, K. Prasad, O. Repic, *Org. Process Res. Dev.* **2008**, *12*, 1137-1141.

[9] J. H. Kim, H. Lee, *Chem. Mater.* **2002**, *14*, 2270-2275.

[10] a) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem. Int. Ed.* **2007**, *46*, 2768-2813; b) G. C. Fortman, S. P. Nolan, *Chem. Soc. Rev.* **2011**, *40*, 5151-5169; c) S. M. P. Vanden Broeck, F. Nahra, C. S. J. Cazin, *Inorganics* **2019**, *7*, 78.

[11] a) E. Marelli, A. Chartoire, G. Le Duc, S. P. Nolan, *ChemCatChem* **2015**, *7*, 4021-4024; b) F. Izquierdo, C. M. Zinser, Y. Minenkov, D. B. Cordes, A. M. Z. Slawin, L. Cavallo, F. Nahra, C. S. J. Cazin, S. P. Nolan, *ChemCatChem* **2018**, *10*, 601-611; c) F. Izquierdo, A. Chartoire, S. P. Nolan, *ACS Catalysis* **2013**, *3*, 2190-2193; d) E. Marelli, Y. Renault, S. V. Sharma, S. P. Nolan, R. J. M. Goss, *Chem. Eur. J.* **2017**, *23*, 3832-2836.

[12] a) K. R. Balinge, P. R. Bhagat, *C. R. Chim.* **2017**, *20*, 773-804, and references cited therein; b) H. Yang, X. Han, G. Li and Y. Wang, *Green Chem.* **2009**, *11*, 1184-1193; c) A.P. Wight, M.E. Davis, *Chem. Rev.* **2002**, *102*, 3589-3614; d) J.-Y. Lee, P.-Y. Cheng, Y.-H. Tsai, G.-R. Lin, S.-P. Liu, M.-H. Sie, H. M. Lee, *Organometallics* **2010**, *29*, 3901-3911; e) T.-T. Gao, A.-P. Jin, L.-X. Shao, *Beilstein J. Org. Chem.* **2012**, *8*, 1916–1919; f) N. Sun, M. Chen, L. Jin, W. Zhao, B. Hu, Z. Shen, X. Hu, *Beilstein J. Org. Chem.* **2017**, *13*, 1735-1744.

[13] a) C. M. Zinser, F. Nahra, M. Brill, R. E. Meadows, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, C. S. J. Cazin, *Chem. Commun.* **2017**, *53*, 7990–7993; b) C. M. Zinser, K. G. Warren, R. E. Meadows, F. Nahra, A. M. Al-Majid, A. Barakat, M. S. Islam, S. P. Nolan, C. S. J. Cazin, *Green Chem.* **2018**, *20*, 3246-3252; c) C. M. Zinser, K. G. Warren, F. Nahra, A. Al-Majid, A. Barakat, M. S. Islam, S. P. Nolan, C. S. J. Cazin, *Organometallics* **2019**, ASAP, doi: 10.1021/acs.organomet.9b00326.

[14] a) R. S. Dothager, K. S. Putt, B. J. Allen, B. J. Leslie, V. Nesterenko, P. J. Hergenrother, *J. Am. Chem. Soc.* **2005**, *127*, 8686-8696; b) B. J. Leslie, C. R. Holaday, T. Nguyen, P. J. Hergenrother, *J. Med. Chem.* **2010**, *53*, 3964-3972; c) Y. Qian, H.-J. Zhang, H. Zhang, C. Xu, J. Zhao, H.-L. Zhu, *Biorg. Med. Chem.* **2010**, *18*, 4991-4996.

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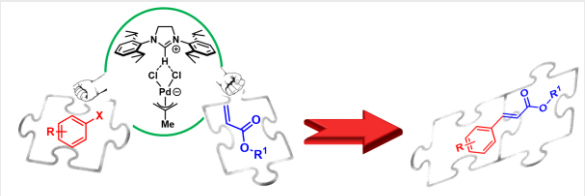

The Mizoroki-Heck reaction involving aryl halides with various acrylates and acrylamides has been studied using air and moisture-stable imidazolium-based palladate pre-catalysts.

Cross-coupling

Mohammad Shahidul Islam , Fady Nahra, Nikolaos V. Tzouras, Assem Barakat, Steven P. Nolan, and Abdullah Mohammed Al-Majid**

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Mizoroki-Heck cross-coupling of acrylate derivatives with aryl halides catalyzed by palladate pre-catalysts