Palladium Catalyzed α,β-Homodiarylation of Vinyl Esters in Aqueous Medium

Damian Trzepizur, Anna Brodzka, Dominik Koszelewski, Monika Wilk, Ryszard Ostaszewski*
Institute of Organic Chemistry, Polish Academy of Science, Kasprowa 44/52, 01-224 Warsaw, Poland
Corresponding author: ryszard.ostaszewski@icho.edu.pl

Abstract:
A palladium catalyzed 1,2-diarylation of vinyl esters with sustainable arylboronic acids in water has been developed. This newly elaborated protocol features good functional group tolerance and provides a one-step access to 1,2-diaryletahol derivatives under mild reaction conditions. The presented reaction can be carried out in water smoothly without the addition of any ligands at ambient temperature what makes this procedure environmentally benign. The transformation occurs within a single catalytic cycle and is feasible due to the modification of transition metal catalytic activity through the influence of π-acceptor olefin (benzoquinone) as well as the polar protic reaction medium (water in particular). Moreover, the protocol allows to generate entire compounds libraries (highly profitable in medicinal chemistry) and utilizes sustainable arylboronic acid as coupling partners under mild conditions.

Keywords: palladium catalysis, diarylation, C-C coupling, vinyl esters, water, benzoquinone, organoboron reagents.

Introduction
1,2-Diarylethanol and its derivatives are an important class of biologically relevant compounds. This includes an antineoplastic combretastatin (Singh and Kaur 2009) and some other molecules with antiviral (Roche et al. 2014; Da Costa et al. 2018), antitubercular (De Vita et al. 2016) or fungicidal (Saiz-Urra et al. 2009; Pinedo-Rivilla et al. 2011) properties. Our recent studies shown that 1,2-diarylethanol and their esters possess also an antimicrobial activity thus they can be used as new potential antibiotics after additional research (Kowalczyk et al. 2021). The common methods for the synthesis of 1,2-diarylethanols (Scheme 1) involve the addition of organometallic reagents to aromatic aldehydes (Narita et al. 2011; Abou Nakad et al. 2018). Nevertheless, the above procedures suffer from several limitations, such as anhydrous conditions, high or very low temperatures as well as the use of harmful reagents. Moreover, most of the literatures known methods are multistep reactions what also is undesirable from the green chemistry point of view. Thus, the development of environmentally friendly protocol for the direct synthesis of 1,2-diarylethanol derivatives are desired.

During our studies on the Heck reaction between arylboronic acid and vinyl acetate (VA) in the presence of 1,4-benzoquinone and palladium (II) acetate, we observed that the change of the reaction medium on the water leads to the formation of target 1,2-diaryl acetates instead of the common Heck product (Meng et al. 2014; Hota et al. 2015). Recently, we have developed the green protocol for the synthesis of 1,2-diaryletanol derivatives using Pd(0) EnCat® 30NP as a catalyst under mild condition (Kowalczyk et al. 2021). Nevertheless, this methodology suffers from several limitation such as narrow scope and low efficiency. The obtained results encouraged us to further studies on the optimization of reaction conditions. Herein, we present a direct reductive α,β-homodiarylation of vinyl esters method leading to 1,2-diarylethanol derivatives. The proposed methodology is characterized by mild reaction conditions and utilizing commercially available substrates.
Scheme 1. The synthesis of 1,2-diarylethanols.

**Previous works:**

Addition of organometallic compounds to aromatic aldehydes

\[ \text{Ar}^-\text{O} + \text{Ar}^1^-\text{X} \rightarrow \text{Ar}^-\text{OH} \text{Ar}^1^- \]

\[ \text{X} = \text{Cl}, \text{Br}, \text{I} \]

This work:

\[ \text{O} \text{R} + \text{Ar}^-\text{B(OH)}_2 \rightarrow \text{Ar}^-\text{O} \text{R} \]

**Experimental**

**Materials and equipment**

The \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra were recorded on Bruker 400 MHz spectrometer using chloroform (CDCl₃) as solvent and tetramethylsilane (TMS) as an internal standard. TLC analyses were done on Kieselgel 60 F\(_{254}\) aluminum sheets. All the new products were further characterized by high-resolution mass spectra (HRMS) or elemental analysis. All reagents of analytical grade were purchased from Sigma-Aldrich or TCI.

**General procedure for α,β-homodiarylation of vinyl esters:** Glass snap cap vial (10 mL), provided with a stir bar, was loaded with solid reagents: arylboronic acid (1; 3 mmol), palladium(II) acetate (5 mol%), 1,4-benzoquinone (BQ, 0.9 mmol), 4 mL of water, and appropriate vinyl ester (2a, 0.75 mmol). The vial was closed and the reaction mixture was stirred at room temperature for 24 hours. Next, methylene chloride (10 mL) was added, resulting in two-phase solution. The organic phase was separated, and the remaining phase was extracted with 20 mL DCM. The combined organic layers were dried with MgSO₄ and residuals of solvent were removed under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/AcOEt as an eluent. The structures of the products were identified by their \(^1\text{H}\) and \(^{13}\text{C}\) NMR in the supplementary information (SI).

**Results and discussion**

**Optimization of reaction parameters**

We begin our studies with the reaction of model phenylboronic acid 1a and vinyl acetate 2a under literature conditions (Pd(OAc)$_2$, DMSO/AcOH, 60°C) (Meng et al. 2014). As a result, styryl acetate 4a was obtained with 33% yield as the only product (Table 1, entry 1). As reaction conditions were harsh, thus in the next step, the reaction was conducted in the H$_2$O/AcOH mixture under ambient temperature (entry 2) (Hota et al. 2015). Besides the expected Heck product 4a, we have also isolated another compound which was identified as the desired 1,2-diphenylethyl acetate 3a. The decrease in reaction temperature resulted in the formation of products with similar yields and selectivity (entry 3). When the reaction was carried out in neat water product 3a was isolated exclusively with 45% yield (entry 4). We have also tested several other solvents, however, none of them was better than water (entries 5-7). After many trials we have found that best results were obtained when the ratio between substrates was 4:1 (entry 8), the presence of palladium catalyst as well as 1,4-benzoquinone was essential. The reaction catalyzed by Pd(0) EnCat® 30NP (Kowalczyk et al 2021) lead to the formation of product 3a with 34%.
Table 1. The optimisation of reaction conditions.

| Entry | Solvent      | Temp. [°C] | Yield [%] of: | Yield [%] of: |
|-------|--------------|------------|---------------|---------------|
| 1     | DMSO/AcOH    | 60         | 0             | 33            |
| 2     | H₂O/AcOH     | 60         | 12            | 36            |
| 3     | H₂O/AcOH     | 25         | 13            | 33            |
| 4     | H₂O          | 25         | 45            | < 0.1         |
| 5     | Dioxane      | 25         | 8             | < 0.1         |
| 6     | CH₂Cl₂       | 25         | < 1.0         | < 0.1         |
| 7     | MeOH         | 25         | 18            | < 0.1         |
| 8     | H₂O          | 25         | 71            | < 0.1         |
| 9     | H₂O          | 25         | 34            | < 0.1         |

*a* Reaction conditions: 1a (1 equiv), 2a (20 equiv), Pd catalyst (5 mol%), BQ (1.2 equiv), solvent: 1 mL/1 mmol of 1a. *b* Yield of isolated product. *c* 1a (4 equiv), 2a (1 equiv), Pd catalyst (5 mol%), BQ (1.2 equiv), solvent: 1 mL/1 mmol of 1a. *d* Pd(0) EnCat® 30NP was used as a catalyst (Kowalczyk et al. 2021).

With the optimized reaction conditions in hand, we proceeded to investigate the scope and limitation (Table 2). The results of the reactions conducted in the presence of Pd(0) EnCat® 30NP as a catalyst (Kowalczyk et al. 2021) were given in parentheses. At first, we investigated the impact of substituents of arylboronic acids (1a-l) in the reactions with vinyl acetate (Table 2, 3a-l). A variety of arylboronic acids bearing both electron-donating groups and electron-withdrawing groups at para position of phenyl rings react with vinyl acetate leading to the formation of corresponding 1,2-diaryl ethyl acetates with good to moderate yield (Table 2, 3b-e, 3h-j) except for para-iodophenylboronic acid (1f) where the product 3f was isolated with 13% yield, due to the limited solubility of reagents and side reactions. The change of bromo substituent from para to meta position resulted in the significant drop of yield from 50% (3e) to 6% (3g). The application of 3,4-dimethoxy-phenylboronic acid 1k, gave product 3k with 33% yield. In case of phenylboronic acid with a protected amino group 1l the formation of by-products reduced target compound 3l yield to 14%.

In the next set of experiment we have studied the impact of vinyl esters (2b-2f) on the developed reaction with model phenylboronic acid 1a. The application of bulkier substrate 2b resulted in the decrease of yield (3m, 25% yield). The reaction of vinyl laurate (2c) was conducted in methanol because of the low solubility of 2c in water; the product 3n was isolated with 21% yield. The same conditions were applied for naproxen vinyl ester 2f; product 3q was obtained with 21% yield. It is worth to mention that we have used the optically pure ester 2f and we have not observed its racemization under the reaction conditions. Other tested vinyl esters gave the corresponding products with respective yields - 33% and 47% (compounds 3o and ).

We have also performed the crossover experiments. Two arylboronic acids with distinct polarity and electronic properties were utilized: 4-((trifluoromethyl)phenylboronic acid 1c and 3,4-dimethoxyphenylboronic acid 1k. Contrary to expectations, only three diarylation products were isolated from complex post-reaction mixture. Also, the product distribution differed from the normal one (Table 2, bottom). The fact that α,β-heterodiarylation is also feasible under developed conditions increases the applicability of the method. At the same time, receiving only one crossover product 3ck indicates that it is possible to control regioselectivity to some extent. Ultimately, gathered results led to the following conclusions: the reaction is prone to both steric and electronic factors and it
proceeds within a single catalytic cycle where two aryl groups are consecutively added to the activated C-C double bond.

**Table 2. Scope of substrates for reductive α,β-homodiarylation.**

| Substrate | Yield (%) (Isolated) |
|-----------|----------------------|
| 3a        | 71% (34%)            |
| 3b        | 40% (19%)            |
| 3c        | 69% (2%)             |
| 3d        | 57% (34%)            |
| 3e        | 50% (6%)             |
| 3f        | 13% (0%)             |
| 3g        | 6% (0%)              |
| 3h        | 60% (4%)             |
| 3i        | 52% (5%)             |
| 3j        | 31% (1%)             |
| 3k        | 33% (33%)            |
| 3l        | 14% (9%)             |
| 3m        | 25% (22%)            |
| 3n        | 21% (0%)             |
| 3o        | 33% (0%)             |
| 3p        | 47% (7%)             |
| 3q        | 21% (0%)             |

Crossover experiment for arylboronic substrates with divergent electronic properties.

---

* Conditions: 1a - p (4 equiv), 2a - f (1 equiv), Pd(OAc)$_2$ (5 mol%), BQ (1.2 equiv), H$_2$O: 1 mL/1 mmol of 1; isolated yields. * In addition, the product of subsequent hydrolysis was obtained (16% yield). Determined by $^1$H NMR. * Reaction was conducted in MeOH. * Conditions: 1c (2 equiv), 1k (2 equiv), 2a (1 equiv), Pd(OAc)$_2$ (5 mol%), BQ (1.2 equiv), H$_2$O (4 mL). * The yields of products obtained for Pd(0) EnCat® 30NP a catalyst (Kowalczyk et al. 2021) were given in parentheses.
Based on the received results and earlier literature reports we propose the mechanism (Scheme 2). The proposed catalytic cycle begins with ester coordination to catalyst A and first transmetalation. The resulted structure B is probably stabilized via coordination between carbonyl O and Pd atoms (Bernocchi et al. 1992; Tian et al. 2002). The following migratory insertion leads to σ-alkyl complex C. After internal arylation, BQ and polar protic solvent molecule (water in particular) coordinate to Pd (structure D), which elucidate the influence of both agents on the reaction course. Contrary to the oxidative Heck reaction, the second transmetalation takes place. Reductive elimination of emerged complex E, in the presence of BQ as a π-acidic ligand, results in target product 4 release, and reduced catalyst F is lastly reoxidated.

**Scheme 2. Presumable reaction mechanism.**

**Conclusion**

In summary, we presented the novel environmentally benign protocol for the synthesis of 1,2-diarylethyl esters. The established procedure is characterized by mild reaction conditions. Moreover, the reaction proceeds well in water what makes it attractive from environmental point of view. It utilizes sustainable arylboronic acids and inexpensive palladium catalyst and offers ready-made one-step access to 1,2-diarylethyl esters. The overall process is atom-efficient, step-economic, and highly functional group-tolerant. Furthermore, the results of crossover experiment indicate that the reaction is chemoselective as only three from four possible products were obtained when two different arylboronic acids are utilized. This feature allows for quick and convenient building up the whole compound library, which is highly desirable in medicinal chemistry.

**Acknowledgements** The authors are greatly thankful to National Science Centre (Poland) for providing financial assistance.

**Funding** This work was supported by the National Science Centre Poland project OPUS No. 2016/23/B/ST5/03307 and 2019/33/B/ST4/01118.

**Conflicts of interest/Competing interests** There are no conflicts to declare.

**Ethics approval** Not applicable

**Ethics approval** Not applicable

**Consent to participate** Not applicable

**Consent for publication** Not applicable

**Availability of data and material** The online version of this article (https://doi.org) contains supplementary material, which is available to authorized users

**Code availability** Not applicable
**Authors' contributions** All authors made considerable contributions to the study design, analysis or interpretation of the data and revised it critically. Material preparation, data collection and analysis were performed by Damian Trzepizur. The first draft of the manuscript was written by Damian Trzepizur, Anna Brodzka and Dominik Koszelewski. All authors approved the final version of the work.

**References**

Abou Nakad E, Bolze F, Specht A (2018) o -Nitrobenzyl photoremovable groups with fluorescence uncaging reporting properties. Org Biomol Chem 16:6115–6122. https://doi.org/10.1039/C8OB01330F

Bernocchi E, Cacchi S, Ciattini PG, et al (1992) Palladium-catalysed vinylation of allylic alcohols with enol triflates. A convenient synthesis of conjugated dienols. Tetrahedron Lett 33:3073–3076. https://doi.org/10.1016/S0040-4039(00)79603-1

Da Costa L, Scheers E, Coluccia A, et al (2018) Structure-Based Drug Design of Potent Pyrazole Derivatives against Rhinovirus Replication. J Med Chem 61:8402–8416. https://doi.org/10.1021/acs.jmedchem.8b00931

De Vita D, Pandolfi F, Cirilli R, et al (2016) Discovery of in vitro antitubercular agents through in silico ligand-based approaches. Eur J Med Chem 121:169–180. https://doi.org/10.1016/j.ejmech.2016.05.032

Hota PK, Vijaykumar G, Pariyar A, et al (2015) An Abnormal N-Heterocyclic Carbene-Based Palladium Dimer: Aqueous Oxidative Heck Coupling Under Ambient Temperature. Adv Synth Catal 357:3162–3170. https://doi.org/10.1002/adsc.201500220

Kowalczyk P, Trzepizur D, Szymczak M, Skiba G, Kramkowski K, Ostaszewski R (2021) 1,2-Diarylethanols—A New Class of Compounds That Are Toxic to E. coli K12, R2–R4 Strains. Materials, 14: https://doi.org/10.3390/ma14041025

Meng L, Liu C, Zhang W, et al (2014) Palladium catalysed β-selective oxidative Heck reaction of an electron-rich olefin. Chem Commun 50:1110–1112. https://doi.org/10.1039/C3CC47045H

Narita K, Nakamura K, Abe Y, Katoh T (2011) Total Synthesis of Bauhinoxepin J: A Biologically Active Dibenzo[b,f]oxepin Isolated from Bauhinia purpurea. European J Org Chem 2011:4985–4988. https://doi.org/10.1002/ejoc.201100845

Pinedo-Rivilla C, Bustillo AJ, Hernández-Galán R, et al (2011) Asymmetric preparation of antifungal 1-(4′-chlorophenyl)-1-cyclopropyl methanol and 1-(4′-chlorophenyl)-2-phenylethanol. Study of the detoxification mechanism by Botrytis cinerea. J Mol Catal B Enzym 70:61–66. https://doi.org/10.1016/j.molcatb.2011.02.005

Roche M, Lacroix C, Khoumeri O, et al (2014) Synthesis, biological activity and structure–activity relationship of 4,5-dimethoxybenzene derivatives inhibitor of rhinovirus 14 infection. Eur J Med Chem 76:445–459. https://doi.org/10.1016/j.ejmech.2014.01.034

Saiz-Urra L, Bustillo Pérez AJ, Cruz-Monteagudo M, et al (2009) Global Antifungal Profile Optimization of Chlorophenyl Derivatives against Botrytis cinerea and Colletotrichum gloeosporioides. J Agric Food Chem 57:4838–4843. https://doi.org/10.1021/jf900375x

Singh R, Kaur H (2009) Advances in Synthetic Approaches for the Preparation of Combretastatin-Based Anti-Cancer Agents. Synthesis (Stuttg) 2009:2471–2491. https://doi.org/10.1055/s-0029-1216891

Tian G, Boyle PD, Novak BM (2002) Synthesis and Crystal Structure of a Dinuclear Palladium Complex Containing C,O-Bridging Ester—Enolato Moieties. Organometallics 21:1462–1465. https://doi.org/10.1021/om010968j