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Towards a Greener Barluenga-Valdés Cross-Coupling: A Microwave Promoted C-C Bond Formation with a Pd/PEG/H₂O Recyclable Catalytic System.

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Supporting Information Placeholder

ABSTRACT: A green Barluenga-Valdés cross-coupling reaction for the synthesis of 1,1-diarylethlenes using palladium catalysis has been developed. The new catalytic system based on Pd/Xphos-SO₃Na or Pd/MeDavephos-CF₃SO₃ in PEG/H₂O under microwave irradiation was found to be the best conditions for this transformation. The recyclability of the palladium catalyst system was also studied and it was found to be active over 9 runs without significant loss in its activity.

The formation of C=C double bonds from carbonyl compounds is among the most important issues in organic synthesis. Alkene units are important constituents in a variety of bioactive compounds.¹ Among them, 1,1-diarylethlenes are identified as an important scaffold in a variety of bioactive molecules such as the antineoplastic agent bexarotene (Targretin®)² or the antivascular compound isoCA-4.³ Among the well-known methods used in the double bond construction, the Wittig,⁴ the Peterson,⁵ the Tebbe-Petasis⁶ and the Julia⁷ reactions constitute major milestones in this chemistry. The main drawbacks of these methods can be summarized as follows: (1) the use of stoichiometric quantities of metal, (2) low reactivity of sterically hindered ketones leading to slow reactions and poor yields, (3) poor chemoselectivity and functional group tolerance due to the use of strong metal bases. In parallel to these methods, metal-catalyzed processes represent general and mild routes for obtaining alkene derivatives.¹,⁸ In 2007, Barluenga and Valdés group developed an interesting Pd-catalyzed Csp²-Csp² bond-forming reaction that employs N-tosylhydrazones (NTH) derived from ketones as nucleophilic partner and organic halides.⁹ This methodology benefits from many advantages including (1) N-tosylhydrazones constitute a reliable in situ source of diazo compounds without the typical decomposition via the Bamford-Stevens reaction, (2) in comparison to classical couplings (Heck, Kumada, Suzuki coupling), this method does not require the use of stoichiometric organometallic reagents, (3) the starting building block (NTH) is obtained easily from carbonyl derivatives.

Scheme 1. Traditional Barluenga-Valdés cross-coupling conditions vs. green conditions.

However, since the pioneering work of Barluenga-Valdés for the formation of Csp²-Csp² bonds, to our knowledge, there is no green protocol available for this efficient coupling. The main drawback of this cross-coupling is related to the use of a toxic solvent (such as dioxane,¹⁰ toluene, or 1,2-dichloroethane¹¹). Moreover, palladium belongs to the list of precious and endangered elements which find major use as a catalyst in many C-C bond constructions.¹² It is therefore important to focus on its recovery and recycling. In this work, we sought to develop a green version of this interesting reaction by using more environmentally benign solvents and recycling the catalytic system (Scheme 1). This approach would enable cross-coupling process in a sustainable manner and can find application in numerous pharmaceutical processes.

To initiate this study, 4-bromoanisole 1a and NTH 2a were chosen as model substrates to explore the cross-coupling reaction conditions (Table 1, and Table S1 in the Supporting Information). With respect to the choice of solvent, we examined the
use of polyethylene glycol (PEG), which was employed in several organic reactions as a green alternative to toxic organic solvents. Indeed, PEGs have been successfully utilized as reaction media for metal-catalyzed coupling reactions, such as a Sonogashira and Heck couplings, hydroisilylation of terminal alkenes, and C-H bond activation.

We started with several mixtures of PEG-400, PEG-600 or glycerol with water at different ratios (entries 1-3), and the best yield of 51% was obtained with the PEG-400:H_2O (2:1) combination (entry 1). The use of glycerol instead PEG led to a decrease of the yield (entry 3). We have then changed the palladium source Pd(0) vs Pd(II), (Table S1) and no improvement of the yield of the reaction was observed. Next, we turned our attention to the base parameter. Excitingly, the use of K_2CO_3 as a base proved to be a good choice, and the yield was significantly increased to 72% after conventional heating at 120 °C for 3 h (entry 4). At this stage, we tried microwave irradiation instead of conventional heating (entries 5-8). We were pleased to observe that the MW-promoted cross-coupling is advantageous in this transformation when compared to the conventional heating; the reaction proved much faster (20 min vs 3 h) with slightly higher yields (entries 4 and 5). Following these results, fine tuning of the temperature parameter (entry 6) led us to find the optimal conditions and provide the desired 1,1-diarylethylene 3a in a 86% yield (entry 6). To prove the importance of MW irradiation in this coupling, we performed the reaction under similar conditions to entry 6, but using conventional heating. In this case, compound 3a was formed in a moderate yield of 50%, emphasizing the importance of MW irradiation. The use of a 1:1 Pd:ligand ratio led to a decrease of the yield from 86% to 62%. Performing the reaction only in PEG-400, or only in water, led to a significant decrease of the yield (entries 7 and 8). Finally, we examined the effect of ligand source on this transformation. As one could expect, the use of non-ionic ligands such as Xphos or Sphos led to a dramatic decrease of the yield (Table S1). However, the use of the home-prepared salt form of DavePhos ligand (MeDavePhos·CF_3SO_3), allowed to obtain the desired product 3a with a good yield (entry 9). For comparison, the use of non-modified Davephos led to a significant drop of the yield (Table S1).

With the optimized conditions in hand, we investigated the substrate scope of this cross-coupling reaction using a series of aryl halides 1 and different NTHs 2. As presented in Scheme 2, the reaction worked efficiently, affording the coupling products in good to high yields (compounds 3a-x). Both electron-donating and electron-withdrawing groups on the aryl halides underwent the reaction to afford the desired products in good to high yields (compounds 3a-c, 3f-i). Also, the reaction proceeded successfully with different substituents at various positions on the aryl halides, including a methoxy group at the ortho position (3e). In addition, the reaction tolerated the use of functional group on the electrophilic partner such as ketone, nitrile, and nitro groups (compounds 3f-i). It should be noted that the coupling tolerates the use of heterocyclic electrophilic partners, and the corresponding products were obtained in good yields (compounds 3k-m). Next, we evaluated the nature of the electrophilic partner (X = Cl, OTf). No reaction was observed when aryl chlorides were used under our standard conditions.

Table 1. Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Base</th>
<th>Solvent</th>
<th>T°C/time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Xphos-SO_4Na</td>
<td>LiOtBu</td>
<td>PEG-400/H_2O (2:1)</td>
<td>120 °C</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>Xphos-SO_4Na</td>
<td>LiOtBu</td>
<td>PEG-600/H_2O (2:1)</td>
<td>120 °C</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>Xphos-SO_4Na</td>
<td>LiOtBu</td>
<td>glycerol/H_2O (2:1)</td>
<td>120 °C</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>Xphos-SO_4Na</td>
<td>KCO_3</td>
<td>PEG-400/H_2O (2:1)</td>
<td>120 °C</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>Xphos-SO_4Na</td>
<td>KCO_3</td>
<td>PEG-400/H_2O (2:1)</td>
<td>120 °C</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>Xphos-SO_4Na</td>
<td>KCO_3</td>
<td>PEG-400/H_2O (2:1)</td>
<td>100 °C</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>Xphos-SO_4Na</td>
<td>KCO_3</td>
<td>PEG-400/H_2O (2:1)</td>
<td>100 °C</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>Xphos-SO_4Na</td>
<td>KCO_3</td>
<td>H_2O</td>
<td>100 °C</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>MeDavePhos-CF_3SO_3</td>
<td>KCO_3</td>
<td>PEG-400/H_2O (2:1)</td>
<td>100 °C</td>
<td>67</td>
</tr>
</tbody>
</table>

a Reaction conditions: substrate 1a (0.25 mmol), NTH 2a (0.3 mmol), [Pd] catalyst (2 mol%), ligand (4 mol%) and base (0.55 mmol) in 2 mL of solvent were used in a sealed tube. bMW heating was applied. cPerforming the reaction in conditions similar to entry 10, in a sealed tube but without MW irradiation led to compound 3a, in only 50% yield. dPerforming the reaction with a ratio of Pd:ligand 1:1 led to 3a in 62% yield.

However, a good yield was obtained by using aryl triflate as electrophilic coupling partners and compounds 3c, 3e, 3g, and 3j were obtained in good yields. It is noteworthy that this coupling is highly chemoselective and tolerates the presence of chlorine atom on the aromatic ring, which is not the case for classical Barluenga-Valdés protocol (compound 3j).19 Circumventing this low reactivity of aryl chlorides would allow for sequential couplings in fragment-based drug discovery or late-stage coupling (vide infra) and therefore open the door for more chemical space. Encouraged by these results, we further examined the substrate scope with respect to the second partner of the cross-coupling. The protocol was effective for a variety of NTH having electron-donating (3n) or electron-withdrawing (3q-t) groups, and the desired products were obtained in good to high yields. Notably, the reaction tolerates the use of heterocyclic NTH (compounds 3u and 3v). Importantly, cyclic and trisubstituted olefins (compounds 3w and 3x) were obtained in satisfactory yields by using the corresponding NTH derivatives. Further, we were interested to demonstrate the synthetic utility of this methodology. As shown in Scheme 3, the gram-scale synthesis (4.5 mmol, 1 g) of compound 3a was realized with a satisfactory yield (73%).

Scheme 2. Substrate scope of the green cross-coupling between electrophilic partner 1 and NTH 2.
Reaction Conditions: substrate 1 (0.25 mmol), NTH 2 (0.3 mmol), Pd₂dba₃·CHCl₃ (2 mol%), XPhos-SO₃Na (4 mol%), K₂CO₃ (0.55 mmol) in 2 mL of solvent in a sealed tube, MW 100 °C, 20 min.

* IsoCombretastatin A-4 (isoCA-4)²⁰ and isoAminocombretastatin A-4 (isoNH₂CA-4)²¹ are two stable isomers of natural combretastatin A-4 with highly cytotoxic and antivascular activity. With the optimized conditions in hand, the reactions proceeded successfully in a one-step fashion, and the two compounds isoCA-4 (3y) and isoNH₂CA-4 (3z) were obtained in good yields (Scheme 3, part b-c). Notably, and in comparison to previous methods, we demonstrated in this application that our new conditions tolerate the presence of free phenol or the aniline group as a cross-coupling partner, without the need for additional steps of protection/deprotection.

Scheme 3. Utility in synthesis: applications of the cross-coupling in PEG400/H₂O to the synthesis of bioactive compounds.

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4 Reaction Conditions: substrate 1 (0.25 mmol), NTH 2 (0.3 mmol), Pd₂dba₃·CHCl₃ (2 mol%), XPhos-SO₃Na (4 mol%), K₂CO₃ (0.55 mmol) in 2 mL of solvent in a sealed tube, MW 100 °C, 20 min.

In comparison, our one-step procedure provides the desired product in 60% yield. Finally, as we demonstrated above that this protocol tolerates the presence of the chlorine atom on the electrophilic partner (Scheme 2, compound 3j), we took advantage of this observation to carry out the synthesis of a key intermediate (3ac) of sertraline (Zoloft®), which is an antidepressant known as a selective serotonin reuptake inhibitor (Scheme 3). The coupling was completely chemoselective, and the desired compound was obtained in a good yield, which constitutes an alternative synthesis to already described methods.

To illustrate the usefulness and the large applications of the cross-coupling method, we tried to further extend the scope of the reaction to 2-phenyl-3-(1-phenylvinyl)-benzo[5]thiophene.
derivatives 4 (Scheme 4). Performing the coupling between 3-
bro-mo-2-(4-methoxyphenyl)benzo[b]thiophene 1 and NTH 2
derived from 3',4',5'-trimethoxycacetophenone under the stand-
ard conditions led to the formation of the desired product 4a in
a low 35% yield. However, changing the Xphos \( \text{SO}_3 \cdot \text{Na} \) ligand for
MeDavephos/\( \text{CF}_3 \text{SO}_3 \), without any other experimental
change, led to a significant improvement of the yield to 65%.
To demonstrate the scope of this ligand, several NTH and
benzo[b]thiophene derivatives having EDG or EWG were cou-
pled successfully in good yield (compounds 4a-f).

Finally, we decided to examine the reusability of the solvent
and the catalytic system (Figure 1, and Figure S1). The cross-
coupling reaction of bromoanisole 1a (1.0 mmol) and N-to-
sylhydrazone 2a (1.2 mmol) was evaluated under our standard
conditions. After completion of the reaction, the yellow reaction
mixture was extracted five times with 2 mL of pentane. The
combined pentane extracts containing the product mixture were
then subjected to purification. The PEG/H\( \text{O} \) layer was then
evaporated with a rotavapor for 10 min to remove traces of pent-
ane and was used for a second reaction by charging with the
same substrates (bromoanisole, N-tosylhydrazone, and \( \text{K}_2\text{CO}_3 \))
without any addition of the catalytic system (Pd\( \text{dba}_3 \) and
Xphos \( \text{SO}_3 \cdot \text{Na} \)).

To our delight, the first reusability trial and 6 successive ex-
periments were consistent in their yields (Fig. 1). Only after the
eighth cycle, a slight decrease in yield was observed.

In conclusion, this work reports a Pd-catalyzed cross-cou-
pling reaction for the synthesis of 1,1-diarylethylene with a
large chemical diversity. The developed methodology employs
an eco-compatible and a green reaction, as it uses a biodegrada-
able solvent. This microwave promoted transformation uses a
homogeneous recyclable catalytic system Pd/PEG-400/H\( \text{O} \) which worked efficiently for the synthesis of 1,1-diarylethylene
products.

![Scheme 4. Substrate scope of the cross-coupling between 3-
bromo-2-phenylbenzo[b]thiophene 1 and NTH 2.](image)

Figure 1. Procedure of the catalytic system recycling at the top.
Efficiency of the recycled catalytic system at the bottom.

Moreover, a variety of bioactive and approved compounds
could be successfully synthesized using this green methodology
with good to excellent yields. Finally, this catalytic system
could be reused up to 7 cycles with no significant loss of cata-
lytic activity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS
Publications website.

Experimental procedures, compound characterizations, \( ^1\text{H} \) and \( ^{13}\text{C} \)
NMR spectra (PDF).

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J.-F.; Bignon, J.; Liu, J.-M.; Wdziecek-Bakala, J.; Thoret, S.; Dubois,
11. DCE is on the REACh authorization list and should not be used anymore at the industrial scale in Europe, without authorization.
13. PEG-400 is an inexpensive, biodegradable, non-halogenated and non-toxic solvent, with an Acute oral toxicity (LD$_{50}$):26800 mg/kg in Rabbit.
18. For the preparation of ligand MeDavePhos.CF$_3$SO$_3$ ligand, please, see the experimental part in the supporting information.