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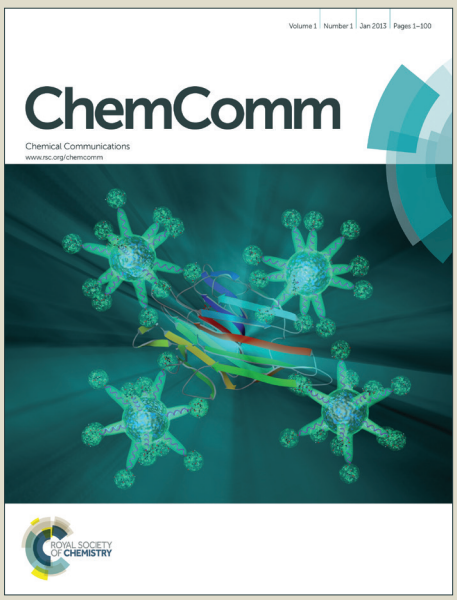





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ARTICLE TYPE

# Stereoselective synthesis of triarylethylenes *via* a copper-palladium catalyzed decarboxylative cross-coupling. Synthesis of (*Z*)-tamoxifen

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**The first Cu/Pd-catalyzed decarboxylative cross-coupling of 3,3-diarylacrylic acids with aryl bromides is described. Triarylethylenes were obtained in high yields and excellent stereoselectivities. This methodology was successfully applied to the stereoselective synthesis of (*Z*)-tamoxifen.**

Stereo- and regioselective synthesis of tri- and tetrasubstituted olefins is very challenging in organic synthesis.[1] Indeed, construction of congested double bond bearing three or four different groups in a stereo- and regioselective manner has always been difficult to achieve. Many efforts were especially reported to synthesize triarylethylenes, an important family of nonsteroidal estrogen agonists and antagonists having interesting biological activities.[2] Their field of application is very large: fertility regulation, breast cancer, osteoporosis as well as nervous central system, cardiovascular and lipid disorders. One of the best known triarylethylenes is (*Z*)-tamoxifen (Figure 1), which is an antagonist of the estrogen receptor used in the treatment of breast cancer.[3]

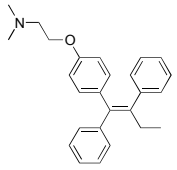
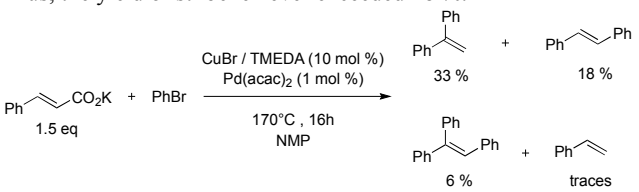


**Figure 1**. (*Z*)-Tamoxifen

Several syntheses of tamoxifen and its derivatives were published. Two strategies were mainly used. The first one is based on the McMurry reaction in which two functionalized ketones are coupled by treating them with low-valent titanium to form an alkene.[4] However, the coupling takes place with poor regio- and stereoselectivity. Moreover, the formation of undesired homocoupling products often limits the synthetic efficiency of the reaction.[5] The key step of the second strategy is the stereoselective carbometalation of diarylacetylenes. The resulting vinylmetal is treated with iodine to form an alkenyl iodide which is then alkylated via a Negishi procedure to give the final product.[6] Other approaches like Pd-catalyzed three-component coupling[7] or oxidative Heck coupling of methyl acrylate with arylboronic acids[8] are also reported.[9] As a rule, it should be noted that all the stereoselective methods require the use of a stoichiometric amount of organometallic compounds. Based on these considerations, it was very tempting to try to perform the synthesis of triarylethylenes such as (*Z*)-tamoxifen *via* a decarboxylative cross-coupling reaction. Indeed, the use of cheap and readily available carboxylic acids as a source of nucleophiles instead of costly preformed stoichiometric organometallic reagents is very attractive.

As part of our ongoing research on decarboxylative cross-coupling reactions, we have recently developed a new simple, cheap and highly efficient copper-based catalytic system (CuBr / TMEDA) for the decarboxylation of aromatic carboxylic acids.[10] This system was successfully used for the synthesis of biaryl compounds. The excellent results obtained encouraged us to extend the scope of the reaction to the stereoselective preparation of triarylethylenes.

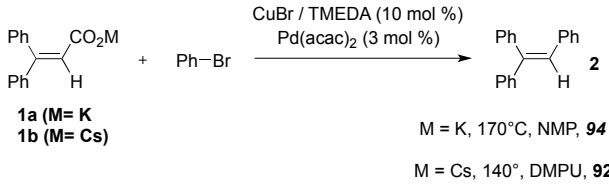
At the best of our knowledge, no attempt to perform the Cu-catalyzed decarboxylative coupling of 3,3-diarylacrylic acids was reported in the literature.[11] It is quite surprising since such a procedure seems very attractive to prepare bioactive molecules like tamoxifen. This is probably due to the poor results obtained with cinnamic acid, one of the simplest commercial arylacrylic acid which is probably frequently used as a model for preliminary experiments. Indeed, our attempts to perform, under our conditions, a Cu/Pd-catalyzed decarboxylative coupling reaction between potassium cinnamate and bromobenzene lead to an untractable mixture of products resulting from both decarboxylative cross-coupling and Heck reactions (scheme 1). Thus, the yield of stilbene never exceeded 18 %.




**Scheme 1.** Decarboxylative cross-coupling of potassium cinnamate with bromobenzene.

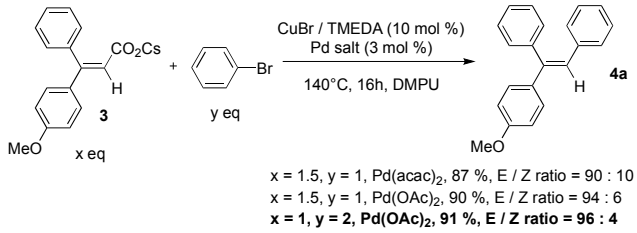
We obtained very similar results by using the conditions described by Goossen[12]and Miura[13] In spite of these discouraging results, we tried to perform the reaction with 3,3-diarylacrylic acids. Indeed, we thought that it would give better results since

the Heck reaction would be less competitive with these substrates. Indeed, as expected we found that, under our conditions, the cross-coupling between potassium 3,3-diphenylacrylate **1a** and bromobenzene gives only the expected coupling product **2** in high yield at 170°C (Scheme 2). The reaction takes place at a lower temperature (140 °C) by using the corresponding caesium carboxylate **1b** in DMPU.




**Scheme 2.** Decarboxylative cross-coupling reaction between potassium or caesium 3,3-diphenylacrylates and bromobenzene

These results prompted us to develop a new stereoselective synthesis of triarylethylenes. At first, we coupled caesium (*E*)-3-anisylcinnamate **3** with bromobenzene to study the stereoselectivity of the decarboxylative cross-coupling reaction under our conditions (Scheme 3).




**Scheme 3.** Optimization of the stereoselectivity of the coupling between caesium (E)-3-anisylcinnamate 3 and bromobenzene.

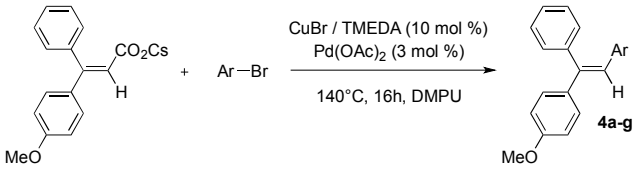
Interestingly, we found that the reaction is quite stereoselective under our conditions (*E*/*Z*= 90:10). Replacement of $Pd(acac)_2$ by $Pd(OAc)_2$ as precatalyst leads to the expected product **4a** in 90-91 % yield with an excellent *E* / *Z* ratio (94:6 to 96:4) (scheme 3).

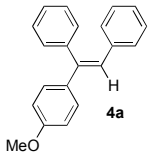
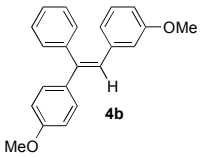
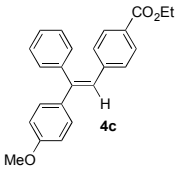
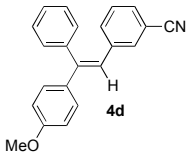
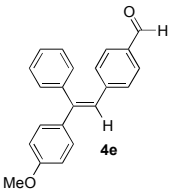
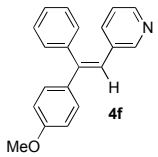
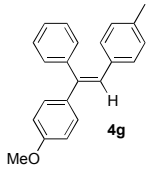
To investigate the scope of the reaction we applied this procedure to various functionalized aryl bromides. As shown in Table 1, the decarboxylative cross-coupling reaction with caesium (*E*)-3-anisylcinnamate is very efficient (yields ranging from 72 % to 91 %) and chemoselective since aldehyde, ester and nitrile are tolerated (Table 1, entries 3 to 5). Furthemore, excellent stereoselectivities were obtained (*E* / *Z* ratio ranges from 96/4 to 99/1).

We also used various caesium 3,3-diarylacrylates (scheme 4). As a rule, excellent yields and stereoselectivities were obtained, it should be noted that 3,3-diarylacrylates bearing a chloro, a fluoro or an acetamido group reacted successfully.

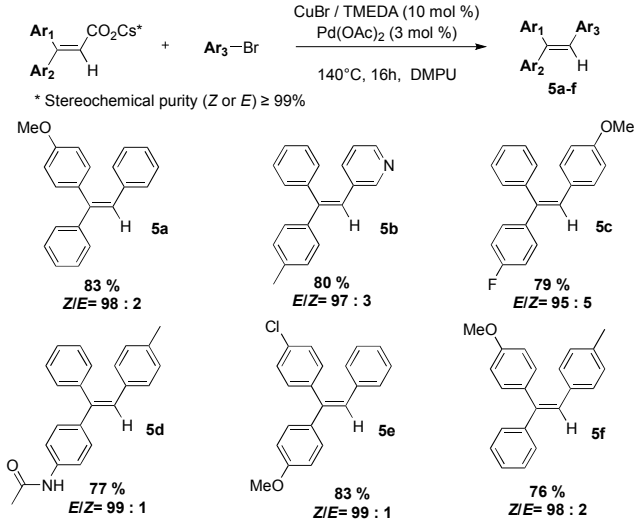
Finally, we applied our procedure to the synthesis of (*Z*)-tamoxifen (Scheme 5). At first, decarboxylative cross-coupling of caesium carboxylate **7** with bromobenzene afforded compound **8** in 84 % yield with a high stereoselectivity (*E* / *Z* = 97 : 3).

**Table 1.** Scope of the decarboxylative cross-coupling reaction between caesium (*E*)-*β*-anisylcinnamate and aryl halides.[a]



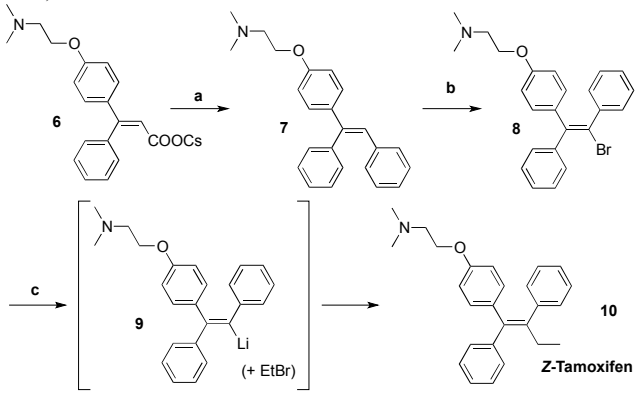

| Entry | Product | Yield (%) | Selectivity |
|---|---|---|---|
| 1 |  **4a** | 91 | 96 : 4 |
| 2 |  **4b** | 90 | 99 : 1 |
| 3 |  **4c** | 90 | 99 : 1 |
| 4 |  **4d** | 86 | 97 : 3 |
| 5 |  **4e** | 72 | 94 : 6 |
| 6 |  **4f** | 84 | 98 : 2 |
| 7 |  **4g** | 87 | 96 : 4 |

According to the procedure developed by Nunes et al.,[14] bromination of **8** in dichloromethane then recristalization in hexanes, gave the *E* isomer **9** (***E***≥ 93%) in 60% yields.




**Scheme 4.** Synthesis of various substituted triarylethylenes *via* a decarboxylative cross-coupling procedure

Generally, (*Z*)-tamoxifen is prepared from **8** *via* a Neghishi reaction with ethylzinc. We propose herein a new and simple way. Alkenylbromide **8** was treated with 1.05 equivalents of ethyllithium. The reaction starts by a lithium-bromide exchange which leads to a mixture of alkenyllithium **9** and ethyl bromide. These two compounds then react rapidly to give (*Z*)-tamoxifen **10** in 70% yield. This original one-pot procedure allows complete retention of the configuration of the starting alkenylbromide ($Z \geq$ 93%).




**Scheme 5.** Synthesis of *Z*-tamoxifen : a) PhBr, CuBr-TMEDA (10 mol %), 3% $Pd(OAc)_2$ (3 mol %), DMPU, 140 °C, 16 h. b) $Br_2$ (1.2 equiv), $CH_2Cl_2$, 0 °C, 16h (60 %, *E* / *Z* = 93 : 7). c) EtLi (1.05 equiv), THF, -78 °C → RT, 1 h (70 %, *E* / *Z* = 93 : 7).

## Conclusions

In summary, we have developed the first decarboxylative cross-coupling of 3,3-diarylacrylic acids with aryl halides by using a simple and cheap decarboxylation catalytic system CuBr / TMEDA. This procedure is very efficient to prepare very stereoselectively various simple and functionalyzed triarylethylenes in excellent yields. In addition, the reaction is displays a high functional group tolerance.

We successfully applied this procedure to the synthesis of *Z*-Tamoxifen.

## Notes and references

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† Electronic Supplementary Information (ESI) available: 1H and 13C NMR spectra, GC/MS analyses

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