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Expedient Access to Unsymmetrical Diarylindolylmethanes through Palladium-Catalyzed Domino Electrophilic Cyclization–Extended Conjugate Addition Approach

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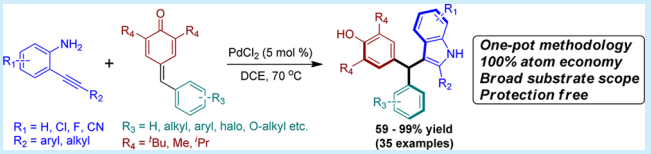
Supporting Information

ABSTRACT: A palladium-catalyzed domino process to access unsymmetrical diarylindolylmethanes has been developed through the annulation of *o*-alkynylanilines followed by 1,6-conjugate addition with *p*-quinone methides (*p*-QMs) under relatively mild conditions. The broad substrate scope of this methodology was demonstrated through the use of a wide range of substituted *o*-alkynylanilines and *p*-quinone methides, and in most cases, the unsymmetrical diarylindolylmethanes could be prepared in moderate to excellent yields. Notably, this method does not require any amino group protection. Moreover, 100% atom economy makes this transformation attractive from a green chemistry perspective.



Triarylmethanes are considered an attractive synthetic target in organic synthesis due to their significant contributions in the dye industry and medicinal chemistry.[1,2] They have also found applications in materials science as fluorescent probes[3] and photochromic agents.[4] The symmetrical triarylmethanes, usually called leuco dyes, are rather easy targets and could be effectually accessed through a Brønsted[5] or Lewis acid[6] catalyzed Friedel–Crafts reaction of aromatic aldehydes or their derivatives with electron-rich arenes and heteroarenes. Nevertheless, the synthesis of unsymmetrical triarylmethanes, which possess various biological properties (Figure 1), still remains a relatively challenging task.

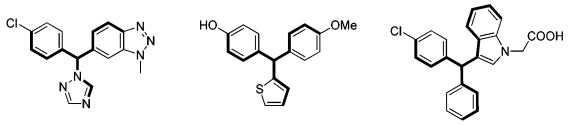
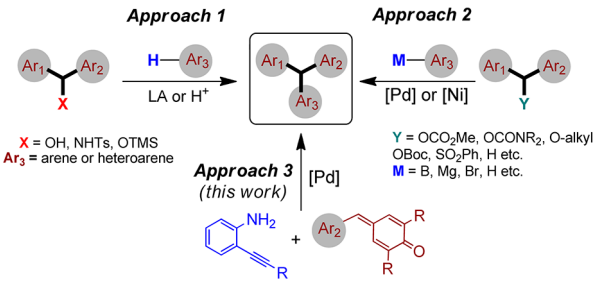


Figure 1. Unsymmetrical triarylmethane-based drugs.

The traditional approach toward unsymmetrical triarylmethanes involves a Friedel–Crafts reaction of electron-rich arenes with unsymmetrical diarylcarbinols or their derivatives under Brønsted or Lewis acid catalyzed conditions (approach 1, Scheme 1).[1e,7] Recently, due to the broad substrate scope, the cross-coupling-based approach has become a unique method for the synthesis of triarylmethanes (approach 2, Scheme 1).

In line with an initial report by Molander's group,[8] Kuwano and co-workers developed an approach to unsymmetrical triarylmethanes through Pd-catalyzed Suzuki–Miyura coupling of boronic acids with diarylmethyl carbonates.[9] Another approach based on Pd-catalyzed direct arylation leading to triarymethanes was developed by the groups of Walsh,[10]

Scheme 1. Approaches toward Unsymmetrical Triarylmethanes



Oshima,[11] and Zhang[12] independently. Watson[13] and Jarvo[14a] reported Ni-catalyzed synthesis of enantioenriched triarylmethanes through coupling of diarylmethanol derivatives with arylboronic acids and boronic esters, respectively. Jarvo's group also developed Ni-catalyzed Kumada coupling of aryl Grignard reagents with diarylmethyl ethers to access enantiomerically enriched triarylmethanes.[14b] Very recently, the group of Crudden and Nambo developed a protocol for the synthesis of unsymmetrical triarymethanes[15a] and triarylacetonitriles[15b] through Pd-catalyzed sequential arylation strategy. Crudden's group also developed a different approach involving enantiospecific Suzuki–Miyura coupling of enantiomerically pure dibenzylic boronic esters with aryl halides.[16] Iron-catalyzed dehydrogenative coupling of diarylmethanes with electron-rich aromatic or heteroaromatic systems was also found to be effective for the synthesis of triarylmethane derivatives.[17] Very recently, Hirano and Miyura reported a Pd-catalyzed C–H/C–O coupling of

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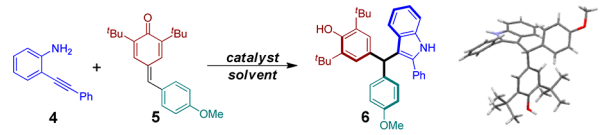
oxazoles with diarylmethanol derivatives leading to oxazole containing triarylmethanes.[18]

In recent years, metal-catalyzed one-pot annulation of *o*-alkynylanilines followed by trapping with suitable electrophiles has become an extremely useful protocol for the construction of 2,3-substituted indoles.[19] Based on this concept, we believed that it is possible to access diarylindolylmethanes through metal-catalyzed annulation of *o*-alkynylanilines followed by trapping with *p*-quinone methides (*p*-QMs). The chemistry of *p*-quinone methides is well explored in organic synthesis and physical organic chemistry.[20a−m] Recently, a few enantioselective transformations have also been reported using *p*-quinone methide as an electrophile.[20n,o] However, to the best of our knowledge, the synthesis of unsymmetrical diarylindolylmethane derivatives[21] through Pd-catalyzed annulation of *o*-alkynylanilines followed by 1,6-conjugate addition with *p*-quinone methides (approach 3, Scheme 1) is still unprecedented in the literature.

We commenced the optimization studies using readily available *o*-alkynylaniline **4** and *p*-quinone methide **5** using a diverse range of palladium catalysts under various reaction conditions (Table 1). Although our initial attempts with

Table 1. Catalyst Screen and Optimization Studies[a]



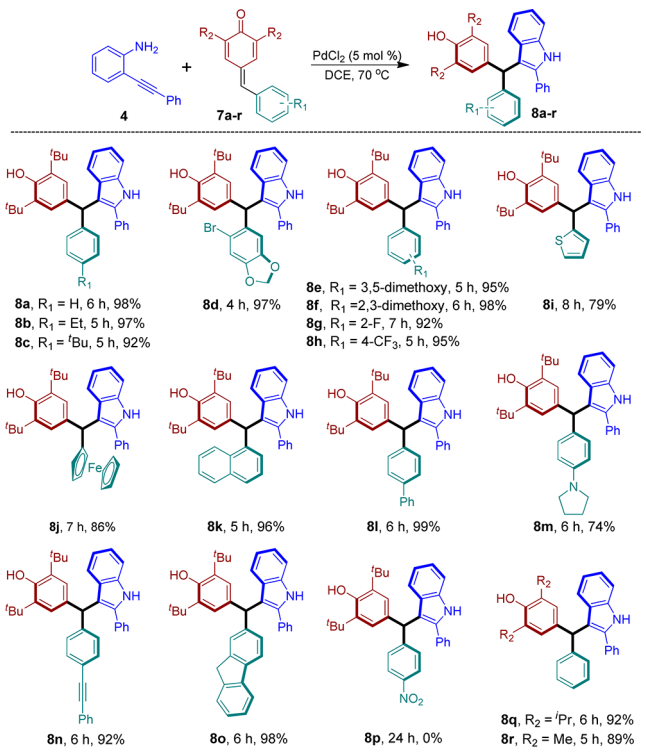
entry	catalyst	solvent	T (°C)	time (h)	yield[b] (%)
1	$PdCl_2(PPh_3)_2$	DCE	rt	36	0
2	$Pd(PPh_3)_4$	DCE	rt	36	0
3	$Pd_2(dba)_3$	DCE	rt	32	0
4	$Pd(OAc)_2$	DCE	rt	36	20
5	$Pd(TFA)_2$	DCE	rt	36	45
6	$PdCl_2$	DCE	rt	36	80
7	**$PdCl_2$**	**DCE**	**70**	**6**	**99**
8	$PdCl_2$	MeCN	70	6	80
9	$PdCl_2$	THF	70	6	92
10	$PdCl_2$	PhMe	70	6	94
11[c]	$PdCl_2$	DCE	70	36	93
12		DCE	rt	36	0

[a]Reaction conditions: 0.04 M solution of **4** in solvent. Pd catalyst (5 mol %) was used. Use of 1.2 equiv of **5** was found to be optimal. [b]Isolated yield. [c]2 mol % of $PdCl_2$ was used. rt = 27−30 °C.

palladium catalysts such as $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, and $Pd_2(dba)_3$ in 1,2-dichloroethane (DCE) at room temperature did not give any fruitful results (entries 1−3, Table 1), extensive optimization experiments revealed that $Pd(OAc)_2$ and $Pd(TFA)_2$ were found to be effective for this transformation at rt, although the yield of **6** was low to moderate (entries 4 and 5). When $PdCl_2$ was used as a catalyst in DCE at rt, the expected product **6** was obtained in 80% yield (entry 6) after 36 h. When the same reaction was carried out at 70 °C, **6** was isolated in almost quantitative yield (entry 7) in just 6 h. The structure of **6** was unambiguously confirmed by NMR as well as X-ray analysis. Further elaboration of optimization was carried out in other solvents at 70 °C. However, in all those cases (entries 8−10), the yield of **6** was found to be inferior when compared to entry 7. Lowering the catalyst loading (2 mol %) did not decrease the yield of the product considerably, but the reaction took a long time to complete (entry 11). No product was observed in the absence of the Pd catalyst (entry 12).

Having optimized conditions in hand (entry 7, Table 1), substrate scope was evaluated using a wide range of *p*-quinone methides (**7a−r**),[20n] and the results are summarized in Scheme 2.

Scheme 2. Substrate Scope with Different *p*-Quinone Methides[a]



[a]Reaction conditions: 0.04 M solution of **4** in DCE. Yields reported are isolated yields.

It is evident from Scheme 2 that this methodology worked very well in the cases of *p*-quinone methides derived from electron-rich (**8a−f,m**) as well as moderately electron poor (**8g,h**) aromatic aldehydes, and in all cases, the expected diarylindolylmethanes were obtained in excellent yields (>90%). In the case of *p*-quinone methide derived from a heteroaromatic aldehyde such as thiophene-2-carboxaldehyde, the product **8i** was isolated in 79% yield. The *p*-quinone methides derived from 2-naphthaldehyde and 4-phenylbenzaldehyde underwent smooth conversion to their corresponding diarylindolylmethane derivatives **8k** and **8l** in 96 and 99% yields, respectively. This transformation was also found to be effective for the synthesis of ferrocene (**8j**), 2-fluorene (**8o**), and 4-(2-phenylethynyl)phenyl (**8n**) substituted triarylmethane derivatives from their corresponding *p*-quinone methides. Unfortunately, the diarylindolylmethane derivative **8p** was not formed in the case of *p*-quinone methide prepared from 4-nitrobenzaldehyde even after 24 h. Other *p*-QMs derived from 2,6-disubstituted phenols such as 2,6-diisopropylphenol (**7q**) and 2,6-dimethylphenol (**7r**) also underwent smooth transformation to their corresponding diarylindolyl derivatives **8q** and **8r** in 92 and 89% yields, respectively.

The scope of this methodology was also extended by treating **5** with a wide range of *o*-alkynylanilines (**9a−p**) under the optimized reaction conditions, and the results are summarized in Scheme 3. Irrespective of the electronic nature of the

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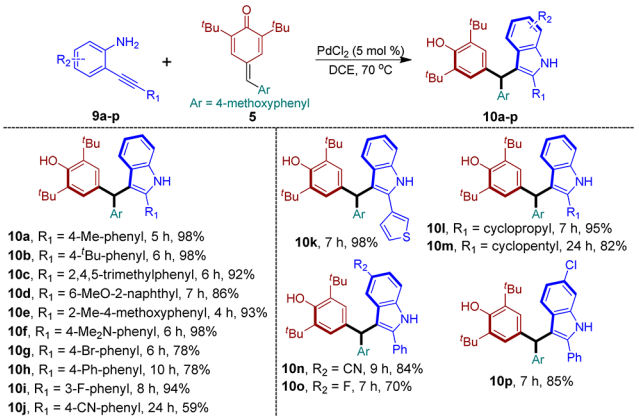
Scheme 3. Substrate Scope with Different Indole Precursors[a]



[a]Reaction conditions: 0.04 M solution of **9** in DCE. Yields reported are isolated yields.

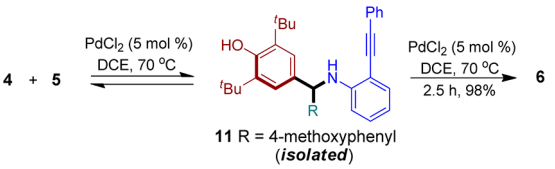
substituents present in the alkyne moiety, the *o*-alkynylanilines (derived from electron-rich as well as electron-deficient arylalkynes) underwent smooth transformation to their corresponding products (**10a−f,i,j**) in moderate to excellent yields. The yields of the product **10g** and **10h** were moderate in the cases of indole precursors derived from 4-bromophenylacetylene and 4-phenylphenylacetylene. The indole precursor prepared from 3-ethynylthiophene was also converted to its corresponding diarylindolylmethane **10k** in excellent yield. The reaction worked pretty well in the cases of indole precursors (**9l** and **9m**) derived from ethynylcyclopropane and ethynylcyclopentane, and the products **10l** and **10m** were obtained in 95 and 82% yields, respectively. We could also synthesize a few other diarylindolylmethanes (**10n−p**) in reasonable yields from *p*-quinone methides derived from *o*-alkynylanilines (**9n−p**) having substituents in the aniline ring.

At this stage, our attention was shifted to elucidate a reasonable mechanism of this transformation. Initially, we believed that the reaction proceeds via 2-substituted indole derivative (through aminopalladation step), which then adds to *p*-QM in 1,6-fashion to generate the diarylindolylmethane derivative. To get a better understanding, a couple of control experiments were performed in which 2-phenylindole (1 equiv) was treated with **5** (1.2 equiv) in the presence or absence Pd catalyst at 70 °C in DCE (please see the Supporting Information for the scheme). In the case of reaction with Pd catalyst, the product **6** was obtained in quantitative yield within 1 h. Unexpectedly, even in the case of the reaction without Pd catalyst, **6** was obtained in 90% yield, although the reaction time was approximately 6 times more than that of the Pd-catalyzed reaction. Therefore, it is obvious that Pd catalyst does help in accelerating the reaction. In the case of reaction without Pd catalyst, we presume that the traces of HCl present in DCE are responsible to effect this transformation by activating the *p*-QM through hydrogen bonding. To confirm the participation of HCl in the reaction, another experiment was conducted where 2-phenylindole was treated with **5** in toluene instead of DCE at 70 °C, but in this case, the product **6** was observed only in trace quantities after 6 h. But, interestingly, when one drop of 1 N aqueous HCl was added, the reaction was completed in 1 h, and **6** was obtained in 71% isolated yield. These experimental observations clearly suggest that HCl is playing important role along with the Pd-catalyst in the 1,6-conjugate addition step to generate the final product. It is also evident that the reaction proceeds through 2-substituted indole intermediate.

On the basis of the above experiments and observations, a plausible mechanism of this transformation has been proposed, which can be found in the Supporting Information.

Notably, we observed that careful monitoring of the reaction between **4** and **5** under standard conditions revealed that the amine addition product **11** was also formed in considerable amounts (Scheme 4), but interestingly, the formation of **11** was found to be reversible. TLC analysis of the reaction mixture indicated that the concentration of **11** was gradually decreasing, and at the same time, the concentration of **6** was steadily increasing during the course of the reaction. Although **11** was unstable under acidic conditions, we could isolate some amounts of **11** by purification through neutral alumina column. The amine addition product **11** was also characterized by spectral techniques. To confirm the reversible nature of this reaction, in an independent experiment, **11** was treated with $PdCl_2$ under standard conditions, and as expected, it was completely converted in to **6** in 2.5 h (Scheme 4).

Scheme 4. Formation of Amine Addition Product 11



In conclusion, an efficient one-pot protocol for the synthesis of heavily substituted unsymmetrical diarylindolylmethane derivatives has been developed through Pd-catalyzed annulation of *o*-alkynylanilines followed by extended conjugate addition to *p*-quinone methides. Broad substrate scope and 100% atom economy are the key features of this methodology. Unlike most of the reported methods for the synthesis of 2,3-substituted indole derivatives, this protocol does not require any protection of the amino group of *o*-alkynylanilines. An enantioselective version of this methodology is currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and characterization data of the products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01030.

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Notes

The authors declare no competing financial interest.

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