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Self-Induced Stereoselective in Situ Trifluoromethylation: Preparation of Spiro[indoline-3,3′-quinoline] via Palladium-Catalyzed Cascade Reaction

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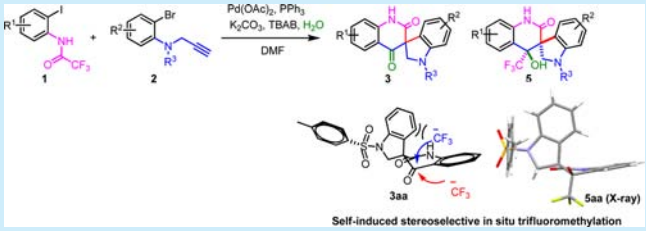
Supporting Information

ABSTRACT: An efficient method to prepare 1′*H*-spiro-[indoline-3,3′-quinoline]-2′,4′-diones and their trifluoromethylated products was developed via a palladium-catalyzed Sonogashira coupling/Wacker-type oxypalladation/cyclization cascade reaction. The amount of water in the reaction system played an important role in the in situ trifluoromethylation reaction, and the trifluoromethylation exhibited excellent molecular self-induced stereoselectivity.



Palladium-catalyzed intramolecular attack of nucleophiles on the π-ligands of palladium−alkyne complexes is a powerful method for the construction of heterocycles.[1] For example, intramolecular aminopalladation and oxypalladation are widely used to synthesize nitrogen- and oxygen-containing heterocyclic compounds, respectively.[2] In addition, oxy/aminopalladation−reductive elimination domino reactions with organopalladium derivatives can be used in the synthesis of regiospecifically substituted heterocyclic compounds.[3] Unlike the reactions mentioned above, intermolecular oxypalladation reactions of alkynes have not been extensively investigated.[4] In this study, we used a palladium-catalyzed Sonogashira coupling/Wacker-type oxypalladation/cyclization cascade reaction to construct a spiro[indoline-3,3′-quinoline]skeleton.

Spirocyclic indoline moieties are found in many natural products[5] and pharmaceuticals.[6] Their biological activities and challenging structures make them attractive synthetic targets, and numerous strategies for their synthesis have recently been developed.[7] Spiro[indoline-3,3′-quinoline] is an important scaffold in various natural products, but only a few synthetic methods, including an $FeCl_3$-catalyzed tandem 1,5-hydride transfer/cyclization,[8] a Michael/Michael cascade reaction,[9] and a domino Heck reaction/C−H arylation,[10] have been reported. In addition, the reported methods have certain limitations: for example, in one case, the starting material is limited to oxindoles, and in other cases, the starting materials are difficult to synthesize. The method described herein provides a new, operationally simple strategy for the synthesis of these spiro compounds from readily accessible starting materials.

Our method arose from a pleasantly surprising discovery we made during an attempt to synthesize 6,7-dihydro-5*H*-indolo-[2,3-*c*]quinoline (**4aa**) from simple precursors **1a** and **2a**. Instead of the expected product, we obtained spiro compound **3aa**, the structure of which was confirmed by X-ray diffraction analysis.[11] This compound was presumed to have formed via an unprecedented competitive intermolecular oxypalladation of the alkyne, in which trace water in the reaction system acted as a nucleophile (Scheme 1). Moreover, we found that the amount of water in the system regulated the in situ trifluoromethylation of the cascade reaction products **3**.[12] Unlike previously reported trifluoromethylation methods,[13] our method relies on a trifluoromethyl source that is generated in situ. Herein, we describe this interesting cascade reaction and the in situ trifluoromethylation reaction in detail, and we discuss the overall mechanism of the process.

Scheme 1. Palladium-Catalyzed Competitive Intermolecular Oxypalladation of Alkynes

First, we optimized the conditions by investigating the palladium catalyst, ligand, base, and solvent (Table 1). With 5 mol % $Pd(OAc)_2$ and 20 mol % PPh_3, Sonogashira coupling product **3aa′** was obtained in 60% yield (entry 1). When the amounts of catalyst and phosphine ligand were doubled, a 15% yield of cascade reaction product **3aa** was obtained in addition to **3aa′** (entry 2). Little to no reaction occurred when triphenylphosphine was replaced by $P(o\text{-tol})_3$ or X-Phos (entries 3 and 4) or when $Pd(OAc)_2$ was replaced with $PdCl_2(MeCN)_2$ or $PdCl_2(PhCN)_2$ (entries 5 and 6). We also tried $Pd_2(dba)_3$ (entry 7) and $Pd(PPh_3)_4$ (entry 8) as catalysts, but the yield of the coupling product was low (35%) with the

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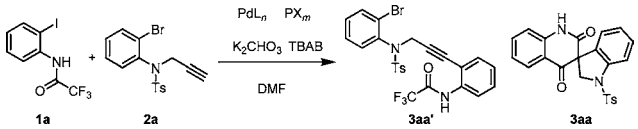
Table 1. Optimization of Reaction Conditions



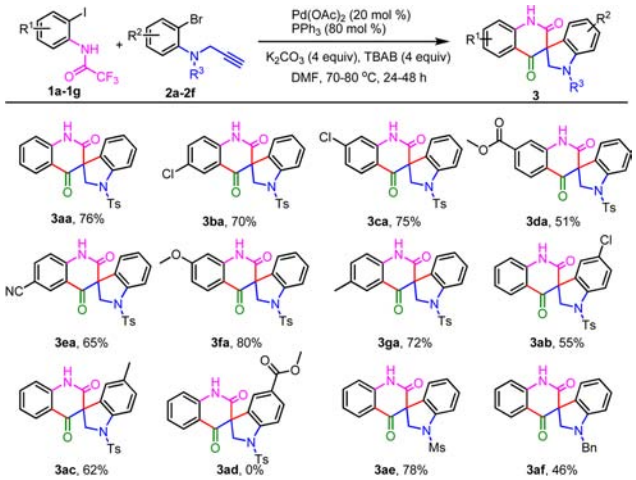
entry	PdL$_n$ (mol %)	PX$_m$ (mol %)	3aa′	3aa
1	Pd(OAc)$_2$ (5%)	PPh$_3$ (20%)	60%	<5%
2	Pd(OAc)$_2$ (10%)	PPh$_3$ (40%)	61%	15%
3	Pd(OAc)$_2$ (10%)	P(*o*-tol)$_3$ (40%)	<5%	–
4	Pd(OAc)$_2$ (10%)	X-Phos (40%)	–	–
5	PdCl$_2$(MeCN)$_2$ (10%)	X-Phos (40%)	–	–
6	PdCl$_2$(PhCN)$_2$ (10%)	X-Phos (40%)	–	–
7	Pd$_2$(dba)$_3$ (5%)	–	35%	–
8	Pd(PPh$_3$)$_4$ (10%)	–	56%	10%
9[a]	Pd(OAc)$_2$ (20%)	PPh$_3$ (80%)	–	76%
10[b]	Pd(OAc)$_2$ (20%)	PPh$_3$ (80%)	35%	15%
11[c]	Pd(OAc)$_2$ (20%)	PPh$_3$ (80%)	49%	–
12[d]	Pd(OAc)$_2$ (20%)	PPh$_3$ (80%)	45%	10%
13[e]	Pd(OAc)$_2$ (20%)	PPh$_3$ (80%)	30%	<5%
14[f]	Pd(OAc)$_2$ (20%)	PPh$_3$ (80%)	5%	22%
15[g]	Pd(OAc)$_2$ (20%)	PPh$_3$ (80%)	51%	–

[a]Isolated yield. [b]4 equiv of Cs_2CO_3 were used instead of K_2CO_3. [c]4 equiv of NEt_3 were used. [d]Acetonitrile was used as the solvent, and the mixture was heated for 48 h. [e]Toluene was used as the solvent, and the mixture was heated for 48 h. [f]Tetrabutylammonium bromide was not added. [g]4 Å molecular sieves were added.

former, and yields similar to those shown in entry 2 were obtained with the latter. To our delight, when we increased the amount of Pd(OAc)$_2$ to 20 mol % and the amount of the PPh$_3$ to 80 mol %, we obtained **3aa** in 76% yield (entry 9). Next we investigated the effect of the base. When Cs_2CO_3 was used instead of K_2CO_3, **3aa′** and **3aa** were obtained in 35% and 15% yields respectively (entry 10). However, with triethylamine, only the coupling product was obtained (49%, entry 11). We also evaluated other solvents: with acetonitrile, **3aa′** and **3aa** were obtained in 45% and 10% yields, respectively, after a prolonged reaction time (entry 12); the yields were even lower in toluene (entry 13). These low yields were probably due to the poor solubility of K_2CO_3 in these solvents. The phase-transfer catalyst strongly influenced the reaction: the yields were much lower in the absence of tetrabutylammonium bromide (entry 14).[14] We also carried out a control reaction with molecular sieves and found that only coupling product **3aa′** was obtained (51% yield, entry 15).

With the optimum conditions in hand, we investigated the substrate scope of the reaction (Scheme 2). First, we evaluated the electronic effects of substituents on the benzene ring of **1** by carrying out reactions of **1a**−**1g** with **2a** to afford compounds **3aa**−**3ga**, respectively. We found that substrates with electron-donating substituents (**1f** and **1g**) and with weak electron-withdrawing substituents (**1b** and **1c**) afforded the desired spiro compounds (**3fa**, **3ga**, **3ba**, and **3ca**, respectively) in good to excellent yields. Even when there was a strong electron-withdrawing group, such as a methoxycarbonyl or a nitrile, on the benzene ring, the desired products (**3da** and **3ea**) were still obtained in moderate yields. The position of the electron-withdrawing Cl substituent had no effect on the reaction (**3ba** and **3ca**). In contrast, the introduction of a substituent on the benzene ring of **2** adversely affected the yields of spiro products **3ab**−**3ad**. In particular, spiro product **3ad** was not obtained from the reaction of ester-substituted aniline **2d** with **1a**. The

Scheme 2. Preparation of 1′*H*-Spiro[indoline-3,3′-quinoline]-2′,4′-diones[a]



[a]The yields given in the scheme are isolated yields.

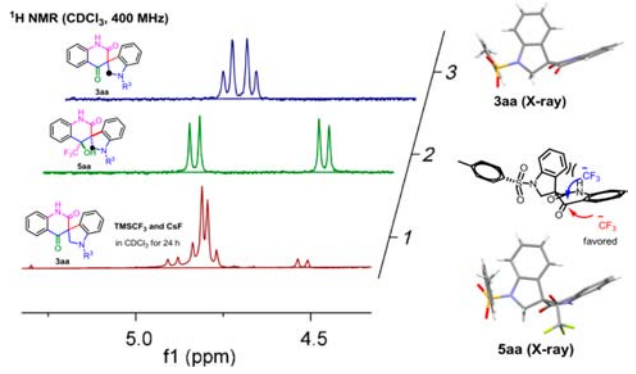
substituent on the nitrogen of **2** had little influence: **3ae** and **3af** were obtained from the reactions of **1a** with **2e** and **2f** in 78% and 46% yields, respectively.

As mentioned above, water regulated the in situ trifluoromethylation of coupling products **3**. To study the effect of the water, we conducted a series of experiments on the relationship between the amount of water and the proportion of trifluoromethylated product **5aa**. We observed that the proportion of **5aa** increased as the amount of water was increased; the proportion peaked at 4 equiv of water. When the amount of water was increased above 4 equiv, an extended reaction time was required and the yield of **5aa** was low (see Supporting Information (SI)).

Notably, the in situ trifluoromethylation reaction exhibited excellent stereoselectivity in the only obtained product, CF_3, and the adjacent phenyl is in a trans position that was confirmed by the X-ray diffraction analysis of **5aa**.[15] Similarly, the reaction of **3aa** with trimethyl(trifluoromethyl)silane also afforded the trifluoromethylation product **5aa** stereospecifically which was determined by the crude ^{1}H NMR spectrum of the reaction mixture (Scheme 3).

We also examined the substrate scope of this new method for introducing a trifluoromethyl group into organic molecules (Scheme 4). Impressively, intentionally adding water (4 equiv) was sufficient to speed up the reaction (see SI). Substituted **1**

Scheme 3. Control Experiments



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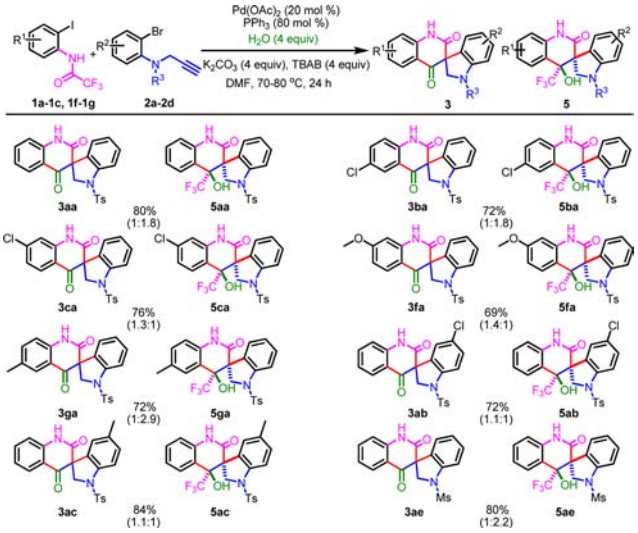
Scheme 4. Water-Regulated Trifluoromethylation of 1′*H*-Spiro[indoline-3,3′-quinoline]-2′,4′-diones[a]

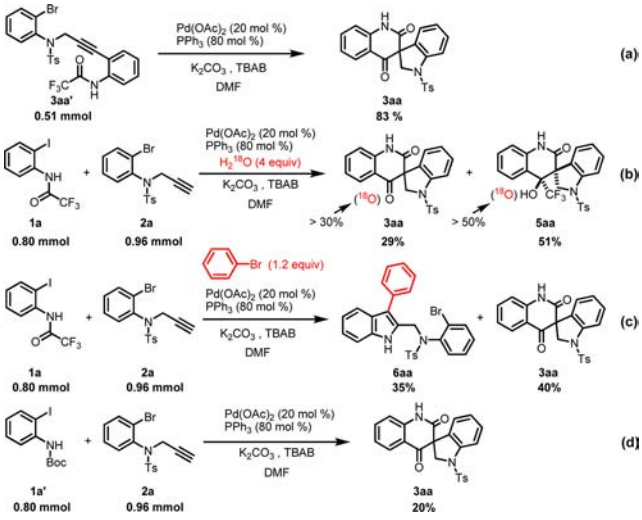


[a]The configuration of compounds **5** is the relative configuration.

reacted with **2** to afford trifluoromethylation products **5** in moderate to good yields. The reaction of methyl-substituted aniline **1g** with **2a** afforded the highest proportion of the trifluoromethylation product (**3ga**/**5ga** = 1:2.9). When 4-methylbenzenesulfonamide **2a** was replaced with methanesulfonamide **2e** in the reaction with **1a**, the proportion of the trifluoromethylation product (**5ae**) increased slightly. In addition, all the products **5** exhibited excellent stereospecificity (see SI).

To gain insight into the mechanism, we performed a series of control experiments (Scheme 5). **3aa**′ could be transformed

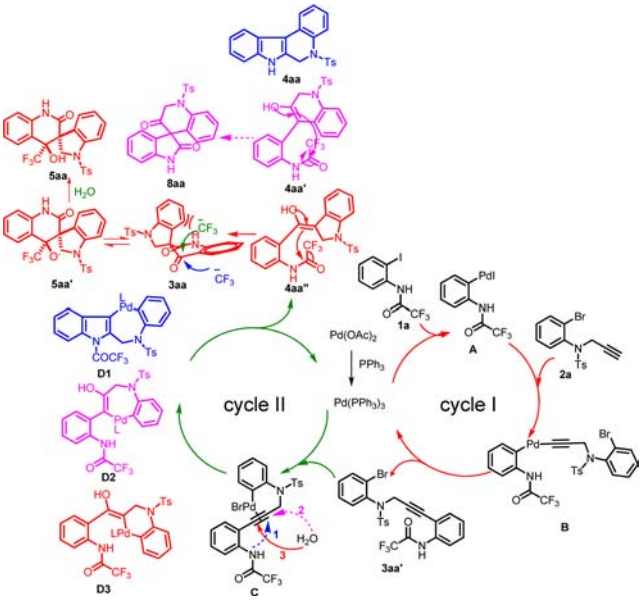
Scheme 5. Control Experiments



into target compound **3aa** under the cascade reaction conditions (Scheme 5a), which indicates the occurrence of a tandem Sonogashira coupling followed by a Wacker-type oxypalladation. To investigate the source of the carbonyl oxygen in the product, we added 4 equiv of $H_2{}^{18}O$ to the reaction system and found that more than 30% of the oxygen-18 was detected in **3aa** and more than 50% was detected in **5aa** (Scheme 5b). Conversely, when 4 Å molecular sieves were added to the reaction system, only Sonogashira coupling product **3aa**′ was obtained (Table 1, entry 15). These results suggest that the oxygen of the carbonyl group comes from water under these reaction conditions. Compound **6aa**, the product of an intramolecular aminopalladation reaction, was obtained when bromobenzene (1.2 equiv) was added to the reaction system (Scheme 5c); this result indicates that the selectivity between the intermolecular Wacker-type oxypalladation and the intramolecular aminopalladation was due to the high reaction energy barrier of intramolecular aminopalladation of **3aa**′. Compound **3aa** could also be obtained in 20% yield from the reaction of **1a** with **2a** (Scheme 5d).

On the basis of the results described above, we propose the reaction mechanism depicted in Scheme 6 for substrates **1a** and

Scheme 6. Proposed Mechanism



2b. First, palladium(II) acetate is reduced to zerovalent palladium by the excess triphenylphosphine. Then, **1a** and **2a** undergo a Sonogashira coupling reaction to form **3aa**′ (cycle I). The π-ligand of palladium−alkyne intermediate **C** forms after oxidative addition of bromobenzene. In the subsequent step, competitive intramolecular aminopalladation (route 1) and regioselective Wacker-type intermolecular oxypalladation (routes 2 and 3) can occur to form three different intermediates (**D1**, **D2**, and **D3**), which lead to three different products (**4aa**, **8aa**, and **3aa**, respectively). **D1** and **D2** are seven-membered cyclic palladium intermediates, whereas **D3** is a six-membered cyclic intermediate. Because we obtained only **3aa**, we speculate that the energy barrier for the formation of **D1** and **D2** is substantially higher than that for the formation of **D3**, which gives the process its high selectivity. Intermediate **4aa**″, which forms by reductive elimination, affords **3aa** by a sequential enol isomerization, nucleophilic attack on the carbonyl carbon of the trifluoroacetyl group, and removal of the trifluoromethyl group. Subsequent stereoselective nucleophilic attack of $^{-}CF_3$ on the ketone carbonyl group of **3aa** affords **5aa**′ which is supposed to be a reversible reaction. In the presence of water, **5aa**′ is readily protonated to give **5aa**, and the amount of water will influence the equilibrium of the reversible reaction and then result in a different ratio of **3aa** and **5aa**.

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In summary, we have developed an efficient method to prepare1′*H*-spiro[indoline-3,3′-quinoline]-2′,4′-diones and their trifluoromethylated products via a palladium-catalyzed Sonogashira coupling/Wacker-type oxypalladation/cyclization cascade reaction. The Wacker-type intermolecular oxypalladation reaction of an alkyne that occurred during this process has rarely been investigated. We found that the amount of water played an important role in the in situ trifluoromethylation reaction and the reaction exhibited excellent stereoselectivity via a molecular self-induced mechanism. Further studies on the application of this cascade reaction are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for **1**, **2**, **3**, **5**, **6**, and related spectra are included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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