Chinese Chemical Letters 34 (2023) 107873

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Palladium-catalyzed carbonylative cyclization of alkene-tethered indoles with phenols or arylboronic acids: Construction of carbonyl-containing indolo[2,1-*a*]isoquinoline derivatives

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ARTICLE INFO

Article history:
Received 12 August 2022
Revised 26 September 2022
Accepted 29 September 2022
Available online 1 October 2022

Keywords:
Carbonylative cyclization
Palladium catalysis
Indolo[2,1-*a*]isoquinolines
Alkene-tethered indoles
Phenols
Arylboronic acids

ABSTRACT

A novel palladium-catalyzed carbonylative cyclization of alkene-tethered indoles with phenols or arylboronic acids is described, which provides a facile approach to access indolo[2,1-*a*]isoquinoline scaffolds. This method employs benzene-1,3,5-triyl triformate (TFBen) as the CO surrogate for the incorporation of a carbonyl group into indolo[2,1-*a*]isoquinoline scaffolds, and a variety of carbonyl-containing indolo[2,1-*a*]isoquinoline derivatives are prepared in good yields.

Indolo[2,1-*a*]isoquinolines represent a class of important scaffolds that is prevalent in numerous natural products and bioactive molecules (Fig. 1) [1–7]. For example, compound **A** was a potent melatonin antagonist to treat sleep problems [1]. Compound **B** was found to inhibit the polymerization of tubulin [2]. Cryptanstoline and cryptowoline were two natural occurring dibenzopyrrocoline alkaloids isolated from a plant *Cryptocarya bowiei* in Queensland [3–5].

To assemble these useful indolo[2,1-*a*]isoquinoline scaffolds, numerous synthetic approaches have been realized in the past several decades. Among them, radical cascade reaction [8–18], C–H annulation [19–25], and metal-catalyzed cyclization [26–35] have been widely studied. For instance, Nevado's group developed an elegant process for the synthesis of CF_3-, SCF_3-, $Ph_2(O)P$-, and N_3-containing indolo[2,1-*a*]isoquinolin-6(5*H*)-ones *via* radical cascade cyclization of *N*-(arylsulfonyl)acrylamides [8]. In 2020, Lei's group discovered a manganese-catalyzed electrochemical radical cascade cyclization of *N*-substituted 2-arylbenzoimidazoles with alkylboronic acids to access a variety of benzo [4,5] imidazo-[2,1-*a*]isoquinolin-6(5*H*)-one derivatives [9]. Recently, Lv, Li and co-workers reported that an iron-catalyzed radical cascade reaction of 2-arylindoles with germanium hydrides for the construction of germanium-substituted indolo[2,1-*a*]isoquinolin-6(5*H*)-ones [10]. Gogoi's group developed a facile and efficient synthesis of indolo[2,1-*a*]isoquinolines through a ruthenium-catalyzed C–H annulation of antipyrine with alkyne [19]. Cui and co-workers revealed a rhodium-catalyzed C–H annulation of 2-phenylindoles with 4-hydroxy–2-alkynoates for the synthesis of a series of furo[3,4-*c*]indolo[2,1-*a*]isoquinolines [20]. Yang and Liang's group demonstrated a palladium-catalyzed cyclization of alkene-tethered aryl halides with *o*-bromobenzoic acids to produce various fused indolo[2,1-*a*]isoquinolines [26]. Despite the significant advance in the synthesis of functionalized indolo[2,1-*a*]isoquinolines, an efficient method for the incorporation of a carbonyl group into indolo[2,1-*a*]isoquinoline scaffolds is undeveloped. In addition, transition-metal-catalyzed carbonylation reactions have been considered as an economic and straightforward approach to access carbonyl-containing molecules [33–39]. Herein, with our recent efforts on carbonylation reactions [40–50], we would like to describe a palladium-catalyzed carbonylative cyclization of alkene-tethered indoles with phenols or arylboronic acids using TFBen as the CO source to furnish a wide range of carbonyl-containing indolo[2,1-*a*]isoquinolines in good yields.

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https://doi.org/10.1016/j.cclet.2022.107873
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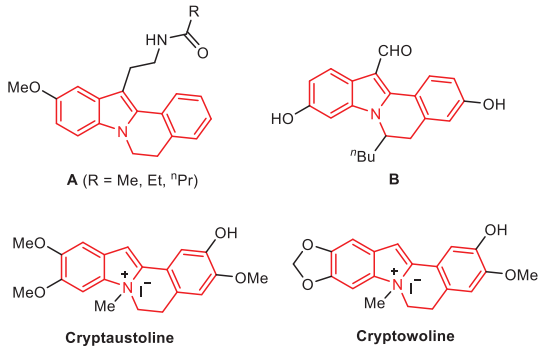
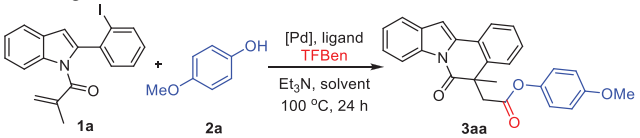


Fig. 1. Selected examples of bioactive molecules with indolo[2,1-*a*]isoquinoline scaffolds.

Our investigation commenced with the reaction of the alkene-tethered indole **1a**, 4-methoxyphenol **2a**, and TFBen in the presence of $Pd(OAc)_2$ as the catalyst and a phosphine ligand (Table 1, entries 1–4). Gratifyingly, the reaction with PCy_3 as the ligand gave the desired product **3aa** in 80% yield (Table 1, entry 2). Next, a series of solvents were screened (Table 1, entries 5–9), and the yield of **3aa** was significantly enhanced to 95% when DMF was used (Table 1, entry 8). It was found that lower reaction yields were obtained when other palladium catalysts such as $PdCl_2$, $Pd(acac)_2$, $Pd(PPh_3)_4$, and $Pd(TFA)_2$ were employed (Table 1, entries 10–13). Moreover, reducing the loading of the catalyst gave 76% yield of **3aa** (Table 1, entry 14). Additionally, when the amount of TFBen was decreased, a relatively lower yield was achieved (Table 1, entry 15). Notably, under our best reaction conditions, a similar yield can be obtained by performing the reaction under CO atmosphere (1 bar).

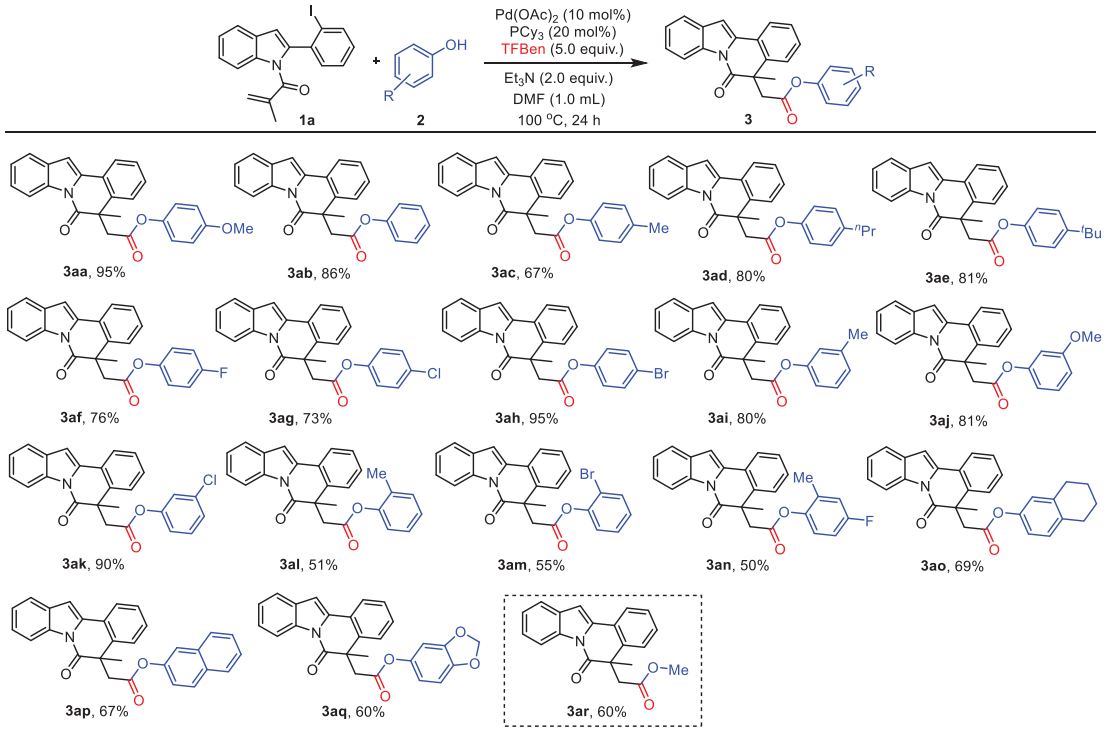
Then, the scopes of phenols were investigated in the reaction with the alkene-tethered indole **1a** under the optimal reaction conditions (Table 1, entry 8). As depicted in Scheme 1, for phenols with *para*-electron-donating or -withdrawing groups, the reaction worked well to give the corresponding products **3aa-3ah** in high to excellent yields. It was shown that the reaction of the *meta*-substituted phenols afforded the desired products **3ai-3ak** in 80%–90% yields. When the *ortho*-substituted phenols were tested, moderate yields of products **3al-3am** were achieved, which could be attributed to the steric hindrance. Furthermore, the di-substituted phenols were successfully converted to product **3an**

Table 1
Screening of the reaction conditions.[a]

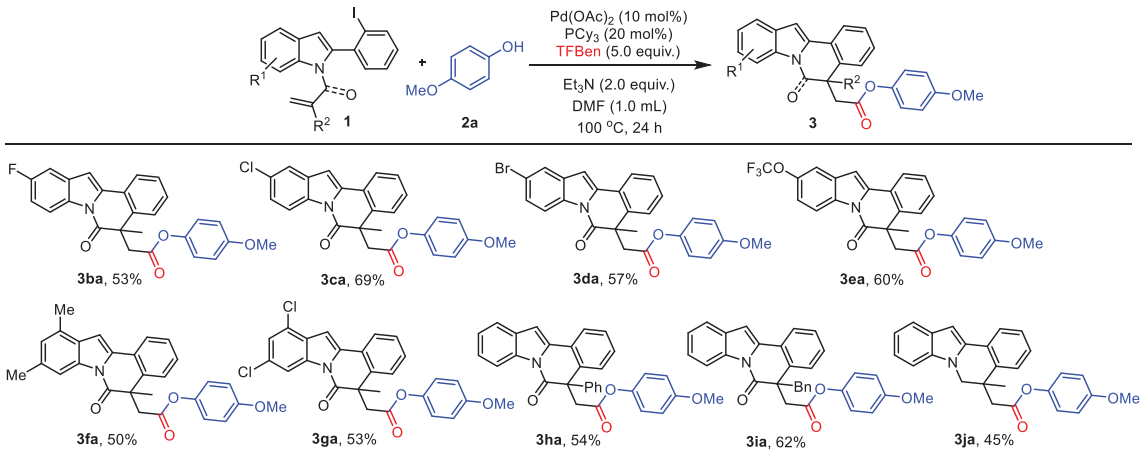


Entry	[Pd]	Ligand	Solvent	Yield (%)
1	$Pd(OAc)_2$	PPh_3	DMSO	78
2	$Pd(OAc)_2$	PCy_3	DMSO	80
3	$Pd(OAc)_2$	dppb	DMSO	54
4	$Pd(OAc)_2$	Xantphos	DMSO	63
5	$Pd(OAc)_2$	PCy_3	toluene	90
6	$Pd(OAc)_2$	PCy_3	dioxane	35
7	$Pd(OAc)_2$	PCy_3	DCE	81
8	$Pd(OAc)_2$	PCy_3	DMF	95
9	$Pd(OAc)_2$	PCy_3	MeCN	59
10	$PdCl_2$	PCy_3	DMF	0
11	$Pd(acac)_2$	PCy_3	DMF	trace
12	$Pd(PPh_3)_4$	PCy_3	DMF	60
13	$Pd(TFA)_2$	PCy_3	DMF	53
14[b]	$Pd(OAc)_2$	PCy_3	DMF	76
15[c]	$Pd(OAc)_2$	PCy_3	DMF	86

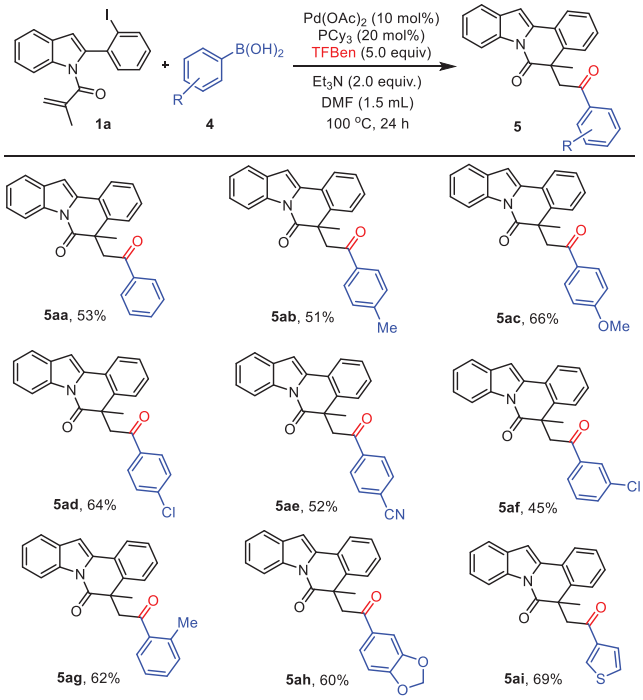
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv.), TFBen (5.0 equiv.), palladium catalyst (10 mol%), monodentate ligand (20 mol%) or bidentate ligand (10 mol%), Et_3N (2.0 equiv.), solvent (1.0 mL), 100 °C, 24 h, isolated yield.
[b] $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%).
[c] TFBen (3.0 equiv).



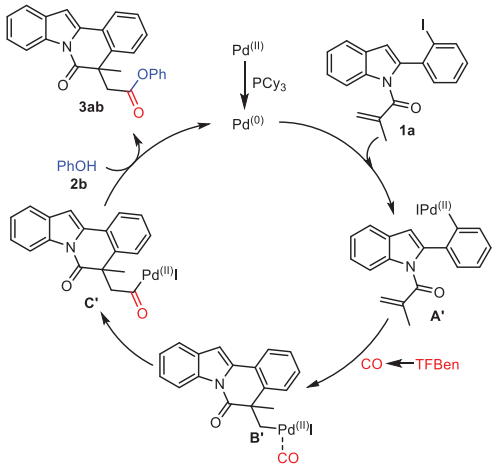
Scheme 1. Scope of phenols. Reaction condition: **1a** (0.2 mmol), **2** (2.0 equiv.), TFBen (5.0 equiv.), $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%), Et_3N (2.0 equiv.), DMF (1.0 mL), 100 °C, 24 h, isolated yield.



Scheme 2. Scope of alkene-tethered indoles. Reaction condition: **1** (0.2 mmol), **2a** (1.5 equiv.), TFBen (5.0 equiv.), $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%), Et_3N (2.0 equiv.), DMF (1.0 mL), 100 °C, 24 h, isolated yield.



Scheme 3. Scope of arylboronic acids. Reaction condition: **1a** (0.2 mmol), **4** (2.5 equiv.), TFBen (5.0 equiv.), $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%), Et_3N (2.0 equiv.), DMF (1.5 mL), 100 °C, 24 h, isolated yield.



Scheme 4. Plausible mechanism.

and **3ao** in 50% and 69% yield, respectively. In addition, 67% yield of product **3ap** was obtained in the reaction with 2-naphthol **2p**. The reaction of sesamol **2q** also proceeded smoothly to give product **3aq** in 60% yield. Notably, methanol could also be transformed to product **3ar** in 60% yield. However, very low yields of the corresponding products were obtained when ethanol, *i*PrOH, *n*BuOH, or amines were tested.

Subsequently, a variety of alkene-tethered indoles were synthesized and tested in the reaction with 4-methoxyphenol **2a** (Scheme 2). For the mono-substituted alkene-tethered indoles, the reaction afforded the desired products **3ba-3ea** in 53%–69% yields. It was found that the reaction of the di-substituted alkene-tethered indoles led to products **3fa-3ga** in moderate yields. It was noted that when substrates bearing a phenyl and benzyl group were tested, the expected product **3ha** and **3ia** were achieved in 54% and 62% yield, respectively. Additionally, the 2-methylallyl-substituted indole **1j** was smoothly converted to product **3ja** in 45% yield.

Furthermore, a series of arylboronic acids were also examined in the reaction with the alkene-tethered indole **1a** as shown in Scheme 3. The reaction of arylboronic acids bearing *para*-electron-donating or -withdrawing substituents proceeded well to give the corresponding products **5aa-5ae** in 51%–66% yields. When 3-chlorophenylboronic acid **4f** was tested, 45% yield of product **5af** was obtained. In addition, the reaction of 2-tolylboronic acid **4g** gave 62% yield of product **5ag**. It was noteworthy that product **5ah** and **5ai** were afforded in high yields in the reaction of arylboronic acids containing a benzo[*d*][1,3]dioxole and thiophene unit.

On the basis of current results and precedent reports [26,30,33], a plausible mechanism for a palladium-catalyzed carbonylative cyclization of alkene-tethered indoles with phenols is proposed (Scheme 4). Initially, the reaction of $Pd(OAc)_2$ with PCy_3 forms the active Pd(0) species, which undergoes oxidative addition with the alkene-tethered indole **1a** to generate the aryl Pd(II) complex **A'**. Then, intramolecular cyclization of **A'** and coordination with CO released from TFBen lead to the intermediate **B'**. Subsequently, migratory insertion of CO in **B'** gives the acyl Pd(II) complex **C'**. Finally, nucleophilic attack of phenol **2b** on **C'** followed by reductive elimination affords the target product **3ab** and regenerates the active Pd(0) species for the next catalytic cycle.

In conclusion, we have developed a facile and efficient method for the construction of indolo[2,1-*a*]isoquinoline scaffolds *via* a novel palladium-catalyzed carbonylative cyclization of alkene-tethered indoles with phenols or arylboronic acids. By using TFBen as the CO source, this protocol enables the incorporation of a carbonyl group into indolo[2,1-*a*]isoquinoline scaffolds, producing various carbonyl-containing indolo[2,1-*a*]isoquinoline derivatives in good yields.

Declaration of competing interest

We have no conflict of interest to declare.

Acknowledgments

We acknowledge the financial supports from the Joint Funds of the Zhejiang Provincial Natural Science Foundation of China (No. LTY21B020001), and the Fundamental Research Funds of Zhejiang Sci-Tech University (No. 2021Q052).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.107873.

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