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C4-arylation and domino C4-arylation/3,2-carbonyl migration of indoles by tuning Pd catalytic modes: Pd(I)–Pd(II) catalysis *vs.* Pd(II) catalysis†

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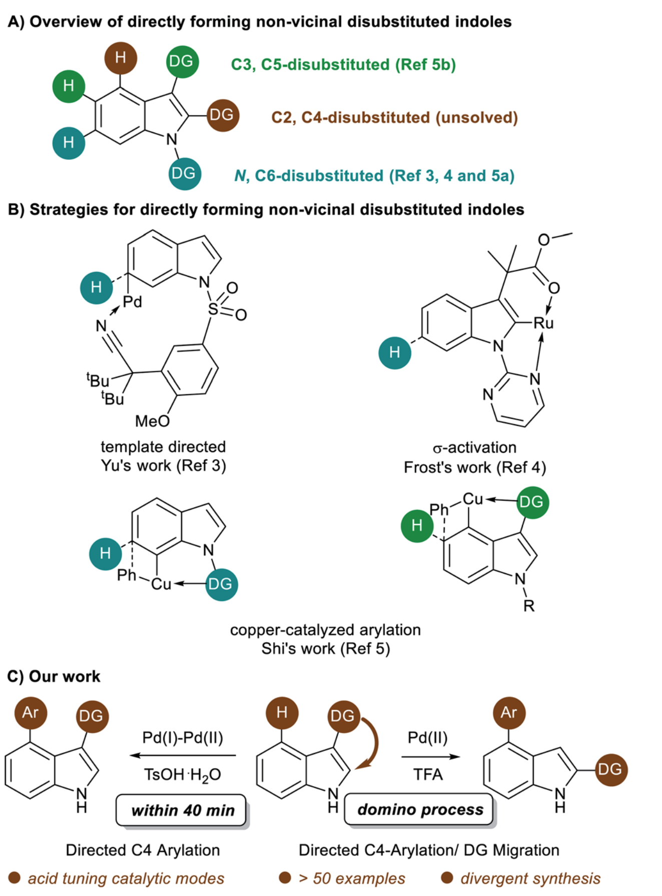
Efficient C4-arylation and domino C4-arylation/3,2-carbonyl migration of indoles have been developed. The former route enables C4-arylation in a highly efficient and mild manner and the latter route provides an alternative straightforward protocol for synthesis of C2/C4 disubstituted indoles. The mechanism studies imply that the different reaction pathways were tuned by the distinct acid additives, which led to either the Pd(I)–Pd(II) pathway or Pd(II) catalysis.

Introduction

Multi-substituted-indoles are key building blocks in a large number of natural products, pharmaceuticals and agrochemicals.[1] Transition-metal-catalyzed directed C–H activation at the benzene moiety has emerged as a powerful synthetic approach to streamline the synthesis of highly substituted indoles.[2] It normally requires an adjacent directing group to the C–H functionalization sites, which leads to the generation of vicinal disubstituted indoles. However, direct formation of non-vicinal disubstituted indoles *via* the directing group's assistance remains challenging.

To achieve this goal, several directed remote C–H functionalization strategies have been developed recently (Scheme 1A). C6-selective olefination of indoles has successfully been achieved by groups of Yu using a combination of a monoprotected amino acid ligand and the nitrile template attached at the indole nitrogen *via* a sulfonamide linkage (Scheme 1B).[3] Frost developed an *N*-pyrimidinyl group assisted cycloruthenation pathway to achieve remote C6-selective alkylation.[4] Shi reported a Cu(II)-diaryliodonium triflate salt catalytic system for N–P(O)^{t}Bu$_2$ directed C6-selective arylation and C3-pivaloyl directed C5-selective arylation.[5] Despite this impressive progress, the scope is limited to the synthesis of 3,5- and *N*,6-disubstituted indoles and strategies other than directed remote C–H activation have been elusive. Herein, we reported the first catalysis mode tuned C4-arylation/directing group migration. With different acidic additives, the different pathways were tuned to either the Pd(I)–Pd(II) pathway or Pd(II) catalysis (Scheme 1C).



Scheme 1 Transition-metal-catalyzed synthesis of non-vicinal disubstituted indoles *via* C–H functionalization.

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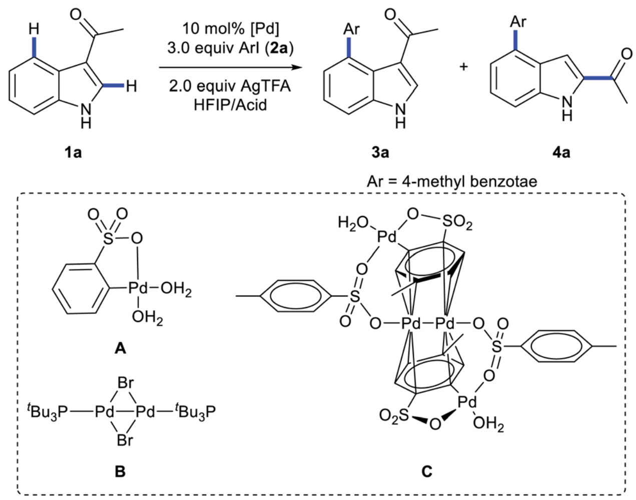
Table 1 Optimization of the reaction conditions[a]



Entry	HFIP/acid	Pd catalyst	Yield% (3a)[b]	Yield% (4a)[b]
1[c]	HFIP/AcOH (3 : 1, v/v)	$Pd(OAc)_2$	50	6
2[d]	$TsOH \cdot H_2O$ (3.75 equiv.)	$Pd(OAc)_2$	90	—
3	$ClCH_2COOH$ (3.75 equiv.)	$Pd(OAc)_2$	20	3
4[e,f]	HFIP/TFA (3 : 1, v/v)	$Pd(OAc)_2$	3	75
5	—	$Pd(OAc)_2$	8	—
6[d]	$TsOH \cdot H_2O$ (3.75 equiv.)	$Pd(OTs)_2(MeCN)_2$	15	—
7[d]	$TsOH \cdot H_2O$ (3.75 equiv.)	**A**	88	—
8[d]	$TsOH \cdot H_2O$ (3.75 equiv.)	**B**	91	—
9[e]	HFIP/TFA (3 : 1, v/v)	$Pd(TFA)_2$	3	75

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (3.0 equiv.), AgTFA (2.0 equiv.), Pd catalyst (10 mol%), HFIP/acid = 3 : 1 (v/v, 1.0 mL), 100 °C, 13 h. [b] Isolated yields. [c] C2-arylation products obtained in 20% yields. [d] The reaction was carried out with 1.0 mL HFIP at 60 °C in 40 minutes. [e] HFIP : TFA = 3 : 1 (v/v, 1.1 mL). [f] C2-arylation products obtained in 6% yields. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, $TsOH \cdot H_2O$ = *p*-toluenesulfonic acid monohydrate, TFA = trifluoroacetate.

The Pd(I)–Pd(II) pathway enables the rapid and mild C4-arylation and the latter Pd(II) catalysis undergoes an unprecedented domino C4-arylation/3,2-carbonyl migration of indoles, which provides a straightforward protocol for synthesis of C2/C4 disubstituted indoles.

Results and discussion

Optimization of reaction conditions

Shi[5a] and Zou[2u] reported C4/C5-arylation of a N–Bn protected indole, and C2/C4-regioselective heteroarylation of N–Me protected indoles has successfully been achieved by You's groups.[2v] Until now, direct C4-arylation of unprotected indoles has not been reported. Thus, we employed unprotected indoles as the starting material. As transient directing group strategies would enhance coordination between Pd catalysts and weak-coordinating directing groups,[6] we commenced our investigation by evaluation of several transient directing groups (TDGs) in C4-arylation of 1-(1*H*-indol-3-yl)ethan-1-one (**1a**) with methyl 4-iodobenzoate (**2a**) using $Pd(OAc)_2$ as the catalyst and AgTFA as the additive. Interestingly, both C4-arylation product **3a** and unexpected **4a** were obtained when using glycine as a transient directing group in the cosolvent of HFIP/HOAc (3/1, v/v, 1.0 mL) (Tables S1 in the ESI†). The structures of **3a** and **4a** were confirmed unambiguously by X-ray crystallography (Schemes 5 and 6, and crystallographic data in the ESI†). Extensive screening of TDGs and solvent revealed that the acid is crucial for the promotion of the reaction (Tables S1 and S2 in the ESI†). Therefore, further investigation was carried out without TDGs. Surprisingly, replacing acetic acid with $TsOH \cdot H_2O$ significantly enabled C4-arylation in a highly efficient and mild manner, providing **3a** as a sole product in 90% yield within 40 minutes (Table 1, entry 2). Notably, with trifluoroacetic acid as a co-solvent, the product **4a** was selectively obtained in 75% yield (Table 1, entry 4). Further screening of other factors didn't improve the reaction efficiency. Thus, $TsOH \cdot H_2O$ is the best acidic additive for **3a** and TFA/HFIP is an optimal cosolvent for **4a**.

Mechanism studies: tuning the catalytic mode *via* acids

To probe the role of $TsOH \cdot H_2O$ in C4-arylation, several control experiments were carried out. According to previous reports, the role of $TsOH \cdot H_2O$ in the Pd-catalyzed reactions can be categorized into two aspects: combination of $Pd(OAc)_2$ with $TsOH \cdot H_2O$ would afford either electrophilic $Pd(OTs)_2(MeCN)_2$

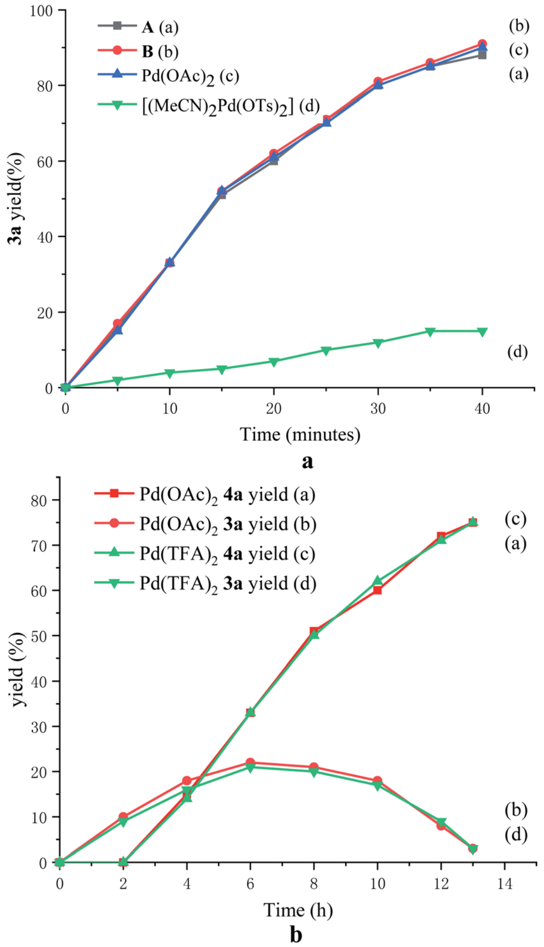


Fig. 1 (a) Time-dependent formation of **3a** using various Pd(I) and Pd(II) catalysts. (b) Time-dependent formation of **3a** and **4a** using $Pd(OAc)_2$ and $Pd(TFA)_2$ catalysts.

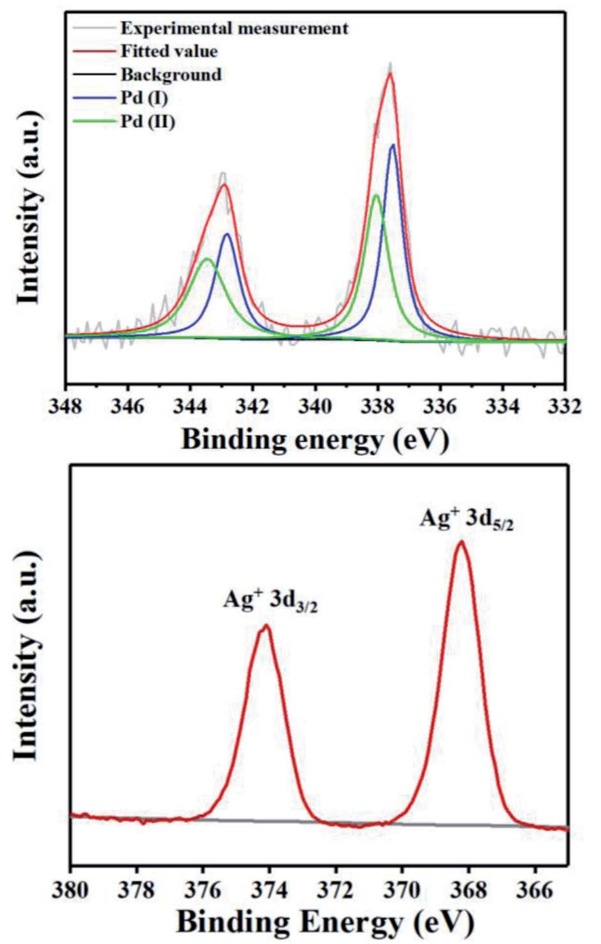
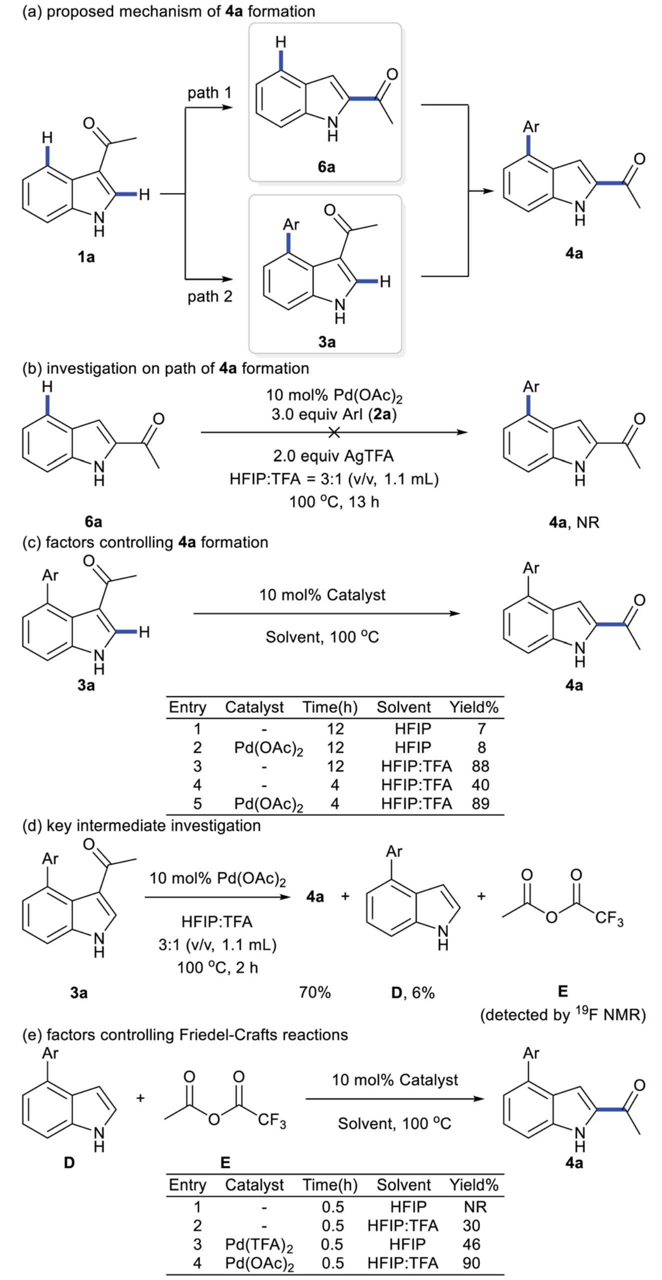


Fig. 2 The X-ray photoelectron spectroscopy (XPS) data of the reaction mixture.

(ref. 7) or complex **A**.[8] $Pd(OTs)_2(MeCN)_2$ instead of $Pd(OAc)_2$ delivered lower yields with an induction period (Table 1, entry 6 and Fig. 1a). In contrast, complex **A**[8] provided **3a** in 88% yield without the induction period (Table 1, entry 7 and Fig. 1a), suggesting that complex **A** would be a competent catalyst. As Bedford and coworkers revealed that complex **A** would be readily converted to unstable Pd(I) species **C** (see Table 1),[8] an investigation of the possible involvement of Pd(I) species in this catalysis process was carried out. A stable dinuclear Pd(I) complex **B**[9] was employed, providing 91% yield without the induction period (Table 1, entry 8 and Fig. 1a).[10] This result is in contrast to that for a previously reported DAF-Pd(I) species, which reduces the catalytic activity in allylic C–H acetoxylation of terminal alkenes and intramolecular aza-Wacker cyclization.[11] These results indicated that $TsOH\cdot H_2O$ together with $Pd(OAc)_2$ would form a reported Pd(I) catalyst **C** *in situ via* complex **A**, which is involved in the catalytic cycle. To explore Pd species in the catalytic cycle, the X-ray photoelectron spectroscopy (XPS) measurement of the reaction mixture using the $Pd(OAc)_2$/$TsOH\cdot H_2O$ system was carried out. The observed peak structures indicate the presence of two distinct oxidation states of Pd species (Fig. 2). These peaks can be attributed to Pd(I) (49.77 at%) and Pd(II) (50.23 at%) without apparent Pd(0) signals,[12] which shows that the C4-arylation reaction may proceed through a Pd(I)–Pd(II) mechanism. In the Pd(I)–Pd(II) catalytic pathway, involvement of silver salts is uncommon. Owing to the halogenophilicity of silver,[13] Ag(I) was reported to abstract halogen during a reported Pd(I)-involved cross-coupling of enamides with α-bromocarbonyls by Loh.[14] In our case, we indeed detected Ag(I) as the only silver species in XPS (Fig. 2),[15] further confirming that Ag(I) acts as a halogen abstractor for aryl iodides instead of an oxidant.[16] To our knowledge, this Pd(I)–Pd(II) catalytic pathway would be the first report of the Pd(I) involved C–H arylation process.[8,9,11,12,14,17,18]

To elucidate the pathway of domino C4-arylation/3,2-carbonyl migration of indoles, several tests were carried out. $Pd(TFA)_2$ instead of $Pd(OAc)_2$ provided **4a** in 75% yield, suggesting that $Pd(OAc)_2$ would be readily converted to $Pd(TFA)_2$ to catalyze reactions (Table 1, entry 9 and Fig. 1b). As we monitored the reaction for **4a**, **3a** was formed before the generation of **4a** and the rate for **4a** formation decreased after maximum



Entry	Catalyst	Time(h)	Solvent	Yield%
1	-	12	HFIP	7
2	$Pd(OAc)_2$	12	HFIP	8
3	-	12	HFIP:TFA	88
4	-	4	HFIP:TFA	40
5	$Pd(OAc)_2$	4	HFIP:TFA	89

Entry	Catalyst	Time(h)	Solvent	Yield%
1	-	0.5	HFIP	NR
2	-	0.5	HFIP:TFA	30
3	$Pd(TFA)_2$	0.5	HFIP	46
4	$Pd(OAc)_2$	0.5	HFIP:TFA	90

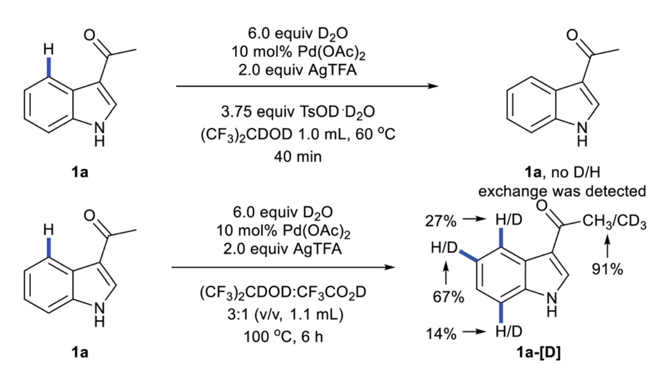
Scheme 2 Pathway of domino C4-arylation/3,2-carbonyl migration of indoles.

production of **3a** (Fig. 1b), indicating a plausible generation of **4a** from **3a** as path 2 (Scheme 2a). Furthermore, 1-(1*H*-indol-2-yl) ethan-1-one (**6a**) was subjected to the standard reaction conditions and failed to give the desired **4a** (Scheme 2b), which ruled out path 1 and suggested a domino C4-arylation/3,2-carbonyl immigration.[19]

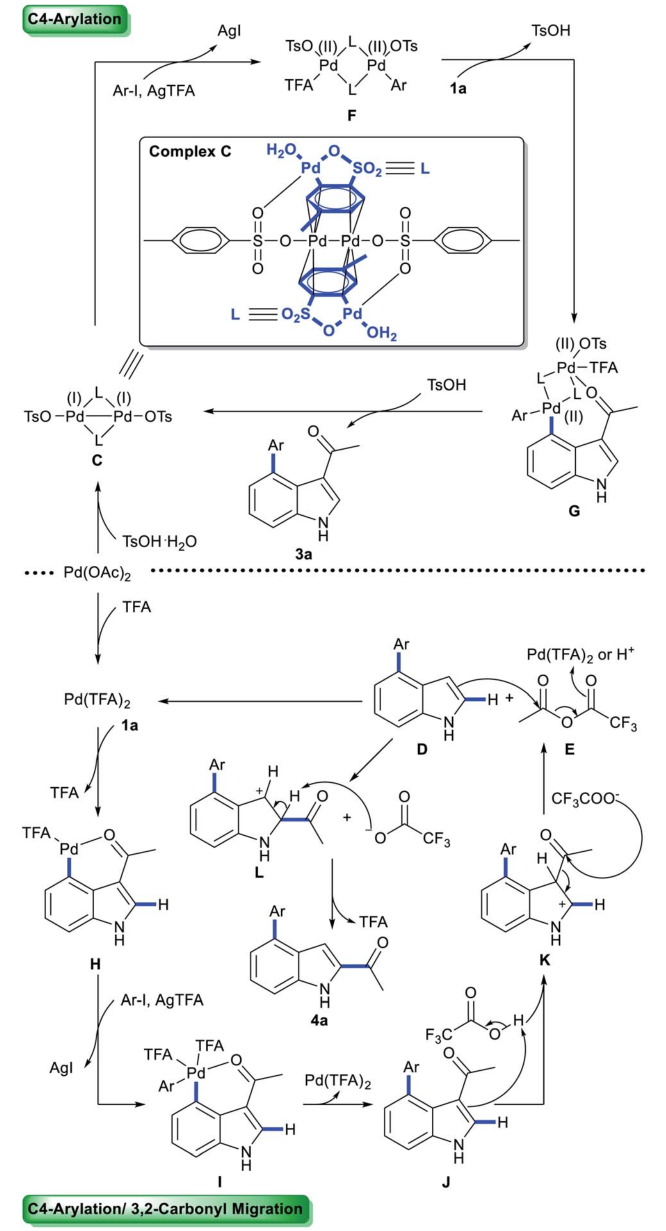
To probe the role of acid in the 3,2-carbonyl migration process, several parallel experiments were conducted (Scheme 2c). HFIP as solvent with or without $Pd(OAc)_2$ only afforded **3a** in 8% or 7% yield, respectively. Addition of TFA delivered **4a** with 40% yield in 4 h and 88% yield of **4a** was obtained by extending the reaction time to 12 h. These results indicate that TFA might be crucial to trigger this reverse Friedel–Crafts reactions *via* protonation of **3a**. Notably, a significant improvement of efficiency was achieved by using TFA and $Pd(OAc)_2$ (89% yield in 4 h), indicating that cooperation of TFA with $Pd(OAc)_2$ prompted the efficient 3,2-carbonyl migration process. Further efforts towards key intermediate trapping were carried out as well. After reacting **3a** with $Pd(OAc)_2$ in HFIP : TFA = 3 : 1 (v/v, 1.1 mL) at 100 °C for 2 h, the ^{19}F NMR spectrum indicated generation of anhydride **E** (Fig. S4 in the ESI†) and **D** was isolated with 6% yield (Scheme 2d). We hypothesized that **E** would react with **D** to afford the product **4a**. Indeed, when **D** was subjected to the reaction with **E**, migration product **4a** was obtained in 90% yield without **3a** (Scheme 2e). These outcomes suggest that reverse Friedel–Crafts reactions of species **3a** might generate intermediates **D** and **E**. Next, Friedel–Crafts reactions of **D** selectively occurred at the C2 position with **E** as an intermolecular reaction, which provided product **4a**. TFA would promote the Friedel–Crafts reaction of **D** with **E** *via* protonation of **E**, which is consistent with results from Scheme 2e: the reaction between **D** and **E** failed in the absence of TFA; addition of TFA delivered **4a** with 30% yield in 0.5 h. Furthermore, comparing the different results in Scheme 2e with or without Pd species, addition of Pd species would increase the reaction rate: a significant improvement of efficiency was achieved by using TFA and $Pd(OAc)_2$ (90% yield in 0.5 h). Thus, we proposed that either $Pd(TFA)_2$ as a Lewis acid or TFA as a Bronsted acid would activate **E** for Friedel–Crafts reaction of **D**.

When **1a** was subjected to C4-arylation conditions using 1,1,1,3,3,3-hexafluoro-2-propanol-d_2 as solvent and $TsOD \cdot D_2O$ as acid additive in the presence of D_2O, no D/H exchange was detected by NMR (Scheme 3). It implies that in the reaction (1) the C–H bond cleavage is an irreversible process and (2) Pd catalysts may undergo oxidative addition with iodobenzenes before C–H activation. In the C4-arylation/3,2-carbonyl migration reaction, D/H exchange was detected by NMR at C4 as well as Me, C5 and C7. It implies that in the domino reaction Pd catalysts may undergo oxidative addition with iodobenzenes after C–H activation.

Based on previous literature[9] and our results, we proposed two catalytic cycles for the aforementioned reactions (Scheme



Scheme 3 H/D exchange experiments.



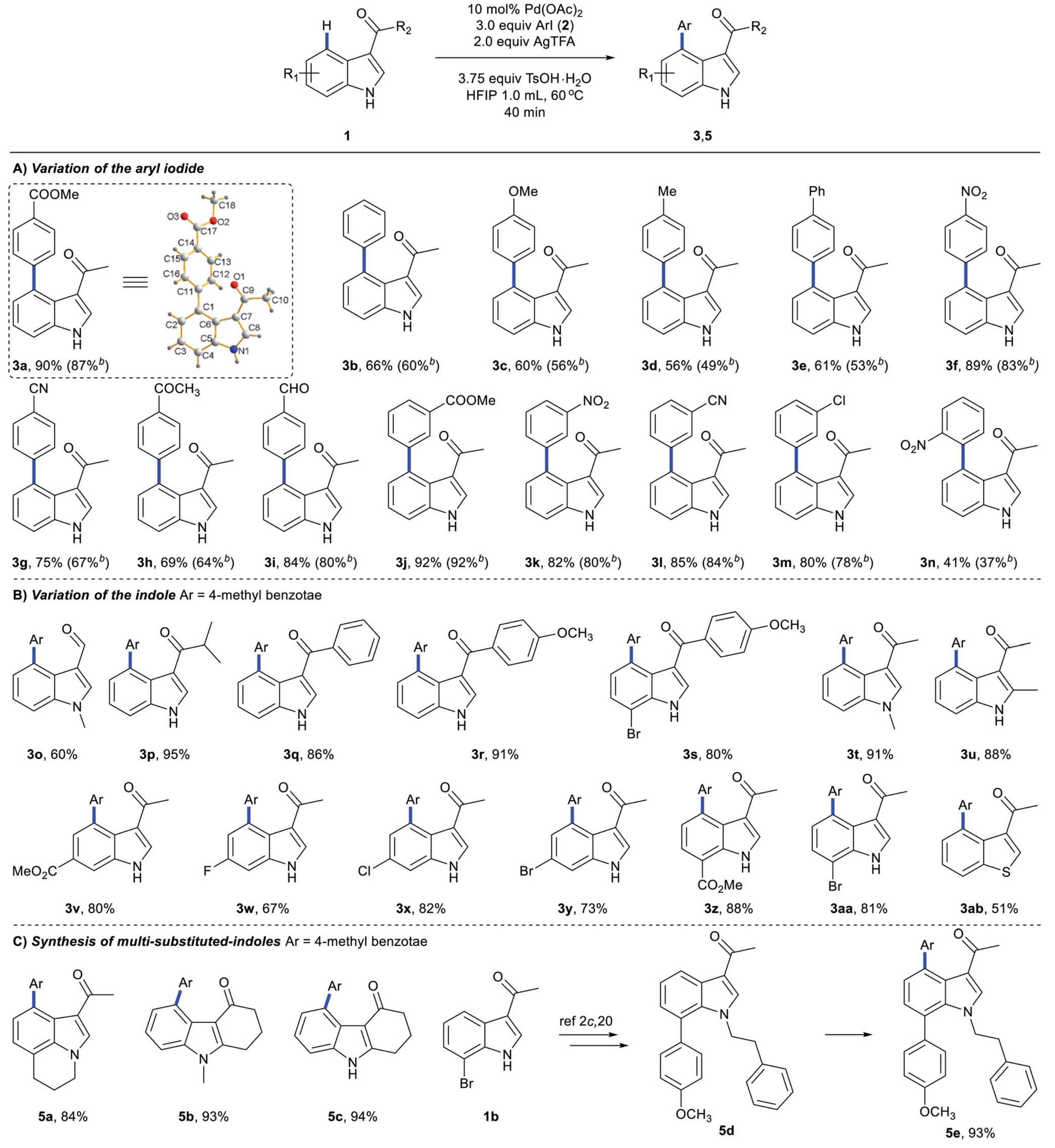
Scheme 4 Proposed mechanism.

4). In the C4-arylation catalysis cycles, $Pd(OAc)_2$ reacts with $TsOH{\cdot}H_2O$ to afford Pd(I) catalytic species **C**,[8] which then readily undergoes oxidative addition with aryl iodides to form Pd(II) species **F**. Subsequent C–H activation of **1a** with **F** affords **G**, which undergoes reductive elimination to give C4-arylation products **3a** and regenerate Pd(I) species **C**. In the domino C4-arylation and 3,2-carbonyl migration of indole catalysis cycles, $Pd(OAc)_2$ reacts with TFA to afford $Pd(TFA)_2$, which undergoes C–H activation with substrate **1a** to afford species **H**. Oxidative addition of **H** with aryl iodides forms **I**, which undergoes reductive elimination to give species **J**. Reverse Friedel–Crafts reactions of **J** begin with the protonation at the C3 positions of indoles, providing **K**. **K** reacts with CF_3COO^- to generate species **D** and **E**. Friedel–Crafts reaction of species **D** and **E** releases **L** and CF_3COO^-, and regenerates $Pd(TFA)_2$. Finally, the process of deprotonation–rearomatization of **L** affords product **4a** and TFA.

Substrate scope

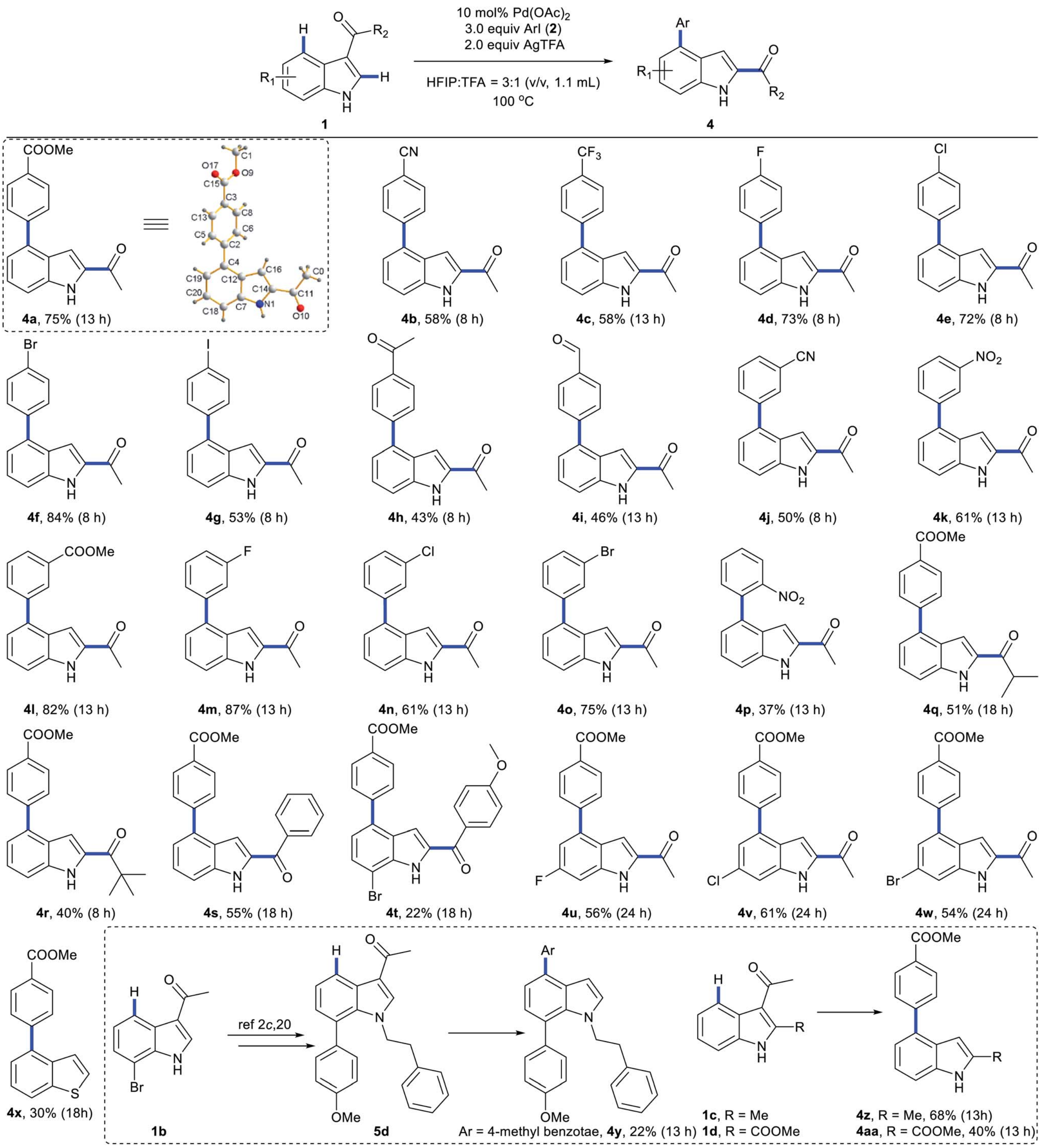
We next explored the scope of C4-arylation under the optimized conditions (Scheme 5). Arylation of indole **1a** with diverse aryl iodides was first examined. A series of aryl iodides with electron-withdrawing or electron-donating groups at the *ortho*, *meta* or *para* position successfully provided arylation products with moderate to good yields in 40 minutes (Scheme 5A). 4-Iodobenzonitrile with a labile cyano group also provided arylation products (**3g** and **3l**) successfully. Although 4-iodobenzaldehyde and 4′-iodoacetophenone were not compatible with basic coupling conditions,[5a] they afforded the products **3h** and **3i** under these optimal conditions. These C4-arylations were previously inaccessible (**3g** and **3i**). Lower aryl iodide loading (1.2 equiv.) also afforded good to excellent yields. Methyl 4-bromobenzoate provided arylation product **3a** in 12% yield as well (Table S11 in the ESI†). With iodobenzene (**2a**) as the coupling partner, diverse indole derivatives were explored (Scheme 5B). In contrast to previous reports, various carbonyl directing groups at the C3 position proved to be viable for directed arylation (**3o–3s**), which provides an alternative route for direct synthesis of 3,4-disubstituted indoles. Furthermore, reactions of indoles with methyl (**3t** and **3u**), esters (**3v** and **3z**), fluoro (**3w**), chloro (**3x**), and bromo substituents (**3y** and **3aa**) afforded the corresponding 4-aryl indoles in moderate to excellent yields. Although aza-indole derived 1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethan-1-one failed to give C4-arylation products (Table S13 in the ESI†), other heterocyclic substrates, such as 1-(benzo[*b*]thiophen-3-yl) ethan-1-one, were compatible with this reaction (**3ab**). Pleasingly, the robustness of this protocol can also be proven by application to highly functionalized indoles in 40 minutes (Scheme 5C). Tri-substituted indoles, such as a lilolidine derivative and bioactive 4-oxocarbazoles, afforded the desired product in excellent yields (**5a–5c**). Notably, this approach didn't afford arylation at the N of pyrrole, which clearly enables the rapid and modular construction of highly substituted indoles (**5e**) from simple and available indole substrates with minimal prefunctionalization.[2c,20] Further screening of the reaction scope revealed that methyl 1*H*-indole-3-carboxylate and (1*H*-indol-3-yl)(morpholino) methanone failed to give C4-arylation products (Table S13 in the ESI†).

We next investigated the scope of C4-arylation and 3,2-carbonyl migration of indole under the optimal conditions (Scheme 6). Iodoarenes containing esters (**4l**), nitriles (**4b** and **4j**), trifluoromethyl (**4c**) and nitro group (**4k** and **4p**) afforded the desired products in moderate to good yields. Notably, reactive ketone and aldehyde functionalities on the aryl iodide remained intact during the reaction (**4h** and **4i**). Aryl iodides containing fluoro, chloro, bromo and iodo substituents are also compatible in the reaction (**4d–4g** and **4m–4o**), thus



Scheme 5 C4-arylation of indoles. [a]Reaction conditions: **1** (0.2 mmol), **2** (3.0 equiv.), AgTFA (2.0 equiv.), $Pd(OAc)_2$ (10 mol%), $TsOH\cdot H_2O$ (3.75 equiv.), HFIP (1.0 mL), 60 °C, 40 minutes. [b]**2** (1.2 equiv.), 90 minutes. [c]Isolated yields.

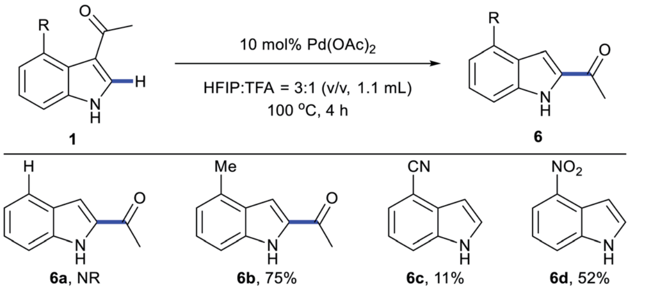
highlighting the potential of this process in combination with further conventional cross-coupling transformations. Besides, various carbonyl directing groups were tolerated well and gave 2,4-disubstituted indole products (**4q–4t**). Indoles containing halide substituents were compatible providing the corresponding products (**4u–4w**) in moderate to good yields. Notably, this approach enables one-pot C4-arylation and directing group removal when a thiophene derivative was employed as a substrate (**4x**). When trisubstituted indole **5d** was subjected to these domino conditions, a similar directing-group-removal product **4y** was obtained, which might be attributed to the bulkiness of the *N*-protecting group. C2-substituted indoles also provided **4z** and **4aa** with directing group removal from their 3-carbonyl indole derivatives with generation of intermediate **E**.



Scheme 6 C4-arylation and 3,2-carbonyl migration of indoles. [a]Reaction conditions: **1** (0.2 mmol), **2** (3.0 equiv.), AgTFA (2.0 equiv.), $Pd(OAc)_2$ (10 mol%), HFIP : TFA = 3 : 1 (v/v, 1.1 mL), 100 °C. [b]Isolated yields.

Given that 2,4-disubstituted indoles are important structural units in biologically active molecules and drugs,[21] this approach would provide an alternative pathway for facile construction of diverse bioactive indole building blocks. Further exploring the reaction scope revealed that 1*H*-indole-3-carbaldehyde, methyl 1*H*-indole-3-carboxylate and (1*H*-indol-3-yl)(morpholino) methanone failed to give C4-arylation/3,2-carbonyl migration products (Table S14 in the ESI†).

We next examined the scope of 3,2-carbonyl migration of C3/C4-disubstituted indoles (Scheme 7). **1a** without C4-substituents failed to react under migration conditions. A 4-methyl indole derivative incorporating C4 electron-donating substituents was compatible in these conditions, providing



Scheme 7 Substrate scope with C3/C4-disubstituted indoles. [a]Standard conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), HFIP : TFA = 3 : 1 (v/v, 1.1 mL), 100 °C, 4 h. [b]Isolated yields.

migration product **6b** in 75% yield. In contrast, indoles bearing electron-withdrawing substituents (CN and NO_2) at the C4 positions afforded **6c** and **6d** with directing group removal.

Conclusions

In summary, we have developed the C4-arylation and domino C4-arylation/3,2-carbonyl migration of indoles. The former route enables C4-arylation in a highly efficient and mild manner employing $TsOH \cdot H_2O$ as acid additive and the latter route provides an alternative straightforward protocol for synthesis of C2/C4 disubstituted indoles. The different reaction pathways were tuned by the distinct acid additives, which led to either the Pd(I)–Pd(II) pathway or Pd(II) catalysis. Given the importance of 3,4- and 2,4-disubstituted indoles in materials science and active pharmaceutical ingredients, it is expected that the reactions will have wide application in organic chemistry, chemical materials and pharmaceutical research.

Author contributions

Y. H. C., S. J. Y. and Y. H. H. conducted all the experimental work. Y. H. C. and G. H. A. collected and analyzed the data. Y. H. C., G. H. A., G. M. L. and Z. Y. Y. wrote the paper. G. H. A., G. M. L. and Z. Y. Y. proposed and supervised the project. All the authors discussed the results and commented on the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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