Synthetic Methods

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# Stereoselective Palladium-Catalyzed Carboaminoxylations of Indoles with Arylboronic Acids and TEMPO**

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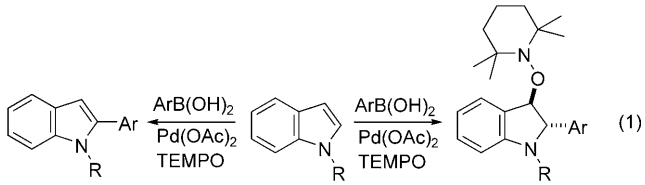
Indoles and their derivatives belong to an important substance class which is often found in natural products and in many pharmaceuticals.[1] Great efforts have recently been devoted to transition-metal-catalyzed chemical modifications of indoles, in particular direct C(2)–H or C(3)–H arylations. Palladium has been heavily used in that regard.[2–7] Herein we present our first results on direct C–H arylations of indoles with arylboronic acids and the 2,2,6,6-tetramethylpiperidine *N*-oxyl radical (TEMPO)[8] as an external mild oxidant (→ **1a–f**) [Eq. (1)]. More importantly, we will show that upon installing a protecting group (PG) on the indole nitrogen atom, the reaction outcome changes and the product formed is that of a highly stereoselective oxidative arylcarboaminoxylation[9] reaction (→**2a–c**). To our knowledge metal-catalyzed arylation of indoles by oxidatively intercepting putative cationic intermediates is unknown.[10]




(1)

We have recently shown that TEMPO can be used as an external oxidant in palladium-catalyzed direct C–H arylations of arenes by using arylboronic acids as aryl sources.[11] We decided to further extend that chemistry to indoles. Pleasingly, we found that indole underwent direct C(2) arylation with phenylboronic acid in the presence of $Pd(OAc)_2$ (10 mol%), KF (4 equiv), and TEMPO (4 equiv) in propionic acid under very mild conditions (room temperature, 1 h) in 81% yield (Table 1, entry 1). As a side product, 3-phenylindole was formed in 10% yield. Surprisingly, in acetic acid only traces of **1a** were formed (thin-layer chromatography (TLC), Table 1; entry 2). The same reaction in butyric acid afforded **1a** in 64% yield (Table 1; entry 3). $Pd(O_2CCF_3)_2$ and $[Pd(acac)_2]$ (acac = acetylacetonate) turned out to be slightly less efficient precatalysts (Table 1; entries 4, 5). The aryl group could readily be varied upon changing the arylboronic acid component (Table 1; entries 6–9). For all acids tested, the 3-arylated indole was formed as a side product. Note that many arylboronic acids are commercially available. Moreover, N-alkyl groups were tolerated as shown for the transformation of *N*-methylindole to 1-methyl-2-phenylindole (**1f**; 68%, Table 1; entry 10).

***Table 1:*** Direct arylation of indole (R = H) with various arylboronic acids [see Eq. (1)].[a]

| Entry | Solvent | Catalyst[b] | Ar | Product | Yield [%][c] |
|---|---|---|---|---|---|
| 1 | $EtCO_2H$ | $Pd(OAc)_2$ | $C_6H_5$ | **1a** | 81 (10) |
| 2 | $MeCO_2H$ | $Pd(OAc)_2$ | $C_6H_5$ | **1a** | < 2 (n.d.) |
| 3 | $nPrCO_2H$ | $Pd(OAc)_2$ | $C_6H_5$ | **1a** | 64 (n.d.) |
| 4 | $EtCO_2H$ | $Pd(O_2CCF_3)_2$ | $C_6H_5$ | **1a** | 75 (n.d.) |
| 5 | $EtCO_2H$ | $[Pd(acac)_2]$ | $C_6H_5$ | **1a** | 62 (n.d.) |
| 6 | $EtCO_2H$ | $Pd(OAc)_2$ | 4-$CH_3C_6H_4$ | **1b** | 73 (10) |
| 7 | $EtCO_2H$ | $Pd(OAc)_2$ | 4-$FC_6H_4$ | **1c** | 78 (9) |
| 8 | $EtCO_2H$ | $Pd(OAc)_2$ | 3-$CH_3C_6H_4$ | **1d** | 71 (10) |
| 9 | $EtCO_2H$ | $Pd(OAc)_2$ | 3-$ClC_6H_4$ | **1e** | 67 (2) |
| 10[d] | $EtCO_2H$ | $Pd(OAc)_2$ | $C_6H_5$ | **1f**[e] | 68 (9) |

[a] Conditions: $ArB(OH)_2$ (4 equiv), TEMPO (4 equiv), KF (4 equiv) in RCOOH at room temperature for 1 h (n.d. = not determined). [b] 10 mol%. [c] In parenthesis yield of the isolated 3-arylated indole. [d] With *N*-methylindole. [e] 1-Methyl-2-phenyl-1*H*-indole (R = Me).

We next tested N-acylated and N-carbamoylated indoles in the direct C–H arylation reaction. Surprisingly, treatment of *N*-acetylindole in acetic acid with phenylboronic acid, KF, and TEMPO in the presence of $Pd(OAc)_2$ (10 mol%) at room temperature for 1 h afforded the arylcarboaminoxylation product **2a** (Ar = Ph) in a moderate yield (55%, Table 2, entry 1). Importantly, **2a** was formed highly diastereoselectively (d.r. > 99:1; HPLC analysis). The relative *trans*-configuration was unambiguously assigned by single-crystal X-ray analysis (Figure 1).[12] In $CF_3CO_2H$, under otherwise identical conditions, **2a** was not formed (Table 2; entry 2). An improved yield was observed upon switching to propionic acid as the solvent (85%, Table 2; entry 3). Butyric acid and valeric acid provided lower yields (Table 2; entries 4, 5). Worse results were achieved in non-acidic solvents such as dichloromethane or dichloroethane (Table 2; entries 6, 7). As for the direct C–H arylation discussed above, $Pd(O_2CCF_3)_2$ and $[Pd(acac)_2]$ turned out to be slightly less efficient precatalysts (Table 2; entries 8, 9). Reducing catalyst loading to 5 mol% did not affect the yield to a great extent (Table 2; entry 10). However, with 2 mol% $Pd(OAc)_2$ the yield dropped significantly (Table 2; entry 11). Reducing the amount of

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TEMPO = 2,2,6,6-tetramethylpiperidine *N*-oxyl radical.

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***Table 2:*** Arylcarboaminoxylation of indoles (Ar = Ph) [see Eq. (1)].[a]

| Entry | Solvent | Catalyst | PG | Product | Yield [%] |
|---|---|---|---|---|---|
| 1 | $MeCO_2H$ | $Pd(OAc)_2$ | Ac | **2a** | 55 |
| 2 | $CF_3CO_2H$ | $Pd(OAc)_2$ | Ac | **2a** | – |
| 3 | $EtCO_2H$ | $Pd(OAc)_2$ | Ac | **2a** | 85 |
| 4 | $nPrCO_2H$ | $Pd(OAc)_2$ | Ac | **2a** | 72 |
| 5 | $nBuCO_2H$ | $Pd(OAc)_2$ | Ac | **2a** | 41 |
| 6 | $CH_2Cl_2$ | $Pd(OAc)_2$ | Ac | **2a** | 20 |
| 7 | $ClCH_2CH_2Cl$ | $Pd(OAc)_2$ | Ac | **2a** | 18 |
| 8 | $EtCO_2H$ | $Pd(O_2CCF_3)_2$ | Ac | **2a** | 76 |
| 9 | $EtCO_2H$ | $[Pd(acac)_2]$ | Ac | **2a** | 73 |
| 10[c] | $EtCO_2H$ | $Pd(OAc)_2$ | Ac | **2a** | 83 |
| 11[d] | $EtCO_2H$ | $Pd(OAc)_2$ | Ac | **2a** | 61 |
| 12[e] | $EtCO_2H$ | $Pd(OAc)_2$ | Ac | **2a** | 52 |
| 13[f] | $EtCO_2H$ | $Pd(OAc)_2$ | Ac | **2a** | 61 |
| 14 | $EtCO_2H$ | $Pd(OAc)_2$ | Bz | **2b** | 91 |
| 15 | $EtCO_2H$ | $Pd(OAc)_2$ | Boc | **2c** | 82 |

[a] Conditions: $PhB(OH)_2$ (4 equiv), TEMPO (4 equiv) and KF (4 equiv) at room temperature for 1 h. [b] 10 mol%. [c] With 5 mol% $Pd(OAc)_2$. [d] With 2 mol% $Pd(OAc)_2$. [e] With 1 equivalent $PhB(OH)_2$ and 1 equivalent KF. [f] With 2 equivalents TEMPO.

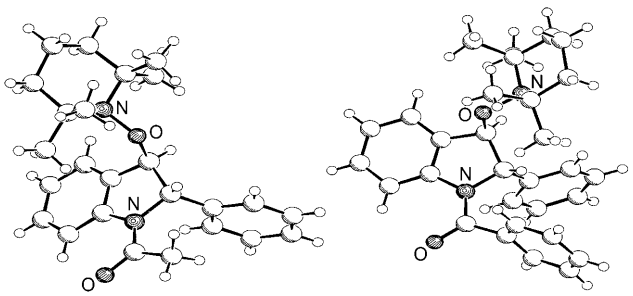
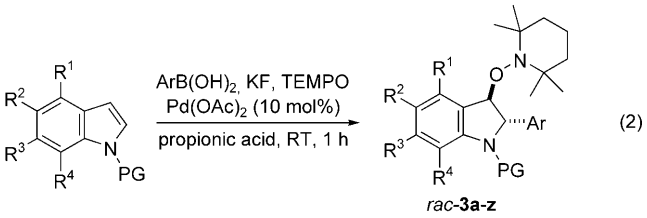


***Figure 1.*** Molecular structure of **2a** (left) and **2b** (right).

$PhB(OH)_2$ (Table 2; entry 12) or TEMPO (Table 2; entry 13) led to lower yields.

The N-protecting group was varied next. Indole with a benzoyl (Bz) protecting group afforded the highest yield (→ **2b**, Ar = Ph, 91%, Table 2; entry 14) and a good yield was also achieved with the *tert*-butoxycarbonyl (Boc) protected indole (→ **2c**, Ar = Ph, 82%, Table 2; entry 15). In both reactions only the *trans*-isomer was formed (HPLC analysis). For **2b** the *trans* configuration was assigned by single-crystal X-ray analysis (see Figure 1) and for **2c** the relative configuration was assigned in analogy to **2a** and **2b**. Biphenyl deriving from oxidative homocoupling of phenylboronic acid was always formed as side product in these arylcarboaminoxylations.[13]

Under optimized conditions various protected indoles were arylcarboaminoxylated with different arylboronic acids [Eq. (2)]. All the reactions conducted delivered only one diastereoisomer (HPLC analysis). The relative *trans* configuration was assigned in analogy to **2a**,**b**. *para*-Substituted arylboronic acids bearing electron-donating or -withdrawing groups afforded the carboaminoxylation product in a good yield (Table 3). This is true for N-acetylated (Table 3; entries 1–3), N-benzoylated (Table 3; entries 5–7), and N-Boc-protected indoles (Table 3; entries 9–11). Similar results were achieved with *meta*-substituted arylboronic acids (Table 3; entries 8, 12, 13). However, with *ortho*-methylphenylboronic acid significantly lower yields were obtained, probably for steric reasons (Table 3; entries 4, 14). Note that arylbromides, which can readily be further manipulated by using transition-metal-based methods, were tolerated under the reaction conditions.




(2)

***Table 3:*** Arylcarboaminoxylation of N-protected indoles with various arylboronic acids.[a]

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Ar | PG | | Yield [%] |
|---|---|---|---|---|---|---|---|---|
| 1 | H | H | H | H | $4\text{-}CH_3C_6H_4$ | Ac | **3a** | 73 |
| 2 | H | H | H | H | $4\text{-}CH_3OC_6H_4$ | Ac | **3b** | 59 |
| 3 | H | H | H | H | $4\text{-}FC_6H_4$ | Ac | **3c** | 80 |
| 4 | H | H | H | H | $2\text{-}CH_3C_6H_4$ | Ac | **3d** | 35 |
| 5 | H | H | H | H | $4\text{-}CH_3C_6H_4$ | Bz | **3e** | 69 |
| 6 | H | H | H | H | $4\text{-}FC_6H_4$ | Bz | **3f** | 91 |
| 7 | H | H | H | H | $4\text{-}BrC_6H_4$ | Bz | **3g** | 52 |
| 8 | H | H | H | H | $3\text{-}CH_3C_6H_4$ | Bz | **3h** | 76 |
| 9 | H | H | H | H | $4\text{-}CH_3C_6H_4$ | Boc | **3i** | 80 |
| 10 | H | H | H | H | $4\text{-}BrC_6H_4$ | Boc | **3j** | 72 |
| 11 | H | H | H | H | $4\text{-}FC_6H_4$ | Boc | **3k** | 78 |
| 12 | H | H | H | H | $3\text{-}CH_3C_6H_4$ | Boc | **3l** | 79 |
| 13 | H | H | H | H | $3\text{-}ClC_6H_4$ | Boc | **3m** | 77 |
| 14 | H | H | H | H | $2\text{-}CH_3C_6H_4$ | Boc | **3n** | 31 |
| 15 | H | Me | H | H | $C_6H_5$ | Ac | **3o** | 78 |
| 16 | H | Br | H | H | $C_6H_5$ | Ac | **3p** | 68 |
| 17 | H | H | Cl | H | $C_6H_5$ | Ac | **3q** | 48 |
| 18 | H | Me | H | H | $C_6H_5$ | Bz | **3r** | 91 |
| 19 | H | $CH_3$ | H | H | $C_6H_5$ | Boc | **3s** | 97 |
| 20 | H | OMe | H | H | $C_6H_5$ | Boc | **3t** | 99 |
| 21 | H | Br | H | H | $C_6H_5$ | Boc | **3u** | 85 |
| 22 | H | H | Cl | H | $C_6H_5$ | Boc | **3v** | 92 |
| 23 | H | H | $CO_2Me$ | H | $C_6H_5$ | Boc | **3w** | 99 |
| 24 | OMe | H | H | H | $C_6H_5$ | Boc | **3x** | 96 |
| 25 | H | H | H | Me | $C_6H_5$ | Boc | **3y** | 94 |
| 26 | H | H | H | Cl | $C_6H_5$ | Boc | **3z** | 93 |

[a] Conditions: $ArB(OH)_2$ (4 equiv), TEMPO (4 equiv), KF (4 equiv), and $Pd(OAc)_2$ (10 mol%) in propionic acid at room temperature for 1 h.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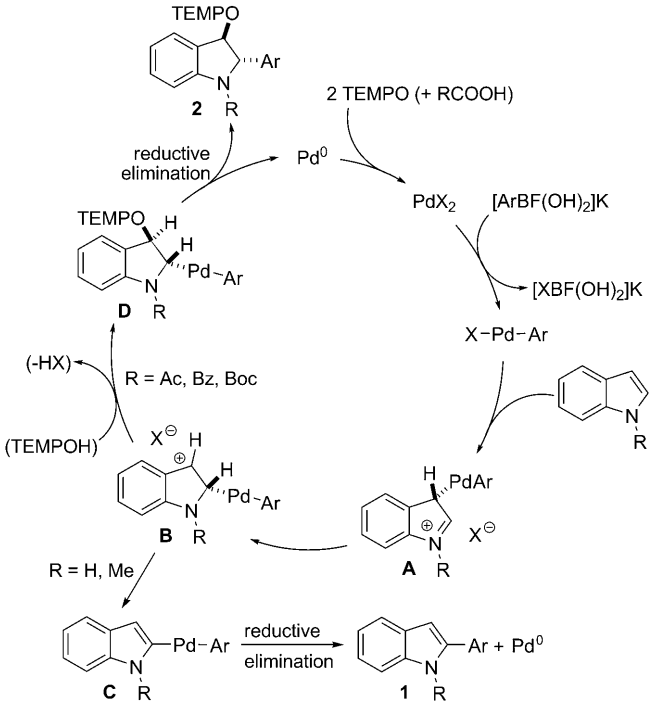
To further study scope and limitations, various N-protected substituted indole derivatives were treated with phenylboronic acid under optimized conditions. Electron-donating and also electron-withdrawing substituents were tolerated in positions 4–7 of the indole core (Table 3; entries 15–26) and good to excellent yields were achieved (48–99%). For substituted indoles, systems bearing the Boc group afforded the highest yields (85–99%, Table 3; entries 19–26). We could further show that for Boc-protected 6-(methoxycarbonyl)indole, for which **3w** was obtained in a quantitative yield under standard conditions (see Table 3; entry 23), the arylcarboaminoxylation could be conducted in good yield (90%) by using only 5 mol% $Pd(OAc)_2$ with 1.5 equivalents of $PhB(OH)_2$, 1.5 equivalents KF, and 3 equivalents TEMPO.

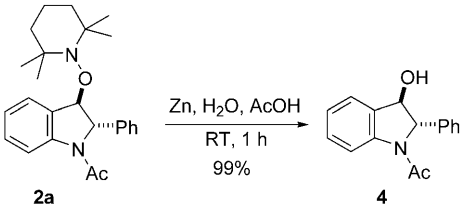
We suggest the following mechanism to explain the observed chemodivergent reaction outcome (Scheme 1).




***Scheme 1.*** Suggested mechanism for the chemodivergent reactions.

Transmetalation from boron to palladium by reaction of $PdX_2$ with $[ArBF(OH)_2]K$ provides an X-Pd-Ar species which adds at the 3-position of the indole to give intermediate **A**, as previously suggested.[3b,4b,6c,7a] 1,2-Metal migration generates intermediate **B**. It has been found that in similar systems under acidic conditions deprotonation of **A** is slower than 1,2-metal migration.[7a] For the free indole or the *N*-methylindole-derived intermediate **B**, deprotonation leads to **C** which upon reductive elimination eventually affords **1** and $Pd^0$. The counteranion $X^-$ acting as a base can either be $EtCO_2^-$ or $TEMPO^-$. For R = Ac, Bz, or Boc intermediate **B** might be stabilized via C=O–Pd interaction. Deprotonation is slowed down and a highly diastereoselective *trans*-trapping of **B** with $X^-$ afforded **D**. Reductive elimination finally gives **2** and $Pd^0$. Since no palladium black was observed during the reaction we believe that TEMPO or TEMPOH helps to stabilize the $Pd^0$ species. Oxidation of $Pd^0$ with 2 equivalents of TEMPO eventually regenerates the $Pd^{II}$ salt. We exclude Heck-type addition of TEMPO-Pd-aryl to indole followed by oxidation to the corresponding $Pd^{IV}$ species and subsequent reductive elimination since TEMPO and the aryl group would have to be *syn*-oriented. Moreover, possible reaction through coordination of the X-Pd-Ar intermediate to the protected indole followed by *anti*-oxypalladation to generate directly intermediate **D** is unlikely, because the polarization of the indole alkene moiety and the electrophilic nature of the X-Pd-Ar species should lead to the opposite regioisomer.

The TEMPO substituent, which is biologically probably not so relevant, can be regarded as a protected hydroxy group. Hence, treatment of **2a** with Zn in $H_2O$/AcOH (3:1) at room temperature for 1 h afforded the 3-hydroxydehydroindole **4** stereospecifically in a quantitative yield [Eq. (3)].[14]




(3)

In conclusion, we presented palladium-catalyzed chemodivergent chemical modifications of various indoles with commercially available arylboronic acids and TEMPO as a commercially available mild oxidant. Depending on the substituent on the indole N atom, either direct C(2) arylation (R = H, Me) or a highly diastereoselective arylcarboaminoxylation (R = Ac, Bz, Boc) occurs. To our knowledge the latter process is unprecedented and delivers biologically interesting structures. Importantly, the reactions occurred under mild conditions (room temperature) in a short time (1 h).

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**Keywords:** C–H activation · chemodivergent reactions · homogeneous catalysis · asymmetric synthesis · transition metals

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