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Elements of Regiocontrol in the Direct Heteroarylation of Indoles/Pyrroles: Synthesis of Bi- and Fused Polycyclic Heteroarenes by Twofold or Tandem Fourfold C–H Activation

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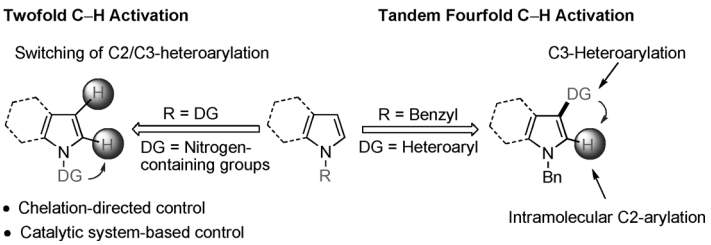
The transition-metal-catalyzed dehydrogenative cross-coupling between two heteroarenes by oxidizing two carbon–hydrogen bonds has emerged as a promising strategy for biheteroaryl formation.[1] This process can avoid the tedious and costly prefunctionalization of substrates that is usually required in C–X/C–M or C–H/C–X coupling reactions. Considering that some significant heterocyclic halides and metallics are difficult to prepare and may be inadequately stable to participate in the coupling reactions, this strategy is even more attractive for the synthesis of biheteroaryl molecules that cannot be achieved by traditional coupling methods. One fundamental challenge in this field is the control of regioselectivity when heteroarene substrates contain multiple reactive C–H bonds. Compared with the cross-coupling of arenes/arenes[2] and arenes/heteroarenes,[3] the dehydrogenative cross-coupling between two heteroarenes is surprisingly under-represented, probably owing to the tendency for homocoupling of heteroarenes and the extra binding of multiple nitrogen atoms to the metal complex. The regiocontrol of the coupling is still in its infancy despite a vital structural feature of biheteroaryl molecules in pharmaceuticals, materials, and natural products.[4] In these limited examples, the reactions generally occur preferentially at the more reactive C–H bonds that are attributed to inherent electronic bias, such as the C3–H of indoles, pyrroles,[4b–e] and indolizine,[4a] and the C2–H of thiophenes, furans,[4a] azoles,[4f,g] and *N*-heteroarene *N*-oxides.[4a–e] Undoubtedly, it is highly desirable to develop powerful strategies to overcome the natural selectivity of heteroarenes and achieve regioselectivity switching.

The C2-heteroarylated indole and pyrrole derivatives, such as (*S*)-nicotine, sempervirine, phorbazole C, granulatimide, and pamicogrel, are among the most important biheteroaryl structural motifs.[5] Although the C2–H arylation of indoles and pyrroles has been well-established in the literature,[6] the C2–H heteroarylation of such molecules still remains challenging, probably owing to the general reluctance of heteroaryl halides to undergo coupling reactions.[7] Therefore, it should be an ideal strategy to solve the problem by dehydrogenative coupling of two heteroarenes. Recently, we and others reported the palladium-catalyzed oxidative C–H/C–H cross-coupling of indoles and pyrroles with various types of heteroarenes (e.g., azoles, indolizines, and pyridine *N*-oxides) at the C3 site.[4b–e] Following our continuing efforts to functionalize indoles/pyrroles, we herein gain switching of the C2/C3 selectivity by the use of two different strategies (Scheme 1). Strategy 1 introduces a coordinating functional group to the nitrogen atom of indoles and pyrroles to lead to C–H activation of the proximal site (C2 site), thus suppressing the naturally preferential C3 selectivity. Strategy 2 is dependent on Pd catalytic systems to regulate the C2/C3 selectivity in C–H functionalizations.



Scheme 1. Strategies for the regiocontrol in the oxidative C–H/C–H couplings of indoles/pyrroles.

These strategies that involve chelation-directed and catalytic-system-based control effectively promote the C2/C3 heteroarylation of indoles and pyrroles with *N*-heteroarene *N*-oxides, xanthines, and indazoles to form biheteroarenes and are further extended to the synthesis of complex fused tri- and tetracyclic heteroarenes by a tandem fourfold C–H activation that involves C3 heteroarylation of indoles/pyrroles and subsequent C3-heteroaryl-directed intramolecular C2 arylation of indoles/pyrroles. During preparation of this manuscript, Miura et al. reported the copper-catalyzed or

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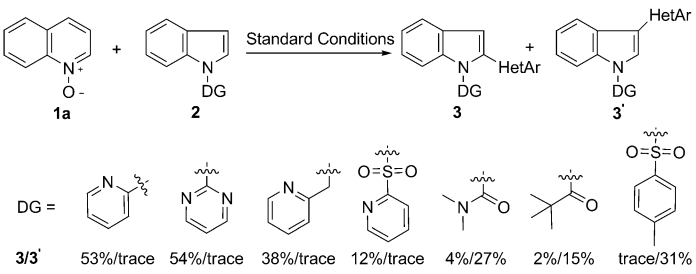
-mediated oxidative C2 heteroarylation of indoles/pyrroles with 5-aryloxazoles and benzoxazoles. Meanwhile, the authors demonstrated that this method was not amenable to other electron-deficient heteroarenes, such as pyridine *N*-oxide.[8] Thus, these two methodologies are complementary to each other.

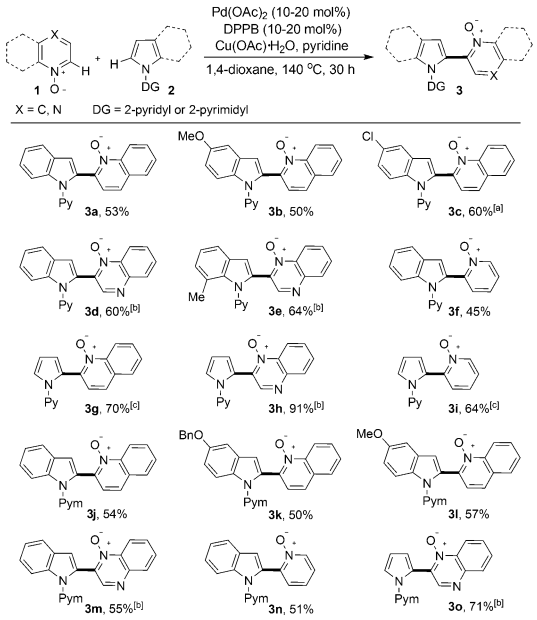
Pyridines and related azine derivatives, such as quinolines and quinoxalines, are important types of heteroarenes, and their corresponding *N*-oxides are also vital intermediates to obtain functionality at neighbouring positions to the nitrogen atom, and they can be deoxygenated to afford free azines.[9] Thus, our investigation started with the dehydrogenative cross-coupling of indoles with quinoline *N*-oxide (**1a**). Chelation-assisted C–H bond activation by using the electrophilic nature of the palladium(II) center constitutes one of the most common strategies towards the *ortho*-C–H functionalization of arenes. However, this strategy is relatively rarely used in the C–H functionalization of heteroarenes. We envisioned that the C2-selective heteroarylation of indoles and pyrroles could be achieved by tethering a suitable directing group at the nitrogen atom (Scheme 1). Considering that the pyridyl group is a widely used directing group for molecular design,[10] 1-(pyridin-2-yl)-1*H*-indole (**2a**) was first employed to optimize the reaction conditions (Table S1 in the Supporting Information). It was anticipated that solvents, ligands, oxidants, and additives would significantly influence the reactivity and selectivity. After screening various conditions, the heterocoupling product **3a** was obtained in 53% yield when $Pd(OAc)_2$ (20 mol%) and 1,4-bis(diphenylphosphino)butane (DPPB) (20 mol%) were used in combination with $Cu(OAc)_2{\cdot}H_2O$ (3.0 equiv) as the oxidant and pyridine (2.0 equiv) as an additive in 1,4-dioxane at 140°C for 30 h. It was suspected that DPPB, which was oxidized to the phosphine oxide under the above conditions,[11] served as a ligand to maintain the high reactivity of the $Pd(OAc)_2$ catalyst. Pyridine might work to stabilize the palladium intermediate and prevent the formation of Pd black.[3a] Notably, the cross-coupling occurred almost exclusively at the indole C2 position. On the other hand, the homocoupling of **2a** and **1a** could also be effectively overcome and gave only 3 and 8% homocoupling yields, respectively.

We next examined a set of potential directing groups under the standard conditions (Scheme 2). Besides 2-pyridyl, the 2-pyrimidyl group was also proven to be a good directing group to afford the desired coupling product in 54% yield, and only trace amounts of the C3 product were detected, along with very small amounts of the homocoupling products. The unsatisfactory directing ability of a one-atom longer group (2-pyridylmethyl and 2-pyridylsulfonyl) on the reaction indicated that a five-membered palladacycle might be involved as an intermediate in the catalytic cycle.

The scope of this methodology with respect to indoles/pyrroles and *N*-heteroarene *N*-oxides was next investigated, and the results are summarized in Scheme 3. To our delight, a variety of substituents on the indole scaffold, such as alkyl, chloride, methoxy, and benzyloxy groups, were well tolerated under the standard conditions. The electron-deficient *N*-heteroarene *N*-oxides, such as pyridine *N*-oxide, quinoline *N*-oxide, and quinoxaline *N*-oxide, all smoothly underwent the dehydrogenative coupling with the 2-pyridyl or 2-pyrimidyl-protected indoles to afford the desired 2-heteroarylated products in acceptable yields. The pyrimidyl group showed a similar reactivity to the pyridyl group in directing this type of coupling reaction. Compared with indoles, the pyrrole derivatives are generally more sensitive to homocoupling and decomposition under oxidative conditions. However, it was interesting to observe that pyrroles could also be involved in the C–H/C–H cross-couplings with *N*-heteroarene *N*-oxides and afforded the desired products in satisfying yields. It should be noted that in all cases indoles/pyrroles



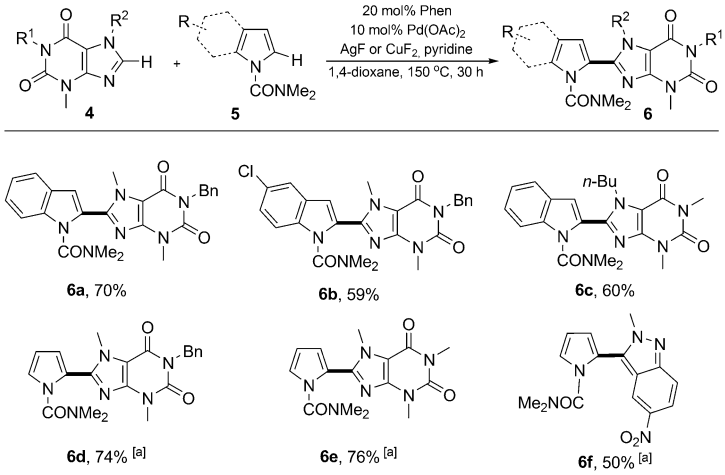
Scheme 2. The effect of different directing groups on the dehydrogenative cross-coupling of *N*-protected indole **2** with quinoline *N*-oxide (**1a**). Standard conditions: indole **2** (0.5 mmol), **1a** (2.0 mmol), $Pd(OAc)_2$ (20 mol%), DPPB (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (1.5 mmol), and pyridine (1.0 mmol) in 1,4-dioxane at 140°C for 30 h under a N_2 atmosphere.



Scheme 3. Highly selective oxidative cross-coupling of indoles/pyrroles with *N*-heteroarene *N*-oxides. Reaction conditions: indole/pyrrole **2** (0.5 mmol), *N*-heteroarene *N*-oxide **1** (2.0 mmol), $Pd(OAc)_2$ (10–20 mol%), DPPB (10–20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (1.5 mmol), and pyridine (1.0 mmol) in 1,4-dioxane at 140°C for 30 h under a N_2 atmosphere. [a] Reaction temperature was 150°C. [b] Reaction temperature was 130°C. [c] 1,4-Dioxane/DMSO (14:1) was used as the solvent. DMSO = dimethyl sulfoxide, Py = 2-pyridyl, Pym = 2-pyrimidyl.

almost exclusively underwent the direct C–H heteroarylation at the C2 position. The structure of **3f** was confirmed by an X-ray analysis of single crystals (Figure S2 in the Supporting Information).[12]

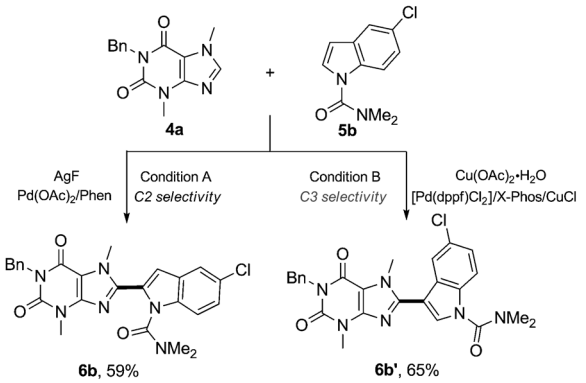
Xanthines, such as caffeine, theophylline and theobromine, are an important type of biologically active alkaloids. However, extending the above-mentioned oxidative reaction to xanthines has proven to be a challenging proposition. In fact, the dehydrogenative coupling of benzylic theobromine **4a** with 1-(pyridin-2-yl)-1*H*-indole (**2a**) only afforded the desired product in 21% yield under the standard conditions. We rationalized that the low reactivity might be attributed to extra binding of multiple nitrogen atoms and oxygen atoms in xanthines to the metal complex, which led to metal sequestration and deactivation. After extensive efforts, we found that the C2/C3 selectivity of heteroarylation of indoles/pyrroles with xanthines could be regulated through the use of different directing groups, oxidants, and ligands (Table S2 in the Supporting Information). The *N*,*N*-dimethylcarbamoyl group was proven to be the best among the directing groups investigated (e.g., *N*,*N*-dimethylcarbamoyl, acetyl, 2-pyridyl, and 2-pyrimidyl). Interestingly, the oxidant containing the F^- counterion was crucial for achieving the regioselectivity switch in this type of cross-coupling reactions. For example, changing the oxidant from Ag_2CO_3 to AgF resulted in a dramatic reversal in the regioselectivity from a 1:7 C2/C3 ratio of 1:7 (in 40% total yield) to a C2/C3 ratio of 1.5:1 (in 85% total yield) under otherwise identical conditions (Table S2, entries 4 and 5). We assumed that the presence of the F^- anion might facilitate the formation of monomeric Pd species rather than trinuclear Pd carboxylate clusters, which favored the C2 site selectivity.[3b,e,4f] Further addition of 1,10-phenanthroline (Phen) to the catalytic system greatly improved the C2/C3 ratio to 4.1:1, and the C2-heteroarylated product was obtained in 70% yield (Table S2, entry 9; Scheme 4, **6a**). Finally, we found that xanthines, such as benzylic theobromine, caffeine, and *n*-butyl theophylline, could all couple with indoles/pyrroles to give the desired products with relatively high C2 selectivities and good yields (Scheme 4; also see the Supporting Information). The structures of **6a** and **6e** were determined by a single-crystal X-ray analysis (Figures S3 and S4 in the Supporting Information).[12] Given their widespread occurrence in biologically important compounds, it was gratifying to see that the current catalytic system was also applicable to an indazole to form the C2-heteroarylated product in 50% yield (Scheme 4, **6f**).



Scheme 4. Selective oxidative cross-coupling of indoles or pyrroles with xanthines. Reaction conditions: xanthine **4** (0.5 mmol), indole or pyrrole **5** (1.5 mmol), $Pd(OAc)_2$ (10 mol%), Phen (20 mol%), AgF (2.0 mmol), and pyridine (0.5 mmol) in 1,4-dioxane (1.5 mL) at 150°C for 30 h under a N_2 atmosphere. Isolated yields of C2-heteroarylated products of indoles or pyrroles. [a] CuF_2 (1.5 mmol) was used as an oxidant.

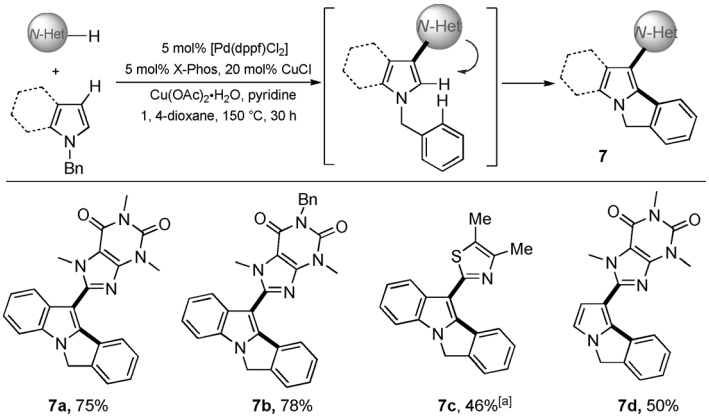
It is worth noting that the catalyst-based control strategy with a judicious choice of oxidant provided a powerful pathway for achieving a reversal of the C2/C3-site selectivity of the oxidative C–H/C–H heteroarylation of indoles or pyrroles with heteroarenes. For example, benzylic theobromine **4a** could react with the *N*,*N*-dimethylcarbamoyl indole **5b** to afford the C2-heteroarylated product in 59% yield by using the optimized catalytic system composed of $Pd(OAc)_2$ and Phen in combination with AgF as oxidant (Scheme 5, Condition A), whereas $[Pd(dppf)Cl_2]$, CuCl, and X-Phos with $Cu(OAc)_2{\cdot}H_2O$ as oxidant mainly gave the C3-heteroarylated product in 65% yield (Scheme 5, Condition B).[13]

Complex fused polycyclic heteroarenes that are widely found in natural products and biologically active pharmaceuticals are often difficult to access by classical synthetic routes.[14] In this work, by taking advantage of Strategy 2, which was mentioned above, N1-benzyl-substituted pyrroles/indoles were designed to undergo a tandem fourfold C–H



Scheme 5. Catalytic system-based switching of the regioselectivity of C–H heteroarylation of indole **5b** with benzylic theobromine (**4a**). Yields of the isolated products are shown. dppf = 1,1′-Bis(diphenylphosphino)ferrocene, X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

activation to concisely synthesize fused tri- and tetracyclic heteroarenes **7a**–**7d** from the corresponding pyrroles and indoles in moderate to good yields (Scheme 6). The structures of **7a** and **7d** were confirmed by X-ray analysis of single

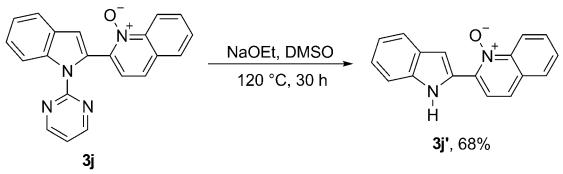


Scheme 6. Palladium-catalyzed tandem coupling reactions of indole or pyrrole derivatives with *N*-heteroarenes. Reaction conditions: *N*-heteroarene (0.5 mmol), indole or pyrrole (1.5 mmol), $[Pd(dppf)Cl_2]$ (5 mol%), X-Phos (5 mol%), CuCl (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (3.0 equiv), and pyridine (1.0 equiv) in 1,4-dioxane (1.5 mL) at 150°C for 30 h under a N_2 atmosphere. [a] In 1,4-dioxane/DMSO (9:1, v/v) at 110°C.

crystals (Figures S5 and S6 in the Supporting Information).[12] The C3-heteroarylated product of *N*-benzylindole with caffeine was observed at the early stage of the reaction and was gradually transformed to the desired product **7a**. Two control experiments illustrated that the intramolecular cross-coupling step did not occur when the *N*-heteroaryl group at the C3 site of indole/pyrroles was changed to the phenyl group, clearly indicating that the *N*-heteroarene moiety played a crucial role in promoting the second coupling process (see the Supporting Information). Thus, this one-pot process might involve the following two sequential oxidative C–H/C–H couplings: 1) the heteroarylation of indoles/pyrroles with various *N*-heteroarenes, such as xanthines and 4,5-dimethylthiazole, first occurred at the C3 position; 2) the N3 atom of azoles was well positioned to further direct C2–H bond activation of indoles/pyrroles to fulfill the intramolecular oxidative C–H/C–H cross-coupling between the indole/pyrrole C2 position and the benzene ring of the benzyl group that is tethered at the indole/pyrrole N1 site.[15] To the best of our knowledge, this is the first palladium-catalyzed cascade reaction involving the cleavage of four C–H bonds and the formation of two C–C bonds.[14]

To further increase the synthetic utility of our methodology, a deprotection was performed to remove the directing group that was tethered to the nitrogen atom of indole. The 2-pyrimidyl group of **3j** could be removed conveniently in the presence of NaOEt in DMSO to afford the corresponding free (N–H) biheteroarene **3j′** in 68% yield (Scheme 7).

In conclusion, the "chelation-directed control" and "catalytic system-based control" strategies can effectively switch the C2/C3 site selectivity in the heteroarylation of indoles



Scheme 7. Deprotection of the pyrimidyl group tethered to the nitrogen atom of indole.

and pyrroles with an array of *N*-heteroarenes by a palladium-catalyzed twofold C–H activation. Interestingly, the resulting C3-heteroaryl indoles/pyrroles can direct the second intramolecular arylation in one pot, leading to a concise approach to complex fused polycyclic heteroarenes through a tandem fourfold C–H activation. Further studies aimed at gaining insight into the mechanism of the oxidative C–H/C–H coupling reactions and extending these strategies to other coupling reactions are currently underway.

Experimental Section

General procedure for the cross-coupling of indole or pyrrole C2–H with *N*-heteroarene *N*-oxides: A flame-dried pressure tube was charged with $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), DPPB (42.6 mg, 0.1 mmol), $Cu(OAc)_2{\cdot}H_2O$ (300 mg, 1.5 mmol), *N*-heteroarene *N*-oxide (2.0 mmol), and the indole or pyrrole derivative (0.5 mmol). The tube was then capped with a rubber septum, evacuated, and backfilled three times with nitrogen. Pyridine and solvent were added by syringe under a N_2 atmosphere. The septum was then replaced by a teflon-coated screw cap, and the mixture was stirred at the indicated temperature for 30 h and then cooled to ambient temperature. The mixture was diluted with CH_2Cl_2 (30 mL), filtered through a Celite pad, and then washed with CH_2Cl_2 (10–20 mL). The combined organic phases were concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel to provide the desired product.

General procedure for the cross-coupling of indole or pyrrole C2–H with xanthines and azoles: A flame-dried pressure tube was charged with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), Phen (18.0 mg, 0.1 mmol), the indole or pyrrole derivative (1.5 mmol), xanthine or azole (0.5 mmol), and an oxidant (1.5 or 2.0 mmol). The tube was then capped with a rubber septum, evacuated, and backfilled three times with nitrogen. Pyridine (39.6 mg, 0.5 mmol) and 1,4-dioxane (1.5 mL) were added by syringe under a N_2 atmosphere. The septum was then replaced by a teflon-coated screw cap, and the mixture was stirred at the indicated temperature for 30 h. The mixture was then cooled to ambient temperature, diluted with CH_2Cl_2 (30 mL), filtered through a Celite pad, and then washed with CH_2Cl_2 (10 mL). The combined organic phases were concentrated under reduced pressure and the residue was purified by column chromatography on silica gel or aluminium oxide (neutral) to provide the desired product.

General procedure for the cross-coupling of indole C3–H and the tandem reaction of indoles or pyrroles with *N*-heteroarenes: A flame-dried pressure tube equipped with a magnetic stir bar was charged with $[Pd(dppf)Cl_2]$ (18.3 mg, 0.025 mmol), X-Phos (11.9 mg, 0.025 mmol), CuCl (10.0 mg, 0.1 mmol), $Cu(OAc)_2{\cdot}H_2O$ (300 mg, 1.5 mmol), the *N*-heterocycle (0.5 mmol), and the indole/pyrrole derivative (1.5 mmol). The tube was then capped with a rubber septum, evacuated, and backfilled three times with nitrogen. Pyridine (39.6 mg, 0.5 mmol) and 1,4-dioxane (1.5 mL) were added by syringe under an N_2 atmosphere. The septum was then replaced by a teflon-coated screw cap, and the mixture was heated at 150°C for 30 h and then cooled to ambient temperature. The mixture was diluted with CH_2Cl_2 (30 mL), filtered through a Celite pad, and then washed with CH_2Cl_2 (10 mL). The combined organic phases

were concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel or aluminium oxide (neutral) to provide the desired product.

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Keywords: C–H activation · cross-coupling · heterocycles · regiocontrol · tandem reactions

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