Multicomponent Reactions

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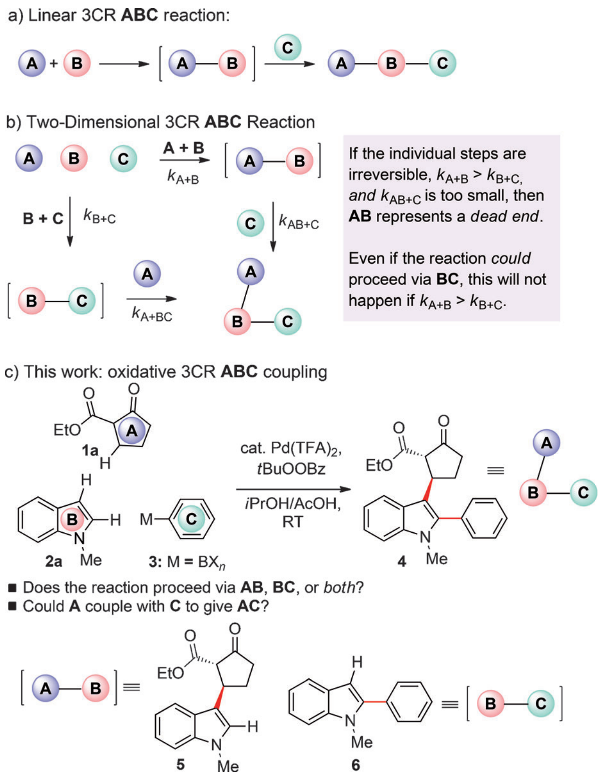
A Three-Component Palladium-Catalyzed Oxidative C−C Coupling Reaction: A Domino Process in Two Dimensions**

*Roshan Y. Nimje, Mikko V. Leskinen, and Petri M. Pihko**

In multicomponent reactions (MCRs), three or more reactants combine in a single chemical step to give a product that contains nearly all the atoms of the individual reactants. Compared with multistep reaction routes, MCRs are highly attractive in terms of step economy.[1,2] Typical MCRs proceed in a linear domino mode: in the first stage, the components **A** and **B** (Scheme 1 a) give rise to a reactive intermediate (**AB**) which then reacts with a third component (**C**), and so on, until the sequence is terminated. Very often, the first steps are reversible, and only the terminating steps are irreversible (type I or type II MCRs).[3,4]

In contrast, if three components **A**, **B**, and **C** could react with each other in any order, such three-component domino reactions (3CR) could proceed through an alternative two-dimensional split domino process (Scheme 1 b). In such a process, there are two kinetic alternatives to give the final **ABC** product, via the **AB** or the **BC** intermediates. If the steps are irreversible, the efficiency of the process could be compromised if one of the pathways leads to a dead end (see the box in Scheme 1 b). Alternatively, unwanted homocoupling or heterocoupling reactions between the components could also jeopardize the projected 3CR process. Given these constraints, it is not surprising that nearly all known MCRs and domino reactions proceed in a strict linear fashion, with the functionalities of the individual components determining the order of events.[5]

Herein, we describe a successful two-dimensional 3CR that proceeds through a mild Pd-catalyzed oxidative coupling between β-ketoesters (component **A**), indoles (component **B**), and aryl boronates (component **C**; Scheme 1 c). This 3CR could theoretically proceed via both **AB** and **BC** intermediates, and we demonstrate herein that both pathways are viable. To the best of our knowledge, catalytic oxidative 3CRs have not been reported in the literature.[6] The 3CR generates densely functionalized 2,3-disubstituted indoles directly from the three components.[7]



Scheme 1. The difference between a) linear and b) two-dimensional multicomponent sequences. Bz = benzoyl, TFA = trifluoroacetate

We hypothesized that the reaction conditions of our previously reported[8] cross-dehydrogenative coupling reaction between β-ketoesters and indoles could also enable other oxidative coupling reactions at the free 2-position of the indole. Two-component oxidative couplings between indoles at the 2-position and arylboronates have previously been reported, by the groups of Shi,[9a] Zhang,[9b] and Studer.[10] However, direct oxidative 2,3-difunctionalization reactions of indoles have not been developed, and we were concerned that owing to the increased steric requirements of such a process a Cu^{II} co-catalyst might be required,[9a,b] and this could compromise the regioselectivity for the β-ketoester.[8a] However, we anticipated that the use of the more-electrophilic Pd^{II} precursor Pd(TFA)$_2$, might overcome these problems, as this catalyst was shown to be superior to other Pd^{II} sources in the cross-dehydrogenative coupling reactions.[8a]

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[*] Dr. R. Y. Nimje, M. V. Leskinen, Prof. Dr. P. M. Pihko
Department of Chemistry and NanoScience Center
University of Jyväskylä
P. O. B. 35, 40014 JYU (Finland)
E-mail: petri.pihko@jyu.fi
Homepage: http://tinyurl.com/pihkogroup

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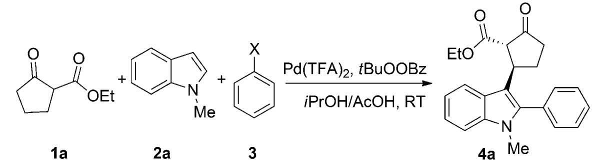
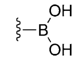
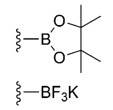
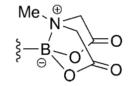
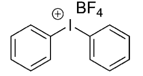
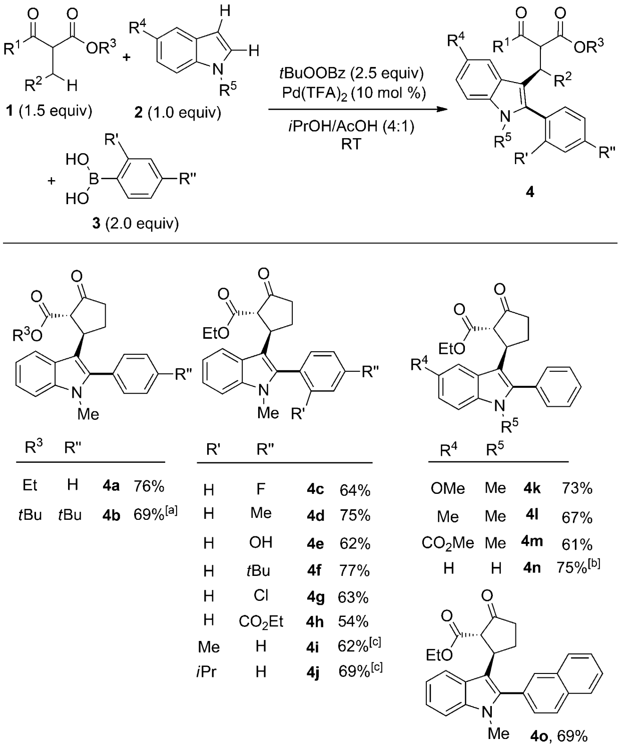
Table 1: Screening of various aryl sources for the 3CR.[a]



Entry	X	t [h]	Yield [%][a]
1		20	83
2		24	11
3	–BF$_3$K	24	59
4		48	0
5	–OTs	48	0
6	–OTf	48	0
7		24	0

[a] Reaction conditions: **1a** (0.6 mmol, 1.5 equiv), **2a** (0.4 mmol, 1 equiv), **3** (0.8 mmol, 2 equiv), Pd(TFA)$_2$ (0.04 mmol, 10 mol%), and *t*BuOOBz (1.0 mmol, 2.5 equiv) in *i*PrOH/AcOH 4:1 (0.5 mL).
[b] Determined by ^{1}H NMR analysis using dibenzyl ether as an internal standard.



R^3	R''		
Et	H	**4a**	76%
*t*Bu	*t*Bu	**4b**	69%[a]

R'	R''		
H	F	**4c**	64%
H	Me	**4d**	75%
H	OH	**4e**	62%
H	*t*Bu	**4f**	77%
H	Cl	**4g**	63%
H	CO$_2$Et	**4h**	54%
Me	H	**4i**	62%[c]
*i*Pr	H	**4j**	69%[c]

R^4	R^5		
OMe	Me	**4k**	73%
Me	Me	**4l**	67%
CO$_2$Me	Me	**4m**	61%
H	H	**4n**	75%[b]

4o, 69%

Scheme 2. Oxidative domino cross-couplings with various arylboronate and indole components. The yields of the products after purification are reported. Reaction conditions, unless otherwise indicated: **1** (1.5 equiv), **2** (0.4 mmol, 1.0 equiv), **3** (0.8 mmol, 2.0 equiv), *t*BuOOBz(2.5 equiv), Pd(TFA)$_2$ (0.1 equiv), *i*PrOH/AcOH (4:1; 0.5 mL) at 25 °C. [a] Dioxane/AcOH (4:1; 0.5 mL) used as a solvent. [b] **2** (3 equiv) used in two installments. [c] 1:1 mixture of atropisomers. The combined yield of two atropisomers is given.

To our delight, when the three components β-ketoester **1a**, indole **2a**, and phenylboronic acid **3** (Table 1) were subjected to our reaction conditions with 2.5 equivalents of the oxidant (*t*BuOOBz), the reaction proceeded cleanly to give the **ABC** product **4a** (83 % conversion, 76 % yield upon isolation). Further studies (Table 1) indicated that phenylboronic acid was indeed the optimal coupling partner. Other oxidants, acid additives, and solvents were also screened (see the Supporting Information) but these generally turned out to be inferior to the optimal conditions.

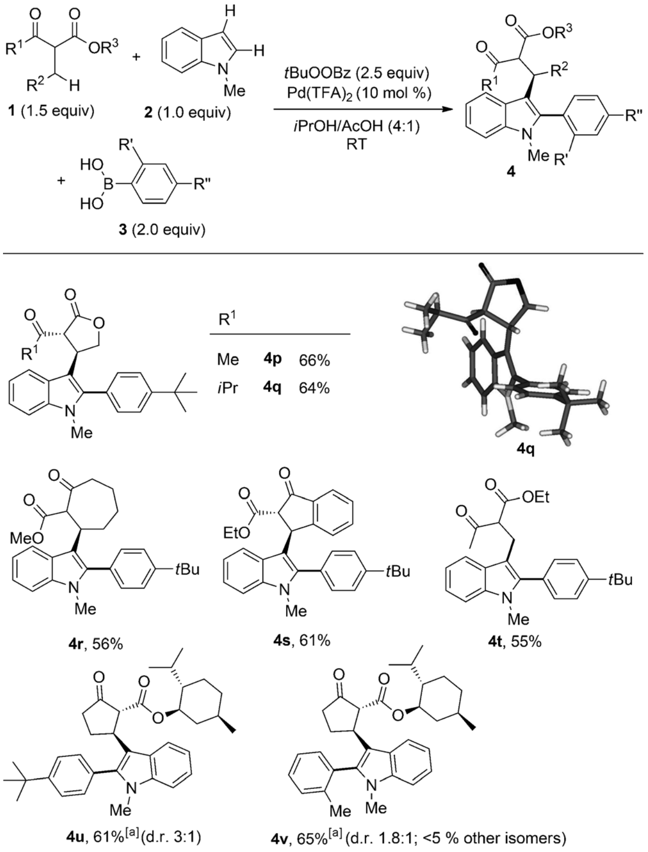
The scope of the reaction turned out to be very wide. Scheme 2 summarizes the exploration of the scope with different arylboronates and indoles. Both electron-donating and electron-withdrawing groups are tolerated on the boronate (products **4c**–**4i**), as well as on indole (**4k**–**4n**). With *o*-tolylboronic acid, the product **4i** was obtained as a 1:1 mixture of two atropisomers. Even compound **4j**, derived from *o*-isopropylphenylboronic acid, was obtained in good yield and the two diastereomeric atropisomers could readily be separated and characterized (see the Supporting Information).[11,12] These experiments also attest to the high steric tolerance of the 3CR process.

Different β-ketoesters are also tolerated (Scheme 3). 3CR products derived from β-keto lactones (**4p**–**4q**), 7-membered β-ketoesters (**4r**), fused β-ketoesters (**4s**), and even open-chain β-ketoesters (**4t**) can be accessed with remarkable ease by this oxidative three-component coupling reaction. Finally, the use of a menthyl ester provides the product with moderate but promising diastereoselectivity (**4u**; 3:1 d.r.), and even more remarkably, with *o*-tolylboronic acid, the reaction gives only two major products in a 1.8:1 ratio (**4v**; presumably the atropisomeric products) instead of the expected statistical mixture of four diastereomers.

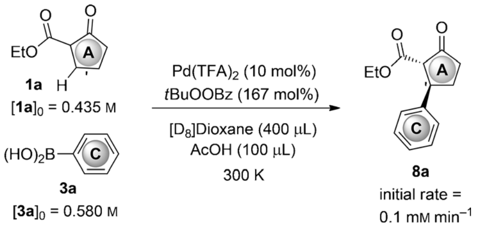
These investigations underline the high tolerance of the reaction to steric effects and suggest that some level of control for the diastereoselectivity should also be possible. The reaction proceeds under very mild reaction conditions, at room temperature, with benign solvents (AcOH + *i*PrOH or dioxane).

In all cases, the reactions proceeded with high regiochemical fidelity: the arylboronate **3** was selectively coupled at the 2-position of indole, and the cross-dehydrogenative coupling of β-ketoester was fully regioselective for the β′ position of the β-ketoester and the 3-position of the indole component.[8–10] What was more remarkable, however, was that the dehydrogenative conditions of the reaction did not result in unwanted coupling between the β-ketoester **1** and the boronate **3** (**A** + **C** coupling). Indeed, even in a control experiment with **1a** and **3a** but no indole component, the rate of the formation of **8a** (**A** + **C** product) was very low (Scheme 4).

To probe whether the 3CR could proceed through both **A** + **B** and **B** + **C** pathways, or whether one of the pathways was dominating, we carried out the following experiments. First, monitoring the reaction progress (Figure 1 a) by ^{1}H NMR spectroscopy indicated that the formation of **5**



Scheme 3. Oxidative domino cross-couplings with different β-ketoesters. Yields of pure products are reported and the X-ray crystallographic structure of **4q** is shown.[15] Reaction conditions, unless otherwise indicated: **1** (1.5 equiv), **2** (0.4 mmol, 1.0 equiv), **3** (0.8 mmol, 2.0 equiv), *t*BuOOBz (2.5 equiv), Pd(TFA)$_2$ (0.1 equiv), *i*PrOH/AcOH (4:1; 0.5 mL) at 25 °C. [a] Combined yield of diastereomers.



Scheme 4. Control experiment to probe the possibility of the formation of the **A** + **C** coupling product.

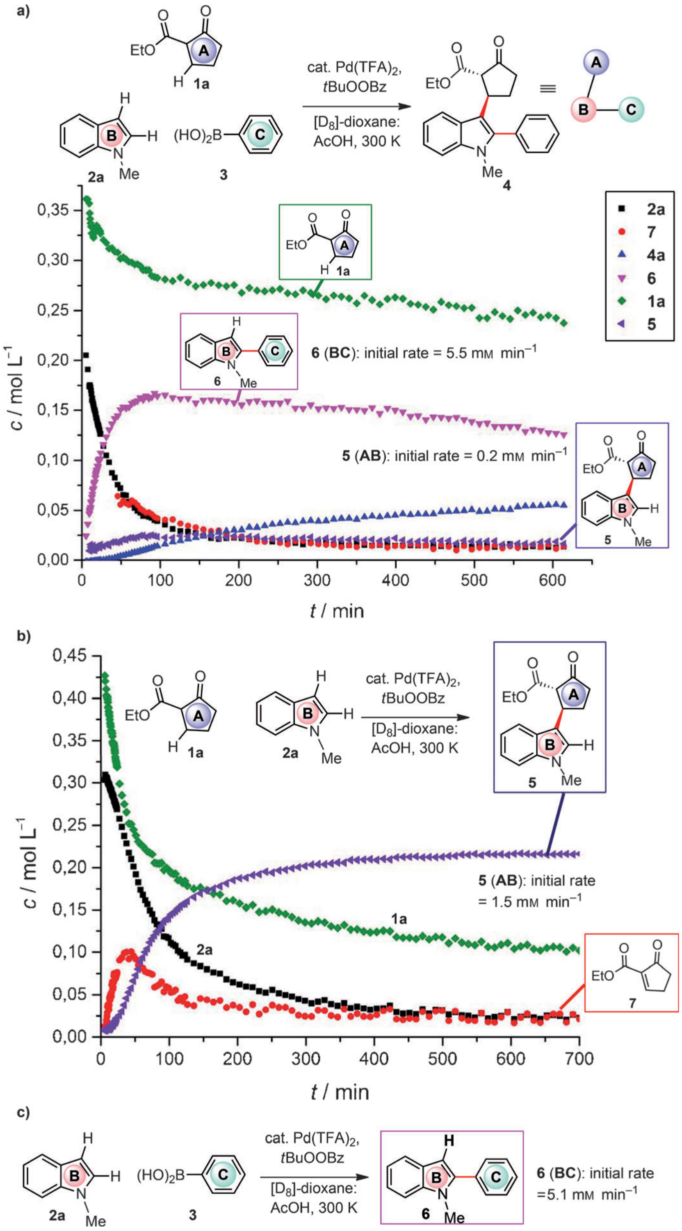


Figure 1. a) Monitoring of the temporal progress of the three-component **A** + **B** + **C** (**1a** + **2a** + **3a**) coupling by ^{1}H NMR spectroscopy. b) Monitoring of the temporal progress of the **A** + **B** (**1a** + **2a**) two-component coupling by ^{1}H NMR spectroscopy. c) Initial rate kinetics of the **B** + **C** (**2a** + **3**) two-component coupling. Reaction conditions: [**1a**]$_0$ = 0.44 M, [**2a**]$_0$ = 0.29 M, [**3**]$_0$ = 0.58 M, [*t*BuOOBz]$_0$ = 0.73 M, 10 mol% Pd(TFA)$_2$, 4:1 [D$_8$]dioxane/AcOH, 300 K. In the three-component coupling, [**7**] could not be reliably monitored in the early stages of the reaction (see the Supporting Information).

(**A** + **B** coupling) was slower than the formation of **6** (**B** + **C**) under the 3CR conditions, with a more than 20-fold initial rate difference between these two competing processes.

Each coupling step of the process was then examined individually by two-component coupling (2CR) experiments under otherwise identical reaction conditions. The initial coupling reactions between **1a** + **2a** (**A** + **B**) and **2a** + **3** (**B** + **C**) were studied first. These experiments revealed that the boronate indole coupling (**2a** + **3**; **B** + **C**) proceeded at nearly identical rates in the 3CR (5.5 mM min^{-1}) and in the 2CR (5.1 mM min^{-1}; Figure 1c). In stark contrast, the cross-dehydrogenative coupling between β-ketoester **1a** and indole **2a** (**A** + **B**) proceeded nearly an order of magnitude faster under the 2CR conditions (1.5 mM min^{-1}) compared to the 3CR conditions (0.2 mM min^{-1}; see Figure 1a). The difference in the rates of the individual 2CRs **A** + **B** and **B** + **C**, thus appears to be amplified in the 3CR.

The second step of the 3CR was studied next. Although the rate of the formation of the **AB** product **5** was marginal under the 3CR conditions, the **AB** + **C** control experiment demonstrated that **5** readily reacted with **3** (**C**) under otherwise identical reaction conditions to give **4** (**ABC** product).[12] Thus, the **AB** + **C**→**ABC** pathway, although slower than the **A** + **BC** pathway, was nevertheless shown to be productive. In turn, a competition experiment with **1a** (**A**) and equimolar concentrations of **2a** (**B**) and **6** (**BC**) indicated that these two competing cross-dehydrogenative coupling reactions to give **5** (**AB**) and **4** (**ABC**) proceed at nearly identical rates.[12] These experiments confirmed that the 3CR proceeds predominantly through the "**B** + **C**, then **A**" pathway, with the dominance established by the faster **B** + **C** coupling relative to the **A** + **B** coupling. However, both pathways are viable routes to the product.

The suppression of the **A** + **B** coupling relative to the **B** + **C** coupling under the 3CR conditions could be due to partitioning of the catalyst between the **A** + **B** and **B** + **C** catalytic cycle, as both reactions are competing for the same Pd catalyst pool. However, the reactions are also competing for the same substrate, indole **2a** (**B**). The sigmoidal shape of the curve for [**5**] in the two-component **A** + **B** coupling is characteristic of a consecutive reaction and suggests that enone **7** is an intermediate (see Figure 1b).[13] The initial delay, inherent in the consecutive nature of the **A** + **B** coupling, gives this reaction a serious kinetic disadvantage compared to the **B** + **C** coupling; by the time the concentration of the intermediate (e.g. enone **7**) reaches its peak, most of the indole **2a** (**B**) has already been consumed. Consequently, the reaction will be diverted towards the **A** + **BC** pathway, possibly with **6** (**BC**) competing with **2a** (**B**) for enone **7**. Although the rate differences between the two-component **A** + **B** and **B** + **C** experiments is small, these differences are amplified in the three-component **A** + **B** + **C** reaction because the **A** + **B** reaction is a consecutive reaction with an induction period, whereas the **B** + **C** reaction starts to consume indole **2a** (**B**) without detectable delay.[14]

Such kinetic amplifications could be useful in designing selective reactions and MCR processes, or for probing the induction periods of reactions. For example, two competing reactions with similar initial rates but different induction periods should display significant rate differences in a competition experiment for the same substrate, even in cases where the intermediates themselves would escape detection.

In summary, palladium-catalyzed oxidative three-component coupling between β-ketoesters, indoles, and arylboronic acids proceeds under very mild reaction conditions with excellent regioselectivity for the products. Even very hindered compounds, such as atropisomeric products **4j** and **4v**, can be accessed in good yields. Indole couples faster with the arylboronic acid than the β-ketoester, and this rate difference is significant under the three-component reaction conditions, possibly because the coupling with β-ketoester involves an enone intermediate. Further implications of this study on the mechanism of both oxidative coupling reactions are being studied and will be reported separately.

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Keywords: homogeneous catalysis · kinetics · multicomponent reactions · oxidative couplings · palladium

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[12] See the Supporting Information for details.

[13] In a three-component control experiment where 250 mol% of enone **7** was used in lieu of β-ketoester **1a** but no additional oxidant was used, the reaction gave exclusively the **A** + **B**

coupling product **5** (see the Supporting Information). This experiment indicates that enone **7** may not be capable of reoxidizing Pd^0 in the catalytic cycle (in order to sustain the **B** + **C** oxidative coupling) and suggests that the concentration of **7** controls the rate of the **A** + **B** coupling. For a previous discussion of the mechanism of the indole-β-ketoester coupling, see Ref. [8a].

[14] We are aware that given the complexity of the system, other factors are likely to play a role as well. For example, most of the species here (**1a**, **2a**, **5**, **6** and **7**) could act as ligands for Pd. For evidence of the involvement of indoles in the formation of **7**, see Ref. [8b] (see the Supporting Information, p. S40).

[15] CCDC 917055 (**4q**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.