ORGANIC
LETTERS

2012
Vol. 14, No. 15
3858–3861

Domino Carbopalladation−Cross-Coupling for the Synthesis of 3,3-Disubstituted Oxindoles

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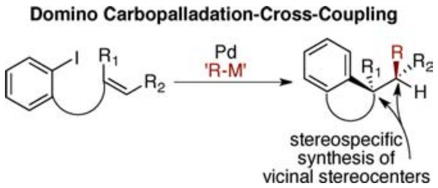
Received June 4, 2012

ABSTRACT



This study examines a domino carbopalladation−cross-coupling reaction for the formation of valuable oxindole scaffolds. Furthermore, the reaction sequence forges vicinal stereocenters in a stereospecific manner through the formation of two carbon−carbon bonds and, thereby, rapidly generates complexity. The reaction gives high yields for a variety of acrylamide substrates, and various organoboranes have also been evaluated for the cross-coupling. This work offers insight into the relative rates determining a successful carbopalladation−cross-coupling reaction and how to favor the desired reaction pathway.

An important aspect of organic synthesis is the development of efficient and practical reaction sequences.[1] The overall efficiency of a particular method or synthesis can be evaluated based on a variety of criteria. These include the yields and selectivities of individual reactions, as well as the total atom, step, and protecting group efficiencies of the entire route. One strategy to address efficiency in organic synthesis is the use of domino processes to forge multiple bonds in a single synthetic operation, since this leads to a net reduction of the total number of manipulations necessary to access a desired skeleton. Consequently, domino reactions have received much attention in recent years.[2]

Transition-metal-mediated domino processes constitute an important class of domino sequences.[3] Expansions of traditional cross-coupling methods, these reactions form multiple bonds in a single step and allow for the synthesis of complex scaffolds from relatively simple starting materials. We have recently developed a domino carbopalladation−carbonylation reaction for substrates possessing pendant β-hydrogens.[4] In this sequence the typical termination event of the Heck reaction, β-hydride elimination, is circumvented and, instead, a carbonylation event ensues. One notable advantage of this sequence is that *syn* carbopalladation of the alkene moiety enforces the diastereospecific synthesis of vicinal stereocenters. We became interested in capitalizing on this diastereocontrol for domino carbopalladation sequences with other types of termination events, such as cross-coupling (Scheme 1). In such a sequence *syn* carbopalladation dictates the relative

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(1) (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281. (b) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233–1246. (c) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010–3021. (d) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657–4673.

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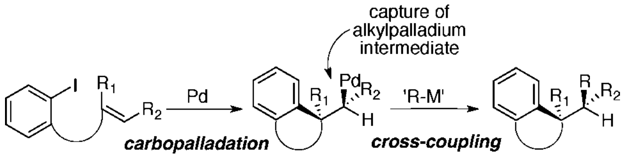
10.1021/ol301539p

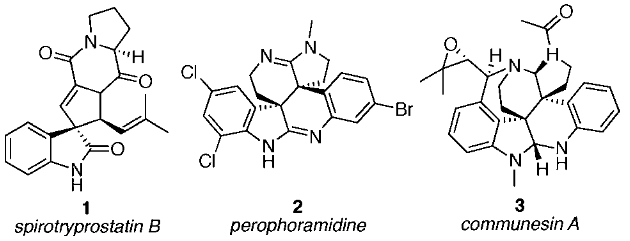
stereochemistry of the newly formed stereocenters and the σ-alkylpalladium intermediate is captured in a cross-coupling event instead of undergoing β-hydride elimination.

Scheme 1. Proposed Domino Carbopalladation−Cross-Coupling Sequence



Domino reactions where carbopalladation is followed by coupling with an organoborane have been explored with considerable success in the literature and have often been referred to as domino Heck−Suzuki reactions.[5] However, there are few examples of this type of domino process in which the inherent diastereospecificity of *syn* carbopalladation is exploited for the construction of two vicinally disposed stereocenters.[6] Therefore, we opted to explore a domino carbopalladation−cross-coupling sequence aimed at accessing 3,3-disubsituted oxindoles bearing a vicinal tertiary center. Oxindoles bearing a quaternary center at C3 are found in a variety of naturally occurring alkaloids and potential pharmaceutical lead compounds and, furthermore, have been found to possess significant biological activity.[7,8] For example, spirotryprostatin B (**1**) has pronounced biological activity and contains the molecular architecture we would like to access, a quaternary stereocenter with an adjacent tertiary stereocenter (Scheme 2).[9] Similar synthetic scaffolds have also been found to suppress the p53-MDM2 protein−protein interaction, which is important for tumor suppression.[10] Moreover, the natural products such as perophoramidine[11] (**2**) and the communesins[12] (e.g., communesin A (**3**)) with vicinally disposed quaternary centers in their core structures have also inspired our synthetic efforts.[13] We envisioned that the proposed reaction sequence, namely domino carbopalladation−cross-coupling, could provide a valuable synthetic tool for the stereospecific construction of the crowded scaffolds found in these three natural products.

Scheme 2. Some Natural Products Containing the 3,3-Disubstituted Oxindole Scaffold



Initially, we began our investigation with amide **4a**, in which β-hydride elimination of alkylpalladium intermediate **6** is precluded. The desired reaction sequence would yield product **7a**, which is equipped with a vinyl moiety for further functionalization and elaboration. First, we examined vinyl trifluoroborate **5a**, since this has been shown to be an air-stable organoborane that is competent in a variety of Suzuki cross-couplings.[14] Subjecting amide **4a** to conditions at 70 °C yielded none of the desired oxindole **7a** (Table 1, entry 1).[15] By simply warming the reaction to 90 °C, the desired domino product could be isolated in 79% yield (entry 2). Switching to $Pd(PPh_3)_4$ gave a slightly higher yield in both toluene and dioxane (entries 3 and 4). By decreasing the catalyst loading the desired product could be obtained in 90% yield when using $Pd(PPh_3)_4$ (entry 6).[16]

With optimized conditions in hand we then explored the influence of the organoborane on the domino reaction, and

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(11) For a recent synthesis, see: Wu, H.; Xue, F.; Xiao, X.; Qin, Y. *J. Am. Chem. Soc.* **2010**, *132*, 14052–14054.

(12) For a recent synthesis, see: Zuo, Z.; Ma, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 12008–12011.

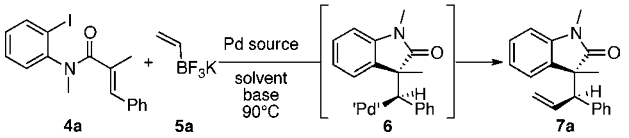
(13) For a related domino approach to these compounds, see: Evans, M. A.; Sacher, J. R.; Weinreb, S. M. *Tetrahedron* **2009**, *65*, 6712–6719.

(14) For example, see: Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107–109.

(15) The relative stereochemistry is assigned in analogy to our previous work, as the reactions are expected to proceed through similar σ-alkylpalladium intermediates. In that case, *syn* carbopalladation of the double bond was confirmed. For further detail, see ref 4.

(16) In entries 3 and 4 in Table 1 there was complete consumption of the starting material, but the corresponding yields could not be isolated. We reasoned that there could be an association of the product with the catalyst and thus tried decreasing the catalyst loading to increase the yield.

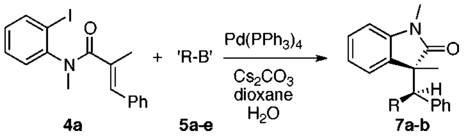
Table 1. Optimization of Domino Carbopalladation−Cross-Coupling Reaction of Amide **4a** with Trifluoroborate Salt **5a**[a]

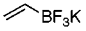
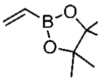
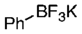
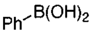
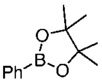


entry	Pd source	Pd (mol %)	yield (%)[b]
1[c]	PdCl$_2$dppf	10	0
2	PdCl$_2$dppf	10	79
3	Pd(PPh$_3$)$_4$	10	84
4[d]	Pd(PPh$_3$)$_4$	10	83
5	PdCl$_2$dppf	2	70
6	Pd(PPh$_3$)$_4$	2	90

[a] Reactions run on a 0.08 mmol scale of **4a** (1 equiv), with Pd (2−10 mol % as in the Table), BF$_3$K salt **5a** (2 equiv), Cs$_2$CO$_3$ (3 equiv), dioxane/H$_2$O (10:1, 0.07 M) at 90 °C. [b] Isolated yield. [c] Reaction run at 70 °C. [d] Toluene was used instead of dioxane.

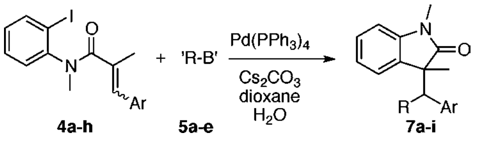
Table 2. Carbopalladation−Cross-Coupling of Substrate **4a** with Various Organoboranes[a]

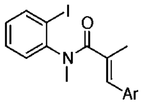
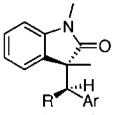
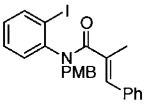
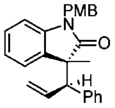
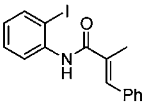
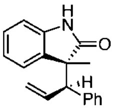
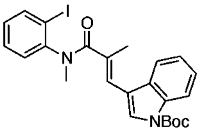
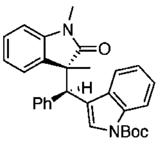
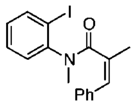
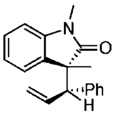


entry	'R-B'	5	7	yield[b]
1		**5a**	**7a**	90
2		**5b**	**7a**	87
3		**5c**	**7b**	81
4		**5d**	**7b**	69
5		**5e**	**7b**	94

[a] Reactions were run on a 0.08 mmol scale of amide **4a** (1 equiv) with organoborane **5a**−**e** (2 equiv), Pd(PPh$_3$)$_4$ (2 mol %), Cs$_2$CO$_3$ (3 equiv), in dioxane/water (10:1, 0.07 M). [b] Isolated yield.

Table 3. Domino Carbopalladation−Cross-Coupling of Acrylamides **4a**−**h**[a]



entry	4	5	7	yield
				
1	**4a**, Ar = Ph	**5a**	**7a**, Ar = Ph, R = vinyl	90
2	**4a**, Ar = Ph	**5e**	**7b**, Ar = Ph, R = Ph	94
3	**4b**, Ar = *p*-MeOC$_6$H$_4$	**5a**	**7c**, Ar = *p*-MeOC$_6$H$_4$, R = vinyl	89
4	**4c**, Ar = *p*-CF$_3$C$_6$H$_4$	**5a**	**7d**, Ar = *p*-CF$_3$C$_6$H$_4$, R = vinyl	85
5[e]	**4d**, Ar = *p*-BrC$_6$H$_4$	**5a**	**7e**, Ar = *p*-BrC$_6$H$_4$, R = vinyl	75
6	 **4e**	**5a**	 **7f**	91
7	 **4f**	**5a**	 **7g**	27
				
8[d]	**4g**	**5e**	**7h**	34
9[e]	**4g**	**5e**	**7h**	53
10[f]	**4g**	**5e**	**7h**	88
				
11	**4h**	**5a**	**7i**	45
12[g]	**4h**	**5b**	**7i**	70[h]

[a] Reactions were run on a 0.13 mmol scale of amide **4** (1 equiv) with organoborane **5** (2 equiv), Pd(PPh$_3$)$_4$ (2 mol %), Cs$_2$CO$_3$ (3 equiv), in dioxane/water (10:1, 0.07 M). [b] Isolated yield. [c] 1.1 equiv of organoborane **5a** was used. [d] 5 mol % Pd(PPh$_3$)$_4$ [e] 50 μL of H$_2$O, 5 mol % Pd(PPh$_3$)$_4$ [f] 3.0 equiv of organoborane **5e**, 5 mol % Pd(PPh$_3$)$_4$, 50 μL of H$_2$O, and 3.5 equiv of Cs$_2$CO$_3$ were used. [g] 3.5 equiv of organoborane **5b** used. [h] NMR yield based on the addition of 1-methoxynaphthalene as an internal standard.

several other organoboranes **5b**−**e** were evaluated in the reaction sequence. The vinyl boronic ester **5b** gave similar results to the vinyl trifluoroborate salt **5a** (Table 2, entries 1 and 2). For phenyl organoboranes the boronic ester **5e** gave the highest yield and the boronic acid **5d** gave the lowest yield, with trifluoroborate salt **5c** in between (entries 3−5). This is a somewhat surprising trend, as the trifluoroborate salts are generally perceived as more reactive, and trifluoroborate **5c** and boronic acid **5d** are both expected to transmetalate via the boronic acid.[17] However, the three organoboranes **5c**−**e** have different rates of hydrolysis and protodeboronation under the reaction conditions, which likely explains the observed results.[18]

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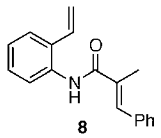
(17) (a) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116–2119. (b) Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5156–5160.

Next a variety of acrylamides **4b**−**h** were examined to determine the scope of the domino reaction. Substituting the aryl ring with electron-donating or -withdrawing groups was well tolerated, giving good yields for both products **7c** and **7d** (Table 3, entries 3,4). For *para*-bromo substrate **4d** a mixture of products was observed when using 2 equiv of organoborane **5a**. However, by decreasing the amount of organoborane to 1.1 equiv, the desired product **7e** could be obtained in 75% yield as a single product (entry 5). The lower yield can be attributed to protodeboronation of organoborane **5a** during the course of the reaction, resulting in incomplete consumption of the starting material. Changing to *para*-methoxy benzyl protected amide **4e** gave the product **7f** in good yield (entry 6). However, when using the unprotected amide **4f**, desired domino product **7g** was isolated in a poor yield (entry 7). The major product of the reaction was noncyclized, cross-coupled product **8**, which was isolated in 62% yield (Figure 1). This indicates that the tertiary amide is essential for the rate of carbopalladation to compete successfully with the rate of early cross-coupling. Similar results were found in our previous study, and in the case of carbonylation none of the desired product was observed, indicating that the carbonylation sequence is faster than the transmetalation sequence.[4b] Initially, heteroaryl substrate **4g** gave a low yield of desired domino product **7h** and the mass balance was unconsumed amide **4g** (entry 8). We reasoned that this was due to a relatively slow cross-coupling step of the intermediate Pd species corresponding to **6**, which would allow more time for protodeboronation of **5e** to occur. Thus, it was reasoned that decreasing the amount of water would slow the rate of protodeboronation and thereby increase the amount of the desired product. Indeed, decreasing the amount of water did lead to an increase in yield (entry 9). Furthermore, increasing the amount of organoborane **5e**, while using a decreased amount of water, furnished product **7h** in good yield (entry 10). The *Z*-isomer of the double bond was also examined, providing the diastereomeric product **7i** (entry 11). In this case, the cross-coupling of the intermediate corresponding to **6** was also slow, as only 45% of the product was isolated using the standard conditions with the mass balance being starting material. Again, by increasing the amount of the organoborane **5b**, product **7i** could be obtained in a higher yield (entry 12).[19]



8

Figure 1. Product **8**.

In conclusion we have developed a domino carbopalladation−cross-coupling reaction for the diastereospecific construction of 3,3-disubstituted oxindoles possessing vicinal stereocenters. To our knowledge this is one of the few examples of a domino reaction that exploits the diastereocontrol that can be imparted by *syn* palladation. This method furnishes the desired oxindole products in good yields for a variety of acrylamides and organoborane species. Key insights into the competing reaction manifolds were drawn, and comparisons of organoborane species were made. Furthermore, how to improve the yield with more recalcitrant substrates was discussed.

Acknowledgment. The authors would like to thank the Knut and Alice Wallenberg Foundation, the Swedish Research Council, and the Estonian Research Council (Grant No. 7808) for funding.

Supporting Information Available. Preparation and characterization of compounds **4a**−**h**, **7a**−**i**, and **8** are included. This material is available free of charge via the Internet at http://pubs.acs.org. The authors declare no competing financial interest.

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(18) Lennox, A. J. J.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 7431–7441.

(19) The **5a** and **5b** perfomed similarly, see Table 2 entries 1 and 2. Also **5a** gave similar yields when increasing the amount of organoborane.

The authors declare no competing financial interest.