JOC*Note*

Heck, Direct Arylation, and Hydrogenation: Two or Three Sequential Reactions from a Single Catalyst

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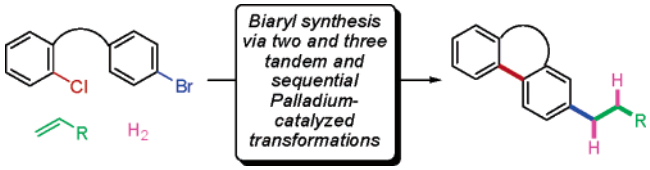

Palladium-catalyzed tandem multifunctional reactions leading to the synthesis of substituted biaryl molecules have been developed including tandem Heck−direct arylation and tandem−sequential Heck−direct arylation−hydrogenation. These reactions occur in good yield and have been employed in the synthesis of a cytotoxic biaryl compound.

The desire to improve efficiency and minimize waste has inspired chemists to develop new catalytic reactions that can substitute the use of stoichiometric reagents with catalytic entities. In addition to new catalysts and reactions, novel strategies have emerged that build on the growing wealth of catalytic transformations. One such strategy involves the use of single catalysts for multiple one-pot transformations, or so-called tandem catalysis.[1] In the ideal situation, one catalyst would be able to perform several mechanistically distinct processes in the same reaction media with little or no alteration of the reaction conditions. Significant success has been achieved under this paradigm as illustrated by the growing number of processes involving two tandem reactions.[2] In contrast, examples of a single catalyst performing three mechanistically distinct tandem and/or sequential catalytic reactions remain rare.[1b]

Discovering a catalyst and reaction conditions that enable two or three distinct processes in one pot is far more complex than independent reaction optimization. In tandem processes, the order of reaction can have a profound influence on reaction outcome, and the byproducts of one transformation can have beneficial or deleterious effects on another in the cascade.[3] Furthermore, the catalyst structure may not be static, but change over the course of one or more steps, making independent reaction optimization fruitless.

In recent years, increased attention has been focused on the use of direct arylation reactions as an alternative to the use of stoichiometric activating groups in the formation of biaryl molecules.[4] Recent work has enabled these reactions to be performed with a growing number of heterocyclic arenes,[5] and the efficient use of some simple aromatic coupling partners is now possible.[6,7] While direct arylation reactions have appeared as the terminating event of a catalytic cascade,[8] little is known about the compatibility of these reactions in the context of sequential, distinct tandem catalytic processes.[9] Being aware of the vast number of palladium-catalyzed transformations[10] and

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(3) Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 11152.

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(8) For example, see: (a) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (b) Ohno, H.; Miyamura, K.; Mizutani, T.; Kadoh, Y.; Takeoka, Y.; Hamaguchi, H.; Tanaka, T. *Chem. Eur. J.* **2005**, *11*, 3728. (c) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78. (d) Cuny, G.; Bois-Choussy, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4774. (e) Mauleon, P.; Nunez, A. A.; Alonzo, I.; Carretero, J. C. *Chem. Eur. J.* **2003**, *9*, 1511. (f) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148.

(9) For a seminal example, see: Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310.

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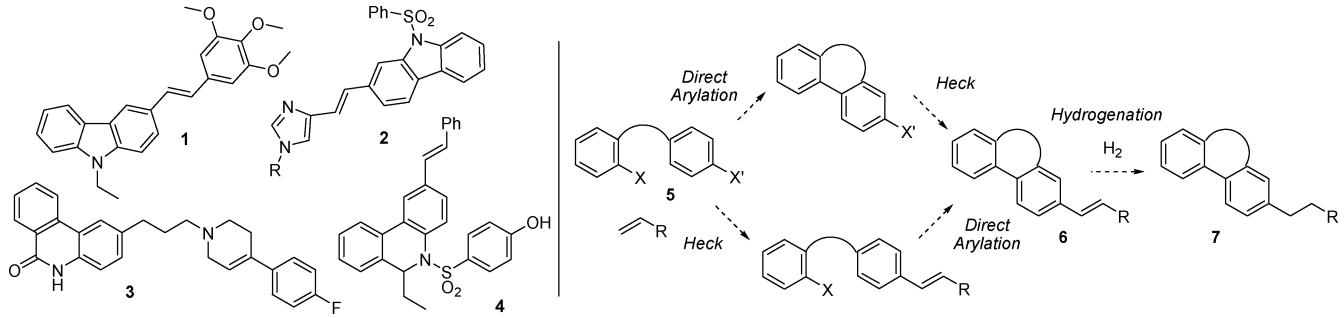
SCHEME 1. Substituted Tricyclic Biaryls in Medicinal Chemistry and a Double-Tandem Catalytic Route for Their Preparation



the significant potential of palladium in tandem catalysis,[1j−m] we sought to investigate the viability of direct arylation in conjunction with other mechanistically distinct processes.[11]

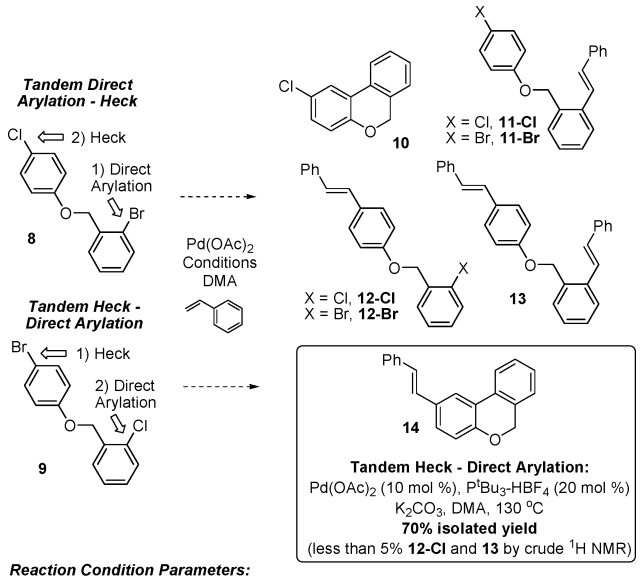
Herein, we describe the development of tandem Heck−direct arylation reactions and tandem−sequential Heck−arylation−hydrogenation reactions. During the course of these studies, we discovered that the optimal catalyst for the tandem processes is nonoptimal for individually run arylation reactions and is completely incompatible with independently run hydrogenation reactions. These results point to a dynamic catalyst structure under the reaction conditions. Furthermore, these results warn against the selection of catalysts for tandem processes based exclusively on discrete reaction phenomena. We also describe the utilization of these reactions in the synthesis of cytotoxic biaryl **1**.

Inspired by molecules that have emerged from medicinal chemistry research, **1**−**4** (Scheme 1),[12] we envisioned that tandem direct arylation−Heck or tandem Heck−direct arylation (depending on the nature of the halides on **5**) could be used to grant rapid and efficient access to these types of molecules, **6**. Furthermore, if the catalyst could be further employed to conduct a third transformation, such as hydrogenation, molecules of type **7** could be achieved via a rare tandem−sequential catalytic protocol.

Initial reaction screens were conducted to determine which reaction sequence was optimal for reactivity and selectivity (Scheme 2). These experiments were performed with bromochloro substrates **8** and **9**. Under no circumstances were acceptable results obtained with substrate **8**, which requires the direct arylation to occur first in the catalytic sequence. Even when the alkene was added after completion of the direct arylation step, low turnovers in the Heck reaction were observed, generating **10** and **11-Cl** as the major products.

More acceptable outcomes were achieved with substrate **9**, which requires the Heck reaction to occur first. Optimal results are obtained when 1 equiv of the alkene is added at the reaction outset, making this a truly tandem catalytic process. With **9**, a

SCHEME 2. Reaction Development and Optimization



Reaction Condition Parameters:
Ligand: 10 phosphine ligands and 2 NHC ligands; **Base:** K_2CO_3, Cs_2CO_3, $NMeCy_2$, KOAc; **Temperature:** 80 to 140 °C; **Equivalents of Alkene:** 0.9 to 3 equivalents

variety of ligands were assayed with different ligand-to-palladium ratios. While tricyclohexylphosphine and di-*tert*-butylmethylphosphine were previously shown to be ideal ligands in the direct arylation reaction,[13] these ligands resulted in inferior outcomes in the tandem reaction. In contrast, tri-*tert*-butylphosphine, which is known to be a good ligand in Heck reactions,[14] but inferior in direct arylation,[13] gave the best tandem catalysis results. Optimized reaction conditions (**9**, styrene (1 equivalent), $Pd(OAc)_2$ (10 mol %), $P^tBu_3-HBF_4$ (20 mol %), K_2CO_3 (four equivalents) in DMA at 130 °C) give a 70% isolated yield of the desired product **14** with less than 5% of other side products being formed. These conditions were employed to investigate the scope of the tandem Heck−direct arylation reaction (Table 1).

In addition to styrene (Table 1, entries 1, 5, 8, and 9), substituted styrenes (entries 2 and 12) and acrylates (entries 3, 4, 6, 7, 10, and 11) are compatible olefin components. Of note, a *p*-acetoxy group on the styrenyl component becomes cleaved under the reaction conditions. While the species responsible for this cleavage has not been determined, it may be thermally induced or through reaction with adventitious water. Both halides may be on the same aromatic ring (entry 3) and when

(11) While the mechanisms of the Heck reaction and hydrogenation reactions are well understood, there is still considerable debate about the precise mechanism of direct arylation of simple arenes. Electrophilic palladation, C−H insertion, and *σ*-bond metathesis have all been advanced as possible mechanisms. See refs 5 and 6.

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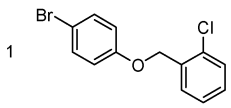
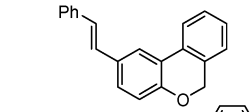
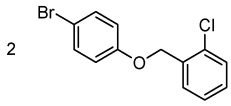
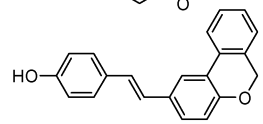
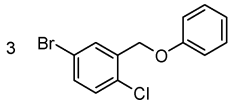
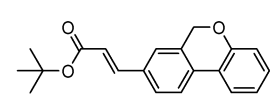
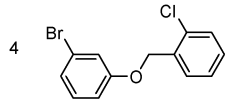
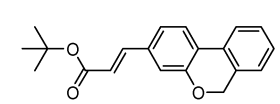
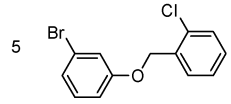
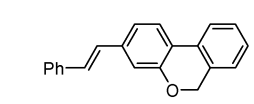
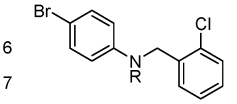
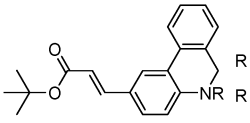
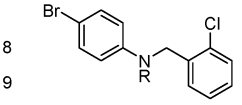
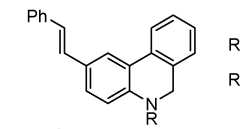
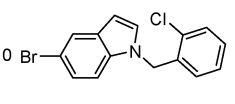
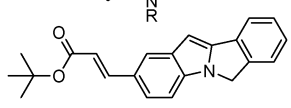
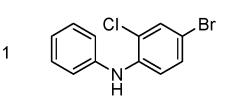
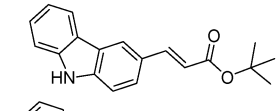
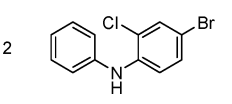
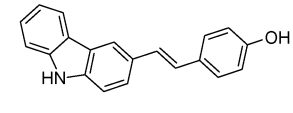
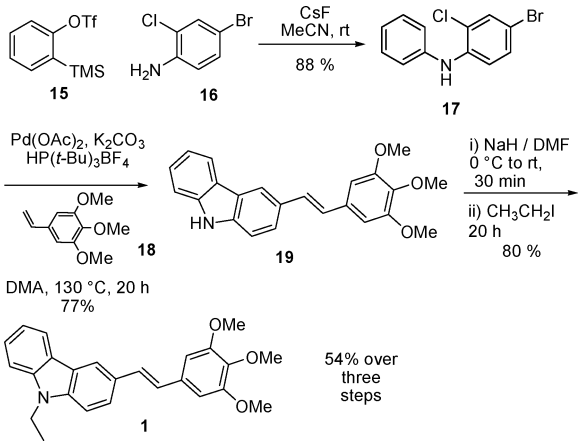
(14) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

TABLE 1. Scope of the Tandem Heck−Direct Arylation Reaction[a]

Entry	Arene	Alkene	Product	Yield (%)[b]
1		A		70
2		B		61
3		C		67
4		C		69
5		A		67
6		C		R = Piv 63
7		C		R = Ms 71
8		A		R = Piv 69
9		A		R = Ms 67
10		C		54
11		C		72
12		B		70

[a] Conditions: Bromochloroarene, $Pd(OAc)_2$ (10 mol %), K_2CO_3 (4 equiv) added to a flask followed by rapid sequential addition of DMA (0.1 M), a stock solution of $P^tBu_3{-}HBF_4$ (20 mol %) in DMA and the alkene (1 equiv) followed by heating to 130 °C. [b] Isolated yield. Alkene **A** = styrene, **B** = 4-acetoxystyrene, **C** = *tert*-butyl acrylate.

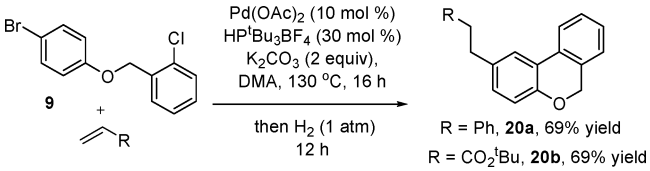
SCHEME 3. Carbazole Synthesis via Tandem Heck, Direct Arylation



a *m*-bromide substrate is employed, high selectivity for direct arylation at the para position is obtained (entries 4 and 5).[15] In addition to ether substrates, nitrogen-containing compounds may also be employed. In these cases, both methanesulfonamide (entries 7 and 9) and pivalamide (entries 6 and 8) functionalities are compatible. In addition to simple arenes, heterocyclic arenes such as indoles can also be reacted (entry 10). This method can also be employed in the synthesis of substituted carbazole molecules (entries 11 and 12). In these cases, protection of the N−H functionality is not required.

This tandem protocol was employed in an efficient synthesis of cytotoxic biaryl **1**[12] (Scheme 3). Reaction of bromochloroaniline **16** with benzyne that is generated in situ from arene **15** occurs in high yield to provide the tandem Heck−direct arylation precursor **17** in 88% yield.[16] Treatment of **17** with trimethoxystyrene **18** under the standard conditions generates substituted carbazole **19** in 77% isolated yield. A final ethylation of the nitrogen atom provides **1** in 54% yield over the three steps.

SCHEME 4. Tandem/Sequential Multifunctional Catalysis: Heck, Direct Arylation, and Hydrogenation



While palladium catalysts are commonly employed in hydrogenation reactions, palladium/phosphine-based catalysts are rarely used. Concerned that such species would not provide acceptable reactivity, we evaluated the compatibility of the tandem Heck−arylation conditions for the hydrogenation of the isolated Heck/arylation product **14**. This concern was borne out, since no hydrogenation was observed after 16 h. On its own, this could indicate that a double tandem Heck−arylation−hydrogenation reaction would not be feasible.

Despite this negative prediction, we were gratified to find that good yields could indeed be achieved when the reactions are run in tandem, despite the fact that the catalyst used at the outset is incompatible with the third reaction of the series. For example, treatment of **9** with 1 equiv of either styrene or *tert*-butyl acrylate under the standard conditions followed by replacement of the nitrogen atmosphere via hydrogen-filled balloon and reaction at 100 °C for an additional 12 h provides **20a** and **20b** in good yield (Scheme 4). This implies that the catalyst is being transformed under the reaction conditions to one that is capable of performing alkene hydrogenation. We observe the formation of insoluble palladium black after the completion of the Heck and arylation steps, which is a common mode of catalyst deactivation in palladium-catalyzed processes. In this case, it is plausible that the palladium colloids are responsible for the hydrogenation chemistry observed. In this way, the sequential process is actually taking advantage of a

(15) See the Supporting Information for regiochemical assignment.
(16) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673.

catalyst deactivation mode to create a catalyst that is capable of carrying out the third reaction in the series. Importantly, this also implies that the reactivity of a single catalyst in individual reactions is not necessarily a good predictor of its behavior in tandem reaction processes. It should also serve as a caution to researchers who may discard the notion of applying a tandem catalytic protocol on the foundation that catalyst reactivity in individual processes is deemed not promising.

In conclusion, we have developed conditions for the preparation of substituted biaryl molecules via tandem Heck−direct arylation and have employed this method in the synthesis of a cytotoxic carbazole compound. We have also reported rare examples of tandem−sequential catalytic Heck−arylation−hydrogenation reactions. In the course of these studies, we discovered that the initial catalyst employed is incompatible with the hydrogenation reactions of the tandem cascade but becomes transformed under the reaction conditions to one capable of achieving the final alkene hydrogenation step.

Experimental Section

Experimental Procedure for the Heck−Direct Arylation Reaction: 2-Styryl-6*H*-benzo[*c*]chromene (14). To an oven-dried Schlenk tube were added 1-(2-chlorobenzyloxy)-4-bromobenzene (106 mg, 0.36 mmol, 1.0 equiv), K_2CO_3 (197 mg, 1.43 mmol, 4.0 equiv), and $Pd(OAc)_2$ (8 mg, 0.036 mmol, 10 mol %). The mixture was then purged with nitrogen for 10 min. Degassed DMA was then added, followed by the addition of a solution containing HP(*t*-Bu)$_3$BF$_4$ (26 mg, 0.071 mmol, 20 mol %) in DMA bringing the reaction concentration to 0.1 M. The reaction mixture was allowed to stir at room temperature for 5 min. Styrene (0.04 mL, 0.36 mmol, 1.0 equiv) was then added, and the reaction temperature was raised to 130 °C. After 20 h, the reaction mixture was filtered through a short pad of Celite using DCM as eluent. DCM was evaporated under reduced pressure, and DMA was removed using a Kugelrohr apparatus. The residue was then purified via chromatotron using 3% dichloromethane in hexane (70%): mp 137−139 °C; IR (ν_{max}/cm^{-1}) 3025, 2926, 2846, 1497, 1447, 1248, 1016, 820; ^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.86 (1H, s), 7.77 (1H, d, J = 7.8 Hz), 7.52 (2H, d, J = 7.5 Hz), 7.43−7.20 (6H, m), 7.16 (1H, d, J = 7.2 Hz), 7.09 (2H, d, J = 9.9 Hz), 5.13 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$, 293K) 154.5, 137.4, 131.5, 131.3, 129.8, 128.7, 128.47, 128.2, 127.8, 127.5, 127.4, 127.2, 126.3, 124.7, 122.9, 122.0, 121.5, 117.7, 68.6; HRMS calcd for $C_{21}H_{16}O$ (M^+) 284.1201, found 284.1181.

Experimental Procedure for the Heck−Direct Arylation−Hydrogenation Reaction: 2-Phenethyl-6*H*-benzo[*c*]chromene (20a). To an oven-dried Schlenk tube were added 1-(2-chlorobenzyloxy)-4-bromobenzene (106 mg, 0.36 mmol, 1.0 equiv), K_2CO_3 (197 mg, 1.43 mmol, 4.0 equiv), and $Pd(OAc)_2$ (8 mg, 0.036 mmol, 10 mol %). The mixture was then purged with nitrogen for 10 min. Degassed DMA was then added, followed by the addition of a stock solution containing HP(*t*-Bu)$_3$BF$_4$ (26 mg, 0.071 mmol, 20 mol %) in DMA bringing the reaction concentration to 0.1 M. The reaction mixture was allowed to stir at room temperature for 5 min. Styrene (0.04 mL, 0.36 mmol, 1.0 equiv) was then added, and the reaction temperature was raised to 130 °C. After 20 h, the atmosphere was replaced with hydrogen via a hydrogen-filled balloon, and the reaction was heated for 24 h at 100 °C under a hydrogen atmosphere. The reaction mixture was then filtered through a short pad of celite using DCM. DCM was evaporated under reduced pressure, and DMA was removed using a Kugelrohr apparatus. The residue was then purified via chromatotron using 5% dichloromethane in hexane (69%): IR (ν_{max}/cm^{-1}) 3062, 3026, 2924, 2855, 1247, 1449, 818, 770; ^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.64 (1H, d, J = 7.5 Hz), 7.50 (1H, d, J = 2.1 Hz), 7.39−7.13 (8H, m), 7.05 (1H, dd, J = 2.4, 6.0 Hz), 6.91 (1H, d, J = 8.1 Hz) 5.09 (2H, s), 2.94 (4H, s); ^{13}C NMR 153.0, 141.7, 135.3, 131.5, 130.2, 129.5, 128.5, 128.3, 127.5, 125.9, 124.6, 123.2, 122.6, 121.9, 117.11, 68.5, 38.2, 37.5; HRMS calcd for $C_{21}H_{18}O$ (M^+) 286.1358, found 286.1355.

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Supporting Information Available: Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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