Heterocycles

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Synthesis of Diversely Functionalized Oxindoles Enabled by Migratory Insertion of Isocyanide to a Transient σ-Alkylpalladium(II) Complex

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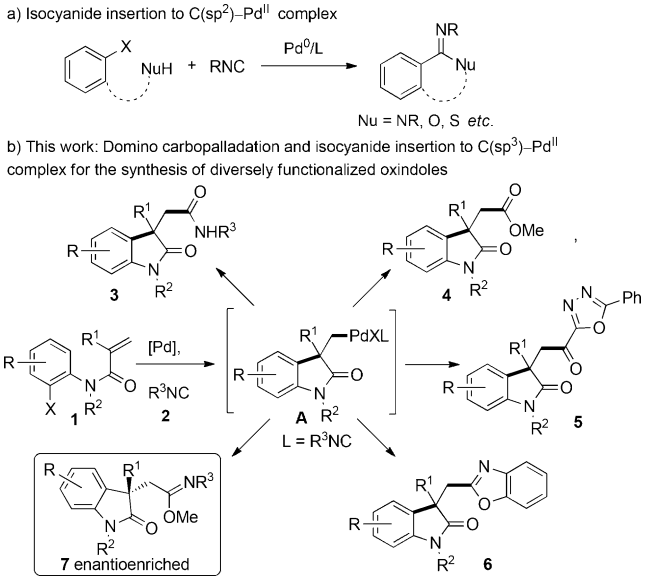
Abstract: *Palladium-catalyzed intramolecular carbopalladation of N-aryl acrylamides followed by migratory insertion of an isocyanide-coordinated C(sp^3)–Pd intermediate afforded an alkylimidoyl–Pd^{II} complex, which can be intercepted by a nucleophile, including heteroarenes. In addition to amides, the alkylimidoyl–Pd^{II} complex was successfully converted into esters, ketones, and bis-heterocyclic compounds. An unprecedented palladium-catalyzed enantioselective domino process involving isocyanide was also documented.*

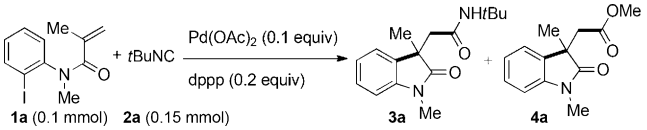
The carbene-like reactivity of the isocyano group has been extensively exploited in the development of multicomponent reactions,[1] insertion reactions,[2] and polymerization processes.[3] Being isoelectronic with carbon monoxide (CO),[4] isocyanides have recently emerged as a valuable C_1 building block in palladium-catalyzed imidoylative/carbonylative coupling reactions.[5] The added advantages of isocyanide relative to CO in such transformations reside on its easy handling, modular reactivity, and ability to bring molecular diversity by its organic residue. Until now, most of the reported imidoylative processes involved a C(sp^2)–Pd^{II} intermediate generated in situ by oxidative addition of palladium to an aryl/vinyl halide (Scheme 1 a). Reactions involving migratory insertion of isocyanide to C(sp^3)–Pd^{II} complexes remain unexploited.[6] In contrast, while the coordinating ability of isocyanide to transition metals has been well appreciated in organometallic chemistry,[7] this property also renders the development of isocyanide-based enantioselective transformations difficult. To the best of our knowledge, only one single example has been reported from the group of Hayashi.[8]

In connection with our interest in palladium-catalyzed domino processes[9] and isocyanide chemistry,[10] we envisaged that an intramolecular carbopalladation of alkenes followed by migratory insertion of the resulting isocyanide-coordinated C(sp^3)–Pd^{II} complex **A** might be an attractive way to form an alkylimidoyl–Pd^{II} species which could be converted into a diversely functionalized oxindoles (Scheme 1 b).[11] We report herein that palladium-catalyzed reactions of N-arylacrylamides (**1**) with isocyanides (**2**) took place smoothly to afford a diverse set of 3,3-disubstituted oxindoles (**3**–**6**) incorporating an amide, an ester, a ketone, and a benzoxazole unit. We also document an unprecedented asymmetric carbopalladation/isocyanide insertion/methoxylation process for the synthesis of enantioenriched imidates (**7**).



Scheme 1. Palladium-catalyzed isocyanide insertion processes.

The reaction between *N*-(2-iodophenyl)-*N*-methyl methacrylamide (**1a**) and *t*BuNC (**2a**) was examined in the presence of a catalytic amount of $Pd(OAc)_2$ and dppp (Scheme 2; see the Supporting Information for a survey of reaction conditions). When the reaction was performed in toluene/H_2O in the presence of Cs_2CO_3, the expected amide **3a** was formed in about 15% yield.[12] After having screened different bases and solvents, we were able to obtain the 3,3-disubstituted oxindole **3a** in 90% yield upon isolation by performing the reaction in toluene/MeOH at 100 °C in the presence of KOH (2.0 equiv). Interestingly, by simply changing the solvent and the base [THF, NaOMe (3 equiv)], the same reaction afforded the ester **4a** in 72% yield upon



Scheme 2. Palladium-catalyzed reaction of the acetanilide **1a** with *t*BuNC (**2a**). Synthesis of the amide **3a** and ester **4a** by small changes in reaction conditions: KOH (2.0 equiv) in toluene/MeOH = 5:1 (2.0 mL) at 100 °C leads to **3a** in 90% yield; and NaOMe (3.0 equiv) in THF (2.0 mL) at 100 °C leads to **4a** in 72% yield. dppp = 1,3-bis(diphenylphosphanyl)propane.

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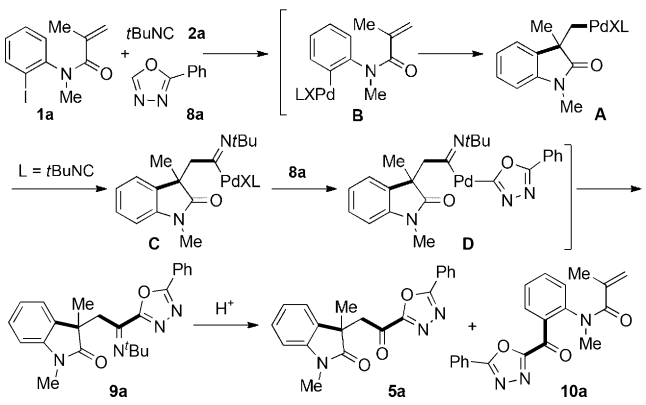
isolation. To the best of our knowledge, direct conversion of isocyanides into esters under imidoylative conditions is unprecedented.

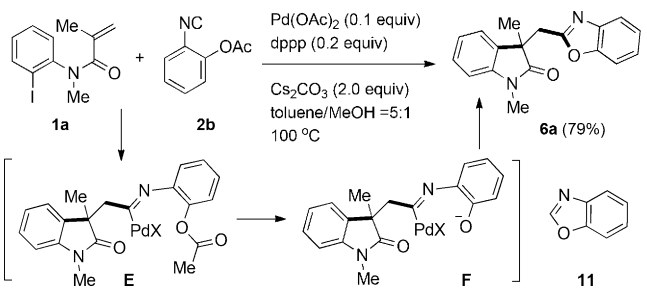
A three-component reaction of **1a**, **2a**, and 2-phenyl-1,3,4-oxadiazole (**8a**) was next investigated. The underlying principle is shown in Scheme 3. Oxidative addition of



Scheme 3. Three-component synthesis of ketone **5**. Optimized reaction conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), *t*BuDavePhos (0.2 equiv), 2-phenyl-1,3,4-oxadiazole (**8a**, 1.5 equiv), **2a** (2.0 equiv), Cs_2CO_3 (2.0 equiv), MeCN (2.0 mL), 110 °C; then HCl (1 N), RT, 2 h. *t*BuDavePhos = 2-Di-*tert*-butylphosphino-2′-(*N*,*N*-dimethylamino)-biphenyl.

isocyanide-ligated palladium(0) to aryliodide would afford **B**, which upon intramolecular carbopalladation, would furnish the $C(sp^3)$–Pd^{II} intermediate **A** (R = H, $R^1 = R^2 = Me$). Migratory insertion of isocyanide would provide the alkylimidoyl–Pd^{II} species **C** which was expected to activate, intermolecularly, the C–H bond of **8a** leading to **D**. Reductive elimination would afford **9a**,[13] whose hydrolysis under acidic conditions would then furnish the ketone **5a**. Three C–C bonds would be created in this multicomponent reaction. After extensive screening of reaction conditions, the desired ketone **5a** was isolated in 72% yield together with **10a** (12%) by performing the reaction in MeCN in the presence of $Pd(OAc)_2$ (0.1 equiv), *t*Bu-Davephos (0.2 equiv), and Cs_2CO_3 (2.0 equiv) at 100 °C. The formation of **10a** could be accounted for by migratory insertion of isocyanide from **B** followed by direct imidoylation of oxadiazole.[14] It is interesting to note that the ligand plays a key role in the product distribution. Using dppp as ligand under otherwise identical reaction conditions, **5a** and **10a** were formed in a one to one ratio (for details, see Table S2 in the Supporting Information). The fact that direct arylation of the palladium(II) intermediates **A** (R = H, $R^1 = R^2 = Me$) and **B** by oxadiazole[15,16] was not observed indicates that migratory insertion of isocyanide from these two complexes was a kinetically faster process. The high chemoselectivity observed is truly remarkable since neither the amide **3a** nor ester **4a** were isolated although methanol was used as a cosolvent.

Reaction of the functionalized isocyanide **2b** with **1a** afforded the bis(heterocyclic) compound **6a** in 79% yield under optimized reaction conditions (Scheme 4; see Table S3).[17] The domino process went presumably via the



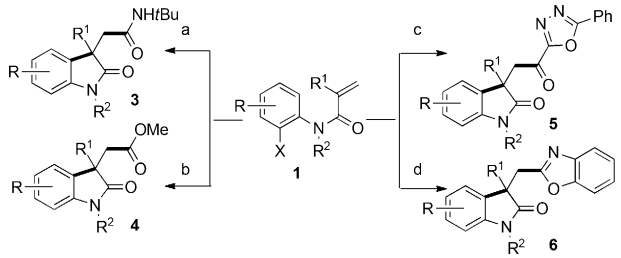
Scheme 4. Synthesis of the oxindole-benzoxazole framework **6a**.

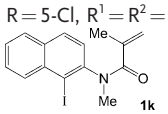
intermediate **E**, which, upon methanolysis, would afford the phenoxide **F**. Ligand exchange followed by reductive elimination would then provide the compound **6a** with concurrent regeneration of the palladium(0) catalyst. Alternatively, rapid hydrolysis of acetate followed by cyclization would convert **2b** into **11**, which can then be alkylated by **A** (R = H, $R^1 = R^2 = Me$) to give **6a**.[18]

The scope and limitations of these new transformations were next examined and the results are shown in Table 1. Reaction of the N-benzyl acetanilide **1b** with *t*BuNC under four sets of reaction conditions afforded four different compounds, **3b**, **4b**, **5b**, and **6a** in good to excellent yields (entry 2). Since the N-benzyl group is readily removed, it constitutes a route to NH oxindoles. The introduction of an *n*-hexyl (**1c**), a methoxymethyl (**1d**), and a phenyl (**1e**) substituent at the C_α-position (R^1) of the acrylamide exerted only a minor effect on the reaction outcome (entries 3–5). Substrates bearing an electron-donating group (**1f–h**; entries 6–8) and an electron-withdrawing group (**1i**, **1j**; entries 9 and 10) on the aniline residue all underwent the domino process efficiently. Even the sterically encumbered C3-substituted aryl iodide **1h** participated in the reaction to provide the desired oxindoles in good yields (entry 8). *N*-(Naphthalen-2-yl)amide **1k** was converted to **3k 4k**, **5k** and **6k**, respectively, without event (entry 11). Finally, reaction of 1,1,3,3-tetramethylbutyl isocyanide with **1a** afforded **3l** and **4a** in yields of 85 and 62%, respectively (for structure of **3l**, see the Supporting Information).

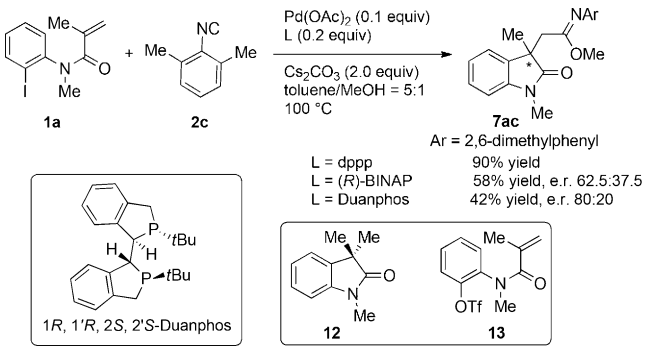
The development of a metal-catalyzed enantioselective isocyanide-based domino process remained exceptionally challenging. Indeed, coordination of isocyanide to the metal/chiral ligand complex could destroy or modify its chiral coordination sphere, hence the asymmetric induction. Our initial efforts on the enantioselective version of the aforementioned transformations using isocyanides **2a** and **2b** met with failure.[19] Reasoning that bulky aryl isocyanides might diminish the adverse coordinative interaction of isocyanide with palladium, 2,6-dimethylphenyl isocyanide **(2c)** was chosen as a reaction partner (Scheme 5). Interestingly, the carboximidate **7ac** was isolated in 90% yield under reaction conditions optimized for the formation of compound **6a** [**1a** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), dppp (0.2 equiv), **2c** (2 equiv), Cs_2CO_3 (2 equiv), toluene/MeOH = 5:1 (2.0 mL), 100 °C].[20] Furthermore, **7ac** was isolated in 58% yield with an enantiomeric ratio (e.r.) of 62.5:37.5 when (*R*)-BINAP was used as a ligand (see Table S4–1).[21] Addition of Ag_3PO_4 as

Table 1: Synthesis of diversely functionalized oxindoles.



Entry	1	Yield [%][a]			
		3	4	5	6
1	R = H, $R^1 = R^2$ = Me (**1a**)	**3a** (90)	**4a** (71)	**5a** (72)	**6a** (79)
2	R = H, R^1 = Me, R^2 = Bn (**1b**)	**3b** (80)	**4b** (70)	**5b** (70)	**6b** (74)
3	R = H, $R^1 = nC_6H_{13}$, R^2 = Me (**1c**)	**3c** (71)	**4c** (78)	**5c** (64)[b]	**6c** (65)
4	R = H, $R^1 = CH_2OMe$, R^2 = Me (**1d**)	**3d** (51)	**4d** (60)	**5d** (68)	**6d** (64)
5	R = H, R^1 = Ph, R^2 = Me (**1e**)	**3e** (72)	**4e** (70)	**5e** (< 5)	**6e** (70)
6	R = 4-*t*Bu, $R^1 = R^2$ = Me (**1f**)	**3f** (83)	**4f** (66)	**5f** (62)	**6f** (78)
7	R = 4-OMe, $R^1 = R^2$ = Me (**1g**)	**3g** (72)	**4g** (70)	**5g** (74)	**6g** (78)
8	R = 3-Me, $R^1 = R^2$ = Me (**1h**)	**3h** (75)	**4h** (66)	**5h** (66)	**6h** (76)
9	R = 4-F, $R^1 = R^2$ = Me (**1i**)	**3i** (74)	**4i** (61)	**5i** (60)	**6i** (73)
10	R = 5-Cl, $R^1 = R^2$ = Me (**1j**)	**3j** (68)	**4j** (55)	**5j** (68)	**6j** (70)
11	 **1k**	**3k** (74)	**4k** (68)	**5k** (67)	**6k** (76)

Reaction conditions: a) **1** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), dppp (0.2 equiv), **2a** (1.5 equiv), KOH (2.0 equiv), toluene/MeOH = 5:1 (1.8 mL), 100 °C. b) **1** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), dppp (0.2 equiv), **2a** (1.5 equiv), NaOMe (5.4 M in MeOH, 0.05 mL), THF (2.0 mL), 100 °C. c) **1** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), *t*BuDavePhos (0.2 equiv), 2-phenyl-1,3,4-oxadiazole (**8a**, 1.5 equiv), **2a** (2.0 equiv), Cs_2CO_3 (2.0 equiv), MeCN (2.0 mL), 110 °C; then HCl (1 N), RT, 2 h. d) **1** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), dppp (0.2 equiv), **2b** (2.0 equiv), Cs_2CO_3 (2.0 equiv), toluene/MeOH = 5:1 (1.8 mL), 100 °C. [a] Yield is that of the isolated product. [b] 2-(4-(trifluoromethoxy)phenyl)-1,3,4-oxadiazole was used instead of **8a**.



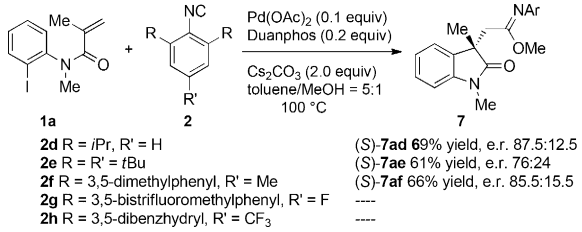
Scheme 5. Enantioselective domino process between **1a** and **2c**. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, Tf = trifluoromethanesulfonyl.

a halide scavenger provided 1,3,3-trimethylindolin-2-one (**12**) as a major product in 50% yield. In line with this result, the aryl triflate **13** failed to afford the desired product.

Encouraged by this preliminary result, a wide range of chiral ligands was screened (Scheme 5; see Table S4–2). An electron-rich and conformationally rigid *P*-stereogenic bis(phospholane) ligand (1*R*,1′*R*,2*S*,2′*S*-Duanphos)[22] proved to be the most effective in terms of enantioselectivity, thus providing **7ac** with a promising e.r. value of 80:20. Aiming at further increasing the enantioselectivity of the process, the structure of the aryl isocyanides was next examined (Scheme 6). Gratefully, using the sterically more demanding 2,6-diisopropylphenyl isocyanide (**2d**), the desired product **7ad** was isolated in 69% yield with an e.r. value of 87.5:12.5. A similar result was obtained with 2,6-di(3,5-dimethylphenyl)-6-methylphenyl isocyanide (**2f**). However, enantioselectivity was reduced with the bulkier isocyanide **2e**. By using electron-deficient isocyanides **2g** (R′ = F) and **2h** (R′ = CF_3), only the reduced product **12** was isolated in yields of 50 and 52%, respectively.

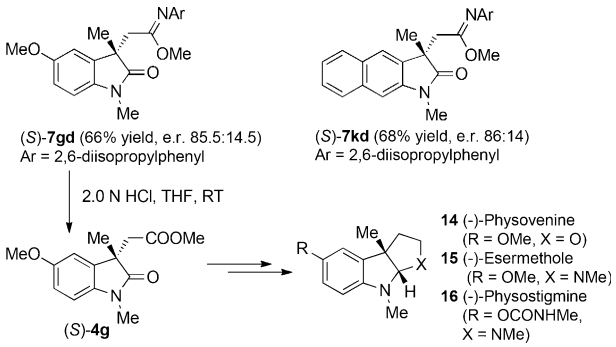
Applying this enantioselective domino imidoylative Heck reaction to **1g** and **1k** led to the formation of the corresponding oxindoles (*S*)-**7gd** and (*S*)-**7kd** with e.r. values of 85.5:14.5 and 86:14, respectively (Scheme 7). Hydrolysis of (*S*)-**7gd** under acidic conditions (2.0 N HCl, THF, RT) afforded the ester **4g** whose absolute configuration was determined to be *S* by comparison of its optical rotation value with that reported in the literature.[23] (*S*)-**4g** is a known precursor of (−)-physovenine (**14**), (−)-esermethole (**15**, and (−)-physostigmine (**16**).[23] We note that previous efforts on the palladium-catalyzed carbonylative Heck reaction of **1a** with CO afforded **4** with an e.r. value of 64:36.[24]

In conclusion, we have developed a series of palladium-catalyzed domino processes involving migratory insertion of isocyanide to the $C(sp^3)$–



Scheme 6. Effect of isocyanide structure on the enantioselectivity of the domino process.

Pd^{II} complex generated by an intramolecular carbopalladation reaction. Depending on the reaction conditions, the reaction can be tuned to generate either the amides **3** or esters **4**.[25] In addition, a three-component reaction involving a key intermolecular direct arylation of an alkylimidoyl–Pd^{II} complex was documented for the first time[26] and a cyclizative heterocoupling reaction[27] leading to the indolinone-benzoxazole framework was achieved using a functionalized isocyanide (**2b**). An enantioselective domino carbopalladation/isocyanide insertion/methoxylation has been developed. Efforts are ongoing to decipher factors controlling the enantioselectivity of transition metal catalyzed processes involving isocyanide as a substrate, a still unsolved problem in asymmetric catalysis.



Scheme 7. Application of enantioselective imidoylative Heck process. THF = tetrahydrofuran.

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Keywords: asymmetric synthesis · heterocycles · multicomponent reactions · palladium · synthetic methods

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