Homogeneous Catalysis

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# Catalytic Enantioselective Aminopalladation–Heck Cascade

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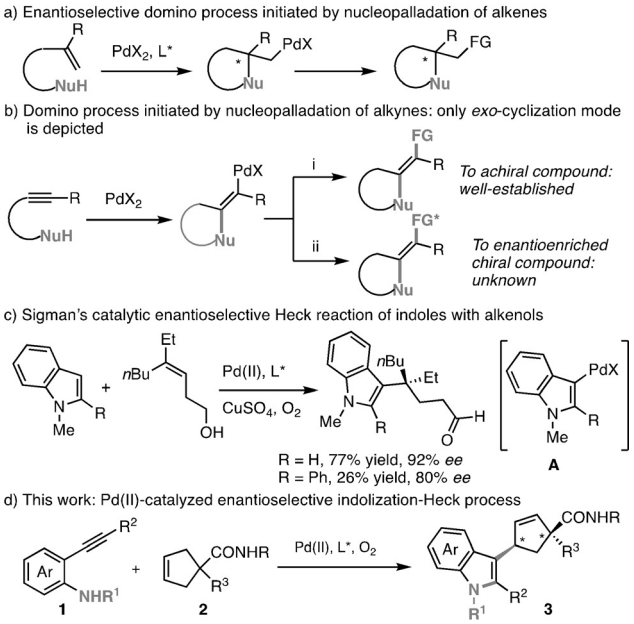
***Abstract:*** *Domino processes initiated by intramolecular nucleopalladation of alkynes have been developed into powerful synthetic tools for the synthesis of functionalized heterocycles. However, a catalytic enantioselective version of this class of reactions remains scarce. We report herein that reaction of 2-alkynylanilines with prochiral cyclopentenes in the presence of a catalytic amount of $Pd(OAc)_2$, a chiral bidentate pyrox ligand and $O_2$ as terminal oxidant affords the structurally diverse indole-cyclopentene conjugates bearing two stereocenters in a highly diastereo- and enantio-selective manner. One of the products is converted to a heavily functionalized tetracyclic indolinone derivative.*

The nucleopalladation of alkenes is an important elementary step in the transitional metal catalyzed transformations. As the reaction generates at least one stereocenter, the development of catalytic enantioselective versions has attracted a great deal of recent attention (Scheme 1 a).[1] In parallel, the nucleopalladation of alkynes followed by trapping of the resulting achiral vinylpalladium intermediates has also been developed into a powerful synthetic tool (Scheme 1 b-i).[2] For example, the $Pd^{II}$-catalyzed 5-*endo* cyclization of 2-alkynylanilines[3] has been successfully combined with Heck reaction,[4] Sonogashira reaction,[5] carbocyclization,[6] Suzuki reaction,[7] amination,[8] carboesterification,[9] alkoxycarbonylation,[10] imidoylation[11] and nucleophilic addition to aldehydes[12] for the synthesis of 2,3-difunctionalized indoles (Scheme 1 b-i). However, applying this strategy to the synthesis of chiral molecules remains scarce (Scheme 1 b-ii). Indeed, except for recent achievement on the synthesis of axially chiral biaryls,[13] enantioselective domino reaction initiated by nucleopalladation of alkynes for the construction of enantioenriched centrally chiral molecules remains, to the best of our knowledge, unknown.

Recent years have witnessed the significant progress in the development of $Pd^{II}$-catalyzed enantioselective oxidative




***Scheme 1.*** Nucleopalladation and oxidative asymmetric Heck reaction: The state of the art and our reaction design.

Heck reaction between arylboronic acids and alkenes.[14–20] However, the heteroarene-derived boronic acids, with few exceptions, are notably absent in the scope exploration of these reports. In this regard, the successful use of 1-tosyl-1*H*-indol-3-yl boronic acid as a reaction partner in the asymmetric redox-relay oxidative arylation of alkenols is noteworthy.[16a] While the enantioselectivity was high, the yield is moderate due to the instability of these boronic acids under the reaction conditions. To address this issue, Sigman developed an enantioselective dehydrogenative Heck reaction of indoles with trisubstituted alkenols (Scheme 1 c).[21] While the reaction works well with 2,3-unsubstituted indoles, the yield of the Heck adduct drops significantly when the 2-substituted indole is used as a reaction partner. The presence of strong electron-withdrawing group in the phenyl ring of the indole is also not tolerated in line with the proposed reaction mechanism. Therefore, a new approach is still needed in order to incorporate the diversely substituted indole moiety to the chiral molecules.

The in situ generated indolylPdX species **A** (Scheme 1 c) is proposed to be the intermediate in the reaction developed by Sigman. Since the $PdX_2$-catalyzed aminopalladation of 2-alkynylaniline **1** generated the same intermediate **A**, we reasoned that it could be interesting to combine this reaction with the enantioselective Heck reaction for the synthesis of indole-containing chiral molecules. We report herein the realization of this endeavour by developing a domino aminopalladation-oxidative Heck reaction of 2-alkynylanilines

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**1** with prochiral cyclopentenes **2** for the synthesis of enantioenriched indole-cyclopentene conjugates **3** (Scheme 1 d).

We began our studies by examining the reaction of *N*-(2-(phenylethynyl)phenyl)methanesulfonamide (**1a**) with *N*-benzyl-1-phenylcyclopent-3-ene-1-carboxamide (**2a**). After initial survey of the reaction parameters, the structure of chiral ligands was fine-tuned by performing the reaction in the presence of $Pd^{II}$ complex (0.1 equiv), a chiral ligand (0.12 equiv) at 50 °C under oxygen atmosphere. Heating a 1,2-dichloroethane solution of **1a** and **2a** in the presence of palladium(II) acetate, Box ligand **L1** (Figure 1) afforded the desired product **3a** in 25 % yield with 70 % *ee* (entry 1, Table 1). Using pyrox ligand **L2** under otherwise identical

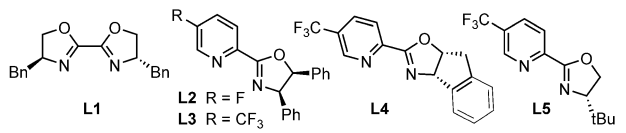
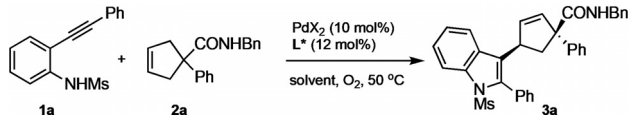



***Figure 1.*** Structure of the chiral ligands.

conditions, the product **3a** was isolated in a slightly increased yields and enantiopurity. Dramatically improved enantioselectivities were observed when $CF_3$-pyrox **L3**–**L5** were employed as ligands and **L5** stood out in terms of enantioselectivity (entry 5). Other palladium(II) salts, such as $Pd(OPiv)_2$ and $Pd(TFA)_2$ gave the product **3a** in lower yields (entries 6–7). After further optimization of the reaction parameters varying the palladium loading, Pd/**L5** ratio, reaction temperature and solvents, the optimum conditions consisted of performing the reaction of **1a** with **2a** in DCE

***Table 1:*** Optimization of reaction conditions.[a]

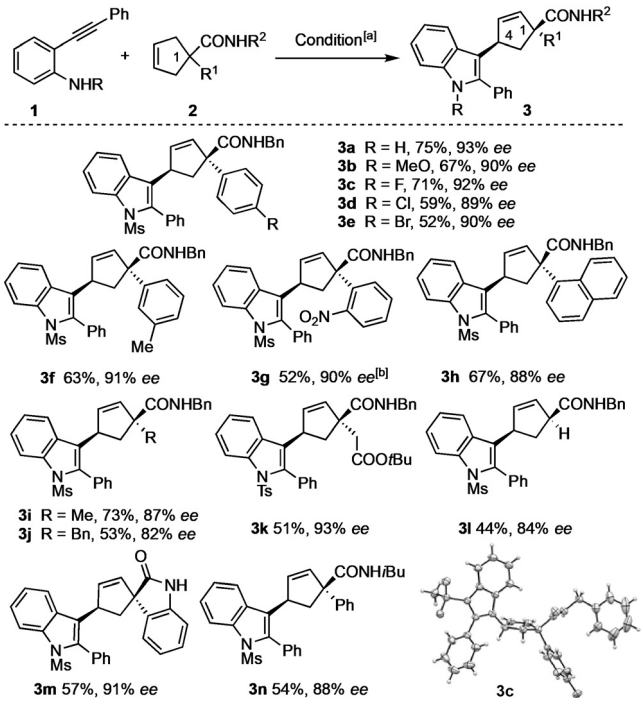



| Entry | L* | $PdX_2$ | Solvent | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **L1** | $Pd(OAc)_2$ | DCE | 25 | 70 |
| 2 | **L2** | $Pd(OAc)_2$ | DCE | 35 | −72 |
| 3 | **L3** | $Pd(OAc)_2$ | DCE | 39 | −88 |
| 4 | **L4** | $Pd(OAc)_2$ | DCE | 43 | 88 |
| 5 | **L5** | $Pd(OAc)_2$ | DCE | 38 | 93 |
| 6 | **L5** | $Pd(OPiv)_2$ | DCE | 15 | ND |
| 7 | **L5** | $Pd(TFA)_2$ | DCE | 18 | ND |
| 8[d] | **L5** | $Pd(OAc)_2$ | DCE | 72 | 93 |
| 9[d] | **L5** | $Pd(OAc)_2$ | Toluene | 67 | 85 |
| 10[d] | **L5** | $Pd(OAc)_2$ | THF | 50 | 85 |
| 11[d] | **L5** | $Pd(OAc)_2$ | DMF | 63 | 91 |
| 12[d] | **L5** | $Pd(OAc)_2$ | $CHCl_3$ | 38 | 93 |
| **13**[e] | **L5** | **$Pd(OAc)_2$** | **DCE** | **75** | **93** |

[a] General conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), chiral Ligand (0.12 equiv), DCE (2.0 mL), 50 °C, $O_2$ balloon, 24 h. [b] Isolated yield, d.r. > 19:1. [c] Determined by SFC analysis on a chiral stationary phase. [d] $Pd(OAc)_2$ (0.15 equiv), chiral Ligand (0.18 equiv) were used, the reaction time was 72 h. [e] **1a** (0.12 mmol), **2a** (0.1 mmol), DCE (0.6 mL) at 60 °C for 72 h.

($c = 0.17$ M, oxygen atmosphere, 60 °C) in the presence of a catalytic amount of $Pd(OAc)_2$ (10 mol %) and **L5** (12 mol %). Under these conditions, **3a** was isolated in 75 % yield with 93 % *ee* (d.r. > 19:1, entry 13). We note that in the absence of oxygen under otherwise identical conditions, reaction of **1a** with **2a** afforded compound **3a** in only 7 % yield corresponding roughly to the catalyst loading.

With the optimized conditions in hands, we proceed to explore the scope of this domino indolization/enantioselective oxidative Heck reaction starting with substituted cyclopentenes **2** (Scheme 2). The C1 aromatic substituent bearing an electron-donating (MeO, Me) and an electron-withdrawing group (F, Cl, Br, $NO_2$) at different positions (*para*, *meta*

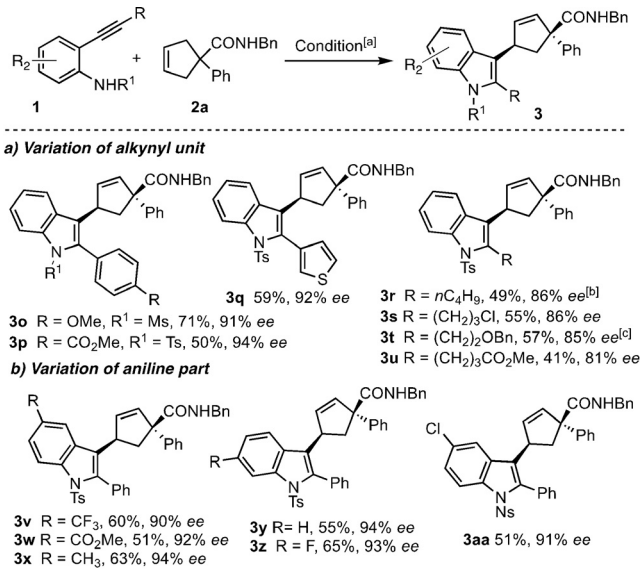



***Scheme 2.*** Scope of cyclopenetenes. [a] General conditions: **1** (0.12 mmol), **2** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), **L5** (12 mol %), DCE (0.17 M), 60 °C, $O_2$ balloon. The *ee* was determined by SFC analysis on a chiral stationary phase. [b] d.r. = 15:1.

and *ortho*) is compatible with the reaction conditions (**3b**–**3g**), so is the α-naphthyl unit (**3h**). The C1 aliphatic substituent including the functionalized one (Me, Bn, $CH_2CO_2tBu$) in compound **2** is well tolerated affording the desired products **3i**–**3k** without event. Finally, the C1 unsubstituted cyclopentene participates in the reaction to afford **3l** in a moderate yield. A cyclopentene containing both an indole and an oxindole moiety **3m** is similarly prepared starting from the corresponding spirooxindole. The amide part can also be varied as showcased by the preparation of compound **3n** bearing an isobutyl carboxyamide. The (1*S*,4*R*)-absolute configuration of **3c** is determined by X-ray crystallographic analysis and the configuration of the other products are assigned in analogy.[22]

A series of structurally diverse 2-alkynylanilines are next evaluated to further probe the reaction scope (Scheme 3).

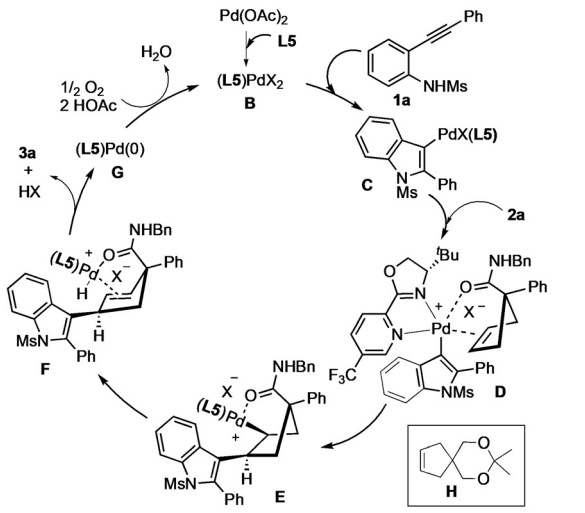
  




***Scheme 3.*** Scope of 2-alkynylanilines. [a] General conditions: **1** (0.12 mmol), **2** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), **L5** (12 mol%), DCE (0.17 M), 60°C, $O_2$ balloon. The *ee* was determined by SFC analysis on a chiral stationary phase. [b] d.r. = 13:1. [c] d.r. = 15:1.

The electron-rich (**3o**, R = OMe) and electron-poor phenyl (**3p**, R = $CO_2$Me) substituent as well as heterocycle (thiophene, **3q**) on the alkynyl part are tolerated. Pleasingly, aliphatic alkynes participate in the reaction leading to the corresponding products (**3r–3u**), albeit with diminished yields. The presence of functional groups such as alkyl chloride (**3s**), alkyl benzyl ether (**3t**) and methoxycarbonyl group (**3u**) is compatible with the reaction conditions. However, the terminal alkyne (R = H) is incompatible with the present oxidative conditions. The presence of diverse functional groups such as halide (**3aa**, R = Cl; **3z** R = F), $CF_3$ (**3v**) and importantly methoxycarbonyl group (**3w**) in the aromatic part of the aniline is well tolerated. As it would be expected, the *N*-Ts (**3q–3z**) and the easily removable *N*-Ns (**3aa**) groups are effective nucleophiles for this transformation. Compound **3aa** is prepared in a gram scale with a similar yield and *ee* (1.18 g, 50%, 91% *ee*) indicating the practicality of the present enantioselective domino process.

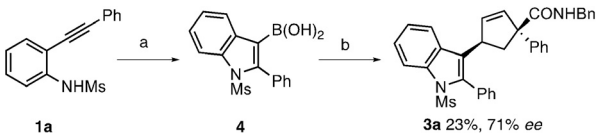
A possible reaction pathway is depicted in Scheme 4 using **1a** and **2a** as reaction partners. An intramolecular aminopalladation of **1a**, catalyzed by (**L5**)$PdX_2$ **B** in situ formed by ligation of pyrox ligand to Pd acetate, would afford the indolylPdX species **C**. Coordination of **C** to the double bond of **2a** directed by the amide function would generate the $Pd^{II}$ complex **D** which defined the face selectivity of the subsequent *syn*-carbopalladation to afford the $Pd^{II}$ species **E**.[23] A β-hydride elimination from **E** would afford **F** which, upon decomplexation and reductive elimination of HX from the resulting HPdX would generate the enantioenriched indole derivative **3a** and $Pd^0$. The latter would be oxidized by oxygen and acetic acid to re-generate the catalytic species **B**,[24] completing therefore the catalytic cycle. We note that in principle compound **2a** could also undergo an intramolecular aminopalladation to afford a 2-azabicyclo[2.2.1]heptanone skeleton. However, this pathway is apparently dominated by




***Scheme 4.*** Possible reaction pathway.

the desired aminopalladation of 2-alkynylaniline **1a**. On the other hand, the reaction of compound **H** (Scheme 4, inset) with **1a** failed to produce the desired product indicating the importance of the amide function for the present transformation.

We have synthesized [1-(methylsulfonyl)-2-phenyl-3-yl]boronic acid (**4**) via $BCl_3$-mediated cyclization of 2-alkynylaniline (Scheme 5).[25] Reaction of **4** with **2a** under our standard conditions afforded **3a** in only 23% yield with 71% *ee*, together with 1-(methylsulfonyl)-2-phenyl-1*H*-indole

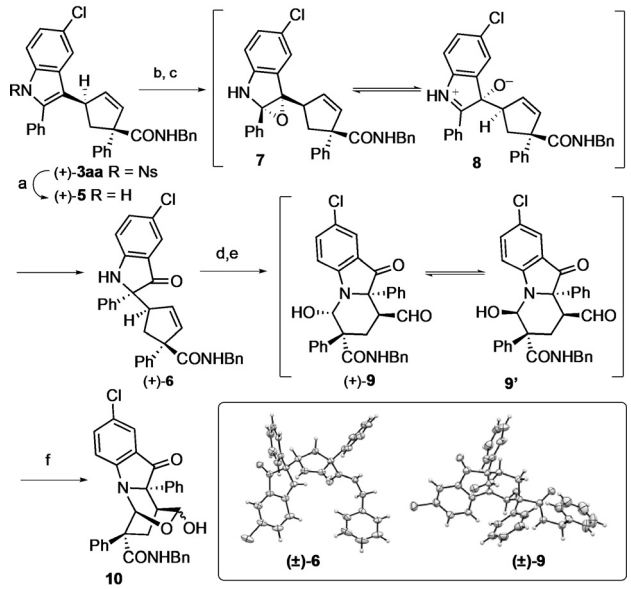



***Scheme 5.*** Results of enantioselective oxidative Heck reaction using pre-synthesized 3-borylated indole as a nucleophile. [a] $BCl_3$, DCM, RT, then $H_2O$. [b] **2a**, $Pd(OAc)_2$ (10 mol%), **L5** (12 mol%), $O_2$, DCE, 60°C.

resulting from the protodeborination of **4** as a major product (65%, structure not shown). This result is in line with Sigman's earlier observations[16a,21] and illustrates clearly the advantage of our domino aminopalladation/oxidative Heck process related to the classical stepwise approach.

Taking advantage of the multiple functionalities in compound **3**, a variety of post-transformations could be envisaged. One of such examples exploiting the selective functionalization of the two double bonds in **3aa** is shown in Scheme 6.[26] Removal of the *N*-Ns group[27] from **3aa** afforded **5** which upon chemoselective epoxidation of indole double bond with the in situ generated dimethyldioxirane followed by scandium triflate promoted Wagner–Meerwein rearrangement furnished oxindole **6** in 53% yield.[28] The relative stereochemistry of **6** was determined by the X-ray structure analysis of its racemic form. It is reasonable to assume that epoxidation occurred preferentially from the α face of the double bond for the steric reason to afford **7** as a major stereoisomer. Ring




***Scheme 6.*** Synthetic transformation of product **3aa**. Reaction conditions: [a] PhSH, $Cs_2CO_3$, MeCN, 50 °C, 76% yield; [b] Oxone, $NaHCO_3$, acetone/$H_2O$, 0 °C; [c] $Sc(OTf)_3$, toluene, 110 °C, 53% yield over two steps; [d] $OsO_4$, NMO, acetone/$H_2O$, 51% yield, 92% based on recovered starting material, d.r. = 1.4:1; [e] $Pb(OAc)_4$, MeCN, 0 °C, 71% yield; [f] $CHCl_3$, 95% yield, d.r. = 1.3:1.

opening of epoxide assisted by the lone pair of nitrogen afforded **8** which, upon a 1,2-suprafacial shift of the cyclopentyl unit, would then provide **6**. Dihydroxylation of the cyclopentene followed by oxidative cleavage of the resulting diol furnished an isolable hemiaminal **9** whose relative stereochemistry was determined by X-ray structural analysis of (±)-**9**. Compound **9**, unstable in solution, was readily converted to the hemiacetal **10** via presumably its epimeric aminal **9′**. The structures of **9** and **10** are reminiscent of the rearranged eburnane alkaloids.[29]

In summary, we have developed the first examples of catalytic enantioselective aminopalladation/Heck reaction cascade for the synthesis of functionalized cyclopentene-indole conjugates with high diastereo- and enantio-selectivities. The indolyl$Pd^{II}$ species generated via aminopalladation has a clear-cut advantage in the oxidative Heck reaction relative to those generated by transmetallation of the indolylboronic acids or by the CH activation. In view of the established efficiency of the nucleopalladation process, we expect that this strategy could be generally applicable to the synthesis of chiral heterocyclic compounds.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** asymmetric synthesis · domino reactions · homogeneous catalysis · nucleopalladation · oxidative Heck reactions

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