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Palladium Catalysis

Orthogonal Regulation of Nucleophilic and Electrophilic Sites in Pd-Catalyzed Regiodivergent Couplings between Indazoles and Isoprene

Wen-Shuang Jiang[+], Ding-Wei Ji[+], Wei-Song Zhang, Gong Zhang, Xiang-Ting Min, Yan-Cheng Hu, Xu-Liang Jiang, and Qing-An Chen**

Abstract: *Depending on the reactant property and reaction mechanism, one major regioisomer can be favored in a reaction that involves multiple active sites. Herein, an orthogonal regulation of nucleophilic and electrophilic sites in the regiodivergent hydroamination of isoprene with indazoles is demonstrated. Under Pd-hydride catalysis, the 1,2- or 4,3-insertion pathway with respect to the electrophilic sites on isoprene could be controlled by the choice of ligands. In terms of the nucleophilic sites on indazoles, the reaction occurs at either the N^1- or N^2-position of indazoles is governed by the acid co-catalysts. Preliminary experimental studies have been performed to rationalize the mechanism and regioselectivity. This study not only contributes a practical tool for selective functionalization of isoprene, but also provides a guide to manipulate the regioselectivity for the N-functionalization of indazoles.*

Introduction

Dimethylallyl-related units are ubiquitous five-carbon (C5) skeletons in natural and bioactive compounds.[1] The existence of these groups usually plays a significant role in enhancing the lipophilicity of molecules and facilitating permeation across the cellular membrane.[2] Therefore, the installation of such motifs into important frameworks has become an active research area in organic chemistry and drug discovery.[3] In nature, prenylated and reverse-prenylated moieties are usually assembled by employing dimethylallyl pyrophosphate (DMAPP) as starting materials through enzyme catalyzed biosynthesis,[4] whereas their isomeric variants are less commonly encountered (Figure 1 A). Owing to its low cost and large-scale production, isoprene can serve as an attractive precursor in the chemical synthesis of dimethylallyl-derived molecules.[5] As a result, tremendous effort has been devoted to the functionalization of isoprene.[6] Among them, the catalytic hydrofunctionalization process represents the most atom-economic protocol.[7] However, most of the established methods focus on the regioselective synthesis of one major isomer, despite multiple isomeric

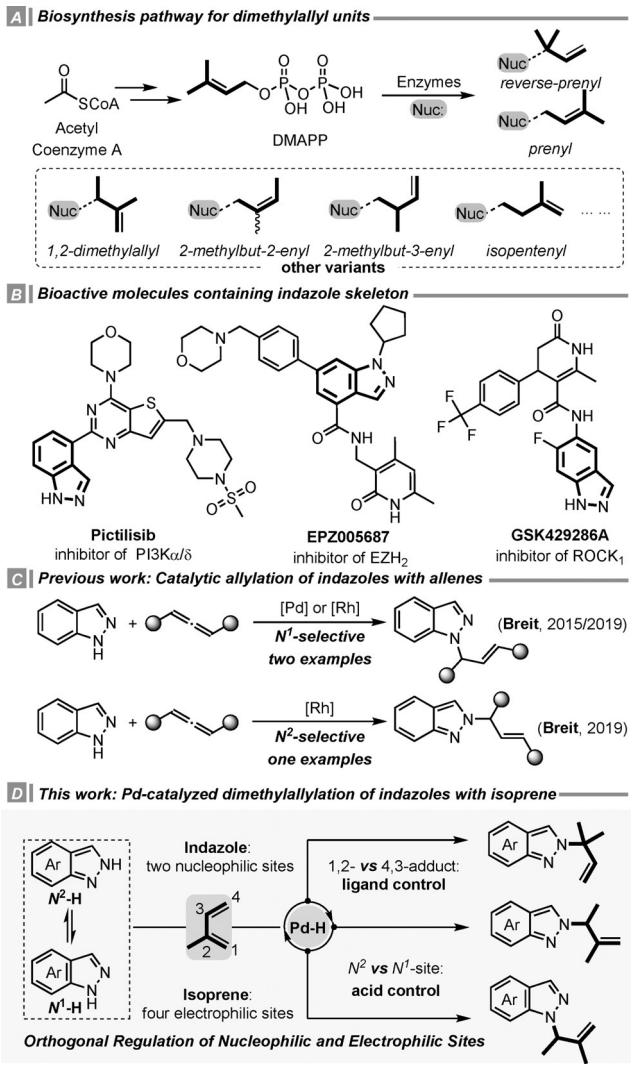

Figure 1. A) Biosynthesis pathway for dimethylallyl units (B) Bioactive molecules containing the indazole skeleton (C) Catalytic allylation of indazoles with allenes (D) Pd-catalytic regiodivergent dimethylallylation of indazole with isoprene.

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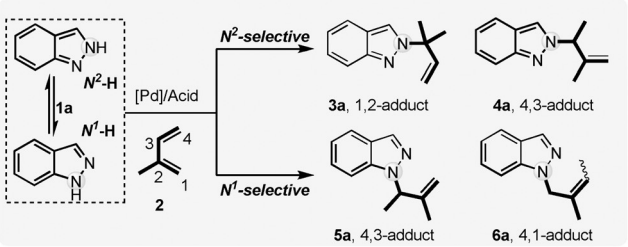
outcomes possible. The development of regiodivergent methodologies, which is of great importance to synthetic efficiency and molecular diversity, still remains in its infancy.[8,9]

Indazoles are pharmacologically important scaffolds that usually serve as indole bioisosteres in medicinal research (Figure 1 B).[10] The direct allylation of indazoles is one of the most efficient methods to derivatize these molecules.[11,12] Nevertheless, the presence of tautomeric forms inevitably introduces site-selectivity challenges. Normally, the direct *N*-allylation of indazoles under basic conditions delivers a mixture of N^1 and N^2-allylic products.[13] The successful discovery of efficient catalysis for the selective *N*-allylation of indazoles is very limited.[14,15] In 2015, Lin and co-workers reported a metal-mediated regioselective N^2-allylation of indazoles with allyl bromides in the presence of stoichiometric gallium or aluminum metal. With the aid of excess amount of titanium tetraisopropoxide, a Pd-catalyzed protocol was also disclosed by Wu et al. for the N^1-selective allylation of the unsubstituted indazole with allylic alcohols. Very recently, Breit's group reported an impressive achievement in metal catalyzed couplings of indazole with allenes (Figure 1 C).[16] In our continued interest towards regiodivergent transformations of isoprene,[6k,9h,j] it is noteworthy that the exploitation of naturally and industrially abundant isoprene in coupling with indazoles is largely absent in the literature. This is speculated to be attributed to obstacles towards regiocontrol: 1) the competitive nucleophilic sites between the N^1 and N^2 positions of indazole; 2) the four electrophilic sites derived from the electronically unbiased alkenyl carbon atoms of isoprene. Herein, we report a ligand and acid-regulated strategy for the Pd-catalyzed regiodivergent coupling reactions between indazoles and isoprene (Figure 1 D). The present protocol features an orthogonal control of nucleophilic and electrophilic sites in catalytic hydrofunctionalization.

Table 1: Acid and ligand effects.[a]



A) Acid effects with L5 as Ligand

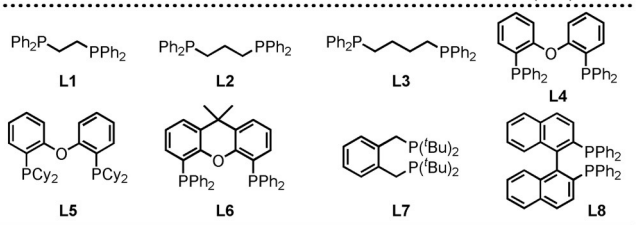
Acid:	$PhCO_2H$	TsOH	$(PhO)_2PO_2H$	$(^nBuO)_2PO_2H$	BEt_3	$Zn(OTf)_2$
N^2 yield(%) **3a/4a**:	25/16	10/2	35/7	**36/23**	**0/4**	0/0
N^1 yield(%) **5a/6a**:	3/0	0/0	0/0	**0/0**	**20/7**	0/0

B) Ligand effects with $(^nBuO)_2PO_2H$ as acid[b]

Ligand:	L1	L2	L3	L4	L5	L6[d]	L7	L8
N^2 yield(%) **3a/4a**:	35/1	44/4	57/15	22/57	**67**/7 (**69**/0)[c]	13/62	25/**66** (1/**82**)[d]	37/17
N^1 yield(%) **5a/6a**:	0/0	0/0	<1/2	4/14	0/0 (0/0)[c]	4/22	5/1 (8/0)[d]	20/4

C) Ligand effects with BEt_3 as acid

Ligand:	L1	L2	L3	L4	L5	L6	L7	L8
N^2 yield(%) **3a/4a**:	0/1	0/2	0/8	0/0	0/5	0/0	0/8 (0/6)[e]	0/3
N^1 yield(%) **5a/6a**:	2/2	3/4	21/22	4/5	22/7	0/0	**18**/0 (**82**/0)[e]	6/16



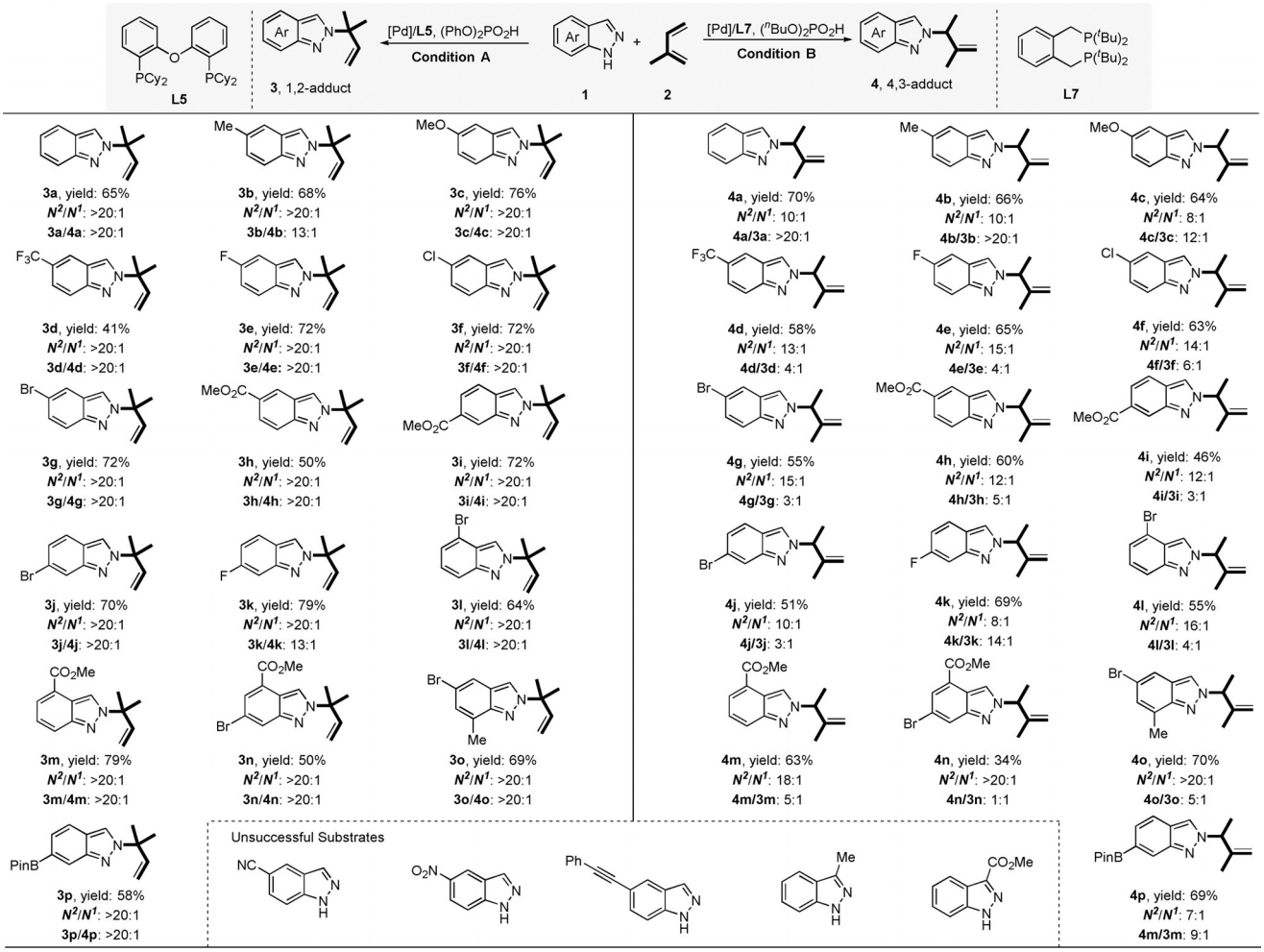
[a]Conditions: **1a** (0.2 mmol), **2** (1.0 mmol), $Pd(PPh_3)_4$ (5 mol%), **L** (5 mol%), acid (20 mol%), ^{i}PrOH (0.25 M), 70 °C, 18 h. Yield was determined by ^{1}H NMR analysis with 1,3,5-trimethoxy-benzene as the internal standard. [b]DCE (0.5 M) . [c]$(PhO)_2PO_2H$ (20 mol%) as acid, DCM instead of DCE. [d]$Pd(P^tBu_3)_2$ instead of $Pd(PPh_3)_4$, $(^nBuO)_2PO_2H$ (50 mol%), 80 °C. [e]$Pd(P^tBu_3)_2$ instead of $Pd(PPh_3)_4$, BEt_3 (75 mol%), 80 °C, 24 h.

Results and Discussion

We began our study with indazole **1a** and isoprene **2** as the model substrates (Table 1). Previous works have shown that an acid co-catalyst can play a crucial role in the generation of the metal-hydride for catalytic hydrofunctionalization of dienes.[17,18] Thereby, various acids were first examined using $Pd(PPh_3)_4$ and **L5** as the catalyst combo (Table 1 A). Delightfully, Brønsted acids, such as carboxylic acid, sulfonic acid and phosphoric acid, all promoted the formation of 1,2 or 4,3-addition products (**3a** and **4a**) in excellent N^2-selectivity. In contrast, the selectivity towards the N^1-allylic product (**5a** and **6a**) was achieved by switching to the Lewis acid BEt_3. Encouraged by these promising results, the evaluation of ligands was subsequently carried out to enhance the reactivity and selectivity (Table 1 B). In the presence of $(^nBuO)_2PO_2H$ (20 mol%), Cy-DPEphos (**L5**) was found to facilitate the formation of N^2-products **3a** and **4a** in good yield (67% and 7%, respectively). The yield of **3a** could be further increased to 69% with excellent regioselectivity when $(PhO)_2PO_2H$ was used instead of $(^nBuO)_2PO_2H$. Interestingly, the bulky ligand **L7** remarkably diverted the regioselectivity to N^2-allyl product **4a** via 4,3-addition. By replacing $Pd(PPh_3)_4$ with $Pd(P^tBu_3)_2$ and increasing the amount of $(^nBuO)_2PO_2H$ to 50 mol%, 82% yield of **4a** could be obtained (Table 1 B). Next, we turned our attention to the N^1-selectivity (Table 1 C). With the aid of BEt_3, all the ligands employed here primarily delivered 4,3-adduct **5a** or 4,1-adduct **6a** as mixtures, and the ligand **L7** exhibiting the best performance in terms of regioselectivity. Using the combination of 5 mol% $Pd(P^tBu_3)_2$ and 75 mol% BEt_3, 82% yield of **5a** was produced in good regioselectivity. Notably, no 1,2-adduct at the N^1-site was observed in all cases.

Having established the optimal conditions, the generality of substrates towards 1,2-adducts at the N^2-site was first explored with the assistance of ligand **L5** and $(PhO)_2PO_2H$. As depicted in Table 2, subjecting unsubstituted indazole **1a** to the standard conditions successfully delivered the reverse-prenylated indazole **3a** in 65% isolated yield. Reverse-prenylation of the 5-Me substituted indazole proceeded smoothly to provide **3b** in 68% yield with good N^2-selectivity. The indazole derivative bearing a methoxy group at the 5-position also reacted well with isoprene and produced **3c** in good yield and excellent regioselectivity. Substrates possess-

Table 2: Substrate scope towards 1,2-adducts and 4,3-adducts at N^2-site.



Condition A: **1** (0.2 mmol), **2** (1.0 mmol), $Pd(PPh_3)_4$ (5 mol%), **L5** (5 mol%), $(PhO)_2PO_2H$ (20 mol%), DCM (0.5 M), 70 °C,18 h. Isolated yield of the major product was given in all cases; regioselectivity was determined by ^1H NMR analysis of the crude reaction mixture.**Condition B:** **1** (0.2 mmol), **2** (1.0 mmol), $Pd(PPh_3)_4$ or $Pd(P^tBu_3)_2$ (5 mol%), **L7** (5 mol%), $(^nBuO)_2PO_2H$ (50 mol%), DCE (0.5 M), 80-90 °C,18 h. Isolated yield of major product was given in all case, regioselectivity was determined by ^1H NMR analysis of crude reaction mixture.

ing electron-withdrawing substituents, such as CF_3, halides, CO_2Me at the 4, 5 or 6-positions of the indazole core all efficiently afforded products **3d**–**3n** in 41–79% yields with regioselectivities consistently maintained at high levels. To our delight, the bromo group, regardless of their positions, was all tolerated under current protocol (**3g**, **3j**, **3l**, **3n** and **3o**). Besides, Indazole possessing a B(pin) group is also compatible in our system (**3p**). These products may be good handles for further functionalization. The regioselectivity for this hydroamination was further confirmed by X-ray analysis of **3i** (see the Supporting Information for detail).

The substrate tolerance towards the 4,3-adducts at the N^2-position was then examined (Table 2, right). By choosing **L7** as the ligand, simple indazole **1a** could be efficiently converted into the 4,3-addition product **4a** in 70% isolated yield with 10:1 selectivity (N^2 vs. N^1). Substrates bearing either electron-withdrawing or electron-donating substituents at the 5-position of indazoles all proceeded smoothly to produce the corresponding products with moderate to good yields and acceptable regioselectivities (**4b**–**4h**). Substituents at the 4 and/or 6-position of indazoles were also compatible under current reaction conditions (**4i**–**4n**), albeit product **4n** was obtained in comparably lower yield. Similar to the 1,2-adducts, substrates with a sensitive group, such as -Br and -B(pin), were accommodated in all case (**4g**, **4j**, **4l** and **4n**–**4p**). 7-Methyl substituted indazole could also be effectively transformed (**4o**). Notably, all these 4,3-addition products **4** could be obtained in pure form after flash chromatography without the contamination of other minor isomers. However, no desired products were observed when substrate having a nitro, cyano or alkynyl group at the 5 or 6-position. Due to the steric hindrance, 3-substituted indazoles were also not suitable under the current protocol.

Subsequently, the generality of current regiodivergent strategy was further examined by important and challenging pyrazole substrates (Table 3). In the presence of **L5** and $(PhO)_2PO_2H$, we were pleased to found that the reactions with various unsymmetrical pyrazoles could exclusively gave the 1,2-adducts in good yields and excellent regioselectivities (**7a**–**7e**). With the assistance of **L7**, the allylic reactions in 4,3-addition also proceeded smoothly to deliver products **8a**–**8e** in 41–86% yields and good to excellent regioselectivities.

Table 3: Substrate scope of substituted pyrazoles.

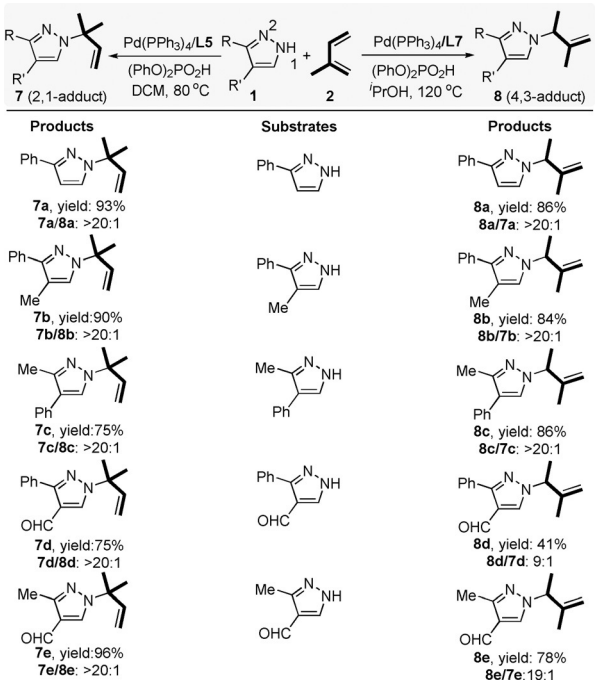
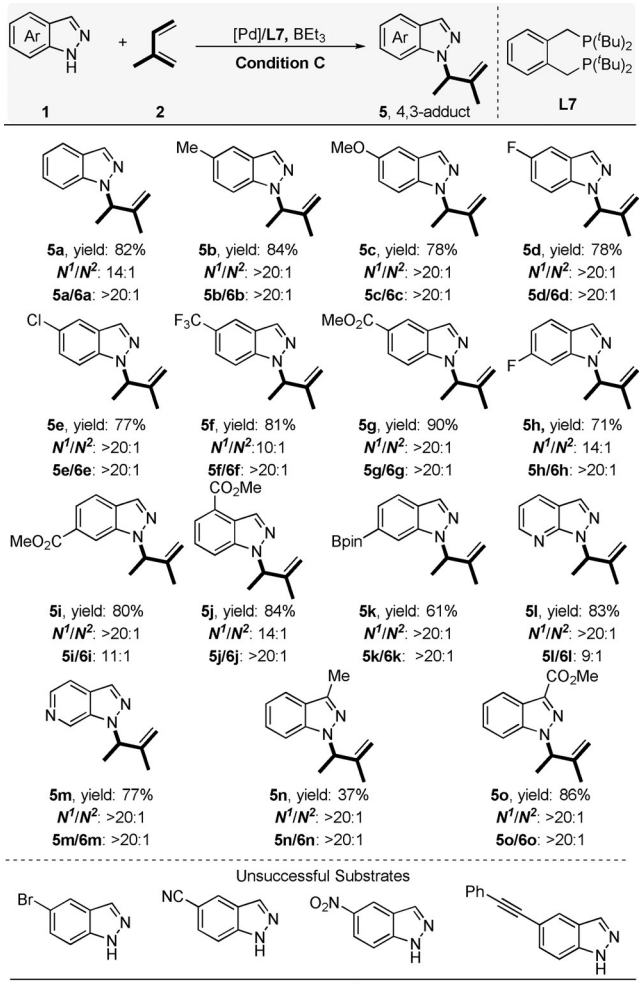


Table 4: Substrate scope towards 4,3-adducts at N^1-site.



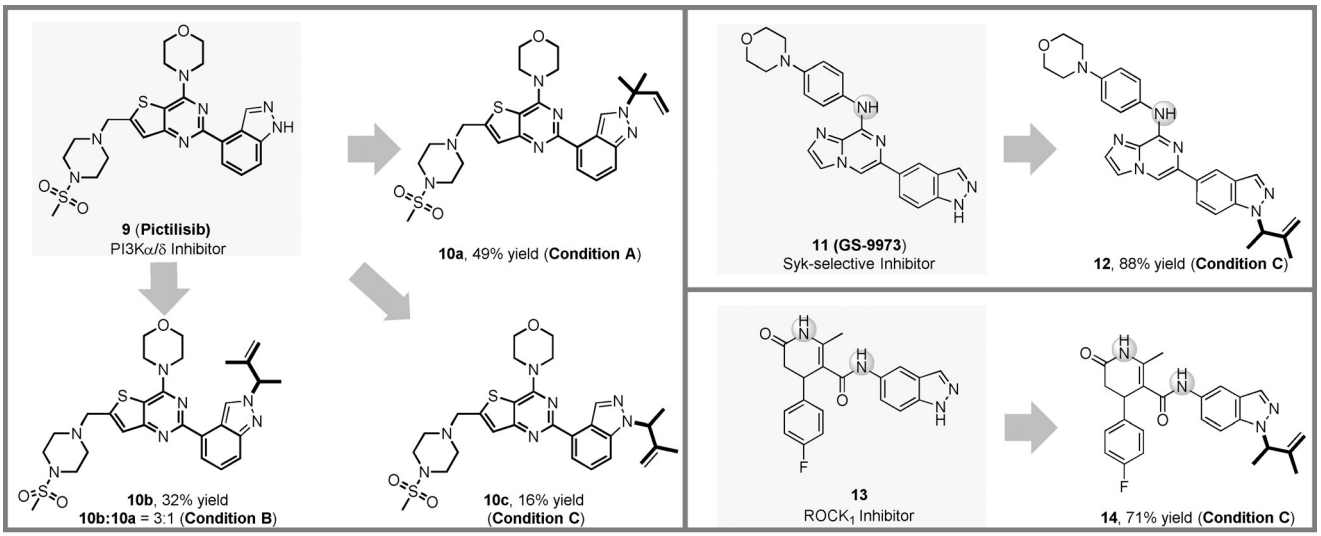
Condition C: **1** (0.2 mmol), **2** (1.0 mmol), $Pd(P^tBu_3)_2$ (5 mol%), **L7** (5 mol%), BEt_3 (75 mol%), ^{i}PrOH (0.25 M), 80 °C, 24 h. Isolated yield of major product was given in all case, regioselectivity was determined by ^{1}H NMR analysis of crude reaction mixture.

Remarkably, pyrazoles with formyl group were all feasible in these cases. The regioselectivity for these hydroamination were further confirmed by X-ray analysis of **7b** and **8c** (see the Supporting Information for detail).

Next we probed the scope of the reaction with respect to N^1-allylation of indazoles (Table 4). The model substrate **1a** could be efficiently converted to product **5a** in 82% yield and 14:1 regioselectivity. Moreover, a range of indazoles bearing 4-, 5 or 6-substituents, including -Me, -OMe, -F, -Cl, $-CF_3$ and $-CO_2Me$, all worked well in this protocol to give products **5b**–**5j** in good yields (71–90%) and high regioselectivities. 6-Boron substituted indazole was successfully employed as well to afford the desired product **5k** in 61% yield and excellent regioselectivity. It is noteworthy that the transformation could be further extended to azaindazoles and the corresponding products **5l** and **5m** were generated in 83% and 77% yields, respectively. In addition, indazoles with a methyl or ester group at 3-position were well applied in this case (**5n** and **5o**). Regrettably, the bromo, nitro, cyano or alkynyl group could not be tolerated.

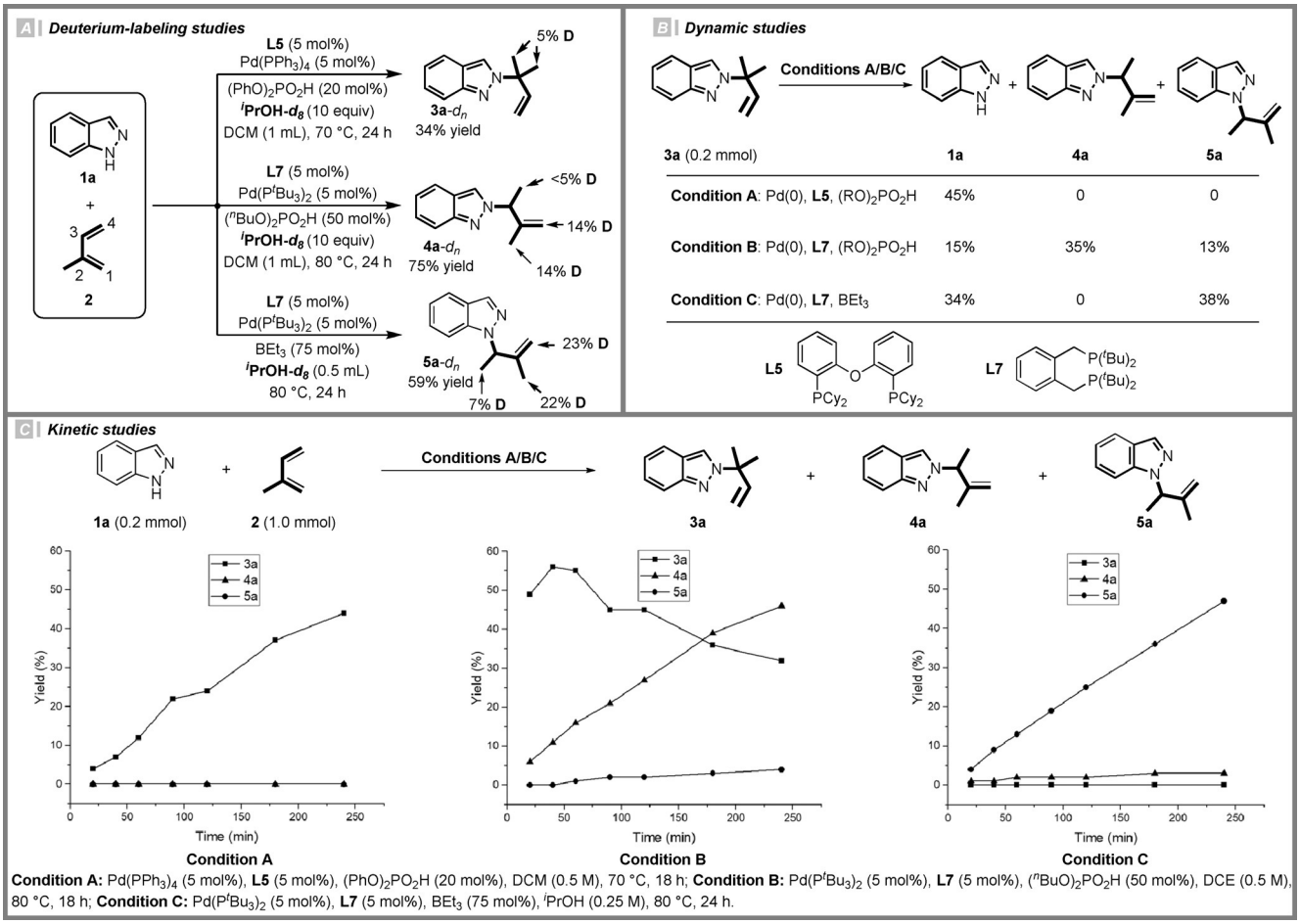
To further demonstrate the practical utility of this protocol, late-stage diversification of several indazole-containing bioactive molecules were examined (Figure 2). Pictilisib (**9**) is an orally available small-molecule inhibitor of the class I phosphatidylinositol-3-kinases (PI3K) and has shown clinically significant antitumor activity.[10e] Pleasingly, this compound reacts favorably under our divergent Pd-hydride catalysis, leading to the N2-allylic product **10a** or **10b** in 49% and 32% yields, respectively. For solubility issue, N^1-selective product **10c** was only obtained in 16% yield under the condition C. Compound **11** is a Syk-selective inhibitor[10d] and compound **13** is a ROCK1 inhibitor,[10a] both of which possess multiple reactive NH groups. Remarkably, these extra NH groups appear to have no obvious effects on both reactivity and selectivity under the condition C, which highlights the broad applicability of this regiodivergent protocol. The structure of **12** was further confirmed by X-ray analysis (see the Supporting Information for detail).

To gain insight into the mechanism of our regiodivergent catalysis, deuterium-labeled experiments were conducted (Figure 3A). When excess ^{i}PrOD-d_8 was employed in the standard condition A, the corresponding allylic product **3a** was obtained only with 5% of deuterium at the methyl group. The low rate of deuterium incorporation may be attributed to the reversible migratory insertion of isoprene into Pd^{II}-hydride. As expected, deuterated isoprene was indeed observed by GC-MS (see the Supporting Information for detail). Furthermore, no obvious deuterium scrambling suggests that the 1,2-addition of Pd-hydride to isoprene is preferred over other inserted orientation in this transformation. In comparison, under condition B and C, deuterium labeling in product **4a** or **5a** was detected at both the two methyl groups and terminal position of alkenes, which indicates that both 1,2-addition and 4,3-addition of the Pd-hydride to isoprene are occurred reversibly.



Condition A: **9** (0.05 mmol), **2** (0.25 mmol), $Pd(PPh_3)_4$ (5 mol%), **L5** (5 mol%), $(PhO)_2PO_2H$ (20 mol%), DCM (0.5 M), 70 °C, 18 h; **Condition B:** **9** (0.05 mmol), **2** (0.25 mmol), $Pd(PPh_3)_4$ (5 mol%), **L7** (5 mol%), $(^nBuO)_2PO_2H$ (50 mol%), DCE (0.5 M), 90 °C,18 h; **Condition C:** **9** or **11** or **13** (0.05 mmol), **2** (0.25 mmol), $Pd(P^tBu_3)_2$ (5 mol%), **L7** (5 mol%), BEt_3 (75 mol%), ^{i}PrOH (0.25 M), 80 °C, 24 h.

Figure 2. Late-stage modification of bioactive molecules.



Condition A: $Pd(PPh_3)_4$ (5 mol%), **L5** (5 mol%), $(PhO)_2PO_2H$ (20 mol%), DCM (0.5 M), 70 °C, 18 h; **Condition B:** $Pd(P^tBu_3)_2$ (5 mol%), **L7** (5 mol%), $(^nBuO)_2PO_2H$ (50 mol%), DCE (0.5 M), 80 °C, 18 h; **Condition C:** $Pd(P^tBu_3)_2$ (5 mol%), **L7** (5 mol%), BEt_3 (75 mol%), ^{i}PrOH (0.25 M), 80 °C, 24 h.

Figure 3. Mechanistic insights.

A general strategy for regiodivergent control in organic reaction stems from interchangeable isomerization between kinetic and thermodynamic products.[19] For better interpretation of the regio-selective alteration principle, product **3a** was isolated and subjected to the three standard conditions (Figure 3B). Under the condition A (with **L5** as ligand and

$(PhO)_2PO_2H$ as acid), substrate **1a** was achieved in 45% yield, no product **4a** or **5a** was produced under this reaction. This result supports the reversibility for the formation of **3a** under condition A. Besides, it is also consistent with the good regioselectivity observed for **3a**. Interestingly, 35% yield of **4a** and 13% yield of **5a** were both obtained in the case of condition B, which indicates that the isomerization from **3a** to **4a** and **5a** indeed occurred with ligand **L7** and $(^nBuO)_2PO_2H$ (condition B). In contrast, only **5a** rather than **4a** was detected when BEt_3 was employed (condition C), which also agrees with the excellent selectivity of **5a** observed in other reactions.

The kinetic experiments were also conducted (Figure 3C). An approximately linear relationship between yield and reaction time was noticed for product **3a** under the condition A at the early stage of the reaction. Similar observations were also obtained under condition C where product **5a** predominates over the time. However, under condition B, an interesting inverted V-shaped formation of **3a** was observed over the time. Meanwhile, an approximately linear increase in yield of product **4a** was found. These results support the conclusion that formation of **3a** from **1a** is reversible.

On the basis of experimental observations and previous reports, we proposed the following mechanism for the ligand-regulated hydroindazoylation of isoprene (Figure 4). First, oxidative addition of acid HX to a Pd^0 precursor leads to coordinatively unsaturated (16 electron) Pd^{II}-hydride species **A**.[20] The last one unoccupied orbital at Pd^{II} center is spared to facilitate the coordination of isoprene **2**. Then, migratory insertion of isoprene into Pd^{II}-hydride delivers the π-allyl-Pd intermediate **B** or **B′**. Based on the analysis of coordination geometry and kinetic studies (Figure 3C), 1,2-insertion is kinetically favored in the presence of the less bulky ligand **L5**, while 4,3-insertion becomes the alternative pathway with the aid of the bulky ligand **L7**. A final nucleophilic substitution of indazole **1a** to **B** or **B′** affords the product **3a** or **4a**, respectively and regenerates the Pd^0 species. The good regioselectivity for product **4a** resulting from that bulky ligand **L7** could facilitate the transformation of kinetic product **3a** to thermodynamic product **4a** under palladium catalysis.

With regard to nucleophilic site regulation towards N^1-hydroamination products, we speculated BEt_3 plays bifunctional roles (Figure 5). First, the BEt_3 can facilitate the formation of 1H-indazole complex by coordinating with N^2 atom (**Int 1**). Theoretically, four possible tautomers (**Int 1**–**4**) could be formed during the complexation of indazole **1a** with BEt_3 (Figure 5A). In terms of thermodynamics, tautomer **Int 1** is preferred over **Int 4** based on density functional theory (DFT) calculations of relative energy difference (5.9 kcal mol^{-1}, Figure 5A, see the Supporting Information for detail). The calculations also suggest tautomer **Int 2** and **3** are too unstable to form. The coordinated site of **Int 1** could be further confirmed as N^2-position by NOESY spectra analysis (see the Supporting Information for detail). A comparison of ^1H NMR spectra between **1a** and **1a** + **BEt_3** also clearly indicated the formation of one single complex with a clear downfield shift (Figure 5B). This is a result of decreasing electron density at the aromatic carbons of indazole through the formation of complex **Int 1**. No obvious changes was found in the case of **1a** + $(RO)_2PO_2H$ (see the Supporting Information for detail). Therefore, the regioselective switch between condition B and C probably results from the deactivation of N^2 atom by BEt_3 in terms of nucleophilicity. On the other hand, a small amount of BEt_3 was expected to undergo oxidative addition with Pd^0 and the subsequent β-hydride elimination to deliver the Et_2B-Pd^{II}-H species.[9h] Subsequent migratory insertion of isoprene into Pd^{II}-hydride and nucleophilic substitution will deliver **5a** (Figure 5B).

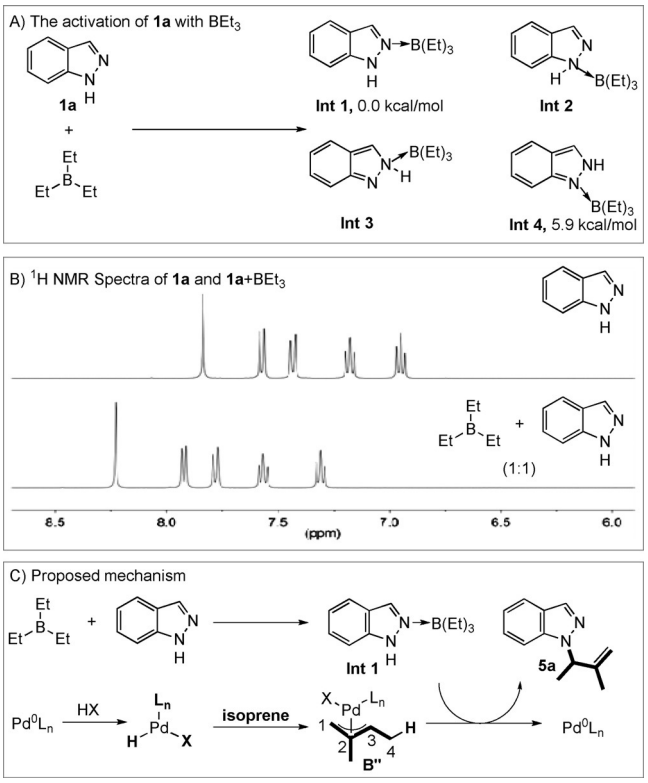


Figure 5. Bifunctional roles of BEt_3 in N^1-hydroamination.

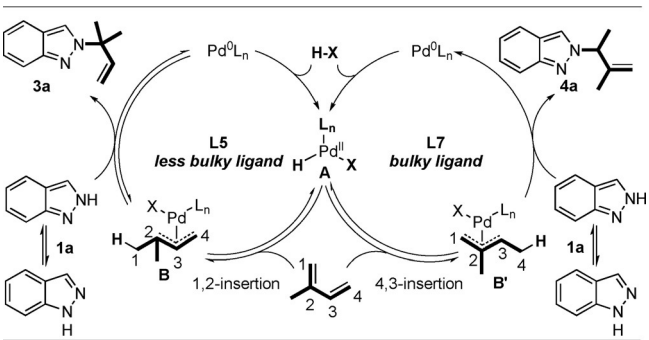


Figure 4. Proposed mechanism towards N^2-hydroamination.

Conclusion

In conclusion, we have developed an orthogonal regulation of nucleophilic and electrophilic sites in regiodivergent couplings between indazoles and isoprene. Under Pd-hydride catalysis, the 1,2- or 4,3-insertion pathways with regard to electrophilic sites is controlled by the choice of ligands. In terms of nucleophilic sites, the reaction occurs at either the N^1- or N^2-position of indazoles and is governed by the acid co-catalysts. Furthermore, regio-divergent late-stage modification of bioactive molecules has been performed to demonstrate the potentially broad applicability of this protocol. This regiodivergent method not only features high atom economy, but also contributes to emerging metal-catalyzed regiodivergent methodologies

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Conflict of interest

The authors declare no conflict of interest.

Keywords: hydroamination · indazole · isoprene · palladium · regiodivergent

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