

## Homogeneous Catalysis

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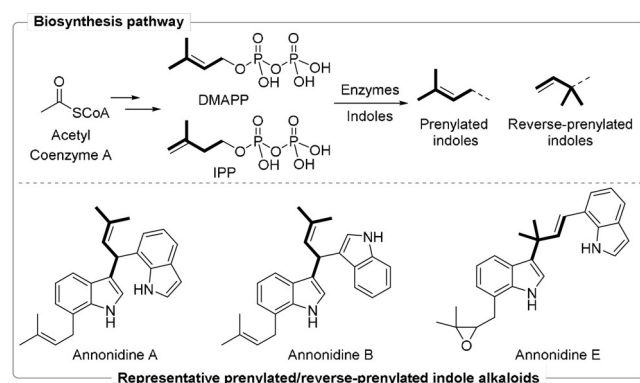
## Catalytic Prenylation and Reverse Prenylation of Indoles with Isoprene: Regioselectivity Manipulation through Choice of Metal Hydride

Yan-Cheng Hu, Ding-Wei Ji, Chao-Yang Zhao, Hao Zheng, and Qing-An Chen\*

Dedicated to the 70th anniversary of the Dalian Institute of Chemical Physics, Chinese Academy of Sciences

**Abstract:** The basic industrial feedstock isoprene was employed as a building block to install prenyl and reverse-prenyl groups onto indoles. The regioselectivity can be manipulated by the choice of metal hydride. Reverse-prenylated indoles were attained with high selectivity when using Rh–H. By switching to a Pd–H catalyst, selectivity toward prenylated indoles was achieved. This regiodivergent method also features high atom economy without stoichiometric byproduct formation.

Nature employs dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP)<sup>[1]</sup> as starting materials for the biosynthesis of numerous prenylated and reverse-prenylated indole alkaloids (Scheme 1).<sup>[2]</sup> The emulation of



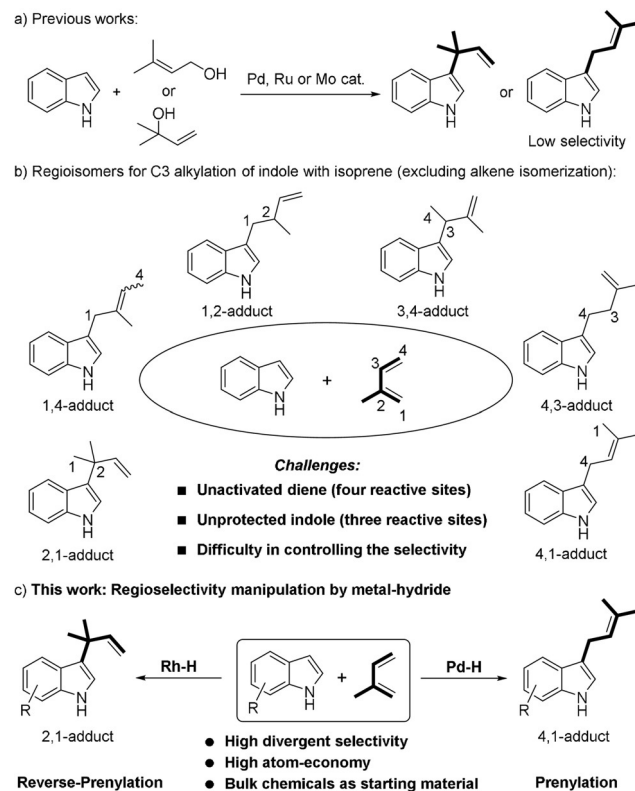
Scheme 1. Prenylation/reverse prenylation of indoles in nature.

such process with chemical reagents has received substantial attention over the past decade.<sup>[3]</sup> Dimethylallyl alcohol and their carbonates are common precursors for the catalytic prenylation and reverse prenylation of indoles.<sup>[4]</sup> The groups of Trost, Carreira, Stark, and You have made significant

contributions to such transformations of C3-substituted indoles.<sup>[5]</sup>

As for simple indole (Scheme 2 a), its reverse-prenylation was first realized by Tamaru et al. in 2005 through Pd<sup>0</sup> catalysis.<sup>[6]</sup> Later, Pd<sup>II</sup><sup>[7]</sup> and Ru<sup>IV</sup><sup>[8]</sup> complexes were designed to catalyze the same transformations. However, only one example has been reported using a Mo catalyst and this gave prenylated indole with low regioselectivity (3:1).<sup>[9]</sup> The success of these methods depends on using hydroxy or carbonate groups as activating groups for the generation of active metal π-allyl intermediates. In this context, developing a divergent strategy to access prenylated and reverse-prenylated indoles from non-activated precursors is in great demand.

Since DMAPP and IPP are also precursors of isoprene emission from plants,<sup>[10]</sup> we envisioned that isoprene may serve as a promising reagent for the prenylation/reverse prenylation of indoles. Furthermore, isoprene is an important



Scheme 2. Biomimetic prenylation/reverse prenylation of indoles.

[\*] Y. C. Hu, D. W. Ji, C. Y. Zhao, H. Zheng, Prof. Dr. Q. A. Chen  
Dalian Institute of Chemical Physics, Chinese Academy of Sciences  
457 Zhongshan Road, Dalian 116023 (China)  
E-mail: qachen@dicp.ac.cn  
Homepage: <http://www.lbcps.dicp.ac.cn>

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bulk chemical that can be produced from both petroleum and biomass.<sup>[11]</sup> From an economical and environmental point of view, direct transformation of such a basic feedstock into value-added indoles is highly appealing. To realize this proposal, we had to address the following challenges (Scheme 2b): 1) Conventional dimethylallyl alcohol is biased significantly through chelation or electronic effects to generate a metal  $\pi$ -allyl intermediate, while with unbiased isoprene, it is more difficult to form that species. 2) The four alkenyl carbons of isoprene are electronically undifferentiated, thereby resulting in six addition modes. Given that indole also has three reactive sites (N, C2, C3), the reaction can theoretically generate 18 possible regioisomers (excluding alkene isomerization). Therefore, the divergent formation of C3 reverse-prenylated (2,1-adduct) and prenylated (4,1-adduct) indoles with high selectivity is a daunting task. Herein, we demonstrated a metal hydride controlled regio-divergent reaction of indoles with isoprene (Scheme 2c).<sup>[12,13]</sup> The use of Rh–H as a catalyst led to reverse-prenylated indoles, while the selectivity switched to prenylated indoles in the presence of Pd–H.

Initially, simple indole (**1a**) and isoprene (**2**) were chosen as the model substrates to test our hypothesis (Table 1). In the presence of [Rh(cod)Cl]<sub>2</sub> (2.5 mol %), PPh<sub>3</sub> (5 mol %), and CSA (25 mol %) in DCE at 70 °C, the reaction resulted in prenylated indole **4a** (4,1-adduct) as main product (entry 1). Surprisingly, upon varying the ligand to bidentate phosphine BINAP or Segphos, reverse-prenylated indole **3a** (2,1-adduct) turned out to be predominant in the mixture (entries 2 and 3). To our delight, when DTBM-Segphos was employed as a ligand, the regioselectivity of **3a** increased to 14:1:1 owing to the steric hindrance of the ligand (entry 4). <sup>t</sup>PrOH and <sup>t</sup>BuOH further improved the yield and selectivity, and the latter gave a better result (entries 5 and 6). The acid additives exerted an influence on the reactivity and selectivity. *p*-TSA afforded **3a** in a slightly decreased yield, whereas TFA and the Lewis acid BEt<sub>3</sub> were found to be ineffective (entries 7–9). Notably, decreasing the amount of CSA (15 mol %) and <sup>t</sup>BuOH (1 M of **1a**) led to **3a** in good yield and 19:1 *rr* (entry 10). The reaction did not occur in the absence of either CSA or Rh<sup>I</sup> (entries 11 and 12), thus implying that Rh<sup>I</sup> and CSA likely form active Rh<sup>III</sup>–H to catalyze the process.

Other precatalysts were further investigated to enhance the selectivity for prenylated indole **4a**. Using Pd(PPh<sub>3</sub>)<sub>4</sub> generated no desired product (entry 13). Gratifyingly, the combination of Pd(PPh<sub>3</sub>)<sub>4</sub>/DTBM-Segphos/BEt<sub>3</sub> switched the main product to **4a** with 3:1 *rr* (entry 14). The utilization of DCE as a solvent dramatically improved the regioselectivity to 14:1 (entry 15). Increasing the amount of **2** and the concentration of **1a** led to the formation of the desired product **4a** in good yield with 17:1 *rr* (entry 16). In addition, the reaction did not proceed without BEt<sub>3</sub> or Pd<sup>0</sup> (entries 17 and 18). It is noteworthy that when using Tamaru's conditions,<sup>[6]</sup> reverse-prenylated indole **3a** became dominant in the mixture with low reactivity (entry 19).

With the optimized conditions in hand, we subsequently explored the substrate scope of this divergent approach (Table 2). For Rh catalysis, subjecting unsubstituted indole **1a** to the standard conditions furnished reverse-prenylated

**Table 1:** Optimization for divergent selectivity.<sup>[a]</sup>

Entry	[M]	L	Additive	Solvent	Yield (%) <sup>[b]</sup>	<i>rr</i> <sup>[c]</sup> <b>3a</b> / <b>4a</b> / <b>A</b> + <b>B</b> + <b>C</b>
1	[Rh]	PPh <sub>3</sub>	CSA	DCE	11	< 1:3:1
2	[Rh]	<b>L1</b>	CSA	DCE	29	3:1:1
3	[Rh]	<b>L2</b>	CSA	DCE	25	1:1:1
4	[Rh]	<b>L3</b>	CSA	DCE	48	14:1:1
5	[Rh]	<b>L3</b>	CSA	<sup>t</sup> PrOH	56	17:1:1
6	[Rh]	<b>L3</b>	CSA	<sup>t</sup> BuOH	70	16: < 1:1
7	[Rh]	<b>L3</b>	<i>p</i> -TSA	<sup>t</sup> BuOH	59	15:1:1
8	[Rh]	<b>L3</b>	TFA	<sup>t</sup> BuOH	N.R.	–
9	[Rh]	<b>L3</b>	BEt <sub>3</sub>	<sup>t</sup> BuOH	N.R.	–
10 <sup>[d]</sup>	[Rh]	<b>L3</b>	CSA	<sup>t</sup> BuOH	77	<b>19</b> : < 1:1
11 <sup>[d]</sup>	[Rh]	<b>L3</b>	–	<sup>t</sup> BuOH	N.R.	–
12 <sup>[d]</sup>	–	–	CSA	<sup>t</sup> BuOH	N.R.	–
13	[Pd]	<b>L3</b>	CSA	<sup>t</sup> BuOH	N.R.	–
14	[Pd]	<b>L3</b>	BEt <sub>3</sub>	<sup>t</sup> BuOH	60	< 1:3:1
15	[Pd]	<b>L3</b>	BEt <sub>3</sub>	DCE	44	< 1:14:1
16 <sup>[e]</sup>	[Pd]	<b>L3</b>	BEt <sub>3</sub>	DCE	<b>83</b>	< 1:17:1
17 <sup>[e]</sup>	[Pd]	<b>L3</b>	–	DCE	N.R.	–
18 <sup>[e]</sup>	–	–	BEt <sub>3</sub>	DCE	N.R.	–
19 <sup>[f]</sup>	[Pd]	–	BEt <sub>3</sub>	–	26	4:1:1

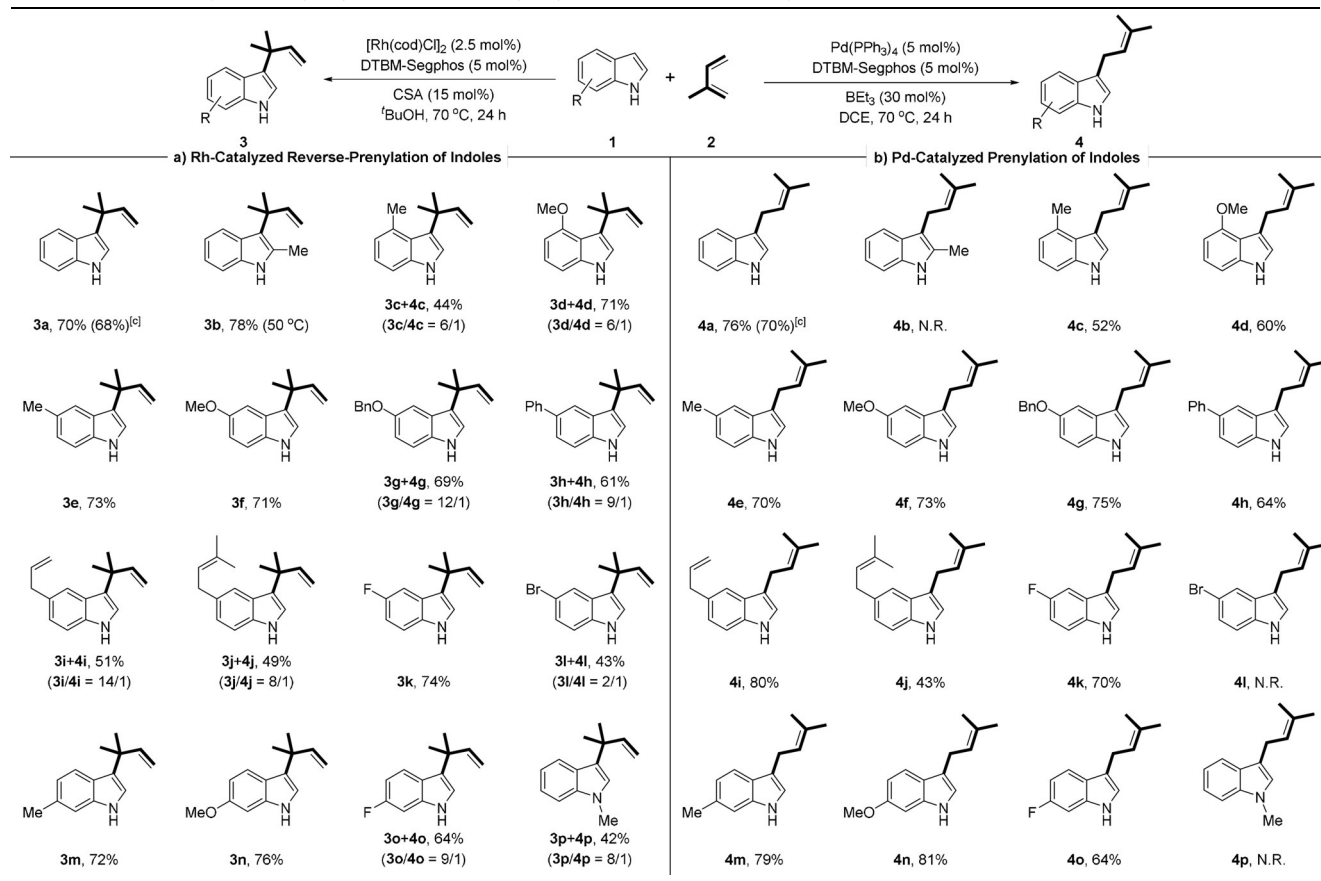
**L1: BINAP**

**L2: Segphos**

**L3: DTBM-Segphos**

[a] Conditions: **1a** (0.20 mmol), **2** (0.60 mmol), [Rh(cod)Cl]<sub>2</sub> (2.5 mol %) or Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol %), L (5 mol %), acid (25 mol %) or BEt<sub>3</sub> (1.0 M in THF, 30 mol %), solvent (0.50 mL), 70 °C, 24 h. [b] Total yield of all isomers, determined by GC-FID with 1,3,5-trimethoxybenzene as the internal standard. [c] Regioselectivity ratio (*rr*), determined by GC-FID. [d] CSA (15 mol %), <sup>t</sup>BuOH (0.20 mL). [e] **2** (0.80 mmol), DCE (0.20 mL). [f] **2** (0.80 mmol), BEt<sub>3</sub> (1.0 M in THF, 0.24 mmol). CSA = camphorsulfonic acid, DCE = dichloroethane, TFA = trifluoroacetic acid, *p*-TSA = *p*-toluenesulfonic acid, N.R. = No reaction.

indole **3a** in 70 % yield. 2-Me indole underwent the reverse prenylation smoothly at 50 °C to provide **3b** in 78 % yield. Me and OMe groups on the phenyl ring, regardless of their positions, were all well-tolerated (**3c–f**, **3m**, **3n**). It is noteworthy that 4-Me (**1c**) and 4-OMe (**1d**) groups presumably impeded the nucleophilic addition pathway of the C3 atom, thus leading to a slightly decreased selectivity. Electron-rich 5-BnO indole (**1g**) was a suitable substrate as well. Aryl and alkyl substituents such as phenyl, allyl and prenyl groups were also compatible with the process, providing the corresponding products **3h–j** in acceptable yields. This transformation can be further extended to halide-substituted indoles (**1k**, **1l**, **1o**). Notably, the reverse prenylation of *N*-Me indole with isoprene delivered the target product **3p** in acceptable yield and selectivity.

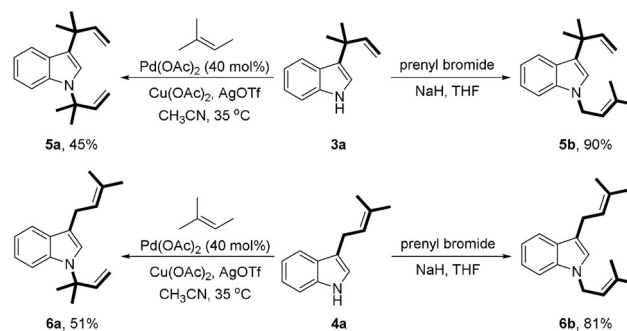
**Table 2:** Substrate scope for the prenylation and reverse prenylation of indoles with isoprene.<sup>[a,b]</sup>

[a] Yield of isolated product. [b] The ratio (3/4) was determined by <sup>1</sup>H NMR; unless otherwise stated, the ratio was > 20:1. [c] Yields of isolated product for reaction on a 2.0 mmol scale.

For Pd-catalyzed prenylation, simple indole **1a** was converted into the desired product **4a** in 76% yield. 2-Me indole and *N*-Me indole were not compatible with the process (**4b**, **4p**) most likely because the methyl group hampers binding of the boron additive to the nitrogen atom. The electronic and steric factors of substituents such as Me, OMe, OBn, and F on phenyl ring had no significant impact on the reactions (**4c–g**, **4k**, **4m–o**). Phenyl-, allyl-, and prenyl-substituted indoles could be successfully applied in this transformation as well (**4h–j**). However, the reaction of 5-Br indole with isoprene did not occur (**4l**), which is probably due to the more favorable oxidative addition of C–Br with Pd<sup>0</sup>.

To illustrate the practical utility of this method, scale-up experiments (2.0 mmol) were performed for indole **1a** and isoprene **2**. Both reactions gave the desired products **3a** (68%) and **4a** (70%) in good yields under the standard conditions (Table 2).

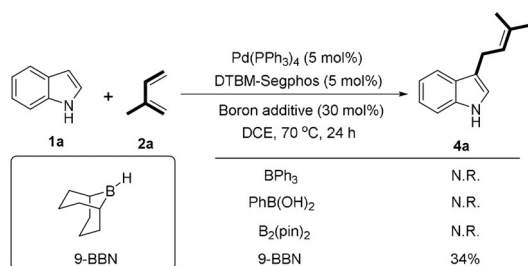
Remarkably, by employing Baran's method,<sup>[14]</sup> reverse *N*-prenylation of **3a** and **4a** occurred, furnishing the corresponding products **5a** and **6a** in moderate yields (Scheme 3). Moreover, treatment of **3a** or **4a** with a mixture of prenyl bromide and NaH successfully introduced prenyl group to *N* atom with high efficiency (Scheme 3). It is worthwhile to mention that reverse prenylated indole **3a** was also the key

**Scheme 3.** Further prenylation and reverse prenylation of indoles **3a** and **4a**.

building block in the total synthesis of the marine natural product hemiasterlin.<sup>[15]</sup>

Additional control experiments were carried out to elucidate the mechanism of Pd catalysis. A mixture of BEt<sub>3</sub> and indole in C<sub>6</sub>D<sub>6</sub> was stirred at 70 °C and analyzed by NMR over time (Figures S4 and S5). Compared with its initial <sup>1</sup>H and <sup>11</sup>B NMR spectra, some new peaks were observed. The new signal at 6.57 ppm (*d*, 3.4 Hz) on <sup>1</sup>H NMR corresponds to C3-H, while the initial C3-H signal of indole appears at 6.53 ppm. This downfield shift suggests an increase in the C3 nucleophilicity. The new resonance at 55.6 ppm on <sup>11</sup>B NMR

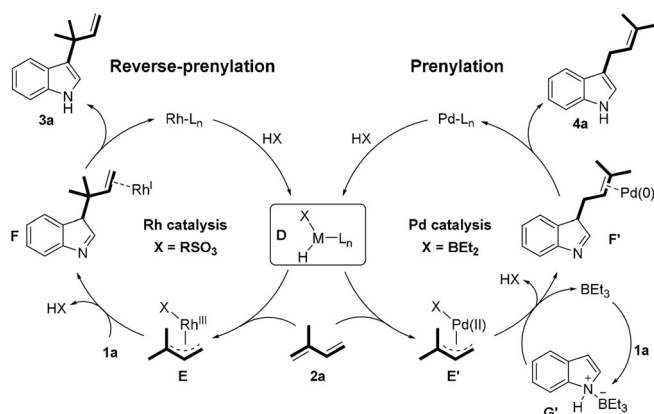
revealed that a new adduct was formed through binding of  $\text{BEt}_3$  to NH of indole (Figure S5). Additives bearing no  $\beta$ -hydrogen, such as  $\text{BPh}_3$ ,  $\text{PhB}(\text{OH})_2$ , and bis(pinacolato)-diboron ( $\text{B}_2(\text{pin})_2$ ), cannot promote the reaction (Scheme 4). In contrast, upon changing the boron additive to 9-BBN, the



**Scheme 4.** Effects of boron additives on Pd-catalyzed prenylation.

prenylation proceeded smoothly. Inspired by the precedents for Pd-catalyzed hydroboration of alkenes,<sup>[16]</sup> oxidative addition of  $\text{Pd}^0$  with B–H of 9-BBN gives a B–Pd<sup>II</sup>–H intermediate, which can activate isoprene to facilitate the coupling with indole.

On the basis of these observations and previous work,<sup>[17]</sup> a plausible mechanism for the divergent selectivity was proposed (Scheme 5). The reverse prenylation begins with



**Scheme 5.** Proposed mechanism for divergent selectivity.

oxidative addition of  $\text{Rh}^I$  with CSA to form active  $\text{Rh}^{III}$ –H species **D**. Subsequently, migratory insertion of isoprene into the Rh–H bond yields  $\pi$ -allyl–Rh complex **E**, which is further attacked by the C3 atom of indole to afford intermediate **F** with the regeneration of CSA. A final aromatization produces reverse-prenylated indole **3a** and regenerates the  $\text{Rh}^I$  catalyst for next catalytic cycle.

For the prenylation process, a catalytic amount of  $\text{BEt}_3$  is sacrificed to give  $\text{Et}_2\text{B}$ –Pd<sup>II</sup>–H intermediate **D** by oxidative addition of  $\text{Pd}^0$  with  $\text{BEt}_3$  and subsequent  $\beta$ -hydride elimination (Scheme 5).  $\text{BEt}_3$  also plays a role in activation of indole through binding of boron to the nitrogen atom, thus resulting in the formation of intermediate **G'**. The active  $\pi$ -allyl–Pd species **E'**, generated by isoprene insertion into Pd–H, is attacked by **G'** to furnish complex **F'** with the release of

$\text{HBEt}_2$  and  $\text{BEt}_3$ . A final aromatization delivers prenylated indole **4a**. It is noted that the formed  $\text{HBEt}_2$  participates in the next cycle to regenerate Pd–H complex **D**. The regiochemical preference probably arises from the respective stabilities of the olefin–metal complexes that form upon outer-sphere nucleophilic attack the  $\pi$ -allyl metal species (**E** or **E'**).<sup>[18]</sup>

In conclusion, a regiodivergent method for the coupling of indoles with isoprene has been developed. Manipulation of the regioselectivity was governed by the choice of metal hydride. Utilization of Rh–H as the active catalyst afforded reverse-prenylated indoles with high selectivity, while a Pd–H catalyst enabled selective synthesis of prenylated indoles. Notably, no stoichiometric byproduct was formed in the process. Further studies on the enantioselective prenylation/reverse prenylation of substituted indoles with isoprene are underway in our laboratory.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** indoles · isoprenes · metal hydrides · prenylation · reverse prenylation

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