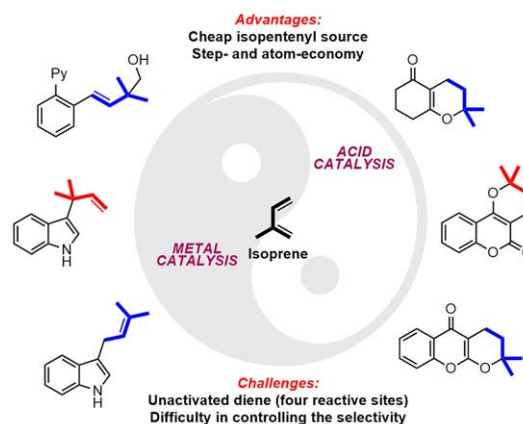


Isoprene: A Promising Coupling Partner in C–H Functionalizations

Wei-Song Zhang^{a,b}
Yan-Cheng Hu^a
Qing-An Chen^{*a}

^a Dalian Institute of Chemical Physics, Chinese Academy of Science, Dalian 116023, P. R. of China

^b University of Chinese Academy of Sciences, Beijing 100049, P. R. of China
qachen@dicp.ac.cn



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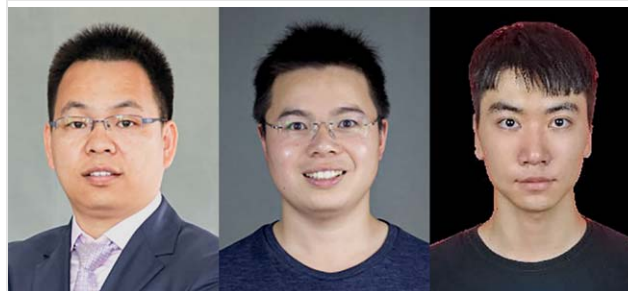
Abstract Five-carbon dimethylallyl units, such as prenyl and reverse-prenyl, are widely distributed in natural indole alkaloids and terpenoids. In conventional methodologies, these valuable motifs are often derived from substrates bearing leaving groups, but these processes are accompanied by the generation of stoichiometric amounts of by-products. From an economical and environmental point of view, the basic industrial feedstock isoprene is an ideal alternative precursor. However, given that electronically unbiased isoprene might undergo six possible addition modes in the coupling reactions, it is difficult to control the selectivity. This article summarizes the strategies we have developed to achieve regioselective C–H functionalizations of isoprene under transition-metal and acid catalysis.

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- 2 Catalytic Coupling of Indoles with Isoprene
- 3 Catalytic Coupling of Formaldehyde, Arenes and Isoprene
- 4 Catalytic Coupling of 4-Hydroxycoumarins with Isoprene
- 5 Catalytic Coupling of Cyclic 1,3-Diketones with Isoprene
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Key words isoprene, prenylation, C–H functionalization, regioselectivity, catalysis

1 Introduction

Five-carbon (C_5) dimethylallyl units, such as 3-methyl-2-butenyl (prenyl) and 2-methyl-3-butenyl (reverse-prenyl), are ubiquitous in nature (Figure 1).¹ Because the presence of these unique groups can enhance the lipophilicity of molecules and facilitate permeation across cellular membrane, these natural products usually exhibit intriguing biological properties. For example, Annonidine B,² isolated from West African medicinal tree *Annonidium mannii*, possesses two prenyl groups at the 3- and 7-positions of the in-

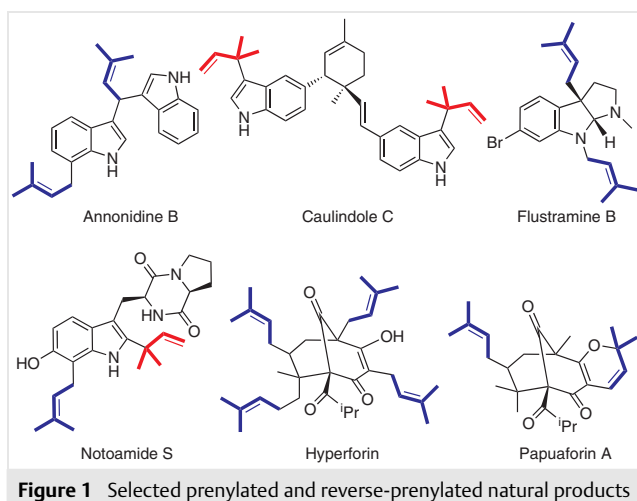


Qing-An Chen was born in 1984 in Fujian Province, China. He received a B.S. degree from the University of Science and Technology of China in 2007 and earned his Ph.D. from the Dalian Institute of Chemical Physics in 2012. He worked with Prof. Vy M. Dong at the University of California Irvine as a postdoctoral fellow from 2012 to 2015. Then he joined Prof. Martin Oestreich's group at Technische Universität Berlin as an Alexander von Humboldt Fellow. In 2017 he began his independent research career at the Dalian Institute of Chemical Physics, Chinese Academy of Sciences, where currently he is Professor of Chemistry. His research interests include the development of catalytic asymmetric reactions, mechanistic elucidation, and asymmetric synthesis. He has authored over 35 publications and received the 2020 Thieme Chemistry Journal Award.

Yan-Cheng Hu was born in Jiangsu Province, China, in 1989. He obtained his B.S. degree from Nanjing Normal University in 2010 and PhD degree from the Dalian Institute of Chemical Physics in 2015, under the supervision of Prof. Boshun Wan. He did his postdoctoral research with Prof. Tao Zhang at the same institute from 2015 to 2018. Later, he worked in the group of Prof. Qing-An Chen, where he is currently an associate professor. His research focuses on transition-metal and acid-catalyzed transformations of isoprene, as well as their applications in the total synthesis of natural products.

Wei-Song Zhang was born in Chongqing Municipality, China, received a B.S. degree from Dalian University of Technology in 2018. Currently, he works in the group of Prof. Qing-An Chen at Dalian Institute of Chemical Physics as a graduate student. His research focuses on transition-metal-catalyzed hydrofunctionalizations of terpenes.

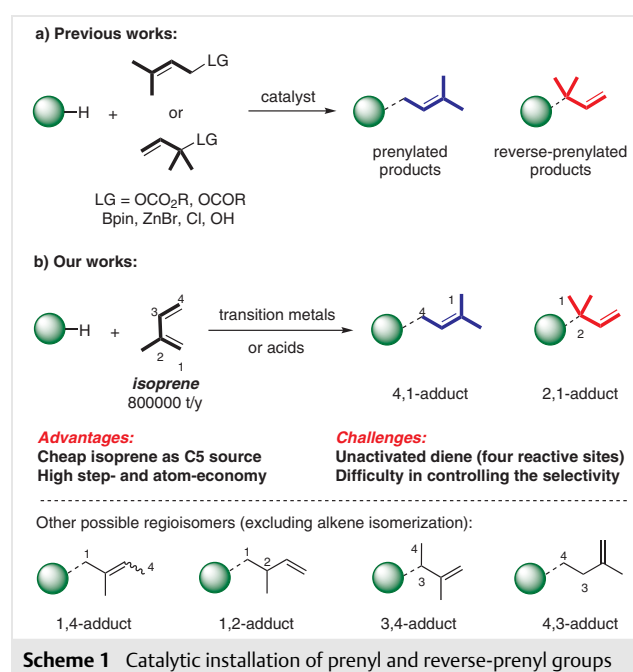
dole ring. Caulindole C,³ a C3 reverse-prenylated indole alkaloid, shows antifungal and antimalarial activities. Flustramine B,⁴ a cyclized N- and C3-prenylated tryptamine derivative, exhibits smooth-muscle relaxant activity. Bearing 2-reverse prenyl and 7-prenyl groups on indole core, Notoamide S⁵ is a common precursor for the biosynthesis of diverse bioactive metabolites in the genus *Aspergillus*. As polycyclic polyprenylated acylphloroglucines (PPAPs) derived from the plants of *Hypericum* family, Hyperforin⁶ and Papaforin A⁷ display potent antibiotic, antitumor and anti-depressant properties. Therefore, the selective incorporation of prenyl and reverse-prenyl motifs into important frameworks has been an active research field in catalysis and synthesis.⁸



Transition-metal-catalyzed allylic substitution and directed C–H activation are two representative strategies for C–H functionalizations with dimethylallylic compounds.⁹ The organic chemistry community has developed some effective C₅ coupling partners such as dimethylallylic alcohols¹⁰ and their derivatives including halides,¹¹ acetates,¹² carbonates¹³ and organometals¹⁴ (Scheme 1a). Leaving groups play a critical role in the process, since they can differentiate the electronic properties of the precursors and facilitate the selective formation of key π -allylmetal intermediates.¹⁵ However, the pre-installation of leaving groups and the consequent generation of stoichiometric by-products diminish both the step and atom economy. In this context, from the viewpoint of green chemistry, the direct use of unactivated C₅ alkenes or dienes as prenyl or reverse-prenyl sources would be highly demanded yet remains seldom explored.

Isoprene is an important C₅ conjugated diene in industry, with a production capacity of approximately 800,000 metric tons per year.¹⁶ Furthermore, isoprene can also be biosynthesized on a large scale via a modified *Escherichia coli* fermentation process.¹⁷ In this respect, isoprene can be regarded as an economic feedstock to some extent. Accord-

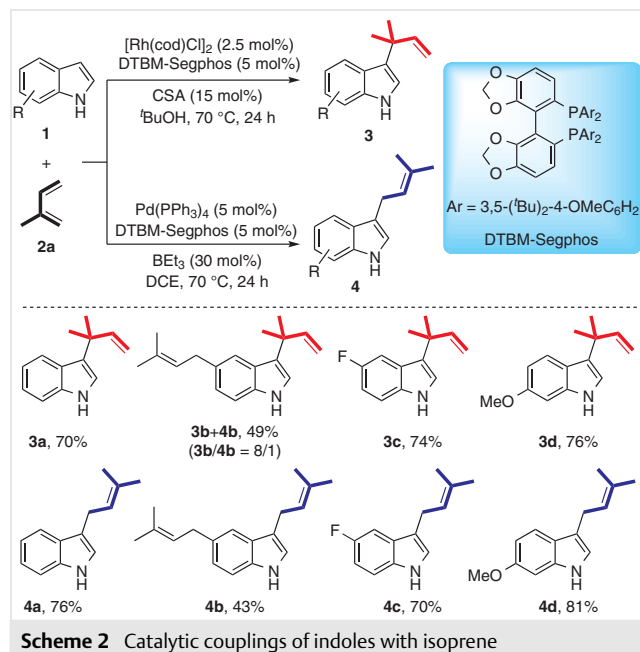
ingly, it would be ideal if isoprene can serve as a building block to install prenyl (4,1-adduct) and reverse-prenyl groups (2,1-adduct) (Scheme 1b). Nevertheless, electronically unbiased isoprene can lead to six possible regioisomers, thus often making it challenging to modulate the product distributions. This account introduces the strategies we have developed to address this issue, by which the selectivity for the isoprene couplings can be manipulated by varying the catalyst.



2 Catalytic Coupling of Indoles with Isoprene

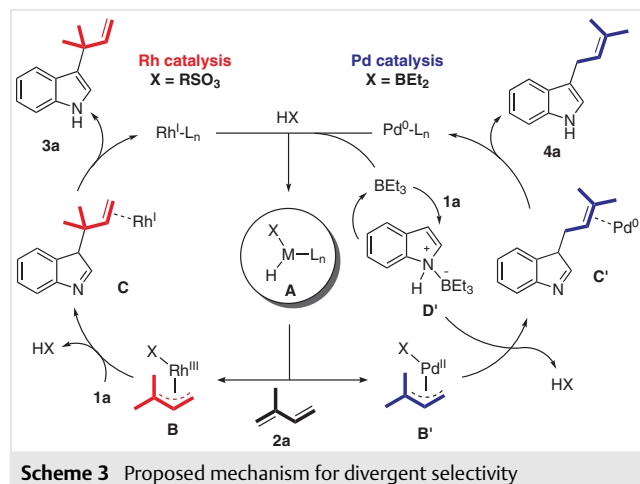
Metal-hydride catalysis has emerged as a powerful tool to promote the hydrofunctionalization of linear 1,3-dienes.¹⁸ In the process, the active metal-hydride species is often generated in situ via oxidative addition of low-valent transition metals such as Pd(0), Ru(0), Rh(I), and Ni(0), with Brønsted acids or alcohols.¹⁹ Compared with the tremendous advances achieved in this area, the metal-hydride catalyzed hydrofunctionalization of isoprene has been rather limited, presumably because of the difficulty in controlling the regioselectivity. We recently developed a regiodivergent coupling of simple indoles with isoprene under metal-hydride catalysis (Scheme 2).²⁰ Reverse-prenylated indoles **3** were furnished with high selectivity when using [Rh(cod)Cl]₂ as a pre-catalyst, DTBM-Segphos as a ligand, and 10-camphorsulfonic acid (CSA) as an additive. In comparison, a combination of Pd(PPh₃)₄, DTBM-Segphos and BEt₃ altered the coupling products to 3-prenylated indoles **4**. 5-Prenyl indole was also compatible with both transformations, albeit with slightly decreased yields (**3b**, **4b**). The

electron-withdrawing (**3c**, **4c**) and electron-donating substituents (**3d**, **4d**) on phenyl ring, regardless of their positions, were all well tolerated.



Scheme 2 Catalytic couplings of indoles with isoprene

A plausible mechanism for the divergent process is depicted in Scheme 3. For Rh catalysis, an initial oxidative addition of Rh(I) pre-catalyst with CSA delivers Rh(III)–H species **A**. A subsequent isoprene insertion into **A** gives π -allyl-Rh intermediate **B**, followed by a nucleophilic attack of indole to furnish complex **C** with release of CSA. An ultimate aromatization results in reverse-prenylated indole **3a** and regenerates Rh(I) catalyst. For Pd catalysis, a small amount of BEt₃ is sacrificed for the generation of Et₂B–Pd(II)–H species **A**, involving oxidative addition of BEt₃ with Pd(0) and subsequent β -hydride elimination. BEt₃ is also likely to in-

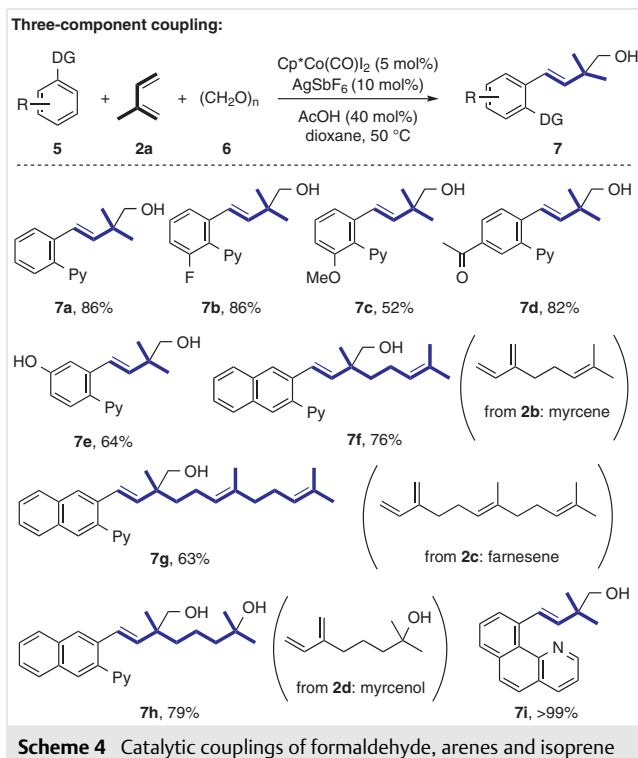


Scheme 3 Proposed mechanism for divergent selectivity

teract with the nitrogen atom of indole, leading to the formation of the adduct **D'**. The π -allyl-Pd intermediate **B'**, formed by isoprene insertion into **A**, undergoes nucleophilic addition with **D'** to produce complex **C'** with the liberation of BEt₃ and HBEt₂. Finally, prenylated indole **4a** is afforded via an aromatization step. It is noteworthy that the released HBEt₂ serves as the hydride source to regenerate Et₂B–Pd(II)–H complex **A** in the next cycle.

3 Catalytic Coupling of Formaldehyde, Arenes and Isoprene

Catalytic multicomponent coupling, featuring one-step formation of multiple new bonds, has become one of the most efficient strategies for the rapid assembly of structural diversity and complexity in organic synthesis.²¹ In recent years, three-component couplings of arenes, dienes and carbonyls via C–H activation processes have attracted particular attention, since they can provide atom-economical access to homoallylic alcohols.²² However, in these studies, the coupling of isoprene often gives low yields and selectivities. In this context, we set out to exploit a catalytic system to achieve regioselective coupling of isoprene, formaldehyde and 2-arylpyridines.²³ It was found that homoallylic alcohols **7** were afforded with exclusive regioselectivities when Cp*Co(CO)I₂ was employed as a catalyst with HOAc and AgSbF₆ as additives (Scheme 4). The electronic and steric factors of the substituents on the phenyl ring had no sig-



Scheme 4 Catalytic couplings of formaldehyde, arenes and isoprene

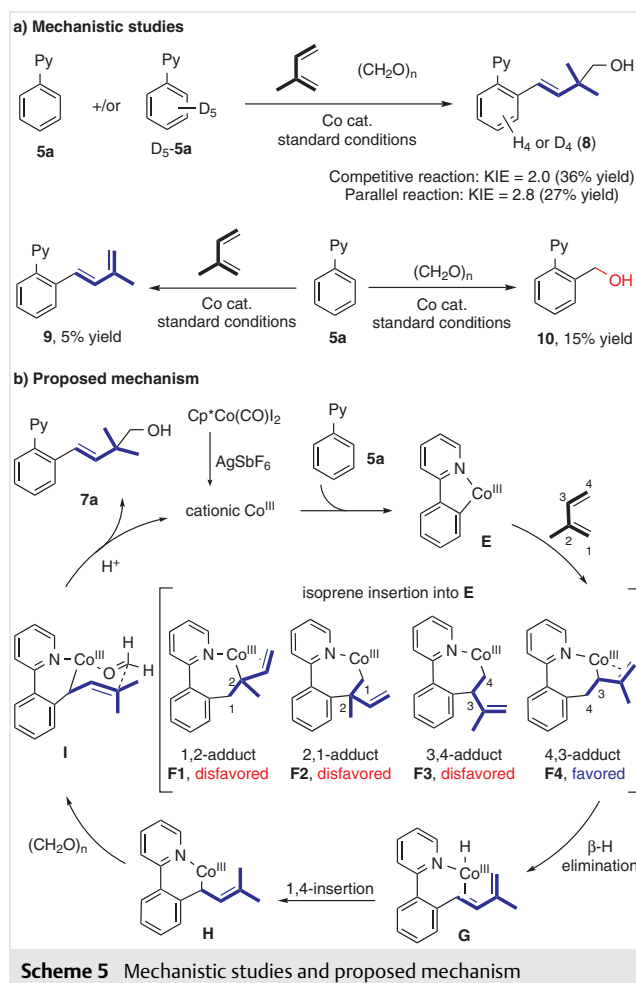
nificant impact on the reaction (**7a–d**), and even free hydroxyl was tolerated (**7e**). Notably, other complex terpene derivatives including myrcene, farnesene, and myrcenol were also suitable coupling partners (**7f–h**). Benzoquinoline could also participate in the three-component coupling, giving the target product **7i** in nearly quantitative yield.

The kinetic isotope effect (KIE) experiments reveal that C–H bond cleavage is likely to be a rate-determining step (Scheme 5a). Subjecting isoprene and 2-phenylpyridine to the standard conditions afforded an oxidative coupling product **9** (Scheme 5a). Additionally, in the absence of isoprene, a two-component coupling of formaldehyde and 2-phenylpyridine could take place to deliver arylmethanol **10** in 15% yield (Scheme 5a). However, neither product was detected under three-component coupling reactions. These results demonstrate that the chemoselectivity stems from coordination ability difference between isoprene and formaldehyde with the five-membered cobaltacycle intermediate generated in situ.

Based on these preliminary results, a plausible mechanism is tentatively outlined in Scheme 5b. In the presence of AgSbF_6 , the pre-catalyst $\text{Cp}^*\text{Co}(\text{CO})_2$ is first converted into an active cationic $\text{Co}(\text{III})$ species, which reacts with 2-phenylpyridine to yield five-membered cyclocobalt complex **E** via a C–H activation step. The subsequent isoprene insertion into **E** has four possible pathways. Owing to the steric hindrance, the generation of adducts **F1** and **F2** can be disfavored. The adduct **F3** is reluctant to undergo β -hydride elimination, thus ruling out this possibility as well. In comparison, a β -hydride elimination of 4,3-adduct **F4** yields $\text{Co}(\text{III})\text{--H}$ species **G**, followed by 1,4-insertion with the isoprene motif to produce prenyl- $\text{Co}(\text{III})$ complex **H**. Eventually, a directed addition of **H** with formaldehyde via a six-membered chair-like transition state **I** furnishes the desired product **7a** with the regeneration of cationic $\text{Co}(\text{III})$ catalyst.

4 Catalytic Coupling of 4-Hydroxycoumarins with Isoprene

Dimethylpyrans, containing a cyclized prenyl, are also widely present in natural products (e.g., papuaforin A in Figure 1),²⁴ which prompted us to construct these important frameworks with isoprene. On the other hand, besides transition-metals, acid catalyst can also activate isoprene to facilitate its coupling reactions.²⁵ In this context, an acid-catalyzed regiodivergent annulation of 4-hydroxycoumarin with isoprene was developed by our group, which provides an atom-economical protocol for the assembly of dimethylpyran skeletons (Scheme 6).²⁶ The utilization of strong Brønsted acid $2,4\text{-(NO}_2)_2\text{C}_6\text{H}_3\text{SO}_3\text{H}$ as catalyst exclusively delivered pyranocoumarins **12**, whereas pyranochromones **13** turned out to be predominant in the presence of Lewis acid $\text{Sm}(\text{OTf})_3$. Both electron-deficient (**12b**, **13b**) and elec-



Scheme 5 Mechanistic studies and proposed mechanism

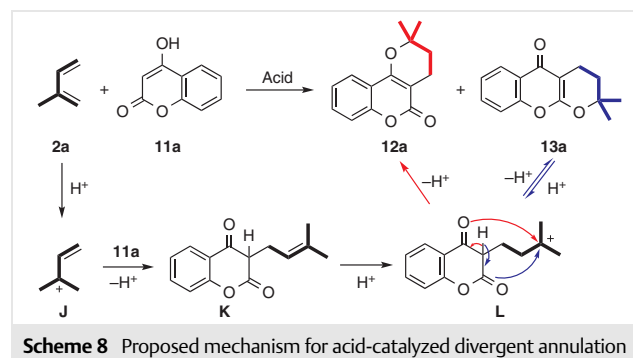
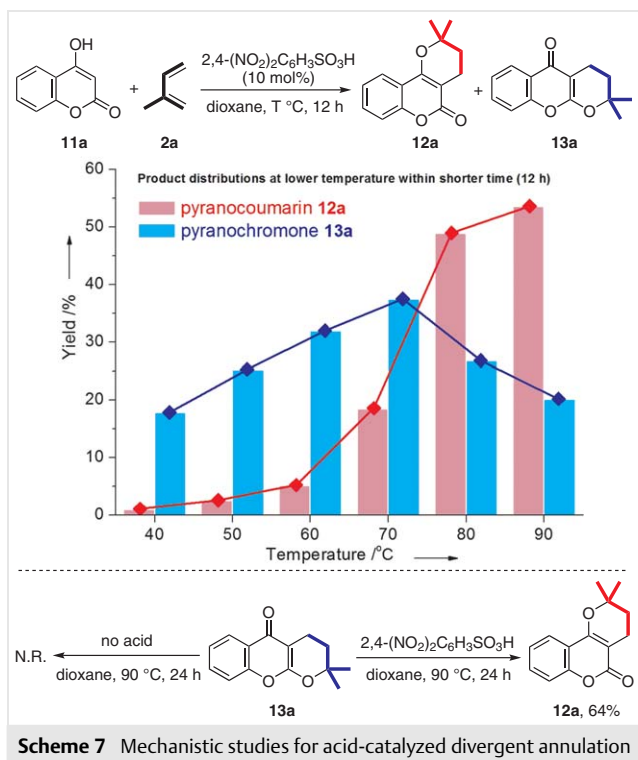
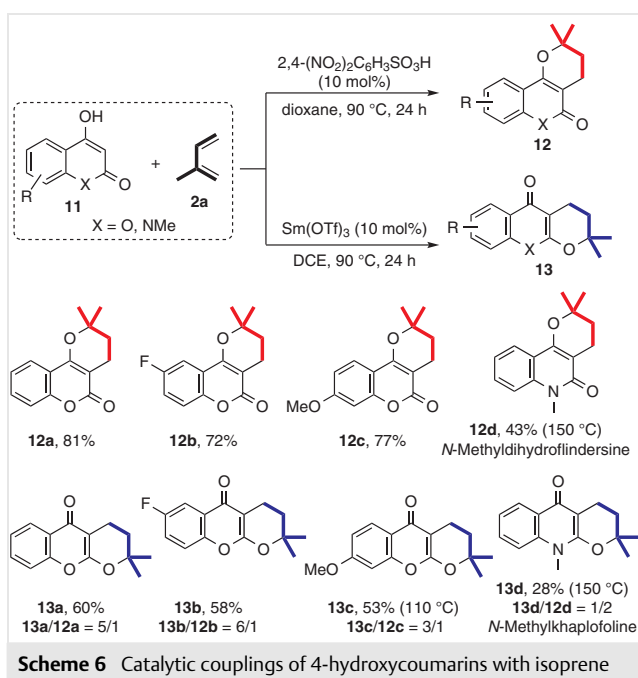
tron-rich (**12c**, **13c**) 4-hydroxycoumarins were applicable to both catalytic systems. Remarkably, 4-hydroxyquinolone was a suitable substrate as well, and the resulting products **12d** and **13d** could be used to synthesize natural alkaloids flindersine and khaplofoline.

To gain a deeper insight into the competitive formation of pyranocoumarin **12a** and pyranochromone **13a**, the experiments were monitored at decreased temperatures within 12 h (Scheme 7, top). With an increment of the temperature ($40 \rightarrow 90^\circ\text{C}$), the yield of **12a** increased significantly, while initial improvement and further decrease of the yield of **13a** were observed. Pyranochromone **13a** could be converted into pyranocoumarin **12a** under the standard conditions (Scheme 7, bottom). These results imply that pyranocoumarin **12a** is the thermodynamically favored product, whereas the formation of pyranochromone **13a** is kinetically favored and reversible.

Based on these experimental results, a plausible mechanism for the generation of pyranocoumarin and pyranochromone is illustrated in Scheme 8. An initial protonation of isoprene results in active isopentenyl cation **J**, which can

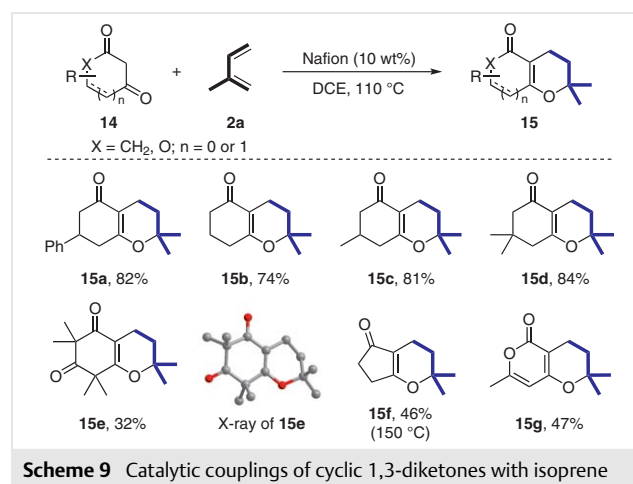
be attacked by the enolate of **11a** to produce prenylated diketone **K**. Finally, an acid-catalyzed intramolecular cyclization of **K** furnishes pyranocoumarin **12a** or pyranochromone **13a** via carbocation intermediate **L**. It is noteworthy that **13a** is produced reversibly, whereas the path-

way to **12a** is irreversible, which can account for the conversion of **13a** into **12a** in the presence of acid at high temperature.

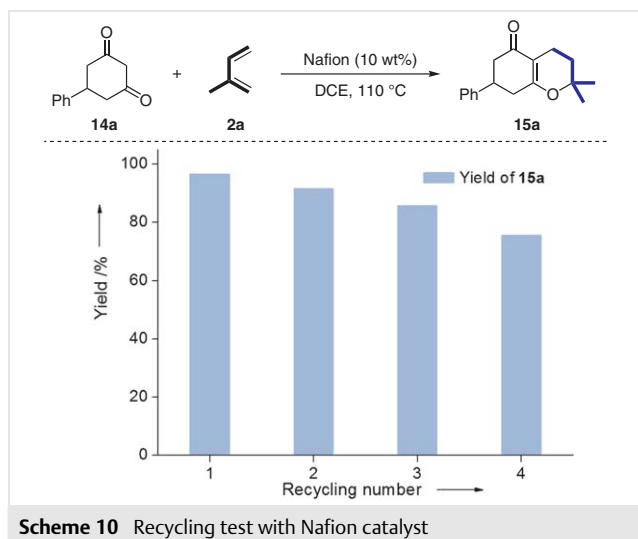


5 Catalytic Coupling of Cyclic 1,3-Diketones with Isoprene

Compared with homogeneous catalysis, the advantages of heterogeneous catalysis include facile separation and recycling of the catalyst, minimal catalyst contamination of the product, low cost, and low environmental impact. With this concept in mind, we further attempted to use solid acids to catalyze the coupling of isoprene.²⁷ It was found that, in the presence of Nafion resin, simple cyclic 1,3-diketones and isoprene could undergo formal [3+3] annulations to afford dimethylpyrans **15** (Scheme 9). A variety of 5-substituted 1,3-cyclohexanediones all worked well (**15a–d**). Submitting sterically hindered syncarpic acid to the standard conditions gave the desired product **15e** in 32% yield; its structure was confirmed by X-ray crystallographic analysis. This protocol could be further extended to other cyclic 1,3-dicarbonyls such as 1,3-cyclopentanedione and 4-hydroxy-2*H*-pyranone (**15f**, **15g**).



The reusability of solid acid Nafion for the annulation of 5-phenyl-1,3-cyclohexanedione and isoprene was tested (Scheme 10). The catalytic activity of Nafion slightly decreased with increasing number of recycling, which is presumably ascribed to coke formation on the catalyst surface via isoprene polymerization. Even so, the yield of **15a** was still acceptable after three cycles.



Scheme 10 Recycling test with Nafion catalyst

6 Conclusion and Outlook

From an economical and environmental point of view, bulk chemical isoprene is an ideal five-carbon source for the installation of valuable prenyl and reverse-prenyl motifs. However, electronically unbiased isoprene might undergo six possible addition modes in the coupling reactions, thus often making it cumbersome to obtain a single isomer. This account summarizes the strategies we have developed to achieve regioselective couplings of isoprene through C–H functionalizations. By varying the metal-hydride catalysts, both prenyl and reverse-prenyl groups could be selectively incorporated into the C3 position of indoles with isoprene. A Co(III)-catalyzed three-component coupling of isoprene, formaldehyde and 2-arylpyridines was developed in which the exclusive regioselectivity derives from the favored 4,3-insertion of isoprene into the Co–C bond. A regiodivergent annulation of 4-hydroxycoumarin with isoprene was achieved with acid catalysis. Furthermore, solid acid Nafion was identified as a promising catalyst for the annulation of cyclic 1,3-diketones with isoprene.

Despite these advances, there is still plenty of room for further exploration. For example, additional theoretical studies will be needed to elucidate the catalyst-controlled divergence, which will presumably provide guidance for the discovery of new couplings. The asymmetric prenylation

and reverse-prenylation of indoles is of great significance in the total synthesis of natural indole alkaloids. Therefore, the development of efficient catalytic systems, non-noble metals in particular, to realize such reactions with isoprene is highly desirable. The regiodivergent formation of C–B, C–N, and C–Si bonds will be another important research area. We anticipate that the studies of isoprene chemistry will also open a new avenue for the total synthesis of terpenoids.

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