Isoprene: A Promising Coupling Partner in C–H Functionalizations

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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.

1 Introduction

Five-carbon (C\textsubscript{5}) dimethylallyl units, such as 3-methyl-2-butenyl (prenyl) and 2-methyl-3-butenyl (reverse-prenyl), are ubiquitous in nature (Figure 1).\textsuperscript{1} Because the presence of these unique groups can enhance the lipophilicity of molecules and facilitate permeation across cellular membranes, these natural products usually exhibit intriguing biological properties. For example, Annonidine B\textsuperscript{2}, isolated from West African medicinal tree \textit{Annonummannii}, possesses two prenyl groups at the 3- and 7-positions of the in-

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Papuaforin A is a 1,2-adduct from the plants of the Hypericum family, Hyperforin and Papuaforin 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.

Transition-metal-catalyzed allylic substitution and directed C–H activation are two representative strategies for C–H functionalizations with dimethylallylic compounds. The organic chemistry community has developed some effective C5 coupling partners such as dimethylallylic alcohols and their derivatives including halides, acetates, carbonates and organometals. 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. 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. Furthermore, isoprene can also be biosynthesized on a large scale via a modified *Escherichia coli* fermentation process. In this respect, isoprene can be regarded as an economic feedstock to some extent. Accordingly, 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-diienes. 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. 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). Reverse-prenylated indoles 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. 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.

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 \( \eta^2 \)-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 \( \eta^1 \) hydride elimination. BEt3 is also likely to interact with the nitrogen atom of indole, leading to the formation of the adduct D'. The \( \eta^1 \)-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. 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. 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. 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-
significant 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 AgSbF6, the pre-catalyst Cp*Co(CO)I2 is first converted into an active cationic Co(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 Co(III)–H species G, followed by 1,4-insertion with the isoprene motif to produce prenyl-Co(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 Co(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-(NO2)2C6H5SO3H as catalyst exclusively delivered pyranocoumarins 12, whereas pyranochromones 13 turned out to be predominant in the presence of Lewis acid Sm(OTf)3. Both electron-deficient (12b, 13b) and electron-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 (40–90 °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 carboxylation intermediate L. It is noteworthy that 13a is produced reversibly, whereas the pathway to 12a is irreversible, which can account for the conversion of 13a into 12a in the presence of acid at high temperature.

Scheme 8 Proposed mechanism for acid-catalyzed divergent annulation

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-2H-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.

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 installation of valuable prenyl and reverse-prenyl moieties 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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References

For selected examples for coupling dienes with electrophiles, see:

For selected examples for coupling dienes with nucleophiles, see:


