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Article

Ni-catalyzed unnatural prenylation and cyclic monoterpenation of heteroarenes with isoprene

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ABSTRACT

Terpenoids, such as hemiterpenoids and monoterpenoids, are the largest class of natural products, which widely exist in plants and marine organisms. Herein, a divergent strategy is developed for the introduction of unnatural prenyl and cyclic monoterpene skeleton through relay catalysis from basic feedstock isoprene. In the presence of catalytic amount of base, the unnatural prenylation of heteroarenes proceeds through Markovnikov addition onto isoprene with less hindered NHC (IMes) ligand under Ni catalysis. With the aid of extra base, a further in situ isomerization of Markovnikov addition products delivered unnatural hemiterpenoids with tetrasubstituted alkene motif in high selectivities. It was found that bulky NHC (IPr) ligand could further promote sequential hydroheteroarylation between isoprene dimers and heterocycles and gave monoterpenoids in one pot. This work provides a new strategy for regulating the synthesis of hemiterpenoids and monoterpenoids.

1. Introduction

Hemiterpenoids and monoterpenoids consisting of one and two isoprene units respectively, which are of extraordinary pharmacological importance covering anticancer, antiviral, antibiotic, and immunosuppressive [1–3]. In nature, dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP) could be transformed to various hemiterpenoids equipped with prenyl and *tert*-prenyl. In addition, they could also be used as starting materials for the biosynthesis of numerous monoterpenoids and their derivatives under monoterpene synthases (Fig. 1(a)) [4–8]. Achieving new catalytic conversion of existing bulk chemicals towards high-value products by mimicking natural process is an eternal goal in academy and industry.

Meanwhile, transition-metal catalyzed hydrofunctionalization of alkenes [9–15] and conjugated dienes [16–29] offers a powerful strategy for the synthesis of complex molecules from easily accessed substrates. Given its low cost and large-scale production [30–32], isoprene is a sustainable precursor for the synthesis of hemi- and monoterpenoids [33–35]. To realize functionalization of isoprene [36–46], we have to address the following challenges: firstly, due to the similarity on electronic properties and steric hindrance, various isomers (up to 14 isomers) could be theoretically formed in hydrofunctionalization of isoprene; secondly, the dimerization of isoprene is a more complicated process under transition metal catalysis, linear and cyclic dimerization may exist simultaneously; in

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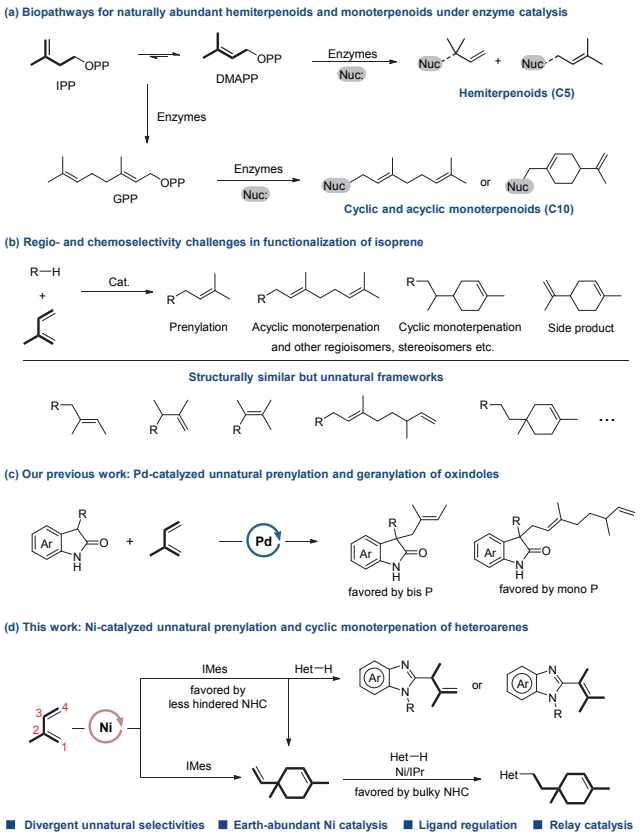


Fig. 1. The creation of natural and unnatural terpenoids.

addition, the follow-up functionalization of these dimers will result in hundreds of isomers, leading to low selectivity and efficiency [47–51]. And the construction of unnatural terpenoids could offer great potential candidates for bioisostere investigations. Therefore, how to effectively construct structurally similar but unnatural hemi- and monoterpene frameworks is of great challenge and highly appealing (Fig. 1(b)).

Nitrogen containing cyclic compounds widely exist in various natural products and pharmaceutical molecules. The catalytic C–H functionalization of heterocycles [52–70] is a straightforward and economic route to achieve post-modification of drugs and active molecules. And the introduction of dimethylallyl-related units (C_5 skeletons) [71–88] into functional molecules often leads to dramatic changes in their lipophilicities and metabolic stabilities. Recently, our group developed a Pd-catalyzed chemoselective coupling of oxindoles with isoprene [89]. The switch of chemoselectivity resulted mainly from the manipulation of coordination number of the phosphine ligand (mono P *vs.* bis P–P) around the Pd center. Given the advantages of earth abundant metal-based catalysis [90–92], we herein developed a Ni-catalyzed divergent strategy for unnatural prenylation and cyclic monoterpenation of heteroarenes from isoprene with high chemo- and regioselectivities (Fig. 1(d)). Less hindered NHC (IMes) favored an unnatural prenylation through the Markovnikov addition of heteroarenes onto isoprene. And bulky NHC (IPr) facilitated a sequential hydroheteroarylation of isoprene dimers for cyclomonoterpenation.

2. Experimental

2.1. General information

^{1}H NMR and ^{13}C NMR and ^{19}F NMR spectra were collected at room temperature in $CDCl_3$ on 400 or 700 MHz instrument. Flash column chromatography was performed on silica gel (200–300 mesh). Subatrates **1** were synthesized according to the literature procedures. Isoprene, nickel catalyst and *N*-heterocyclic carbene ligands were commercially available.

2.2. Typical procedure for the preparation of allylated products

In a glove box, a solution of $Ni(COD)_2$ (10 mol%), IMes·HCl (10 mol%), ^{t}BuONa (10 mol%) in hexane (1.0 mL) was stirred at room temperature for 20 min. Then, the solution was transferred into a reaction tube charged with **1** (0.20 mmol), **2** (0.80 mmol), and hexane (1.0 mL). After being sealed with a teflon screw cap, the reaction tube was removed from the glove box. Then, the reaction mixture was stirred at 100 °C for 24 h. Upon completion, the mixture was filtered through a short pad of celite, concentrated in vacuo, and purified by silica chromatography to give the product **3**.

2.3. Typical procedure for the preparation of alkenylated products

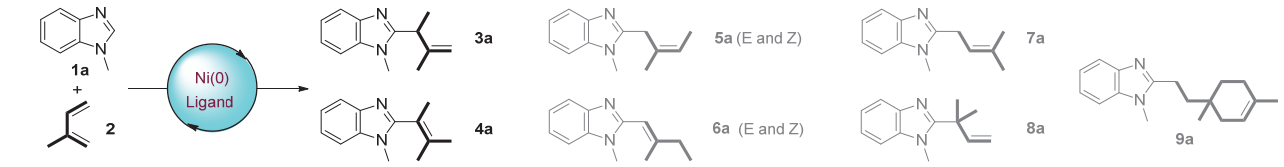
In a glove box, a reaction tube was charged with **1** (1.0 equiv.), **2** (4.0 equiv.), $Ni(COD)_2$ (5 mol%), IMes·HCl (5 mol%), EtONa (1.0 equiv.) and hexane (1.0 mL). After being sealed with a teflon screw cap, the reaction tube was removed from the glove box. Then, the reaction mixture was stirred at 100 °C for 24 h. Upon completion, the mixture was filtered through a short pad of celite, concentrated in vacuo, and purified by silica chromatography to give the product **4**.

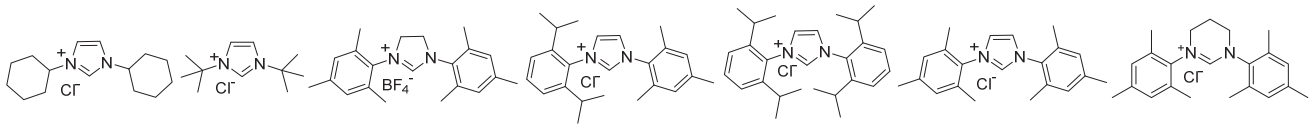
3. Results and discussion

3.1. Optimization for Ni-Catalyzed Unnatural Prenylation Heteroarenes with Isoprene

We began our investigation by the coupling of benzimidazole **1a** and isoprene **2** (Table 1). Initially, earth abundant nickel was chosen as catalyst to evaluate the influence of different *N*-heterocyclic carbene ligands (NHC) on the activity and selectivity in the presence of catalytic amount of ^{t}BuONa. Promising but low chemo- and regioselectivity for 4,3-adduct (**3a**), 4,1-adduct (**5a**) and 1,4-adduct (**7a**) of benzimidazole were observed with the use of **L1** as ligand (entry 1). And *tert*-butyl substituted NHC (**L2**) was found to be ineffective (entry 2). Then we turned our attention to aryl substituted NHC ligands. The common NHC ligand SIMes·HBF_4 (**L3**) gave 28% yield of **3a** (entry 3). Although the reaction with **L4** provided only trace amounts of 4,3-adduct (**3a**), bulkier ligand **L5** gave 4,3-adduct (**3a**) and telomer **9a** in 13% and 28% yield respectively (entries 4 and 5). It is surprisingly that IMes·HCl (**L6**) delivered the Markovnikov addition product (**3a**) in 82% yield accompanied

Table 1
Optimization for the nickel-catalyzed unnatural prenylation of benzimidazole with isoprene.





Entry [a]	Ligand	Base (mol%)	**3a** (%)	**4a** (%)	**5a** [c] (%)	**6a** [c] (%)	**7a** (%)	**8a** (%)	**9a** (%)
1	**L1**	^{t}BuONa (10)	12	0	15/5	0	3	0	0
2	**L2**	^{t}BuONa (10)	0	0	0	0	0	0	0
3	**L3**	^{t}BuONa (10)	28	0	10/4	0	2	2	0
4	**L4**	^{t}BuONa (10)	13	0	0	0	0	0	0
5	**L5**	^{t}BuONa (10)	13	0	0	0	0	0	28
6	**L6**	^{t}BuONa (10)	82	1	4/5	0	3	0	0
7	**L7**	^{t}BuONa (10)	0	0	0	0	0	0	0
8	**L6**	^{t}BuOLi (10)	0	0	0	0	0	0	0
9	**L6**	MeONa (10)	60	0	5/6	0	3	0	0
10	**L6**	^{t}BuONa (50)	0	11	0	16/10	0	1	0
11 [b]	**L6**	^{t}BuONa (100)	0	14	0	34/18	0	2	0
12 [b]	**L6**	EtONa (100)	6	81	0	7/4	0	2	0
13 [b]	**L6**	MeONa (100)	29	43	0	11/6	0	2	0

[a] **1a** (0.20 mmol), **2** (0.80 mmol), Ni(COD)$_2$ (10 mol%), ligand (10 mol%), hexane (2 mL), 100 °C, 24 h. The yield was determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [b] Ni(COD)$_2$ (5 mol%), **L6** (5 mol%), hexane (1 mL). [c] Compounds **5a** and **6a** were obtained as a mixture of E and Z stereoisomers.

by small amount of other isomers (entry 6). Ligand **L7** with an expansion of ring size resulted in no activity (entry 7). These results indicated that compound **9** can only be generated under the Ni/IPr catalytic system. When ^{t}BuOLi was employed as the additive, no products were observed (entry 8). In contrast, MeONa gave the 4,3-adduct **3a** in 60% yield (entry 9). Interestingly, the tetrasubstituted olefin product **4a** was obtained in 14% yield with the increase of the loading of ^{t}BuONa (entries 10 and 11). In the presence of excess EtONa, isomerized product **4a** was selectively formed in 81% yield (entry 12). However, MeONa did not perform well in the desired transformation (entry 13).

3.2. Substrate scope

Having identified optimized conditions, the scope of the hydroheteroarylation between different substituted benzimidazoles and isoprene **2** was evaluated (Fig. 2(a)). In general, benzimidazoles with different alkyl substituents in the nitrogen atom, such as *n*-propyl, *n*-butyl, methoxymethyl, benzyl, could all be well adapted to this protocol (**3a**–**3d**). An array of tethered alkenes was explored to test the generality of the reaction. The substrates with prenyl (**3f**), homoallyl (**3g**) and elongated allyl (**3h**) offered the desired product in high yields. It was showed that either electron-donating groups such as methyl (**3i**–**3k**) and methoxyl (**3l**–**3m**) or electron-withdrawing groups such as –Cl (**3n**–**3o**) and carboxylate (**3p**) on phenyl ring, regardless of their positions, had no significant impact on the reactions and desired products were produced in 41%–87% yields. Other *N*-containing heterocycle (**3q**) worked well and delivered the allylated product in 72% yield. Pleasingly, highly functionalized benzimidazole isomers **1r** and **1s** also reacted smoothly with isoprene under standard conditions to produce allylated products **3r** and **3s** in decent yields. Notably, the prenylation of *N*-methylbenzimidazole **1a** still worked well on a scale-up reaction and **3a** was delivered in 1.12 g with 70% yield.

Next, the versatility of the Ni-catalyzed C–H alkenylation strategy was explored (Fig. 2(b)). This method was found to be widely applicable to benzimidazoles containing different substituents on nitrogen atom, such as alkyl (**4a**–**4c**), methoxymethyl (**4d**), and benzyl (**4e**), the target products were generated in 73%–86% yields. This method was also applicable to benzimidazoles containing internal or terminal alkenyl groups (**4f**–**4h**). The electronic factors of substituents such as –Me, –OMe, –Cl and –CO_2Me on phenyl ring, did not significantly affect the catalytic activities, yielding the alkenylated products (**4i**–**4p**) in good yields. It should be pointed out that **1p** can be converted into ethyl ester **4q** in the presence of stoichiometric amounts of EtONa. Biologically relevant pyridine derivatives likewise underwent the catalytic C–H activation to give desired products (**4r** and **4s**). In addition, the coupling naphthoimidaz-

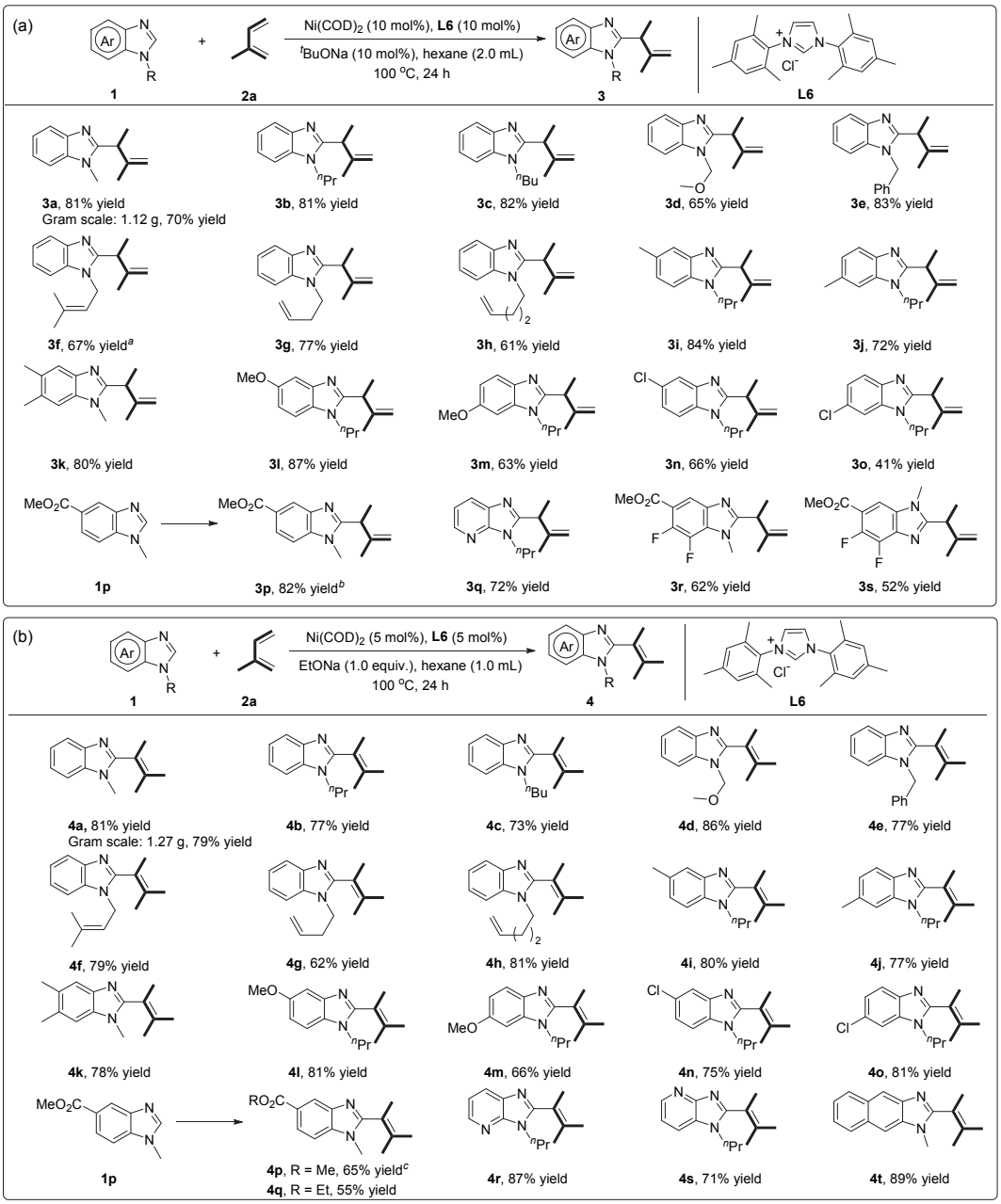


Fig. 2. The substrates scope of hydroheteroarylation of isoprene and isomerization. [a]Ni(COD)$_2$ (5 mol%), IMes·HCl (5 mol%), MeONa (10 mol%), *n*-hexane (0.4 mL). [b]MeONa (10 mol%), toluene (1.0 mL). [c]MeONa (1.0 equiv.).

ole with isoprene also occurred efficiently to produce **4t** in high yield. Gram-scale experiment was performed for heterocycle **1a** and gave desired product **4a** in 1.27 g with 79% yield.

3.3. Mechanistic investigation

To gain insight into the Ni-catalyzed the regiodivergent hydroheteroarylation of isoprene, preliminary mechanistic investigations have been conducted (Fig. 3). First, interconversion experiments between **3a** and **4a** were performed to figure out which one is thermodynamic product. In the presence of free IMes ligand without base, terminal alkene **3a** could be isomerized to form internal alkene **4a** in 22% yield (Fig. 3(a), Eq. (1)). With the aid of a stoichiometric amount of base, higher yield (90%) of product **4a** was obtained without nickel catalyst. When using **4a** as substrate, no Markovnikov addition product **3a** was detected under either above conditions or **3a**'s generation condition. These isomerization studies suggest that the product **4a** is generated from the isomerization of **3a** which is promoted by strong base, but nickel-catalyzed process is not precluded (Fig. 3(a), Eq. (2)). Next, deuterium labeling studies were conducted with ***d*-1a**, the expected product ***d*-3a** was achieved with 35% and 9% of D incorporation at the methyl and terminal alkenyl position in the absence of base (Fig. 3(b), Eq. (3)). This incomplete deuterium-transfer may be caused by the reversible migratory insertion of Ni^{II}-H into isoprene. Under

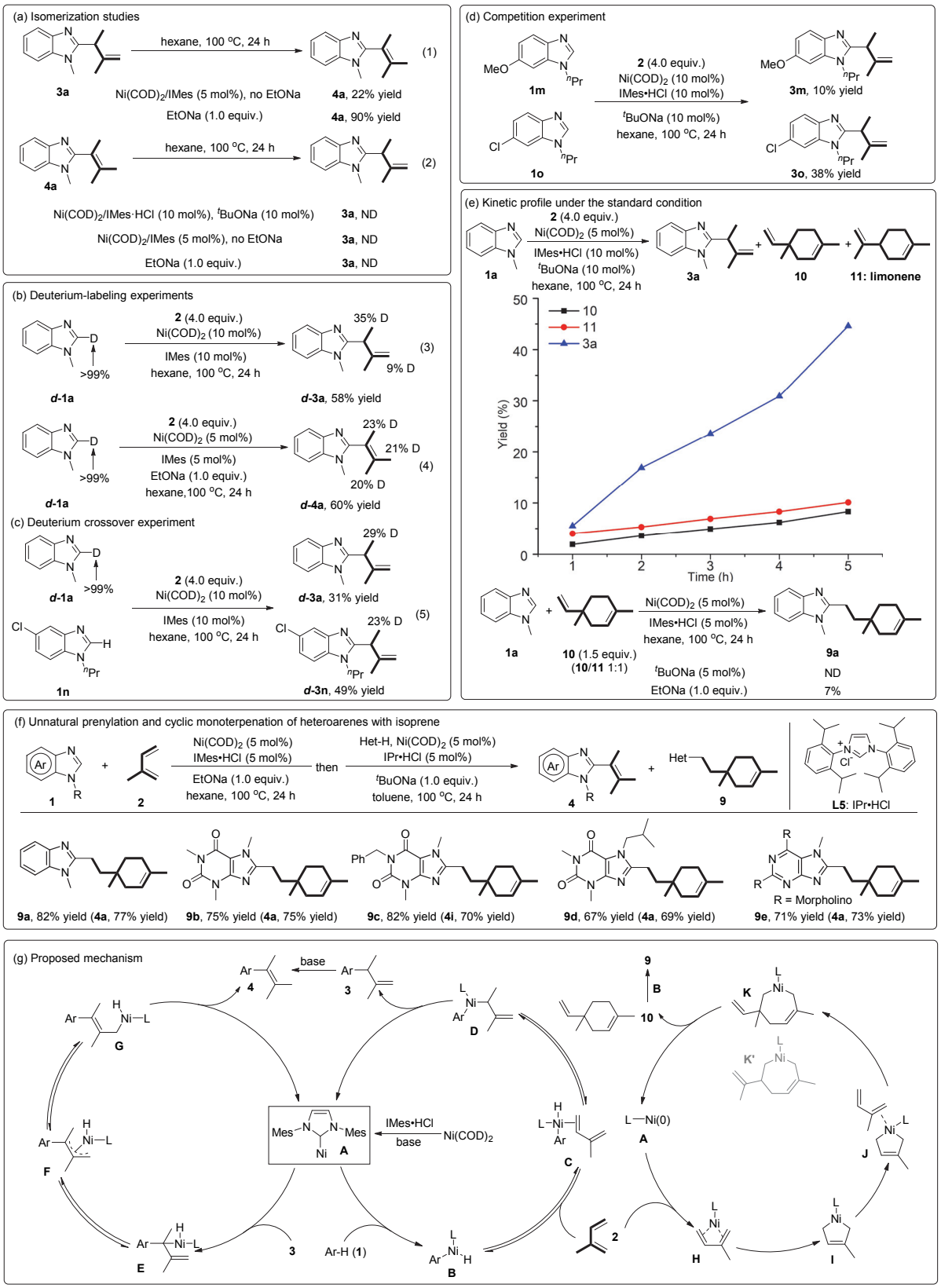


Fig. 3. Mechanistic studies and the substrates scope of monoterpenation under relay catalysis.

stoichiometric amount of EtONa, deuterium scrambling was detected at three methyl groups of product ***d*-4a** (Fig. 3(b), Eq. (4)). The even deuterium distribution probably results from the alkene isomerization promoted by EtONa. The subsequent deuterium crossover experiment was performed with ***d*-1a** and **1n** in one pot, there was a deuterium scrambling distribution

between these two products (Fig. 3(c)). This result supports the aforementioned reversible migratory insertion of Ni^{II}-hydride. It also indicates a reversible coordination of isoprene with Ni complex. Higher yield was obtained for benzimidazole bearing more electron-withdrawing group (**1o** *vs.* **1m**) in the competition experiment (Fig. 3(d)). It could be attributed to the decrease of electron density on the reactive C–H bond which undergoes oxidative addition with Ni(0) easier.

In addition, the kinetic investigations were executed to reveal the reaction process (Fig. 3(e)). With the increasing of reaction time, the yield of Markovnikov addition product **3a** increased gradually. It was surprising that the cyclodimerization product **10** and limonene (**11**) were detected during the reaction, but the formation rate of **3a** was obviously greater than that of dimers **10** and limonene **11**. The yield of **3a**, **10** and limonene **11** was 82%, 27% and 30% after the completion of the reaction respectively. In addition, the reaction between substrate **1a** and isolated mixture **10** and **11** did not give any products under a catalytic amount of ^{t}BuONa (Fig. 3(e)). Unnatural monoterpenoid **9a** was generated in only 7% yield in the presence of a stoichiometric amount of EtONa. These results indicate that less hindered NHC (IMes) ligand was not able to effectively promote the hydroheteroarylation of dimer **10**. However, bulky NHC IPr could facilitate hydroheteroarylation of dimer **10** to give an unnatural monoterpenoid **9a** with 82% yield (Fig. 3(f)). And the unnatural hemiterpenoid **4a** was also obtained with 77% yield in one pot. The combination of benzimidazole and caffeine and purine analogues was compatible and gave the corresponding products in 67%–82% yields (**9b**–**9e**). It should be noted that the formation of two desired products (**4** and **9**) is independent and both of them were obtained simultaneously from the column chromatography. This unique protocol demonstrates that ligands can act a key role in modulating the chemoselectivity (C5 *vs.* C10) of terpene synthesis like enzymes in nature.

Based on the above results and literature precedents [41,51,64], a proposed mechanism was shown in Fig. 3(g). Initially, a ligand exchange process between $Ni(COD)_2$ and IMes·HCl generates active catalyst Ni(IMes) **A** in the presence of base. This Ni(0) species undergoes a subsequent oxidative addition with aromatic heterocycles to yield Ni–H intermediate **B**. Next, the complexation of Ni-hydride intermediate **B** with isoprene **2** promotes the migratory insertion to give allylic Ni(II) **D**. Subsequently, a reductive elimination gives the Markovnikov addition product **3** and regenerates the Ni catalyst **A**. For the formation of isomerized product **4**, one route is that the generated product **3** firstly coordinates with Ni(0) species **A**. Subsequently, the intramolecular 1,3-H shift is triggered by an allylic C–H bond activation to form allyl Ni(II) complex **E**. A next tautomerization of allyl Ni(II) **E** *via* π-allyl intermediate **F** gives the other allyl Ni(II) complex **G**. Finally, reductive elimination delivers the isomerized product **4** and regenerates catalyst **A**. Besides this pathway, the addition of a stoichiometric amount of base could also promote the isomerization of terminal alkene **3** to internal alkene **4**.

For the formation of unnatural monoterpenoid **9** from isoprene, Ni^{0} (NHC) species **A** coordinates with isoprene **2** to produce the complex **H**, which undergoes cyclometallation to generate a nickelacycle **I**. A 16e Ni(II) complex **J** is formed through the coordination of second isoprene **2** with nickelacycle **I**. Then the obtained Ni(II) complex **J** undergoes migratory insertion to yield a seven-member nickelacycle **K**. The desired unnatural monoterpene **10** is generated from the reductive elimination of Ni(II) species **K**. A subsequent coordination of monoterpene **10** with Ni–H **B** triggers a hydroarylation to give product **9**. And natural monoterpene limonene **11** can also be produced via the reductive elimination of the other seven-member nickelacycle **K'** which is formed from similar pathway. A final migratory insertion and reductive elimination from the reaction of unnatural monoterpene **10** with Ni–H intermediate **B** delivers unnatural monoterpenoid **9** and regenerates the nickel catalyst **A**.

4. Conclusions

In conclusion, a Ni-catalyzed divergent unnatural prenylation and cyclic monoterpenylation of heteroarenes with isoprene was demonstrated via C–H bond activation with a relay catalysis strategy. A series of Markovnikov addition products, tetrasubstituted internal olefins and cyclic monoterpenoids were obtained in high regio- and chemoselectivities. Investigation of mechanism demonstrated that the steric hindrance of NHC ligands has a big influence on catalytic activity of metal center. The less hindered IMes not only promotes the hydroheteroarylation of isoprene but also facilitates the dimerization of isoprene. On the other hand, the addition of bulkier NHC ligand IPr further expedites the sequential hydroheteroarylation of isoprene dimer. This work demonstrates an efficient strategy for regulating the synthesis of hemi- and monoterpenoids. Further studies on the application of this approach are underway in our lab.

Electronic supporting information

Supporting information is available in the online version of this article.

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Graphical Abstract

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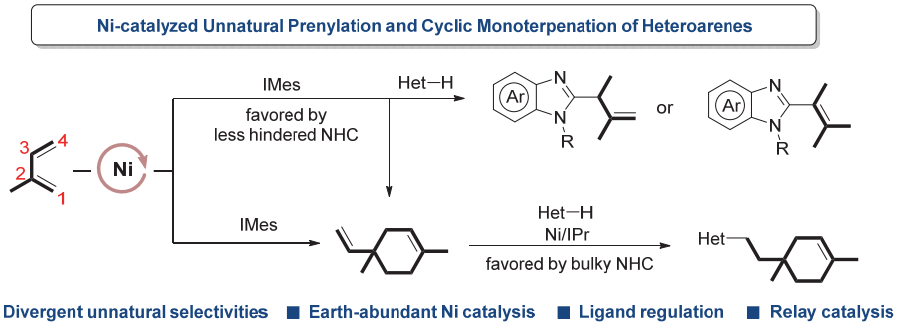

A Ni-catalyzed divergent strategy has been developed for unnatural prenylation and cyclic monoterpenation of heteroarenes from isoprene. Less hindered NHC favored a Markovnikov addition of heteroarenes onto isoprene. And bulky hindered NHC facilitated a sequential hydroheteroarylation of isoprene dimers for cyclomonoterpenation.

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镍催化杂芳烃的非天然戊烯基化及环状单萜化反应

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摘要: 萜类化合物, 如半萜类和单萜类, 是天然产物中种类最繁多、结构最多样的一类, 广泛存在于植物和海洋生物中, 在人类的日常生活中具有重要的应用价值. 自然界中, 二甲基烯丙基焦磷酸酯(DMAPP)和异戊烯基焦磷酸酯(IPP)在各种酶的作用下经过偶联、重排、环化以及异构化等反应合成萜类化合物. 传统的人工方法大多依赖于过渡金属催化的异戊烯基以及反异戊烯基前体的反应, 该反应不仅需要当量的金属试剂, 且反应过程中也会产生当量的副产物, 不符合绿色环保以及原子经济性原则. 异戊二烯作为一种廉价易得的大宗化学品, 其高附加值转化一直是学术界和工业界关注的焦点. 但由于异戊二烯具有反应活性低以及区域选择性调控难的特点, 氢芳基化产物最多可达到十四种异构体. 此外, 异戊二烯容易发生二聚、三聚以及调聚等反应, 产生复杂产物. 上述问题使得异戊二烯的高附加值转化具有很大挑战性.

在前期关于异戊二烯氢官能团化以及手性二聚研究的基础上, 本文提出了一种以异戊二烯为原料, 通过接力催化策略, 在杂芳环中引入非天然戊烯基和环状单萜骨架的方法. 具体而言, 使用廉价金属镍作为催化剂, 小位阻的氮杂环卡宾作为配体, 在当量碱的条件下, 通过马氏加成得到异戊二烯4,3-氢杂芳基化产物, 该策略具有广泛的底物普适性, 较好的选择性和产率. 机理研究表明, 反应首先经过杂环化合物的C–H键氧化加成, 再通过异戊二烯的配位以及迁移插入, 最后通过还原消除获得目标产物. 反应过程中没有当量副产物生成, 符合原子经济性原则. 而当体系中加入当量碱时, 4,3-氢杂芳基化产物

通过原位异构化获得了含有四取代烯烃的非天然半萜. 机理研究表明,碱诱导的异构化和镍催化的分子内氢迁移的机理可能同时存在. 进一步研究表明,通过控制不同位阻卡宾配体的添加过程,可以实现“一锅两步法”生成含有四取代烯烃的半萜衍生物和环状单萜衍生物; 具体为先加入小位阻卡宾配体催化生成四取代烯烃,再加入大位阻卡宾配体以及杂环化合物,催化生成环状单萜衍生物.

综上,本文不仅有助于大宗化学品异戊二烯的高效转化,而且发展的配体调控为半萜类化合物和单萜类化合物的发散性合成提供了新思路,具有潜在的应用价值.

关键词: 萜类化合物; 异戊二烯; 非天然戊烯基化; 镍催化; 氮杂环卡宾配体; 四取代烯烃

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