How to cite: *Angew. Chem. Int. Ed.* **2022,** *61,* e202207202
International Edition: doi.org/10.1002/anie.202207202
German Edition: doi.org/10.1002/ange.202207202

Transition-Metal Catalysis

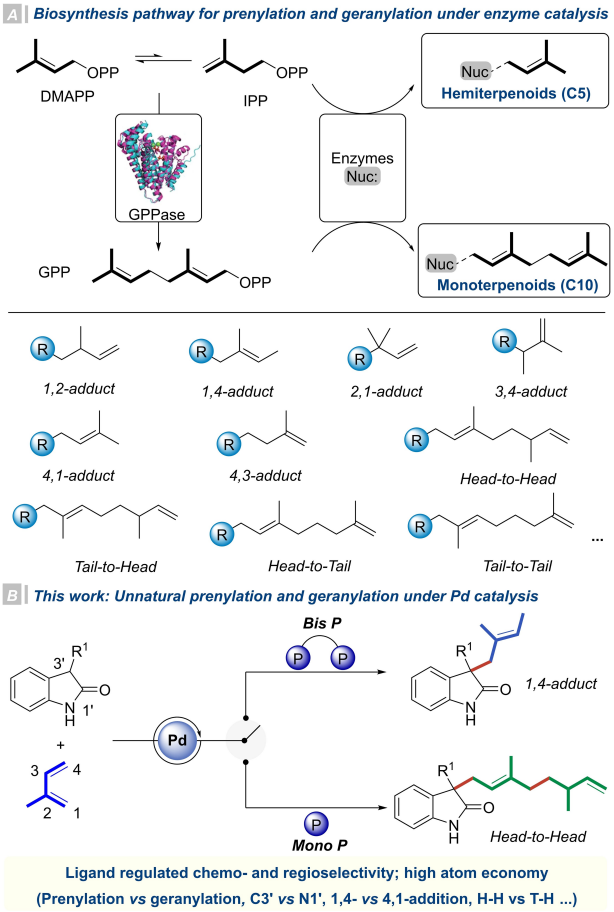
Bioinspired and Ligand-Regulated Unnatural Prenylation and Geranylation of Oxindoles with Isoprene under Pd Catalysis

*Chao-Yang Zhao, Ying-Ying Liu, Xiang-Xin Zhang, Gu-Cheng He, Heng Liu, Ding-Wei Ji, Yan-Cheng Hu, and Qing-An Chen**

Abstract: In nature, prenylation and geranylation are two important metabolic processes for the creation of hemiterpenoids and monoterpenoids under enzyme catalysis. Herein, we have demonstrated bioinspired unnatural prenylation and geranylation of oxindoles using the basic industrial feedstock isoprene through ligand regulation under Pd catalysis. Pentenylated oxindoles (with C_5 added) were attained with high selectivity when using a bisphosphine ligand, whereas upon switching to a monophosphine ligand, selectivity toward geranylated oxindoles (with C_{10} added) was achieved. Moreover, the head-to-head product could be further isomerized to an internal skipped diene under Pd–H catalysis. No stoichiometric by-product was formed in the process.

As the largest class of natural products, terpenoids are not only widely found in plants, but also can be extracted from marine organisms.[1] Hemi- and monoterpenoids are the two major ingredients for terpenoids.[2] In organisms, dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP) can not only generate a series of hemiterpenoids, but also could undergo condensation reaction to produce geranyl diphosphate (GPP) with the help of geranyl pyrophosphate synthase (GPPase). Under the catalysis of enzymes, GPP can generate a series of bioactive monoterpenoids (Scheme 1A). Accordingly, it is of great significance to achieve straight-forward prenylation[3] and geranylation for terpenoids synthesis through artificial catalysis.[4]

Oxindole[5,6] and its derivatives are crucial transcription factor inhibitors and have enzyme inhibitory activity in life.[7] Although Trost[8] and co-workers have developed elegant prenylations of oxindoles, dimethylallyl alcohol carbonates and protecting group on nitrogen are indispensable for their protocol. Recognized as the most prominent hemiterpene, basic feedstock isoprene[9] is theoretically the ideal precursor for the construction of hemi- and monoterpenoids with regards to high atom economy.[10] However, compared with common preactivated C_5 precursors such as dimethylallyl alcohol[11] and their analogues,[12] the direct assembly of isoprene into oxindole poses a greater challenge. Firstly, the four olefin carbons of isoprene are difficult to distinguish in terms of electronic properties and steric hindrance, therefore, leading to 6 addition modes. Secondly, it will be more complicated for the telomerization process of isoprene[13] which would in theory generate up to more than 60 acyclic isomers and over 90 cyclic isomers (See Scheme S1 and S2 in Supporting Information). Thirdly, it is worth emphasizing that oxindole also has two reactive sites



Scheme 1. Bioinspired unnatural prenylation and geranylation of oxindoles.

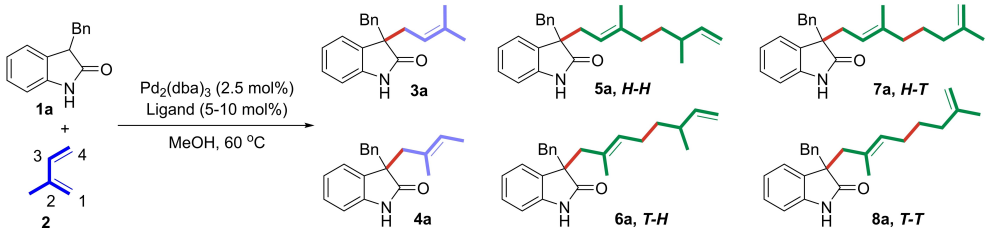
[*] C.-Y. Zhao, Y.-Y. Liu, X.-X. Zhang, G.-C. He, H. Liu, D.-W. Ji, Y.-C. Hu, Prof. Dr. Q.-A. Chen
Dalian Institute of Chemical Physics, Chinese Academy of Sciences
457 Zhongshan Road, Dalian 116023 (China)
E-mail: qachen@dicp.ac.cn
Homepage: http://www.lbcs.dicp.ac.cn
C.-Y. Zhao, Y.-Y. Liu, X.-X. Zhang, G.-C. He, H. Liu, Prof. Dr. Q.-A. Chen
University of Chinese Academy of Sciences
Beijing 100049 (People's Republic of China)

(N, C3), which doubles the diversity of reactions and the difficulty of regulation. Thus, the divergent formation of isoprenylated (with C_5 added) and monoterpenylated (with C_{10} added) oxindole with high selectivity is a daunting task. Herein, following our long-standing interest in pursuing divergent selective transformations of terpenes,[14] we sought to develop a ligand-regulated bioinspired chemoselective unnatural prenylation and geranylation of oxindole with isoprene under Pd catalysis (Scheme 1B).

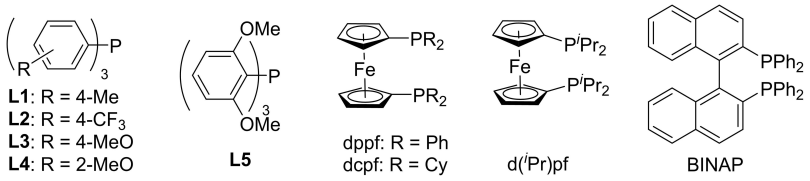
Initially, 3-Bn oxindole (**1a**) and isoprene (**2**) served as the model substrates to test our hypothesis under Pd catalysis (Table 1). Promising but low chemo- and regioselective prenylations (**3a** and **4a**) and geranylations (**5a**–**8a**) of oxindole were observed with the use of PPh_3 (entry 1). The subsequent evaluation of monophosphine ligand suggested PPh_2Cy favored the prenylation and $PPhCy_2$ favored geranylation (entries 2–4). Notably, up to six isomers (**3a**–**8a**) could be observed in the presence of P(2-furyl)$_3$ (entry 5). The investigation on the substituent effect on PPh_3 showed that electron-rich phosphorus ligands had higher catalytic activities (entries 6–10). To our delight, monophosphine **L5** facilitated the formation of geranylated product **5a** in 61 % yield with high chemo- and regioselectivity (entry 10). And the electron-poor phosphorus ligand **L2** could not promote the desired transformation (entry 7). By reducing the loading of **L5**, the yield of **5a** had been significantly increased to 87 % (entry 11). Interestingly, switching to bidentate ligand significantly favored the formation of prenylated (C_5) products (**3a** and **4a**) over geranylated (C_{10}) products **5a**–**8a** (entries 12–15). Delightedly, 1,4-adduct prenylated product **4a** was obtained in 77 % yield with high regioselectivity using d(^{i}Pr)pf as the ligand (entry 14). The yield and selectivity of **4a** could be further improved by increasing the reaction temperature to 80 °C (85 % yield, >20:1 *rr*, entry 16).

With the optimized conditions in hand, the generality of oxindole substrates was subsequently tested (Table 2A). For Pd-catalyzed 1,4-addition, the 3-Bn oxindole **1a** was converted to the desired product **4a** in 83 % yield and >20:1 *rr*. The stereo configuration of **4a** was unambiguously determined by two-dimensional nuclear magnetic resonance (NOESY) spectroscopy and X-ray analysis (Table 2A).[15] Similarly, oxindoles with different substituents (CF_3, F, Ph, ^{t}Bu or Me) in the para position of the benzyl group, could

Table 1: Bioinspired prenylation and geranylation of oxindole.[a]

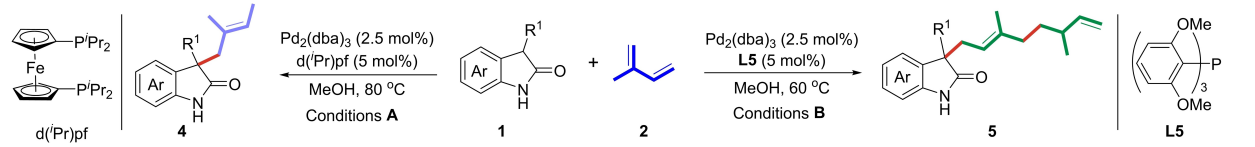


Entry	Ligand	Yield [%][b]					
		3a	**4a**	**5a**	**6a**	**7a**	**8a**
1	PPh_3	4	5	4	10	1	1
2	PPh_2Cy	3	12	1	5	1	–
3	$PPhCy_2$	–	3	10	18	–	1
4	PCy_3	–	–	3	4	–	–
5	P(2-furyl)$_3$	2	4	5	18	4	5
6	**L1**	18	26	3	4	–	–
7	**L2**	–	–	–	–	–	–
8	**L3**	20	27	6	12	–	1
9	**L4**	12	19	28	24	–	–
10	**L5**	–	–	61	–	–	–
11[c]	**L5**	–	–	87	–	–	–
12	dppf	25	27	–	–	–	–
13	dcpf	6	65	–	–	–	–
14	d(^{i}Pr)pf	4	77	–	–	–	–
15	BINAP	8	10	–	–	–	–
16[d]	d(^{i}Pr)pf	3	85	–	–	–	–

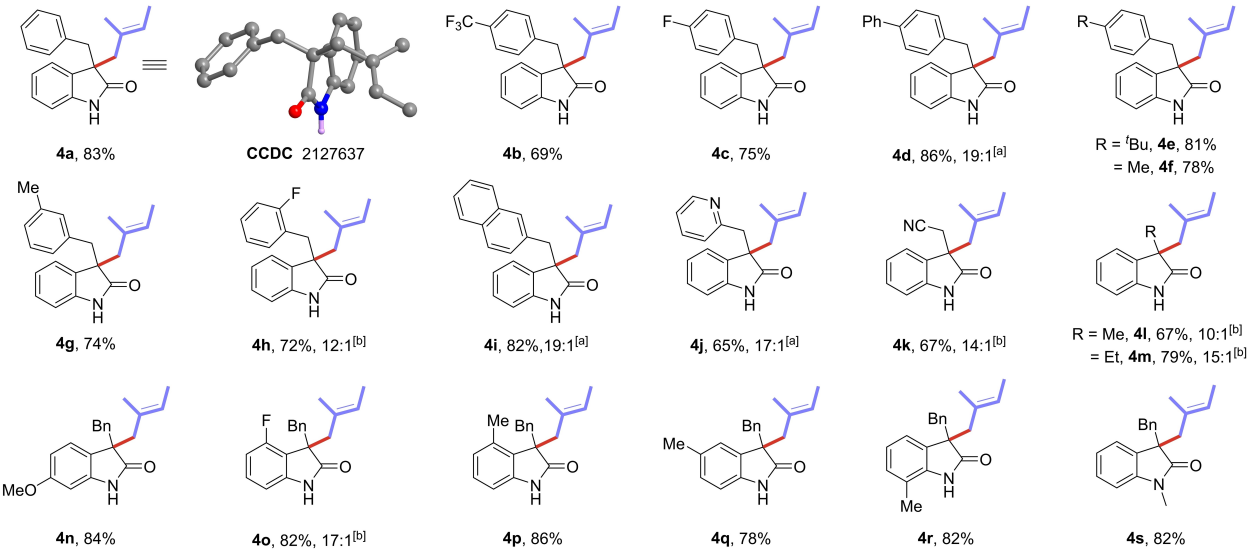


[a] Conditions: **1a** (0.10 mmol), **2** (0.40 mmol), $Pd_2(dba)_3$ (2.5 mol %), Mono P (10 mol %) *or* Bis P (5 mol %), MeOH (0.4 mL), 60 °C. [b] Determined by GC-FID analysis of the crude product mixture using mesitylene as internal standard. [c] **L5** (5 mol %). [d] 80 °C; H–H: Head to Head, T–H: Tail to Head, H–T: Head to Tail, T–T: Tail to Tail. Cy = Cyclohexyl, Bn = Benzyl, dba = dibenzylideneacetone.

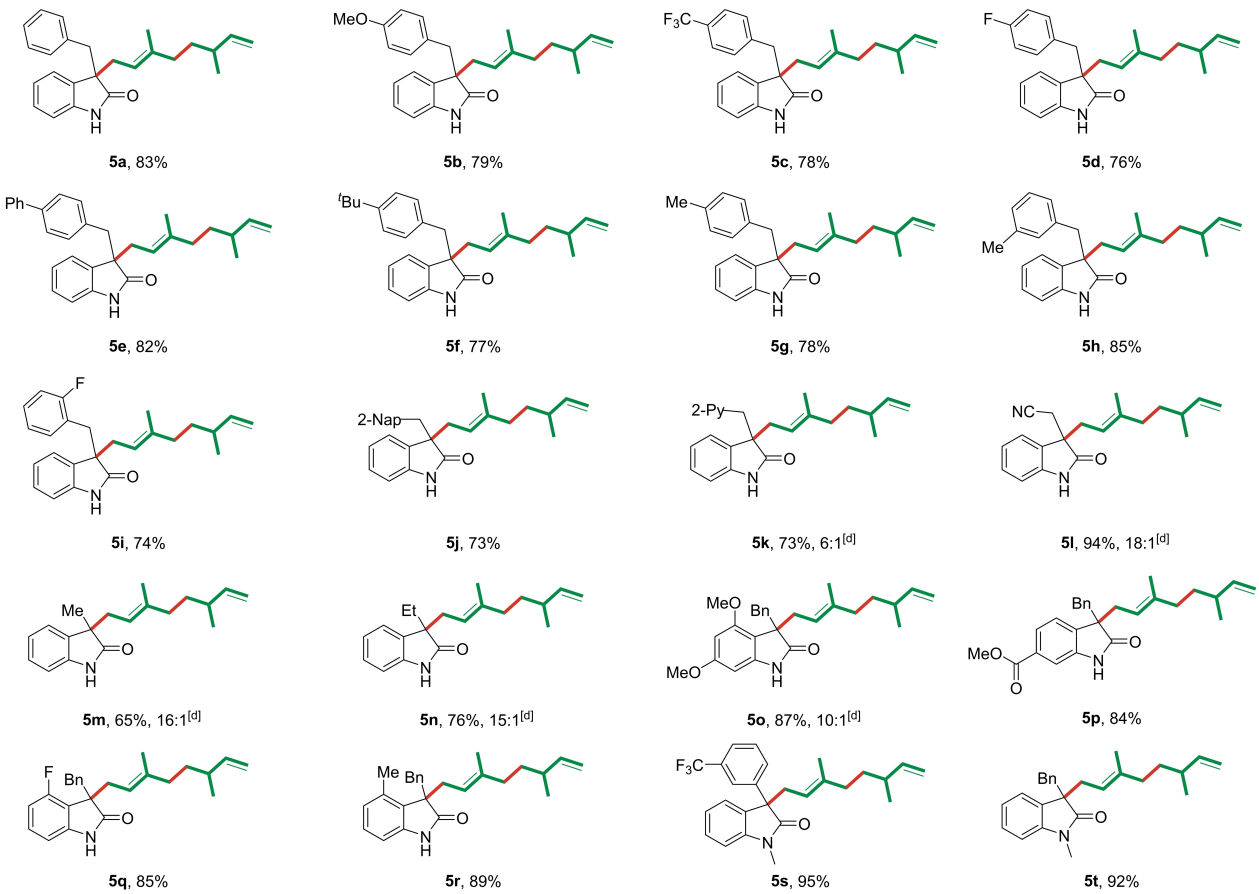
Table 2: Oxindole scope for Pd-catalyzed unnatural prenylation and geranylation.



A) Biomimetic prenylation of oxindoles under Conditions A



B) Biomimetic geranylation of oxindoles under Conditions B[c]



[a] Minor product is prenylation product **3**; [b] Minor product is reverse-prenylation product; [c] All the *dr* of **5** is 1:1; [d] Minor product is *T-H* (**6**) product.

all be well adapted to the reaction process (**4b–f**). In addition, substrate bearing meta-substituted group also showed good performance on both reactivity and selectivity and exclusively delivered **4g** in 74 % yield. It was worth noting that 3-(2′-F-Bn), 3-(CH_2CN), 3-Me and 3-Et substituted oxindoles would generate a little corresponding reverse-prenylation products (**4h, 4j–m**). Naphthyl or pyridyl instead of phenyl of benzyl all reacted smoothly under the current condition (**4i–j**). Besides, oxindoles having a substituent on the benzene ring were further investigated, which could successfully generate the desired products (**4n–o**). Me group on the phenyl ring, regardless of their positions, were all well-tolerated (**4p–r**). Finally, when the N–H on the oxindole was protected by methyl, the reaction process could still proceed well (**4s**).

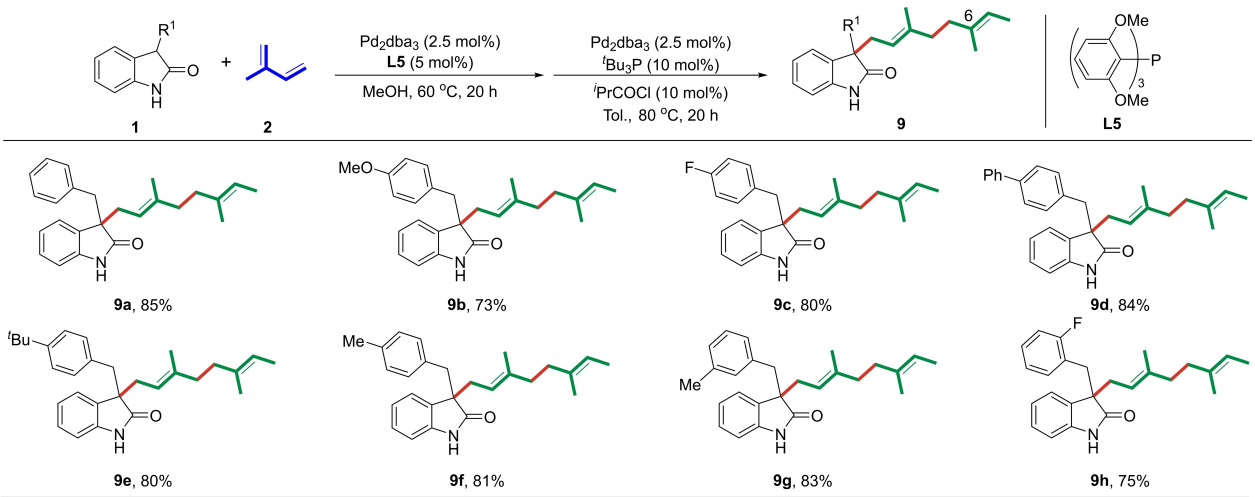
We next set about to assess the scope of oxindoles with respect to the geranylation (Table 2B). Firstly, subjecting 3-Bn substituted oxindole **1a** to the standard conditions furnished geranylated oxindole **5a** in 84 % yield. Also, the stereo configuration of product **5a** was determined as single *E*-type via NOESY. 4′-MeO-Bn substituted oxindole also underwent the geranylation smoothly to provide **5b** in 81 % yield. The benzyl groups, bearing regardless of the electron withdrawing groups (CF_3, F, or Ph) or the electron donating groups (^{t}Bu or Me) on the para position, were all well-tolerated under this protocol (**5c–g**). Moreover, 3-(3′-Me-Bn) and 3-(2′-F-Bn) substituted oxindoles were both suitable substrates as well (**5h–i**). When the naphthyl replaced the phenyl on benzyl, compound **5j** could also be delivered in good yield. It was worth mentioning that the heterocyclic substituent was also compatible with the catalytic system, but the selectivity was significantly decreased (**5k**). Additionally, alkyl (such as methyl and ethyl) and 3-cyanomethyl substituents were all compatible with the process, providing the corresponding products **5l–n** in acceptable to good yields (65–95 %). Methoxy group on the benzene ring could also proceed smoothly accompanied by a small amount of **6o** (*T-H*). Oxindoles with different substituents on the benzene ring were suitable substrates as well (**5o–r**). The reactivities could be further enhanced through the protection of N atom on oxindole (**5s–t**).

To further showcase the applicability of the method, gram-scale experiments (5.0 mmol) were performed for oxindole **1a** and isoprene **2**. The desired prenylated product **4a** and the geranylated product **5a** could both be obtained in higher yield (88 %, 1.285 g and 94 %, 1.690 g, respectively) with only the half loading of the catalyst (Scheme 2a).

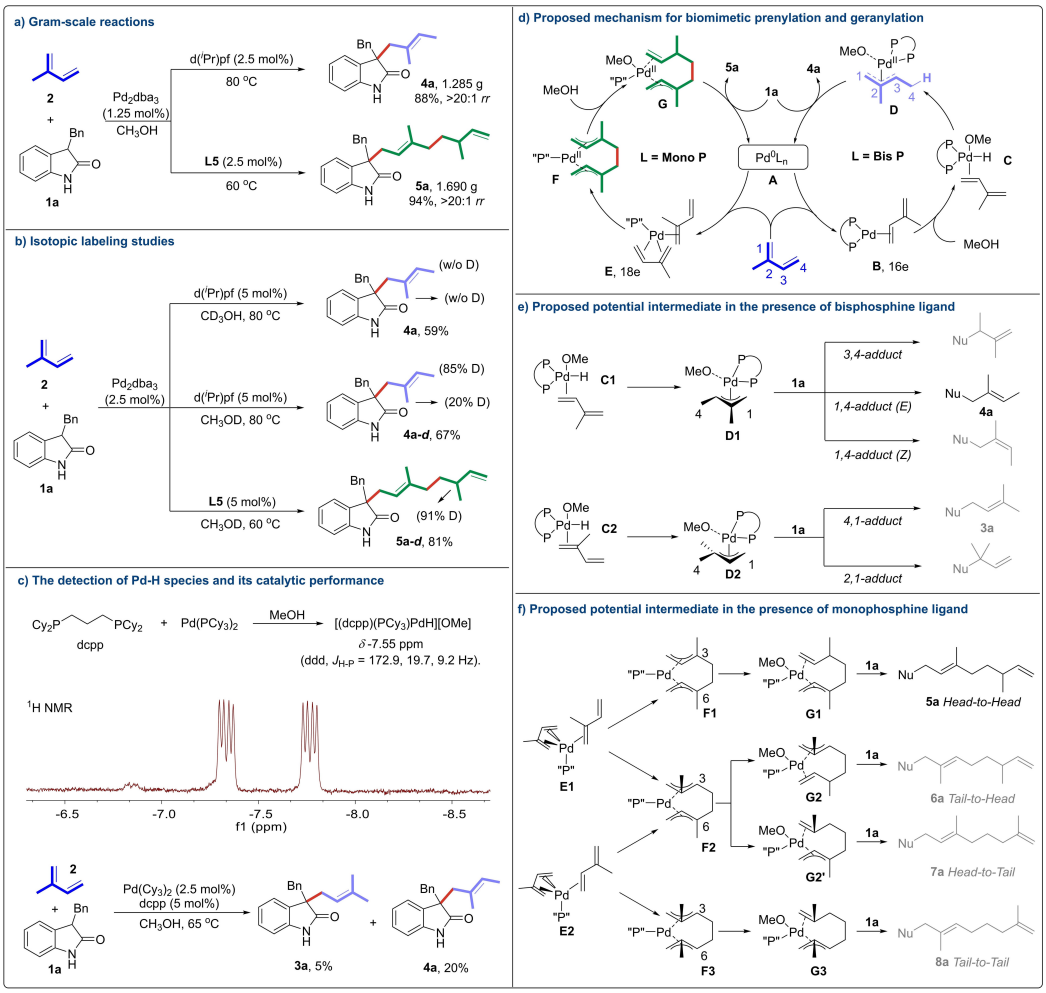
To gain insight into the mechanism of the bioinspired prenylation and geranylation, deuterium-labeled experiments were conducted (Scheme 2b). Using CD_3OH as solvent, there was no deuterium observed in the product **4a**. But when MeOD was employed as the solvent in the standard condition A, 20 % and 85 % of deuterium incorporation were observed respectively at the two methyl groups of the obtained product **4a-*d***. Among them, deuterium mainly exists on the C4 position, indicating that Pd–H and isoprene mainly undergo 4,3-insertion during the reaction. Besides, the presence of deuterium on both methyl groups indicates that there is a hydrogen tautomerism process in the reaction. In comparison, under the condition B, using MeOD instead of MeOH yielded the target product **5a-*d*** with 91 % of deuterium on tertiary carbon. It suggests no hydrogen tautomerism process occurs on the isoprene **2** and a protonation probably be involved in the geranylation.

With the intention to understand the mechanism of the prenylation, additional mechanistic experiments were designed (Scheme 2c). Owing to a transient property of active Pd–H species, we were not able to observe it from ^{1}H NMR spectroscopy under standard condition or related control experiments. However, a stabilized Pd–H species could be detected with the help of additional phosphine ligand PCy_3.[16] The ^{1}H NMR spectrum displayed a unique resonance centered at −7.55 ppm characterized with three different J_{H-P} coupling constants (172.9, 19.7 and 9.2 Hz, Scheme 2c). The largest splitting (J_{H-P} = 172.9 Hz) of the hydride resonance resulted from a trans influence on its

Table 3: Bioinspired geranylation through relay Pd catalysis.[a]



[a] *6E/6Z* of **9** is between 2:1 and 3:1.



Scheme 2. Scale up reactions and mechanistic studies.

coupling with a phosphorus atom of the dcpp ligand. The presence of multiple cyclohexyl groups on the phosphine ligands probably makes the palladium center too crowded to coordinate directly with the methoxy anion.[16] Further control experiments also confirmed the catalytic ability of the obtained Pd–H in prenylation (Scheme 2c).

On the basis of experimental observations and previous reports,[17] a plausible mechanism for this chemo- and regiodivergent couplings was shown in Scheme 2d. For prenylation facalitated by bisphosphine ligand, Pd^0 species **A** coordinates with one molecule of isoprene to form species **B**. Subsequently, MeO–Pd^{II}–H intermediate **C** is generated via the oxidative addition of MeOH with Pd^0 species **B**. A subsequent migratory insertion of isoprene into Pd^{II}–H **C** delivers π-allyl-Pd^{II} species **D**, which is attacked by oxindole **1a** to furnish the desired 1,4-addition product **4a** and regenerate the Pd^0 species **A**. For geranylation promoted by monophosphine ligand, the spared vacant coordination site allows Pd^0 to interact with two molecules of isoprene simultaneously. Next, the formed Pd^0 species **E** undergoes oxidative cyclopalladation to give bis-π-allyl-Pd^{II} intermediate **F**. Then, intermediate **G** is delivered by protonolysis of Pd^{II} complex **F** in the presence of MeOH. A final nucleophilic substitution of **G** with oxindole affords the product **5a** and regenerates the Pd^0 catalyst.

Based on the analysis of coordination geometry of Pd complex, the potential intermediates for the elucidation of regioselective manipulation were purposed in Scheme 2e and f. In the presence of bisphosphine ligand, although Pd^0 could coordinate with two molecules of isoprene or chelate with one molecule of isoprene, it tends to form inactive resting species off the catalytic cycle. Instead, Pd^{II}-hydride intermediate **C1** or **C2** in which palladium coordinates with one molecule of isoprene will be expected to form in the catalytic cycle. Subsequently, the allyl-Pd species **D1** or **D2** could be generated and delivers five regioselective and constitutional isomers. In the presence of d(iPr)pf, since the hydride in Pd–H is relatively nucleophilic, the migration insertion into the relatively electron-deficient double bond is preferred (Scheme 2e, **C1** vs. **C2**). Besides, deuterium experiments (Scheme 2b) further support this speculation. When two methyl groups are orientated in a syn form of the π allyl group, the intermediate **D1** is more thermodynamic stable. At last, the nucleophilic substitution occurs at the less hindered site and gives **4a** as preferential product.

On the contrary, with the aid of the monophosphine ligand, one extra coordination site is spared to facilitate the complexation of two molecules of isoprene with Pd^0 (Scheme 2f). Therefore, it provides the possibility for the dimerization of isoprene. Due to the different coordination modes of isoprene and Pd^0 (**E1** and **E2**), three different palladacycles **F1**–**3** can be produced through oxidative cyclometallation. Structurally, intermediates **F1** and **F3** are symmetric while **F2** is nonsymmetric. Therefore, the subsequent protonolysis of **F2** could theoretically give two different allyl palladium species **G2** and **G2′**. Eventually, 4 different products (**5a**–**8a**) could be delivered via the coupling of allyl palladium **G** and **1a**. The presence of methyl group on the C2 position of isoprene make the attached C=C bond with higher electron density than the other one. Therefore, more electron-rich complex **E1** is favored over **E2** to undergo oxidative cyclometallation. With the increasing the steric hindrance effect between the monophosphine ligand (**L3**–**5**, Table 1, entries 8–10) and substrate, the intermediate **F1** with two distant methyl groups is more preferred than **F2** for the cross coupling. Overall, the regulation of prenylation (C_5) and geranylation (C_{10}) is accomplished by tuning the coordination geometry of Pd catalytic center.

Olefins represent key structural features in a plethora of naturally and non-naturally occurring compounds,[18] as well as being precursors for the industrial synthesis of polymers. What's more, catalytic isomerizations are perceived as nearly ideal transformations due to atom economy and institutional diversity.[19] The geranylated product **5a** can be further isomerized to generate internal skipped diene **9a** under Pd catalyst. After further optimization, **9a** could be obtained with 85 % yield in one pot transformation from **1a** with good substrate applicability (Table 3). For example, substrates bearing with either electron donating groups (**9b**) or electron-withdrawing groups (**9c**, **9d, 9h**) were all compatible under current process and provided the corresponding products in acceptable to good yields (73–84 %). Obviously, substrates containing alkyl substituent (such as, ^{t}Bu, Me) delivered **9e** in 80 % yield, **9f** in 81 % yield and **9g** in 83 % yield, respectively.

In conclusion, a practical strategy has been developed for ligand-regulated chemoselective unnatural prenylation and geranylation of oxindoles with isoprene under Pd catalysis. Manipulation of the selectivity was governed by modulating the coordination geometry of Pd catalyst. Utilization of bisphosphine ligand d(^{i}Pr)pf afforded 1,4-addition products (with C_5 added) with high selectivity, while monophosphine ligand **L5** enabled selective synthesis of the geranylated products (with C_{10} added). Additionally, the geranylated products can be further isomerized to internal unconjugated dienes in the presence of Pd–H catalyst. Furthermore, the reaction process features high atom economy without stoichiometric by-product formation. Further studies on regiodivergent telomerization of oxindole with isoprene are underway in our laboratory.

Acknowledgements

We thank Prof. Yong-Gui Zhou (DICP) for helpful discussions and manuscript revisions. Financial support from Dalian Outstanding Young Scientific Talent (2020RJ05), and the National Natural Science Foundation of China (22071239) is acknowledged.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Geranylation · Isoprene · Oxindoles · Palladium · Prenylation

[1] a) E. Oldfield, F.-Y. Lin, *Angew. Chem. Int. Ed.* **2012**, *51*, 1124; *Angew. Chem.* **2012**, *124*, 1150; b) R. Long, J. Huang, J. Gong, Z. Yang, *Nat. Prod. Rep.* **2015**, *32*, 1584; c) Z. G. Brill, M. L. Condakes, C. P. Ting, T. J. Maimone, *Chem. Rev.* **2017**, *117*, 11753; d) Y. J. Zhou, E. J. Kerkhoven, J. Nielsen, *Nat. Energy* **2018**, *3*, 925.

[2] M. Ishikura, T. Abe, T. Choshi, S. Hibino, *Nat. Prod. Rep.* **2013**, *30*, 694.

[3] a) S.-M. Li, *Nat. Prod. Rep.* **2010**, *27*, 57; b) M. E. Tanner, *Nat. Prod. Rep.* **2015**, *32*, 88.

[4] a) N. Funken, Y.-Q. Zhang, A. Gansaeuer, *Chem. Eur. J.* **2017**, *23*, 19; b) C. Nájera, I. P. Beletskaya, M. Yus, *Chem. Soc. Rev.* **2019**, *48*, 4515.

[5] a) W. C. Sumpter, *Chem. Rev.* **1945**, *37*, 443; b) A. Deiters, M. Pettersson, S. F. Martin, *J. Org. Chem.* **2006**, *71*, 6547; c) G. Chen, Y.-Q. Miao, R. Zhou, L. Zhang, J. Zhang, X.-J. Hao, *Res. Chem. Intermed.* **2013**, *39*, 2445; d) K. Balaraman, C. Wolf, *Angew. Chem. Int. Ed.* **2017**, *56*, 1390; *Angew. Chem.* **2017**, *129*, 1411; e) J. Bariwal, L. G. Voskressensky, E. V. Van der Eycken, *Chem. Soc. Rev.* **2018**, *47*, 3831; f) A. Ding, M. Meazza, H. Guo, J. W. Yang, R. Rios, *Chem. Soc. Rev.* **2018**, *47*, 5946; g) Y. M. Khetmalis, M. Shivani, S. Murugesan, K. V. G. C. Sekhar, *Biomed. Pharmacother.* **2021**, *141*, 111842.

[6] For selective works on the catalytic transformation of oxindoles, see: a) B. M. Trost, J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6314; b) W.-B. Liu, H. He, L.-X. Dai, S.-L. You, *Org. Lett.* **2008**, *10*, 1815; c) B. Sundararaju, M. Achard, B. Demerseman, L. Toupet, G. V. M. Sharma, C. Bruneau, *Angew. Chem. Int. Ed.* **2010**, *49*, 2782; *Angew. Chem.* **2010**, *122*, 2842; d) Z. Cao, Y. Liu, Z. Liu, X. Feng, M. Zhuang, H. Du, *Org. Lett.* **2011**, *13*, 2164; e) A. Lin, J. Yang, M. Hashim, *Org. Lett.* **2013**, *15*, 1950; f) X. Zhang, L. Han, S.-L. You, *Chem. Sci.* **2014**, *5*, 1059; g) X. Zhang, W.-B. Liu, H.-F. Tu, S.-L. You, *Chem. Sci.* **2015**, *6*, 4525; h) Q. A. Chen, H. F. Klare, M. Oestreich, *J. Am. Chem. Soc.* **2016**, *138*, 7868; i) F. A. Cruz, Y. Zhu, Q. D. Tercenio, Z. Shen, V. M. Doneta, *J. Am. Chem. Soc.* **2017**, *139*, 10641.

[7] a) K. M. Depew, S. J. Danishefsky, N. Rosen, L. SeppLorenzino, *J. Am. Chem. Soc.* **1996**, *118*, 12463; b) S. Edmondson, S. J. Danishefsky, L. Sepp-Lorenzino, N. Rosen, *J. Am. Chem. Soc.* **1999**, *121*, 2147; c) J. M. Schkeryantz, J. C. G. Woo, P.

Siliphaivanh, K. M. Depew, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 11964; d) B. M. Trost, D. T. Stiles, *Org. Lett.* **2007**, *9*, 2763; e) B. M. Trost, M. Osipov, *Angew. Chem. Int. Ed.* **2013**, *52*, 9176; *Angew. Chem.* **2013**, *125*, 9346; f) J. Ruchti, E. M. Carreira, *J. Am. Chem. Soc.* **2014**, *136*, 16756; g) J. H. Lang, P. G. Jones, T. Lindel, *Chem. Eur. J.* **2017**, *23*, 12714; h) B. M. Trost, W.-J. Bai, C. Hohn, Y. Bai, J. J. Cregg, *J. Am. Chem. Soc.* **2018**, *140*, 6710; i) F. Zhou, L. Zhu, B.-W. Pan, Y. Shi, Y.-L. Liu, J. Zhou, *Chem. Sci.* **2020**, *11*, 9341.

[8] a) B. M. Trost, S. Malhotra, W. H. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 7328; b) B. M. Trost, W. H. Chan, S. Malhotra, *Chem. Eur. J.* **2017**, *23*, 4405.

[9] T. D. Sharkey, A. E. Wiberley, A. R. Donohue, *Ann. Bot.* **2008**, *101*, 5.

[10] a) M. Kimura, A. Ezoe, M. Mori, K. Iwata, Y. Tamaru, *J. Am. Chem. Soc.* **2006**, *128*, 8559; b) A. M. Johns, Z. Liu, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2007**, *46*, 7259; *Angew. Chem.* **2007**, *119*, 7397; c) S. Omura, T. Fukuyama, J. Horiguchi, Y. Murakami, I. Ryu, *J. Am. Chem. Soc.* **2008**, *130*, 14094; d) F. Shibahara, J. F. Bower, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 6338; e) T. Smejkal, H. Han, B. Breit, M. J. Krische, *J. Am. Chem. Soc.* **2009**, *131*, 10366; f) J. C. Leung, L. M. Geary, T.-Y. Chen, J. R. Zbieg, M. J. Krische, *J. Am. Chem. Soc.* **2012**, *134*, 15700; g) L. M. Geary, B. W. Glasspoole, M. M. Kim, M. J. Krische, *J. Am. Chem. Soc.* **2013**, *135*, 3796; h) A. Köpfer, B. Sam, B. Breit, M. J. Krische, *Chem. Sci.* **2013**, *4*, 1876; i) D. Banerjee, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 1630; *Angew. Chem.* **2014**, *126*, 1656; j) Q. A. Chen, D. K. Kim, V. M. Dong, *J. Am. Chem. Soc.* **2014**, *136*, 3772; k) X. Fang, H. Li, R. Jackstell, M. Beller, *J. Am. Chem. Soc.* **2014**, *136*, 16039; l) X.-H. Yang, A. Lu, V. M. Dong, *J. Am. Chem. Soc.* **2017**, *139*, 14049.

[11] a) M. Kimura, M. Futamata, R. Mukai, Y. Tamaru, *J. Am. Chem. Soc.* **2005**, *127*, 4592; b) L. Usui, S. Schmidt, M. Keller, B. Breit, *Org. Lett.* **2008**, *10*, 1207; c) X. Zhang, Z.-P. Yang, C. Liu, S.-L. You, *Chem. Sci.* **2013**, *4*, 3239; d) S. Tanaka, S. Shiomi, H. Ishikawa, *J. Nat. Prod.* **2017**, *80*, 2371; e) Y.-C. Hu, Y. Li, D.-W. Ji, H. Liu, H. Zheng, G. Zhang, Q.-A. Chen, *Chin. J. Catal.* **2021**, *42*, 1593; f) C.-Y. Zhao, D.-W. Ji, H. Zheng, G.-C. He, H. Liu, Y.-C. Hu, Q.-A. Chen, *ACS Catal.* **2021**, *11*, 6825.

[12] a) P. Zhang, H. Le, R. E. Kyne, J. P. Morken, *J. Am. Chem. Soc.* **2011**, *133*, 9716; b) Y. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 10642; c) Y. Yang, T. J. L. Mustard, P. H.-Y. Cheong, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 14098; *Angew. Chem.* **2013**, *125*, 14348; d) C. Zheng, C.-X. Zhuo, S.-L. You, *J. Am. Chem. Soc.* **2014**, *136*, 16251; e) R. Alam, C. Diner, S. Jonker, L. Eriksson, K. J. Szabo, *Angew. Chem. Int. Ed.* **2016**, *55*, 14417; *Angew. Chem.* **2016**, *128*, 14629; f) J. M. Müller, C. B. W. Stark, *Angew. Chem. Int. Ed.* **2016**, *55*, 4798; *Angew. Chem.* **2016**, *128*, 4877; g) S. Priya, J. D. Weaver, *J. Am. Chem. Soc.* **2018**, *140*, 16020; h) H.-F. Tu, X. Zhang, C. Zheng, M. Zhu, S.-L. You, *Nat. Catal.* **2018**, *1*, 601; i) F.-L. Yu, D.-C. Bai, X.-Y. Liu, Y.-J. Jiang, C.-H. Ding, X.-L. Hou, *ACS Catal.* **2018**, *8*, 3317.

[13] a) E. J. Smutny, *J. Am. Chem. Soc.* **1967**, *89*, 6793; b) S. Takahashi, T. Shibano, N. Hagihara, *Tetrahedron Lett.* **1967**, *8*, 2451; c) W. Keim, M. Roper, *J. Org. Chem.* **1981**, *46*, 3702; d) M. Hidai, H. Mizuta, H. Yagi, Y. Nagai, K. Hata, Y. Uchida, *J. Organomet. Chem.* **1982**, *232*, 89; e) W. Keim, K. R. Kurtz, M. Roper, *J. Mol. Catal.* **1983**, *20*, 129; f) S. M. Maddock, M. G. Finn, *Organometallics* **2000**, *19*, 2684; g) F. Leca, R. Reau, *J. Catal.* **2006**, *238*, 425; h) R. Jackstell, A. Grotevendt, D. Michalik, L. El Firdoussi, M. Beller, *J. Organomet. Chem.* **2007**, *692*, 4737; i) A. Behr, M. Becker, T. Beckmann, L. Johnen, J. Leschinski, S. Reyer, *Angew. Chem. Int. Ed.* **2009**, *48*, 3598; *Angew. Chem.* **2009**, *121*, 3652; j) A. Gordillo, L. D. Pachon, E. de Jesus, G. Rothenberg, *Adv. Synth. Catal.* **2009**, *351*, 325; k) P. J. C. Hausoul, A. N. Parvulescu, M. Lutz, A. L. Spek, P. C. A. Bruijnincx, B. M. Weckhuysen, R. Gebbink, *Angew. Chem. Int. Ed.* **2010**, *49*, 7972; *Angew. Chem.* **2010**, *122*, 8144; l) C. F. Huo, R. Jackstell, M. Beller, H. J. Jiao, *J. Mol. Model.* **2010**, *16*, 431; m) I. Maluenda, M.-T. Chen, D. Guest, S. M. Roe, M. L. Turner, O. Navarro, *Catal. Sci. Technol.* **2015**, *5*, 1447; n) T. A. Faßbach, A. J. Vorholt, W. Leitner, *ChemCatChem* **2019**, *11*, 1153.

[14] a) Y. C. Hu, D. W. Ji, C. Y. Zhao, H. Zheng, Q. A. Chen, *Angew. Chem. Int. Ed.* **2019**, *58*, 5438; *Angew. Chem.* **2019**, *131*, 5492; b) Y. Li, Y.-C. Hu, H. Zheng, D.-W. Ji, Y.-F. Cong, Q.-A. Chen, *Eur. J. Org. Chem.* **2019**, 6510; c) J. Yang, D. W. Ji, Y. C. Hu, X. T. Min, X. Zhou, Q. A. Chen, *Chem. Sci.* **2019**, *10*, 9560; d) C. S. Kuai, D. W. Ji, C. Y. Zhao, H. Liu, Y. C. Hu, Q. A. Chen, *Angew. Chem. Int. Ed.* **2020**, *59*, 19115; *Angew. Chem.* **2020**, *132*, 19277; e) Y. Li, Y.-C. Hu, D.-W. Ji, W.-S. Zhang, G.-C. He, Y.-F. Cong, Q.-A. Chen, *Chin. J. Catal.* **2020**, *41*, 1401; f) C.-Y. Zhao, H. Zheng, D.-W. Ji, X.-T. Min, Y.-C. Hu, Q.-A. Chen, *Cell Rep. Phys. Sci.* **2020**, *1*, 100067; g) W.-S. Jiang, D.-W. Ji, W.-S. Zhang, G. Zhang, X.-T. Min, Y.-C. Hu, X.-L. Jiang, Q.-A. Chen, *Angew. Chem. Int. Ed.* **2021**, *60*, 8321; *Angew. Chem.* **2021**, *133*, 8402.

[15] Deposition Number 2127637 (for **4a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[16] a) M. Portnoy, D. Milstein, *Organometallics* **1994**, *13*, 600; b) J. C. Calabrese, E. E. Bunel, *Organometallics* **2001**, *20*, 337.

[17] a) M. J. L. Tschan, E. J. Garcia-Suarez, Z. Freixa, H. Launay, H. Hagen, J. Benet-Buchholz, P. van Leeuwen, *J. Am. Chem. Soc.* **2010**, *132*, 6463; b) J. Colavida, J. A. Lleberia, A. Salom-Català, A. Gual, A. Collado, E. Zangrando, J. M. Ricart, C. Godard, C. Claver, J. J. Carbó, S. Castillon, *ACS Catal.* **2020**, *10*, 11458.

[18] a) Y. J. Zhang, E. Skucas, M. J. Krische, *Org. Lett.* **2009**, *11*, 4248; b) J. R. Zbieg, E. Yamaguchi, E. L. McInturff, M. J. Krische, *Science* **2012**, *336*, 324; c) C. C. Roberts, D. M. Matias, M. J. Goldfogel, S. J. Meek, *J. Am. Chem. Soc.* **2015**, *137*, 6488; d) J. S. Marcum, C. C. Roberts, R. S. Manan, T. N. Cervarich, S. J. Meek, *J. Am. Chem. Soc.* **2017**, *139*, 15580; e) X.-H. Yang, V. M. Dong, *J. Am. Chem. Soc.* **2017**, *139*, 1774; f) H.-C. Shen, Y.-F. Wu, Y. Zhang, L.-F. Fan, Z.-Y. Han, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2018**, *57*, 2372; *Angew. Chem.* **2018**, *130*, 2396; g) X.-H. Yang, R. T. Davison, V. M. Dong, *J. Am. Chem. Soc.* **2018**, *140*, 10443; h) D. W. Ji, Y. C. Hu, H. Zheng, C. Y. Zhao, Q. A. Chen, V. M. Dong, *Chem. Sci.* **2019**, *10*, 6311; i) D. W. Ji, G. C. He, W. S. Zhang, C. Y. Zhao, Y. C. Hu, Q. A. Chen, *Chem. Commun.* **2020**, *56*, 7431.

[19] a) D. Gauthier, A. T. Lindhardt, E. P. K. Olsen, J. Overgaard, T. Skrydstrup, *J. Am. Chem. Soc.* **2010**, *132*, 7998; b) E. Larionov, H. Li, C. Mazet, *Chem. Commun.* **2014**, *50*, 9816; c) M. Holmes, L. A. Schwartz, M. J. Krische, *Chem. Rev.* **2018**, *118*, 6026.

Manuscript received: May 16, 2022
Accepted manuscript online: June 1, 2022
Version of record online: June 23, 2022