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Asymmetric Hydroxymethylative Etherification of 1,3-Dienes with Isatins and Alcohols via Pd(0)-π-Lewis Base Catalysis

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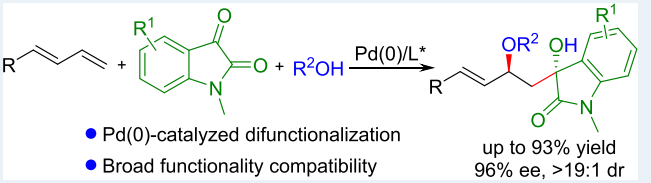
ABSTRACT: Although the asymmetric hydroalkoxylation of 1,3-dienes has been achieved recently, the development of a modular and mechanistically distinct strategy for concurrently introducing an alkoxyl group and another chiral moiety into 1,3-dienes remains to be disclosed. Presented herein is a palladium(0)-π-Lewis base-catalyzed asymmetric hydroxymethylative etherification reaction of 1,3-dienes, isatins, and aliphatic alcohols, proceeding through a cascade vinylogous addition and allylic etherification sequence. This three-component reaction exhibits a broad substrate scope and good functionality tolerance under mild catalytic conditions, generally furnishing structurally diverse chiral 1,3-diol derivatives bearing two stereogenic centers with moderate-to-high levels of diastereo- and enantioselectivity, which can be further converted to valuable frameworks with higher molecular complexity. In addition, a few control experiments were conducted to elucidate the reaction process.



KEYWORDS: *hydroxymethylative etherification, palladium, π-Lewis base catalysis, 1,3-diene, isatin, alcohol*

INTRODUCTION

Optically pure allylic ethers, as a class of prominent structural motifs, not only are witnessed in diverse bioactive natural products and marketed pharmaceutical agents[1] but also serve as versatile building blocks in organic synthesis.[2] Among various approaches available for constructing chiral allylic ethers, the transition metal (TM)-catalyzed asymmetric substitution of allylic derivatives with oxygen-containing nucleophiles proved to be one of the most straightforward and efficient strategies.[3] Compared with phenols,[4] aliphatic alcohols were scarcely employed in allylic etherification reactions, mainly because of their poor nucleophilicity.[5] External activators (such as Et_3B,[5a,b] Et_2Zn,[5c] Bu_3SnOR,[5d] etc.[5e,f]) or specially tailored ligands[6] were typically required for alcohol-engaged Tsuji−Trost-type reactions, which sometimes significantly restricted functional group tolerance. In recent years, TM-mediated enantioselective hydroalkoxylation of C−C multiple bonds emerged as a more atom- and step-economic protocol for the production of allylic ethers, since it allowed net addition of alcohols to readily accessible allenes or alkynes straightforwardly.[7] As the latest effort, He[8a] and Yang[9a] successfully extended the hydroalkoxylation strategy to abundant 1,3-dienes, via asymmetric palladium and nickel catalysis, respectively (Scheme 1a).[8,9] Although elegant advances have been achieved, the hydroalkoxylation of unsaturated hydrocarbons has mainly generated simple allylic ether derivatives. It would be highly facilitating but challenging that alkoxyl groups and another privileged pharmacophore rather than simple hydrogen could be simultaneously installed into C−C multiple bonds of simple starting materials, especially in a catalytic diastereo- and enantioselective manner. Nevertheless, this concept still remains to be developed.

In 2021, Huang documented a rare strategy for enantioselective aminomethylative etherification of 1,3-dienes by using in situ generated aminomethyl cyclopalladated complexes from *N*,*O*-acetals and aliphatic alcohols, affording valuable chiral 1,3-aminol ethers, albeit with a single stereogenic center (Scheme 1b).[10] As a result, the development of a modular and mechanistically distinct strategy for concurrently introducing an alkoxyl group and another chiral moiety into 1,3-dienes is highly desirable, which could significantly enrich the structural and stereochemical diversity and complexity. In line with our continuous interest in developing new transformations based on Pd(0)-π-Lewis base catalysis,[11] we envisaged that HOMO (the highest occupied molecular orbital) energy-raised complexes **I** of 1,3-dienes **1** and Pd(0) upon η^2-coordination would undergo vinylogous addition to electrophiles, such as biorelevant isatins **2**, enantioselectively. As illustrated in Scheme 1c, the resultant five-membered cyclopalladium complexes **II** would isomerize to π-allylpalladium species **III**, which would activate hard aliphatic alcohols **3** by a hydrogen-bonding interaction, facilitating subsequent allylic alkylation to deliver 1,3-diol derivatives **4**. Several challenges need to be

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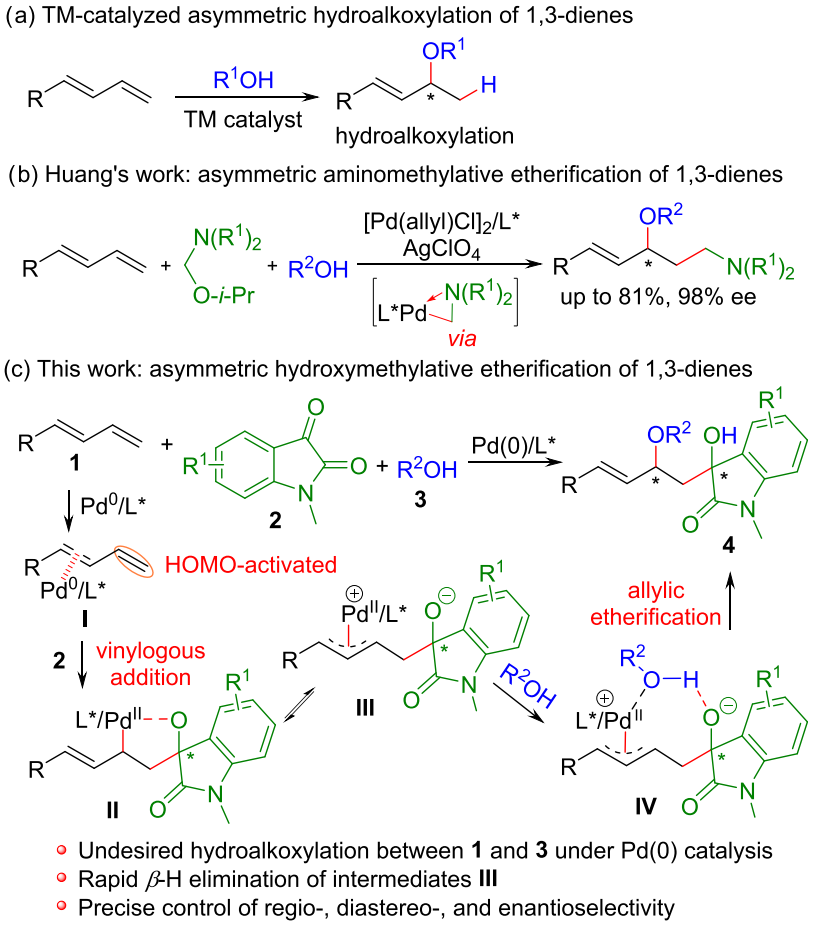
Scheme 1. Strategies for Asymmetric Etherification Reactions of 1,3-Dienes



conquered to realize the above conception: (1) 1,3-Dienes **1** might undertake competitive hydroalkoxylation with alcohols **3** in the presence of Pd(0), as demonstrated in He's work.[8a] (2) Our previous work indicated that π-allylpalladium intermediates **III** were liable to undergo β-H elimination to deliver the undesired 2,4-dienyl alcohols, especially when hard alcohols **3** are used as the final pronucleophiles.[11a] (3) Generated allylic ether products **4** might also suffer oxidative addition with palladium(0) to form allyl intermediates, which would lead to the erosions of stereoselectivity or degradations of the products.[12] These possible side reactions would significantly complicate the reaction profiles and precise control of regio-, diastereo-, and enantioselectivity, presenting another formidable task.

RESULTS AND DISCUSSION

Catalytic Condition Screenings. We initiated the investigation by examining the reaction between 1-phenyl-1,3-butadiene **1a**, *N*-methyl isatin **2a**, and MeOH (10 equiv) in toluene under the catalysis of $Pd(PPh_3)_4$. The reaction proceeded smoothly at 80 °C, but only undesired dienyl alcohol **5a** was isolated in a good yield after 24 h (Table 1, entry 1). Fortunately, conducting the reaction in neat MeOH efficiently switched the unwanted β-H elimination into an allylic etherification process, thus providing expected difunctionalized product **4a** as separable diastereomers in excellent yield and regio- and *E*/*Z* selectivity (>19:1), albeit with poor diastereoselectivity (entry 2). Our effort was then turned to the realization of the catalytic asymmetric synthesis of **4a** by using $Pd_2(dba)_3$ in combination with various chiral ligands. While phosphoramidite ligand **L1** and monophosphine **L2** favored the formation of **5a** (entries 3 and 4), pleasingly, bulky bidentate **L3** exclusively delivered chiral **4a** in promising yield and enantioselectivity, but with low diastereoselectivity (entry 5). Further ligand evaluations (**L4**−**7**, entries 6−9) revealed that dipyridyl bisphosphine **L6** outperformed others in terms of enantiocontrol (entry 8), whereas comparable yield and diastereoselectivity were observed. Changing MeOH to EtOH led to a marginal improvement in stereoselectivity, but the yield decreased dramatically (entry 10). A survey of additives (entries 11−15) demonstrated that NaI significantly increased the yield of **4b**, which probably functioned as an anion counterion to disrupt cyclopalladated complex **II**,[13] thus facilitating the isomerization to η^3-allylpalladium species **III** (entry 15). Screenings of palladium sources (entries 16−18) identified $Pd(dba)_2$ as the optimal choice, though a prolonged time was necessary to achieve better conversions (entry 18). Other parameters, including ligand loadings and concentrations, were further explored (entries 19−21), and a good yield was observed by conducting the reaction in a higher (0.4 M) concentration (entry 21).[14]

Substrate Scope and Limitations. With the optimized catalytic conditions in hand, the substrate scope of isatins was first investigated in the assemblies with 1-phenyl-1,3-butadiene **1a** in neat EtOH at 80 °C in the presence of $Pd(dba)_2$/**L6** and NaI. An array of isatins **2** with either electron-donating or -withdrawing groups at different positions of the indole ring performed well to afford corresponding products **4b**−**l** in good

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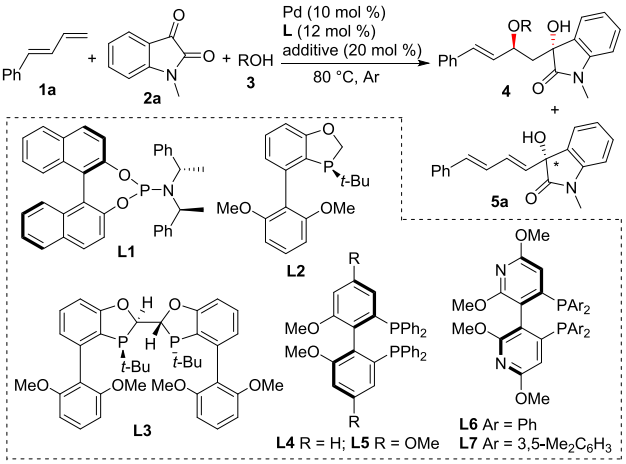
Table 1. Screening Conditions for Asymmetric Hydroalkoxylative Etherification of 1,3-Diene 1a, Isatin 2a, and Alcohols 3[a]



entry	Pd/L	3	add.	t (h)	yield (%)[b]	dr[c]	ee (%)[d]
1[e]	$Pd(PPh_3)_4$	MeOH		24	**5a**, 72		
2	$Pd(PPh_3)_4$	MeOH		24	**4a**, 95	2.5:1	
3	$Pd_2(dba)_3$/**L1**	MeOH		24	**5a**, 65		13
4	$Pd_2(dba)_3$/**L2**	MeOH		24	**5a**, 68		9
5	$Pd_2(dba)_3$/**L3**	MeOH		48	**4a**, 66	2:1	79, 11
6	$Pd_2(dba)_3$/**L4**	MeOH		48	**4a**, 70	2.5:1	64, 33
7	$Pd_2(dba)_3$/**L5**	MeOH		48	**4a**, 66	4:1	73, 66
8	$Pd_2(dba)_3$/**L6**	MeOH		48	**4a**, 64	3:1	86, 71
9	$Pd_2(dba)_3$/**L7**	MeOH		48	**4a**, 60	3:1	63, 30
10	$Pd_2(dba)_3$/**L6**	EtOH		48	**4b**, 29	4:1	93, 65
11	$Pd_2(dba)_3$/**L6**	EtOH	BzOH	48	**4b**, 16	3:1	63, 23
					5a, 48		23
12	$Pd_2(dba)_3$/**L6**	EtOH	K_2CO_3	48	NR		
13	$Pd_2(dba)_3$/**L6**	EtOH	TBAB	48	**4b**, 22	5:1	93, 59
14	$Pd_2(dba)_3$/**L6**	EtOH	KI	48	**4b**, 36	6:1	93, 62
15	$Pd_2(dba)_3$/**L6**	EtOH	NaI	48	**4b**, 49	7:1	93, 61
16	Pd(allyl)Cp/**L6**	EtOH	NaI	24	**4b**, 87	2:1	67, 42
17	$Pd(OAc)_2$/**L6**	EtOH	NaI	48	trace		
18	$Pd(dba)_2$/**L6**	EtOH	NaI	72	**4b**, 77	7:1	93, 63
19[f]	$Pd(dba)_2$/**L6**	EtOH	NaI	72	**4b**, 74	7:1	93, 63
20[g]	$Pd(dba)_2$/**L6**	EtOH	NaI	72	**4b**, 50	5:1	93, 63
21[h]	$Pd(dba)_2$/**L6**	EtOH	NaI	72	**4b**, 82	7:1	93, 63

[a]Unless noted otherwise, reactions were carried out with **1a** (0.1 mmol), **2a** (0.05 mmol), Pd (10 mol %), **L** (12 mol %), and additive (20 mol %) in alcohol (0.25 mL) at 80 °C under Ar. [b]Yield of the isolated product. [c]dr = *anti*-**4**/*syn*-**4**, determined by ^{1}H NMR analysis. [d]Ee of *anti*-**4**/*syn*-**4**, determined by HPLC analysis on a chiral stationary phase. [e]In toluene (0.25 mL). [f]With **L6** (20 mol %). [g]With **L6** (6 mol %). [h]In EtOH (0.125 mL).

yields with excellent enantioselectivity. While moderate diastereoselectivities were generally observed, it was interesting that outstanding diastereocontrol was obtained when 4-substituted isatins were used, delivering *anti*-allylic ethers **4c−e** as single diastereomers, even on a 1.0 mmol scale reaction (product **4e**), probably owing to the steric effect. Isatins with other *N*-protecting groups also reacted smoothly to give products **4m** and **4n** with similar good results. Subsequently, the scope and limitations of 1,3-dienes **1** and alcohols **3** were explored, employing 4-chloroisatin **2d** as the electrophilic partner. As illustrated in Scheme 2b, moderate-to-good yields with excellent diastereo- and enantioselectivity were generally obtained for products **4o−u** when an array of 1-aryl or heteroaryl 1,3-dienes **1** were applied. 1-Alkyl-tethered 1,3-dienes exhibited lower reactivity, furnishing products **4v−y** in low-to-fair yields but still with high stereocontrol. In addition, a triene or simple 1,3-butadiene was applicable, delivering product **4z** or **4aa**, respectively, with good enantioselectivity, albeit in low yields.

It would be highly important that diverse alcohols **3**, especially those with various functionalities, could be directly utilized; thus, different types of ether products would be constructed stereoselectively via the same strategy. As outlined in Scheme 2c, pleasingly, a broad spectrum of primary alcohols, including MeOH, *n*-BuOH, and diverse benzyl-type alcohols, were smoothly assembled with 1,3-diene **1a** and 4-chloroisatin **2d** under the standard catalytic conditions, and corresponding products **4ab−ai** were generally furnished in fair-to-moderate yields with good-to-excellent enantioselectivity. In a few cases with unsatisfactory data, using MeCN as the solvent could slightly improve the results. Conducting the reaction in simple allyl alcohol efficiently afforded product **4aj** with high enantiocontrol. While poor results were observed when neat propargyl alcohols were employed, probably due to the strong

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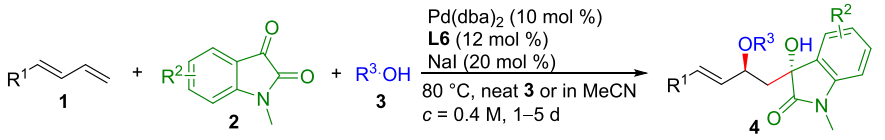
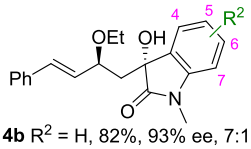
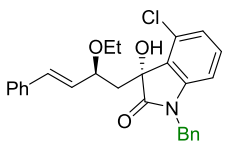
Scheme 2. Substrate Scope and Limitations of Asymmetric Hydroalkoxylative Etherification Reaction[a]



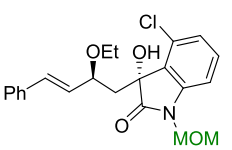
(a) Scope of isatins 2



4b R^2 = H, 82%, 93% ee, 7:1 dr
4c R^2 = 4-Me, 45%, 92% ee, >19:1 dr
4d R^2 = 4-Ph, 71%, 91% ee, >19:1 dr
4e R^2 = 4-Cl, 82%, 93% ee, >19:1 dr[b] (1.0 mmol, 76%, 93% ee, >19:1 dr)
4f R^2 = 5-MeO, 85%, 92% ee, 6:1 dr
4g R^2 = 5-F, 81%, 93% ee, 5:1 dr
4h R^2 = 5-Br, 66%, 93% ee, 6:1 dr
4i R^2 = 5-NO_2, 93%, 92% ee, 4:1 dr[c]
4j R^2 = 5-CF_3O, 71%, 93% ee, 8:1 dr
4k R^2 = 6-Cl, 61%, 93% ee, 3:1 dr
4l R^2 = 7-Cl, 66%, 92% ee, 3:1 dr

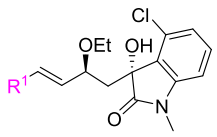


4m 70%, 93% ee, >19:1 dr

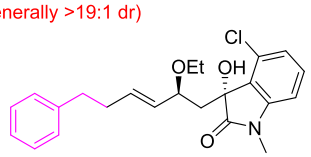


4n 53%, 90% ee, >19:1 dr

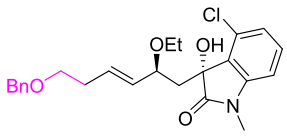
(b) Scope of dienes 1 (generally >19:1 dr)



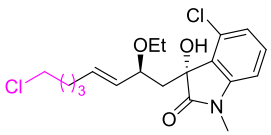
4o R^1 = 2-$MeOC_6H_4$, 67%, 94% ee
4p R^1 = 3,4-$(MeO)_2C_6H_3$, 73%, 92% ee
4q R^1 = 2-ClC_6H_4, 57%, 93% ee
4r R^1 = 3-$CF_3C_6H_4$, 84%, 93% ee
4s R^1 = 4-$CO_2EtC_6H_4$, 79%, 94% ee
4t R^1 = 2-naphthyl, 82%, 86% ee
4u R^1 = 2-furyl, 43%, 92% ee



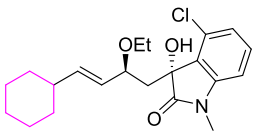
4v 46%, 88% ee



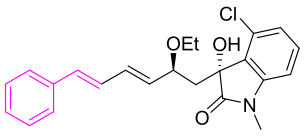
4w 49%, 90% ee



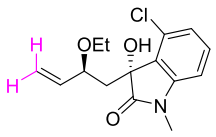
4x 21%, 85% ee



4y 18%, 90% ee

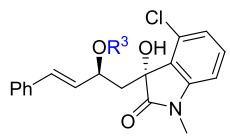


4z 25%, 91% ee[d]

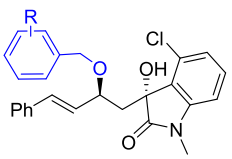


4aa 26%, 86% ee

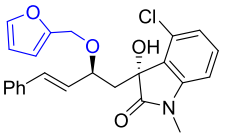
(c) Scope of alcohols 3 (generally >19:1 dr)



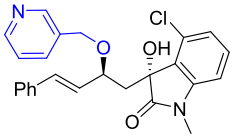
4ab R^3 = Me, 83%, 86% ee
4ac R^3 = *n*-Bu, 66%, 93% ee



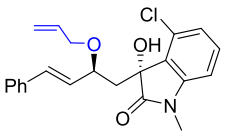
4ad R = H, 63%, 91% ee
4ae R = 4-MeO, 49%, 94% ee
4af R = 2-Cl, 36%, 79% ee (in MeCN: 34%, 94% ee[e])
4ag R = 4-F, 52%, 77% ee (in MeCN: 54%, 77% ee[e])



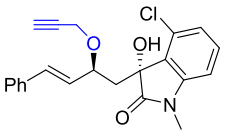
4ah 60%, 82% ee (in MeCN: 56%, 91% ee)



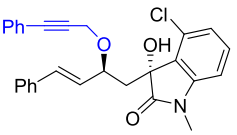
4ai 53%, 91% ee



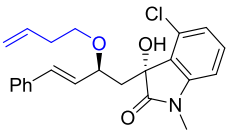
4aj 85%, 91% ee



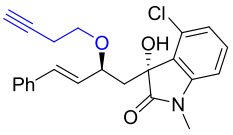
4ak 18%, 77% ee (in MeCN: 35%, 81% ee)



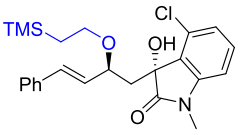
4al 53%, 61% ee (in MeCN: 56%, 82% ee)



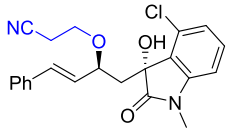
4am 71%, 93% ee



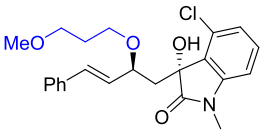
4an 63%, 90% ee



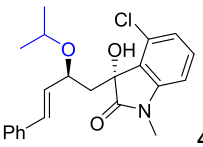
4ao 58%, 90% ee



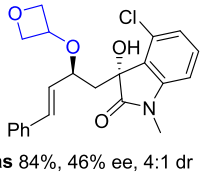
4ap 49%, 50% ee, 8:1 dr (in MeCN: 46%, 86% ee[e])



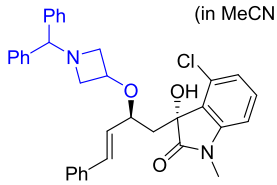
4aq 48%, 94% ee



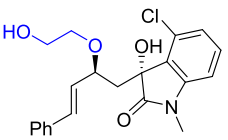
4ar 33%, 96% ee



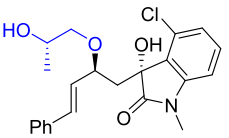
4as 84%, 46% ee, 4:1 dr (in MeCN: 52%, 88% ee[e])



4at 32%, 93% ee[d] (in MeCN)



4au 75%, 88% ee[e] (in MeCN)



4av 44%, >19:1 dr[e] (in MeCN)

[b]The absolute configuration of **4e** was determined by X-ray analysis after conversion to **6**. The other products were assigned by analogy. [c]At 100 °C and without NaI. [d]At 60 °C. [e]At 100 °C. [a]Unless noted otherwise, reactions were carried out with **1** (0.2 mmol), **2** (0.1 mmol), $Pd(dba)_2$ (10 mol %), **L6** (12 mol %), and NaI (20 mol %) in **3** (0.25 mL) or **3** (5−10 equiv) in MeCN (0.25 mL) at 80 °C under Ar.

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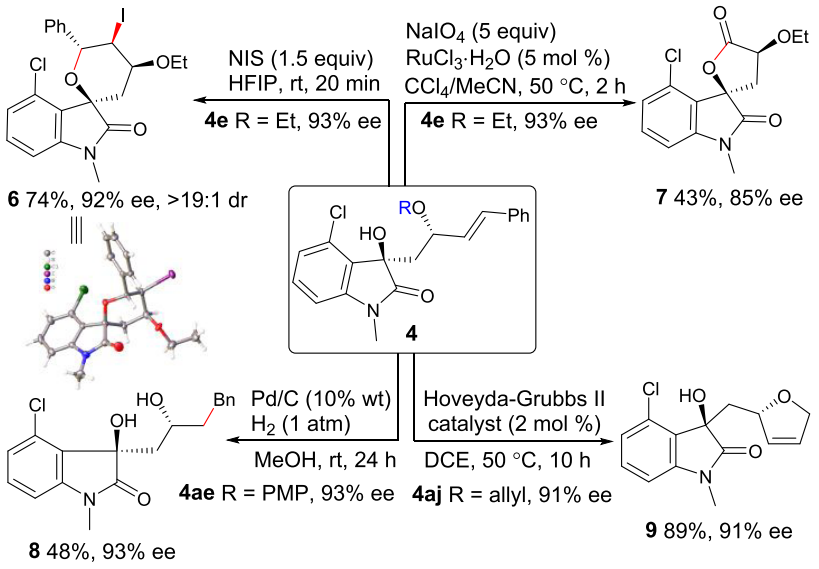
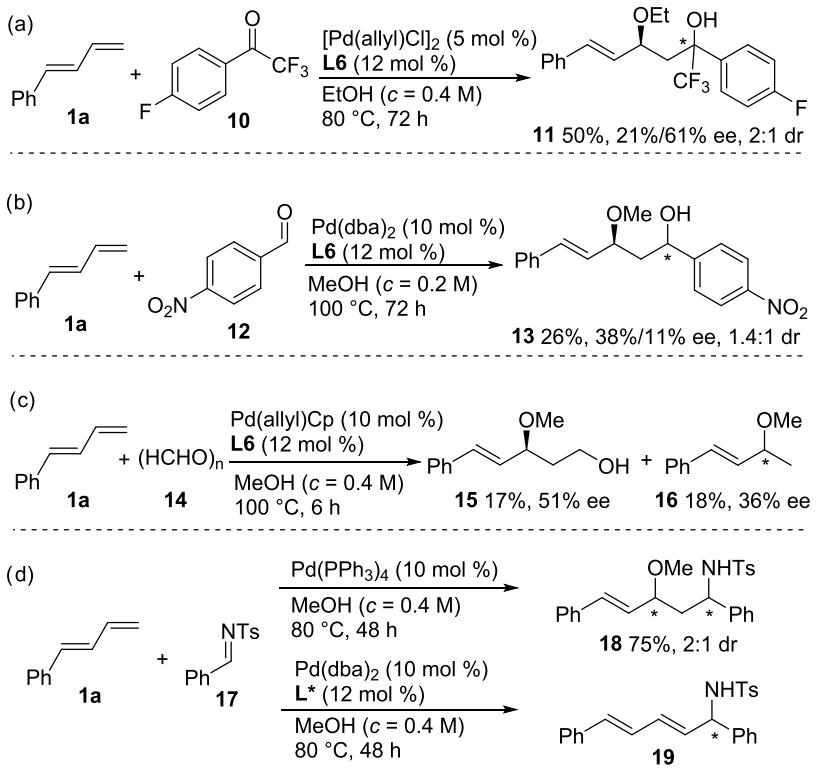
Scheme 3. Synthetic Transformations of Various Adducts



Scheme 4. Exploration of More Electrophiles



affinity to palladium, desired products **4ak** and **4al** in better results could be attained in MeCN. Impressively, a number of functionalized linear alcohols were well compatible, thus delivering chiral allylic ethers **4am**−**aq** capable of versatile latent transformations. More challenging secondary alcohols, which were not suitable for previous palladium-catalyzed hydroalkoxylation of 1,3-dienes,[8a] could also participate in the current allylic etherification reaction enantioselectively, though the yields were needed to be improved (**4ar**−**at**). Notably, ethylene glycol could be monoallylated to deliver **4au** in satisfactory yield and stereoselectivity, and the primary hydroxyl group of (*S*)-propane-1,2-diol was chemoselectively allylated to give product **4av** with remarkable diastereoselectivity.

Synthetic Transformations. The multifunctional allylic ether products enable further transformations to construct complex and potentially useful chiral frameworks. As outlined in Scheme 3, iodoetherification of **4e** with NIS in HFIP afforded spirooxindole **6** in a moderate yield with excellent regio- and diastereoselectivity.[15] Additionally, oxidative cleavage of the double bond of **4e** by $RuCl_3/NaIO_4$ successfully furnished lactone **7** in a fair yield but with a reduced ee value.[16] Hydrogenation and concurrent debenzylation of **4ae** were conducted to deliver 1,3-diol **8**. Moreover, oxindole **9**

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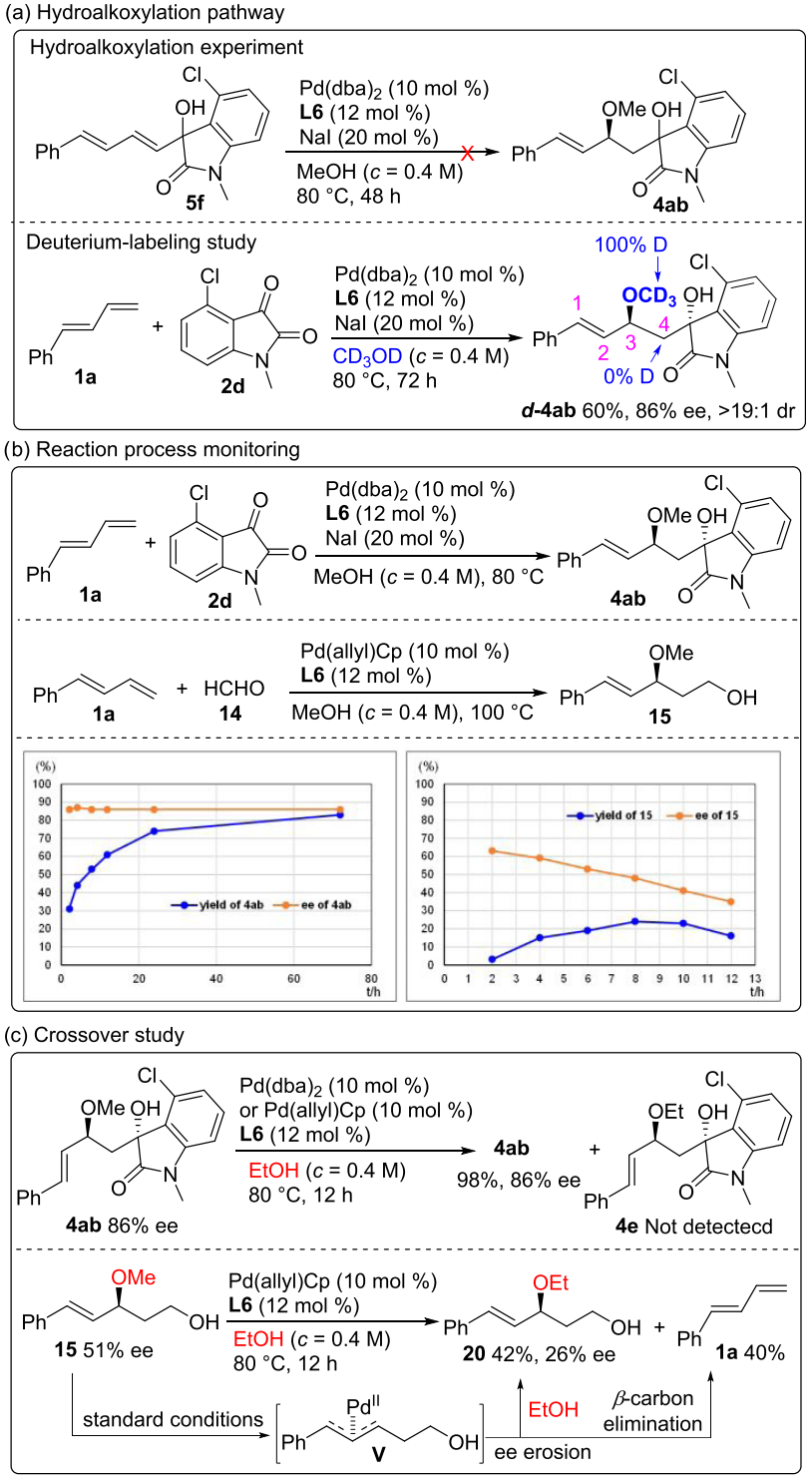
Scheme 5. Control Experiments for Preliminary Mechanism Investigation



incorporating a 2,5-dihydrofuryl motif was efficiently constructed via a ring-closing metathesis reaction of adduct **4aj**.

Exploration of More Electrophiles and Preliminary Mechanism Investigation. Apart from isatins, other types of electrophiles were also applicable to the current difunctionalization strategy. As depicted in Scheme 4a,b, trifluoroacetophenone **10** and *p*-nitrobenzaldehyde **12** could be assembled with 1,3-diene **1a** in neat alcohol catalyzed by Pd/**L6**, but poor stereoselectivity was observed for both products **11** and **13**. Paraformaldehyde **14** was also viable for this protocol, furnishing hydroxymethylative etherification adduct **15** and hydromethoxylation adduct **16** with low chemo- and enantioselectivity (Scheme 4c). In addition, aldimine **17** underwent similar coupling with 1,3-diene **1a** in MeOH to provide racemic allylic 1,3-amino ether **18** when $Pd(PPh_3)_4$ was utilized, but only β-H elimination byproduct **19** was detected by using a chiral palladium complex (Scheme 4d).[17] These results indicated that the employment of isatin-based electrophiles was crucial for achieving high reactivity and stereoselectivity.

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A number of control experiments were conducted to gain some insights into the reaction mechanism. No obvious conversions were observed by treating dienyl alcohol **5f** with MeOH under standard catalytic conditions. Additionally, the reaction between **1a** and **2d** in CD_3OD delivered product ***d*-4ab**, and no deuterium atoms were incorporated into the C-4 position (Scheme 5a). These collective data indicated that allylic ether product **4ab** was not generated from **5f** via hydroalkoxylation, and the in situ formed η^3-complex was directly trapped by alcohol. As the enantioselectivity for isatin-involved hydroxymethylative etherification was significantly superior to that of other electrophiles (Scheme 4), the reaction processes for two different electrophiles were monitored. While the enantioselectivity for product **4ab** remained unchanged during the reaction, the ee value of product **15** eroded along with the time (Scheme 5b). Crossover studies were further conducted to validate the reversibility of the final *O*-allylic alkylation step. When product **4ab** was subjected to EtOH under standard conditions, no cross-coupling product **4e** was detected, and **4ab** was recovered in a quantitative yield with a maintained ee value. In contrast, apparent crossover coupling products **20** and 1,3-diene **1a** were observed from adduct **15** under identical conditions. These experimental results well demonstrated that allylic ether **15** was more liable to undergo reversible oxidative addition with Pd(0) to form π-allylpalladium species **V**, thus leading to not only the observed decreased enantiomeric ratio but also production of 1,3-diene **1** through the β-carbon elimination event.[18] As a result, the steric hindrance of the oxindole moiety and low oxidative potential of relevant products prevented similar oxidative addition of **4ab** with Pd(0), resulting in high chemoselectivity and stereoselectivity.

CONCLUSIONS

In summary, we developed a Pd(0)-catalyzed asymmetric three-component hydroxymethylative etherification reaction of 1,3-dienes with isatins and aliphatic alcohols. This protocol proceeded through vinylogous addition of HOMO-raised η^2-complexes of 1,3-dienes and Pd(0) to isatins enantioselectively, and a tandem intermolecular allylic etherification with alcohols was followed by trapping the in situ formed π-allylpalladium species. The electron-neutral features of Pd(0)-π-Lewis base catalysis and free of external acidic or basic activators rendered the current approach successful, exhibiting broad applicability and substantial functional group compatibility. A diversity of chiral allylic ether products, bearing nonadjacent quaternary and tertiary stereogenic centers, were straightforwardly and efficiently constructed in fair-to-good yields with moderate-to-excellent diastereo- and enantioselectivity, which could be elaborated to access architectures with higher molecular complexity. Apart from isatins, other electrophiles, including activated arylaldehydes, trifluoroacetophenones, and aldimines, could be assembled with 1,3-dienes and alcohols, though reactivity and stereoselectivity remained to be improved. A series of control experiments were conducted to rationalize the reaction process, which would be helpful for future development. The unique property of Pd(0)-π-Lewis base catalysis could be further applied to realize the difunctionalization of other multiply unsaturated systems.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c05346.

More screening experiments; complete experimental procedures; characterization of new products; NMR; HRMS spectra; and HPLC chromatograms (PDF)

Accession Codes

CCDC 2304729 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected examples, see: (a) Lamb, Y. N. Pacritinib: First Approval. *Drugs* **2022**, *82*, 831−838. (b) Asari, T.; Ishikawa, S.; Sasaki, T.; Katada, J.; Hayashi, Y.; Harada, T.; Yano, M.; Yasuda, E.; Uno, I.; Ojima, I. Development of New Non-Peptide GPIIb/IIIa Antagonists, NSL-95315 and NSL-95317, Isosteres of NSL-95300. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2099−2104. (c) Crowley, P. J.; Berry, E. A.; Cromartie, T.; Daldal, F.; Godfrey, C. R. A.; Lee, D.-W.; Phillips, J. E.; Taylor, A.; Viner, R. The Role of Molecular Modeling in the Design of Analogues of the Fungicidal Natural Products Crocacins A and D. *Bioorg. Med. Chem.* **2008**, *16*, 10345−10355.

(2) For selected reviews and examples, see: (a) Lumbroso, A.; Cooke, M. L.; Breit, B. Catalytic Asymmetric Synthesis of Allylic Alcohols and Derivatives and Their Applications in Organic Synthesis. *Angew. Chem., Int. Ed.* **2013**, *52*, 1890−1932. (b) Butt, N. A.; Zhang, W. Transition Metal-Catalyzed Allylic Substitution Reactions with Unactivated Allylic Substrates. *Chem. Soc. Rev.* **2015**, *44*, 7929−7967. (c) Tu, H.-F.; Zheng, C.; Xu, R.-Q.; Liu, X.-J.; You, S.-L. Iridium-Catalyzed Intermolecular Asymmetric Dearomatization of *β*-Naphthols with Allyl Alcohols or Allyl Ethers. *Angew. Chem., Int. Ed.* **2017**, *56*, 3237−3241.

(3) For selected reviews, see: (a) Trost, B. M.; Zhang, T.; Sieber, J. D. Catalytic Asymmetric Allylic Alkylation Employing Heteroatom Nucleophiles: A Powerful Method for C−X Bond Formation. *Chem. Sci.* **2010**, *1*, 427−440. (b) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855−1969. (c) Pàmies, O.; Margalef, J.; Cañellas, S.; James, J.; Judge, E.; Guiry, P. J.; Moberg, C.; Bäckvall, J.-E.; Pfaltz, A.; Pericàs, M. A.; Diéguez, M. Recent Advances in Enantioselective Pd-Catalyzed Allylic Substitution: From Design to Applications. *Chem. Rev.* **2021**, *121*, 4373−4505.

(4) For selected examples, see: (a) Trost, B. M.; Toste, F. D. Asymmetric O- and C-Alkylation of Phenols. *J. Am. Chem. Soc.* **1998**, *120*, 815−816. (b) Evans, P. A.; Leahy, D. K.; Andrews, W. J.; Uraguchi, D. Stereodivergent Construction of Cyclic Ethers by a Regioselective and Enantiospecific Rhodium−Catalyzed Allylic Etherification: Total Synthesis of Gaur Acid. *Angew. Chem., Int. Ed.* **2004**, *43*, 4788−4791. (c) Kim, H.; Men, H.; Lee, C. Stereoselective Palladium-Catalyzed *O*-Glycosylation Using Glycals. *J. Am. Chem. Soc.* **2004**, *126*, 1336−1337. (d) Xie, J.; Guo, W.; Cai, A.; Escudero-Adán, E. C.; Kleij, A. W. Pd-Catalyzed Enantio- and Regioselective Formation of Allylic Aryl Ethers. *Org. Lett.* **2017**, *19*, 6388−6391. (e) Huang, H.-M.; Bellotti, P.; Pflüger, P. M.; Schwarz, J. L.; Heidrich, B.; Glorius, F. Three-Component, Interrupted Radical Heck/Allylic Substitution Cascade Involving Unactivated Alkyl Bromides. *J. Am. Chem. Soc.* **2020**, *142*, 10173−10183.

(5) For selected examples, see: (a) Trost, B. M.; McEachern, E. J.; Toste, F. D. A Two-Component Catalyst System for Asymmetric Allylic Alkylations with Alcohol Pronucleophiles. *J. Am. Chem. Soc.* **1998**, *120*, 12702−12703. (b) Khan, A.; Khan, S.; Khan, I.; Zhao, C.; Mao, Y.; Chen, Y.; Zhang, Y. J. Enantioselective Construction of Tertiary C−O Bond via Allylic Substitution of Vinylethylene Carbonates with Water and Alcohols. *J. Am. Chem. Soc.* **2017**, *139*, 10733−10741. (c) Kim, H.; Lee, C. A Mild and Efficient Method for the Stereoselective Formation of C-O Bonds: Palladium-Catalyzed Allylic Etherification Using Zinc(II) Alkoxides. *Org. Lett.* **2002**, *4*, 4369−4371. (d) Keinan, E.; Sahai, M.; Roth, Z.; Nudelman, A.; Herzig, J. Organotin Nucleophiles. 6. Palladium-Catalyzed Allylic Etherification with Tin Alkoxides. *J. Org. Chem.* **1985**, *50*, 3558−3566. (e) Evans, P. A.; Leahy, D. K. Regio- and Enantiospecific Rhodium-Catalyzed Allylic Etherification Reactions Using Copper(I) Alkoxides: Influence of the Copper Halide Salt on Selectivity. *J. Am. Chem. Soc.* **2002**, *124*, 7882−7883. (f) Shu, C.; Hartwig, J. F. Iridium-Catalyzed Intermolecular Allylic Etherification with Aliphatic Alkoxides: Asymmetric Synthesis of Dihydropyrans and Dihydrofurans. *Angew. Chem., Int. Ed.* **2004**, *43*, 4794−4797.

(6) (a) Lam, F. L.; Au-Yeung, T. T.-L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. Palladium−(*S*,p*R*)-FerroNPS-Catalyzed Asymmetric Allylic Etherification: Electronic Effect of Nonconjugated Substituents on Benzylic Alcohols on Enantioselectivity. *Angew. Chem., Int. Ed.* **2008**, *47*, 1280−1283. (b) Ye, F.; Zheng, Z.-J.; Li, L.; Yang, K.-F.; Xia, C.-G.; Xu, L.-W. Development of a Novel Multifunctional N,P Ligand for Highly Enantioselective Palladium-Catalyzed Asymmetric Allylic Etherification of Alcohols and Silanols. *Chem. - Eur. J.* **2013**, *19*, 15452−15457. (c) Ueno, S.; Hartwig, J. F. Direct, Iridium-Catalyzed Enantioselective and Regioselective Allylic Etherification with Aliphatic Alcohols. *Angew. Chem., Int. Ed.* **2008**, *47*, 1928−1931.

(7) For selected reviews and examples, see: (a) Kennemur, J. L.; Maji, R.; Scharf, M. J.; List, B. Catalytic Asymmetric Hydroalkoxylation of C−C Multiple Bonds. *Chem. Rev.* **2021**, *121*, 14649−14681. (b) Nanda, S. K.; Mallik, R. Transition Metal-Catalyzed Hydroalkoxylation of Alkynes: An Overview. *Chem. - Eur. J.* **2021**, *27*, 15571−15604. (c) Lim, W.; Kim, J.; Rhee, Y. H. Pd-Catalyzed Asymmetric Intermolecular Hydroalkoxylation of Allene: An Entry to Cyclic Acetals with Activating Group-Free and Flexible Anomeric Control. *J. Am. Chem. Soc.* **2014**, *136*, 13618−13621. (d) Liu, Z.; Breit, B. Rhodium-Catalyzed Enantioselective Intermolecular Hydroalkoxylation of Allenes and Alkynes with Alcohols: Synthesis of Branched Allylic Ethers. *Angew. Chem., Int. Ed.* **2016**, *55*, 8440−8443.

(8) (a) Yang, S.-Q.; Han, A.-J.; Liu, Y.; Tang, X.-Y.; Lin, G.-Q.; He, Z.-T. Catalytic Asymmetric Hydroalkoxylation and Formal Hydration and Hydroaminoxylation of Conjugated Dienes. *J. Am. Chem. Soc.* **2023**, *145*, 3915−3925. For nonasymmetric examples, see: (b) Utsunomiya, M.; Kawatsura, M.; Hartwig, J. F. Palladium-Catalyzed Equilibrium Addition of Acidic OH Groups Across Dienes. *Angew. Chem., Int. Ed.* **2003**, *42*, 5865−5868. (c) Fernandes, R. A.; Chandra, N.; Gangani, A. J.; Khatun, G. N. Palladium-Catalyzed Regioselective Intermolecular Hydroalkoxylation of 1-Arylbutadienes. *J. Org. Chem.* **2023**, *88*, 10339−10354.

(9) (a) Li, Q.; Wang, Z.; Dong, V. M.; Yang, X.-H. Enantioselective Hydroalkoxylation of 1,3-Dienes via Ni-Catalysis. *J. Am. Chem. Soc.* **2023**, *145*, 3909−3914. (b) Mifleur, A.; Suisse, I.; Mortreux, A.; Sauthier, M. Enantioselective Nickel Catalyzed Butadiene Hydroalkoxylation with Ethanol: from Experimental Results to Kinetics Parameters. *Catal. Lett.* **2021**, *151*, 27−35. For nonasymmetric examples, see: (c) Mifleur, A.; Mérel, D. S.; Mortreux, A.; Suisse, I.; Capet, F.; Trivelli, X.; Sauthier, M.; Macgregor, S. A. Deciphering the Mechanism of the Nickel-Catalyzed Hydroalkoxylation Reaction: A Combined Experimental and Computational Study. *ACS Catal.* **2017**, *7*, 6915−6923. (d) Mifleur, A.; Mortreux, A.; Suisse, I.; Sauthier, M. Synthesis of C4 Chain Glyceryl Ethers via Nickel-Catalyzed Butadiene Hydroalkoxylation Reaction. *Mol. Catal.* **2017**, *427*, 25−30. (e) Mifleur, A.; Ledru, H.; Lopes, A.; Suisse, I.; Mortreux, A.; Sauthier, M. Synthesis of Short-Chain Alkenyl Ethers from Primary and Bio-sourced Alcohols via the Nickel-Catalyzed Hydroalkoxylation Reaction of Butadiene and Derivatives. *Adv. Synth. Catal.* **2016**, *358*, 110−121. (f) Tran, G.; Mazet, C. Ni-Catalyzed Regioselective Hydroalkoxylation of Branched 1,3-Dienes. *Org. Lett.* **2019**, *21*, 9124−9127.

(10) (a) Chang, R.; Cai, S.; Yang, G.; Yan, X.; Huang, H. Asymmetric Aminomethylative Etherification of Conjugated Dienes with Aliphatic Alcohols Facilitated by Hydrogen Bonding. *J. Am. Chem. Soc.* **2021**, *143*, 12467−12472. (b) Huang, Y.; Zou, S.; Yu, B.; Yan, X.; Liu, S.; Huang, H. Highly Regioselective and Diastereodivergent Aminomethylative Annulation of Dienyl Alcohols Enabled by a Hydrogen-bonding Assisting Effect. *Chem. Sci.* **2022**, *13*, 2317−2323.

(11) (a) Xiao, B.-X.; Jiang, B.; Yan, R.-J.; Zhu, J.-X.; Xie, K.; Gao, X.-Y.; Ouyang, Q.; Du, W.; Chen, Y.-C. A Palladium Complex as an Asymmetric *π*-Lewis Base Catalyst for Activating 1,3-Dienes. *J. Am. Chem. Soc.* **2021**, *143*, 4809−4816. (b) Zhu, J.-X.; Chen, Z.-C.; Du, W.; Chen, Y.-C. Asymmetric Auto-Tandem Palladium Catalysis for 2,4-Dienyl Carbonates: Ligand-Controlled Divergent Synthesis. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202200880. (c) Chen, P.; Tan, S.-Z.; Zhu, L.; Ouyang, Q.; Jia, Z.-J.; Du, W.; Chen, Y.-C.

https://doi.org/10.1021/acscatal.3c05346
ACS Catal. 2024, 14, 628−636

Palladium-Catalyzed Inverse and Normal Dehydrogenative Aza-Morita−Baylis−Hillman Reactions with γ,δ-Unsaturated Compounds. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202301519. (d) Tan, S.-Z.; Chen, P.; Zhu, L.; Gan, M.-Q.; Ouyang, Q.; Du, W.; Chen, Y.-C. Use of (*E*,*E*)-Dienoic Acids as Switchable (*E*,*E*)- and (*Z*,*E*)-Dienyl Anion Surrogates via Ligand-Controlled Palladium Catalysis. *J. Am. Chem. Soc.* **2022**, *144*, 22689−22697. (e) Liu, X.-L.; Lin, H.-Z.; Tan, L.-Q.; Peng, J.-B. Palladium- and Brønsted Acid-Catalyzed Enantio-, Site- and *E*/*Z*-Selective Addition of Alkylidenecyclopropanes with Imines. *Chem. Sci.* **2023**, *14*, 2348−2352.

(12) (a) Huo, X.; Quan, M.; Yang, G.; Zhao, X.; Liu, D.; Liu, Y.; Zhang, W. Hydrogen-Bond-Activated Palladium-Catalyzed Allylic Alkylation via Allylic Alkyl Ethers: Challenging Leaving Groups. *Org. Lett.* **2014**, *16*, 1570−1573. (b) Mukai, R.; Horino, Y.; Tanaka, S.; Tamaru, Y.; Kimura, M. Pd(0)-Catalyzed Amphiphilic Activation of Bis-allyl Alcohol and Ether. *J. Am. Chem. Soc.* **2004**, *126*, 11138−11139. (c) Zhu, J.; Mao, M.; Ji, H.-J.; Xu, J.-Y.; Wu, L. Palladium-Catalyzed Cleavage of α-Allenylic Aryl Ether toward Pyrazole-methylene-Substituted Phosphinyl Allenes and Their Transformations via Alkenyl C−P(O) Cleavage. *Org. Lett.* **2017**, *19*, 1946−1949.

(13) For selcted review and examples, see: (a) Fagnou, K.; Lautens, M. Halide Effects in Transition Metal Catalysis. *Angew. Chem., Int. Ed.* **2002**, *41*, 26−47. (b) Lowe, M. A.; Ostovar, M.; Ferrini, S.; Chen, C. C.; Lawrence, P. G.; Fontana, F.; Calabrese, A. A.; Aggarwal, V. K. Palladium-Mediated Annulation of Vinyl Aziridines with Michael Acceptors: Stereocontrolled Synthesis of Substituted Pyrrolidines and Its Application in a Formal Synthesis of (−)-α-Kainic Acid. *Angew. Chem., Int. Ed.* **2011**, *50*, 6370−6374. (c) Knight, J. G.; Stoker, P. A.; Tchabanenko, K.; Harwood, S. J.; Lawrie, K. W. M. Synthesis of Highly Substituted Pyrrolidines via Palladium-Catalyzed Cyclization of 5-Vinyloxazolidinones and Activated Alkenes. *Tetrahedron* **2008**, *64*, 3744−3750. (d) Cantat, T.; Agenet, N.; Jutand, A.; Pleixats, R.; Moreno-Manas, M. The Effect of Chloride Ions on the Mechanism of the Oxidative Addition of Cyclic Allylic Carbonates to Pd^0 Complexes by Formation of Neutral $[(\eta^1\text{-allyl})PdClL^2]$ Complexes. *Eur. J. Org. Chem.* **2005**, *2005*, 4277−4283.

(14) For more screening details, see the Supporting Information.

(15) Cui, H.-L.; Chouthaiwale, P. V.; Yin, F.; Tanaka, F. Catalytic Asymmetric Hetero-Diels−Alder Reactions of Enones with Isatins to Access Functionalized Spirooxindole Tetrahydropyrans: Scope, Derivatization, and Discovery of Bioactives. *Org. Biomol. Chem.* **2016**, *14*, 1777−1783.

(16) Rana, S.; Kour, S.; Kizhake, S.; King, H. M.; Mallareddy, J. R.; Case, A. J.; Huxford, T.; Natarajan, A. Dimers of Isatin Derived α-Methylene-γ-Butyrolactone as Potent Anti-Cancer Agents. *Bioorg. Med. Chem. Lett.* **2022**, *65*, No. 128713.

(17) For the exploration of asymmetric version, see the Supporting Information.

(18) Harayama, H.; Kimura, M.; Tanaka, S.; Tamaru, Y. Selective Reaction of π-Allyl(alkyloxy)palladium(II) Complexes toward β-Decarbopalladation, β-Dehydropalladation, and Reductive Elimination. *Tetrahedron Lett.* **1998**, *39*, 8475−8478.

https://doi.org/10.1021/acscatal.3c05346
ACS Catal. 2024, 14, 628−636