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Communication

Asymmetric Formal Nucleophilic *o*-Cresolylation with Morita–Baylis–Hillman Carbonates of 2-Cyclohexenones via Palladium Catalysis

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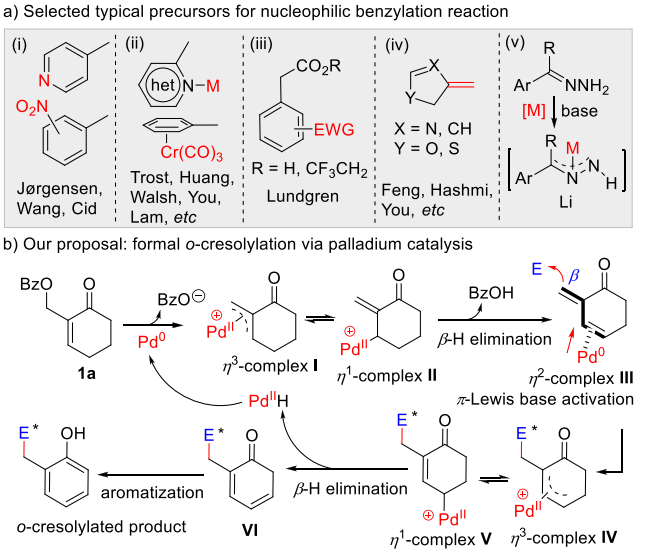
ABSTRACT: Here we report an asymmetric formal nucleophilic *o*-cresolylation reaction with the Morita–Baylis–Hillman (MBH) carbonates from 2-cyclohexanones and diverse aldehydes under palladium catalysis, by in situ generation of electron-neutral and HOMO-raised η^2-Pd(0)-dienone complexes via an oxidative insertion/π–σ-isomerization/β-H elimination activation sequence. The subsequent umpolung vinylogous addition to a variety of imines is realized upon Pd(0)-mediated π-Lewis base catalysis, finally furnishing *o*-cresolylated products followed by another cascade of a π–σ-isomerization/β-H elimination/aromatization process. Moderate to excellent diastereo- and enantioselectivity are achieved for substantial substrate assemblies by employing a newly designed bulky chiral phosphonamidite ligand, and the resultant multifunctional products can be facilely elaborated to access diverse enantioenriched architectures. In addition, the catalytic reaction pathway is finely illuminated by control experiments.

The introduction of a benzyl group into molecules, including the asymmetric version, represents a fundamental reaction in organic chemistry. Hence the benzylation process, especially in a catalytic manner, has been widely investigated by chemists. Some new protocols, such as direct benzylic C(sp^3)–H activation[1] and cross-coupling reaction of benzylic halides under transition metal[2] or photocatalysis,[3] have illustrated the capability to produce the benzylated substances, but some challenges remain to be resolved for enantioselective reactions. Traditional electrophilic benzylation processes, usually involving the S_N1 or S_N2 mechanism mediated substitution reaction of benzyl (pseudo)halides[4] and dearomative benzylic π-allylmetal complexes,[5] or even pre-prepared and in situ generated quinone methides with a driven force to aromatization via 1,4-addition or [4 + *n*] annulations,[6] contributed tremendously. Not surprisingly, the alternative nucleophilic benzylation reaction has also received broad attention. Since the benzylic C–H without activation of an adjacent functional group is not easily deprotonated to generate the carbanion species,[7] the methyl-substituted electron-deficient heteroarenes or arenes bearing strong electron-withdrawing groups, are commonly employed, and excess strong Brønsted bases and/or Lewis acid activation are usually necessary for the relevant nucleophilic benzylation reaction, as illustrated in Scheme 1a, (i)[8] and (ii).[9] Lundgren disclosed a decarboxylative allylic benzylation with aryl acetic acids or esters, but the substrates having an electron-deficient (hetero)aryl group must be used [Scheme 1a, (iii)].[10] Moreover, there is a type of specific cyclic diene nucleophiles, which easily undergo an ene reaction with electrophiles to furnish the formal benzylation after aromatization, but these are generally limited to five-membered azaarenes [Scheme 1a, (iv)].[11] Recently, the hydrazones have been successfully utilized as benzyl carbanion equivalents via ruthenium- or palladium-catalyzed Wolff–Kishner (WK) reduction [Scheme 1a, (v)].[12] Despite remarkable advances in this field, most reliable asymmetric examples presented were focused on the

Scheme 1. Summary of Diverse Nucleophilic Benzylation Strategies and Proposal of Formal *o*-Cresolylation via Palladium Catalysis[8−12]



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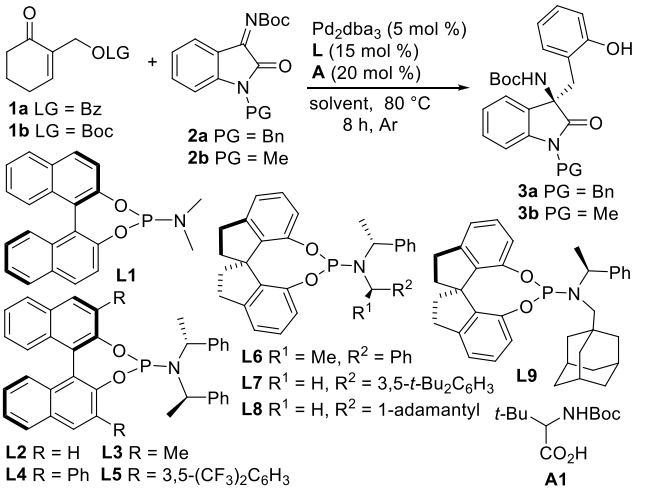
classical allylic alkylation-type reaction; in particular, the above-mentioned nucleophilic benzylation strategies, involving carbanion species, are not applicable for yielding the products with electron-donating groups, which significantly limits their structural and functional diversity.

As outlined in Scheme 1b, we envisaged that Morita–Baylis–Hillman (MBH) benzoate **1a**, readily available from 2-cyclohexenone and formaldehyde, would generate π-allylpalladium complex **I** under Pd(0) catalysis. Although the allylic alkylation of complex **I** with a nucleophilic reagent has been established,[13] it would instead isomerize to corresponding η^1-complex **II** in the absence of a nucleophile and undergo β-H elimination to deliver a dienone intermediate, which could coordinate to Pd(0) in an electron-neutral η^2-pattern. According to our recently uncovered π-Lewis base activation mode, resultant η^2-complex **III** would be HOMO-raised and umpolung the reactivity of *exo*-β-carbon of the enone motif based on the principle of vinylogy.[14] Consequently, the enantioselective nucleophilic attack toward a suitable electrophile, followed by another sequence of π–σ-isomerization, β-H elimination, and aromatization (**IV**–**VI**), would finally accomplish an unprecedented asymmetric formal *o*-cresolylation reaction. Through this unusual palladium activation mode, the MBH adduct serves as a nucleophilic benzylic surrogate and adopts an electron-rich phenol ring into products efficiently and enantioselectively.

We commenced our study on the reaction of MBH benzoate **1a** and isatin-derived imine **2a** in toluene under the catalysis of Pd_2dba_3 and PPh_3, but very poor conversions were observed after heating at 80 °C for 24 h (Table 1, entry 1). Pleasingly, using chiral BINOL-derived phosphonamidite ligand **L1** dramatically improved the reaction, and the desired formal *o*-cresolylated adduct, **3a**, was isolated in a good yield, albeit with bad enantioselectivity (entry 2). Encouraged by these results, a few chiral phosphonamidite ligands **L2**–**5** with bulky substituents were explored, and significantly improved enantiocontrol was obtained (entries 2–6). Notably, the enantioselectivity was even switched by using ligand **L5** with the same chiral skeleton (entry 6). Chiral SPINOL-based phosphonamidite ligands **L6**–**8** were tested as well (entries 7–9), and a higher ee value was attained by using newly designed **L8** with an unsymmetrical amine moiety (entry 9). Using *N*-methyl imine **2b** slightly increased the enantioselectivity (entry 10). Considering the stoichiometric benzoic acid would be formed in the reaction with substrate **1a**, carbonate **1b** was studied but with inferior results (entry 11). Adding catalytic amounts of benzoic acid was beneficial for the reaction (entry 12), and (L)-**A1** proved to be a better choice (entry 13 vs 14), indicating that the acid additive would be actively involved in the addition process, probably as an H-bond donor for imine substrate.[14a] Moreover, ligand **L9** was found to be better matched (entry 15). In addition, excellent results were afforded in $PhCF_3$ (entry 16), and comparable data were still obtained with much lower catalyst loadings (entry 17) or on a larger scale (entry 18).[15]

Consequently, we examined the scope and limitations of this asymmetric formal nucleophilic *o*-cresolylation reaction. The results are summarized in Scheme 2. An array of ketimines **2** derived from diversely substituted isatins were well-tolerated in the reactions with MBH carbonate **1b** in $PhCF_3$ under the catalysis of Pd_2dba_3 and ligand **L9**, and desired adducts **3a**–**m** were generally obtained in excellent yields and enantioselectivity. The imine with a 4-substituent led to a bad conversion

Table 1. Condition Optimizations of Asymmetric Formal *o*-Cresolylation Reaction[a]



entry	L	1	A	solvent	yield (%)[b]	ee (%)[c]
1	PPh_3	**1a**		toluene	trace	
2	**L1**	**1a**		toluene	**3a**, 80	−8
3	**L2**	**1a**		toluene	**3a**, 99	−40
4	**L3**	**1a**		toluene	**3a**, 99	−64
5	**L4**	**1a**		toluene	**3a**, 99	−30
6	**L5**	**1a**		toluene	**3a**, 99	71
7	**L6**	**1a**		toluene	**3a**, 81	78
8	**L7**	**1a**		toluene	**3a**, 99	60
9	**L8**	**1a**		toluene	**3a**, 99	86
10[d]	**L8**	**1a**		toluene	**3b**, 99	89
11[d]	**L8**	**1b**		toluene	**3b**, 96	81
12[d]	**L8**	**1b**	BzOH	toluene	**3b**, 99	89
13[d]	**L8**	**1b**	(L)-**A1**	toluene	**3b**, 91	93
14[d]	**L8**	**1b**	(D)-**A1**	toluene	**3b**, 99	90
15[d]	**L9**	**1b**	(L)-**A1**	toluene	**3b**, 99	93
16[d]	**L9**	**1b**	(L)-**A1**	$PhCF_3$	**3b**, 99	95
17[d,e]	**L9**	**1b**	(L)-**A1**	$PhCF_3$	**3b**, 94	92
18[d,f]	**L9**	**1b**	(L)-**A1**	$PhCF_3$	**3b**, 98	97

[a]Unless noted otherwise, reactions were carried out with **1** (0.065 mmol), **2a** (0.05 mmol), Pd_2dba_3 (5 mol %), **L** (15 mol %), and acid additive **A** (20 mol %), in toluene (0.5 mL) at 80 °C for 8 h under Ar. [b]Yield of the isolated product. [c]Determined by HPLC analysis on a chiral stationary phase. [d]**2b** was used. [e]With Pd_2dba_3 (1 mol %) and **L9** (3 mol %) in $PhCF_3$ (0.2 mL) for 12 h on a 0.1 mmol scale. [f]On a 1.0 mmol scale.

probably due to steric reasons (**3i**). In addition, the 7-azaoxindole-based imine was compatible, albeit with slightly reduced yield and enantioselectivity (**3n**). Besides the simple MBH carbonate from 2-cyclohexenone and formaldehyde, pleasingly, the substrates from aryl- and heteroaryl aldehydes exhibited high reactivity in the assemblies with imine **2b**, by using the same catalytic combination in toluene. As outlined in Scheme 2a, corresponding products **3o**–**ab**, bearing more challenging adjacent tertiary and quaternary stereogenic centers, were efficiently constructed in moderate to excellent yields with uniformly outstanding enantio- and diastereoselectivity. An acetaldehyde-derived MBH carbonate showed reasonable reactivity, albeit with reduced enantiocontrol (**3ac**). Although a mixture was obtained by using the cinnamaldehyde-derived MBH carbonate, probably because of regioselectivity, pure product **3ad′** was isolated in a fair yield with a high ee value after *O*-acetylation. It was noteworthy that the

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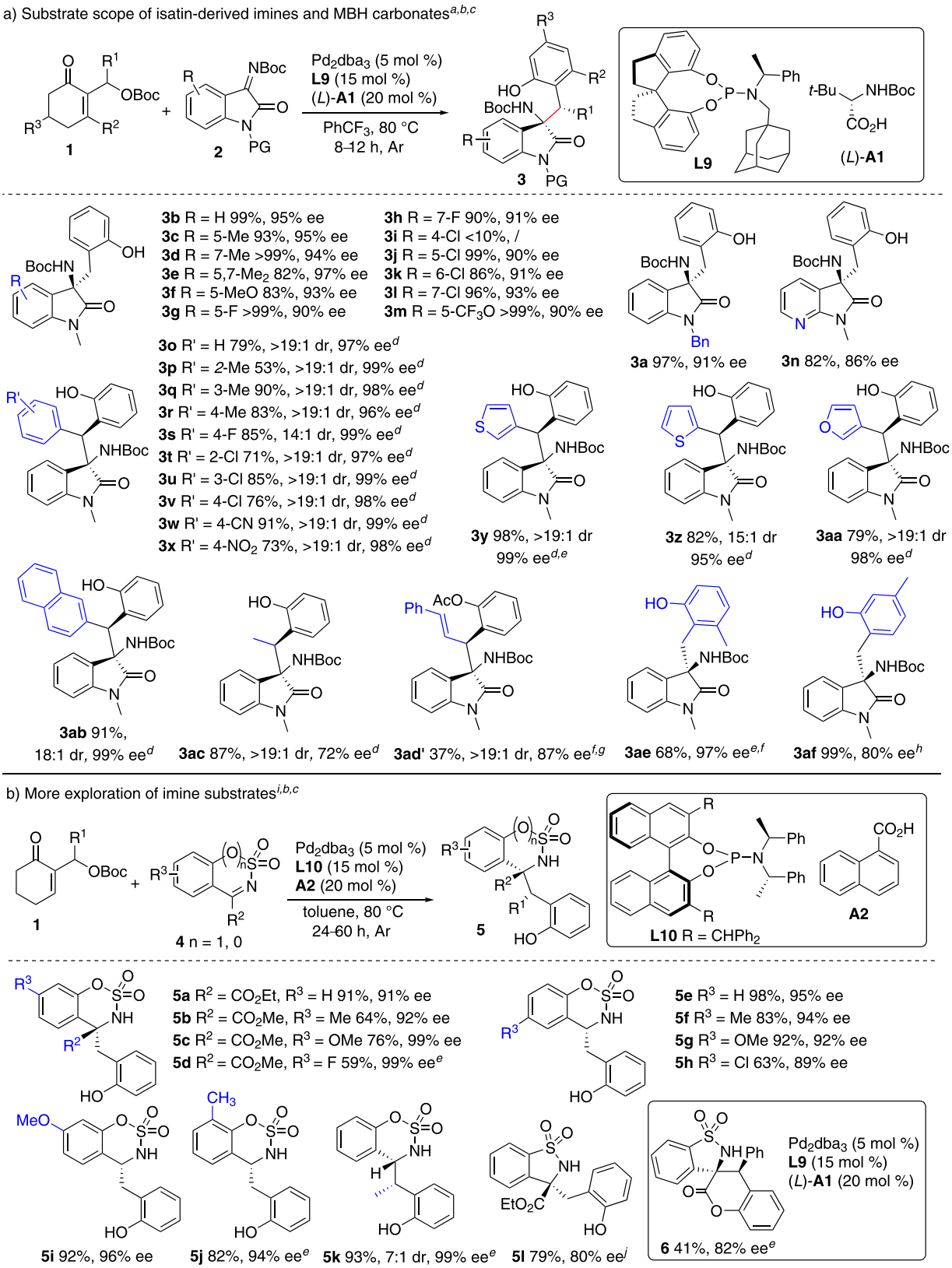
Scheme 2. Substrate Scope of Asymmetric Formal *o*-Cresolylation Reaction



[a]Unless noted otherwise, reactions were carried out with MBH carbonate **1** (0.13 mmol), imine **2** (0.10 mmol), Pd_2dba_3 (5 mol %), **L9** (15 mol %), and acid (L)-**A1** (20 mol %) in $PhCF_3$ (1.0 mL) at 80 °C for 8−12 h under Ar. [b]Yield of the isolated product. [c]As determined by HPLC analysis on a chiral stationary phase. [d]In toluene (0.50 mL). [e]The absolute configurations of enantiopure *ent*-**3y**, **3ae**, **5d**, **5j**, derivative of **5k** (**5k′**), and relative configuration of **6** were determined by X-ray analysis. The other products were assigned by analogy. [f]In THF (1.0 mL). [g]After acetylation. [h]In toluene at 60 °C. [i]Unless noted otherwise, reactions were carried out with MBH carbonate **1** (0.13 mmol), imine **4** (0.10 mmol), Pd_2dba_3 (5 mol %), **L10** (15 mol %), and acid **A2** (20 mol %) in toluene (1.0 mL) at 80 °C for 24−60 h under Ar. [j]In EtOAc (1.0 mL).

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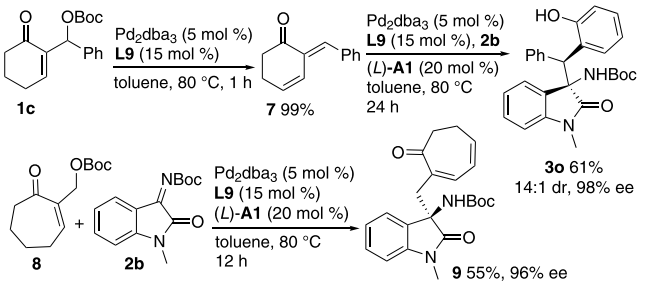
MBH carbonate with a 3-methyl group was applicable, and expected product **3ae** was attained in a moderate yield with remarkable enantioselectivity, indicating this η^2-coordination and activation mode of Pd(0) is not very sensitive to steric hindrance. Even the 5-methyl-substituted MBH carbonate, used in a racemic form, showed comparable reactivity, though the enantioselectivity of product **3af** was slightly reduced.

In order to further expand the synthetic utility of the current palladium activation strategy, more electrophilic reagents were investigated. As summarized in Scheme 2b, activated cyclic ketimines **4**, possessing a benzo[*e*][1,2,3]oxathiazine 2,2-dioxide moiety, were compatible in the reactions with carbonate **1b** under the catalysis of Pd_2dba_3, **L10**, and acid **A2**.[15] Relevant products **5a−d** were smoothly furnished in moderate to high yields with excellent enantioselectivity. Importantly, cyclic imines **4** derived from salicylaldehydes also showed high reactivity, generally affording expected adducts **5e−k** in high yields and stereoselectivity. In addition, a benzo[*d*]isothiazole 1,1-dioxide-type ketimine delivered desired product **5l** in moderate results. Its combination with phenyl-substituted carbonate **1c** was successful under the catalysis of Pd_2dba_3 and **L9**; interestingly, spirocyclic lactone **6** was obtained in a fair yield with good enantioselectivity after transesterification.[15]

In order to understand the reaction mechanism better, MBH carbonate **1c** was converted to isolable dienone **7** quantitatively under palladium catalysis (Scheme 3). The subsequent

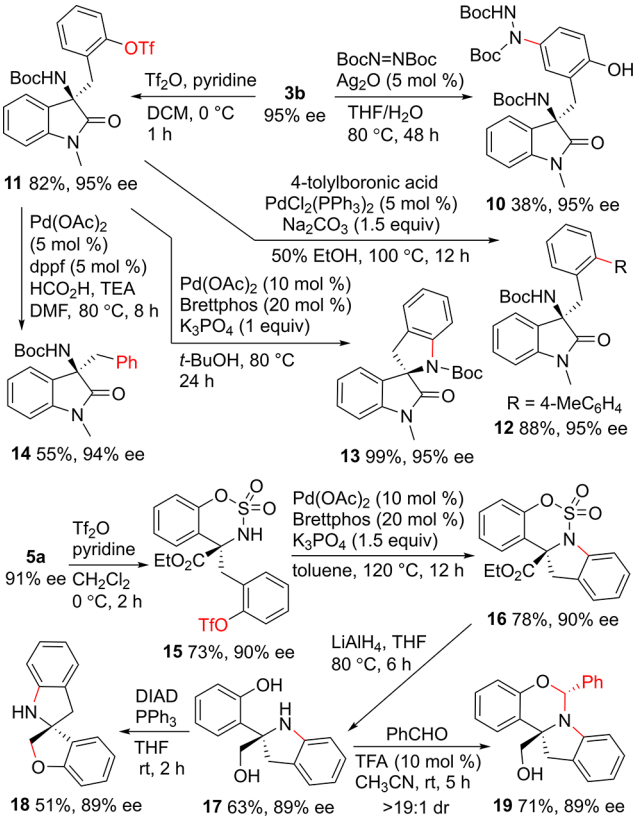
Scheme 3. Control Experiments for Mechanism Elucidation



umpolung coupling of **7** and imine **2b** proceeded smoothly under the identical palladium catalysis, and desired adduct **3o** was yielded with comparable stereocontrol, verifying the proposed η^2-Pd(0)-dienone complex, **III** (Scheme 1b), which would be the key nucleophilic species.[16] Furthermore, the assembly of 2-cycloheptenone-derived MBH carbonate **8** and imine **2b** was successful under the optimal catalytic conditions, and product **9**, having an *endo*-dienone motif, was furnished in a moderate yield with excellent enantioselectivity, further verifying the suggested reaction pathway outlined in Scheme 1b.

As illustrated in Scheme 4, the installed phenol group enables facile transformations to access a variety of functionalized molecules. *para*-Selective amination product **10** was generated in a fair yield upon treating **3b** and an azodicarboxylate under the catalysis of Ag_2O. In addition, after conversion to triflate **11**, the Pd-catalyzed Suzuki coupling or intramolecular amination occurred, efficiently furnishing product **12** or 2′-spiropyrrolidine oxindole framework **13**,[17] respectively, whereas using formic acid as the reductant

Scheme 4. Synthetic Elaborations of Products



delivered benzyl product **14**. In contrast, the same triflation and Pd-catalyzed coupling sequence of adduct **5a** provided fused framework **16**. After reduction with $LiAlH_4$, an intramolecular Mitsunobu reaction with resultant alcohol **17** straightforwardly afforded unique spiro heterocycle **18**, while aminal product **19** was obtained with exclusive diastereoselectivity by treating **17** with benzaldehye and an acid catalyst.[18]

In summary, we have developed an unprecedented formal nucleophilic *o*-cresolylation reaction under palladium catalysis, by employing readily available Morita−Baylis−Hillman carbonates condensed from 2-cyclohexenones and a variety of aldehydes as the surrogates. This process relied on an unusual multiple activation process of palladium for the carbonate substrates, which could generate the key HOMO-raised η^2-Pd(0)-dienone complexes with umpolung nucleophilicity. Their assemblies with a diversity of activated ketimines and salicylaldehydes-derived cyclic imines were effectively realized, finally furnishing a broad spectrum of homobenzyl amine products bearing a free hydroxyl group with moderate to excellent stereoselectivity. More results in regard to this effective palladium-based multiple activation strategy will be presented in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c04101.

More screening conditions, complete experimental procedures, characterization of new products, ^{1}H NMR

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and preliminary density functional theory (DFT) calculation studies of η^2-Pd(0)-dienone complexes, NMR and HRMS spectra, and HPLC chromatograms (PDF)

Accession Codes

CCDC 2166845−2166850 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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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 reviews, see (a) Vanjari, R.; Singh, K. N. Utilization of Methylarenes as Versatile Building Blocks in Organic Synthesis. *Chem. Soc. Rev.* **2015**, *44*, 8062−8096. (b) Saint-Denis, T. G.; Zhu, R.-Y.; Chen, G.; Wu, Q.-F.; Yu, J.-Q. Enantioselective C(sp^3)−H Bond Activation by Chiral Transition Metal Catalysts. *Science* **2018**, *359*, No. eaao4798.

(2) For selected review and examples, see (a) Liégault, B.; Renaud, J.-L.; Bruneau, C. Activation and Functionalization of Benzylic Derivatives by Palladium Catalysts. *Chem. Soc. Rev.* **2008**, *37*, 290−299. (b) Saito, B.; Fu, G. C. Enantioselective Alkyl−Alkyl Suzuki Cross-Couplings of Unactivated Homobenzylic Halides. *J. Am. Chem. Soc.* **2008**, *130*, 6694−6695. (c) Binder, J. T.; Cordier, C. J.; Fu, G. C. Catalytic Enantioselective Cross-Couplings of Secondary Alkyl Electrophiles with Secondary Alkylmetal Nucleophiles: Negishi Reactions of Racemic Benzylic Bromides with Achiral Alkylzinc Reagents. *J. Am. Chem. Soc.* **2012**, *134*, 17003−17006. (d) Huang, W.; Wan, X.; Shen, Q. Enantioselective Construction of Trifluoromethoxylated Stereogenic Centers by a Nickel-Catalyzed Asymmetric Suzuki−Miyaura Coupling of Secondary Benzyl Bromides. *Angew. Chem., Int. Ed.* **2017**, *56*, 11986−11989. (e) Jiang, S.-P.; Dong, X.-Y.; Gu, Q.-S.; Ye, L.; Li, Z.-L.; Liu, X.-Y. Copper-Catalyzed Enantioconvergent Radical Suzuki−Miyaura C(sp^3)−C(sp^2) Cross-Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 19652−19659.

(3) For selected examples, see (a) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. Visible-Light Excitation of Iminium Ions Enables the Enantioselective Catalytic β-Alkylation of Enals. *Nat. Chem.* **2017**, *9*, 868−873. (b) Mazzarella, D.; Crisenza, G. E. M.; Melchiorre, P. Asymmetric Photocatalytic C−H Functionalization of Toluene and Derivatives. *J. Am. Chem. Soc.* **2018**, *140*, 8439−8443. (c) Le Saux, E.; Zanini, M.; Melchiorre, P. Photochemical Organocatalytic Benzylation of Allylic C−H Bonds. *J. Am. Chem. Soc.* **2022**, *144*, 1113−1118. (d) Nacsa, E. D.; MacMillan, D. W. C. Spin-Center Shift-Enabled Direct Enantioselective α-Benzylation of Aldehydes with Alcohols. *J. Am. Chem. Soc.* **2018**, *140*, 3322−3330. (e) Zhang, H.-H.; Zhao, J.-J.; Yu, S. Enantioselective Allylic Alkylation with 4-Alkyl-1,4-dihydro-pyridines Enabled by Photoredox/Palladium Cocatalysis. *J. Am. Chem. Soc.* **2018**, *140*, 16914−16919. (f) Li, F.; Tian, D.; Fan, Y.; Lee, R.; Lu, G.; Yin, Y.; Qiao, B.; Zhao, X.; Xiao, Z.; Jiang, Z. Chiral Acid-Catalysed Enantioselective C−H Functionalization of Toluene and Its Derivatives Driven by Visible Light. *Nat. Commun.* **2019**, *10*, 1774. (g) Li, Y.; Lei, M.; Gong, L. Photocatalytic Regio- and Stereoselective C(sp^3)−H Functionalization of Benzylic and Allylic Hydrocarbons as well as Unactivated Alkanes. *Nat. Catal.* **2019**, *2*, 1016−1026. (h) Song, C.; Zhang, H.-H.; Yu, S. Regio- and Enantioselective Decarboxylative Allylic Benzylation Enabled by Dual Palladium/Photoredox Catalysis. *ACS Catal.* **2022**, *12*, 1428−1432.

(4) (a) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. Catalytic Asymmetric Benzylation of Achiral Lithium Enolates Using a Chiral Ligand for Lithium in the Presence of an Achiral Ligand. *J. Am. Chem. Soc.* **1994**, *116*, 8829−8830. (b) Cozzi, P. G.; Benfatti, F.; Zoli, L. Organocatalytic Asymmetric Alkylation of Aldehydes by S_N1-Type Reaction of Alcohols. *Angew. Chem., Int. Ed.* **2009**, *48*, 1313−1316. (c) List, B.; Čorić, I.; Grygorenko, O. O.; Kaib, P. S. J.; Komarov, I.; Lee, A.; Leutzsch, M.; Chandra Pan, S.; Tymtsunik, A. V.; van Gemmeren, M. The Catalytic Asymmetric α-Benzylation of Aldehydes. *Angew. Chem., Int. Ed.* **2014**, *53*, 282−285.

(5) For selected reviews, see (a) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. Transition Metal-Catalyzed Decarboxylative Allylation and Benzylation Reactions. *Chem. Rev.* **2011**, *111*, 1846−1913. (b) Trost, B. M.; Czabaniuk, L. C. Structure and Reactivity of Late Transition Metal η^3-Benzyl Complexes. *Angew. Chem., Int. Ed.* **2014**, *53*, 2826−2851. (c) Le Bras, J.; Muzart, J. Production of Csp^3−Csp^3 Bonds through Palladium-Catalyzed Tsuji−Trost-Type Reactions of (Hetero)Benzylic Substrates. *Eur. J. Org. Chem.* **2016**, *2016*, 2565−2593.

(6) For selected reviews, see (a) Amouri, H.; Le Bras, J. Taming Reactive Phenol Tautomers and *o*-Quinone Methides with Transition Metals: A Structure−Reactivity Relationship. *Acc. Chem. Res.* **2002**,

35, 501−510. (b) Caruana, L.; Fochi, M.; Bernardi, L. The Emergence of Quinone Methides in Asymmetric Organocatalysis. *Molecules* **2015**, *20*, 11733−11764.
(7) For selected nonasymmetric examples, see (a) Liu, Y.-F.; Zhai, D.-D.; Zhang, X.-Y.; Guan, B.-T. Potassium-Zincate-Catalyzed Benzylic C−H Bond Addition of Diarylmethanes to Styrenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 8245−8249. (b) Bao, C.-C.; Luo, Y.-L.; Du, H.-Z.; Guan, B.-T. Benzylic Aroylation of Toluenes with Unactivated Tertiary Benzamides Promoted by Directed *ortho*-Lithiation. *Sci. China Chem.* **2021**, *64*, 1349−1354. (c) Gu, Y.; Zhang, Z.; Wang, Y.-E.; Dai, Z.; Yuan, Y.; Xiong, D.; Li, J.; Walsh, P. J.; Mao, J. Benzylic Aroylation of Toluenes Mediated by a $LiN(SiMe_3)_2/Cs^+$ System. *J. Org. Chem.* **2022**, *87*, 406−418. (d) For an asymmetric example, see Hirata, T.; Sato, I.; Yamashita, Y.; Kobayashi, S. Asymmetric $C(sp^3)$−H Functionalization of Unactivated Alkylarenes such as Toluene Enabled by Chiral Brønsted Base Catalysts. *Commun. Chem.* **2021**, *4*, 36.
(8) (a) Dell'Amico, L.; Companyó, X.; Naicker, T.; Bräuer, T. M.; Jørgensen, K. A. Asymmetric Organocatalytic Benzylation of α,β-Unsaturated Aldehydes with Toluenes. *Eur. J. Org. Chem.* **2013**, *2013*, 5262−5265. (b) Duce, S.; Mateo, A.; Alonso, I.; García Ruano, J. L.; Cid, M. B. Role of Quaternary Ammonium Salts as New Additives in the Enantioselective Organocatalytic β-Benzylation of Enals. *Chem. Commun.* **2012**, *48*, 5184−5186. (c) Li, T.; Zhu, J.; Wu, D.; Li, X.; Wang, S.; Li, H.; Li, J.; Wang, W. A Strategy Enabling Enantioselective Direct Conjugate Addition of Inert Aryl Methane Nucleophiles to Enals with a Chiral Amine Catalyst under Mild Conditions. *Chem. - Eur. J.* **2013**, *19*, 9147−9150.
(9) (a) Trost, B. M.; Thaisrivongs, D. A. Strategy for Employing Unstabilized Nucleophiles in Palladium-Catalyzed Asymmetric Allylic Alkylations. *J. Am. Chem. Soc.* **2008**, *130*, 14092−14093. (b) Trost, B. M.; Thaisrivongs, D. A. Palladium-Catalyzed Regio-, Diastereo-, and Enantioselective Benzylic Allylation of 2-Substituted Pyridines. *J. Am. Chem. Soc.* **2009**, *131*, 12056−12057. (c) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. Palladium-Catalyzed Benzylic Addition of 2-Methyl Azaarenes to N-Sulfonyl Aldimines via C−H BondActivation. *J. Am. Chem. Soc.* **2010**, *132*, 3650−3651. (d) Best, D.; Kujawa, S.; Lam, H. W. Diastereo- and Enantioselective Pd(II)-Catalyzed Additions of 2-Alkylazaarenes to N-Boc Imines and Nitroalkenes. *J. Am. Chem. Soc.* **2012**, *134*, 18193−18196. (e) Mao, J.; Zhang, J.; Jiang, H.; Bellomo, A.; Zhang, M.; Gao, Z.; Dreher, S. D.; Walsh, P. J. Palladium-Catalyzed Asymmetric Allylic Alkylations with Toluene Derivatives as Pronucleophiles. *Angew. Chem., Int. Ed.* **2016**, *55*, 2526−2530. (f) Liu, X.-J.; You, S.-L. Enantioselective Iridium-Catalyzed Allylic Substitution with 2-Methylpyridines. *Angew. Chem., Int. Ed.* **2017**, *56*, 4002−4005. (g) Murakami, R.; Sano, K.; Iwai, T.; Taniguchi, T.; Monde, K.; Sawamura, M. Palladium-Catalyzed Asymmetric $C(sp^3)$−H Allylation of 2-Alkylpyridines. *Angew. Chem., Int. Ed.* **2018**, *57*, 9465−9469. (h) Liu, X.-J.; Zhang, W.-Y.; Zheng, C.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution of Methyl Azaarenes. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202200164.
(10) (a) Doyle, M. G. J.; Gabbey, A. L.; McNutt, W.; Lundgren, R. J. Enantioselective Tertiary Electrophile (Hetero)Benzylation: Pd-Catalyzed Substitution of Isoprene Monoxide with Arylacetates. *Angew. Chem., Int. Ed.* **2021**, *60*, 26495−26499. (b) Moon, P. J.; Wei, Z.; Lundgren, R. J. Direct Catalytic Enantioselective Benzylation from Aryl Acetic Acids. *J. Am. Chem. Soc.* **2018**, *140*, 17418−17422.
(11) For selected examples, see (a) Luo, W.; Zhao, J.; Yin, C.; Liu, X.; Lin, L.; Feng, X. Catalytic Hetero-Ene Reactions of 5-Methyleneoxazolines: Highly Enantioselective Synthesis of 2,5-Disubstituted Oxazole Derivatives. *Chem. Commun.* **2014**, *50*, 7524−7526. (b) Nalivela, K. S.; Rudolph, M.; Baeissa, E. S.; Alhogbi, B. G.; Mkhalid, I. A. I.; Hashmi, A. S. K. Sequential Au/Cu Catalysis: A Two Catalyst One-Pot Protocol for the Enantioselective Synthesis of Oxazole α-Hydroxy Esters via Intramolecular Cyclization/Intermolecular Alder-Ene Reaction. *Adv. Synth. Catal.* **2018**, *360*, 2183−2190. (c) Liu, X.-J.; Zheng, C.; Yang, Y.-H.; Jin, S.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Aromatization Reaction. *Angew. Chem., Int. Ed.* **2019**, *58*, 10493−10499.
(12) (a) Chen, N.; Dai, X.-J.; Wang, H.; Li, C.-J. Umpolung Addition of Aldehydes to Aryl Imines. *Angew. Chem., Int. Ed.* **2017**, *56*, 6260−6263. (b) Wang, H.; Dai, X.-J.; Li, C.-J. Aldehydes as Alkyl Carbanion Equivalents for Additions to Carbonyl Compounds. *Nat. Chem.* **2017**, *9*, 374−378.
(13) Trost, B. M.; Tsui, H. C.; Toste, F. D. Deracemization of Baylis−Hillman Adducts. *J. Am. Chem. Soc.* **2000**, *122*, 3534−3535.
(14) (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) Yang, X.-X.; Yan, R.-J.; Ran, G.-Y.; Chen, C.; Yue, J.-F.; Yan, X.; Ouyang, Q.; Du, W.; Chen, Y.-C. π-Lewis-Base-Catalyzed Asymmetric Vinylogous Umpolung Reactions of Cyclopentadienones and Tropone. *Angew. Chem., Int. Ed.* **2021**, *60*, 26762−26768.
(15) For more details, see the Supporting Information.
(16) For ^{1}H NMR and DFT calculation studies of η^2-Pd(0)-dienone complexes, see the Supporting Information.
(17) (a) Wang, D.; Zhang, W.; Lu, X.; Zhou, H.; Zhong, F. Cinchona Alkaloid Derived Iodide Catalyzed Enantioselective Oxidative α-Amination of Carbonyl Compounds toward the Construction of Spiroindolyloxindole. *Org. Lett.* **2022**, *24*, 842−847. (b) Liu, R.-R.; Xu, Y.; Liang, R.-X.; Xiang, B.; Xie, H.-J.; Gao, J.-R.; Jia, Y.-X. Spirooxindole Synthesis via Palladium-Catalyzed Dearomative Reductive-Heck Reaction. *Org. Biomol. Chem.* **2017**, *15*, 2711−2715.
(18) Mangion, I. K.; Chen, C.-y.; Li, H.; Maligres, P.; Chen, Y.; Christensen, M.; Cohen, R.; Jeon, I.; Klapars, A.; Krska, S.; Nguyen, H.; Reamer, R. A.; Sherry, B. D.; Zavialov, I. Enantioselective Synthesis of an HCV NS5a Antagonist. *Org. Lett.* **2014**, *16*, 2310−2313.

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