OL | Organic Letters

pubs.acs.org/OrgLett Letter

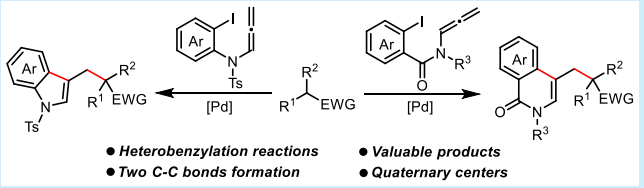
Palladium-Catalyzed Allenamide Carbopalladation/Allylation with Active Methine Compounds

Xiaoyi Zhu, Ruibo Li, Hequan Yao,* and Aijun Lin*

Cite This: *Org. Lett.* 2021, 23, 4630–4634 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A palladium-catalyzed allenamide carbopalladation/allylation with active methine compounds has been developed. Various indoles and isoquinolinones bearing a quaternary carbon center were achieved with good efficiency, a broad substrate scope and good functional group tolerance. This reaction underwent cascade oxidative addition, carbopalladation, and allylic alkylation, and two new C−C bonds were formed in one pot.



All-carbon quaternary centers are widely distributed in natural products and pharmaceuticals, which can greatly increase the three-dimensionality of molecules and significantly improve the target selectivity, metabolic stability, and other pharmacy-related properties.[1] The construction of quaternary carbon skeleton has always been an important research topic in organic synthetic chemistry,[2] and it is also a challenging task. Over the past several decades, the alkylation,[3] arylation,[4] and allylic alkylation[5] of active methine compounds have been well explored, which has provided efficient routes to access quaternary carbon frameworks. However, benzylation, in particular, the heterobenzylation reaction, has rarely been reported, and the benzylic reagents are mainly confined to activated benzyl bromides,[6] benzyl alcohols,[7] and their derivatives[8] (Scheme 1a).

Indoles and isoquinolinones are two kinds of important heterocyclic skeletons that are frequently found in bioactive substances exhibiting broad biological and pharmacological effects such as antioxidant, anti-inflammatory, and antihypertensive activities.[9] Given the importance of quaternary carbon skeletons and heterocycles to the pharmaceutical properties,

Scheme 1. Benzylation of Active Methine Compounds

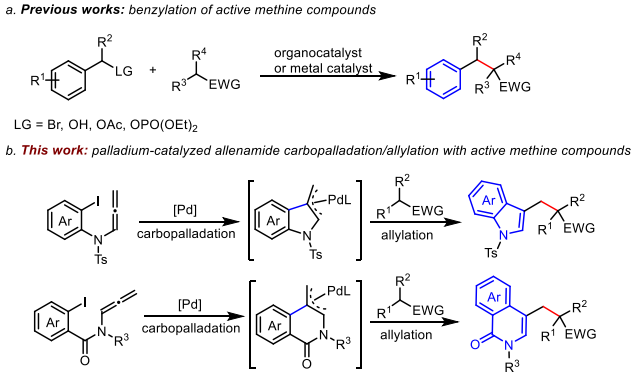
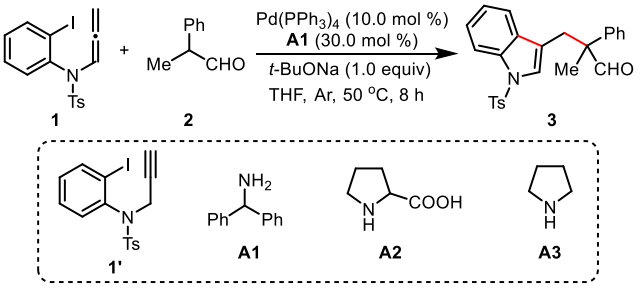


Table 1. Optimization of Reaction Conditions[a,b]



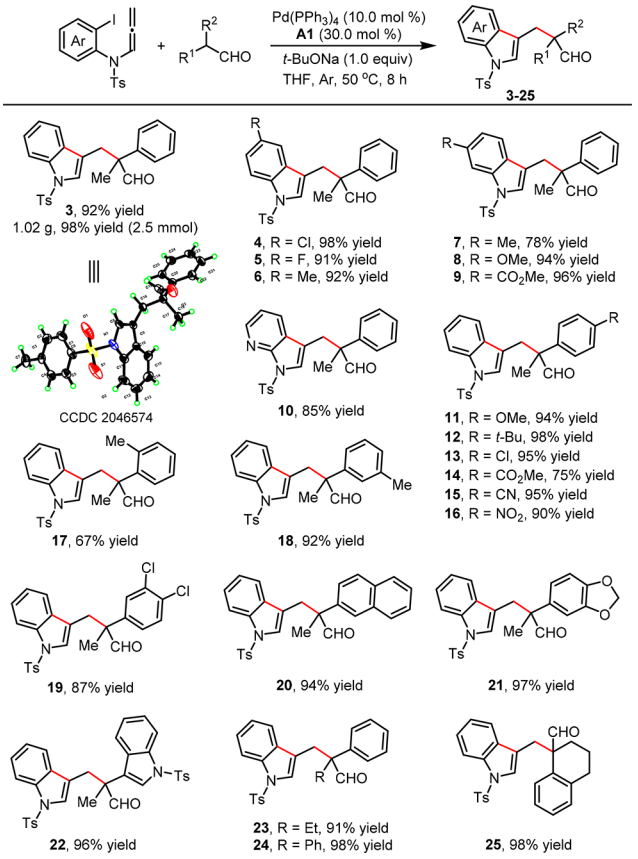
entry	deviation of standard conditions[a]	yield (%)[b]
1	none	92
2	$Pd(P^tBu_3)_2$ instead of $Pd(PPh_3)_4$	38
3	$Pd_2(dba)_3$ instead of $Pd(PPh_3)_4$	trace
4	**A2** instead of **A1**	21
5	**A3** instead of **A1**	26
6	Cs_2CO_3 instead of *t*-BuONa	51
7	K_3PO_4 instead of *t*-BuONa	12
8	Et_3N instead of *t*-BuONa	trace
9	PhMe instead of THF	36
10	MeCN instead of THF	45
11	DMSO instead of THF	23
12	without $Pd(PPh_3)_4$	NR[c]
13	without **A1**	40
14	**1′** instead of **1**	53

[a]Standard conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(PPh_3)_4$ (10.0 mol %), **A1** (30.0 mol %), *t*-BuONa (0.2 mmol), THF (1.0 mL), 50 °C (oil bath temperature), under an Ar atmosphere for 8 h, sealed tube. [b]Isolated yields. [c]NR, no reaction.

Received: April 20, 2021
Published: May 28, 2021

https://doi.org/10.1021/acs.orglett.1c01369
Org. Lett. 2021, 23, 4630–4634

Scheme 2. Substrate Scope for the Synthesis of Indoles[a,b]

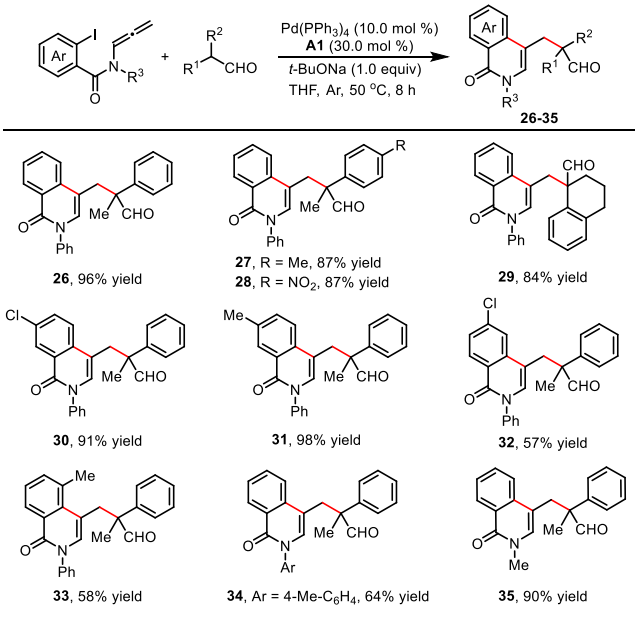


[a]Reaction conditions: allenamide (0.2 mmol), aldehyde (0.4 mmol), $Pd(PPh_3)_4$ (10.0 mol %), **A1** (30.0 mol %), *t*-BuONa (0.2 mmol), THF (1.0 mL), 50 °C (oil bath temperature), under an Ar atmosphere for 8 h. [b]Isolated yields.

herein we describe a palladium-catalyzed carbopalladation/allylation of allenamides[10] with active methine compounds for the first time. Many indoles and isoquinolinones bearing a quaternary carbon center were achieved with good efficiency (Scheme 1b). This reaction underwent cascade oxidative addition, carbopalladation, and allylic alkylation, and two new C−C bonds were formed in one pot.

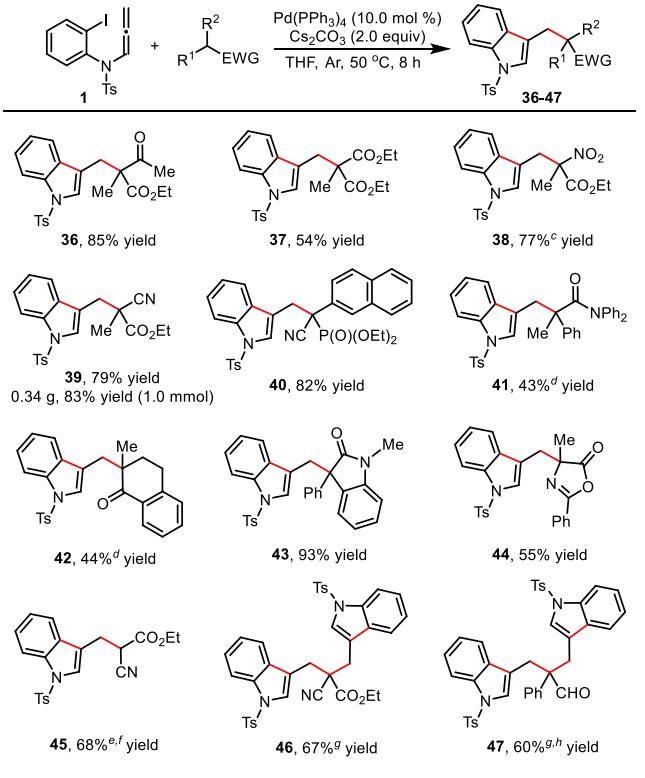
We commenced our study with *N*-(*o*-iodophenyl)allenamide **1** and 2-phenylpropanal **2** as the model substrates. After systematic screening of the reaction conditions (see the Supporting Information (SI) for details), the desired product **3** could be obtained in 92% yield by employing 10.0 mol % $Pd(PPh_3)_4$ and 30.0 mol % diphenylmethanamine **A1** as the catalysts and *t*-BuONa as the base in THF at 50 °C for 8 h (Table 1, entry 1). When $Pd(P^tBu_3)_2$ was used, the reaction proceeded in 38% yield, and $Pd_2(dba)_3$ retarded the transformation (Table 1, entries 2 and 3). Proline **A2** and pyrrolidine **A3** finished the reaction with low efficiency (Table 1, entries 4 and 5). Other bases, such as Cs_2CO_3 and K_3PO_4, offered **3** in diminished yields (Table 1, entries 6 and 7), and organic base such as Et_3N failed in facilitating the reaction (Table 1, entry 8). When the reaction was carried out in toluene, acetonitrile, or DMSO, product **3** was isolated in 23−45% yield (Table1, entries 9−11). Control experiments showed that the palladium catalyst was essential to this reaction (Table 1, entry 12). A low yield of **3** was detected in the absence of **A1** (Table 1, entry 13). We also employed

Scheme 3. Substrate Scope for the Synthesis of Isoquinolinones[a,b]



[a]Reaction conditions: allenamide (0.2 mmol), aldehyde (0.4 mmol), $Pd(PPh_3)_4$ (10.0 mol %), **A1** (30.0 mol %), *t*-BuONa (0.2 mmol), THF (1.0 mL), 50 °C (oil bath temperature), under an Ar atmosphere for 8 h. [b]Isolated yields.

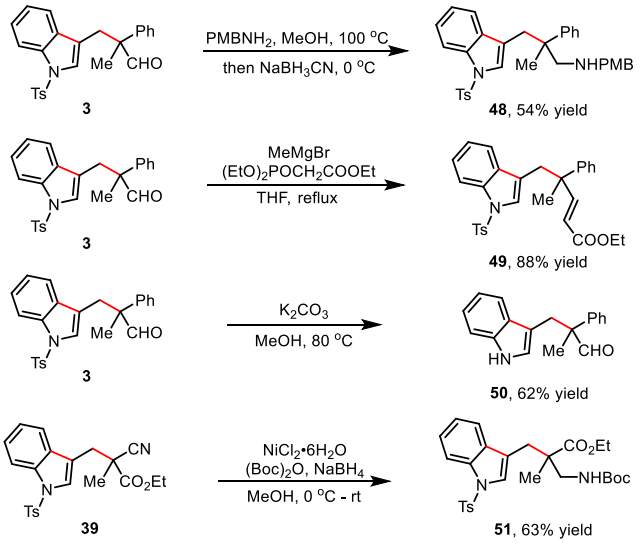
Scheme 4. Substrate Scope of Pronucleophiles[a,b]



[a]Reaction conditions: allenamide **1** (0.2 mmol), pronucleophile (0.4 mmol), $Pd(PPh_3)_4$ (10.0 mol %), Cs_2CO_3 (0.4 mmol), THF (1.0 mL), 50 °C (oil bath temperature), under an Ar atmosphere for 8 h. [b]Isolated yields. [c]DBU (0.4 mmol). [d]LDA (0.4 mmol). [e]Cs_2CO_3 (1.0 equiv). [f]Pronucleophile (4.0 equiv). [g]Allenamide **1** (2.0 equiv). [h]**A1** (30 mol %).

https://doi.org/10.1021/acs.orglett.1c01369
Org. Lett. 2021, 23, 4630−4634

Scheme 5. Synthetic Transformations



progargylamide **1′** as the starting material, which offered **3** in 53% yield (Table 1, entry 14) (see the SI for details). The structure of **3** was confirmed by the single-crystal X-ray diffraction studies (see the SI for details).

With the optimized conditions in hand, we then checked the substrate scope for the synthesis of indole-containing compounds (Scheme 2). The allenamides with various groups on the benzene ring, such as methyl, methoxyl, halogen, and carboxyl groups, performed the reaction well, offering products **4**−**9** in 78−98% yield. When pyridine-derived allenamide was applied, the corresponding azaindole product **10** could be obtained in 85% yield. The generality of α-branched aldehydes was also examined. 2-Arylpropanals with versatile substituent groups offered the products **11**−**16** and **18**−**21** in good to excellent yields. Product **17** was isolated in 67% yield due to the steric hindrance. Product **22** with two indole units was synthesized in 96% yield. The 2-phenylbutanal, 2,2-diphenylacetaldehyde, and 1,2,3,4-tetrahydronaphthalene-1-carbaldehyde were also good participants, affording the products **23**−**25** in excellent yields. Product **3** (1.02 g) could be achieved in 98% yield on a 2.5 mmol scale under the optimal conditions.

After exploring the generality for the synthesis of indole frameworks, we then extended this protocol to synthesize isoquinolinones, and the corresponding products **26**−**35** were achieved in 57−98% yield under the standard reaction conditions (Scheme 3).

In addition, we also extended this method to other active methine compounds (Scheme 4), such as β-ketoester, diethyl methylmalonate, 2-nitropropanoate, 2-cyanopropionate, cyanophosphonate, amide, ketone, oxindole, and azlactone, and the corresponding products **36**−**44** were isolated in 43−93% yield. Notably, this method could also be applied to active methylene nucleophiles. The benzylic product **45** and dibenzylic product **46** could be achieved in 68 and 67% yield by altering the ratio of the substrates and the equivalent of base (see the SI for details). Moreover, the dibenzylic product **47** was obtained in 60% yield when 2-phenylacetaldehyde was used.

To further demonstrate the synthetic utility of the method, synthetic transformations of product **3** and **39** were carried out (Scheme 5). After condensation of **3** with (4-methoxyphenyl)-methanamine followed by reduction with $NaBH_3CN$, compound **48** was isolated in 54% yield in one pot. Compound **49** could be achieved in 88% yield through the Wittig reaction. The *N*-tosyl protecting group could be expediently removed in the presence of K_2CO_3 to give **50** in 62% yield. Treating compound **39** with $NiCl_2{\cdot}6H_2O$ and $NaBH_4$ offered β-amino acid derivative **51** in 63% yield. We also attempted the asymmetric version of this method. After screening a series of chiral ligands and chiral amine catalysts (see the SI for details), product **3** could be achieved in 89% yield with 40% ee.

In conclusion, we have established a palladium-catalyzed sequential oxidative addition, carbopalladation, and allylic alkylation of allenamides with active methine and methylene compounds for the first time. This protocol highlighted a generalizable strategy to construct indoles and isoquinolinones with a quaternary carbon center with good efficiency.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01369.

Experiment procedures, detailed reaction optimization, compound characterization, and NMR spectra (PDF)

Accession Codes

CCDC 2046574 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, 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.

■ AUTHOR INFORMATION

Corresponding Authors

Hequan Yao − *State Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of Bioactive Natural Product Research, Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, P. R. China;* orcid.org/0000-0003-4865-820X; Email: hyao@cpu.edu.cn, cpuhyao@126.com

Aijun Lin − *State Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of Bioactive Natural Product Research, Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, P. R. China;* orcid.org/0000-0001-5786-4537; Email: ajlin@cpu.edu.cn

Authors

Xiaoyi Zhu − *State Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of Bioactive Natural Product Research, Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, P. R. China*

Ruibo Li − *State Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of Bioactive Natural Product Research, Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01369

Notes

The authors declare no competing financial interest.

https://doi.org/10.1021/acs.orglett.1c01369
Org. Lett. 2021, 23, 4630−4634

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (NSFC22071267), the Foundation of the Open Project of State Key Laboratory of Natural Medicines (SKLNMZZ202023), and the Innovation Team of "the Double-First Class" Disciplines (CPU2018GY35) for the financial support.

■ REFERENCES

(1) For a recent review, see: (a) Talele, T. T. Opportunities for Tapping into Three-Dimensional Chemical Space through a Quaternary Carbon. *J. Med. Chem.* **2020**, *63*, 13291−13315. For selected examples, see: (b) Mould, D. P.; Alli, C.; Bremberg, U.; Cartic, S.; Jordan, A. M.; Geitmann, M.; Maiques-Diaz, A.; McGonagle, A. E.; Somervaille, T. C. P.; Spencer, G. J.; Turlais, F.; Ogilvie, D. Development of (4-Cyano-phenyl)glycine Derivatives as Reversible Inhibitors of Lysine Specific Demethylase 1. *J. Med. Chem.* **2017**, *60*, 7984−7999. (c) Zheng, X.; Liang, C.; Wang, L.; Wang, B.; Liu, Y.; Feng, S.; Wu, J. Z.; Gao, L.; Feng, L.; Chen, L.; Guo, T.; Shen, H. C.; Yun, H. Discovery of Benzoazepinequinoline (BAQ) Derivatives as Novel, Potent, Orally Bioavailable Respiratory Syncytial Virus Fusion Inhibitors. *J. Med. Chem.* **2018**, *61*, 10228−10241. (d) Michaelides, M. R.; Kluge, A.; Patane, M.; Van Drie, J. H.; Wang, C.; Hansen, T. M.; Risi, R. M.; Mantei, R.; Hertel, C.; Karukurichi, K.; Nesterov, A.; McElligott, D.; de Vries, P.; Langston, J. W.; Cole, P. A.; Marmorstein, R.; Liu, H.; Lasko, L.; Bromberg, K. D.; Lai, A.; Kesicki, E. A. Discovery of spiro oxazolidinediones as selective, orally bioavailable inhibitors of p300/CBP histone acetyltransferases. *ACS Med. Chem. Lett.* **2018**, *9*, 28−33. (e) Li, Y.; Zhao, J.; Gutgesell, L. M.; Shen, Z.; Ratia, K.; Dye, K.; Dubrovskyi, O.; Zhao, H.; Huang, F.; Tonetti, D. A.; Thatcher, G. R. J.; Xiong, R. Novel Pyrrolopyridone Bromodomain and Extra-Terminal Motif (BET) Inhibitors Effective in Endocrine-Resistant ER+ Breast Cancer with Acquired Resistance to Fulvestrant and Palbociclib. *J. Med. Chem.* **2020**, *63*, 7186−7210.

(2) For selected reviews, see: (a) Fuji, K. Asymmetric Creation of Quaternary Carbon Centers. *Chem. Rev.* **1993**, *93*, 2037−2066. (b) Quasdorf, K. W.; Overman, L. E. Catalytic Enantioselective Synthesis of Quaternary Carbon Stereocentres. *Nature* **2014**, *516*, 181−191. (c) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. Catalytic Enantioselective Construction of Quaternary Stereocenters: Assembly of Key Building Blocks for the Synthesis of Biologically Active Molecules. *Acc. Chem. Res.* **2015**, *48*, 740−751. (d) Zeng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. Catalytic Enantioselective Desymmetrization Reactions to All-Carbon Quaternary Stereocenters. *Chem. Rev.* **2016**, *116*, 7330−7396. (e) Feng, J.; Holmes, M.; Krische, M. J. Acyclic Quaternary Carbon Stereocenters via Enantioselective Transition Metal Catalysis. *Chem. Rev.* **2017**, *117*, 12564−12580. (f) Li, C.; Ragab, S. S.; Liu, G.; Tang, W. Enantioselective Formation of Quaternary Carbon Stereocenters in Natural Product Synthesis: a Recent Update. *Nat. Prod. Rep.* **2020**, *37*, 276−292.

(3) For selected examples, see: (a) Sawamura, M.; Hamashima, H.; Ito, Y. Catalytic Asymmetric Synthesis with Trans-Chelating Chiral Diphosphine Ligand TRAP: Rhodium-Catalyzed Asymmetric Michael Addition of α-Cyano Carboxylates. *J. Am. Chem. Soc.* **1992**, *114*, 8295−8296. (b) Hamashima, Y.; Hotta, D.; Sodeoka, M. Direct Generation of Nucleophilic Chiral Palladium Enolate from 1,3-Dicarbonyl Compounds: Catalytic Enantioselective Michael Reaction with Enones. *J. Am. Chem. Soc.* **2002**, *124*, 11240−11241. (c) Mase, N.; Tanaka, F.; Barbas, C. F., III Synthesis of β-Hydroxyaldehydes with Stereogenic Quaternary Carbon Centers by Direct Organocatalytic Asymmetric Aldol Reactions. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420−2423. (d) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. A Chiral Primary Amine Thiourea Catalyst for the Highly Enantioselective Direct Conjugate Addition of α,α-Disubstituted Aldehydes to Nitroalkenes. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366−6370. (e) Jautze, S.; Peters, R. Enantioselective Bimetallic Catalysis of Michael Additions Forming Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2008**, *47*, 9284−9288. (f) Hashimoto, T.; Sakata, K.; Maruoka, K. α-Chiral Acetylenes Having an All-Carbon Quaternary Center: Phase Transfer Catalyzed Enantioselective a Alkylation of α-Alkyl-α-alkynyl Esters. *Angew. Chem., Int. Ed.* **2009**, *48*, 5014−5017.

(4) For selected examples, see: (a) Xie, X.; Chen, Y.; Ma, D. Enantioselective Arylation of 2-Methylacetoacetates Catalyzed by CuI/trans-4-Hydroxy-L-proline at Low Reaction Temperatures. *J. Am. Chem. Soc.* **2006**, *128*, 16050−16051. (b) Martín, R.; Buchwald, S. L. A General Method for the Direct α-Arylation of Aldehydes with Aryl Bromides and Chlorides. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236−7239. (c) Vo, G. D.; Hartwig, J. F. Palladium-Catalyzed α-Arylation of Aldehydes with Bromo- and Chloroarenes Catalyzed by [{Pd(allyl)-Cl}$_2$] and dppf or Q-phos. *Angew. Chem., Int. Ed.* **2008**, *47*, 2127−2130. (d) Jiao, Z.; Chee, K. W.; Zhou, J. S. Palladium-Catalyzed Asymmetric α-Arylation of Alkylnitriles. *J. Am. Chem. Soc.* **2016**, *138*, 16240−16243.

(5) For selected examples, see: (a) Jiang, G.; List, B. Direct Asymmetric α-Allylation of Aldehydes with Simple Allylic Alcohols Enabled by the Concerted Action of Three Different Catalysts. *Angew. Chem., Int. Ed.* **2011**, *50*, 9471−9474. (b) Liu, W.-B.; Reeves, C. M.; Stoltz, B. M. Enantio-, Diastereo-, and Regioselective Iridium-Catalyzed Asymmetric Allylic Alkylation of Acyclic β-Ketoesters. *J. Am. Chem. Soc.* **2013**, *135*, 17298−17301. (c) Turnbull, B. W. H.; Evans, P. A. Enantioselective Rhodium-Catalyzed Allylic Substitution with a Nitrile Anion: Construction of Acyclic Quaternary Carbon Stereogenic Centers. *J. Am. Chem. Soc.* **2015**, *137*, 6156−6159. (d) Kita, Y.; Kavthe, R. D.; Oda, H.; Mashima, K. Asymmetric Allylic Alkylation of β-Ketoesters with Allylic Alcohols by a Nickel/Diphosphine Catalyst. *Angew. Chem., Int. Ed.* **2016**, *55*, 1098−1101. (e) Cruz, F. A.; Dong, V. M. Stereodivergent Coupling of Aldehydes and Alkynes via Synergistic Catalysis Using Rh and Jacobsen's Amine. *J. Am. Chem. Soc.* **2017**, *139*, 1029−1032.

(6) For selected examples, see: (a) Ooi, T.; Miki, T.; Fukumoto, K.; Maruoka, K. Asymmetric Synthesis of α-Acyl-γ-butyrolactones Possessing All-Carbon Quaternary Stereocenters by Phase-Transfer-Catalyzed Alkylation. *Adv. Synth. Catal.* **2006**, *348*, 1539−1542. (b) Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. Enantioselective Catalytic α-Alkylation of Aldehydes via an S_N1 Pathway. *J. Am. Chem. Soc.* **2010**, *132*, 9286−9288. (c) Park, Y.; Lee, Y. J.; Hong, S.; Kim, M.-h.; Lee, M.; Kim, T.-S.; Lee, J. K.; Jew, S.-s.; Park, H.-g. Highly Enantioselective Phase-Transfer Catalytic α-Alkylation of α-tert-Butoxycarbonyllactams: Construction of β-Quaternary Chiral Pyrrolidine and Piperidine Systems. *Adv. Synth. Catal.* **2011**, *353*, 3313−3318. (d) List, B.; Coric, 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. (e) Zhu, Y.; Zhang, W.-Z.; Zhang, L.; Luo, S. Chiral Primary Amine Catalyzed Asymmetric α-Benzylation with In Situ Generated ortho-Quinone Methides. *Chem. - Eur. J.* **2017**, *23*, 1253−1257.

(7) For selected examples, see: (a) Sanz, R.; Miguel, D.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. Brønsted Acid-Catalyzed Benzylation of 1,3-Dicarbonyl Derivatives. *Org. Lett.* **2007**, *9*, 2027−2030. (b) Xing, C.; Sun, H.; Zhang, J.; Li, G.; Chi, Y. R. Brønsted Acid Catalyzed α-Alkylation of Aldehydes with Diaryl Methyl Alcohols. *Chem. - Eur. J.* **2011**, *17*, 12272−12275. (c) Maji, T.; Ramakumar, K.; Tunge, J. A. Retro-Claisen Benzylation: Direct Use of Benzyl Alcohols in Pd-catalyzed Couplings with Nitriles. *Chem. Commun.* **2014**, *50*, 14045−14048.

(8) For selected examples, see: (a) Torregrosa, R. R. P.; Ariyarathna, Y.; Chattopadhyay, K.; Tunge, J. A. Decarboxylative Benzylations of Alkynes and Ketones. *J. Am. Chem. Soc.* **2010**, *132*, 9280−9282. (b) Trost, B. M.; Czabaniuk, L. C. Palladium-Catalyzed Asymmetric Benzylation of 3-Aryl Oxindoles. *J. Am. Chem. Soc.* **2010**, *132*, 15534−15536. (c) Trost, B. M.; Czabaniuk, L. C. Benzylic Phosphates as Electrophiles in the Palladium-Catalyzed Asymmetric Benzylation of Azlactones. *J. Am. Chem. Soc.* **2012**, *134*, 5778−5781. (d) Trost, B. M.; Czabaniuk, L. C. Palladium-Catalyzed Asymmetric Benzylation of Azlactones. *Chem. - Eur. J.* **2013**, *19*, 15210−15218. (e) Franzoni, I.; Guénée, L.; Mazet, C. A General Pd-catalyzed α- and γ-Benzylation of

https://doi.org/10.1021/acs.orglett.1c01369
Org. Lett. 2021, 23, 4630−4634

Aldehydes for the Formation of Quaternary Centers. *Org. Biomol. Chem.* **2015**, *13*, 6338−6343. (f) Tsuji, H.; Hashimoto, K.; Kawatsura, M. Nickel-Catalyzed Benzylic Substitution of Benzyl Esters with Malonates as a Soft Carbon Nucleophile. *Org. Lett.* **2019**, *21*, 8837−8841.

(9) For selected drug molecules containing indole and isoquinolinone motifs, see: (a) Jagtap, P. G.; Baloglu, E.; Southan, G. J.; Mabley, J. G.; Li, H.; Zhou, J.; van Duzer, J.; Salzman, A. L.; Szabo, C. Discovery of Potent Poly(ADP-ribose) Polymerase-1 Inhibitors from the Modification of Indeno[1,2-c]isoquinolinone. *J. Med. Chem.* **2005**, *48*, 5100−5103. (b) Biradar, J. S.; Sasidhar, B. S.; Parveen, R. Synthesis, Antioxidant and DNA Cleavage Activities of Novel Indole Derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 4074−4078. (c) Pereira, R.; Benedetti, R.; Perez-Rodríguez, S.; Nebbioso, A.; García-Rodríguez, J.; Carafa, V.; Stuhldreier, M.; Conte, M.; Rodríguez-Barrios, F.; Stunnenberg, H. G.; Gronemeyer, H.; Altucci, L.; de Lera, A. R. Indole-Derived Psammaplin A Analogues as Epigenetic Modulators with Multiple Inhibitory Activities. *J. Med. Chem.* **2012**, *55*, 9467−9491. (d) Kaila, N.; Follows, B.; Leung, L.; Thomason, J.; Huang, A.; Moretto, A.; Janz, K.; Lowe, M.; Mansour, T. S.; Hubeau, C.; Page, K.; Morgan, P.; Fish, S.; Xu, X.; Williams, C.; Saiah, E. Discovery of Isoquinolinone Indole Acetic Acids as Antagonists of Chemoattractant Receptor Homologous Molecule Expressed on Th2 Cells (CRTH2) for the Treatment of Allergic Inflammatory Diseases. *J. Med. Chem.* **2014**, *57*, 1299−1322. (e) Singh, P.; Kaur, S.; Sharma, A.; Kaur, G.; Bhatti, R. TNF-α and IL-6 Inhibitors: Conjugates of N-substituted Indole and Aminophenylmorpholin-3-one as Anti-inflammatory Agents. *Eur. J. Med. Chem.* **2017**, *140*, 92−103.

(10) For selected reviews, see: (a) Lu, T.; Lu, Z.; Ma, Z.-X.; Zhang, Y.; Hsung, R. P. Allenamides: A Powerful and Versatile Building Block in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 4862−4904. (b) Blieck, R.; Taillefer, M.; Monnier, F. Metal-Catalyzed Intermolecular Hydrofunctionalization of Allenes: Easy Access to Allylic Structures via the Selective Formation of C−N, C−C, and C−O Bonds. *Chem. Rev.* **2020**, *120*, 13545−13598. For selected examples, see: (c) Braun, M.-G.; Katcher, M. H.; Doyle, A. G. Carbofluorination via a Palladium-Catalyzed Cascade Reaction. *Chem. Sci.* **2013**, *4*, 1216−1220. (d) Higuchi, Y.; Mita, T.; Sato, Y. Palladium-Catalyzed Intramolecular Arylative Carboxylation of Allenes with CO_2 for the Construction of 3-Substituted Indole-2-carboxylic Acids. *Org. Lett.* **2017**, *19*, 2710−2713. (e) Hédouin, J.; Schneider, C.; Gillaizeau, I.; Hoarau, C. Palladium-Catalyzed Domino Allenamide Carbopalladation/Direct C−H Allylation of Heteroarenes: Synthesis of Primprinine and Papaverine Analogues. *Org. Lett.* **2018**, *20*, 6027−6032. (f) Hédouin, J.; Carpentier, V.; Renard, R. M. Q.; Schneider, C.; Gillaizeau, I.; Hoarau, C. Regioselective Pd-Catalyzed Carbopalladation/Decarboxylative Allylic Alkynylation of ortho-Iodoallenamides with Alkynyl Carboxylic Acids. *J. Org. Chem.* **2019**, *84*, 10535−10545. (g) Xiong, W.; Cheng, R.; Wu, B.; Wu, W.; Qi, C.; Jiang, H. Palladium-Catalyzed Regioselective Cascade Reaction of Carbon Dioxide, Amines and Allenes for the Synthesis of Functionalized Carbamates. *Sci. China: Chem.* **2020**, *63*, 331−335.

https://doi.org/10.1021/acs.orglett.1c01369
Org. Lett. 2021, 23, 4630−4634