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Total Synthesis of Galanthamine and Lycoramine Featuring an Early-Stage C−C and a Late-Stage Dehydrogenation via C−H Activation

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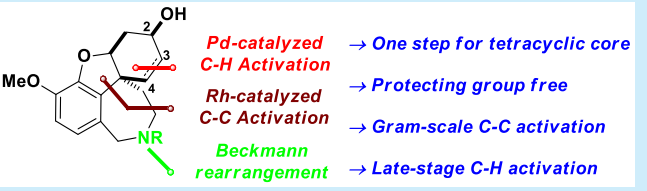
Supporting Information

ABSTRACT: Herein, we report a novel strategy toward galanthamine and lycoramine. The concise synthesis was enabled by a Rh-catalyzed gram-scale C−C activation for the tetracyclic carbon framework and a regioselective Pd-catalyzed C−H activation for double-bond introduction. An aqueous-phase Beckmann rearrangement was performed for nitrogen atom insertion. Galanthamine and lycoramine were completed in 11 and 10 steps, respectively.



Alzheimer's (AD) and other neurodegenerative diseases have plagued modern society for more than 50 years,[1] exerting a huge financial burden on the world.[2] Unfortunately, we still do not have a cure yet. The complicated nature and unmet clinical needs promise research around AD will be continued and reinforced.[1a] (−)-Galanthamine (**1**) is a reversible acetylcholinesterase inhibitor and is used as a primary drug to decelerate AD progression.[1,3] Galanthamine (**1**) and lycoramine (**2**) isolated[4] from *Narcissus* spp. *daffodil* show various neuron-protective activities.[3] Structurally, their polyfused tetracyclic ring skeleton as well as the key all-carbon quaternary stereocenter (shared by opioid alkaloids **3** and **4** shown in Figure 1) have attracted worldwide interest from the synthetic community ever since the first isolation.[5]

Galanthamine-type alkaloids[6] feature a linearly fused 6−5−6 tricycle (A−B−C rings in Figure 2), decorated with a D-ring of a 7-membered azepane. These structural features bring many

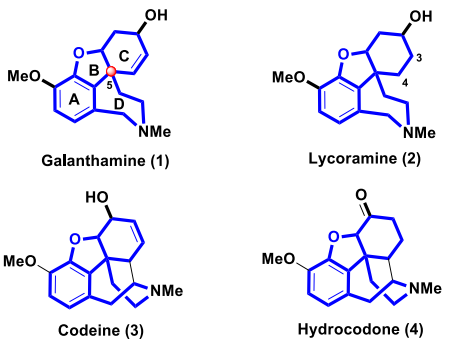


Figure 1. Galanthamine, lycoramine, and related alkaloids.

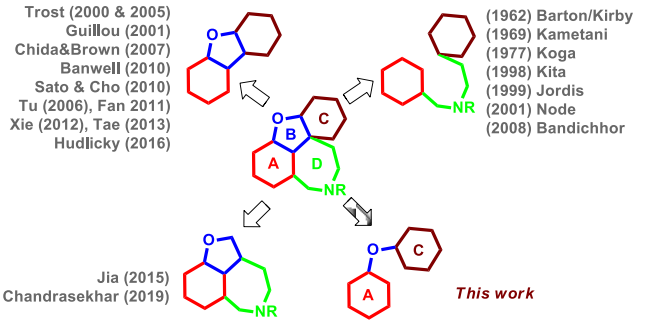


Figure 2. Strategies toward the core of galanthamine.

strategies focusing on constructing the A−B−C tricycle first, followed by a cyclization reaction for the D-ring,[7] and two examples of constructing the C ring at last after installing A−B−D rings.[8] Although an industrialized route toward (±)-galanthamine features a biomimetic[9f] oxidative coupling for tetracyclic ring formation, the galanthamine-type molecules continue to serve as a "touch stone" inspiring new strategies demonstrated by a recent review from Hudlicky and co-workers.[5b]

The development of transition-metal (TM) catalyzed C−C bond activation[10] of benzocyclobutenones, pioneered by Dong, gave us new tools for polyfused ring construction.[11] On the other hand, the late-stage C−H functionalization[12] was an attractive idea in multistep synthesis because redox adjustment can be avoided at an early stage. It is postulated

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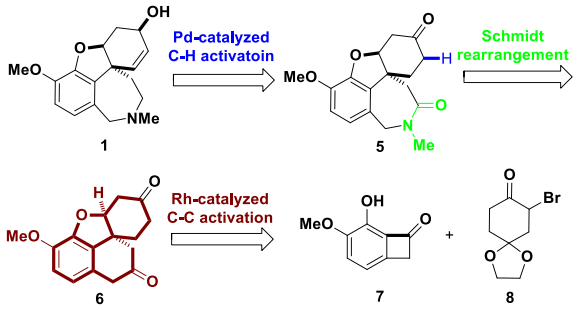
that the overall efficiency and diversity will be dramatically increased if we combine the advantages of the above, ideally, TM catalyzed C−C activation for carbon skeleton and C−H activation for functional group introduction. We herein extend such an example toward total synthesis of galanthamine and lycoramine.

Our retrosynthetic analysis is summarized in Scheme 1. Galanthamine (**1**) can be obtained through a regioselective Pd-catalyzed C−H activation[13] from ketone **5**. The nitrogen atom in **5** was postulated to be introduced by a Schmidt rearrangement from the tetracyclic intermediate **6**, which had possessed the A−B−C−D carbon framework of the target molecule. The tetracyclic ketone **6** can be reached through a Rh-catalyzed "cut and sew" annulation via C−C activation[11] from the coupling product between benzocyclobutenone **7** and the known bromocyclohexanone **8** (see the Supporting Information for details).

Scheme 1. Retrosynthetic Analysis



With the above strategy in mind, we commenced with preparation of benzylcyclobutenone **7**. The compound **9** was treated with freshly prepared LiTMP at −78 °C within the presence of lithium enolate (in situ generated from THF and *n*BuLi in a separate vessel). The [2 + 2] cycloaddition took place satisfactorily to afford benzocyclobutanol **10** in 64% yield on a decagram scale. Benzocycloubutenone **7** was achieved in 79% overall yield on a decagram scale through Dess−Martin oxidation followed by MOM removal under acidic conditions. A coupling between **7** and known compound **8** followed by Wittig olefination, provided the key C−C activation precursor **11** in 45% overall yield over two steps (Scheme 2). The moderate yield was mainly due to a competitive olefination of the four-membered ketone. Nevertheless, the key precursor **11** was prepared on a multigram scale.

The designed C−C activation was attempted on the basis of Dong's classical conditions (entry 1, Table 1).[11a] The desired

Scheme 2. Synthesis of the Key Reaction Precursor 11

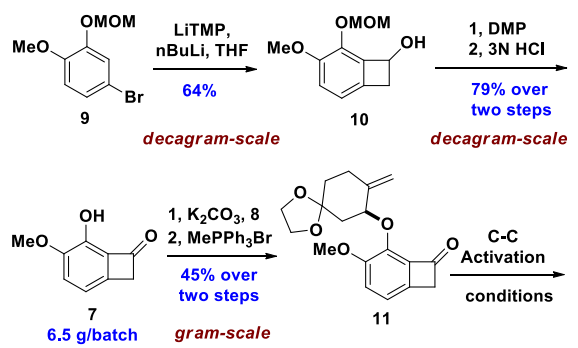
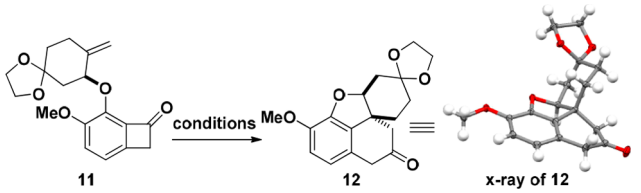


Table 1. Selected Condition Optimization for C−C Activation



entry[a]	precatalyst	ligand	conversion (%)	yield[b] (%)
1	$[Rh(cod)Cl]_2$	DPPB	30	15 (50)
2	$[Rh(C_2H_4)_2Cl]_2$	DPPB	40	32 (80)
3	$[Rh(coe)_2Cl]_2$	DPPB	32	17 (53)
4	$[Rh(CO)_2Cl]_2$	DPPB	34	28 (82)
5[c]	$[Rh(CO)_2Cl]_2$	PPh_3	40	23 (58)
6	$[Rh(CO)_2Cl]_2$	rac-BINAP	61	18 (30)
7[c]	$[Rh(CO)_2Cl]_2$	$P(3,5\text{-}C_6H_3(CF_3)_2)_3$	34	12 (35)
8[c]	$\mathbf{[Rh(CO)_2Cl]_2}$	$\mathbf{P(C_6F_5)_3}$	**90**	**71 (79)**
9[d]	$\mathbf{[Rh(CO)_2Cl]_2}$	$\mathbf{P(C_6F_5)_3}$	**100**	**77**

[a]All reactions were run with 5 mol % precatalyst and 12 mol % ligand on a 0.1 mmol scale in dioxane at 130 °C for 15 h unless otherwise noted; conversion were determined based on recycled starting material after isolation. [b]Isolated yield, numbers in parentheses are brsm yield. [c]22 mol % of ligand was used. [d]The reactions were run with 5 mol % $[Rh(CO)_2Cl]_2$ and 22 mol % $P(C_6F_5)_3$ on a 1 g scale of **11** in dioxane at 130 °C for 19 h.

tetracyclic product **12** was obtained, but only in 15% yield. Gratifyingly, a single crystal was successfully obtained, verifying the relative stereochemistry of **12**, as expected (Table 1). The 1,1-disubstituted *exo*-olefin of a cyclohexane was blamed for causing remote steric repulsion, which might account for the slow conversion and low yield. A screening of precatalysts only led to low conversion (30−40%) and moderate yields (15−32%, entries 1−3, Table 1). Surprisingly, 5 mol % $[Rh(CO)_2Cl]_2$ together with 12 mol % bidentate DPPB resulted in a 28% isolated yield (82% brsm, entry 4). This encouraging results lead us to search for other ligands (entries 5−8). Delightfully, the ketone **12** was obtained as a single diastereoisomer in 71% isolated yield (79% brsm) when 5 mol % $[Rh(CO)_2Cl]_2$ and 22 mol % monodentate $P(C_6F_5)_3$ were used.[11c] With the optimized conditions in hand, we further tested its robustness on challenging substrates (Scheme 3). The key "cut and sew" carboacylation reaction was found to be compatible with an ester group, as product **12a** was successfully isolated in 61% yield (inseparable 1:1 mixture derived from corresponding starting material, see the SI for details). It was found that different masking groups led to different diastereoselectivity.[11m] Compound **12b** was isolated as the only product (70% yield), although it bears a dr ratio in the corresponding starting material (see the SI for details). We tried *exo*-olefins bearing different ring sizes from cyclopentanemethelene to cycloheptanemethelene, and the reaction yielded the corresponding products **12c** and **12d** in 88% and 50% (75% brsm) yields, respectively. As in the case of cycloheptanemethelene, a pair of diastereoisomers **12e** (33% yield) and **12e′** (33% yield) was obtained, indicating that the migratory insertion step of the carboacylation reaction could be altered through the conformation control of the pedant olefin. *To the best of our knowledge, this accounted for the only*

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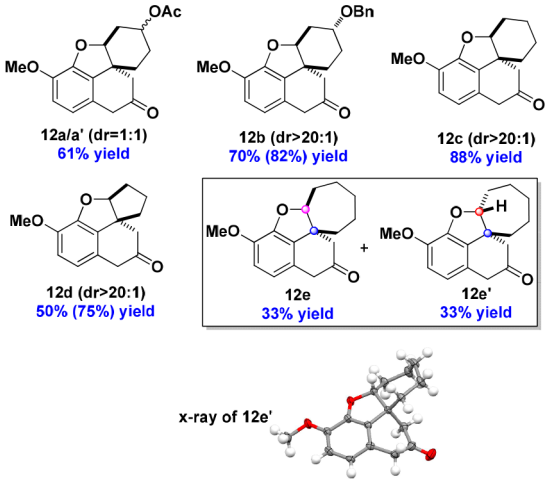
Scheme 3. Viable Substrate Scopes for C−C Activation



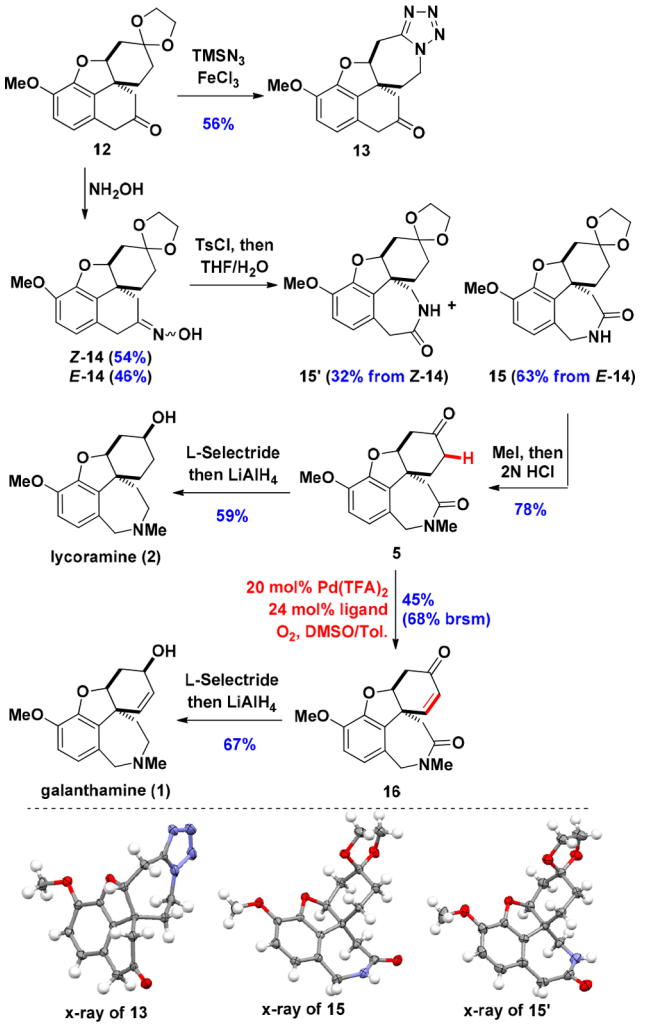
example of migratory insertion forming trans-fused ring systems in the carboacylation reaction initiated by C−C activation.

With a robust condition in hand, we tentatively tried the key reaction with 1 g of **11**; it turned out that the carboacylation reaction proceeded faithfully with improved efficiency (100% conversion) and 77% isolation yield, demonstrating practicality of the key C−C activation (entry 9, Table 1). Our synthesis was continued with the task of introducing nitrogen atom in the D ring.

First, a Schmidt rearrangement[14] was performed in the hope of introducing nitrogen in a regioselective fashion based on the assumption that benzyl group's migrating ability is better than a neopentyl group. To our disappointment, only tetrazole **13** was isolated through extensive condition screening. It was reasoned that the Lewis acid activated ketal first, which rendered the C-ring expansion (Scheme 4). Crystallographic analysis of **13** unambiguously showed its structure. Toward this end, other N-insertion reactions were sought after, e.g., Beckmann rearrangement.[14] Tetracycle ketone **12** was condensed with hydroxyl amine quantitatively. The resulting oxime **14** (1:1.2 *E*/*Z* isomers) was treated by tosylation and stirring at mild temperature.[15] The Beckmann rearrangement occurred spontaneously in a THF/water solvent without any other additives, yielding the desired amide **15** (63% yield) and its regioisomer **15′** (32% yield). A crystallographic analysis of amide **15** and **15′** confirmed their structures as well as stereochemistry. The key diversifiable intermediate **5** was isolated in 78% yield upon methylation and acidic workup.

With keto-amide **5** in hand, we attempted the Pd-catalyzed regioslelctive C−H activation reaction using Stahl's procedure.[13] Gratifyingly, using 20 mol % $Pd(TFA)_2$ and 24 mol % of ligand (premixed with DMSO and added in six portions), the desired oxidation took place, providing unsaturated ketone **16** in 45% isolated yield (68% based on recovered starting material). The reaction was found to be sensitive to scale, and **5** was decomposed in the reaction media (for full optimization details, see the SI). In the meantime, **5** was converted to racemic lycoramine (**2**) through consecutive double reduction using L-Selectride/$LiAlH_4$ in 59% yield. The same procedure also successfully elaborated **16** to galanthamine (**1**) diastereoselectively in 67% yield. The spectroscopic data of galanthamine (**1**) and lycormaine (**2**) were in good accordance with the reported data.[7k]

Scheme 4. Synthesis of Lycoramine



In summary, we have completed the total synthesis of galanthamine and lycoramine in 11 and 10 steps featuring a gram-scale Rh-catalyzed C−C activation initiated "cut and sew" carbolacylation and a late-stage Pd-catalyzed dehydrogenation via C−H activation. The tetracyclic carbon framework A−B−C−D of galanthamine-type alkloids was constructed in one step based on the strategic application of C−C activation. No protecting groups were needed. This synthesis represented the first example of strategic combining TM-catalyzed C−C and C−H activation in natural product synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04337.

Experimental procedures; spectral data (PDF)

Accession Codes

CCDC 1968259 and 1968489−1968492 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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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Patterson, C. *World Alzheimer Report*; Alzheimer's Disease International, 2018. (b) Dobson, C. M. *Rend. Fis. Acc. Lincei.* **2015**, *26*, 251−262. (c) Young, A. B. *J. Neurosci.* **2009**, *29*, 12722−12728.

(2) (a) Gooch, C. L.; Pracht, E.; Borenstein, A. R. *Ann. Neurol.* **2017**, *81*, 479−484. (b) Lin, P.-J.; Neumann, P. J. *Alzheimer's Dementia* **2013**, *9*, 58−62.

(3) For studies of galanthamineandAChE, see: Mashkovskii, M. D. *Pharmacol. Toxicol.* **1955**, *18*, 21. (b) Irwin, R. L.; Smith, H. J. *Biochem. Pharmacol.* **1960**, *3*, 147. (c) Caricati-Neto, A.; D'angelo, L. C.; Reuter, H.; Jurkiewicz, N. H.; Garcia, A. G.; Jurkiewicz, A. *Eur. J. Pharmacol.* **2004**, *503*, 191.

(4) For the first isolation, see: (a) Proskurnina, N. F.; Yakoleva, A. P. *J. Gen. Chem.* **1952**, *22*, 1899. (b) Kondo, H.; Tomimura, K.; Ishiwata, S. *J. Pharm. Soc. Jpn.* **1932**, *52*, 51.

(5) For selected leading reviews of galanthamine, see: (a) Marco-Contelles, J.; Carreiras, M. D.; Rodriguez, C.; Villarroya, M.; Garcia, A. G. *Chem. Rev.* **2006**, *106*, 116−133. (b) Rinner, U.; Dank, C.; Hudlicky, T. *Targets in Heterocyclic Systems* **2016**, *20*, 283−315.

(6) (a) Hoshino, O. The Amaryllidaceae Alkaloids. In *The Alkaloids: Chemistry and Biology*; Geoffrey, A. C., Ed.; Academic Press, 1998; Vol. *51*, pp 323−424. (b) Martin, S. F. The AmaryllidaceaeAlkaloids. In *The Alkaloids: Chemistry and Pharmacology*, Arnold, B., Ed.; Academic Press, 1987; Vol.*30*, pp 251−376.

(7) For the ABC−D construction sequence toward total synthesis of galanthamine, see: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262. (b) Guillou, C.; Beunard, J.-L.; Gras, E.; Thal, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 4745. (c) Trost, B. M.; Tang, W. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2795. (d) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785. (e) Hu, X.-D.; Tu, Y.-Q.; Zhang, E.; Gao, S.; Wang, S.; Wang, A.; Fan, C.-A.; Wang, M. *Org. Lett.* **2006**, *8*, 1823. (f) Tanimoto, H.; Kato, T.; Chida, N. *Tetrahedron Lett.* **2007**, *48*, 6267. (g) Satcharoen, V.; McLean, N. J.; Kemp, S. C.; Camp, N. P.; Brown, R. C. D. *Org. Lett.* **2007**, *9*, 1867. (h) Ishikawa, T.; Kudo, K.; Kuroyabu, K.; Uchida, S.; Kudoh, T.; Saito, S. *J. Org. Chem.* **2008**, *73*, 7498. (i) Chang, J. H.; Kang, H.-U.; Jung, I.-H.; Cho, C.-G. *Org. Lett.* **2010**, *12*, 2016. (j) Banwell, M. G.; Ma, X.; Karunaratne, O. P.; Willis, A. C. *Aust. J. Chem.* **2010**, *63*, 1437. (k) Chen, J.-Q.; Xie, J.-H.; Bao, D.-H.; Liu, S.; Zhou, Q.-L. *Org. Lett.* **2012**, *14*, 2714. (l) Choi, J.; Kim, H.; Park, S.; Tae, J. *Synlett* **2013**, *24*, 379. (m) Nugent, J.; Matousova, E.; Banwell, M. G. *Eur. J. Org. Chem.* **2015**, *2015*, 3771. (n) Endoma-Arias, M. A.; Hudlicky, T. *Chem. - Eur. J.* **2016**, *22*, 14540. (o) Nugent, J.; Banwell, M. G. *Eur. J. Org. Chem.* **2016**, *2016*, 5862. (p) Zhang, Q.; Zhang, F.-M.; Zhang, C.-S.; Liu, S.-Z.; Tian, J.-M.; Wang, S.-H.; Zhang, X.-M.; Tu, Y.-Q. *J. Org. Chem.* **2019**, *84*, 12664.

(8) For the ABD−C construction sequence toward total synthesis of galanthamine, see: (a) Li, L.; Yang, Q.; Wang, Y.; Jia, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 6255. (b) Venkatesh, T.; Mainkar, P. S.; Chandrasekhar, S. *Org. Biomol. Chem.* **2019**, *17*, 2192.

(9) For the biomimetic oxidative coupling strategy toward total synthesis of galanthamine, see: (a) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806. (b) Kametani, T.; Yamaki, K.; Yagi, H.; Fukumoto, K. *J. Chem. Soc. C* **1969**, *0*, 2602. (c) Kametani, T.; Yamaki, K.; Yagi, H.; Fukomuto, K. *J. Chem. Soc. D* **1969**, *0*, 425. (d) Shimizu, K.; Tomioka, K.; Yamada, S. I.; Koga, K. *Heterocycles* **1977**, *8*, 277. (e) Kita, Y.; Arisawa, M.; Gyoten, M.; Nakajima, M.; Hamada, R.; Tohma, H.; Takada, T. *J. Org. Chem.* **1998**, *63*, 6625. (f) Küenburg, B.; Czollner, L.; Fröhlich, J.; Jordis, U. *Org. Process Res. Dev.* **1999**, *3*, 425. (g) Node, M.; Kodama, S.; Hamashima, Y.; Katoh, T.; Nishide, K.; Kajimoto, T. *Chem. Pharm. Bull.* **2006**, *54*, 1662.

(10) For selected reviews on C−C activation, see: (a) Jones, W. D. *Nature* **1993**, *364*, 676. (b) Murakami, M.; Ito, Y. *Top. Organomet. Chem.* **1999**, *3*, 97. (c) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (d) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610. (e) Satoh, T.; Miura, M. *Top. Organomet. Chem.* **2005**, *14*, 1. (f) Necas, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566. (g) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (h) Ruhland, K. *Eur. J. Org. Chem.* **2012**, *2012*, 2683. (i) Korotvicka, A.; Necas, D.; Kotora, M. *Curr. Org. Chem.* **2012**, *16*, 1170. (j) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740. (k) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (l) Dermenci, A.; Coe, P. W.; Dong, G. *Org. Chem. Front.* **2014**, *1*, 567. (m) C-C Bond Activation. *Topics in Current Chemistry*; Dong, G., Ed.; Springer-Verlag: Berlin, 2014. (n) Chen, F.; Wang, T.; Jiao, N. *Chem. Rev.* **2014**, *114*, 8613. (o) Souillart, L.; Cramer, N. *Chem. Rev.* **2015**, *115*, 9410. (p) Shaw, M. H.; Bower, J. F. *Chem. Commun.* **2016**, *52*, 10817. (q) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *117*, 9404. (r) Chen, P.-H.; Billett, B. A.; Tsukamoto, T.; Dong, G. *ACS Catal.* **2017**, *7*, 1340.

(11) For pioneering and seminal examples by Dong and co-workers, see: (a) Deng, L.; Jin, L.; Dong, G. *Angew. Chem., Int. Ed.* **2018**, *57*, 2702. (b) Deng, L.; Xu, T.; Li, H.; Dong, G. *J. Am. Chem. Soc.* **2016**, *138*, 369. (c) Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7567. (d) Xu, T.; Ko, H. M.; Savage, N. A.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 20005. (e) Xu, T.; Savage, N. A.; Dong, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1891. (f) Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 10733. (g) Chen, P.-H.; Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1674. (h) Chen, P.-h.; Sieber, J.; Senanayake, C. H.; Dong, G. *Chem. Sci.* **2015**, *6*, 5440−5445. (i) For recent applications, see: Li, K.; Wang, Y.-F.; Li, X.-M.; Wang, W.-J.; Ai, X.-Z.; Li, X.; Yang, S.-Q.; Gloer, J. B.; Wang, B.-G.; Xu, T. *Org. Lett.* **2018**, *20*, 417. (j) Qiu, B.; Li, X.-T.; Zhang, J.-Y.; Zhan, J.-L.; Huang, S.-P.; Xu, T. *Org. Lett.* **2018**, *20*, 7689. (k) Yu, H.; Zong, Y.; Xu, T. *Chem. Sci.* **2020**, DOI: 10.1039/C9SC05252F. (l) Sun, T.; Zhang, Y.; Qiu, B.; Wang, Y.; Qin, Y.; Dong, G.; Xu, T. *Angew. Chem.* **2018**, *130*, 2909. (m) Deng, L.; Fu, Y.; Lee, S. Y.; Wang, C.; Liu, P.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 16260.

(12) For selected reviews on late stage C−H functionalization, see: (a) White, M. C. *Science* **2012**, *335*, 807. (b) White, M. C. *Synlett* **2012**, *23*, 2746. (c) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (e) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (f) Malik, H. A.; Taylor, B. L.; Kerrigan, J. R.; Grob, J. E.; Houk, K. N.; Du Bois, J.; Hamann, L. G.; Patterson, A. W. *Chem. Sci.* **2014**, *5*, 2352. (g) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. *Nat. Chem.* **2018**, *10*, 383. (h) Karimov, R. R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2018**, *57*, 4234. (i) White, M. C.; Zhao, J. J. *J. Am. Chem. Soc.* **2018**, *140*, 13988−14009. (j) For pioneering work on late-stage C−H activation in synthesis, see: Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C.

DOI: 10.1021/acs.orglett.9b04337
Org. Lett. XXXX, XXX, XXX−XXX

Org. Lett. **2005**, *7*, 223. (k) Covell, D. J.; Vermeulen, N. A.; Labenz, N. A.; White, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 8217.

(13) (a) Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. *Chem. Rev.* **2018**, *118*, 2636. (b) Diao, T.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 14566. (c) Diao, T.; Wadzinski, T. J.; Stahl, S. S. *Chem. Sci.* **2012**, *3*, 887. (d) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2017**, *139*, 7757. (e) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 14889.

(14) (a) Grecian, S.; Aube, J. Schmidt Rearrangement Reactions with Alkyl Azides. In *Organic Azides: Syntheses and Applications*; Brase, J., Banert, K., Eds.; Wiley, 2009; pp439−469. (b) Mailyan, A. K.; Eickhoff, J. A.; Minakova, A. S.; Gu, Z.; Lu, P.; Zakarian, A. *Chem. Rev.* **2016**, *116*, 4441−4557. (c) For Beckmann rearrangement, see: Beckmann, E. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 988. (d) Chandrasekhar, S. *Comprehensive Organic Synthesis II*, 2nd ed.; Elsevier: Amsterdam, 2014; Vol. 7, pp 770−800. (e) Touchette, S. J.; Dunkley, E. M.; Lowder, L. L.; Wu, J. *Chem. Sci.* **2019**, *10*, 7812.

(15) *E*-**14** can be readily isomerized to *Z*-**14** by heating or elongate reaction time and the reverse isomerization was not observed, indicating the latter's a thermodynamic product.

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