JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Two-Carbon Ring Expansion of 1-Indanones via Insertion of Ethylene into Carbon-Carbon Bonds

Ying Xia, Shusuke Ochi, and Guangbin Dong

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.9b07445 • Publication Date (Web): 07 Aug 2019

Two-Carbon Ring Expansion of 1-Indanones via Insertion of Ethylene into Carbon−Carbon Bonds

Ying Xia, Shusuke Ochi and Guangbin Dong*

Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States

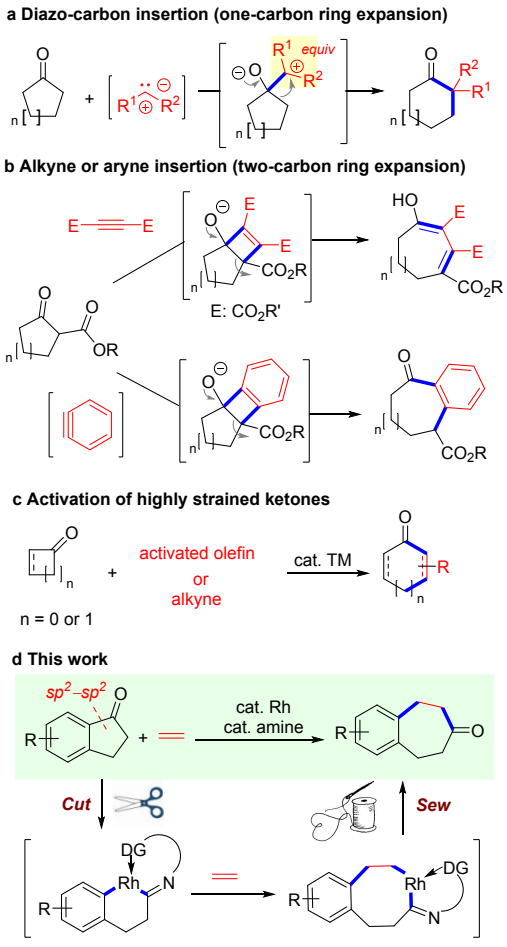
Supporting Information Placeholder

ABSTRACT: A rhodium-catalyzed direct insertion of ethylene into a relatively unstrained carbon–carbon bond in 1-indanones is reported, which provides a two-carbon ring-expansion strategy for preparing seven-membered cyclic ketones. As many 1-indanones are commercially available and ethylene is inexpensive, this strategy simplifies synthesis of benzocycloheptenones that are valuable synthetic intermediates for bioactive compounds but challenging to prepare otherwise. In addition, the reaction is byproduct-free, redox neutral, and tolerant of a wide range of functional groups, which may have implications on unconventional strategic bond disconnections for preparing complex cyclic molecules.

Ring expansion reactions of carbonyl compounds, such as Baeyer−Villiger oxidation, Beckmann rearrangement and various carbon-insertion reactions, are highly valuable transformations and have been frequently utilized in complex molecule syntheses.[1] With a few exceptions, most direct ring-expansion reactions could add only a one-atom unit to the existing structures. Compared to the well-established one-carbon homologation methods[2] (Scheme 1a), limited approaches are known for direct two-carbon ring expansions of ketones.[3] After an accidental discovery in 1974, Proctor elucidated that carbocyclic β-ketoesters could undergo a [2+2] cycloaddition with an activated alkyne, followed by an accelerated retro-4π cyclization, to give two-carbon extended products[4] (Scheme 1b). Later, Kuninobu and Takai discovered a similar but efficient rhenium-catalyzed reaction for insertion of terminal alkynes with β-ketoesters[5], though the reaction was not suitable for preparing 7-membered rings. As a mechanistically related transformation, Caubere[6], and Stoltz[7], reported an intriguing two-carbon ring expansion method via benzyne insertion (Scheme 1b).

Alternatively, it could be attractive to directly insert a common unsaturated unit into a cyclic ketone through transition metal-catalyzed C−C activation[8-10], which should offer a straightforward and byproduct-free approach for multi-atom ring expansions. The reaction involves oxidative addition of C−C bond to a low-valent transition metal[8b], followed by 2π-insertion to give an enlarged metallocycle and C−C reductive elimination. Such a transformation, also known as a "cut-and-sew" process[9b], has been extensively demonstrated in strained three- and four-membered ring systems (Scheme 1c).[11] However, for unstrained systems,[10] the scope of the process has been primarily limited to the use of polar C−CN bonds[12] or some special intramolecular reactions[13]. In addition, ethylene, as the most highly produced organic compound, may serve as an appealing two-carbon coupling partner; to the best of our knowledge, the "cut-and-sew" reaction using ethylene as a 2π unit has been elusive for either strained or unstrained systems. Moreover, the preference to break the stronger aryl−carbonyl bond (e.g. in 1-indanones), enabled by transition-metal catalysts, could offer complementary selectivity to the conventional[1] or radical-mediated C−C cleavage reactions[14]. Herein, we describe our preliminary development of a Rh-catalyzed two-carbon ring expansion of 1-indanones via insertion of ethylene into C−C bonds (Scheme 1d).

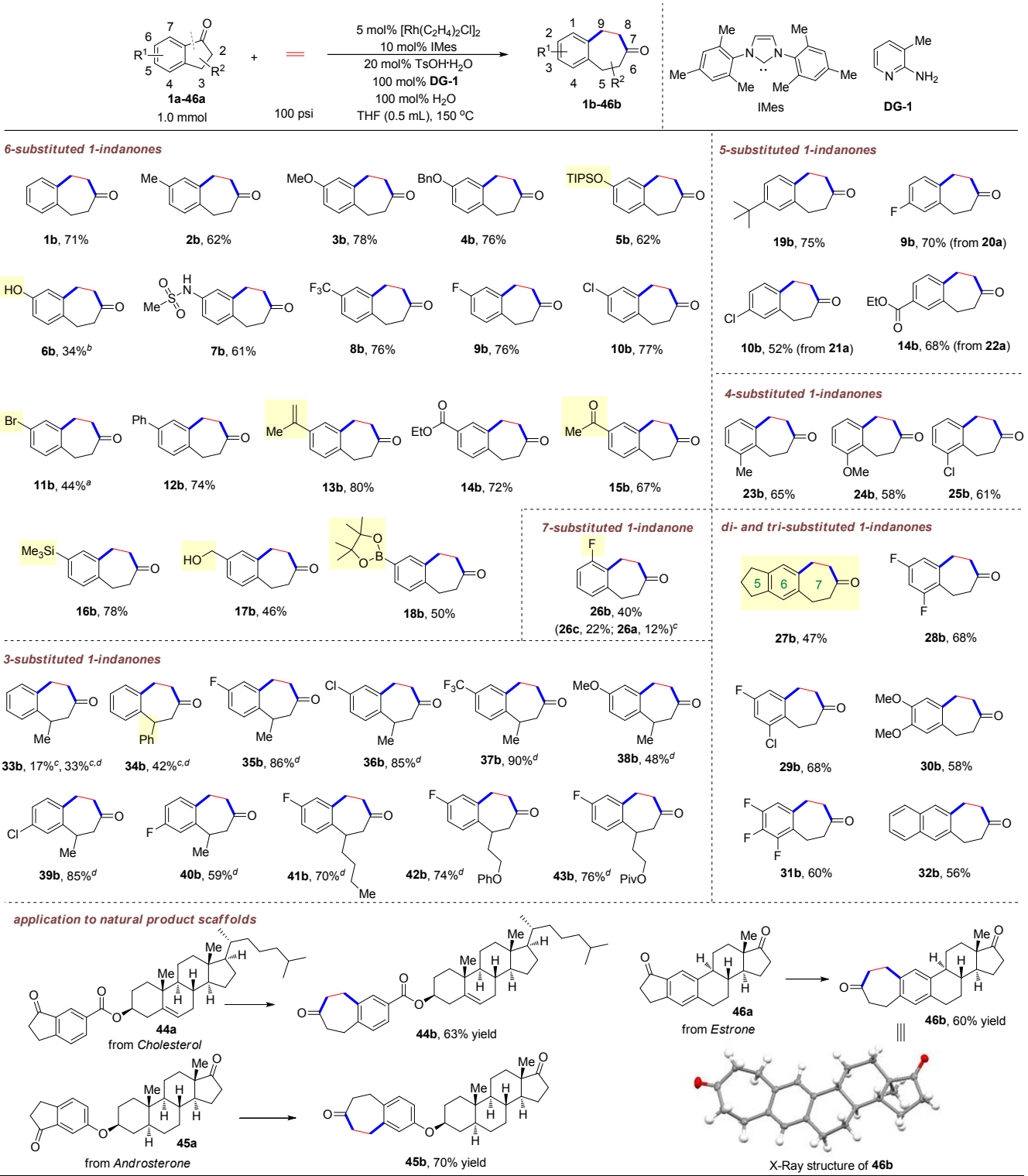
Scheme 1. Representative direct methods for ring expansion of cyclic ketones



To explore the proposed ethylene-insertion reaction, unsubstituted 1-indanone (**1a**) was used as the model substrate, and the Jun's ketimine directing mode[8d,10b] was employed for C−C activation. The reaction parameters, including different aminopyridines (serving as the temporary directing group),

ligands, solvents, additives, temperature and pressure of ethylene, were carefully

Chart 1. Scope of the Ethylene-Insertion Reaction[a]



[a]Unless otherwise noted, all the reactions were carried out on 1.0 mmol scale in 72 hours under the standard conditions and yields are of material isolated by silica gel chromatography. [b]The reaction was carried out at 130 °C. [c]Yields were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [d]In the absence of IMes ligand and use of 50 mol% water. For details, see Supporting Information.

optimized (see Table S1). Ultimately, the desired benzocycloheptenone product **1b** was obtained in 76% yield from 1-indanone (**1a**) and ethylene gas (100 psi) in the presence of 5 mol% $[Rh(C_2H_4)_2Cl]_2$, 10 mol% 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes), 20 mol% *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$), 100 mol% 2-amino-3-picoline (**DG-1**) and 100 mol% H_2O in THF (Table S1, entry 1). The only observable side product was the ketone α-C−H

insertion product,[15] 2-ethyl-1-indanone (**1c**), which was formed in 8% yield. Interestingly, in the absence of the strong σ-donating IMes ligand, the reaction still afforded the desired product **1b** in 60% yield, but gave a poorer selectivity with the α-alkylation product formed in 15% yield (Table S1, entry 2). The Rh catalyst, $TsOH{\cdot}H_2O$ and the **DG-1** are all critical for this transformation, and no desired product can be produced without any of them (Table S1, entries 3-5). When decreasing **DG-1** to 30 mol% and 50 mol%, the seven-membered ring product **1b** could still be obtained in 54% and 69% yield, respectively (Table S1, entries 6 and 7), suggesting that **DG-1** exhibits some catalytic activity. Other temporary directing groups were found either less efficient or less selective (Table S1, entries 8-11), but it is worth noting that simple 2-aminopyridine **DG-2** favors forming the ketone α-alkylation product (For more control experiments, see *Supporting Information, Section 3*).

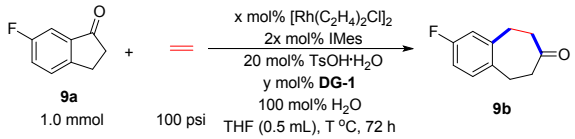
With the optimized conditions in hand, the substrate scope of this ethylene-insertion reaction was then explored (Chart 1). First, C6-substituted 1-indanone substrates were tested. The electronic property of the 6-substituent only had a marginal influence on this reaction, as 1-indanones bearing either electron-donating (**2a-7a**) or -withdrawing groups (**8a-15a**) all gave comparable results to the model substrate **1a**. A series of functional groups, including free phenol (**6a**), sulfonamide (**7a**), chloride (**10a**), ester (**14a**), methyl ketone (**15a**), silyl (**16a**) and free hydroxyl group (**17a**), are tolerated. Besides, substrates containing aryl bromide (**11a**) and boronate (**18a**), which are generally reactive moieties in transition-metal catalysis, still afforded the desired products in moderate yields. Notably, for the substrate that contains two ketone carbonyls (**15a**), C−C activation occurred exclusively at the indanone site. 1-Indanones bearing substituents at the 4- or 5-position exhibited similar reactivity, yielding the corresponding benzocycloheptenones in 52-75% yields (**19a-25a**). As expected, substitutions at the 7-position resulted in lower reactivity due to the increased steric hindrance around the carbonyl functionality (**26a**). In addition, several disubstituted 1-indanones (**27a-31a**) or naphthyl-fused cyclopentanone (**32a**) proved to be competent substrates, affording the desired seven-membered ring products in moderate to good yields.

After examining the steric and electronic influence of the arene part on reactivity, the substitution effect at the aliphatic positions of 1-indanones was next investigated. 3-Methyl-1-indanone (**33a**) showed substantially reduced reactivity under the standard conditions; however, the yield could be improved in the absence of the IMes ligand with a reduced amount of water (50 mol%). Under these new reaction conditions, 3-phenyl 1-indanone (**34a**) afforded the desired product in 42% yield. Gratifyingly, the reaction efficiency was significantly improved when substrates containing an additional substituent on the benzene ring (**35a-40a**), though the exact reason is unclear. For example, 6-trifluoromethyl-3-methyl-1-indanone (**37a**) produced the desired product (**37b**) in 90% yield. Besides methyl and phenyl groups, other alkyl substituents at the 3-position were also tolerated (**41b-43b**). Unsurprisingly, substitution at the α-position (C2) of 1-indanones shut down the reactivity because the steric congestion around the ketone would inhibit forming the imine intermediate. Finally, this reaction can be applied to natural product-derived or tethered indanones. Indanone **44a** with an ester-linked cholesterol and **45a** with an ether-linked androsterone smoothly participated in this two-carbon ring-expansion reaction. Similarly, starting from estrone-fused cyclopentanone **46a**, a seven-membered ketone moiety can be efficiently introduced to give a unique 7-6-6-6-5 pentacyclic structure, which was unambiguously confirmed by X-ray crystallography.

From a practical viewpoint, the limits of the reaction condition, i.e. the lowest catalyst loading/temperature that could still afford good synthetic efficiency, were probed. To our delight, when decreasing the loading of the rhodium/IMes from 10 mol% to *3 mol%* and decreasing **DG-1** from 100 mol% to *50 mol%*, the reaction still worked well to give 85% conversion and 65% yield of product **9b** (Scheme 2a, entry 2 *vs.* entry 1). Using 5 mol% rhodium/IMes and 50 mol% **DG-1**, the reaction efficiency almost reached to the level of the original conditions (Scheme 2a, entry 3). Besides, when running at a lower temperature (130 °C), the reaction still proceeded smoothly even with 5 mol% rhodium/ligand (Scheme 2a, entry 4). The reaction is also scalable. On gram scales, good yields could still be obtained with 1-indanones bearing either an electron-donating or -withdrawing group, and **DG-1** could be easily recycled (Scheme 2b). Moreover, synthesis of enantiomerically enriched 5-substituted benzocycloheptanone (Scheme 2c) could be achieved using chiral 1-indanone *R*-**35a** that was prepared in three steps from commercially available arylboronic acid **47** and α,β-unsaturated ester **48** via asymmetric conjugate addition[16]. The slight erosion of enantioselectivity was likely due to the unproductive C−C activation at the C1−C2 position, which led to reversible β-hydrogen elimination[17].

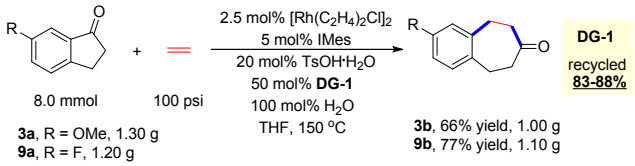
Scheme 2. Synthetic applications

a Pushing the limits of the reaction conditions

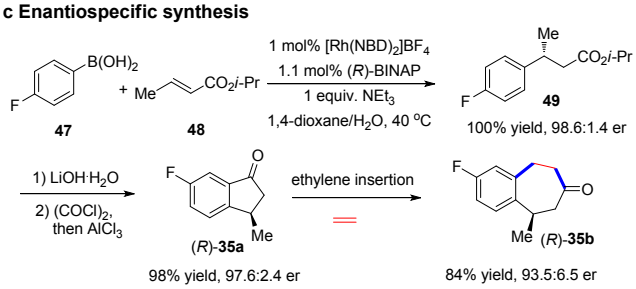


Entry	$[Rh(C_2H_4)_2Cl]_2$/IMes	DG-1	T	Conversion	Yield
1	5 mol%/10 mol%	100 mol%	150 °C	>95%	77%
2	**1.5 mol%/3 mol%**	50 mol%	150 °C	85%	65%
3	2.5 mol%/5 mol%	**50 mol%**	150 °C	>95%	74%
4	2.5 mol%/5 mol%	100 mol%	**130 °C**	86%	74%

b Gram-scale syntheses



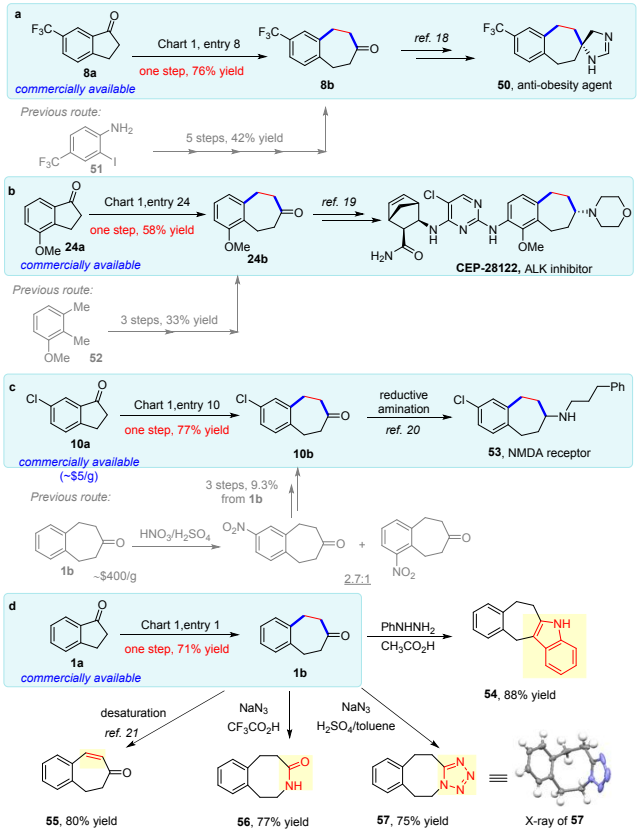
c Enantiospecific synthesis



Benzocycloheptenones have been frequently used in the synthesis of bioactive compounds that contain seven-membered rings; however, the conventional approaches for preparing benzocycloheptenones are often inefficient[18-20] (Scheme 3). Thus, this two-carbon homologation approach could contribute to shortening the syntheses of those complex pharmaceutical agents. For example, the trifluoromethyl-substituted benzocycloheptanone (**8b**), prepared in a single step using this method, was the key intermediate in the synthesis of anti-obesity agent **50** (Scheme 3a). As a comparison, the prior approach

required five steps from 2-iodo-4-trifluoromethyl-aniline **51**[18]. In the second case, CEP-28122 is a highly potent and selective inhibitor of ALK (anaplastic lymphoma kinase), showing promising antitumor activity in human cancers[19]. One key structural motif is the benzocycloheptene moiety, which was synthesized from methoxyl-substituted benzocycloheptenone **24b**. The previous synthesis of **24b** used three steps from 1-methoxy-2,3-dimethylbenzene **52** with a 33% overall yield[19]. Now, **24b** can be prepared straightforwardly via the "cut-and-sew" process from commercially available 4-methoxy-1-indanone **24a** (Scheme 3b). The third example involves the synthesis of amine **53**, which is a NMDA (*N*-methyl-D-aspartate) receptor for the potential treatment of various neurological disorders.[20] The existing route prepared the key intermediate **10b** in three steps from unsubstituted benzocycloheptenone **1b** that is either very expensive or requires an additional two or three steps for preparation. In addition, the electrophilic aromatic substitution used in this synthetic route exhibited poor site-selectivity, leading to a low overall yield. Analogously, through the two-carbon homologation, compound **10b** was made available in one-step from relatively inexpensive 6-chloro-1-indanone **10a** (Scheme 3c). Moreover, simple transformations of the benzocycloheptanone moiety could afford a range of synthetically useful scaffolds, and here symmetrical benzocycloheptenone **1b** was used to avoid forming regioisomers. For instance, tetracyclic compound **54** was afforded in 88% yield via Fischer indole synthesis. Conjugated seven-membered enone **55** can be prepared in a good yield via ketone desaturation.[21] Treatment with sodium azide under different conditions delivered either eight-membered lactam **56** (77% yield) or tetrazole-fused 6-8-5 tricycle **57** (75% yield), in which the structure of **57** was unambiguously confirmed by X-ray crystallography (Scheme 3d).

Scheme 3. Application Potentials in the Syntheses of Bioactive Molecules



In summary, we disclose a two-carbon ring expansion method that inserts ethylene into relatively unstrained C–C bonds in 1-indanones, which offers a straightforward but strategically distinct approach for preparing benzocycloheptenones. The reaction is chemoselective, scalable and redox-neutral, which could be used to simplify the syntheses of benzocycloheptene-derived bioactive compounds. Efforts on extending the reaction scope to other cyclic ketones and unsaturated coupling partners,[22] as well as detailed mechanistic studies, are ongoing.

ASSOCIATED CONTENT

Supporting Information Experimental procedures; crystallographic data of **46b** and **57**; spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

gbdong@uchicago.edu

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This project was supported by NIGMS (R01GM109054). We thank Mr. Ki-Young Yoon for X-ray crystallography and thank Dr. Jun Zhu for checking the experiment. Chiral Technologies is acknowledged for their generous donation of chiral HPLC columns. We also thank Umicore AG & Co. KG for generous donation of rhodium salts.

REFERENCES

(1) For recent reviews of ring expansion reactions, see: (a) Hesse, M. *Ring Enlargement in Organic Chemistry*. VCH: Weinheim, Germany, 1991. (b) Roxburgh, C. J. Syntheses of Medium Sized Rings by Ring Expansion Reactions. *Tetrahedron* **1993**, *49*, 10749–10784. (c) Kantorowski, E. J.; Kurth, M. J. Expansion to Seven-membered Rings. *Tetrahedron* **2000**, *56*, 4317–4353. (d) Donald, J. R.; Unsworth, W. P. Ring-expansion Reactions in the Synthesis of Macrocycles and Medium-sized Rings. *Chem. Eur. J.* **2017**, *23*, 8780–8799.

(2) For a recent review, see: Candeias, N. R.; Paterna, R.; Gois, P. M. P. Homologation Reaction of Ketones with Diazo Compounds. *Chem. Rev.* **2016**, *116*, 2937–2981.

(3) Dowd, P.; Zhang, W. Free Radical-mediated Ring Expansion and Related Annulations. *Chem. Rev.* **1993**, *93*, 2091–2115.

(4) (a) Lennon, M.; McLean, A.; McWatt, I.; Proctor, G. R. Azabenzocycloheptenones. Some Substitution Reactions in Tetrahydro-l-benzazepin-5-ones. *J. Chem. Soc., Perkin Trans. I* **1974**, 1828–1833. (b) Frew, A. J.; Proctor, G. R. Ring-expansion of Carbocyclic π-Ketoesters with Acetylenic Esters. *J. Chem. Soc., Perkin Trans. I* **1980**, 1245–1250.

(5) Kuninobu, Y.; Kawata, A.; Kazuhiko, T. Efficient Catalytic Insertion of Acetylenes into a Carbon−carbon Single bond of Nonstrained Cyclic Compounds under Mild Conditions. *J. Am. Chem. Soc.* **2006**, *128*, 11368–11369.

(6) Caubere, P.; Guillaumet, G.; Mourad, M. S. Synthese Generale de Benzocyclenones Non Substituees; Mecanisme de Condensation du Benzyne Surles Enolates de Cetones. *Tetrahedron* **1973**, *29*, 1857–1863.

(7) Tambar, U. K.; Stoltz, B. M. The Direct Acyl-alkylation of Arynes. *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341.

(8) (a) Rybtchiski, B.; Milstein, D. Metal Insertion into C−C Bonds in Solution. *Angew. Chem. Int. Ed.* **1999**, *38*, 870–883. (b) Souillart, L.; Cramer, N. Catalytic C–C bond Activations via Oxidative Addition to Transition Metals. *Chem. Rev.* **2015**, *115*, 9410−9464. (c) Murakami, M.; Ishida, N. Potential of Metal-catalyzed C–C Single Bond Cleavage for Organic Synthesis. *J. Am. Chem. Soc.* **2016**, *138*, 13759–13769. (d) Kim, D.-S.; Park, W.-J.; Jun, C.-H. Metal–organic Cooperative Catalysis in C–H and C–C Bond Activation. *Chem. Rev.* **2017**, *117*, 8977–9015.

(9) (a) Fumagalli, G.; Stanton, S.; Bower, J. F. Recent Methodologies That Exploit C–C Single-Bond Cleavage of Strained Ring Systems by Transition Metal Complexes. *Chem. Rev.* **2017**, *117*, 9404–9432. (b) Chen, P.; Billett, B.; Tsukamoto, T.; Dong, G. "Cut and Sew" Transformations via Transition-metal-catalyzed Carbon–Carbon Bond Activation. *ACS Catal.* **2017**, *7*, 1340–1360.

(10) (a) Murakami, M.; Amii, H.; Ito, Y. Selective Activation of Carbon−Carbon Bonds next to a Carbonyl Group. *Nature* **1994**, *370*, 540−541. (b) Jun, C.-H.; Lee, H. Catalytic Carbon−Carbon Bond Activation of Unstrained Ketone by Soluble Transition-Metal Complex. *J. Am. Chem. Soc.* **1999**, *121*, 880−881. (c) Chen, F.; Wang, T.; Jiao, N. Recent Advances in Transition-metal-catalyzed Functionalization of Unstrained Carbon–Carbon Bonds. *Chem. Rev.* **2014**, *114*, 8613–8661. (d) Song, F.; Gou, T.; Wang, B.-Q.; Shi, Z.-J. Catalytic Activations of Unstrained C–C Bond Involving Organometallic Intermediates. *Chem. Soc. Rev.* **2018**, *47*, 7078–97115.

(11) For examples on two-carbon ring expansion via transition metal-catalyzed C−C activation of highly strained ketones with activated olefins or alkynes, see: (a) Kondo, T.; Nakamura, A.; Okada, T.; Suzuki, N.; Wada, K.; Mitsudo, T.-a. Ruthenium-catalyzed Reconstructive Synthesis of Cyclopentenones by Unusual Coupling of Cyclobutenediones with Alkenes Involving Carbon−Carbon Bond Cleavage. *J. Am. Chem. Soc.* **2000**, *122*, 6319−6320. (b) Kondo, T.; Taguchi, Y.; Kaneko, Y.; Niimi, M.; Mitsudo, T.-a. Ru- and Rh-catalyzed C−C Bond Cleavage of Cyclobutenones: Reconstructive and Selective Synthesis of 2-Pyranones, Cyclopentenes, and Cyclohexanones. *Angew. Chem. Int. Ed.* **2004**, *43*, 5369−5372. (c) Kondo, T.; Niimi, M.; Nomura, M.; Wada, K.; Mitsudo, T.-a. Rhodium-catalyzed Rapid Synthesis of Substituted Phenols from Cyclobutenones and Alkynes or Alkenes via C–C Bond Cleavage. *Tetrahedron Lett.* **2007**, *48*, 2837−2839. (d) Juliá-Hernández, F.; Ziadi, A.; Nishimura, A.; Martin, R. Nickel-catalyzed Chemo-, Regio- and Diastereoselective Bond Formation through Proximal C−C Cleavage of Benzocyclobutenones. *Angew. Chem. Int. Ed.* **2015**, *54*, 9537−9541.

(12) Tobisu, M.; Chatani, N. Catalytic Reactions Involving the Cleavage of Carbon–Cyano and Carbon–Carbon Triple Bonds. *Chem. Soc. Rev.* **2008**, *37*, 300–307.

(13) Though not ring expansion reactions, some related examples are: (a) Dreis, A. M.; Douglas, C. J. Catalytic Carbon−Carbon σ Bond Activation: An Intramolecular Carbo-acylation Reaction with Acylquinolines. *J. Am. Chem. Soc.* **2009**, *131*, 412−413. (b) Wentzel, M. T.; Reddy, V. J.; Hyster, T. K.; Douglas, C. J. Chemoselectivity in Catalytic C−C and C−H Bond Activation: Controlling Intermolecular Carboacylation and Hydroarylation of Alkenes. *Angew. Chem. Int. Ed.* **2009**, *48*, 6121−6123. (c) Rong, Z.-Q.; Lim, H. N.; Dong, G. Intramolecular Acetyl Transfer to Olefins via Catalytic C−C Bond Activation of Unstrained Ketones. *Angew. Chem. Int. Ed*. **2018**, *57*, 475−479.

(14) (a) Hu, A.; Chen, Y.; Guo, J.-J.; Yu, N.; An, Q.; Zuo, Z. Cerium-Catalyzed Formal Cycloaddition of Cycloalkanols with Alkenes through Dual Photoexcitation. *J. Am. Chem. Soc.* **2018**, *140*, 13580−13585. (b) Zhao, K.; Yamashita, K.; Carpenter, J. E.; Sherwood, T. C.; Ewing, W. R.; Cheng, P. T. W.; Knowles, R. R. Catalytic Ring Expansions of Cyclic Alcohols Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2019**, *141*, 8752−8757.

(15) Mo, F.; Dong, G. Regioselective Ketone α-Alkylation with Simple Olefins via Dual Activation. *Science* **2014**, *345*, 68–72.

(16) Itooka, R.; Iguchi, Y.; Miyaura, N. Rhodium-catalyzed 1,4-Addition of Arylboronic Acids to α, β-Unsaturated Carbonyl Compounds: Large Accelerating Effects of Bases and Ligands. *J. Org. Chem.* **2003**, *68*, 6000–6004.

(17) Xia, Y.; Lu, G.; Liu, P.; Dong, G. Catalytic Activation of Carbon-Carbon Bonds in Cyclopentanones. *Nature* **2016**, *539*, 546–550.

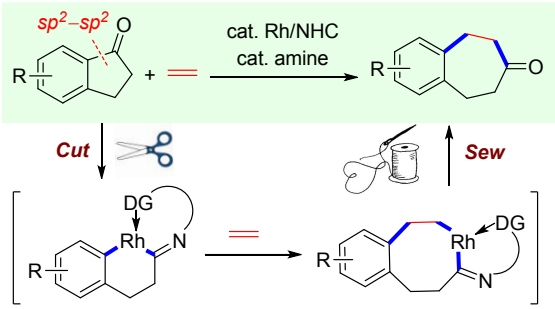
(18) Boussard, M.-F.; Guette, J. P.; Wierzbicki, M.; Beal, P.; Fournier, J.; Boulanger, M.; Della-Zuanad, O.; Duhault, J. Preparation and Pharmacological Profile of 2-Trifluoromethyl-benzo(8,9)-1,3-diaza-spiro(4,6)-undeca-2,8-diene and Its Enantiomers As New Anti-obesity Agents. *Arzneim.-Forsch./Drug Res*. **2000**, *50*, 1084–1092.

(19) Gingrich, D. E; Lisko, J. G.; Curry, M. A.; Cheng, M.; Quail, M.; Lu, L.; Wan, W.; Albom, M. S.; Angeles, T. S.; Aimone, L. D.; Curtis Haltiwanger, R.; Wells-Knecht, K.; Ott, G. R.; Ghose, A. K.; Ator, M. A.; Ruggeri, B.; Dorsey, B. D. Discovery of an Orally Efficacious Inhibitor of Anaplastic Lymphoma Kinase. *J. Med. Chem.* **2012**, *55*, 4580−4593.

(20) Gawaskar, S.; Temme, L.; Schreiber, J. A.; Schepmann, D.; Bonifazi, A.; Robaa, D.; Sippl, W.; Strutz-Seebohm, N.; Seebohm, G.; Wünsch, B. Design, Synthesis, Pharmacological Evaluation and Docking Studies of Glun2b-Selective NMDA Receptor Antagonists with a Benzo[7]annulen-7-amine Scaffold. *ChemMedChem* **2017**, *12*, 1212−1222.

(21) Albrecht, S.; Al-Lakkis-Wehbe, M.; Orsini, A.; Defoin, A.; Pale, P.; Salomon, E.; Tarnus, C.; Weibel, J.-M. Amino-benzosuberone: A Novel Warhead for Selective Inhibition of Human Aminopeptidase-N/CD13. *Bioorg. Med. Chem.* **2011**, *19*, 1434–1449.

(22) Use of non-ethylene olefins or saturated cyclopentanones is challenging at this initial stage, likely due to a slow migratory insertion step.


sp2–sp2
O
R
+
cat. Rh/NHC
cat. amine
R
O
Cut
Sew
DG
Rh
N
R
DG
Rh
N
R