Organic Syntheses

Discussion Addendum for:

Rh(I)-Catalyzed Allenic Pauson–Khand Reaction

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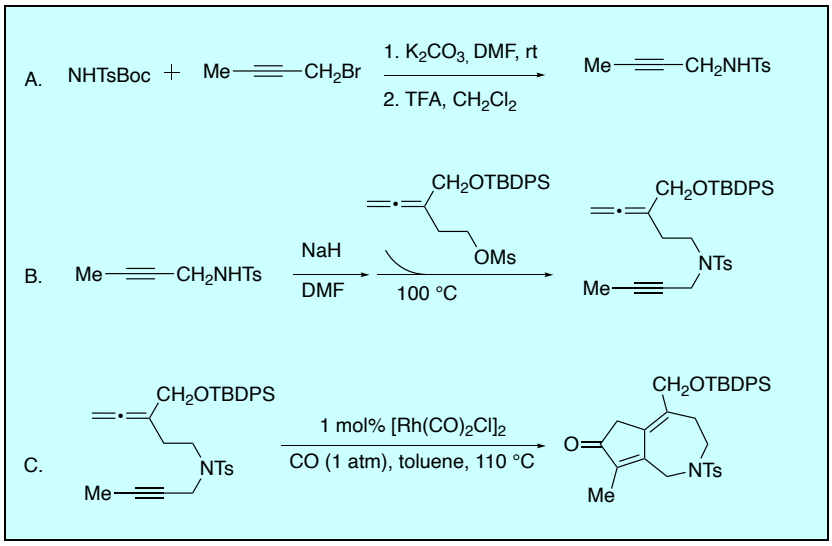
Original Article: Burchick, Jr. J.E.; Wells, S.M.; Brummond, K.M.; Org. Synth. ***2017***, *94*, 123–135.



The intramolecular Rh(I)-catalyzed *allenic* Pauson–Khand reaction (APKR) is a powerful synthetic method for constructing ring-fused cyclopentenones. Our group's interest in the APKR extends back to 1992 when we submitted original research proposals for applications to academic positions. At that time, there were two independent reports of allenes being used in the PKR–only Aumann's demonstrated the feasibility of an *intermolecular* Fe(0)-catalyzed process.[2a] In 1994, Narasaka demonstrated three examples of an intramolecular APKR using *allenyl sulfides* and an iron carbonyl complex.[3] In 1995, we reported a successful *intramolecular* APKR reaction of *unfunctionalized allenes*[4] using stoichiometric $Mo(CO)_6$–a transition metal complex that had recently been reported by Jeong for the enyne PKR.[5]

DOI: 10.15227/orgsyn.100.0029

Also, in 1995, Narasaka reported trace amounts of a cycloadduct for a simple allene-yne using Fe(0)-catalysis,[6] and Cazes successfully demonstrated an *intermolecular* APKR using $Co_2(CO)_8$ and NMO.[7] In July of 2000, an undergraduate researcher, Brenden Rickards, working in our lab demonstrated a Rh(I)-catalyzed APKR using $[Rh(CO)_2Cl]_2$–a catalyst previously reported by Narasaka for an *enyne* PKR.[8] This result established for the first time that a Rh(I) transition metal catalyst afforded complete selectivity for the distal double bond of the allene whereas $Mo(CO)_6$ afforded selectivity for the proximal double bond affording a different constitutional isomer.

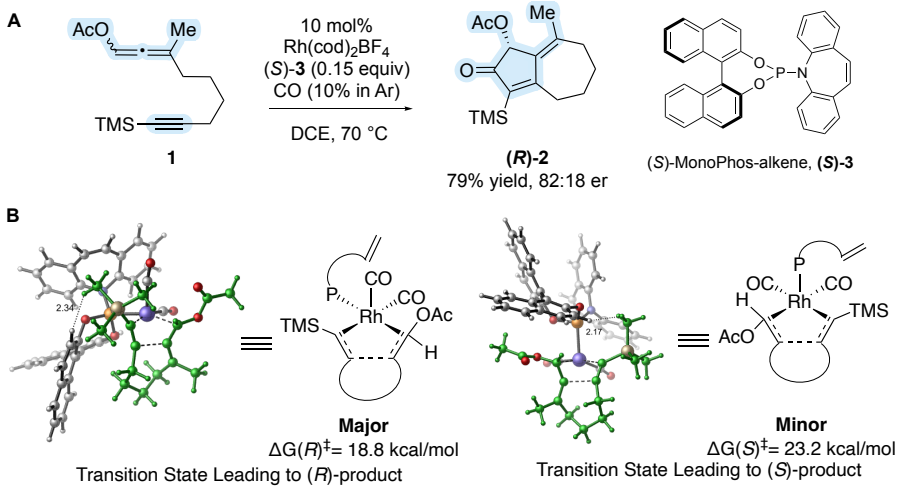
In 2001, while our group was expanding the scope of this unprecedented, catalyst-controlled double bond selectivity for Mo(0) and Rh(I) on a number of alkynyl allenes,[9a,b] including an APKR approach to the natural product guanacastepene A,[9c] Narasaka published a manuscript describing the scope and limitations of $[Rh(CO)_2Cl]_2$-catalyzed *enyne* PKR where he also described the reaction of a single alkynyl allene showing that the reaction occurred with the distal double bond.[10] In early 2002, Dr. Hongfeng Chen, a postdoctoral fellow in our group, demonstrated that *unfunctionalized allenes* could be used in the APKR to form [5,7]-ring systems by exploiting the Rh(I) catalyst controlled double bond selectivity,[9b] and Mukai reported that *allenyl sulfones* could also be employed to prepare [5,7]-ring systems.[11] This independent co-discovery of a metal catalyzed control of double bond selectivity to form seven-membered rings has inspired our group and others in the application of this powerful method for synthesizing complex molecular compounds.

This discussion addendum informs on a few recent advances made regarding expansion of the scope of the APKR and its application to target-oriented synthesis. We have divided this addendum into the following topics: Asymmetric Allenic Pauson–Khand Reaction; Transfer of Allene Axial Chirality in APKR; Rh(I)-Catalyzed APKR Double Bond Selectivity, Mechanism, and Reaction Optimization; and APKR Approach to Natural Products and Other Bioactive Compounds.

Asymmetric Allenic Pauson–Khand Reaction

Burrows, Jesikiewicz, Liu, and Brummond recently showed that through a combination of experiment and theory *racemic* allene-yne **1** could be transformed to bicyclo[5.3.0]decadienone **2** in 79% yield with an 82:18 enantiomeric ratio (er) using a chiral non-racemic Rh(I) catalyst (Scheme 1A).[12] A transformation made possible through rapid scrambling of the axial

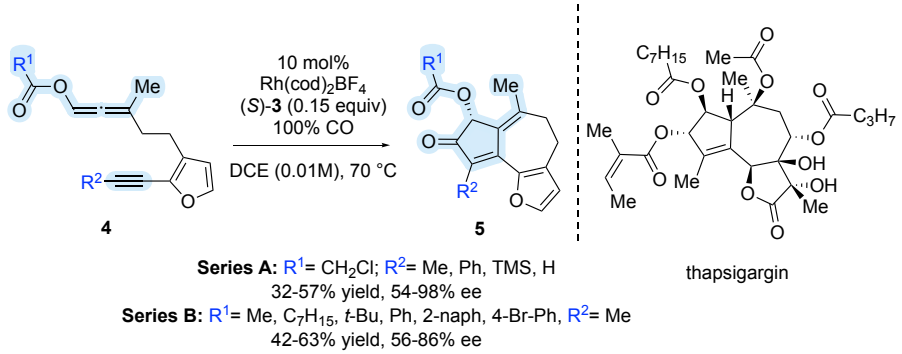
chirality of the allenyl acetate under the reaction conditions and selective reaction of one enantiomer. This represents the first Rh(I)-catalyzed asymmetric carbocyclization reaction of this type outside of a 1,6-enyne. In contrast to more traditional catalyst design strategies involving high throughput experimentation, high enantioselectivity was realized after testing only seven different chiral catalysts using wet-lab experimentation–representing an immense savings in resources. The key to our success was a deep mechanistic understanding where experiment and computation informed selection of the next catalyst. For example, activation barriers for the enantioselectivity-determining oxidative cyclization step were computed to reveal the origins of catalyst reactivity ($\Delta G^{\ddagger}$) and selectivity ($\Delta\Delta G^{\ddagger}$) and experiments in a flask were performed to test catalyst efficiency (yield) and stereo-directing ability (er) (Scheme 1B). This mechanistically complex process involving a dynamic kinetic asymmetric transformation (DyKAT) is a powerful demonstration of catalyst design made possible through the tight integration of experiment and computation.



Scheme 1. DyKAT process realized in the asymmetric APKR

Deihl and Brummond expanded the asymmetric APKR to include furanyl tethered allene-ynes to access the core ring system present in the guaianolide natural product thapsigargin (Tg).[13] The APKR of several furanyl tethered allene-ynes **4** afforded products **5** in good yields with high

enantioselectivities when using the chiral monodentate ligand **S-(3)** (Scheme 2). *Interestingly, while several allenyl carboxy groups were examined (Series B), only allenyl chloroacetates afforded products in upwards of 98% ee (Series A)!* The group on the terminus of the alkyne played a key factor in the yield and enantioselectivity of the APKR with a terminal alkyne affording product in 32% yield and 54% ee and a phenyl alkyne affording product in 46% yield and 98% ee. The methyl-substituted alkyne with an allenyl chloroacetate afforded product in 57% yield and 94% ee. DFT calculations of this reaction show a favorable π-π interaction between the furanyl ring and phosphoramidite ligand that lowers the energy of the transition state leading to the major product. The transition state leading to the minor enantiomer, lacks this favorable π-π interaction.[13]



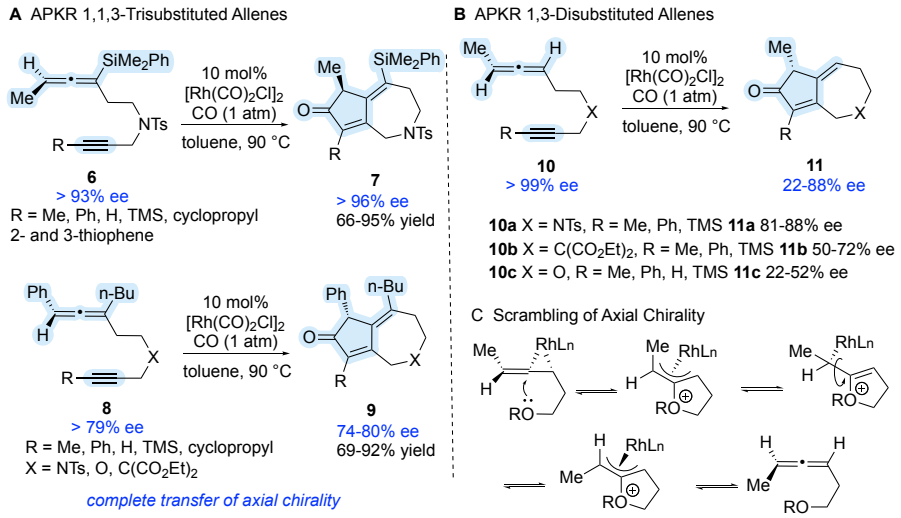
Series A: R^1= CH_2Cl; R^2= Me, Ph, TMS, H
32-57% yield, 54-98% ee
Series B: R^1= Me, C_7H_{15}, *t*-Bu, Ph, 2-naph, 4-Br-Ph, R^2= Me
42-63% yield, 56-86% ee

Scheme 2. APKR of furan-tethered allene-yne affording the Tg core

Transfer of Allene Axial Chirality in the APKR

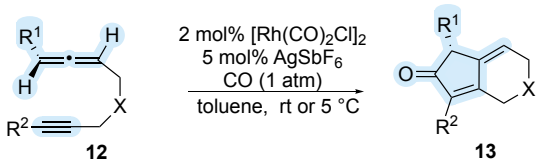
The transfer of chiral information from the allene to the cyclocarbonylation product for the APKR of non-racemic allenes has also been demonstrated. Grillet and Brummond showed that reacting enantioenriched *1,3,3-trisubstituted* allenes **6** and **8** to the Rh(I)-catalyzed APKR afforded bicyclo[5.3.0]decadienone products **7** and **9** with complete transfer of chiral information for 17 substrates (Scheme 3A).[14] Success was realized for allene-ynes having variety of groups on the alkyne terminus (Me, Ph, H, TMS, 2-, 3-thiophenyl, cyclopropyl), allene (Ph, Me, n-Bu, $SiMe_2Ph$), and tether (X = NTs, $C(CO_2Et)_2$, O). In the case of *1,3-disubstituted* allenes, the degree of chirality transferred depended upon the tether identity and the alkynyl group (Scheme 3B). For example, allene-yne **10a** (X = NTs, R= TMS) afforded **11a** in 83% yield in 84% ee, whereas allene-yne **10b** (X = $C(CO_2Et)_2$,

R= TMS) and **10c** (X = O, R= TMS) provided the products **11b** and **11c** in good yield but with 50% and 22% ee, respectively. Reaction monitoring using chiral HPLC analysis provided strong evidence for scrambling of the axial chirality of the allenyl precursor and not epimerization of the APKR product. Scrambling of the axial chirality of the allene is postulated to involve an intramolecular nucleophilic attack of the rhodium complexed allene by the heteroatom in the tether (Scheme 3C).[14]



Scheme 3. Transfer of allene axial chirality in the Rh(I)-catalyzed APKR to access bicyclo[5.3.0]decadienones enantioselectively

Ma and coworkers have shown that chiral non-racemic 1,3-disubstituted allenes **12** afford bicyclo[4.3.0]nonadienones **13** with complete transfer of chirality (Scheme 4).[15] Low reaction temperatures and silver salt additives were critical to the success of the preferred mechanistic pathway affording the cyclocarbonylation product. Higher temperatures in the absence of silver hexafluoroantimonate afforded the corresponding cross conjugated triene via a formal Alder-ene process. High yields and enantiospecificities were reported for the APKR of ten allene-ynes.



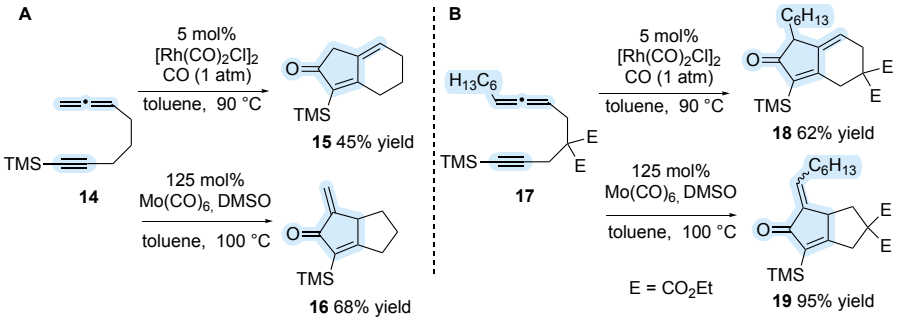
X = NTs, R^1 = n-Pr, R^2 = Ph, Ar, CH_3, TMS 88-97% yield, 90-94% ee
X = $C(CO_2Et)_2$, R^1 = Cy, R^2 = Ph, CH_3, TMS 64-96% yield, 93-96% ee
X = O, R^1 = n-Pr, CH_2Bn, R^2 = CH_3 81-85% yield, 91-92% ee

complete transfer of axial chirality

Scheme 4. Transfer of allene axial chirality in the Rh(I)-catalyzed APKR to access chiral non-racemic bicyclo[4.3.0]nonadienones

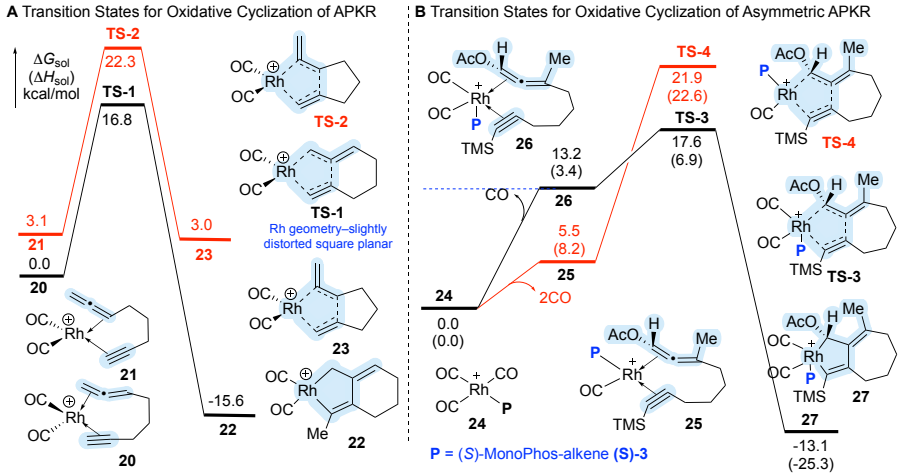
Rh(I)-Catalyzed APKR Double Bond Selectivity, Mechanism, and Reaction Optimization

Rhodium and molybdenum are the most used transition metals for catalyzing the *intramolecular* APKR with each showing a different reactivity preference towards the double bonds of the allene. For example, rhodium biscarbonyl chloride dimer $[Rh(CO)_2Cl]_2$ reacts preferentially with the distal double bond of the allenes **14** and **17** to afford products **15** and **18**, while molybdenum hexacarbonyl $[Mo(CO)_6]$ reacts with the proximal double bond to afford **16** and **19**. This transition metal controlled selectivity has been used to form either α-methylene cyclopentenone or 4-alkylidene cyclopentenone products (Scheme 5).[9a,b]



Scheme 5. Catalyst-controlled double bond selectivity for APKR

The preferential reactivity of one double bond over the other has been described using Density Functional Theory (DFT) where calculations show the *metal geometry in the oxidative cyclization (OxCycl) transition state–the rate determining step in the reaction energy profile–as a key control element*.[16] For example, the rhodium catalyzed reaction shows an early transition state (TS) with all low energy TS structures for the OxCycl step having a four-coordinate rhodium metal complexed to the distal allene double bond (**TS-1**) and adopting a slightly distorted square planar geometry to afford metallocycle **22** (Scheme 6A). Whereas all low energy TS structures for the OxCycl step for the five-coordinate molybdenum having a trigonal bipyramidal geometry show the proximal double bond as complexing to the axial position due to conformational constraints (not shown) The CO insertion step was found to be the rate-determining step for molybdenum; however, the free energy of this step was lower than that for the OxCycl of the metal to the distal double bond of the allene (not shown).[16]

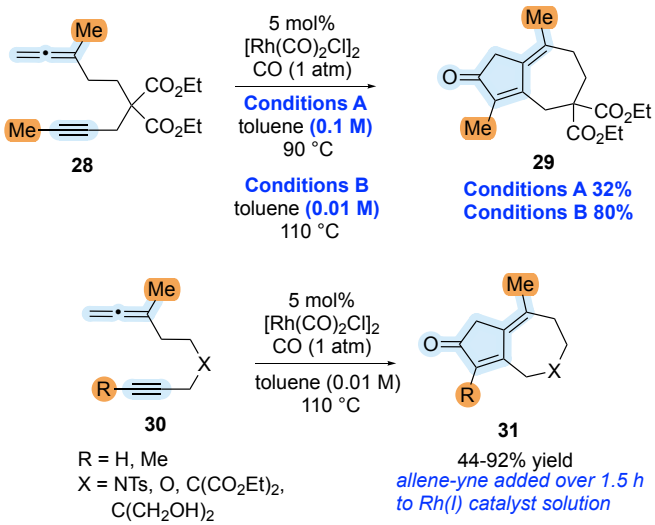


Scheme 6. DFT studies on the oxidative cyclization step of the Rh(I)-catalyzed APKR and asymmetric APKR

The computed reaction energy profile for the asymmetric Rh(I)-catalyzed APKR shows the oxidative cyclization step as stereo- but not rate-determining (Scheme 6B).[12] Complexation of the allene-yne to the resting state of the catalyst **24** occurs with the loss of two CO's to afford **25** having a square planar geometry which is 7.7 kcal/mol lower in energy than the square-based pyramidal complex **26**, which results from the loss of one CO

(Scheme 6B). Nonetheless, the OxCycl step for the five-coordinate **TS-3** has a lower calculated activation barrier than the four-coordinate **TS-4** by 4.3 kcal/mol. Stabilization of **TS-3** (18-electron) over **TS-4** (16-electron) by the additional CO ligand was attributed to the acetoxy group on the allene. Interestingly, DFT predicts that both reaction pathways afford the same enantiomeric product. Whereas, in the Rh(I)-catalyzed PKR of enynes, the reaction pathways involving the four- and five-coordinate complexes afford different enantiomeric products.[17]

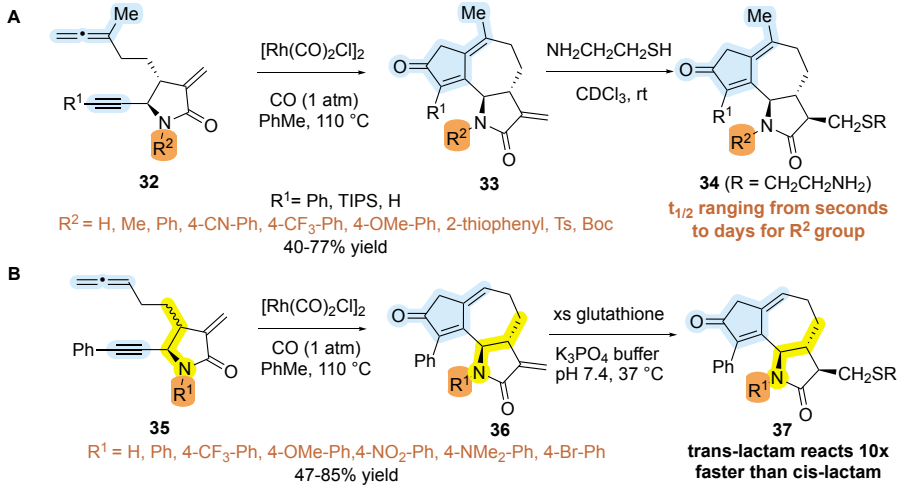
During application of the APKR involving an early-stage installation of C4 and C10 methyl groups present in the 6,12-guaianolides, a byproduct was formed in substantial quantities for methyl substituted allenes and alkynes as well as terminal alkynes. ^{1}H NMR spectroscopy and ESI mass spectrometry analysis supported a byproduct resulting from a dimerization of the allene-yne precursor **28**. Performing the reaction by dropwise addition of allene-ynes **28** to the Rh(I) catalyst under Conditions B (0.01 M) gave an 80% yield of **29**, much higher than Conditions A which afforded **29** in 32% yield**.** High yields were afforded for nearly all substrates examined when using these modified conditions (Scheme 7).[18] These same conditions were used for APKR protocol published in Organic Syntheses on a 6-g scale in 88% yield using 1 mol% of $[Rh(CO)_2Cl]_2$.[19]



Scheme 7. Optimized conditions for Rh(I)-catalyzed APKR

APKR Approach to Natural Products and Other Bioactive Compounds

The APKR is a key step in the synthesis of the core structure of several natural products and other bioactive compounds. Jackson and Brummond demonstrated that the Rh(I)-catalyzed APKR of lactam tethered allene-ynes **32** enabled rapid access to several guaianolide analogs **33**, which are equipped with an electronically tunable covalent reactive group, an α-methylene–γ-lactam (Scheme 8A).[20] These analogs were designed for tunable thiol reactivity thus enabling an understanding of structure activity relationships for bioactive compounds with an α-methylene–γ-lactone that are otherwise too reactive. Reaction of compound **33** with excess cysteamine showed thiol addition with half-lives ranging from seconds to days depending upon the electronics of the R^2 group.

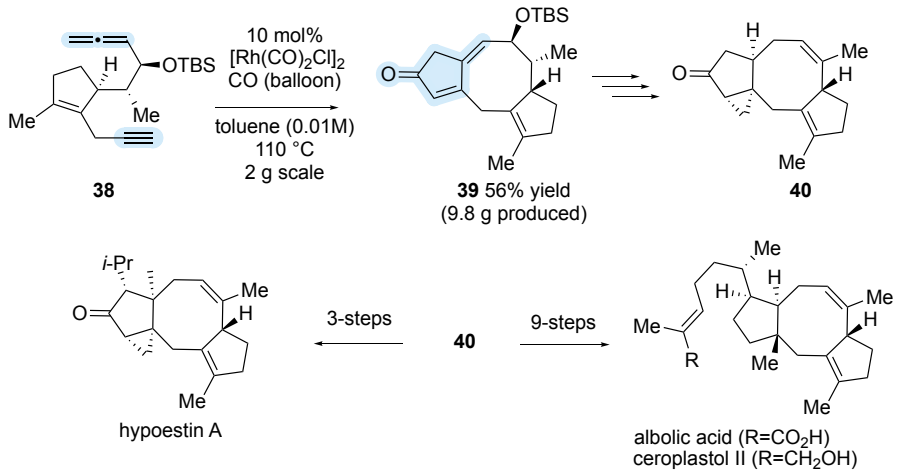


Scheme 8. APKR approach to guaianolide analogs with tunable thiol reactivity and bioactivity

Dempe and Brummond have shown that reaction of cis and trans-annulated lactams **35** to the Rh(I) conditions afforded APKR products **36** in yields ranging from 47–85% (Scheme 8B). Reaction times for the APKR varied considerably across this series of lactams with the trans-allene-ynes reacting 2–4× faster than the cis-isomers. Furthermore, lactam **36** reacted with excess glutathione 10x faster than cis-annulated lactams under biologically relevant conditions (Scheme 8B).[21] DFT calculations revealed this higher reactivity of

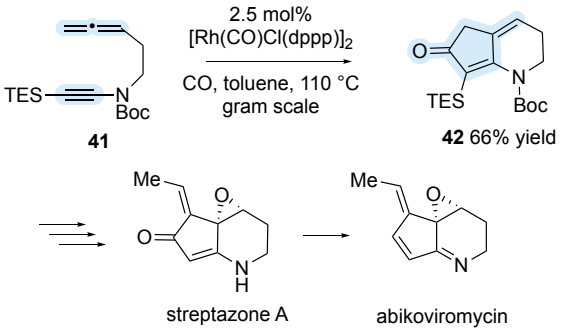
the trans-annulated stereoisomer is due to release of ring strain in the thiol-Michael addition transition state. These studies support the α-methylene-γ-lactam as a novel covalent reactive group and its value in the rational design of inhibitors by having thiol reactivity within a range of the widely used and therapeutically proven acrylamide.[21,22]

In 2022, the Li group reported the first use of APKR of an unfunctionalized allene **38** to form an eight-membered-ring to achieve the asymmetric total synthesis of hypoestin A, albolic acid, and ceroplastol II from the common intermediate **40** (Scheme 9).[23,24] Several rhodium catalysts and additives were screened identifying the standard APKR conditions ([$(Rh(CO)_2Cl]_2$, toluene, CO balloon, 110 °C) as optimal for achieving the 5,8,5-ring system **39** in 56% yield. The APKR could be performed reliably on a 2-g scale and the generality of the method was demonstrated on ten additional substrates with various functionality affording 5,8,5-ring systems in 40–86% yields.



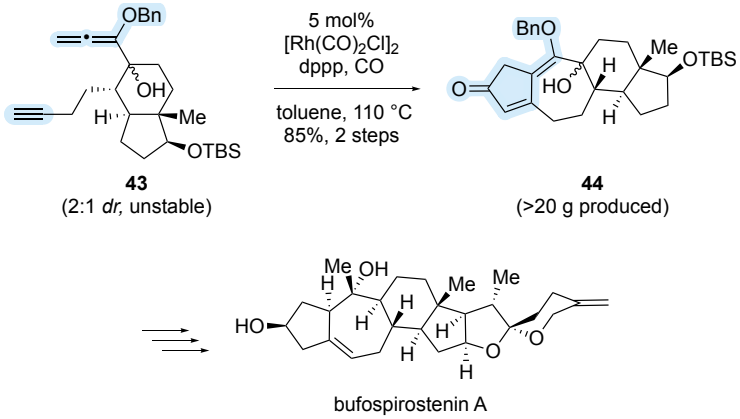
Scheme 9. APKR approach to a 5,8,5-ring system

In 2021, the Poulsen group reported an APKR on an allene-ynamide **41** to deliver the azabicyclo[4.3.0] core **42** via reaction with the distal double bond of the allene in 66% yield. This reaction was performed on a gram-scale using either a constant flow of CO (10% CO mixed with 90% argon) or COgen–a bench stable CO precursor–in a two-chamber system to generate carbon monoxide in situ. Compound **42** was taken on to afford concise syntheses of streptazone A, and abikoviromycin (Scheme 10).[25]



Scheme 10. APKR approach to 5,6-ring system–Total synthesis of streptazone A and abikoviromycin

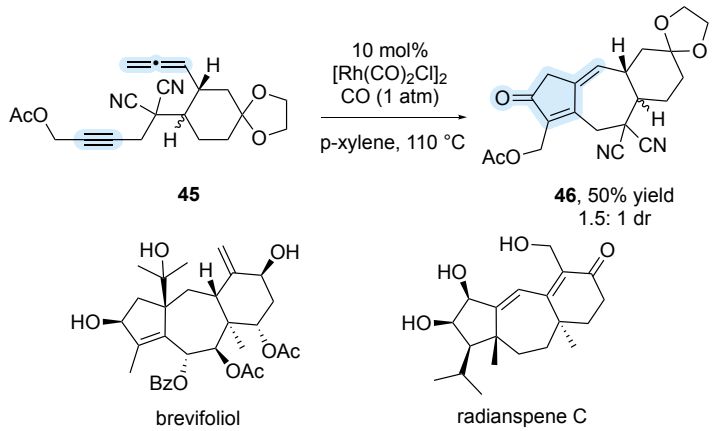
The Li group used an APKR of benzyloxyallene-yne **43** to construct the 5,7,6,5- tetracyclic ring system **44** in the total synthesis of sterically compact bufospirostenin A (Scheme 11).[26] Extensive experimentation revealed that the ligand additive 1,3-bis(diphenylphosphino)propane (dppp) and the syringe pump addition of allene-yne to the rhodium catalyst afforded the desired product in 85% yield as a 2:1 mixture of diastereomers separable by column chromatography on large scale (>20 g).



Scheme 11. APKR approach to 5,7,6,5-ring system

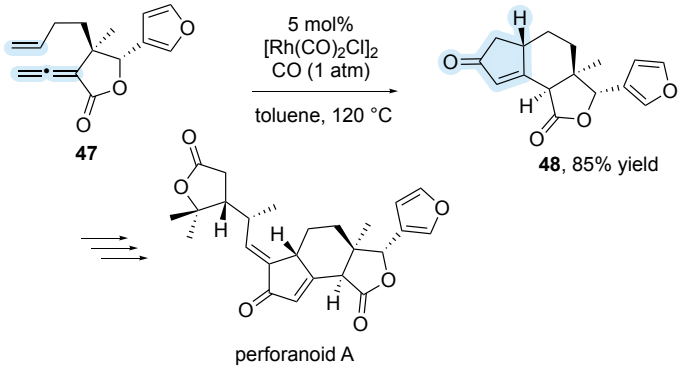
In 2017, the Grenning group combined a deconjugative propargylation and a Cope rearrangement to afford **45**, which was reacted to the Rh(I)-catalyzed APKR to rapidly assemble the 6,7,5-ring system of **46**–a terpenoid

core represented in several natural products including brevifoliol and radianspene C (Scheme 12).[27]



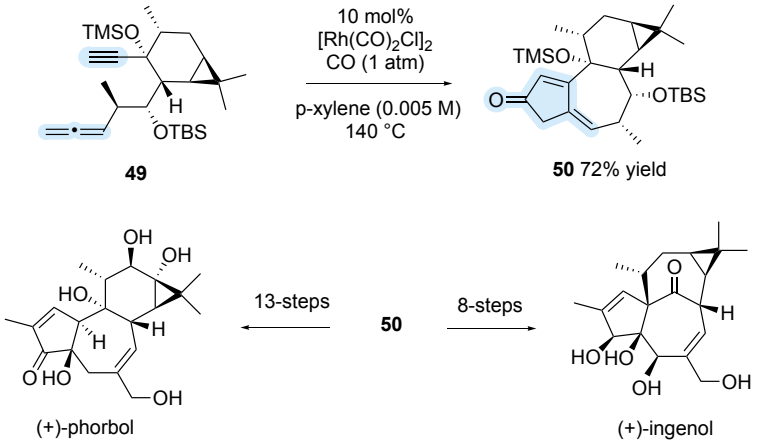
Scheme 12. Rapid assembly of 6,7,5-ring system of a terpenoid core

The Yang group reported using ene-allene **47** in a Rh(I)-catalyzed cyclocarbonylation reaction to from a tricyclic core **48** as a single isomer that was used to complete the total synthesis of perforanoid A (Scheme 13).[28] The use of an ene-allene in this transformation was the result of an alkyne isomerization prior to the cyclocarbonylation which ultimately afforded the desired product as that of an enyne due to isomerization of the double bond into conjugation with the ketone. While not technically an APKR, the high yielding cyclocarbonylation of ene-allene **47** demonstrates the extraordinary scope, and potential, of the Rh(I)-catalysis conditions.



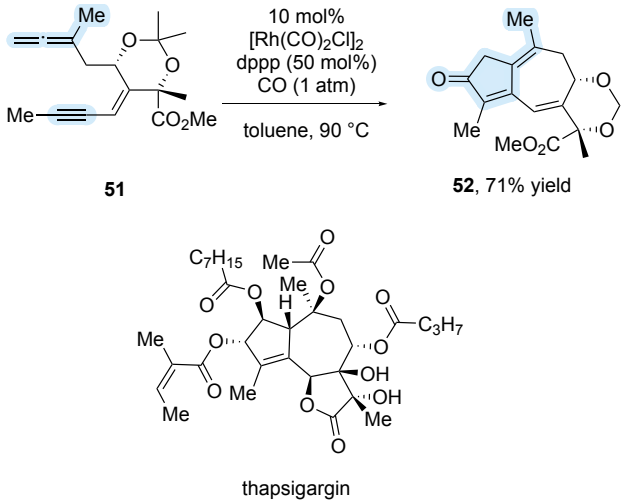
Scheme 13. Cyclocarbonylation of ene-allene

Baran and coworkers have demonstrated the APKR of allene-yne **49** to prepare **50** which was used in the total syntheses of ingenol and phorbol (Scheme 14).[29, 30] Protection of the diol as silyl ethers, high temperature, and high dilution conditions were essential to this high yielding APKR on gram scale.



Scheme 14. APKR approach to a 5,7-ring system

Ardisson and coworkers have shown that a Rh(I)-catalyzed APKR performed using racemic allene-yne **51** affords the 5,7-ring system of the tricyclic **52** in 71% yield in an approach to the natural product thapsigargin (Scheme 15).[31] The structure of **52** was confirmed by X-ray crystallography. The APKR conditions were modified to include 1,3-bis(diphenylphosphino)propane (dppp). These conditions have previously been demonstrated to give a dramatic yield enhancement for some allene-ynes, including: allenyl carbamates, and benzyl and para-methoxy benzyl ethers. Interestingly, the catalyst and ligand were added successively to the allene-yne whereas most protocols involve the addition of the allene-yne to the Rh(I)-catalyst.[32, 33]



Scheme 15. APKR approach to a 5,7-ring system of thapsigargin

In summary, the APKR has played an important role in target-oriented organic synthesis. And, amongst different metals including Fe, Mo, and Co being used as the catalyst in APKR, Rh is the most prominent in the recent advances in this area. Finally, for additional insight and information on the APKR several reviews have been published.[34]

References

1. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA, 15260. Email: kbrummon@pitt.edu; orchid.org/0000-0003-3595-6806. We thank the University of Pittsburgh for financial support.
2. (a) Aumann, R.; Weidenhaupt H.-J. Organische synthesen mit übergangsmetallkomplexen, 19 ß-methylencyclopentenone durch templatgesteuerte [2 + 2 + 1]-cycloaddition von alkinen an allene und kohlenmonoxid mit eisencarbonyl. *Chem. Ber.* **1987**, *120*, 23–27, doi.org/10.1002/cber.19871200106; (b) See note 24 in, Pauson, P.L. The Khand reaction: A convenient and general route to a wide range of cyclopentenone derivatives. *Tetrahedron* **1985**, *41*, 5855–5860 citing unpublished results where 1,2-cyclononadiene reacted readily but the structure of the product was not firmly established.

3. Narasaka, K.; Shibata, T. Conversion of 1-(ω-alkynyl)-1,2-propadienyl sulfides to bicyclic dienones by the use of iron carbonyl complex. *Chem. Lett*. **1994**, 315. doi.org/10.1246/cl.1994.315
4. Kent, J. L.; Wan, H.; Brummond, K. M. A new allenic Pauson-Khand cycloaddition for the preparation of α-methylene cyclopentenones. *Tetrahedron Lett*. **1995**, *36*, 2407. doi.org/10.1016/0040-4039(95)00315-4
5. Jeong, N.; Lee, S. J.; Lee, B.Y.; Chung, K.Y. Molybdenium mediated preparation of cyclopentenones. *Tetrahedron Lett*. **1993**, *34*, 4027. doi.org/10.1016/S0040-4039(00)60607-X
6. Shibata, T.; Koga, Y.; Narasaka, K. Intra- and intermolecular allene–alkyne coupling reactions by the use of $Fe(CO)_4(NMe_3)$. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 911–919. doi.org/10.1246/bcsj.68.911
7. Ahmar, M.; Antras, F.; Cazes, B. Pauson-Khand reaction with allenic compounds I: Synthesis of 4-alkylidene-2-cyclopentenones. *Tetrahedron Lett*. **1995**, *36*, 4417–4420. doi.org/10.1016/0040-4039(95)00735-U
8. (a) Koga, Y.; Kobayashi, T.; Narasaka, K. Rhodium-catalyzed intramolecular Pauson-Khand reaction. *Chem. Lett*., **1998**, 249–250. doi.org/10.1246/cl.1998.249 (b) Independently, Jeong and coworkers reported an enyne PKR using *trans*-$[Rh(Cl)(CO)(dppp)]_2$, see: Jeong, N.; Lee, S.; Sung, B. K. Rhodium(I)-catalyzed intramolecular Pauson−Khand reaction. *Organometallics* **1998**, *17*, 3642–3644. doi.org/10.1021/om980410k
9. (a) Brummond, K.M.; Rickards, B.; Sill, P.C.; Geib, S.J. A silicon-tethered allenic Pauson–Khand reaction. *Tetrahedron Lett.* **2002**, *43*, 3735–3738. doi.org/10.1016/S0040-4039(02)00633-0; (b) Brummond, K. M.; Chen, H.; Fisher, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C; Geib, S.J . An allenic Pauson−Khand-type reaction: A reversal in π-bond selectivity and the formation of seven-membered rings. *Org. Lett*. **2002**, *4*, 1931–1934. doi.org/10.1021/ol025955w; (c) Brummond, K. M.; Gao, D. Unique strategy for the assembly of the carbon skeleton of guanacastepene A using an allenic Pauson−Khand-type reaction. *Org. Lett*. **2003**, *5*, 3491–3494. doi.org/10.1021/ol035322x
10. Kobayashi, T.; Koga, Y.; Narasaka, K. The rhodium-catalyzed Pauson–Khand reaction *J. Organomet. Chem.* **2001**, *624*, 73–87. doi.org/10.1016/S0022-328X(00)00835-4
11. Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M. Rh(I)-catalyzed intramolecular allenic Pauson−Khand reaction: construction of a bicyclo[5.3.0]dec-1,7-dien-9-one skeleton. *Org. Lett.* **2002**, *4*, 1755–1758. doi.org/10.1021/ol020051w

12. Burrows, L. C.; Jesikiewicz, L. T.; Lu, G.; Geib, S. J.; Liu, P.; Brummond, K. M. Computationally guided catalyst design in the Type I dynamic kinetic asymmetric Pauson–Khand reaction of allenyl acetates. *J. Am. Chem. Soc.* **2017**, *139*, 15022–15032. doi.org/10.1021/jacs.7b07121
13. Deihl, E. D.; Jesikiewicz, L. T.; Newman, L. J.; Liu, P.; Brummond, K. M., Rh(I)-catalyzed allenic Pauson–Khand reaction to access the thapsigargin core: Influence of furan and allenyl chloroacetate groups on enantioselectivity. *Org. Lett.* **2022**, *24*, 995–999. doi.org/10.1021/acs.orglett.1c03951
14. Grillet, F.; Brummond, K. M. Enantioselective synthesis of 5,7-bicyclic ring systems from axially chiral allenes using a Rh(I)-catalyzed cyclocarbonylation reaction. *J. Org. Chem.* **2013**, *78*, 3737–3754. doi.org/10.1021/jo4002432
15. Han, Y.; Zhao, Y.; Ma, S. Rhodium-catalyzed Pauson–Khand-type cyclization of 1,5-allene-alkynes: A chirality transfer strategy for optically active bicyclic ketones. *Chem. Eur. J.* **2019**, *25*, 9529–9533. doi.org/10.1002/chem.201900963
16. Bayden, A. S.; Brummond, K. M.; Jordan, K. D. Computational insight concerning catalytic decision points of the transition metal catalyzed [2 + 2 + 1] cyclocarbonylation reaction of allenes. *Organometallics* **2006**, *25*, 5204–5206. doi.org/10.1021/om0607503
17. Burrows, L. C.; Jesikowicz, L. T.; Liu, P.; Brummond, K. M. Mechanism and origins of enantioselectivity in the Rh(I)-catalyzed Pauson–Khand reaction: comparison of bidentate and monodentate chiral ligands. *ACS Catalysis* **2021**, *11*, 323–336. doi.org/10.1021/acscatal.0c03774
18. Wells, S. M.; Brummond, K. M. Conditions for a Rh(I)-catalyzed [2+2+1] cycloaddition reaction with methyl substituted allenes and alkynes. *Tetrahedron Lett*. **2015**, *56*, 3546–3549. doi.org/10.1016/j.tetlet.2015.01.075
19. Burchick. Jr., J. E.; Wells, S. M.; Brummond, K. M. Rh(I)-Catalyzed Allenic Pauson–Khand Reaction. *Org. Synth.* ***2017***, *94*, 123–135. doi: 10.15227/orgsyn.094.0123
20. Jackson, P. A.; Schares, H. A. M.; Jones, K. F. M.; Widen, J. F.; Dempe, D. P.; Cuellar, M. E.; Walters, M. A.; Harki, D. A.; Brummond, K. M. Synthesis of guaianolide analogues with a tunable α-methylene-γ-lactam electrophile and correlating bioactivity with thiol reactivity. *J. Med. Chem*. **2020**, *63*, 14951–14978. doi.org/10.1021/acs.jmedchem.0c01464
21. Dempe, D. P.; Ji, C.-L.; Liu, P.; Brummond, K. M. Thiol reactivity of N-aryl α-methylene-γ-lactams: influence of the guaianolide structure. *J. Org. Chem*. **2022**, 87, 11204–11217. doi.org/10.1021/acs.joc.2c01530

22. Erbay, T. G.; Dempe, D. P.; Godugu, B.; Liu, P.; Brummond, K. M. Thiol reactivity of N-aryl α-methylene-γ-lactams: a reactive group for targeted covalent inhibitor design. *J. Org. Chem*. **2021**, *86*, 11926–11936. doi.org/10.1021/acs.joc.1c01335
23. Wang, Y.-Q.; Xu, K.; Min, L.; Li, C. -C. Asymmetric total syntheses of hypoestin A, albolic acid, and ceroplastol II. *J. Am. Chem. Soc.* **2022**, *144*, 10162–10167. doi.org/10.1021/jacs.2c04633
24. Mukai and coworkers were the first to demonstrate the formation of an eight-membered ring using an allenyl sulfone in the APKR, see: Mukai, C.; Hirose, T.; Teremoto, S.; Kitagaki, S. Rh(I)-catalyzed allenic Pauson–Khand reaction: first construction of the bicyclo[6.3.0]undecadienone ring system. *Tetrahedron* **2005**, *61*, 10983–10994. doi.org/10.1016/j.tet.2005.08.088
25. Wørmer, G. J.; Villadsen, N. L.; Nørby, P.; Poulsen, T. B. Concise Asymmetric syntheses of streptazone A and abikoviromycin. *Angew. Chem., Int. Ed*. **2021**, *60*, 10521–10525. doi.org/10.1002/anie.202101439
26. Cheng, M.-J.; Zhong, L.-P.; Gu, C.-C.; Zhu, X.-J.; Chen, B.; Liu, J.-S.; Wang, L.; Ye, W.-C.; Li, C.-C. Asymmetric total synthesis of bufospirostenin A. *J. Am. Chem. Soc.* **2020**, *142*, 12602−12607. doi.org/10.1021/jacs.0c05479
27. Scott, S. K.; Grenning, A. J. An enyne Cope rearrangement enables polycycloalkane synthesis from readily available starting materials. *Angew. Chem., Int. Ed.* **2017**, *56*, 8125–8129. doi.org/10.1002/anie.201703186
28. Lv, C.; Tu, Q.; Gong, J.; Hao, X.; Yang, Z. Asymmetric total synthesis of (−)-perforanoid A. *Tetrahedron* **2017**, *73*, 3612–3621. doi.org/10.1016/j.tet.2017.03.072; Lv, C.; Yan, X.; Tu, Q.; Di, Y.; Yuan, C.; Fang, X.; Ben-David, Y.; Xia, L.; Gong, J.; Shen, Y.; Yang, Z.; Hao, X. Isolation and asymmetric total synthesis of perforanoid A. *Angew. Chem., Int. Ed*. **2016**, *55*, 7539–7543. doi.org/10.1002/anie.201602783
29. Jørgensen, L.; McKerrall, L. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. 14-Step synthesis of (+)-ingenol from (+)-3-carene. *Science* **2013**, *341*, 878–882. doi: 10.1126/science.1241606
30. Kawamura, S., Chu, H., Felding, J.; Baran, P. S. Nineteen-step total synthesis of (+)-phorbol. *Nature* **2016**, *532*, 90–93.
31. Sanogo, Y.; Othman, R.B.; Dhambri, S.; Selkti, M.; Jeuken, A.; Prunet, J.; Férézou, J.-P.; Ardisson, J.; Lannou, M. I.; Sorin, G. Ti(II) and Rh(I) complexes as reagents toward a thapsigargin core. *J. Org. Chem*. **2019**, *84*, 5821–5830. doi.org/10.1021/acs.joc.8b03249

32. Tap, A.; Lecourt, C.; Dhambri, S.; Arnould, M.; Galvani, G.; Nguyen Van Buu, O.; Jouanneau, M.; Ferezou, J.-P.; Ardisson, J.; Lannou, M. I.; Sorin, G. Alkoxyallene-ynes: Selective preparation of bicyclo[5.3.0] ring systems including a γ-alkoxy cyclopentadienone. *Chem. Eur. J.* **2016**, *22*, 4938–4944. doi.org/10.1002/chem.201504753
33. Tap, A.; Jouanneau, M.; Galvani, G.; Sorin, G.; Lannou, M. I. ; Ferezou, J.-P.; Ardisson, J. Asymmetric synthesis of a highly functionalized enantioenriched system close to thapsigargin framework. *Org. Biomol. Chem.* **2012**, *10*, 8140–8146. doi.org/10.1039/C2OB26194D
34. (a) Burnie, A.J.; Evans, P.A. Recent developments in rhodium-catalyzed carbonylation reactions, in *Top. Organomet. Chem*. **2018**, *61*, 167-230, Springer, Cham.; (b) Kitagaki, S.; Inagaki, F.; Mukai, C. [2+2+1] Cyclization of allenes. *Chem. Soc. Rev*. **2014**, *43*, 2956–2978. doi.org/10.1039/C3CS60382B; (c) Brummond, K. M.; Mitasev, B. Rhodium-catalyzed cycloisomerization reactions of allenes in diversity oriented synthesis. In Strategies and Tactics in Organic Synthesis, *7*, **2008**, 328–366. (d) Alcaide, B.; Almendros, P. The allenic Pauson−Khand reaction in synthesis. *Eur. J. Org. Chem*. **2004**, 3377–3383. doi.org/10.1002/ejoc.200400023. (e) Brummond, K. M.; Chen, H. Allenes in natural product synthesis, in Modern Allene Chemistry, N. Krause, ed., Wiley VCH, **2004**, Volume 2, pp. 1041–1090. (f) Brummond, K. M. An Allenic [2 + 2 + 1] cycloaddition, in Advances in Cycloaddition Chemistry, Volume 6, Harmata, M. ed., JAI Press Inc., Stamford, Connecticut, **1999**, pp. 211–237.

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