Communication

One-Pot Synthesis of Benzene-Fused Medium-Ring Ketones: Gold Catalysis-Enabled Enolate Umpolung Reactivity

Zhou Xu, Hongyi Chen, Zhixun Wang, Anguo Ying, and Liming Zhang

Just Accepted

One-Pot Synthesis of Benzene-Fused Medium-Ring Ketones: Gold Catalysis-Enabled Enolate Umpolung Reactivity

Zhou Xu,[a,b,†] Hongyi Chen,[a,†] Zhixun Wang[a] and Anguo Ying, Liming Zhang[a]*

[a] Department of Chemistry & Biochemistry, University of California, Santa Barbara, CA 93106

[b] Department of Chemistry, Xuzhou Medical College, Xuzhou, China 221004

Supporting Information Placeholder

ABSTRACT: Enolate umpolung reactivities offer valuable and potentially unique alternatives over the enolate counterparts for the construction of ubiquitous carbonyl compounds. We disclose in this report that *N*-alkenoxypyridinium salts, generated readily upon gold-catalyzed additions of protonated pyridine *N*-oxide to C-C triple bonds of unactivated terminal alkynes, display versatile enolate umpolung chemistry upon heating and react with tethered arene nucleophiles in an S_N2' manner. In a synthetically efficient one-pot, two-step process, this chemistry enables expedient preparation of valuable benzo-fused 7-/8-membered cyclic ketones, including those of *O*-/*N*-heterocycles, from easily accessible aryl-substituted linear alkyne substrates. The overall reaction yields can be up to 87%.

We have recently developed an intermolecular oxidative gold catalysis, which permits facile and general access to α-oxo gold carbene intermediates (e.g., **A**) from benign and readily available alkynes instead of hazardous α-diazo ketones (Scheme 1A).[1] Mechanistically, the carbene formation commences with a cationic Au(I)-promoted addition of a pyridine/quinoline *N*-oxide to a C-C triple bond to afford the gold-substituted *N*-alkenoxyheteroarenium intermediate **B**, which would in turn heterolytically fragment the weak N-O bond to arrive at **A**. Based on this oxidative approach, a variety of versatile synthetic methods[1b-g,2] including cyclopropanations of tethered alkenes[1e,1f,2j,2k] and insertions into C-H bonds[1g,2g] have been developed from alkyne precursors.

Our early intramolecular work in 2009,[3] 2011,[4] and 2013[1d] showed that the initial adducts related to **B**, where SR_2 or NR_3 replaces the *N*-heteroarene, do not always undergo fragmentation to form α-oxo gold carbenes of type **A**, but instead proceed through more facile alternative processes. Other studies utilizing the intermolecular strategy shown in Scheme 1A have also revealed alternative reaction pathways undertaken by **B**,[2d,2h] or related other metal intermediates,[5] where the metal-attached C(sp²) reacts with tethered nucleophiles without the involvement of the α-oxo metal carbene intermediate **A**. Importantly, Hashmi[6] showed that the related *N*-alkenoxypyridinium intermediate **C**, generated from electron-rich and activated phenoxyethyne in the presence of HBF_4, is also electrophilic at the terminal alkene end despite without metal substitution, and its subsequent cyclization renders benzofuranones (Scheme 1B). Gong[7] earlier reported a related metal-free oxidation.

We envisioned that the metal-less *N*-alkenoxypyridinium **D** of general scope could be generated from typical unactivated alkynes via sequential gold-promoted formation of **B** and its subsequent protodeauration (Scheme 1C). It is surmised that such a species

might offer a new range of versatile reactivities complementary to the chemistry featuring oxidatively generated and highly reactive α-oxo gold carbenes (i.e., **A**). In particular, it is anticipated that **D** could react with nucleophiles in an S_N2' manner and, as such, behave as a surrogate of highly reactive and little utilized acylcarbenium ions[8] and display novel enolate umpolung reactivities. Notably, approaches to achieving enolate umpolung have been reported but are limited in scopes and utilities.[9] Herein, we disclose our preliminary results in this regard, which reveals highly facile oxidative constructions of benzene-fused 7-/8-membered alkenones from readily available linear arylalkyne substrates. Medium-ring ketones of these types are synthetically useful and often prepared via ring expansion or from diazo substrates,[10] both of which, however, could require multi-steps and/or necessitate the use of hazardous diazo compounds.
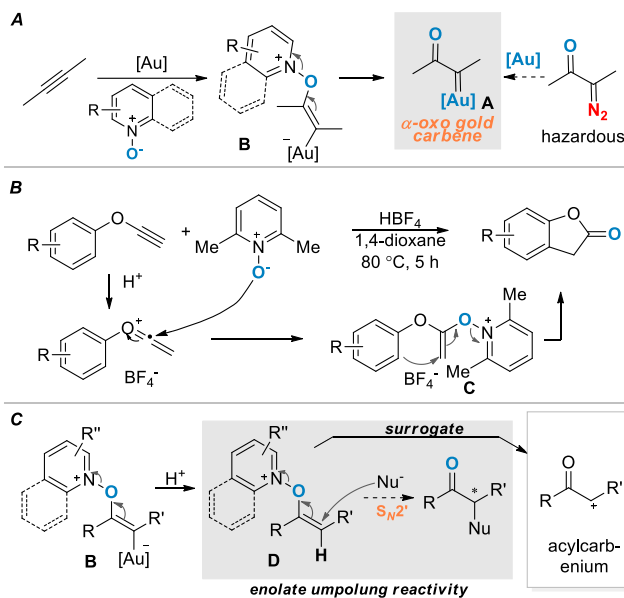
Scheme 1. A) Generation of α-oxo gold carbenes via oxidative gold catalysis. B) Hashmi's work using electron-rich alkynyl phenyl ethers. C) Our design

At the outset, we employed 5-phenylpent-1-yne as the substrate for the preparation of the desired *N*-alkenoxypyridinium salt **2a** (Table 1). Moreover, we surmised that **2a** might undergo Friedel-Crafts-type cyclization to deliver the benzene-fused cycloheptenone **3a**. After considerable effort on condition discovery and optimization, we were indeed able to implement both transformations in a two-step, one-pot process.

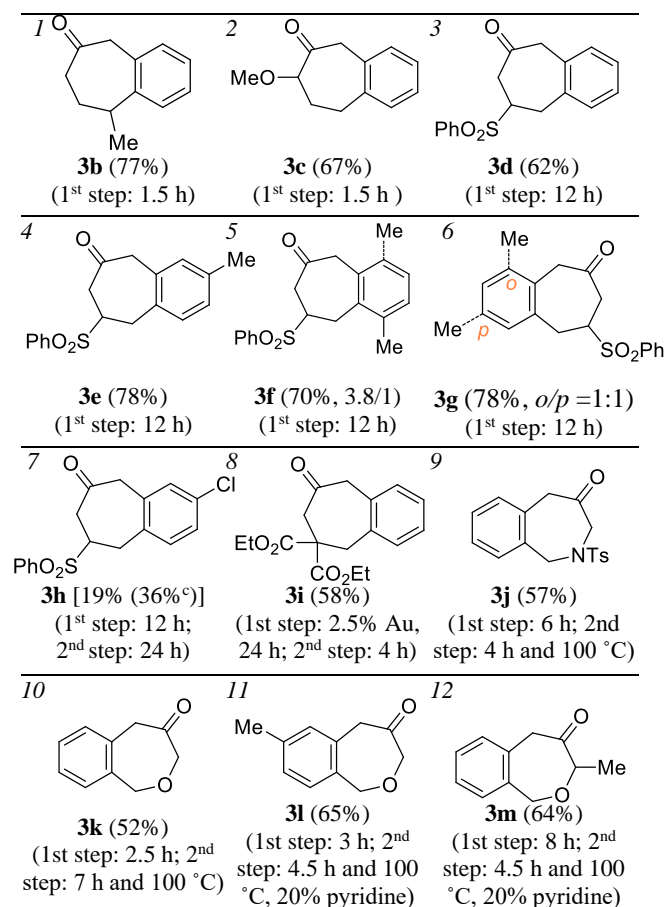**Table 1.** Initial reaction discovery and condition optimization.
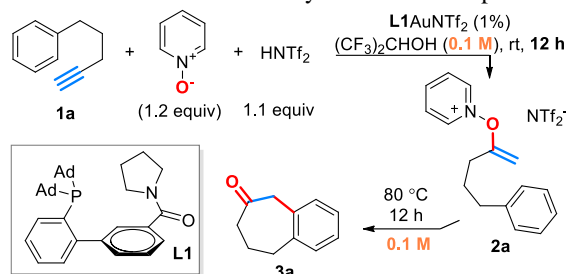
en-try	Deviation from the initially optimized conditions [a]	yield	
		1st step	overall
1	-	90%	71%
2	Ph₃P as ligand	84% [b]	-
3	IPr as ligand	7% [b]	-
4	JohnPhos as ligand	27% [b]	-
5	(2,6-^{t}Bu₂C₆H₃O)₃P as ligand	18% [b]	-
6	CF₃CH₂OH as solvent	90%	57%
7	DCE as solvent	79% [b]	35%
8	CH₃CN as solvent	61%	-
9	THF as solvent	trace	-
10	4-methylpyridine N-oxide instead	86%	30% [c]
11	2-bromopyridine N-oxide instead	72%	25%
12	2-ethoxylpyridine N-oxide instead	48%	-
13	quinoline N-oxide instead	98%	48% [d]
14	HOTf as acid	90%	71%
15	pyridine N-oxide (1 eq.) and Tf₂NH (1.2 eq) instead	N.R.	-
16	[1a] = 1.0 M and 0.5 mol% L1AuNTf₂, 1 h; 90 °C and 3 h for the 2nd step	98%	75% [e] (70% [f])

[a] Reactions run in vials; yields as determined by ^{1}H NMR. [b] Reaction time: 24 h; no alkyne left. [c] 35% of the pyridinium intermediate remained. [d] 26% of methyl ketone formed. [e] ~77% NMR obtained by using 5 mol% of Ph₃PAuNTf₂. [f] Isolated yield.

With the initially optimized conditions, **3a** was formed in a good 71% overall yield (entry 1). The reaction conditions, as shown in the equation in Table 1, include the use of **L1** as the most effective ligand, hexafluoroisopropanol as the optimal solvent, and cheap and commercially available pyridine N-oxide as the oxidant. The first step proceeded smoothly at ambient temperature in 12 h, affording **2a** in 90% NMR yield; the second step required heating at 80 °C for 16 h. Notably, **2a** is a stable species and was isolated in 88% yield and fully characterized. It needs to be pointed out that intermediates of this type has rarely been isolated before.[11] Dissolving **2a** in (CF₃)₂CHOH and heating the solution at 80 °C again afforded **3a** in 75% NMR yield, which is comparable to the estimated yield of the second step in the one-pot process (i.e., ~79%). This result confirms that in the one-pot reaction the remaining gold catalyst, the excess oxidant and its protonated form did not interfere the desired cyclization. The ligand **L1** was previously developed by us as a bifunctional ligand for gold-catalyzed highly efficient addition of carboxylic acid to alkynes.[12] Indeed, other typical ligands including JohnPhos, IPr, and (2,6-
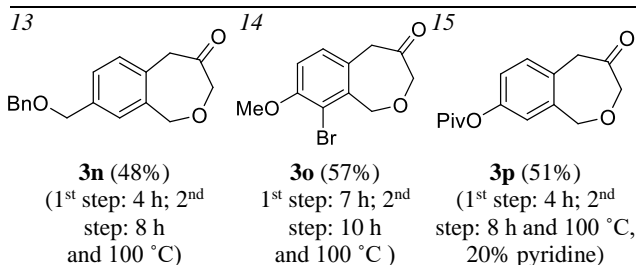
^{t}Bu₂C₆H₃O)₃P all fared worse than **L1** in terms of reaction rate and efficiency (entries 3-5). The reaction solvent turned out to be critical for both steps. While CF₃CH₂OH is equally effective in the first step, the yield of the cyclization is lower (entry 6). Other solvents such as DCE, CH₃CN and THF are less or not conducive to the initial gold catalysis (entries 7-9). The replacment of pyridine N-oxide with substituted ones led to poor yields (entries 10-12). In the case of quinoline N-oxide (entry 13), though the first step was more efficient, the cyclization turned out to be inferior and, moreover, the corresponding methyl ketone was formed in 26% yield. This side product, also observed with other N-oxides albeit to a much less extent (<8%), is likely formed upon nucleophile attack at the C2 of the quinoline ring followed by rearomatization. TfOH was as efficient an acid as HNTf₂ (entry 14). It is interesting, though, that little **2a** was detected when the acid HNTf₂ was used in excess to the oxidant in the gold catalysis step (entry 15), which can be attributed to the much decreased concentration of the nucleophilic free oxidant. Finally, the conditions could be further improved by running the first step at a higher initial concentration (i.e., 1 M), which permitted the use of only 0.5 mol% of the gold catalyst while offering a near quantitative yield in only 1 h, and the second step at 90 °C, which allowed the completion of the cyclization in a much shorter 3 h (entry 16). As such, the overall one-pot process afforded **3a** in 75% NMR and 70% isolated yield. Of note, with 5 mol% Ph₃PAuNTf₂ as the gold catalysis, the overall yield is comparable. Gagosz and co-workers have demonstrated that a related one-step gold catalysis via a gold-containing intermediate of type **B** enables efficient oxidative cyclization of 3-arylpropynes, but no **3a** was formed from **1a** by following the same protocol, even in the presence of MsOH,[2d] highlighting the complementary nature of our umpolung approach.

Table 2. Formation of benzene-fused 7-membered ketones: reaction scopes.[a,b]

3b (77%) (1st step: 1.5 h)
3c (67%) (1st step: 1.5 h)
3d (62%) (1st step: 12 h)

3e (78%) (1st step: 12 h)
3f (70%, 3.8/1) (1st step: 12 h)
3g (78%, o/p =1:1) (1st step: 12 h)

3h [19% (36% [c])] (1st step: 12 h; 2nd step: 24 h)
3i (58%) (1st step: 2.5% Au, 24 h; 2nd step: 4 h)
3j (57%) (1st step: 6 h; 2nd step: 4 h and 100 °C)

3k (52%) (1st step: 2.5 h; 2nd step: 7 h and 100 °C)
3l (65%) (1st step: 3 h; 2nd step: 4.5 h and 100 °C, 20% pyridine)
3m (64%) (1st step: 8 h; 2nd step: 4.5 h and 100 °C, 20% pyridine)

3n (48%) (1st step: 4 h; 2nd step: 8 h and 100 °C)
3o (57%) (1st step: 7 h; 2nd step: 10 h and 100 °C)
3p (51%) (1st step: 4 h; 2nd step: 8 h and 100 °C, 20% pyridine)

[a] Typical reaction conditions: i) pyridine *N*-oxide (1.2 equiv), HNTf$_2$ (1.1 equiv), **L1**AuNTf$_2$ (0.5 mol%), (CF$_3$)$_2$CHOH (1 M), rt, 3 h; ii) (CF$_3$)$_2$CHOH (0.1 M), 90 ˚C, 3 h. [b] Isolated yield. [c] The yield of the corresponding methyl ketone **3h'**.

With the optimal conditions (cf. Table 1, entry 16) in hand, we then set out to explore the scope of the novel umpolung chemistry in the context of constructing benzene-fused 7-membered ketones. As shown in Table 2, a methyl (entry 1), a methoxy (entry 2) or a sulfonyl (entry 3) substitution at the propylene tether between the phenyl ring and the C-C triple bond were readily allowed, and the corresponding benzene-fused heptenones were formed in fair to good yields. Considering the two-step nature of the oxidative cyclization, the average single step yields in these cases are still near or exceeding 80%. In entry 3, the sulfonyl substrate was easily prepared via propargylation of deprotonated (phenethylsulfonyl)benzene. This flexible access to the aryl alkynes enabled expedient examination of the impact of a methyl substituent at different positions of the benzene ring. As shown in entries 4-6, these reactions proceeded smoothly and efficiently. In the case of an *ortho*-Me (entry 5), an inseparable minor isomer was formed, the structure of which was assigned based on NMR spectra and correlation to a later case (*vide infra*). In the case of a *meta*-Me, no regioselectivity was detected, consistent with the low steric demand of an unsubstituted alkene end (entry 6). With a moderately deactivating *p*-Cl on the benzene ring, the desired product **3h** was isolated in a poor 19% yield, while the major product was the corresponding methyl ketone, despite the high yielding of the initial gold catalysis (~94%). This result, while consistent with the Friedel-Crafts nature of the cyclization, indicates that the undesired nucleophilic attack at the pyridine ring (*vide supra*) can dominate over the desired cyclization with deactivated arene rings. Notably, with all the sulfone substrates (i.e., entries 3-7), the initial gold catalysis required a much longer 12 h reaction time. With a malonate-derived substrate, the initial gold catalysis was even slower, requiring 24 h in the presence of 2.5 mol% of the gold catalyst, and afforded a lower 84% NMR yield (entry 8). These slow gold catalyses can be attributed to the decreased reactivities of the C-C triple bonds due to induction by the electron-withdrawing substituents. Nevertheless, the umpolung reactions remained mostly efficient.

This one-pot oxidative cyclization could be smoothly applied to the readily accessible benzyl propargyl amides and ethers (entries 9-15), thereby affording benzo-fused dihydroazepinones or dihydrooxepinones, some functionalized with benzyloxy ether (**3n**), bromo (**3o**), or carboxy (**3p**). In these cases, the umpolung step was slow, and a higher temperature, i.e., 100 ˚C, resulted reasonable reaction times. Notably, in entries 11 and 12 and 15, the initial adducts, i.e., the *N*-alkenoxypyridinium salts of type **D**, appeared to decompose under the acidic environment at the elevated temperature. With the buffering of 20 mol% of pyridine, the reactions proceeded smoothly to deliver the anticipated heterocycles in fairly good yields. Extension of the chemistry to phenyl homopropargyl ether, *N*-homopropargylaniline or substrates with electron-rich heteroaromatic rings such as furan, pyrrole and indole was not successful. In entries 3, 9 and 10, we also tested Ph$_3$PAuNTf$_2$ (5 mol%) instead of **L1**AuNTf$_2$ (0.5 mol%), but the gold catalysis was much less efficient, with yields typically <60%. When Table 2, entry 12 was performed using the (*R*)-substrate, (*R*)-**3m** was formed without detectable *e.e.* erosion (Eq.1).
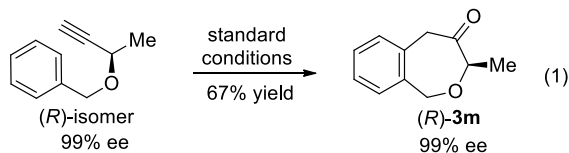
With the success in the formations of benzene-fused 7-membered rings, we then explored the more challenging 8-membered ring formation. Not surprisingly, the reaction of 6-phenylhex-1-yne was poor, and the yield of the cyclization step was ~20%. Much to our delight, the reactions using the easily accessible propargyl ethers as substrates were efficient, affording the dihydrobenzooxocinones in generally good to excellent yields (entries 1-4). Of note are that the unsubstituted product **4a** (entry 1) was formed in a better yield than its 7-membered counterpart (Table 2, entry 10), and electron-donating substituents enable further improved reaction efficiencies (entries 2-4).

Table 3. Formation of benzene-fused 8-membered ketones: reaction scopes.[a,b]

Typical reaction conditions: i) pyridine N-oxide (1.2 equiv), HNTf$_2$ (1.1 equiv), **L1**AuNTf$_2$ (0.5 mol%), (CF$_3$)$_2$CHOH (1 M), rt; ii) (CF$_3$)$_2$CHOH (0.1 M), 100 ˚C, 6 h. [b] Isolated yield.

As shown in Scheme 2, , with 2-methylphenethyl propargyl ether as the substrate, besides the expected product **4e**, its structural isomer **4e'** was also isolated. The competitive skeleton rearrangement in this case can be rationalized by invoking the formation of the spirobenzenium **F**, which can be followed by the migration of its alkyl group instead of the acylmethyl group. The occurance of this reation pathway could be attributed to the comparable stability of benzenium moieties **F** and the expected cyclization intermediate **E** as a consequence of the *ortho*-methyl group. This rationale could likewise explain the formation of the minor isomer of **3f** (cf. Table 2, entry 5).
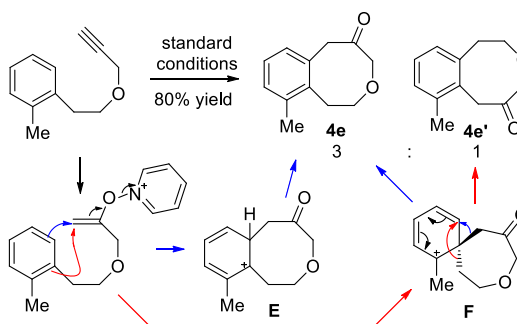
Scheme 2. Proposed mechanism of the formation of **4e/4e'**

The reactions with naphthalene-based substrates are interesting. With a 2-naphthyl substrate in entry 5, cyclization to the ring 3-position yielding **4f'** competes with that to the 1-position; another site competition was observed with the 1-naphthyl substrate, where cyclization to the *peri* position en route to a 9-membered ketone (i.e., **4g'**) was significant (entry 6). To our delight, the reaction also permits a one-step preparation of the tetrahydrobenzo[*d*]azocinone **4h** from a *N*-propargylsulfonamide (e.g., entry 7). Importantly, the reaction was surprisingly efficient, and the overall yield (i.e., 78%) is better than that of its dihydroazepinone counterpart (57% in Table 2, entry 9). Among the substrates with *N* or *O* atoms at other locations of the tether, phenyl bihomopropargyl ether is the only one affording a decent yield (entry 8).

Of interest is that the sulfonyl groups used to enable rapid substrate assembly, as in Table 2, entries 3-7, reside β to the nascent carbonyl group. It is anticipated that they could be eliminated under basic conditions to yield versatile medium-ring conjugated enones.[13] Indeed, when **3d** was treated with DBU in THF in 10 min, the benzo-fused cycloheptadienone **5** was formed in 71% isolated yield (Eq.1). Overall, the sulfonyl group acts as a versatile yet traceless facilitator of the umpolung chemistry.

$$\text{3d} \xrightarrow[\text{THF, rt, 10 min}]{\text{DBU (2 equiv.)}} \text{5} \quad (2)$$

71%
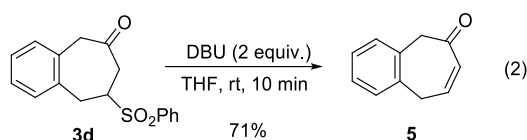
In conclusion, we have demonstrated that novel *N*-alkenoxypyridinium salts exhibit versatile enolate umpolung reactivities. These intermediates can be readily accessed upon gold-catalyzed addition of protonated pyridine *N*-oxide to C-C triple bonds of unactivated terminal alkynes and easily activated upon heating to react with tethered arene nucleophiles in an S_N2' manner. The significant synthetic value of this approach is demonstrated in this work via expedient one-pot preparation of valuable benzo-fused medium-ring ketones from easily accessible aryl-substituted linear alkynes. This novel strategy possesses the potential of revolutionizing the enolate umpolung reactivities and offering highly valuable alternatives for the synthesis of various carbonyl compounds. Studies on challenging intermolecular reactions will be next pursued.

ASSOCIATED CONTENT /

Supporting Information

Experimental details, compound characterization and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

zhang@chem.ucsb.edu

Notes

[†] These authors contributed equally.

The authors declare no competing financial interests.

ACKNOWLEDGMENT

REFERENCES

(1) a) Zhang, L. *Acc. Chem. Res.* **2014**, *47*, 877–888; b) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258-3259; c) Wang, Y.; Ji, K.; Lan, S.; Zhang, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1915-1918; d) Lu, B.; Li, Y.; Wang, Y.; Aue, D. H.; Luo, Y.; Zhang, L. *J. Am. Chem. Soc.* **2013**, *135*, 8512-8524; e) Ji, K.; Zhang, L. *Org. Chem. Front.* **2014**, *1*, 34-38; f) Ji, K.; Zheng, Z.; Wang, Z.; Zhang, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 1245-1249; g) Wang, Y.; Zheng, Z.; Zhang, L. *J. Am. Chem. Soc.* **2015**, *137*, 5316–5319.

(2) a) Dateer, R. B.; Pati, K.; Liu, R.-S. *Chem. Commun.* **2012**, *48*, 7200-7202; b) Qian, D.; Zhang, J. *Chem. Commun.* **2012**, *48*, 7082-7084; c) Davies, P. W.; Cremonesi, A.; Martin, N. *Chem. Commun.* **2011**, *47*, 379-381; d) Henrion, G.; Chavas, T. E. J.; Le Goff, X.; Gagosz, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 6277-6282; e) Wang, T.; Shi, S.; Hansmann, M. M.; Rettenmeier, E.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 3715–3719; f) Sun, N.; Chen, M.; Liu, Y. *J. Org. Chem.* **2014**, *79*, 4055–4067; g) Bhunia, S.; Ghorpade, S.; Huple, D. B.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2939-2942; h) Chen, M.; Chen, Y.; Sun, N.; Zhao, J.; Liu, Y.; Li, Y. *Angew. Chem., Int. Ed.* **2015**, 1200-1204; i) Shu, C.; Liu, R.; Liu, S.; Li, J.-Q.; Yu, Y.-F.; He, Q.; Lu, X.; Ye, L.-W. *Chem. - Asian J.* **2015**, *10*, 91-95; j) Qian, D.; Zhang, J. *Chem. Commun.* **2011**, *47*, 11152-11154; k) Vasu, D.; Hung, H.-H.; Bhunia, S.; Gawade, S. A.; Das, A.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2011**, *50*, 6911-6914.

(3) Cui, L.; Zhang, G.; Peng, Y.; Zhang, L. *Org. Lett.* **2009**, *11*, 1225-1228.

(4) Noey, E. L.; Luo, Y.; Zhang, L.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *134*, 1078-1084.

(5) Li, L.; Zhou, B.; Wang, Y.-H.; Shu, C.; Pan, Y.-F.; Lu, X.; Ye, L.-W. *Angew. Chem. Int. Ed.* **2015**, *54*, 8245–8249.

(6) Graf, K.; Rühl, C. L.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 12727-12731.

(7) Chen, D.-F.; Han, Z.-Y.; He, Y.-P.; Yu, J.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 12307-12310.

(8) Begue, J. P.; Charpentier-Morize, M. *Acc. Chem. Res.* **1980**, *13*, 207-212.

(9) a) Miyata, O.; Miyoshi, T.; Ueda, M. *Arkivoc* **2013**, *2013*, 60-81; b) Gilchrist, T. L. *Chem. Soc. Rev.* **1983**, *12*, 53-73; c) Coe, J. W.; Bianco, K. E.; Boscoe, B. P.; Brooks, P. R.; Cox, E. D.; Vetelino, M. G. *J. Org. Chem.* **2003**, *68*, 9964-9970; d) Edstrom, E. D.; Yu, T. *J. Org. Chem.* **1995**, *60*, 5382-5383; e) Malapel-Andrieu, B.; Mérour, J.-Y. *Tetrahedron* **1998**, *54*, 11095-11110; f) Zhdankin, V. V. *Arkivoc* **2009**, *1*, 1-62; g) Parra, A.; Reboredo, S. *Chem. - Eur. J.* **2013**, *19*, 17244-17260.

(10) Scott, P. J. H. *Seven-Membered and Larger-Ring Cyclic Ketones* In *Science of Synthesis Knowledge Updates*; Thieme Chemistry: 2013; Vol. 4, p 243-299.

(11) Justik, M. W.; Kristufek, S. L.; Protasiewicz, J. D.; Deligonul, N. *Synthesis* **2010**, *2010*, 2345-2347.

(12) Wang, Y.; Wang, Z.; Li, Y.; Wu, G.; Cao, Z.; Zhang, L. *Nature Commun.* **2014**, doi: 10.1038/ncomms4470.

(13) Jiang, Y.; Ichikawa, Y.; Isobe, M. *Synlett* **1995**, *1995*, 285-288.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60