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Introduction

The insertion of a hypervalent atom into an unactivated C–H bond is an attractive strategy for bond formation as it can lead to more efficient and more concise synthetic routes.^{1–5} Importantly, unlike most bond forming reactions that require the presence of two reactive functional groups, insertion reactions take advantage of a typically inert C–H bond and a single additional functional group. Minimizing the number of functional groups present in a system decreases the need for protecting groups and oxidation state changes during a synthetic sequence, which makes a synthetic route greener and more efficient from a time and cost perspective.^{6–8} This type of reactivity is exemplified by the intramolecular insertion of metal carbenes, derived from diazo precursors, into gamma C–H bonds as reported by Wenkert^{9,10} and Taber¹¹ (Fig. 1a). Advances in efficiency and stereoselectivity have since made rhodium carbene insertions valuable synthetic transformations especially for the formation of γ -lactones and γ -lactams.^{1–3} The strategic advantages that C–H insertion reactions offer synthetic chemists make identifying additional methods to effect these types of ring forming reactions a worthwhile pursuit, particularly if these new methods can provide structures that existing methods cannot. Herein we report an alternative strategy to exploit the diazo functional group in a C–H insertion reaction that can provide products not accessible by the transition metal catalyzed procedures. Specifically, β -hydroxy- α -diazo ketones react with Lewis acids by a rearrangement and subsequent C–H

insertion to give cyclopentenone products in good yield (Fig. 1b).

Cyclopentenones are versatile synthetic intermediates that are commonly used to make more-highly functionalized cyclopentanes, which are one of the most common ring systems found in biologically active organic structures (Fig. 1c).¹² Cyclopentenones are often prepared by the Nazarov cyclization^{13–15} or the Pauson–Khand reaction,^{16–20} but reactivity and selectivity issues and the need for stoichiometric quantities of reagents can limit the generality of these reactions.

Results and discussion

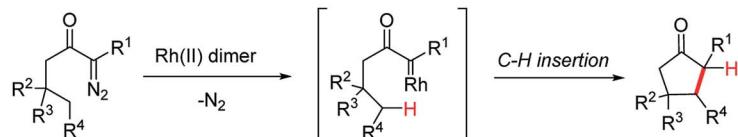
Our discovery of the insertion sequence shown in Fig. 1b stemmed from our work on the Lewis acid mediated ring fragmentation of γ -silyloxy- β -hydroxy- α -diazo esters (Fig. 2).^{21–24} In that reaction, a vinyl cation,^{25,26} formed from the diazo alcohol by the process described by Pellicciari²⁷ and Padwa,²⁸ underwent a Grob-type fragmentation that was facilitated by the γ -silyloxy group. We hypothesized that a β -hydroxy- α -diazo ketone that lacks a fragmentation-promoting group at the γ position might instead react by a C–H insertion pathway. This hypothesis was based on Schegolev's initial reports^{29–31} that vinyl cations, generated by the acylation of alkynes, can participate in C–H insertion reactions.^{32,33} We began our studies by preparing diazo ketones **1** and **3** (Scheme 1) by adding lithiated 1-diazo-3,3-dimethyl-2-butanone or lithiated 1-diazo-3-methyl-2-butanone to cyclohexanone. Treating these materials with SnCl_4 at $-20\text{ }^\circ\text{C}$ gave the hexahydro-1-azulenones **2** and **4** in 83% and 70% yield respectively, thus confirming that β -hydroxy- α -diazo ketones could serve as C–H insertion precursors. Importantly, cyclopentenone **2**, which has a quaternary carbon adjacent to the carbonyl, could not be made by a rhodium catalyzed C–H insertion.

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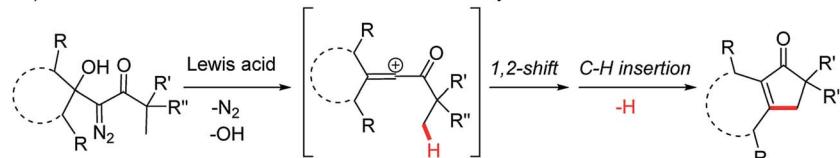
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7sc02768k



a) Known: Transition metal catalyzed C-H insertions



b) This work: Lewis acid mediated C-H insertion of a vinyl cation



c) Representative examples of biologically active cyclopentanes

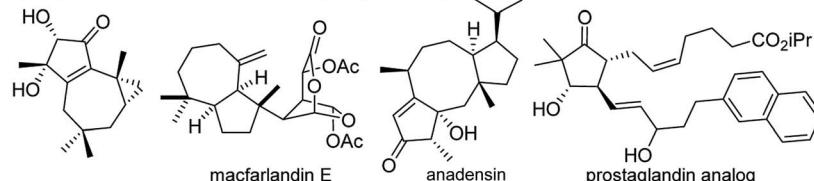
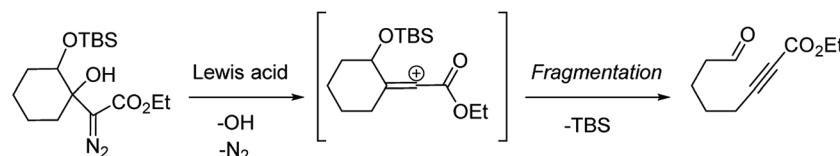


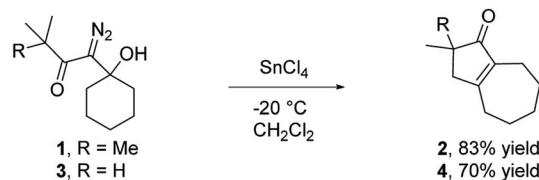
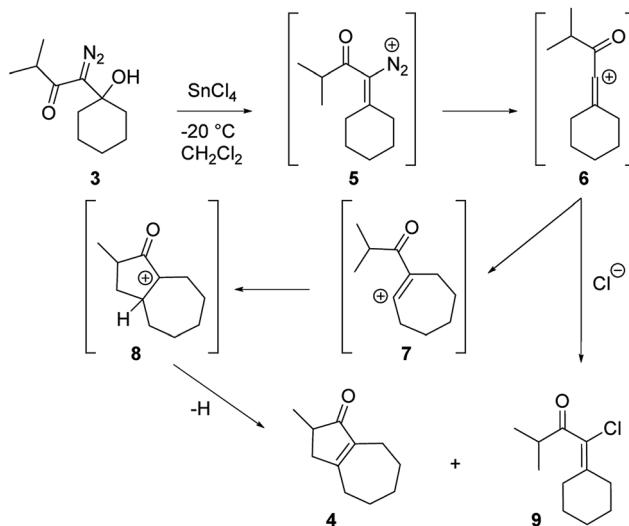
Fig. 1 C-H insertions leading to 5-membered carbocycles and examples of biologically active cyclopentanes.

Fig. 2 Lewis acid mediated ring fragmentation of a γ -silyloxy- β -hydroxy- α -diazo ester.

We propose that this transformation occurs by the sequence shown in Scheme 2.²⁸ Lewis acid mediated elimination of the tertiary hydroxide would give vinyl diazonium ion 5, which would lose nitrogen to give vinyl cation 6. Carbonyl groups typically stabilize cations on adjacent carbons through resonance.³⁴ However, in this system the p-orbitals of the carbonyl would be orthogonal to the cation's vacant p-orbital, thus preventing resonance stabilization. Instead, the cation would be destabilized by the inductively withdrawing carbonyl, which would facilitate a 1,2-shift across the alkene²⁵ to give the ring expanded cyclic vinyl cation 7. Remote C-H insertion of the vinyl cation into a non-activated pendent methyl C-H bond would provide tertiary cation 8, and subsequent loss of a proton would give the cyclopentenone product (4). In line with this sequence, vinyl chloride 9 (Scheme 2), which could be formed

by trapping vinyl cation 6 with chloride, was also isolated from the reaction mixture.

To optimize hexahydro-1-azulenone formation we evaluated other Lewis acid promoters. While $\text{BF}_3 \cdot \text{Et}_2\text{O}$, $\text{In}(\text{OTf})_3$, and

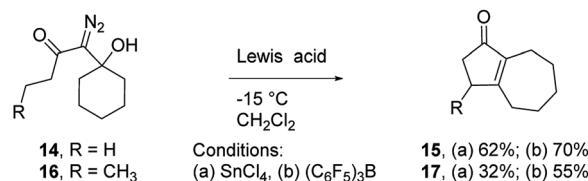
Scheme 1 Lewis acid mediated conversion of β -hydroxy- α -diazo ketones to bicyclic cyclopentenones.

Scheme 2 Proposed sequence for bicyclic cyclopentenone and vinyl chloride formation.

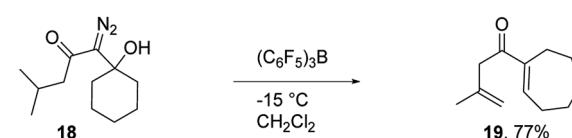


FeCl_3 were all less effective at promoting the reaction, tris(pentafluorophenyl)borane (BCF) gave **2** and **4** in 88% and 82% yield respectively (Table 1, entries 1 and 2). We next examined how temperature affected the conversion of **3** to **4** with both SnCl_4 and BCF as Lewis acids. There was negligible change in yield when the reaction was run at temperatures between -35°C and room temperature, but for both Lewis acids the yield decreased to 71% when the reaction was run at 40°C (entry 3). It is noteworthy that reducing the quantity of BCF to 20 mol% provided the desired product (**4**) in only a slightly diminished yield of 67% (entry 4), while running the reaction with 30 mol% BCF in the presence of 1 equiv. of MgSO_4 returned the product in 80% yield (entry 5). We also prepared two analogs of **1** that have substituents at the 4 position of the ring (**10** and **12**; entries 6 and 7). Both of these substrates reacted productively, albeit in slightly diminished yields as compared to the unsubstituted analog.

To assess the scope of the reaction with respect to the diazo ketone portion of the molecule, we prepared diazo ketones **14**, **16**, and **18** (shown in Schemes 3 and 4) and treated them with both SnCl_4 and BCF. The ethyl ketone derivative (**14**) gave cyclopentenone **15** in 62% yield on treatment with SnCl_4 , whereas BCF returned the product in 70% yield. The trend that insertion products **2**, **4**, and **15** are isolated in decreasing yields (88%, 82% and 70% respectively) might be a reflection of the changing number of possible sites of insertion for these different substrates, or could indicate that the Thorpe–Ingold effect is playing a role in promoting the ring closure. The *n*-propyl ketone derivative (**16**) was prepared to determine if insertion could occur at a methylene rather than methyl position. In this case, the SnCl_4 mediated reaction returned the desired insertion product in only 32% yield, whereas the BCF mediated reaction gave the desired product in a more useful 55% yield. Further investigation will be required to determine why insertion at a methylene position is less productive than insertion at a methyl position. Finally, we prepared isobutyl ketone derivative **18** (Scheme 4) to see if insertion would occur



Scheme 3 Variation at the site of insertion.



Scheme 4 Hydride transfer from a tertiary carbon.

at a tertiary carbon to give an all carbon quaternary center. When reacted with BCF, this material returned diene **19** in 77% yield, whereas treatment with SnCl_4 returned diene **19** and chloride trapped products as an inseparable mixture. To form **19**, it appears that hydride transfer occurred from the tertiary center to the vinyl cation, but ring closure did not ensue, which may be a ramification of the stability of the tertiary carbocation formed upon hydride transfer. A similar hydride transfer–elimination sequence was not apparent for *n*-propyl substrate **16**, which indicates that the degree of concertedness of the insertion step likely depends on the nature of the point of insertion.

With these results in hand, we prepared a series of diazo ketones by adding lithiated 1-diazo-3-methyl-2-butanone to various cyclic ketones and have reacted each of these diazo ketones with SnCl_4 and BCF (Table 2). When treated with SnCl_4 , the cyclobutanone and cyclopentanone derivatives (**20** and **23**) gave their respective insertion products in only trace quantities and 21% yield respectively (entries 1 and 2). In these smaller ring systems, rearrangement of the initially formed linear vinyl cation to the cyclic vinyl cation intermediate would be less favorable because of increased ring strain in the rearranged

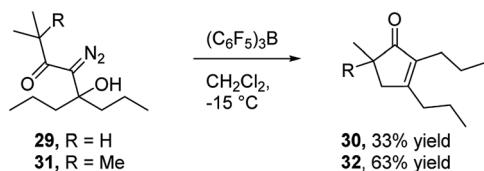
Table 1 Initial optimization studies

Entry	Compound	R	R'	R''	Temp	Mol% BCF	Product	% Yield
1	1	Me	H	H	-15°C	100	2	88
2	3	H	H	H	-15°C	100	4	82
3	3	H	H	H	40°C	100	4	71
4	3	H	H	H	-15°C	20	4	67
5	3	H	H	H	-15°C	30	4	80 ^a
6	10	Me	Me	Me	-15°C	100	11	78
7	12	Me	<i>t</i> -Bu	H	-15°C	100	13	66 ^a

^a 1 equiv. MgSO_4 was included.Table 2 Affect of β -hydroxy- α -diazo ketone ring size on reaction outcome

Entry	Compound	n	Lewis acid	Product	Yield	Product	Yield
1	20	1	SnCl_4	21	<5%	22	68%
2	23	2	SnCl_4	24	21%	25	30%
3	26	4	SnCl_4	27	42%	28	24%
4	20	1	$(\text{C}_6\text{F}_5)_3\text{B}$	21	0%		
5	23	2	$(\text{C}_6\text{F}_5)_3\text{B}$	24	60%		
6	26	4	$(\text{C}_6\text{F}_5)_3\text{B}$	27	66%		





Scheme 5 Preparation of monocyclic cyclopentenone derivative.

product, and the initially formed linear vinyl cations were instead captured by chloride to give vinyl chlorides 22 and 25 as the major products of the reactions. Switching the Lewis acid to BCF did not result in the productive formation of cyclopentenone 21 (entry 4), but the yield of cyclopentenone 24 increased to 60% (entry 5). The increased yield in this case can be attributed to the fact that BCF does not contain a moiety that could readily capture the vinyl cation intermediate, thus allowing the rearrangement and insertion to occur. The cycloheptyl derivative (26) reacted with SnCl_4 to give the desired 5,8-fused bicyclic 27 in 42% yield along with a significant quantity (24% yield) of vinyl chloride 28 (entry 3). It is not clear to us why capture by chloride is an important pathway in this larger ring system. In the presence of BCF, diazo ketone 26 returned cyclopentenone 27 in 66% yield (entry 6).

In view of the important role that monocyclic cyclopentenone derivatives play as synthetic intermediates, and the fact that prostaglandins and their analogs (e.g. Fig. 1c³⁵) are important biologically active compounds derived from these scaffolds, we were interested to determine if this reaction could provide monocyclic cyclopentenone products. To this end, we prepared diazo ketones 29 and 31 (Scheme 5) from 4-heptanone. Treating these substrates with BCF returned the desired 2,3-disubstituted cyclopentenones 30 and 32 respectively, indicating the potential of this methodology to provide new access to prostaglandin analogs.

Conclusions

In summary, we have shown that β -hydroxy- α -diazo ketones, which are simple to prepare, can serve as convenient vinyl cation precursors for C–H insertion reactions that lead to monocyclic or bicyclic cyclopentenone products. This reaction sequence appears to be fairly general, and gives good to excellent yields of ring fused 5,6-, 5,7-, and 5,8-bicyclic and 2,3-disubstituted monocyclic products. While insertion occurred productively at methyl and methylene positions, a methyne position acted as a hydride donor without subsequent C–C bond formation. In this later case, a concerted insertion process is clearly precluded, but further studies are needed to probe the mechanism of the insertion step at methyl and methylene positions. Overall, this reaction sequence represents a new approach to making common and important cyclopentenone scaffolds, including systems that cannot be made by transition metal catalyzed C–H insertion reactions. In addition to studying this reaction further, we are currently investigating alternative uses for vinyl cation intermediates formed from β -hydroxy- α -diazo carbonyl compounds.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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References

- 1 M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704–724.
- 2 H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417–424.
- 3 H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861–2904.
- 4 Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247–9301.
- 5 T. A. Ramirez, B. Zhao and Y. Shi, *Chem. Soc. Rev.*, 2012, **41**, 931–942.
- 6 W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976–1991.
- 7 L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885–1898.
- 8 J. F. Hartwig, *J. Am. Chem. Soc.*, 2016, **138**, 2–24.
- 9 E. Wenkert, L. L. Davis, B. L. Mylari, M. F. Solomon, R. R. Da Silva, S. Shulman, R. J. Warnet, P. Ceccherelli, M. Curini and R. Pellicciari, *J. Org. Chem.*, 1982, **47**, 3242–3247.
- 10 P. Ceccherelli, M. Curini, M. C. Marcotullio, O. Rosati and E. Wenkert, *J. Org. Chem.*, 1990, **55**, 311–315.
- 11 D. F. Taber and E. H. Petty, *J. Org. Chem.*, 1982, **47**, 4808–4809.
- 12 S. P. Simeonov, J. P. M. Nunes, K. Guerra, V. B. Kurteva and C. A. M. Afonso, *Chem. Rev.*, 2016, **116**, 5744–5893.
- 13 A. J. Frontier and C. Collison, *Tetrahedron*, 2005, **61**, 7577–7606.
- 14 M. A. Tius, *Acc. Chem. Res.*, 2003, **36**, 284–290.
- 15 S. E. Denmark and T. K. Jones, *J. Am. Chem. Soc.*, 1982, **104**, 2642–2645.
- 16 I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts and M. I. Foreman, *J. Chem. Soc., Perkin Trans. 1*, 1973, 977–981.
- 17 K. M. Brummond and J. L. Kent, *Tetrahedron*, 2000, **56**, 3263–3283.
- 18 J. Blanco-Urgoiti, L. Anorbe, L. Perez-Serrano, G. Dominguez and J. Perez-Castells, *Chem. Soc. Rev.*, 2004, **33**, 32–42.
- 19 N. E. Schore, in *Organic Reactions*, John Wiley & Sons, Inc., 2004, DOI: 10.1002/0471264180.or040.01.
- 20 V. B. Kurteva and C. A. M. Afonso, *Chem. Rev.*, 2009, **109**, 6809–6857.



21 C. Draghici and M. Brewer, *J. Am. Chem. Soc.*, 2008, **130**, 3766–3767.

22 A. Bayir, C. Draghici and M. Brewer, *J. Org. Chem.*, 2010, **75**, 296–302.

23 N. P. Tsvetkov, A. Bayir, S. Schneider and M. Brewer, *Org. Lett.*, 2012, **14**, 264–267.

24 A. Bayir and M. Brewer, *J. Org. Chem.*, 2014, **79**, 6037–6046.

25 P. J. Stang, Z. Rappoport, M. Hanack and L. B. Subramanian, *Vinyl Cations*, Academic Press, New York, 1979.

26 Z. Rappoport and P. J. Stang, *Dicoordinated carbocations*, Wiley, Chichester, New York, 1997.

27 R. Pellicciari, B. Natalini, B. M. Sadeghpour, G. C. Rosato and A. Ursini, *Chem. Commun.*, 1993, 1798–1800.

28 R. Pellicciari, B. Natalini, B. M. Sadeghpour, M. Marinozzi, J. P. Snyder, B. L. Williamson, J. T. Kuethe and A. Padwa, *J. Am. Chem. Soc.*, 1996, **118**, 1–12.

29 A. A. Schegolev, W. A. Smit, G. V. Roitburd and V. F. Kucherov, *Tetrahedron Lett.*, 1974, **15**, 3373–3376.

30 A. A. Schegolev, W. A. Smit, V. F. Kucherov and R. Caple, *J. Am. Chem. Soc.*, 1975, **97**, 6604–6606.

31 M. I. Kanishchev, A. A. Shegolev, W. A. Smit, R. Caple and M. J. Kelner, *J. Am. Chem. Soc.*, 1979, **101**, 5660–5671.

32 Metzger, *et al.*, have shown that vinyl cations generated by the addition of carbocations to alkynes undergo intramolecular insertion reactions to give cyclopentane products in the presence of a reductant. See ref. 33.

33 U. Biermann, R. Koch and J. O. Metzger, *Angew. Chem., Int. Ed. Engl.*, 2006, **45**, 3076–3079.

34 D. A. Dixon, R. A. Eades, R. Frey, P. G. Gassman, M. L. Hendewerk, M. N. Paddon-Row and K. N. Houk, *J. Am. Chem. Soc.*, 1984, **106**, 3885–3891.

35 D. Yariv, WO2006113571, 2006.

