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Catalytic Homologation of Cycloalkanones with Substituted Diazomethanes. Mild and Efficient Single-Step Access to α-Tertiary and α-Quaternary Carbonyl Compounds

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The homologation of cyclic ketones with diazoalkanes is a strategically useful ring expansion, with origins dating back to the early twentieth century.[1] Scheme 1 (**1** + **2**→**4**) shows the widely accepted mechanism for carbon insertion involving (1) nucleophilic attack by the diazoalkyl carbon on the carbonyl group to form a tetrahedral intermediate (diazonium betaine) and (2) 1,2-C−C bond migration with concerted loss of dinitrogen. Water and alcohol additives have long enhanced the efficiency and utility of this process, whereby protonation of the oxyanion (**3**, LA = H^+) in the transition state for rate-determining diazoalkyl addition can serve to discourage its collapse to epoxide byproducts.[2] Other Lewis acids, namely BF_3 and $AlCl_3$, are also known to promote carbon insertion.[1] Decomposition of the nucleophile, however, is a competitive problem when using these and other agents.[3] Indeed, nearly[4] all documented examples rely on superstoichiometric amounts of both diazoalkane and promoter (or methanol as cosolvent), affording low yields of product and, in the case of reactive substrates, mixtures derived from multiple homologation.

In 1994, Yamamoto and co-workers recorded the state of the art in this area upon observing efficient single homologation of various ketones in the presence of stoichiometric quantities of methyl aluminum *bis*(2,6-di-*tert*-butyl-4-methyl-phenoxide) (MAD).[5] Unfortunately, experimentation with more functional nucleophiles was limited to diazoethane, diazohexane, and diazopropene, and thus application of internal (disubstituted) diazoalkanes to carbon insertion events has remained elusive. Recently, we began a program to develop *broadly applicable, catalytic*[6] carbon insertion methodology (Scheme 1), with the ultimate intent of introducing inexpensive chiral ligands for enantioselective variants. In this Communication, we report the discovery that simple Sc^{3+} salts are uniquely effective catalysts for diazoalkyl insertion with cycloalkanone electrophiles.

At the outset, our work benefited from three outstanding protocols for *nonstabilized*[7] diazoalkane synthesis based on hydrazone oxidation.[8] Save one exception (**5c**, *p*-methoxy-phenyldiazomethane), all aryl-substituted nucleophiles were accessed by Brewer's method[8a] with dimethylchlorosulfonium chloride. For high-purity solutions of the more challenging mono- and dialkyldiazomethanes, we chose to blend known approaches by capitalizing on a modification of the Myers' *N*-silyl hydrazone protection strategy[8b] and the Shechter DMF/tetramethylguanidine solvent combination[8c] which facilitates extraction of diazoalkane products into a hydrocarbon layer.[9]

Studies to identify a suitable carbon insertion catalyst began with **5a** (Table 1) and cyclobutanone to ensure high reactivity. Various electron-rich Al- and B-based Lewis acids were tested because of the literature precedence,[1,5] but attempts to achieve turnover were not successful. An even greater survey of potential H-bond donors was carried out (alcohols, biphenols, diols, ureas, thioureas, and electronically activated versions thereof),[10] again with discouraging results. Finally, a screen of lanthanide triflates was highly rewarding. Dropwise addition of **5a** (1.1 equiv) to a stirring mixture of ketone and 5 mol % $Sc(OTf)_3$[11] affords **6a** in near quantitative yield (entry 1). No special precautions were taken to purify or dry the commercial Sc salt, so a control experiment was performed to preclude protic catalysis of the reaction.[12] Entries 2 and 3 confirm that the reaction tolerates electronic changes to the nucleophile, although **5c** gave a modest yield (45%) of product at 1.1 equiv and required the less Lewis acidic $Sc(acac)_3$,[13] suggesting that more electron-rich species could be problematic. As seen in entries 4 and 6, a workable solution to counteract diazoalkane instability[13] is to employ a slight excess of the reagents; that they are available in just two steps from the corresponding aldehyde or ketone makes this approach feasible.[9] Reactions in entries 4−7 further underscore

Scheme 1

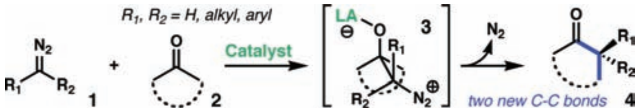
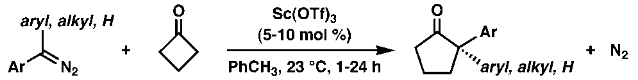
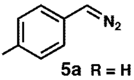
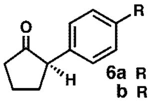
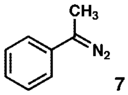
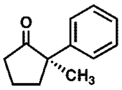
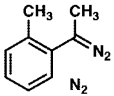
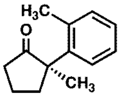
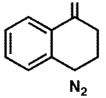
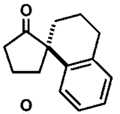
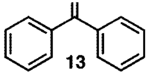
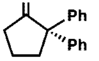


Table 1. Complex Cyclopentanones through Catalytic Carbon Insertion[a]



entry	aryldiazoalkane	diazoalkane yield (%)	equiv of nucleophile	insertion product	yield (%)
1	 **5a** R = H	51	1.1	 **6a** R = H	98[b]
2	**b** R = NO_2	94	1.1	**b** R = NO_2	98[b]
3	**c** R = OCH_3	41	1.1	**c** R = OCH_3	45[c]
4	 **7**	51	1.5	 **8**	88
5	 **9**	58	1.1	 **10**	72
6	 **11**	40	4.0	 **12**	96[d]
7	 **13**	85	1.1	 **14**	80

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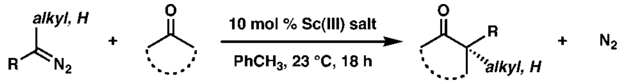
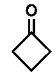
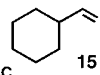
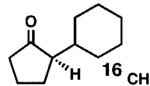
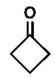
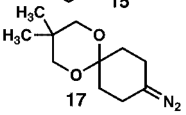
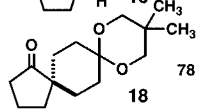
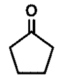
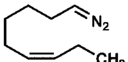
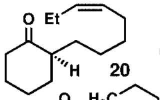
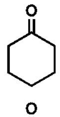
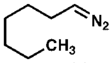
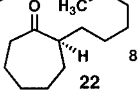
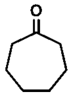
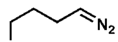
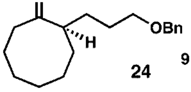
[a] Conditions: 10 mol % $Sc(OTf)_3$, 23 °C, 0.2 M in $PhCH_3$; isolated yields after chromatography. [b] Run with 5 mol % catalyst. [c] Run with 10 mol % $Sc(acac)_3$. [d] Run @ −50 °C.

10.1021/ja809220j CCC: $40.75

Table 2. Catalytic Ring Enlargement with Aliphatic Diazo Compounds[a]



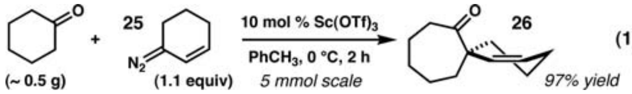
entry	electrophile	nucleophile	diazoalkane yield (%)[b]	equiv of nucleophile	insertion product	yield (%)
1		 15	35	2.2	 16	85[c]
2		 17	34	2.2	 18	78
3		 19	40	2.2	 20	60
4		 21	38	2.0	 22	86
5		 23	38	2.0	 24	91

[a] Conditions: 10 mol % Sc(TMHD)$_3$, 23 °C, PhCH$_3$, isolated yields. [b] Over three steps based on esterification. [c] Run with Sc(acac)$_3$. TMHD = 2,2,6,6-tetramethyl-3,5-heptanedianato.

the remarkable facility with which sterically congested, all-carbon-substituted quaternary centers can be installed in a single step under mild conditions.

Additional features of these processes include the following: (1) Only 1.5 equiv of methyl phenyl diazomethane (**7**) is required to provide α-quaternary cyclopentanone **8** in 88% yield. (2) *ortho* substitution (see **9**) does not adversely affect reaction efficiency from the standpoint of either chemical yield (72% of **10**) or the need for an excess of the nucleophile (1.1 equiv). (3) Tetralone-derived **11** is especially prone to Sc-catalyzed decomposition to the corresponding azine,[13] but a 96% yield of complex spirocycle **12** is achieved with optimal temperature and stoichiometry (−50 °C, 4 equiv). (4) Efficient carbon insertion with diphenyldiazomethane (**13**) suggests that the method further permits access to useful α-diaryl carbonyls.

An opening investigation with aliphatic nucleophiles is also indicative of considerable promise for this method (Table 2): (1) Steric congestion in the form of *β*-branched (**15**) or ketone-derived nucleophiles (**17**) is well-tolerated (entries 1 and 2). (2) Competing cyclopropanation of alkene double bonds is not observed (entry 3). (3) The reaction conditions accept some common protecting groups (ketal or Bn ether, entries 2 and 5). (4) Four-carbon ring strain is not crucial, since five-, six-, and seven-membered ring substrates undergo carbon insertion in good yield (entries 3−5). In most of these cases, an additional refinement is made possible with a switch to *tert*-butyl-acac (TMHD) as supporting ligation for Sc^{3+}, possibly due to added steric protection of the trication and enhanced diazoalkane longevity. Even more noteworthy are the facts that quaternary carbon synthesis is feasible with unstrained precursors and the method has proven scalable (eq 1). Catalytic merger of ∼0.5 g (5 mmol) cyclohexanone and 3-diazocyclohexene (**25**) to give **26**—a structure not easily accessed by classic metalloenamine or enolate alkylation chemistry—perhaps best demonstrates a setting where the present method can be preparatively useful.



(1)

Efficient, stereoselective α-elaboration of “naked” ketone carbonyls[14] has been a longstanding challenge to the field, and recently considerable progress was made through catalytic asymmetric alkylation[14a,g] and decarboxylative Tsuji allylation processes.[14b,c] Methods described herein confront the problem in a different way, merging formation of two new C−C bonds with a powerful and enabling ring expansion. Chemists often prepare the higher homologue of a given alkanone from a lower one that is inexpensive or more accessible. Our findings add both complexity and stereochemistry to this fundamental operation and should prove to be of value for both small and complex molecule synthesis. Further studies are underway.

Acknowledgment. We thank the ACS Petroleum Research Fund (grant 5001009) and Boston College for generous support of this research. The Boston College Mass Spectrometry Facility is supported by the NSF (grant DBI-0619576).

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) (a) Gutsche, C. D. *Org. React.* **1954**, *8*, 364–429. (b) Hauptmann, S.; Hirschberg, K. *J. Prakt. Chem.* **1966**, *34*, 272–282. (c) Gutsche, C. D; Redmore, D. In *Carbocyclic Ring Expansion Reactions*; Hart, H., Karabatsos, G. J., Eds.; Academic Press: New York, 1968, 81−98. (d) Krow, G. R. *Tetrahedron* **1987**, *43*, 3–38 For a projected application in sesquiterpenoid total synthesis, see: (e) Corey, E. J.; Ohno, M.; Mitra, R. B.; Vatakencherry, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 478–485.

(2) In this manner, one intercepts the same intermediate formed by treating *β*-amino alcohols with nitrous acid in the related Tiffeneau-Demjanov reaction: Smith, P. A. S.; Baer, D. R. *Org. React.* **1960**, *11*, 157–188.

(3) For example, CH$_2$N$_2$ forms polymethylene and N$_2$ with trialkylborates; see: Buckley, G. D.; Ray, N. H. *J. Chem. Soc.* **1952**, 3701−3704.

(4) For a notable exception of catalysis, see: Johnson, W. S.; Neeman, M.; Birkeland, S. P.; Fedoruk, N. A. *J. Am. Chem. Soc.* **1962**, *84*, 989–992.

(5) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, 1283.

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(7) A new diazocarbonyl synthesis and lead references for *stabilized* diazos: Toma, T.; Shimokawa, J.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 3195–3197.

(8) (a) Javed, M. I.; Brewer, M. *Org. Lett.* **2007**, *9*, 1789–1792. (b) Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 12222–12223. (c) Holton, T. L.; Shechter, H. *J. Org. Chem.* **1995**, *60*, 4725–4729.

(9) The merits of this procedure will be disclosed elsewhere. Though lower diazoalkanes are toxic, explosive gases at 23 °C, the higher weight derivatives shown here have been *safely and without incident* prepared in pure form as solids or viscous oils. See the Supporting Information.

(10) For an overview of catalysis by hydrogen bond donors, see: Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543.

(11) Sc(III) was chosen for development given its proven utility with cheap chiral ligands; for a recent review, see: Jimmy Wu, Ph.D. Thesis. Harvard University, Cambridge, MA, 2005.

(12) In the event, exposure of cyclobutyl ketone and phenyldiazomethane to 1 mol % TfOH (PhCH$_3$, 23 °C) gave no **6a** and only stilbene (∼1:1 *E*:*Z*).

(13) As an illustration of dramatic ligand effects on diazoalkane stability, ReactIR $T_{1/2}$ values for azine formation with strongly Lewis basic **5c** are 40 s and 16 h (respectively) in the presence of 10 mol % Sc(OTf)$_3$ and Sc(acac)$_3$. Precedent for Rh-catalyzed decomposition to azines: Shankar, B. K. R.; Shechter, H. *Tetrahedron Lett.* **1982**, *23*, 2277–2280.

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JA809220J