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Catalytic and Regioselective Ring Expansion of Arylcyclobutanones with Trimethylsilyldiazomethane. Ligand-Dependent Entry to β-Ketosilane or Enolsilane Adducts

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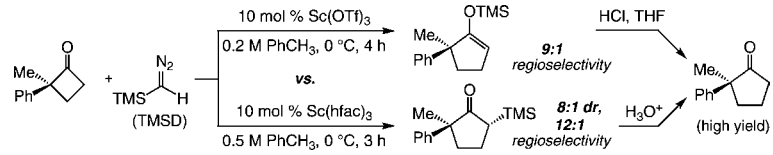
ABSTRACT



Divergent reactivity is uncovered in the homologation of arylcyclobutanones with trimethylsilyldiazomethane. With $Sc(OTf)_3$ as catalyst, enolsilanes are obtained with a high preference for methylene migration. By contrast, $Sc(hfac)_3$ gives β-ketosilanes with both regio- and diastereocontrol. Each adduct affords the cyclopentanone upon hydrolysis.

Ring expansion reactions rank among the most strategically useful in synthesis, since many natural products consist of polycyclic networks of carbon. Methylene insertion can be effected with diazomethane in protic solvents[1] or with trimethylsilyldiazomethane (TMSD) in the presence of BF_3 and Al-based promotors.[2] Achieving reliable and efficient regiocontrol over 1,2-migration in unsymmetrical ketones, however, remains problematic. With few exceptions,[3] the known cases[4] of regioselective (>3:1, see Scheme 1) 1-C homologation rely on the presence of a deactivating C−Cl or C−O α-substituent. Further, the accepted[1b] hierarchy of migratory aptitudes for diazoalkyl insertion (phenyl ∼ vinyl > methyl > *n*-propyl > isopropyl ∼ benzyl > *tert*-butyl) is strictly empirical in origin and bears little resemblance to the trends that predictably govern Baeyer−Villiger, Criegee, and pinacol rearrangements.[5] Building upon our interest in the study of noncarbonyl-stabilized diazoalkanes as carbon nucleophiles in synthesis,[6] we have begun to explore the regiochemistry of carbon insertion under conditions of true catalysis.[7] Herein, we report a TMSD-based ring expansion of arylcyclobutanones that proceeds with high regiocontrol. α-Ter-

[†] These authors contributed equally to this paper.

(1) Reviews: (a) Gutsche, C. D. *Org. React.* **1954**, *8*, 364–429. (b) Gutsche, C. D.; Redmore, D. In *Carbocyclic Ring Expansion Reactions*; Hart, H., Karabatsos, G. J., Eds.; Academic Press: New York, 1969; pp 81−98.

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(5) (a) Goodman, R. M.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9392–9393. (b) Nakamura, K.; Osamura, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9112–9120. (c) Berson, J. A.; Suzuki, S. *J. Am. Chem. Soc.* **1959**, *81*, 4088–4094.

(6) (a) Moebius, D. C.; Kingsbury, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 878–879. (b) Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. *Org. Lett.* **2009**, *11*, 3202–3205.

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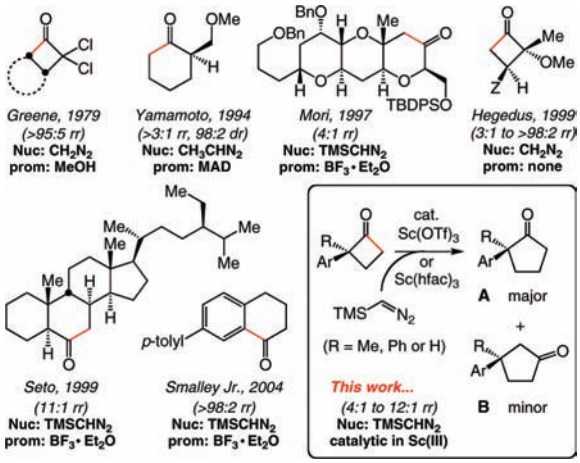
Scheme 1. Representative Cases of Regioselective Homologation[a]



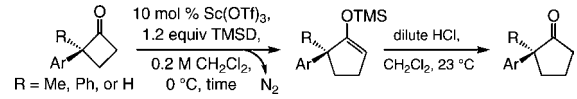
[a] The preferred migrating group has been colored in each substrate (rr = regioisomer ratio, Nuc = nucleophile, prom = promoter).

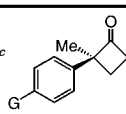
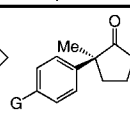
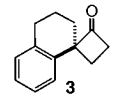
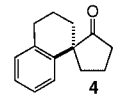
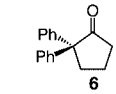
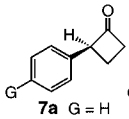
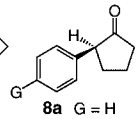
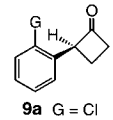
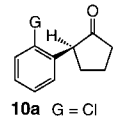
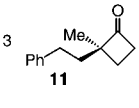
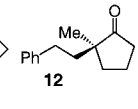
tiary and -quaternary arylcyclopentanones form in up to 12:1 selectivity (**A**:**B**, Scheme 1) after protodesilylation.

Enantioenriched 2-aryl cyclopentanones are synthesized by catalytic arylation of ketone enolates[8] or by asymmetric epoxidation/rearrangement of benzylidenecyclobutanes.[9] Noting that benzyl is second only to *tert*-butyl in rank (vide supra) as a poor migrating group for diazoalkyl insertion,[1b] we chose cyclobutanone **1a** (Table 1) for opening studies on the regioselectivity of Sc-catalyzed 1-C insertion. The hypothesis was that the incorporation of both phenyl and methyl groups would render the α carbon benzylic and tertiary, thereby even less prone to 1,2-migration. A variety of 2-aryl cyclobutanones were prepared in two steps[10] by spiroannelation of the corresponding aldehyde or ketone so that inductive and resonance effects could be investigated. TMSD[11] was chosen as the preferred one-carbon source, offering greater stability[12] and regioselectivity[2a] than diazomethane and a way to access useful organosilicon products.

Dropwise addition of commercial TMSD to a toluene[6] solution of **1a** at 0 °C containing 10 mol % of suspended $Sc(OTf)_3$ led to visible N_2 evolution and rapid consumption of starting material. A basic aqueous workup gives a clean mixture of regioisomeric enol silanes, but the ratio of *n*-alkyl:*tert*-alkyl migration (9:1) was initially assessed after hydrolysis to the corresponding cyclopentanones (**A**:**B**). **2a** is readily separable from its β-quaternary isomer by column chromatography (85% yield, 94% mass balance). A solvent screen established that

Table 1. Scope of Catalytic CH_2 Insertion for Arylcyclobutanones



entry	substrate	major product	time	convn(%)[a]	regioisomer ratio[a]	isolated yield[b]
1[c]	 **1a** G = H	 **2a** G = H	1 h	>98	9:1	85% (94%)
2	**b** G = OMe	**b** G = OMe	1 h	>98	8:1	83% (93%)
3	**c** G = CF_3	**c** G = CF_3	12 h	>98	4:1	73% (91%)
4	**d** G = Br	**d** G = Br	1 h	>98	6:1	66% (77%)
5	**e** G = Cl	**e** G = Cl	1.5 h	>98	6:1	74% (85%)
6	 **3**	 **4**	4 h	87	9:1	60% (67%)
7[d]	 **5**	 **6**	24 h	>98	7:1	72% (84%)
8	 **7a** G = H	 **8a** G = H	1 h	>98	7:1	76% (88%)
9	**b** G = OMe	**b** G = OMe	0.5 h	>98	10:1	78% (87%)
10	 **9a** G = Cl	 **10a** G = Cl	0.5 h	>98	5:1	63% (78%)
11	**b** G = Br	**b** G = Br	0.5 h	>98	6:1	70% (82%)
12	**c** G = OMe	**c** G = OMe	1 h	>98	5:1	72% (88%)
13	 **11**	 **12**	1 h	>98	3:1	70% (92%)

[a] Determined by ^1H NMR analysis. [b] Yield of the major regioisomer shown; combined yields given in parentheses. [c] Toluene as solvent. [d] Run at 23 °C.

highly coordinating solvents (e.g., Et_2O, THF, or MeCN) were not effective, but near identical regioselectivity and a faster reaction rate was observed with CH_2Cl_2, perhaps due to the greater solubility of $Sc(OTf)_3$.

The remaining entries in Table 1 confirm that useful levels of regiocontrol are maintained in the homologation of a range of aryl-substituted cyclobutanones. Trimethylsilyl enol ethers are the exclusive products, yet in these cases direct hydrolysis (1 N HCl, biphasic) of the mixture was carried out before the workup to allow for isolation of the major cyclopentanone in good yield. Inductive effects can influence reaction time and regioselectivity, but methoxy, trifluoromethyl, and halogen groups are all tolerated at the para position of the arene, giving the α-quaternary ketones in ≥66% yield (entries 2−5, → **2b**−**e**). A spirocyclic analogue of methyl phenyl cyclobutanone (**3**) underwent insertion with identical selectivity (9:1, entry 6) but was slower to react, giving 60% of **4** at 87% conversion. Despite even greater steric hindrance, diphenylcyclobutanone **5** is consumed after 24 h of stirring with similar levels of efficiency (7:1 selectivity, 72% **6**, entry 7). Bond-selective ring expansion is also possible with α-tertiary electrophiles. 2-Phenylcyclobutanone (**7a**) and its *p*-methoxy variant (**7b**)

(7) An $InCl_3$-catalyzed merger of TMSD and aldehydes to give α-silyl ketones: Li, J.; Sun, C.; Lee, D. *J. Am. Chem. Soc.* **2010**, *132*, 6640–6641.

(8) (a) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261–1268. (b) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195–200.

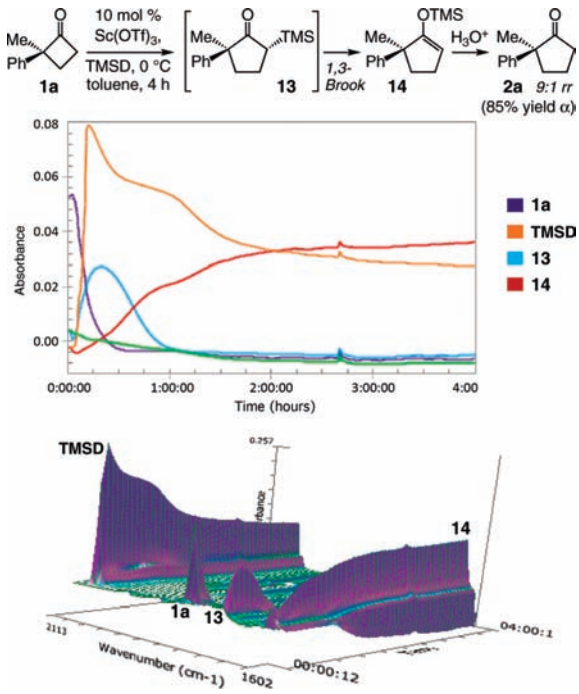
(9) (a) Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455–5458. (b) Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 1429–1432.

(10) (a) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321–5334. (b) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 3088–3100. (c) Gadwood, R.; Rubino, M. R.; Nagarajan, S. C.; Michel, S. T. *J. Org. Chem.* **1985**, *50*, 3255–3260.

undergo regioselective (7 and 10:1 rr) methylene insertion to give cyclopentanones **8a** and **8b** in >75% yield (entries 8 and 9). We have also demonstrated tolerance for ortho substitution within the monoarylated series. As shown in entries 10−12, *o*-chloro-, *o*-bromo-, and *o*-methoxyphenyl cyclobutanones transform to the corresponding 5-C ring ketones with ≥5:1 regioselectivity and 63−72% yield. A representative dialkyl cyclobutanone (**11**) was tested as well. Selectivity falls to 3:1 in the absence of the bulky arene substituent, but in this case the α-quaternary cyclopentanone (**12**) is still recovered with good efficiency (70% yield).

Closer analysis of the reaction pathway for homologation of ketone **1a** was revealing. As shown in Scheme 2, real-time

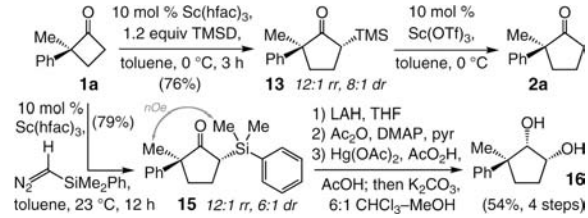
Scheme 2. Carbosilane Intermediate Detected by reactIR Analysis



monitoring of the event by reactIR spectroscopy confirms a short-lived (1 h) intermediacy of β-keto silane **13**, whose carbonyl stretch (1717 cm^{-1}) is easily discernible from that of the starting **1a** (1775 cm^{-1}). Since authentic **13** is a stable species (vide infra), $Sc(OTf)_3$ appears to play a dual role in the transformation, catalyzing (1) rapid (<30 min) insertion of the TMSCH moiety into the less hindered α C−C bond of **1a** and (2) a more gradual 1,3-Brook rearrangement[13] of **13** to **14**. At this point, we sought to gain access to carbosilane **13** by other means so that C → O Si transfer could be studied under more controlled conditions. While synthetic methods exist[14a] for such useful intermediates,[14b] it was intriguing to consider that a less Lewis acidic Sc trication might halt reaction at β-keto silane **13**, especially since the kinetics of carbon insertion appeared faster than Brook isomerization.

In a screen with other commercial Sc(III) salts, $Sc(acac)_3$ and $Sc(tmhd)_3$ were completely ineffective (<2% conv), but $Sc(hfac)_3$ gave the desired outcome. With 10 mol % catalyst, homologation of **1a** proceeds cleanly to an 8:1 mixture of diastereomeric β-keto silanes with a 12:1 predominance of secondary vs quaternary carbon migration (Scheme 3). The

Scheme 3. Diversifying Reactions Made Possible by hfac Ligation



major product (**13**, 76%) is stable to silica gel and readily separable from the minor components of the reaction.[15] Its 2,5-trans configuration is assigned by analogy to the more enabling transformation depicted at the bottom of Scheme 3. Thus, $Sc(hfac)_3$-catalyzed reaction with $PhMe_2SiCHN_2$[16] smoothly converts **1a** to organosilane **15** with comparable diastereo- and regioselectivity. Comparative NOE analysis on both diastereomers established the relative configuration in **15** as that shown. After stereoselective LAH reduction to a secondary alcohol, repeated attempts to oxidize the C−Si bond gave product mixtures. Silyl protecting groups did not hold up to the acidic conditions needed, but reaction on the derived acetate was favorable. Cyclopentanediol **16** can be accessed in 54% yield over four steps that include Fleming oxidation[17] of the acetoxy silane and acetate ester removal. Subsequent acetalization with *p*-bromobenzaldehyde gives a cis-configured dioxolane, confirming the stereochemistry of the reduction. Interestingly, upon revisiting the issue of $Sc(OTf)_3$ catalysis of Brook rearrangement in **13**, we found protodesilylation (to **2a**) as the exclusive result (Scheme 3). At this time, it is not clear why enol silane **14**, if generated catalytically from **13**, is stable only under the preparative conditions for 1-C ring expansion. A possible role for the donor−acceptor nucleophile in mediating silicon transfer is considered next in a discussion of reaction mechanism.

(11) Other recent literature on the utility of this reagent: (a) Dias, E. L.; Brookhart, M.; White, P. S. *J. Am. Chem. Soc.* **2001**, *123*, 2442–2443. (b) Greenman, K. L.; Carter, D. S.; Van Vranken, D. L. *Tetrahedron* **2001**, *57*, 5219–5225. (c) Aggarwal, V. K.; Sheldon, C. G.; Macdonald, G. J.; Martin, W. P. *J. Am. Chem. Soc.* **2002**, *124*, 10300–10301. (d) Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 320–328. (e) Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 11162–11163. (f) Kühnel, E.; Laffan, D. D. P.; Lloyd-Jones, G. C.; del Campo, T. M.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7075–7078. (g) Reference 7.

(12) For commentary on this trend, see: Seyferth, D.; Dow, A. W.; Menzel, H.; Flood, T. C. *J. Am. Chem. Soc.* **1968**, *90*, 1080–1082.

(13) (a) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77–84. (b) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065–2084. (c) Brook, A. G.; Limburg, W. W.; MacRae, D. M.; Fieldhouse, S. A. *J. Am. Chem. Soc.* **1967**, *89*, 704–706.

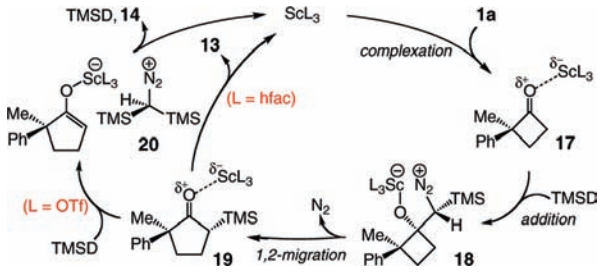
(14) (a) Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1984**, *25*, 4345–4348. (b) Obayashi, M.; Utimoto, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1760–1764.

(15) The regioisomeric α-silyl, β-quaternary ketone was recovered as a single diastereomer (6% yield) along with 10% of the α-silyl epimer of **13**.

(16) Prepared by a procedure for TMSD from (chloromethyl)dimethylphenylsilane: Shiori, T.; Aoyama, T.; Mori, S. *Org. Synth.* **1990**, *68*, 1−4.

(17) Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, *28*, 4229.

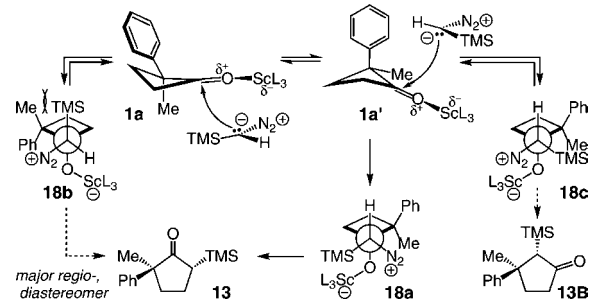
Scheme 4. Plausible Mechanistic Rationale for Product Selectivity



The catalytic cycle depicted in Scheme 4 can account for the ligand-dependent product formation. After Lewis acid coordination to the sterically more accessible carbonyl lone pair (→ **17**), C−C bond formation leads to the Sc-complexed diazonium alkoxide **18**. Collapse of this intermediate with 1,2-shift of the carbon antiperiplanar to the leaving group provides **19**. Perhaps as a result of attenuated Lewis acidity and bulkier bidentate ligands, simple turnover ensues from **19** when L = hfac. On the other hand, with the smaller and more electron-withdrawing triflate counterion, activation in **19** facilitates net 1,3-transfer of the trimethylsilyl unit from carbon to oxygen. Since protodesilylation to **2a** occurs in the absence of nucleophile, even with rigorously dried $Sc(OTf)_3$ (Scheme 3), we postulate that the Lewis basic TMSD, present in excess, acts as a temporary sink for trimethylsilyl cation. Ion pair **20** is the result, and subsequent *O*-silylation of the Sc enolate releases the silyl enol ether product **14**, regenerates TMSD, and completes the catalytic cycle.

A preliminary basis for regiochemical control can also be advanced. Substitution of a methyl and phenyl group at the same carbon atom in cyclohexane results in a preference[18] for axial phenyl despite its larger *A* value (3.0 versus 1.7). The effect is attributed[18] to the ability of the phenyl group to orient itself perpendicular to the axis of the $C-CH_3$ bond (compare **1a** and **1a′**, Scheme 5). In this conformation, a preferred approach of

Scheme 5. Carbonyl Addition Model Explains the Regioselectivity



TMSD *syn* to the phenyl ring places hydrogen over the top face of the cyclobutane ring and the linear diazonium group near the quaternary center. This mode of addition situates the less substituted C−C bond syncoplanar with the antibonding (σ^*_{C-N}) orbital, directly provides the major product upon rearrangement (**18a** → **13**), and is consistent with Bassindale's model for the approach of prochiral carbanions at the carbonyl group.[19] The extent to which steric interactions between the TMS group and bulky (hexafluoroacetyl)acetonate counterions on scandium serve to destabilize betaine **18a** is not clear at this time. An alternative mechanism for the selective formation of **13** involves addition *syn* to the methyl group, as illustrated in butterfly conformation **1a**. Molecular models show that the resulting intermediate **18b** experiences severe nonbonding interactions between its methyl and TMS groups regardless of whether they arise (1) during nucleophilic attack (as shown) or (2) during counterclockwise, 120° rotation about the newly formed bond in order to attain the proper orbital alignment for ring expansion. This model[20] also accounts for the diminished levels of regioselectivity (3:1) observed with α-dialkylcyclobutanones (**11**, Table 1). Addition to **1a′** from the opposite face of the reagent gives betaine **18c** in which the fully substituted carbon is poised for 1,2-shift. The presence of the TMS group proximal to the quaternary center appears to be better accommodated in less hindered cyclobutanone substrates. Experiments are now underway to confirm that the carbonyl addition event is both rate- and regiochemistry-determining, as the current model predicts.

A foundation for exploiting utility in the Sc-catalyzed, regioselective diazoalkane−carbonyl homologation reaction is in place. Lewis acidity at Sc^{3+} is tuned by electronic and steric changes to the ligand, a fact that permits a switchable entry to enolsilane or carbosilane products during catalytic trialkylsilylmethine insertion. The preliminary scope of this process confers access to both quaternary[8,9a] and tertiary[9b] 2-aryl cyclopentanones through a simple, one-flask protocol. The minor influence of arene electronics is in agreement with a model for regioselectivity, one based exclusively on sterics. Application of this methodology to the total synthesis of complex quinonoid natural products will be the subject of future reports from these laboratories.

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Supporting Information Available: Characterization data and full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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