COMMUNICATION

OBC
www.rsc.org/obc

Silicon and tin-directed Tiffeneau–Demjanov reaction†

Leonie Chow, Melanie McClure and Jonathan White*
School of Chemistry, The University of Melbourne, Parkville 3010, Melbourne, Australia.
E-mail: whitejm@unimelb.edu.au

Received 20th November 2003, Accepted 12th January 2004
First published as an Advance Article on the web 27th January 2004

Silicon and tin substituents surprisingly have only a moderate directing effect on the Tiffeneau–Demjanov reaction. The low selectivity is rationalised as being due to the reactive nature of the diazonium ion leaving group, the weaker oxydiazene leaving group was found to give better yields of the silicon-directed ring expanded product.

The stabilisation of positive charge at the β position by group 4 metal substituents (the so called 'β effect') has been well established.[1–7] The magnitude of this stabilisation increases down the group Si < Ge << Sn and is related to the ability of the C–metal bond to donate electrons to the carbenium ion p orbital by hyperconjugation (Fig. 1).[6,7]

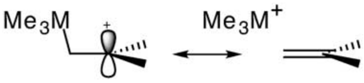
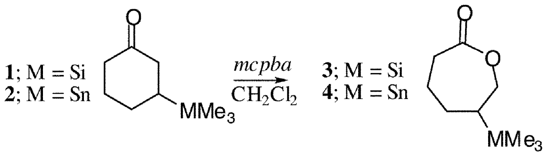


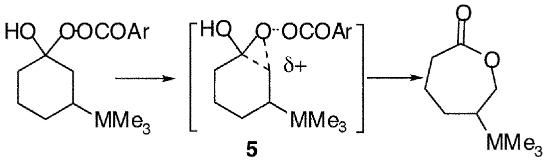
Fig. 1

The β effect (particularly that of silicon) has been widely exploited in synthetic organic chemistry.[8–16] Silicon directs the outcome of reactions, or rearrangements, which involve carbenium ion intermediates or polarised transition states. These reactions are biased towards pathways which result in the development of positive charge on the carbon β to the metal substituent. For example, both silicon and tin substituents have been demonstrated to exert a high degree of regiochemical control on the Baeyer–Villiger reaction of the cyclic ketones **1** and **2** resulting in the exclusive formation of the lactones **3** and **4** by preferential insertion of the oxygen adjacent to the carbon which is β to the silicon or tin substituent (Scheme 1).[14–16]



Scheme 1

The directing effect of the silicon or tin substituent is believed to manifest in the breakdown of the tetrahedral intermediate **5** (Scheme 2), the migrating carbon develops a partial positive charge at the transition state, thus the carbon which is β to the silicon or tin substituent migrates preferentially.



Scheme 2

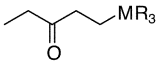
The strength of the directing effect is exemplified by the observation that a 1° carbon, which is β to silicon has a migratory aptitude between that of a 2° and 3° carbon in the Baeyer–Villiger reaction, while β-Tin raises the migratory aptitude of a 1° carbon to be above that of a 3° carbon.

The Tiffeneau–Demjanov ring enlargement of cyclic ketones is shown in Scheme 3 and involves the intermediate diazonium species **6**.[17] Breakdown of the diazonium intermediate **6** has similarities with the breakdown of the tetrahedral intermediate **5** in the Baeyer–Villiger reaction (Scheme 2). Given the strong directing influence that silicon and tin have on the Baeyer–Villiger reaction, we were interested to establish whether these substituents would exert a similar degree of control over the Tiffeneau–Demjanov ring enlargement of cyclic ketones and on the related chain extension reaction of acyclic ketones.

To test this proposal we prepared the series of the silicon and tin substituted cyclic ketones **7**–**11** by conjugate addition of trimethylsilyllithium or trimethylstannyllithium to precursor enones. These were converted to the primary amines **12**–**16** (which are the precursors to the Tiffeneau–Demjanov reaction) by two different methods; Method A (Scheme 4) involved treatment of ketones **7**–**11** with trimethylsilylcyanide followed by reduction with lithium aluminium hydride.[18] By this method the amines **12**, **13**, **14** and **16** were obtained as inseparable mixtures of diastereoisomers which were used without further purification. The *trans*-isomer of **15** was the major product from application of Method A to the cyclohexanones **9** and **10**.

The *cis*-isomers of amines **14** and **15** were prepared by epoxidation of the ketones **9** and **10** with Corey's ylide (Method B, Scheme 5),[19] ring opened with azide ion[20] and the intermediate azides **17** and **18** reduced with sodium borohydride.[21]

The acyclic ketones **19** and **20** were prepared by literature methods[22,23] and converted to the amino alcohols **21** and **22** using Method A.



19; M = Si, R = Me
20; M = Sn, R = Bu

Tiffeneau–Demjanov reactions of **12**–**16**, **21** and **22** were effected by treating the amines with sodium nitrite in acetic acid overnight.[24,25] The product mixtures were analysed by ^1H and ^{13}C NMR, identification was made by comparison with known compounds. The results of these are summarised in Table 1.

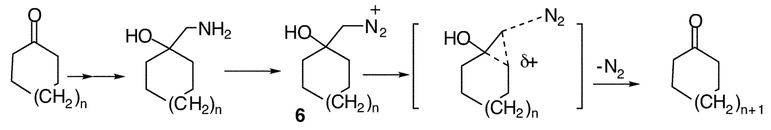
It is clear from the results summarised in Table 1 that both silicon and tin direct the course of the Tiffeneau–Demjanov ring expansion and chain extension reactions, however the degree of regioselectivity is surprisingly low, although comparison of the regioselectivities for the ring expansions of both isomers of **14** and **15** suggests that the regioselectivity is slightly higher for the *cis*-isomers. This contrasts with the powerful directing influence that these substituents have on the Baeyer–Villiger reaction. A possible rationalisation of this disappointing result can be made by comparing the transition states for these two reactions (Fig. 2).

There are two fundamental differences between these two transition states; the nature of the leaving group being

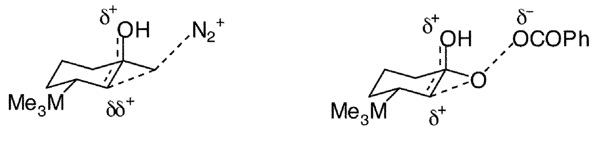
---

† Electronic supplementary information (ESI) available: experimental details and spectra. See http://www.rsc.org/suppdata/ob/b3/b314923d/

DOI: 10.1039/b314923d



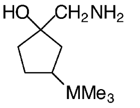
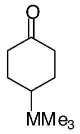
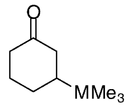
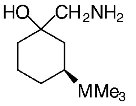
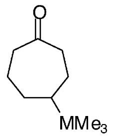
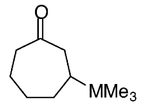
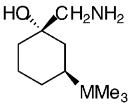
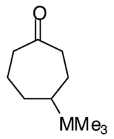
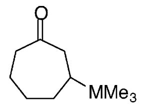
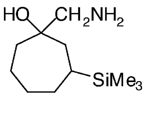
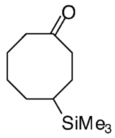
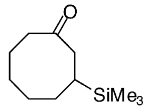
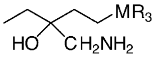
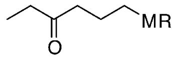
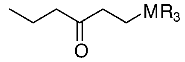
Scheme 3



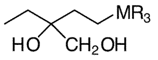
Tiffeneau-Demjanov Baeyer-Villiger

Fig. 2

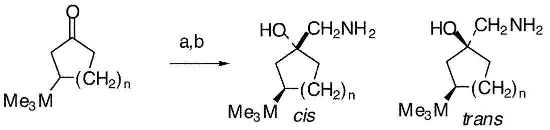
Table 1

		
12; M = Si (2 : 1) **13**; M = Sn (1.1 : 1)	**23** 58% **24** 63%	**9** 42% **10** 37%
		
14; M = Si (1 : 1) **15**; M = Sn (70% trans)	**25** 58% **26** 72%	**11** 42% **27** 28%
		
cis-**14**; M = Si *cis*-**15**; M = Sn	**25** 72% **26** 87%	**11** 28% **27** 13%
		
16	**28** 63%	**29** 37%
		
21; $SiMe_3$ **22**; $SnBu_3$	**30** 67%[a] **31** 64%	**32** 33% **33** 36%

[a] Small quantities of the diol **34** ca. 10% were isolated from the reaction.



34



a) KCN/18-crown-6, Me_3Si-CN, b) $LiAlH_4$

7; M = Si, n=1
8; M = Sn, n = 1
9; M = Si, n = 2
10; M = Sn, n = 2
11; M = Si, n = 3

12; n = 1, R = H, M = Si (2:1)
13; n = 1, R = H, M = Sn 1.1:1
14; n = 2, R = H, M = Si (1:1)
15; n = 2, R = H, M = Sn 71% trans
16, n = 3, R = H, M = Si (2.2:1)

Scheme 4

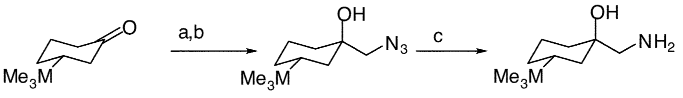
displaced and the nature of the atom being inserted during the ring expansion. In the Tiffeneau–Demjanov transition state the excellent diazonium leaving group is displaced as molecular nitrogen, this leaving group would require very little nucleophilic 'push' by the migrating C–C bond, and would involve an early transition state with a low degree of positive charge development on the migrating carbon. In contrast the Baeyer–Villiger transition state involves the displacement of a weaker carboxylate leaving group which would require a greater nucleophilic 'push' by the migrating carbon, this later transition state would involve a greater charge build up on the migrating carbon, furthermore the carbon is migrating to oxygen which should also lead to further polarisation of the developing bond. Thus the migrating carbon in the Baeyer–Villiger reaction is expected to have a larger degree of positive charge than the migrating carbon in the Tiffeneau–Demjanov reaction, and therefore the metal substituent (Si, Sn) would be expected to exert a stronger influence.

To investigate the effect that a weaker leaving group has on the regioselectivity of the silicon-directed Tiffeneau–Demjanov ring expansion, we chose to investigate the *tert*-butoxydiazene leaving group.[26] The oxydiazene substituent can be prepared by rearrangement of a nitroso-pivaloylamide derivative and has been used recently to initiate cationic polymerisation.[26]

Thus the *cis*- and *trans*- amines **14** were converted to the pivaloyl amide derivatives **35** and **36** (Scheme 6), which were then nitrosated by treatment with a solution of sodium nitrite in acetic acid. The resulting product was found to be a mixture of the ring expanded ketones **25** and **11** in the ratio 5 : 1 (from cis-**14**) and 4 : 1 (from trans-**14**). The expected nitrosamide intermediates **37** could not be isolated but clearly rearranged under the reaction conditions to the *tert*-butoxydiazene derivative **38** (Scheme 7) which then broke down with subsequent ring enlargement.

The improved regioselectivity of the ring enlargement is consistent with the less reactive oxydiazene leaving group requiring a greater push by the migrating carbon. Unfortunately we were unable to ascertain the directing effect of a tin substituent using this reaction as the conditions required to affect the nitrosation of the corresponding tin-substituted pivaloylamides derived from **15** resulted in complex mixtures and loss of the tin-substituent.

We are continuing to investigate the silicon and tin-directed Tiffeneau–Demjanov using alternative leaving groups on the exocyclic methylene to further improve the regioselectivity.



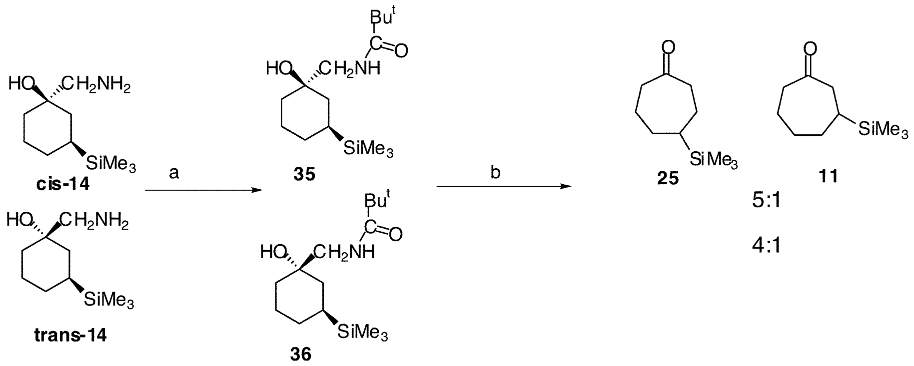
a) $CH_2SO(CH_3)_2$/THF b) NaN_3/CH_3OH, c) $NaBH_4/CH_3OH$

9; M = Si
10; M = Sn

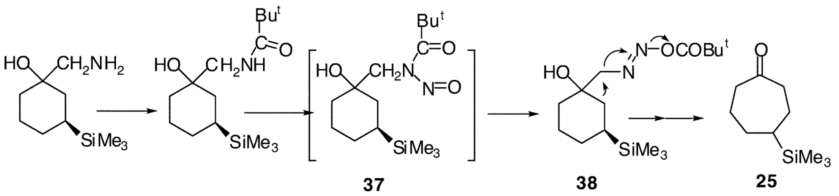
17; M = Si
18; M = Sn

14; M = Si
15; M = Sn

Scheme 5



Scheme 6 *Reagents*: a) pivaloyl chloride/pyridine; b) $NaNO_2/CH_3CO_2H$.



Scheme 7

Acknowledgements

Our thanks to the Australian Research Council for the award of an APRA (MM).

Notes and references

1 J. B. Lambert, *Tetrahedron*, 1990, **46**, 2677.
2 J. M. White, *Aust. J. Chem.*, 1995, **48**, 1227.
3 C. I. Clark and J. M. White, *Topics in Stereochemistry*, Volume 22, Ed. Scott E. Denmark, John Wiley and Sons, New York.
4 E. Colvin, *Silicon in Organic Synthesis*, Butterworths Monographs in Chemistry, Butterworth, Boston, 1981.
5 J. B. Lambert, G-t. Wang, R. B. Finzel and D. H. Teramura, *J. Am. Chem. Soc.*, 1987, **109**, 7838.
6 S. G. Wierschke, J. Chandrasekhar and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1985, **107**, 1496.
7 M. R. Ibrahim and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1989, **111**, 819.
8 I. Fleming and S. K. Patel, *Tetrahedron Lett.*, 1981, **22**, 2321.
9 A. Hosomi, *Acc. Chem. Res.*, 1988, **21**, 200.
10 T. H. Chan and I. Fleming, *Synthesis*, 1979, 761.
11 F. Badali, A. Karalis, W. Y. Tham and J. M. White, *Aust. J. Chem.*, 1996, **49**, 1293.
12 D. Seyferth, S. S. Washburne, C. J. Attridge and K. Yamamoto, *J. Am. Chem. Soc.*, 1970, **92**, 4405.
13 D. Seyferth, R. Damrauer and S. S. Washburne, *J. Am. Chem. Soc.*, 1967, **89**, 1538.
14 P. F. Hudrlik, A. M. Hudrlik, G. Nagendrappa, T. Yimenu, E. T. Zellers and E. Chin, *J. Am. Chem. Soc.*, 1980, **102**, 6894.
15 T. Aida, M. Asaoka, S. Sonoda and H. Takei, *Heterocycles*, 1993, **36**, 427.
16 S. Horvat, P. Karallas and J. M. White, *J. Chem. Soc. Perkin Trans. 2*, 1998, 2151.
17 M. Hesse, *Ring Enlargement in Organic Chemistry*, VCH, Weinheim, Federal Republic of Germany, 1991.
18 R. W. Thies and J. R. Pierce, *J. Org. Chem.*, 1982, **47**, 798.
19 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.
20 G. Swift and D. Swern, *J. Org. Chem.*, 1966, **31**, 4226.
21 K. Soai, S. Yokoyama and A. Ookawa, *Synthesis*, 1987, 48.
22 H. Nakahira, I. Ryu, A. Ogawa, N. Kambe and N. Sonoda, *Organometallics*, 1990, **9**, 277.
23 G. Wickham, H. A. Olszowy and W. Kitching, *J. Org. Chem.*, 1982, **47**, 3788.
24 P. A. S. Smith and D. R. Baer, *Org. React.*, 1960, **11**, 157.
25 K. Schank, in *The Chemistry Of Diazonium and Diazo groups*, Ed. S. Patai, Wiley, New York, 1978, pp. 645–657.
26 R. W. Darbeau, M. S. Delaney, U. Ramelow and K. R. James, *Org. Lett.*, 1999, **1**, 761.