Early Transition Metal Induced Intramolecular Cocyclisation / Elaboration Reactions Using a Cleavable Silicon Linker

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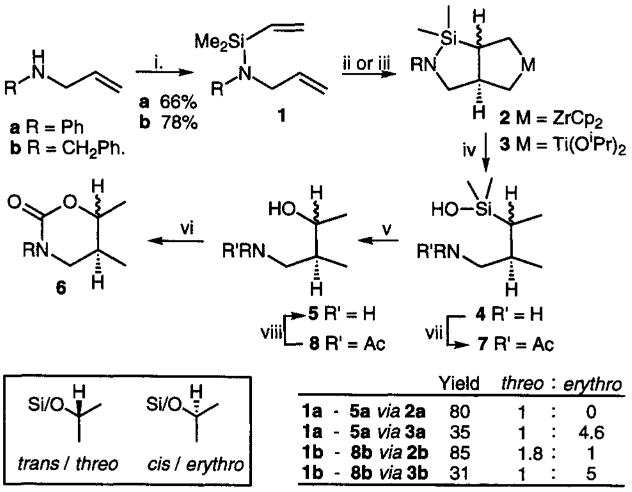
Abstract: 1,6- and 1,7-dienes and -enynes incorporating a silicon-oxygen or silicon-nitrogen link are co-cyclised with zirconocene(1-butene) or diisopropoxytitanium(propene) to give metallabicycles. Further elaboration followed by cleavage of the silicon-carbon bond using Tamao oxidation affords a wide variety of organic products.

The early transition metal induced intramolecular co-cyclisation of 1,n-dienes, -enynes, and -diynes to give metallacyclopent-anes, -enes, and -dienes is a useful method for carbon-carbon bond formation.[1] The wide variety of methods which have been developed for further elaboration of these metallacycles[2] promises to make them important intermediates in the synthesis of mono- and bicyclic compounds. Unfortunately the intermolecular co-cyclisation of alkenes and alkynes is a far more limited process[3] so that routes to acyclic and monocyclic products are restricted. One potential solution is to temporarily connect the two π-components. Silicon has been widely used as a cleavable linker in Diels-Alder and 1,3-dipolar cycloadditions, and in radical chemistry[4] where there are also great benefits from intramolecular reactions. In transition metal chemistry silaketal linkers have been used in ring closing metathesis cyclisations, and Dötz benzannulation reactions.[5] We report below our initial results using a silicon linker in zirconium and titanium induced co-cyclisation reactions.

We chose to examine cases where a heteroatom - silicon bond is formed / cleaved during the temporary connection processes. Advantages included the fast and quantitative formation of N-Si and O-Si bonds, and that Tamao oxidation of carbon-silicon bonds (our chosen cleavage method) works well when the silicon carries an oxygen or nitrogen substituent.[6]

Reaction of *N*-allylaniline with chlorodimethylvinylsilane gave the diene **1a**. Cocyclisation induced by zirconocene(1-butene), generated *in situ* from dibutylzirconocene (the 'Negishi reagent')[7] gave cleanly the zirconacycle ***trans*-2a**. In the analogous cyclisation of diallylaniline a 1 : 2.6 mixture of *trans*- and *cis*- fused zirconabicycles is formed initially, isomerising to a 2.5 : 1 mixture on heating.[8] Heating the zirconacycle ***trans*-2a** (60°C, 4 h) did not cause any isomerisation. It is notable that 1,6-heptadiene gives exclusively the *trans*-fused zirconabicycle[2b] so **1a** resembles the all carbon analogue, rather than the amine where carbon replaces the silicon group. Aqueous work-up of **2a** gave the silanol ***threo*-4a**.[9] Tamao oxidation[6] of the crude product gave the aminoalcohol **5a**[10] as a the single *threo*-isomer. The stereochemistry of ***threo*-5a** was proven by conversion to the cyclic carbamate ***trans*-6a** and ^{1}H NMR studies.[11] A large excess of hydrogen peroxide was required for the Tamao oxidation (zirconium residues probably catalyse decomposition of hydrogen peroxide) and timing was critical for good yields. Isolation of substantial amounts of nitrobenzene when the reaction was left overnight confirmed that oxidation of the nitrogen was occurring. Acylation of the intermediate amino-silanol **4a** gave a more reliable oxidation (≈90% yield, and not time critical), but the overall yield was comparable.

It would be desirable to be able to vary the stereochemistry of the initial co-cyclisation. Treatment of **1a** with the Ti(O^{i}Pr)$_4$ / 2 ^{i}PrMgCl reagent [*in situ* (^{i}PrO)$_2$Ti(CH$_2$=CHCH$_3$)] recently developed by Sato[12] followed by protonation gave the silanol **4a** as a ≈ 1 : 4 *threo* : *erythro* mixture indicating that the presumed intermediate titanabicycle **3a** was predominantly *cis*-fused. Tamao oxidation gave a 4.6 : 1 mixture of the amino alcohols *erythro*-**5a** and *threo*-**5a** in 35% overall yield from **1a**.



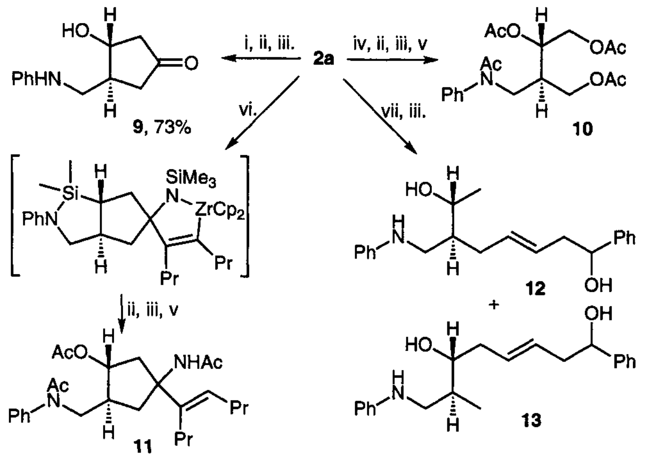
	Yield	*threo* : *erythro*
1a - **5a** *via* **2a**	80	1 : 0
1a - **5a** *via* **3a**	35	1 : 4.6
1b - **8b** *via* **2b**	85	1.8 : 1
1b - **8b** *via* **3b**	31	1 : 5

Scheme 1. i. a. BuLi, -40°C, THF; b. Me$_2$(CH$_2$=CH)SiCl, 20°C, 1h. ii. Cp$_2$ZrCl$_2$ + 2 BuLi, -78°C - 20°C, 2h. iii. Ti(O^{i}Pr)$_4$, 2 ^{i}PrMgCl, -40°C, 2h. iv H$_2$O, 20°C, 16h. v. KHCO$_3$, KF, H$_2$O$_2$, MeOH/THF, 20°C, 2 - 16h. vi. CO(CCl$_3$)$_2$, benzene, 80°C, 12h. vii. Ac$_2$O, pyridine, cat. DMAP. viii. 2M HCl aq, reflux, 6h

The potentially more useful *N*-benzyl substrate **1b** was examined next. Cyclisation with zirconocene(1-butene) followed by hydrolysis gave the silanols **4b** as a 2 : 1 mixture of *threo*- and *erythro*- isomers. Heating the intermediate zirconacycle did not change the ratio. Attempted Tamao oxidation of **4b** failed, presumably because the nitrogen is more easily oxidised than in **4a**. *N*-Acylation of the crude silanols followed by Tamao oxidation gave a 1.8 : 1 mixture of the easily separable *N*-acyl aminoalcohols ***threo*-** and ***erythro*-8b** in an excellent overall yield. Deacylation and formation of the cyclic carbamates **6b** was used to prove the relative stereochemistries.[11] Cyclisation of **1b** with Ti(O^{i}Pr)$_4$ / 2 ^{i}PrMgCl followed by aqueous work-up gave a 1 : 5 mixture of ***threo*-** and ***erythro*-4b** indicating that the *cis*-fused titanacycle **3b** predominates. Acylation and Tamao oxidation gave **8b** in 31% yield as a 5 : 1 mixture of *erythro* : *threo* diastereoisomers.

Further elaboration of the zirconacycle intermediates is essential if efficient use is to be made of the metal. Carbonylation,[2a] air oxidation,[2b] and trimethylsilyl cyanide insertion / 4-octyne trapping[2c] of **2a** followed by aqueous work-up and Tamao oxidation gave the highly elaborated products **9**, **10**, and **11** in reasonable overall yields from *N*-allyl-*N*-(dimethylvinylsilyl)aniline **1a** (Scheme 2). The dramatic increase in complexity in these sequences is a testament to the efficient use of the transition metal. Insertion of lithium chloroallylide, generated *in situ* from allyl chloride and lithium 2,2,6,6-tetramethylpiperidide (LiTMP), into **2a** occurred without selection between the two available carbon-zirconium bonds to give a 1 : 1 mixture of **12** and **13** after work up with benzaldehyde[2d] followed by protonolysis and Tamao oxidation.

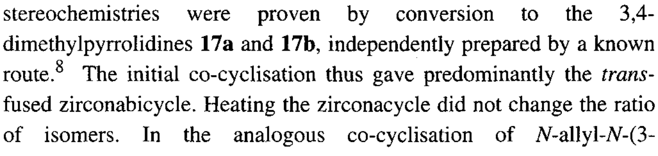
Reaction of *N*-allylaniline with allylchlorodimethylsilane to give **14** followed by zirconocene induced co-cyclisation gave the metallacycle



42%, 2:1 mixture of diastereomers 52%. **12** : **13** :: 1 : 1

Scheme 2. Yields based on **1a**. i. a. 1 atm CO, -40 - 20°C; b. O_2, 20°C, 1h. ii. H_2O. iii. $KHCO_3$, KF, H_2O_2., THF/MeOH, 2 - 16h. iv. dry air. v. Ac_2O, pyridine, DMAP. vi. Me_3SiCN, 4-octyne, 50°C, 12h. vii. a. $CH_2{=}CHCH_2Cl$, LiTMP, -85°C; b. PhCHO, $BF_3.Et_2O$, -78°C - 20°C; c. $NaHCO_3$aq.

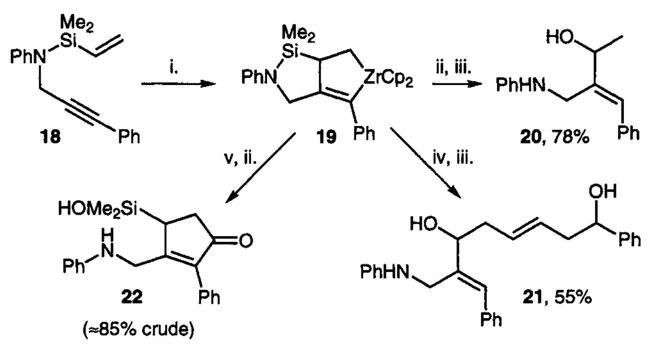
15 as a 4 : 1 ratio of isomers (Scheme 3). Protonolysis and Tamao oxidation gave the aminoalcohols **16a** and **16b** in a 4 : 1 ratio. The stereochemistries were proven by conversion to the 3,4-dimethylpyrrolidines **17a** and **17b**, independently prepared by a known route.[8] The initial co-cyclisation thus gave predominantly the *trans*-fused zirconabicycle. Heating the zirconacycle did not change the ratio of isomers. In the analogous co-cyclisation of *N*-allyl-*N*-(3-butenyl)benzylamine the kinetic product is a 4 : 1 mixture of *cis* : *trans* ring fusion, and the thermodynamic product a 1 : 1 mixture.[13] With 1,7-octadiene the kinetic product is >80% *cis*-fused[8,14] and the thermodynamic product >97% *trans*-fused.



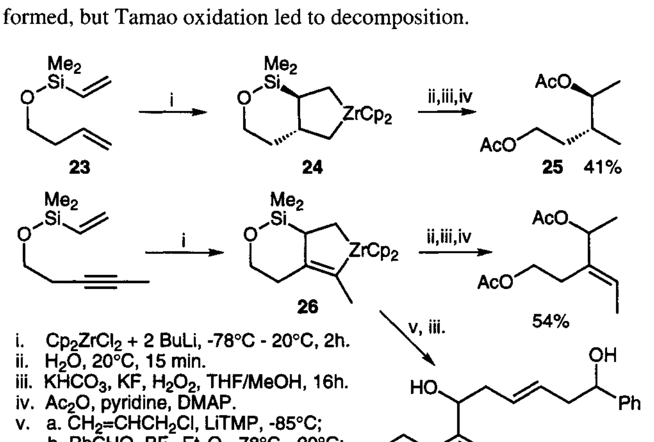
Scheme 3. i. a. BuLi. b. $Me_2(CH_2{=}CHCH_2)SiCl$. ii. Cp_2ZrCl_2 + 2 BuLi, -78 - 20°C. iii. MeOH, $NaHCO_3$. iv. H_2O_2, KF, $KHCO_3$, MeOH/THF. v. a. 1 eq. BuLi. b. 1 eq. MsCl

The elaboration of a propargylic amine was examined next. Reaction between *N*-(3-phenyl-2-propynyl)aniline and dimethylchlorovinylsilane gave the cyclisation precursor **18**. Zirconocene induced co-cyclisation formed the zirconacycle **19** which underwent protonation and Tamao oxidation to give the aminoalcohol **20** in good yield (Scheme 4). Further elaboration of **19** by regiospecific insertion of lithium chloroallylide into the alkyl-zirconium bond[15] followed by addition of benzaldehyde and Tamao oxidation gave the aminodiol **21**. Carbonylation of **19** gave the silanol **22** in good yield, but unfortunately all attempts at Tamao oxidation lead only to decomposition.

Zirconocene induced co-cyclisation of -dienes and -enynes derived from allylic or propargylic alcohols and chlorodimethylvinylsilane failed as expected - rearrangement of the intermediate β-alkoxy-zirconocene η^2-alkene or -alkyne moieties to allyl or propargyl zirconium species being well precedented.[16] Homoallylic alcohols and homopropargylic alcohols do not suffer from the rearrangement problem and gave reasonable yields of elaborated products on reaction with chlorodimethylvinylsilane / cocyclisation / elaboration and Tamao oxidation (Scheme 5). Of note is that cyclisation of the 1,7-diene **23** gave exclusively the *trans*-fused zirconabicycle **24** and hence diacetate **25**, the stereochemistry of the later being proven by independent synthesis.[17] Carbonylation of the unsaturated zirconacycle **26** suffered the same fate as with **19** - the silicon substituted cyclopentenone was formed, but Tamao oxidation led to decomposition.



Scheme 4. i. Cp_2ZrCl_2 + 2 BuLi, -78 - 20°C. ii. MeOH, $NaHCO_3$. iii. H_2O_2, KF, $KHCO_3$, MeOH/THF. iv. a. $CH_2{=}CHCH_2Cl$, LiTMP, -80°C; b. PhCHO, $BF_3.Et_2O$, -78-20°C, 2h then $NaHCO_3$ aq. v. CO (1 atm)

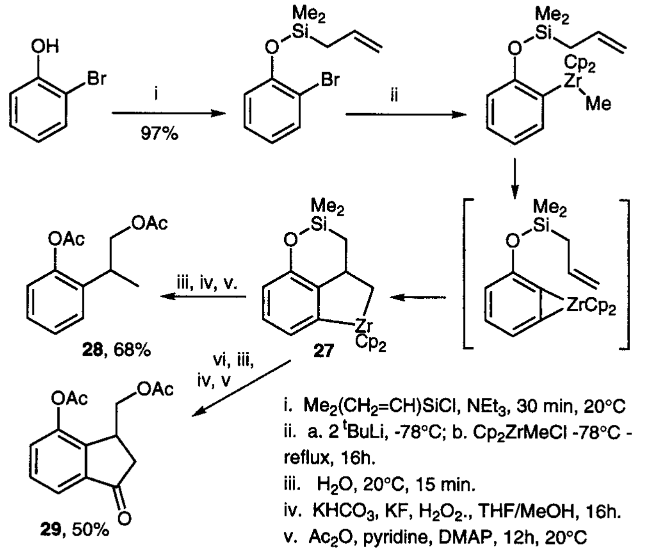


i. Cp_2ZrCl_2 + 2 BuLi, -78°C - 20°C, 2h.
ii. H_2O, 20°C, 15 min.
iii. $KHCO_3$, KF, H_2O_2, THF/MeOH, 16h.
iv. Ac_2O, pyridine, DMAP.
v. a. $CH_2{=}CHCH_2Cl$, LiTMP, -85°C;
b. PhCHO, $BF_3.Et_2O$, -78°C - 20°C;
c. $NaHCO_3$aq.

Scheme 5

The formation and reactions of zirconocene(benzyne) complexes has been developed by Erker and Buchwald but intermolecular trapping with terminal alkenes is generally inefficient.[18] Reaction of o-bromophenol with allylchlorodimethylsilane followed by bromine/ lithium exchange, addition of (methyl)zirconocene chloride, and thermolysis gave the adduct **27** by intramolecular trapping of the *in situ* generated zirconocene(benzyne) complex (Scheme 6). Protonolysis, or carbonylation followed by protonolysis, then Tamao oxidation and acylation gave the products **28** and **29** in reasonable overall yields. The analogous zirconocene(benzyne) complex derived from 2-bromoanisole inserts alkenes exclusively into the bond remote to the methoxy group so the methods are complementary.

In conclusion we have shown that the early transition metal induced intramolecular co-cyclisation of dienes and enynes incorporating a cleavable silicon linker is an efficient process. Further elaboration of the intermediates has the potential to give a very wide range of organic structures, a few of which we have illustrated. The transformation may also be viewed as a heteroatom directed carbometallation of alkenes and



i. $Me_2(CH_2{=}CH)SiCl$, NEt_3, 30 min, 20°C
ii. a. 2 ^tBuLi, -78°C; b. $Cp_2ZrMeCl$ -78°C - reflux, 16h.
iii. H_2O, 20°C, 15 min.
iv. $KHCO_3$, KF, H_2O_2., THF/MeOH, 16h.
v. Ac_2O, pyridine, DMAP, 12h, 20°C
vi. CO (1 atm).

Scheme 6

alkynes. The co-cyclisation reaction of 1,6 and 1,7-dienes containing silicon-oxygen or silicon-nitrogen links in the connecting chain gives unexpected stereochemical results. Generally these resemble the all-carbon analogues, rather than the oxygen or nitrogen containing equivalents where the silicon is replaced by carbon. A qualification is that the presence of the heteroatom speeds equilibration of the zirconacycles so that only thermodynamic mixtures are observed.

Rel-(2_S_,3_R_)-4-anilino-3-methylbutan-2-ol (5a)

To a solution of zirconocene dichloride (0.584 g, 2 mMol) in THF (10 mL) at -70°C under argon was added dropwise n-butyllithium solution (1.60 mL, 2.5 M in hexanes, 4 mMol), followed 15 min later by *N*-allyl-*N*-(1,1-dimethyl-1-vinylsilyl)-*N*-phenylamine (0.434 g, 2 mMol). The solution was warmed to room temperature and stirred for 2 h to give an orange solution. Addition of methanol (5 mL) and stirring for 15 min gave a cloudy pale yellow mixture which was poured onto water (150 mL). Extraction with diethyl ether (3 x 50 mL), drying of the combined organic layers with anhydrous magnesium sulphate and the removal of solvent by rotary evaporation gave *rel*-((1*S*,2*R*)-3-anilino-1,2-dimethylpropyl) (hydroxy)dimethylsilane as a yellow oil (0.603 g). To a solution of the crude product in methanol (8 mL) and THF (8 mL) was added potassium hydrogen carbonate (0.200 g, 2 mMol) and potassium fluoride (0.116 g, 2 mMol) giving a green solution. After cooling in an ice-bath 30% aqueous hydrogen peroxide solution (10 mL) was added. The reaction flask was allowed to warm to room temperature over 2 h and monitored by t.l.c. analysis. If necessary more hydrogen peroxide was added to effect complete oxidation of the starting material. With ice-bath cooling 5% palladium on carbon (≈20 mg) was added and stirring continued overnight at room temperature. The reaction mixture was the filtered through a thin layer of Celite and the solids washed with ethyl acetate (50 mL). The solution was extracted with ethyl acetate, (3 x 50 mL), the combined organic layers washed with brine (100 mL) and the solvent removed by rotary evaporation to yield a crude product. Chromatography on grade III neutral alumina (petrol - diethyl ether gradient) gave the *title aminoalcohol* as a colourless oil (0.286 g, 80%).

^1H NMR ($CDCl_3$, 300 MHz): δ 7.23 (2H, t, J=7.4 Hz), 6.78 (1H, t, J=7.4 Hz), 6.70 (2H, t, J=7.6 Hz), 4.04 (1H, bs), 3.75 (1H, quintet, J=6.5 Hz), 3.23 (1H, dd, J=12.4, 7.1 Hz), 3.11 (1H, dd, J=12.3, 5.2 Hz), 2.6 (1H, br s), 1.69 (1H, septet, J=6.3 Hz), 1.24 (3H, d, J=6.3 Hz), 0.98 (3H, d, J=6.9 Hz) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.27 (s), 129.25 (d, 2C), 118.10 (d), 113.64 (d, 2C), 72.60 (d), 49.26 (t), 40.01 (d), 21.32 (q), 14.98 (q) ppm.

IR: 3374 (bs), 2964 (s), 1603 (s), 1506 (s), 1381 (m), 1257 (m), 749 (m), 733 (m) cm^{-1}.

HRMS (CI): found (M^++1) 180.1394. $C_{11}H_{18}NO$ requires 180.1389.

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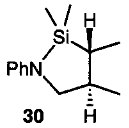
(9) Depending on the precise work-up procedure the amino-silanols e.g. **4** were often contaminated with the ring closed form e.g. **30**. Chromatography on silica, or Kugelrohr distillation gave mostly or exclusively the closed form (stirring in water reversed the process). Oxygen linked systems were always isolated in the cyclic-siloxane form.



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(10) All non-silicon containing compounds were characterised by high field ^{1}H and ^{13}C NMR, IR, MS, and HRMS or combustion analysis. Isomers **11**, **12/13**, and **16** were not separated.

(11) For the oxazolines *trans-* and *cis*-**6a** and -**6b** the stereochemical assignment was clear from the coupling constant between the two C*H*Me protons. For *trans-* and *cis*-**6a** it is 9.9 and 3.3 Hz, for **6b** 9.6 and 1.8 Hz, and for the known parent 2,3-dimethyloxazoline (**6**, R = H) 10 and 3.5 Hz respectively (Fisyuk, A. S.; Ryzhiva, E. V.; Unkovskii, B. V. *Chem. Hetero. Comp.* **1994**, *30*, 238).

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