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A bidirectional synthesis of spiroacetals via Rh(II)-catalysed C–H insertion

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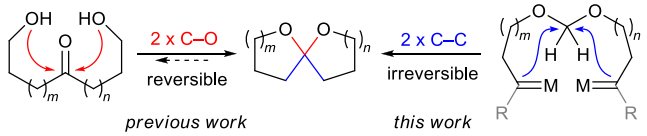
Acyclic methylene acetals bearing two diazoester subunits have been converted to [5,5]-spiroacetals via bidirectional C–H insertion under Rh(II) catalysis. Using a chiral Rh(II) catalyst, the major diastereomer can be produced in high enantiomeric excess (89%).

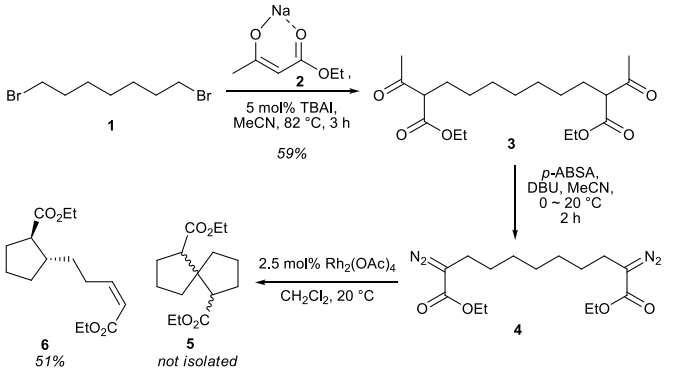
Spiroacetals are common in a wide variety of biologically active natural products, from insect pheromones to highly potent anti-cancer agents.[1] Many commonly employed methods for spiroacetal synthesis involve formation of one or both of the C–O bonds, concomitant with spirocycle formation. The most highly utilised methodology is intramolecular acetalisation of appropriately masked dihydroxyketone precursors, which proceeds via intermediate oxonium ions and is generally reversible (Scheme 1). A notable exception is the strategy for non-anomerically stabilised spiroacetal synthesis developed by Rychnovsky and co-workers, involving reductive lithiation of ortho ester-derived anomeric cyanides and *in situ* intramolecular alkylation onto a pendant alkyl chloride.[2]



Scheme 1 Spirocyclisation via C–O vs. C–C bond formations.

As an alternative approach, we sought to develop a method for spiroacetal synthesis, based on consecutive C–C bond-forming reactions of simple acyclic acetal precursors. To achieve this aim, we envisioned a one-pot double-C–H insertion procedure involving methylene acetals bearing pendant metal carbene groups. We postulated that the activating influence of oxygen atoms adjacent to the C–H bonds undergoing insertion could be key to the possible success of this approach.[3] A related bidirectional C-H insertion strategy has been reported for synthesis of spiro[4.4]nonane-2,7-diones [4a,b] and 1,1'-spirobi[indan-3,3'-dione],[4c] with substrates that cannot undergo β-elimination.

Given the known proclivity of rhodium carbenes to favour 5-membered ring-formation in intramolecular C–H insertion reactions, we focused our attention on substrates that would allow this to occur. For comparison purposes, a substrate that lacks activating oxygen atoms, and therefore a potential precursor for spirocarbacycle synthesis, was initially prepared (Scheme 2). Reaction of 1,7-dibromoheptane (**1**) with the sodium salt of ethyl acetoacetate (**2**) provided the bis β-ketoester **3**. Double de-acetylative diazo transfer using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and DBU in MeCN gave the bis α-diazoester **4**.[5]



Scheme 2 Attempted spirocarbacycle formation.

With **4** in hand, the rhodium(II)-catalysed double C–H insertion was attempted. Treatment with 2.5 mol% $Rh_2(OAc)_4$ in CH_2Cl_2 at room temperature failed to deliver any spirocyclic products **5**. Disubstituted cyclopentane **6** was afforded in 51% yield, along with a complex mixture of side products. Similar results were obtained using Rh_2(*S*-PTAD)$_4$ in PhMe. The formation of **6** suggests that, although the first C–H insertion occurs to some extent, β-elimination of the second Rh(II) carbene competes with the challenging second C–H insertion. β-Hydride

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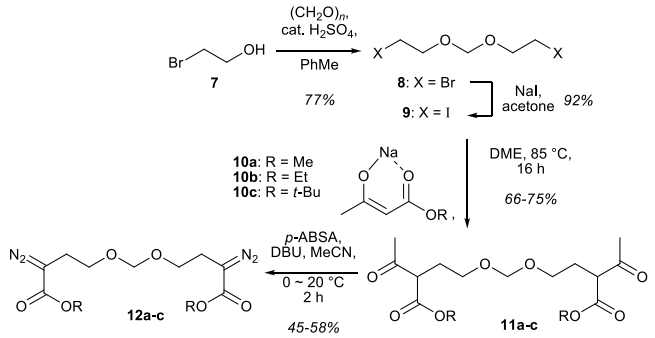
elimination is a well-known and characterised alternative pathway to intramolecular C–H insertion for ester stabilised Rh(II) carbenes, with the relative rates being influenced by substrate and catalyst sterics and electronic factors.[6] Steric hindrance at the desired methine position is exacerbated by the adjacent, sterically congested ester-bearing methine carbon. Furthermore, the electron-withdrawing ester group also acts to disfavour 1,5-C–H insertion, a process which is heavily influenced by electronic factors.[7]

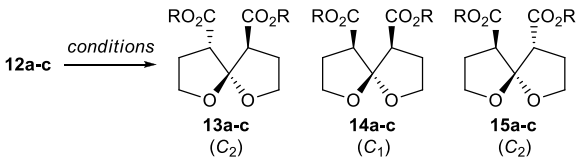
Our attention turned to the formation of spiroacetals from substrates that incorporate oxygen atoms adjacent to the site of C–H insertion. 2-Bromoethanol (**7**) was reacted with paraformaldehyde in the presence of H_2SO_4 under Dean–Stark conditions to give methylene acetal **8**, [8] which was subsequently converted to the corresponding bis iodide **9** using NaI in acetone (Scheme 3). Treatment of **9** with the sodium salts of methyl, ethyl and *tert*-butyl acetoacetate (**10a-c**) in DME gave intermediate bis β-ketoesters **11a-c**, which were converted to the corresponding bis α-diazoesters **12a-c** using *p*-ABSA and DBU.



Scheme 3 Spiroacetal precursor synthesis.

Pleasingly, treatment of bis diazo compound **12b** with $Rh_2(oct)_4$ in PhMe provided an inseparable *ca*. 66:17:17 mixture of 5,5-spiroacetal diastereomers **13b**, **14b** and **15b**, respectively, in 58% yield (Table 1, entry 1). Use of the more electrophilic $Rh_2(TFA)_4$ as catalyst gave only mono-cyclised products in low yield and none of the desired spiroacetals (entry 2). The less electrophilic, but bulky catalyst, $Rh_2(TPA)_4$, resulted in a reversal of selectivity, providing the unsymmetric diastereomer **14b** as the major diastereomer (entry 3). Using $Rh_2(esp)_2$, which bears bulky bridging dicarboxylate ligands,[9] and the methyl ester substrate **12a** gave exceptional selectivity for **13a** (entry 4). By comparison, the more sterically demanding ethyl and *tert*-butyl ester substrates **12b** and **12c**, respectively, with $Rh_2(esp)_2$ gave a modest decrease in diastereoselectivity (entries 5 and 6). The chiral catalysts Rh_2(*S*-DOSP)$_4$ [10] and Rh_2(*S*-PTAD)$_4$ [11] were effective for this transformation, giving similar diastereoselectivities to $Rh_2(oct)_4$ (entries 7 and 8).

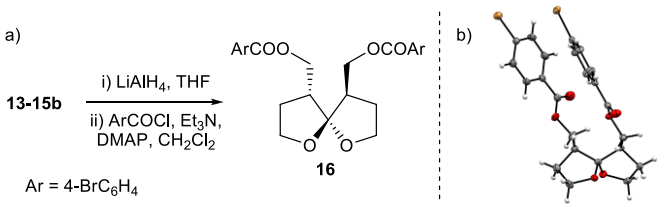
Table 1 Synthesis of 5,5-spiroacetals.



Entry	SM	Conditions[a]	Ratio	Yield (%)
1	**12b**	1 mol% $Rh_2(oct)_4$, –78 → 0 °C, 2 h	66:17:17	58
2	**12b**	1 mol% $Rh_2(TFA)_4$,–78 → 0 °C, 2 h	n.d.	0
3	**12b**	1 mol% $Rh_2(TPA)_4$, –78 → 0 °C, 2 h	14:84:2	67
4	**12a**	0.1 mol% $Rh_2(esp)_2$,–78 → 0 °C, 2 h	98:<1:<1	56
5	**12b**	0.1 mol% $Rh_2(esp)_2$,–78 → 0 °C, 2 h	89:11:<1	67
6	**12c**	0.1 mol% $Rh_2(esp)_2$,–78 → 0 °C, 2 h	89:11:<1	50
7	**12b**	1 mol% Rh_2(*S*-DOSP)$_4$,–78 → 0 °C, 2 h	74:17:9	52[b]
8	**12b**	1 mol% Rh_2(*S*-PTAD)$_4$,–78 → 0 °C, 2 h	62:33:5	69[c]

[a]All reactions were conducted in PhMe. [b]Major diastereomer **14b** 74% ee by chiral HPLC of a derivative. [c]Major diastereomer **14b** 89% ee by chiral HPLC of a derivative.

Although the C_1 spiroacetal diastereomer **14b** could be readily identified in the mixture, and distinguished from the other isomers **13b** and **15b** by ^{1}H and ^{13}C NMR, the C_2 diastereomers could not be distinguished from each other spectroscopically. As such, the mixture of diastereomers was reduced using $LiAlH_4$ and the resultant alcohols converted to a separable mixture of *p*-bromobenzoates, from which **16** was provided in 39% yield (Scheme 4). The Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-PTAD)$_4$-catalysed reactions provided *p*-bromobenzoates derived from the major spiroacetal **13b**, in 74 and 89% ee, respectively. The relative and absolute configuration (Flack Parameter = -0.012(7)) of this crystalline derivative resulting from Rh_2(*S*-PTAD)$_4$-mediated C–H insertion (Scheme 4) was determined by x-ray crystallography.‡

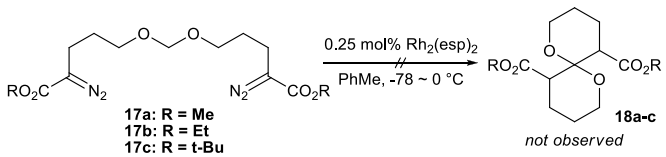


Scheme 4 a) Spiroacetal derivatisation. b) ORTEP diagram for **16**.

It is interesting to note that both chiral catalysts, Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-PTAD)$_4$, provide the same enantiomer of **13b**, despite previous observations of opposite enantioinduction using these catalysts to mediate intramolecular C–H insertion of donor/acceptor carbenes.[11] Further work is ongoing to investigate the mechanism of this bidirectional synthesis, with particular interest in whether one or both of the C–H insertion steps proceed via a non-concerted mechanism involving hydride transfer from the acetal carbon to the carbene,[12] since this has important ramifications for the stereochemical course of the reaction.

In an attempt to extend the methodology to 6,6-spiroacetals, bis α-diazoesters **17a-c** were synthesised by an analogous route to that used for **12a-c** starting from 3-chloro-1-propanol

(Scheme 3). Unfortunately, treatment of **17a-c** with $Rh_2(esp)_2$ under a variety of conditions failed to provide any of the desired 6,6-spiroacetals **18a-c** (Scheme 5). Indeed, a complex mixture of products was obtained in each case, showing evidence for β-elimination, O–H insertion into water and oxidation (presumably from adventitious oxygen) at the carbene site. No cyclic products, resulting from C–H insertion, were observed. While disappointing, this result was not unexpected, given the known preference for 1,5-C–H vs 1,6-C–H insertion and proclivity shown by ester-stabilised Rh(II) carbenes to undergo β-Hydride elimination.[6]



Scheme 5 Attempted 6,6-spiroacetal formation.

In conclusion, we have demonstrated the bidirectional synthesis of 5,5-spiroacetals from simple methylene acetal precursors via Rh(II)-catalysed double C–H insertion. The procedure creates two rings and three new stereogenic centres in one pot from simple, achiral precursors. The diastereoselectivity of the reaction can be influenced by appropriate choice of catalyst, and chiral catalysts can be used to provide the major diastereomer in excellent enantioselectivity. The product spiroacetals represent interesting chiral, 3-dimensional scaffolds for future drug discovery, asymmetric synthesis and catalysis. Work is ongoing to extend this strategy to the synthesis of other spirocyclic scaffolds and other bicyclic topologies.

Notes and references

‡ Crystal data for **16**. $C_{23}H_{22}Br_2O_6$, M = 554.22, T = 130.0 K, λ = 1.54184, Orthorhombic, space group P $2_12_12_1$, a = 6.0088(1) b = 14.4880(1), c =25.2409(2) *Å*, V = 2197.36(2) *Å*^{3}, Z = 4 , D_c = 1.675 mg M^{-3} μ(Cu-Kα) 5.007 mm^{-1}, F(000) =1112, crystal size 0.55 x 0.27 x 0.22 mm^3, 15254 reflections measured, 4594 independent reflections [R(int) = 0.0272], the final R was 0.0259[I > 2σ(I)] and *w*R(F^2) was 0.0703 (all data), Flack parameter -0.012(7). CCDC deposit code 1519781.

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