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Highly diastereoselective hydrosilylations of allylic alcohols†

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The highly *syn*-selective hydrosilylation of allylic alcohols was developed which, following oxidation, provided 1,3 alcohols containing two contiguous stereocentres. Through judicious choice of silane the complementary *anti*-selective hydrosilylation was also developed. This protocol was applied to the synthesis of an all *syn* polyketide stereotriad.

Organosilicon compounds are important tools in organic synthesis, with their use as protecting groups being demonstrated in numerous total syntheses. Their use as a synthetic handle for building molecular complexity is much less developed with a few notable exceptions. Organosilanes can be used as the transmetallating partner in Hiyama and Denmark–Hiyama cross coupling reactions,[1] as a masked hydroxyl group *via* the Fleming–Tamao oxidation,[2] and as a precursor to many facile halogenation reactions.[3] More recently, these versatile compounds have also found use in medicinal chemistry, with several drug candidates containing organosilicon functionality.[4]

Due to the increased uses of these important compounds, the need for new, highly efficient and robust protocols to afford stereochemically defined organosilanes has increased, with transition metal catalysis proving invaluable. Alkene hydrosilylation has become a cornerstone in this endeavour.[5] Traditionally, this C–Si bond formation has been catalysed by highly active catalysts such as Speier's [H_2PtCl_6][6] or Karstedt's (Pt_2dvs_3) catalyst.[7] In spite of their high reactivity, these platinum catalysed hydrosilylation reactions have drawbacks. They suffer from unwanted side reactions, as well as having issues with regio- and stereocontrol.

The anti-Markovnikov addition of hydrosilanes to 1,1-disubstituted olefins can result in the formation of a new stereogenic centre. Stereoselectivity can be imparted into this reaction *via* two strategies: reagent control and substrate control. The former requires chiral catalysts to be able to differentiate between the two prochiral faces of the alkene. This approach is still in its infancy with several notable examples, however the scope of these reactions tends to be poor.[8] The more developed field is to use a pre-existing stereogenic centre to direct the addition to one of the faces of the alkene thus forming diastereoisomers in the process.[9]

Tamao and Ito reported an intramolecular hydrosilylation of silyl ethers onto 1,1-disubstituted alkenes using H_2PtCl_6 as the catalyst.[10] Following oxidation, 1,3-diols were produced with two contiguous stereogenic centres being formed in moderate to good selectivity in most cases with the *syn*-diastereomer predominating.[11] Since this work, other groups have reported a range of hydrofunctionalisations followed by *in situ* oxidations to afford these important scaffolds.[12] Previously we demonstrated, the combination of $PtCl_2$ and XPhos as a catalyst system provides excellent regio and stereocontrol in the hydrosilylation of alkynes.[13] We hypothesised that the use of bulky phosphine ligands would also improve the stereochemical outcome of this reaction. In particular, the judicious use of ligand could achieve high levels of diastereocontrol.[14] Herein we report the use of bulky phosphine ligands to enhance the *syn* stereochemical outcome and a complementary intermolecular *anti* hydrosilylation of allylic alcohols.

Optimisation. Our optimisation studies began by examining allylic alcohol **1a** (Table 1). This substrate was reported by Tamao and Ito to perform the hydrosilylation in 83 : 17 diastereoselectivity.[10] In this report, they required the pre-formation of the silyl ether prior to the hydrosilylation step. We reasoned that the both these steps could be performed concomitantly to provide a one-step procedure. Indeed, the use of Speier's catalyst and Et_2NSiMe_2H provided the requisite diol following oxidation in the same diastereoselectivity as reported by Tamao and Ito, albeit in reduced yield. To improve the reactivity and stereoselectivity, we next examined the effect of bulky phosphine ligands and found XPhos **L1** provided the optimal result in a 96 : 4 diastereomeric ratio and a much improved yield. Further optimisation came from a slightly modified oxidation procedure which allowed us to obtain the diol in excellent yields and diastereoselectivities. The use of $ClSiMe_2H$ provided similar levels of diastereoselectivity with a much reduced yield and $MeOSiMe_2H$ failed to react. With these conditions in hand, we began to examine the substrate scope for this reaction (Table 2).

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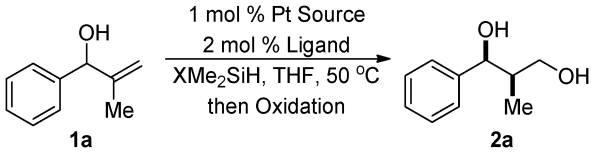
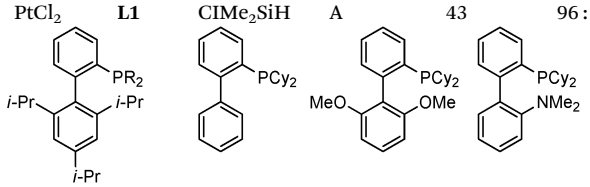
Table 1 Optimisation studies



1a 2a

Entry	Pt source	Ligand	XMe_2SiH	Oxidation[a]	Yield[b] (%)	d.r.[c]
1	H_2PtCl_6	—	Et_2NMe_2SiH	A	37	84 : 16
2	$PtCl_2$	PCy_3	Et_2NMe_2SiH	A	12	80 : 20
3	$PtCl_2$	**L1**	Et_2NMe_2SiH	A	71	96 : 4
4	$PtCl_2$	**L2**	Et_2NMe_2SiH	A	47	90 : 10
5	$PtCl_2$	**L3**	Et_2NMe_2SiH	A	40	85 : 15
6	$PtCl_2$	**L4**	Et_2NMe_2SiH	A	35	80 : 20
7	$PtCl_2$	**L5**	Et_2NMe_2SiH	A	n.r.	—
8	**$PtCl_2$**	**L1**	**Et_2NMe_2SiH**	**B**	**83**	**96 : 4**
9	$PtCl_2$	**L1**	$MeOMe_2SiH$	A	n.r.	—
10	$PtCl_2$	**L1**	$ClMe_2SiH$	A	43	96 : 4



[R=Cy]; XPhos (**L1**) Cy-JohnPhos (**L3**) SPhos (**L4**) DavePhos (**L5**)
[R=*t*-Bu]; *t*-Bu-XPhos (**L2**)

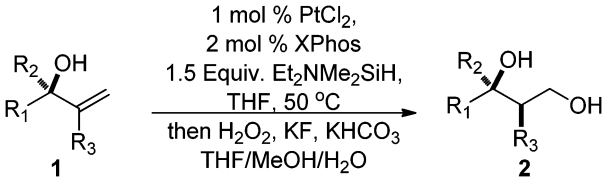
[a] Conditions A: H_2O_2, KF, $NaHCO_3$, THF, MeOH, H_2O; B: H_2O_2, KF, $KHCO_3$, THF, MeOH, H_2O. [b] Combined yield of diastereoisomers. [c] Determined by ^1H NMR analysis of the crude.

Syn-selective intramolecular hydrosilylation. The reaction is tolerant of a wide range of functional groups with substituted aromatic substrates **2b–d** reacting in a similar fashion to the parent phenyl substrate. Heteroaromatic substrates are also well tolerated with furan and pyrrazole substrates **2e–f** formed, albeit in slightly reduced diastereoselectivities. The role of sterics is very clearly exemplified by the alkyl substituents **2g–i** where the more hindered the substrate the higher the diastereoselectivity, with the *tert*-butyl substrate **1i** providing a single diastereoisomer. When tertiary allylic alcohols are used, moderate diastereoselectivity is observed as there is much less of a steric bias between the two substituents at the alcohol centre. Finally, we examined the effect of substituents at the central position (R_3) of the allylic group and found that other alkyl groups are well tolerated and can boost the diastereoselectivity of the reaction when sterically encumbered groups are present **2k–l**. We were also able to hydrosilylate enol ethers to form 1,2,3-triol type products **2m–p**. These reactions were highly diastereoselective and in all cases provided higher stereoselectivities than the parent methyl analogues. To our knowledge, this is the first example of a platinum catalysed hydrosilylation of an enol ether substrate (Table 2).

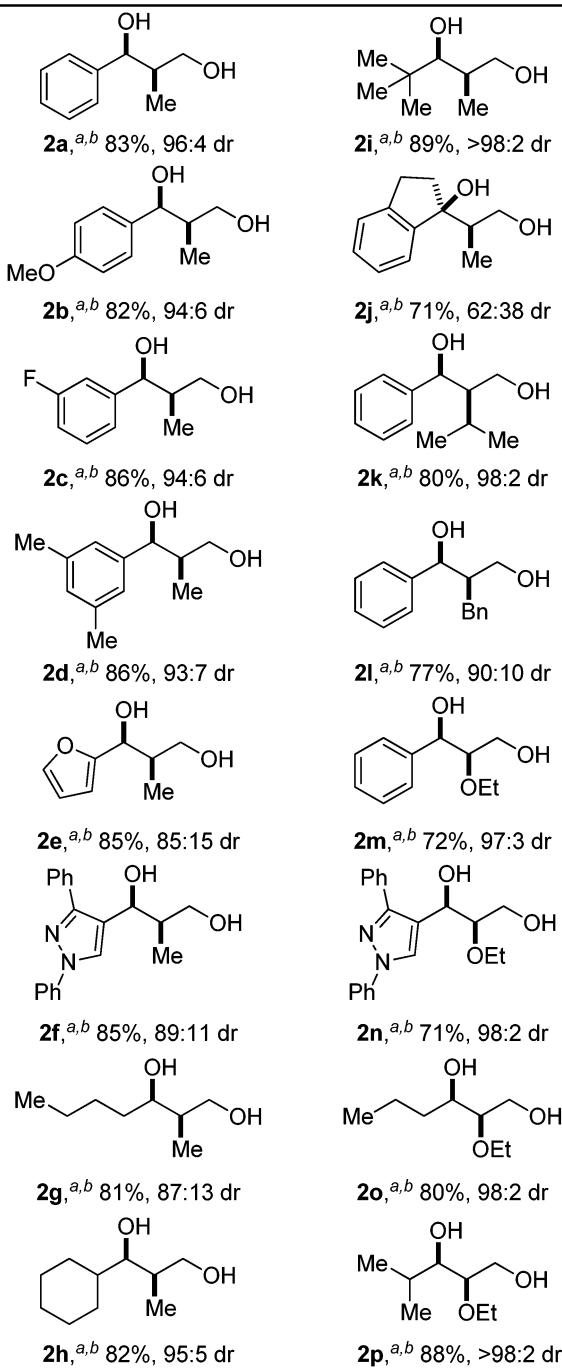
To highlight this method we prepared a small polyketide fragment. There are numerous methods to form polypropionate fragments, however, the formation of the stereotriad with *syn–syn* configuration **6** can be challenging.[15,16] This motif is found in many natural products including: swinholide A, erythromycin A and discodermolide.[17]

Utilizing *O*-Piv-protected allylic alcohol (2*S*,3*S*)-**5**, which was readily prepared,[18] we performed our intramolecular hydrosilylation reaction which, following oxidation, provided the corresponding *syn,syn* diol **6** in high diastereoselectivity. Cossy reported all other diastereoisomers of **6** *via* an oxymercuration of cyclopropylcarbinols and this confirmed the stereochemistry of the product to be the *syn,syn* form (Scheme 1).[19]

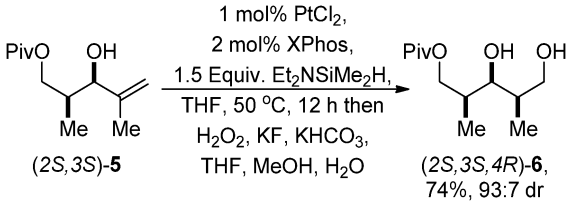
Table 2 Substrate scope



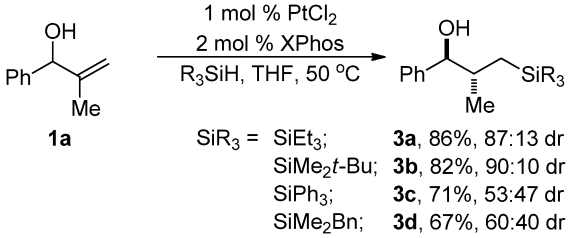
1 2



[a] Combined yield of diastereoisomers. [b] Diastereoselectivity determined by ^1H NMR analysis of the crude reaction.



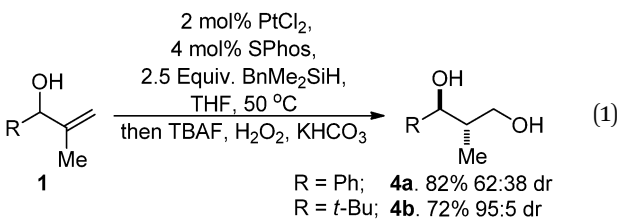
Scheme 1 Synthesis of all *syn* polyketide type fragment.



Scheme 2 *Anti*-selective intermolecular hydrosilylation–oxidation.

Anti-selective intermolecular hydrosilylation. As the *syn*-products are formed *via* an intramolecular hydrosilylation, we next examined the intermolecular variant. We envisaged that the intermolecular pathway would provide the complementary *anti*-stereoisomer, and this was found to be the case. When Et_3SiH was utilized an 87 : 13 diastereomeric ratio of **3a** was obtained with the *anti* diastereomer predominating. *t*-$BuMe_2SiH$ gave similar results with good *anti* diastereoselectivity of **3b** being obtained, however, both **3a** and **3b** were inert to oxidation conditions.[2] The more easily oxidized silanes, Ph_3SiH and $BnMe_2SiH$ were used and provided products **3c–d** albeit in a much less diastereoselective fashion.

The use of $BnMe_2SiH$ allowed for a one-pot hydrosilylation–oxidation procedure, similar to the intramolecular variant (Scheme 2). Modulation of the ligand from XPhos to SPhos resulted in higher yields and a small increase in diastereoselectivity, providing diol **4a** in a modest 62 : 38 diastereoselectivity. The use of more sterically encumbered substrates, such as *tert*-butyl derivative **1b**, afforded excellent diastereoselectivity with **4b** being formed in 95 : 5 diastereoselectivity, with the *anti* diastereoisomer predominating.



(1)

The stereochemical model for the observed reactivity is highlighted in Fig. 1. As was mentioned earlier we believe that Et_2NSiMe_2H performs an intramolecular hydrosilylation reaction through the intermediacy of a silyl ether analogous to what had previously been reported by Tamao and Ito,[10] albeit with significantly higher stereocontrol. The molecule is constrained with the oxygen functionality on the same side as the incoming Pt–H bond. The stereoselectivity is therefore determined by the minimization of $A_{1,2}$ strain between the R_2 group and either a hydrogen or R_1 substituent (**A** *versus* **B**). When either R_1 or R_2 is increased in size the stereoselectivity also increases and the reaction is particularly efficient when –OEt groups are present at R_2 position.

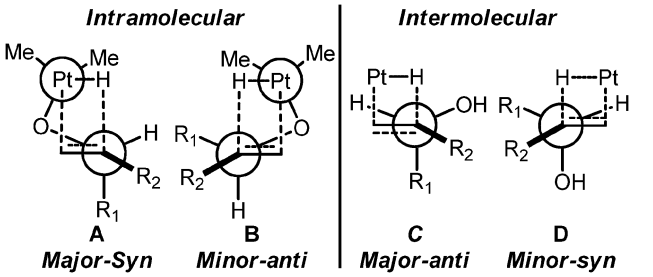


Fig. 1 Model for stereoselectivity.

In the intermolecular reaction there are no constraints on the molecule and the stereoselectivity is governed by a combination of both steric and electronic factors. The minimization of $A_{1,2}$ strain plays a role as in the intramolecular case however, positioning the OH group antiperiplanar to the incoming hydridic nucleophile minimizes the buildup of negative charge analogous to the polar Felkin–Anh model (**C** *versus* **D**).[20] When R_1 = Ph, the steric and electronic factors almost cancel each other out whereas when the steric bulk is increased the steric factors override any electronic bias there may be thus providing the *anti* product in excellent diastereoselectivity.

In conclusion, we have developed a highly diastereoselective hydrosilylation protocol that provides the *syn* diastereomer in high levels of diastereoselectivity. The reaction is very tolerant of many functional groups providing 1,3-diols with two contiguous stereogenic centers following oxidation. This method has been applied to the synthesis of a small polyketide fragment. We have also developed an *anti* selective variant which is particularly efficient for trialkylsilanes and sterically encumbered allylic alcohols.

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