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Platinum Catalysed Hydrostannylation of Terminal Alkynes; Highly Selective Synthesis of Vinyl Stannanes

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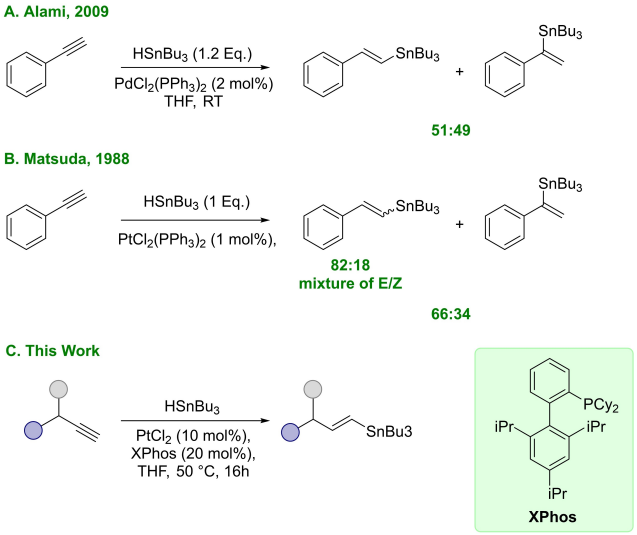
Abstract: We present the first study on the application of platinum complexes in the hydrostannylation of terminal alkynes. A range of platinum complexes were screened, with $PtCl_2$/XPhos proving to provide the best selectivity for the β-(E)-vinyl stannane. The catalyst system is able to provide the corresponding vinyl stannane in selectivities which surpasses that which is typically afforded under palladium catalysis. Additionally, a telescoped hydrometallation/cross-coupling sequence has been developed, allowing for application of the vinyl stannanes without excessive manipulation or purification of the intermediate stannane.

Keywords: Platinum; Organostannanes; Hydrometallation; Cross-Coupling

Organostannanes are highly versatile synthetic intermediates which find widespread application in cross-coupling reactions as well as having various other applications in organic synthesis.[1–4] Resultantly, a variety of elegant methods to access organostannanes have been reported.[5,6] The hydrostannylation of alkynes represents a highly atom-economical method of accessing vinyl stannanes from widely available precursors, and as such, the method has received significant attention from the synthetic community.[7] Typically, alkyne hydrostannylation is carried out under transition metal catalysis, although hydrostannylation via radical chemistry or by Lewis acid catalyzed processes have also been well studied.[8,9] Notably, the stereochemical and regiochemical outcome of the transformation is intrinsically linked to the method of choice and controlling this selectivity represents a fundamental challenge in the synthesis of alkenyl stannanes.[7]

By some distance, palladium represents the most widely utilized transition metal for the hydrostannylation of alkynes. The method predominantly affords the E-vinyl stannane arising from a *syn*-hydrometallation mechanism. While little kinetic data has been reported to provide clear evidence of a particular mechanism, it is generally accepted that the reaction proceeds through a similar mechanism to the widely studied Chalk-Harrod hydrosilylation mechanism.[10,11] While an effective method, the selectivity afforded is often controlled by the steric and electronic nature of the substrate in question. For example, linear alkyl substituted alkynes are hydrostannylated with almost no regioselectivity with $PdCl_2(PPh_3)_2$, while branched derivatives almost exclusively afford the β-*E*-vinyl stannane, thus demonstrating the dependency on steric bias to achieve high regioselectivity (Scheme 1).[12] In 2009, Alami and co-workers reported a study on the palladium catalyzed hydrostannylation of a range of functionalized phenylacetylene derivatives, with the reaction found to the be highly dependent on the electronic nature of the ring. In the absence of electronic bias, the reaction affords effectively a 1:1 mixture of regioisomers.[13] Work by Chong and co-workers in 2008 demonstrated that the regioselectivity of palladium catalysed processes can be dramatically increased by judicious choice of ligand, with bulky electron rich ligands such as Cy_3P and tBu_3P. In comparison to Pd complexes bearing Ph_3P ligands, this process is able to afford hydrometallated alcohols in much higher selectivities.[14] While palladium has dominated the majority of catalytic hydrostannylation reactions, it should be noted that other metals have



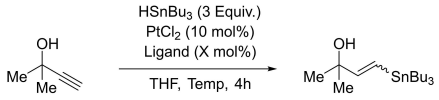
Scheme 1. Previous examples of catalytic alkyne hydrostannylation and the proposed work.

also been studied as hydrostannylation catalysts, with molybdenum and ruthenium being particularly notable for the unique regiochemical outcomes they provide.[15,16]

Given the extensive application of platinum complexes as hydrosilylation catalysts, it is perhaps surprising that little work exists on platinum catalysis in the context of alkyne hydrostannylation.[17–19] Beyond a single entry in a systematic screening of transition metals for the hydrostannylation of phenyl acetylene in 1988 by Matsuda and co-workers, little has been reported in this context.[20] Due to our group's interest in the application of platinum complexes in the stereoselective and regioselective synthesis of vinyl organometalloids under platinum catalysis, we wished to study the activity of platinum-phosphine complexes towards alkyne hydrostannylation.[21,22] We were particularly keen to study if these complexes were able to achieve superior selectivities to those which can be achieved under the more typical palladium catalysed processes.

We began our investigation by treating propargylic alcohol **1 a** with tributyltin hydride in the presence of $PtCl_2$ as a catalyst (Table 1). While this resulted in incomplete consumption of the starting material, we additionally noted the formation of several different olefinic products. Based on the analogous hydrosilylation chemistry, we envisaged the activity and selectivity of the reaction could be increased by the addition of phosphine ligands into the reaction mixture, and so screened both monodentate (entries 2 & 3) and bidentate (entries 4–9) ligands.[23] In all cases, the linear isomers were predominantly formed, but we were surprised to note a relationship between ligand denticity and stereochemical outcome of the hydro-

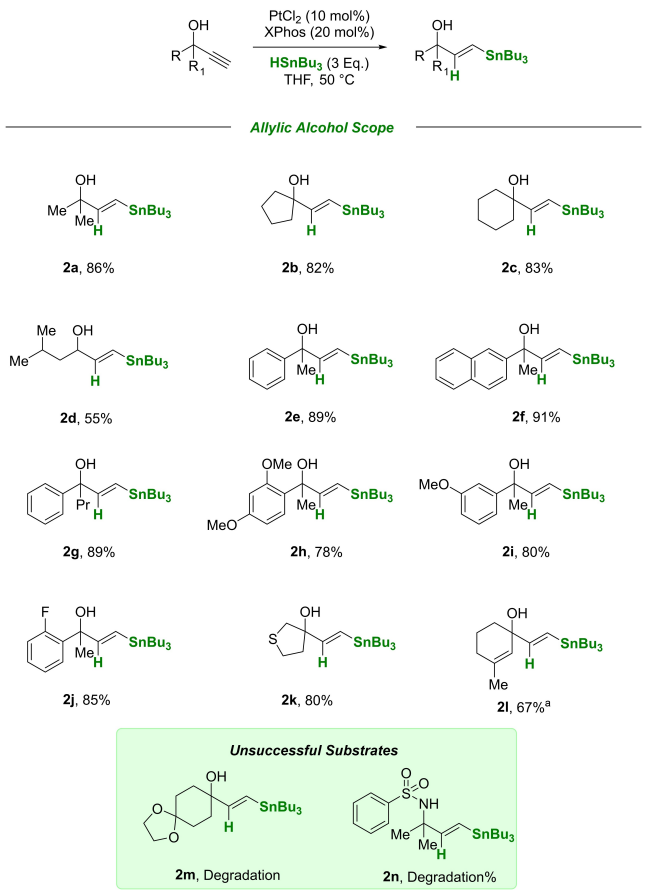
Table 1. Optimisation data from ligand screen. Conversions and selectivity ratios calculated from ^{1}H NMR analysis of the crude reaction mixture.



Entry	Ligand	Ligand Loading (X)	Temperature	E/Z	Conversion
1	x	0	50	x	x
2	XPhos	20	50	99:1>	64%
3	PPh_3	20	50	54:46	>99%
4	XantPhos	10	50	20:80	>99%
5	BINAP	10	50	17:83	56%
6	BINAP	10	40	12:88	44%
7	3,5-dimethylSEGPHOS	10	50	x	x
8	DPPF	10	50	16:84	78%
9	DPPF	10	40	8:92	50%

stannylation. Whilst previous studies have noted competing alkyne hydrogenation, under the conditions screened here, this was not observed.[14] In all cases, changes to the ligand: metal ratio resulted in neglible effect on the stereochemical and regiochemical outcome of the reaction. While bulky monodentante ligand XPhos is highly selective for the formation of the *E*-vinyl stannane, bidentate ligands XantPhos, BINAP and DPPF all predominantly formed the corresponding *Z*-vinyl stannane, albeit with moderate selectivity. Despite the similarity in structure to BINAP, SEGPHOS ligands proved to be unsuitable for the reaction, resulting in for the formation of a complex mixture of products. The selectivity for this surprising *anti*-hydrometallation could be increased by lowering reaction temperature, although this did result in a decrease in conversion. We propose the mondentate phosphine complexes provides the *E* vinyl stannane through the more sterically favourable hydroplatination, although at this stage demetallation of the alkyne cannot be ruled out. The rationale behind the formation of the Z isomer when bidentate ligands are employed is less obvious at this stage. As a direct *anti*-hydrostannylation is unlikely, this is presumably formed by a *syn*-hydrostannylation/isomerization pathway, as has been previously reported for various hydrogermylation and hydrosilylation catalyst systems.[24] Attempts to decrease the catalytic loading below 10% resulted in a sluggish reaction and incomplete consumption of the starting alkyne. Attempts to lower the loading of tin was likewise unsuccessful due to competing homocoupling of the stannane to form hexabutylditin.

With optimized conditions in hand, we turned our attention to investigating the scope of propargylic alcohols which could undergo hydrostannylation (Scheme 2). Carbocyclic alcohols **1 b** and **1 c** proved to be viable substrates, affording the desired stannanes in 82% and 83% yields respectively, with ring size having little effect on reaction yield. Secondary alcohol **1 d** also was amenable to the reaction, albeit with a

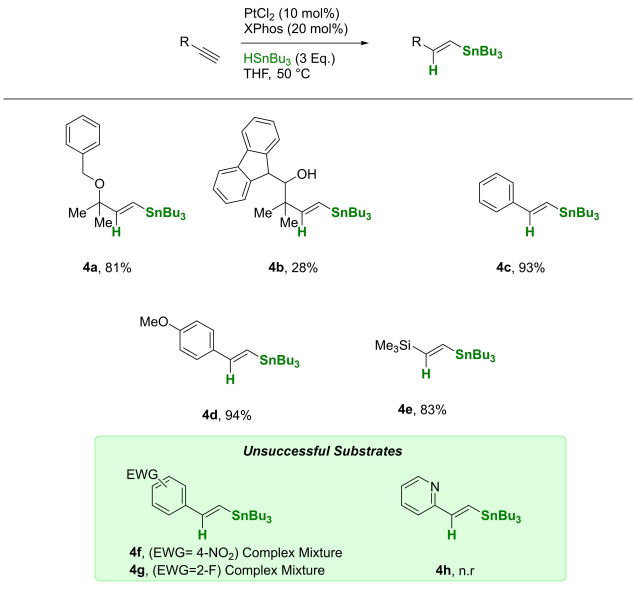


Scheme 2. Scope of propargylic alcohols screened as hydrostannylation substrates. Isolated yields. [a] 2 equiv. of tributyltin hydride used.

noticeable decrease in isolated yield (55%), which is in keeping with previous reports on platinum catalyzed hydrometallation.[25]

Moving to substrates containing aromatic substituents in the propargylic position, we were delighted to note acetophenone-derived alcohol **1e** underwent hydrostannylation smoothly to afford **2e** in an 89% yield as a single isomer. Increasing the size of the aromatic group to a significantly more sterically cumbersome naphthyl group also appeared to have little effect on the efficacy of the reaction, with **2f** afforded in excellent yield. Equally, sequentially increasing the steric bulk of the methyl group to a propyl chain also had little effect on the reaction, with **2g** afforded in excellent yields as a single isomer. We were pleased to note that the reaction was tolerant to substrates bearing aryl groups containing *ortho*, *meta* and *para* substituents, as shown by aryl ethers **1h** and **1i**, additionally showing tolerance to electron rich aromatic systems, as these alcohols afforded stananes **2h** and **2i** in 78% and 80% yields respectively. Gratifyingly, the reaction was also tolerant to more electron deficient aromatic systems, as shown by the synthesis of **2j** in 85% yield. Heterocyclic alcohol **1k** was also readily hydrometallated under the optimized conditions, affording heterocyclic stannane **2k** in 80% yield. Substrates containing both an alkene and alkyne also proved viable, although the tin loading was decreased in order to minimize unwanted olefin reduction, leading to a diminished yield. Nonetheless, diallylic alcohol **2l** was accessed in a synthetically useful 67% yield. Under the optimized conditions, ketal **1n** led to the formation of a complex mixture of products, likely to the acid-sensitive nature of the acetonide. Likewise, sulfonamide **1o** also proved to be unsuitable as a substrate, although the issues associated with hydrometallation of nitrogen containing substrates has previously been documented.[26]

We wished to explore whether the presence of the hydroxyl group was playing a role in inducing catalyst/substrate interaction and therefore potentially influencing selectivity and reactivity (Scheme 3). We therefore prepared the benzylated derivative of 1a as a method to probe this. With benzyl ether 3a in hand, we subjected it to the optimized conditions, and were delighted to observe clean conversion to the corresponding vinyl stannane in an 81% yield. Notably, the reaction only affords the stannane as a single regio and steroisomer. Utilising a homologated system in homopropargylic alcohol 3b did however result in a dramatic decrease in yield, with only 28% of the desired olefin observed in the ^{1}H NMR of the crude reaction mixture, alongside several other olefinic products. This is perhaps unsurprising, as the detrimental effect of heteroatoms at the



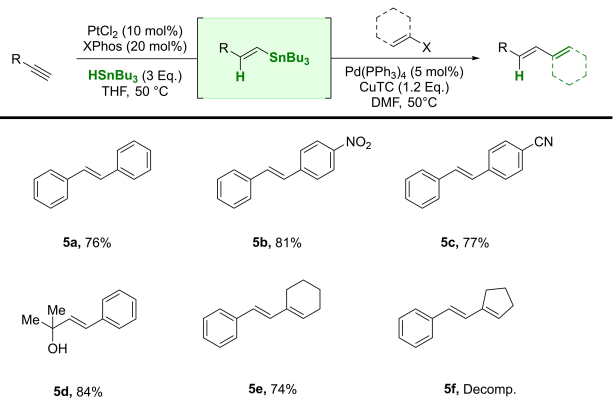
Scheme 3. Scope of non-propargylic alcohol substrates. Yield determined by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

homopropargylic position of alkynes has previously been studied.[27]

We next investigated substrates derived from phenyl acetylene, substrates which typically show little to no selectivity in hydrostannylation reactions.[28] Phenylacetylene itself proved to be an excellent substrate for hydrostannylation under platinum catalysis, with an 93% yield observed alongside excellent selectivity, unlike the analogous process catalysed by $PdCl_2(PPh_3)_2$. Likewise, 4-methoxyphenylacetylene also resulted in a high yielding and selective reaction, with stannane 4d formed in 94% yield, with the more polarised alkyne having negligible effect on reaction efficacy. When 4-nitrophenyl acetylene was utilised in this reaction, we observed the formation of a complex mixture of products, with no desired olefin observed in the ^{1}H NMR of the reaction mixture. This same poor reactivity was observed when 2-fluorophenyl acetylene was employed as a substrate, rather than seeing directed metalation as has been previously reported,[29] we instead saw decomposition of the starting alkyne, suggesting a limitation when electron poor alkynes are employed. Likewise, 2-ethynylpyridine also proved unviable as a substrate, with no conversion observed, likely to the aforementioned catalyst deactivation in the presence of nitrogenous groups.[26] We then carried out the hydrostannylation of trimethylsilylacetylene, with the corresponding 1,2-bismetallated olefin cleanly formed in 83% yield. We were pleased to note that the known polarizing effect of the silyl group on the alkyne had negligible effect on the selectivity of the metalation.

As previously discussed, one of the typical applications of vinyl stannanes in organic synthesis is in the Stille cross-coupling. To this end, we wished to explore the viability of performing a telescoped hydrometallation/cross-coupling sequence to afford a range of highly functionalized dienes and styrenes, whilst minimizing the number of chromatography steps. To this end, starting with 3c, we first carried out a hydrostannylation under the optimized conditions, affording intermediate 4c, which after filtration through silica to remove residual platinum complexes could undergo Stille coupling with iodobenzene to afford 5a in 76% yield, with stannane by-products readily separable via flash chromatography. It is of note that the removal of the hydrometallation catalyst is key; attempting the cross coupling with the platinum complex present typically results in the formation of a complex mixture of products, though this is readily achieved via filtration of the hydrometallation mixture through a plug of celite.

With a streamlined hydrometallation/cross-coupling sequence now developed, we explored the scope of compounds which could be accessed via this method (Scheme 4). We expanded the range of stilbene derivatives which could be accessed using this



Scheme 4. Scope of olefins accessed via telescoped hydrometallation/cross-coupling sequence.

sequence, and were able to access 5b and 5c in excellent yields by cross-coupling with the corresponding aryl bromide, and were pleased to note no decrease in the geometric purity of the olefin. We were likewise able to apply the sequence to the synthesis of allylic alcohol 5d, by hydrometallation/cross-coupling of 1a with iodobenzene, affording 5d in an 84% yield. We next applied the sequence to the synthesis of dienes, accessing 5e in 74% yield via coupling of the intermediate stannane with 1-cyclohexenyl triflate

In summary, the first study of platinum catalysed alkyne hydrostannylation has been performed. A range of platinum complexes were screened, with $PtCl_2$/XPhos proving to be the most selective for the linear E-vinyl stannane. Interestingly, switching the ligand denticity has a profound effect on the stereoselectivity of the hydrometallation, with bidentate phosphines preferentially forming the Z-alkene, suggesting two, ligand dependent, stereodivergent reaction mechanisms.

Using a $PtCl_2$/XPhos complex, a range of diverse alkynes readily undergo highly selective hydrostannylation, providing an operationally simple method to selectively access these high-value intermediates. The application of these products was then explored with the development of a telescoped hydrometallation/cross-coupling sequence, which avoids purification of the intermediate stannane, aside from filtration to remove the residual platinum salts. This avoids the risk of silica-mediated protodestannylation whilst also minimizing the need to manipulate the stannane, lowering toxicity concerns. Using this method, a range of stilbene, styrene and dienes have been accessed in excellent yields. We are currently working to elucidate the nature of the aforementioned ligand-dependent stereodivergence and how this may likewise be applied to the stereocontrolled synthesis of polyolefinic units. This mechanistic work and its subsequent application will be disclosed in a subsequent manuscript.

Experimental Section

General Procedure for Alkyne Hydrostannylation

To an oven dried 22 mL vial equipped with a magnetic stirrer was added $PtCl_2$ (10 mol%) and 2- Dicyclohexylphosphino-2,4,6-triisopropylbiphenyl (XPhos) (20 mol%). The flask was then flushed quickly with nitrogen and dry THF was added to form a 0.1 M solution relative to the alkyne. The mixture was then stirred at 50 °C for 20 minutes until a yellow homogeneous mixture was obtained indicating the formation of the active catalyst, $PtCl_2(XPhos)_2$. The corresponding alkyne (1 eq.) was added followed by the stannane (3 eq.) via syringe (CAUTION: Rapid evolution of hydrogen gas) and the solution was stirred at 50 °C for 15 hours. The solvent was evaporated, and the crude mixture was applied to the top of a column and chromatographed to afford the requisite (*E*) – vinyl stannane.

Acknowledgements

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