Catalytic, Oxidant-Free, Direct Olefination of Alcohols using Wittig Reagents

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Reported here is the catalytic, acceptorless coupling of alcohols with *in-situ* generated, non-stabilized phosphonium ylides to form olefins as major products. The reaction uses low catalyst loadings and does not require added oxidants. Hydrogenation of the product is minimized and the reaction leads to *Z* (aliphatic) or *E* (benzylic) stereospecificity.

Since its discovery in 1953,[1] the Wittig olefination reaction has been recognized as one of the most important carbon-carbon bond forming transformations in organic chemistry as it is carried out under mild conditions and shows good tolerance towards various functional groups.[2] However, the reaction requires a carbonyl functionality for the ylide to react, and good, selective reactivity is limited to aldehydes and ketones.[3]

A few years ago the Williams group developed an elegant ‘borrowing hydrogen’ procedure for the synthesis of alkanes from alcohols, using an indirect Wittig reaction where the alcohol moiety was dehydrogenated by an iridium or ruthenium catalyst into an aldehyde intermediate that reacted with a stabilized ylide, leading to alkanes as major products, rather than olefins.[4] Aiming at olefins, a number of one-pot examples, where *in-situ* oxidation by various oxidants is carried out with an alcohol and it is later coupled to a stabilized Wittig reagent, usually a carboethoxymethylene-triphenylphosphorane, were described.[5] Crucially, the vast number of possible Wittig reagents are unstable under these conditions, as they themselves react with oxidants, severely limiting the application of these methods. Even one of the mildest oxidants, oxygen,[6] is incompatible with most ylides and causes formation of carbonyl compounds which subsequently react with remaining ylide. One-pot oxidative coupling of benzyl alcohols with Wittig reagents to form stilbenes, promoted by Ni nanoparticles which requires a stoichiometric (or greater) amount of nickel, was reported.[5i]

Direct catalytic reaction of an ylide with an alcohol to selectively yield an olefin, with liberation of hydrogen gas, avoiding the use of oxidants, would be a significant advance in light of the ubiquitous nature of the Wittig transformation in modern organic synthesis (Eq 1). It also might be a valuable transformation where the aldehyde is an unstable species under ambient conditions.

$R\text{-}CH_2\text{-}OH + R'\text{-}CH{=}PPh_3 \rightarrow R\text{-}CH{=}CH\text{-}R' + OPPh_3 + H_2$ [Eq 1]

In the current report, we describe for the first time such a process. This new Ru catalyzed reaction is applicable to both benzylic and aliphatic alcohols, and a good range of Wittig salts, giving the corresponding olefins in high yields (often quantitative conversion and >80% isolated yields after chromatography), using 1 – 0.02 mol% catalyst, with evolution of H_2. The reaction is tolerant of a number of functional groups including nitriles, CF_3, double bonds, amines, and to a lesser extent, of pyridines and halogens. To our knowledge, the catalytic conversion of alcohols to olefins as the major products using unstabilized Wittig reagents is unprecedented, even when oxidants are used. Moreover, no oxidants are required in the reaction reported here.

We have recently reported a range of Ru pincer complexes that catalyse the acceptorless dehydrogenation of various substrates[7] to form esters,[8] amides,[9] and carboxylic acid salts,[10] from alcohols, amines and their reactions in organic solvents[8,9] and water.[10] In the mechanism for many of the transformations, it is assumed that an aldehyde intermediate that may, or may not be released to solution[11] reacts with another equivalent of alcohol, with an amine, or with water, to give an intermediate that is further dehydrogenated towards the final product.

A recent report from our group describes the direct olefination of alcohols with sulfones. However, the reaction is limited to benzylic and allylic alcohols, while aliphatic alcohols give complicated mixtures, and only methyl and phenyl sulfones were reported.[12] In light of these intriguing results, we decided to explore the reactivity of alcohols with Wittig salts, which are ubiquitous and easy to prepare.

We hypothesized that if an aldehyde is indeed a long-lived intermediate species in the catalytic process, either liberated into solution or existing bound to the metal, then it may have an

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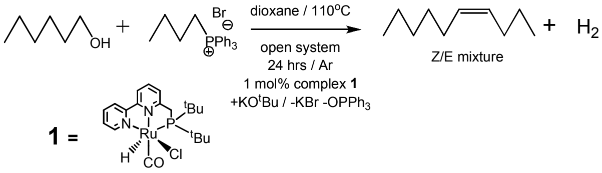
Electronic Supplementary Information (ESI) available: NMR spectra of products, discussion of experimental outcomes and identification of isomers is included. See DOI: 10.1039/x0xx00000x opportunity to react with an *in-situ* formed ylide to form the product olefin (Scheme 1).



Scheme 1. First reaction demonstrating the validity of the olefination of alcohols using Wittig reagents

Equimolar amounts of an aliphatic alcohol, an aliphatic Wittig salt, and a slight excess of base in dioxane solvent were refluxed under argon, with efficient removal of the hydrogen gas formed. A slight excess of base is needed in order to deprotonate complex **1** to the dearomatized catalyst.[8-11] Gratifyingly, the first reaction tried, using n-hexanol and n-butyl-triphenylphosphonium bromide with 1 mol% of complex **1** and 1.2 mol% KO^{t}Bu in refluxing dioxane for 24 hrs (Scheme 1) was successful, giving ~90% conversion of the alcohol and an 85% yield of the corresponding olefin, with no alkane formation, as determined by GC and GC/MS, with the NMR being consistent with 4-decene product only. Interestingly, no traces of ester or other alcohol-derived products were found in this reaction. The NMR spectrum of the crude mixture showed that 72%/28% *Z/E* isomers were formed, as is expected from the basic stereochemistry of the Wittig reaction,

With this first result in hand, we explored the scope of the reaction, as well as its stereochemistry. After a short initial screening it was found that in order to get consistent results and accurately estimate conversion, the alcohol should be taken as the limiting reagent, with a slight (1.1 eq) excess of the Wittig salt and accordingly a 1.2 eq of base. In examples 15-21 in Table 1, it was found that 1.7 eq of base gave better results, perhaps as a result of some acidic impurities in the substrates.[13]

The reactions were carried out in refluxing dioxane using 1 mol% complex **1** for 14 hrs (Table 1). GC yields were calibrated with an internal standard and were further confirmed by isolated yields. The reaction proved robust, often giving full conversion of the alcohol, with the only products of the reactant alcohol being the resulting olefins and in some cases small amounts of hydrogenated products, except in entry 9, where 14% of hydrogenated product is seen. However, only small amounts of this alkane are observed under milder conditions (*vide infra* Table 2). By comparison, it is notable that in the iridium catalyzed chemistry earlier reported by Williams[4] alkanes are the major products and olefins are trace or minor species. Noteworthy, this high catalytic activity took place despite the large amount of OPPh$_3$ formed, and to a much lesser extent PPh$_3$ present in solution due to the decomposition of some Wittig salts during the reaction, respectively. It's likely that the bulky environment around the metal center significantly raises the energy of the PPh$_3$ or OPPh$_3$ bound Ru(II) species, leading to preferential coordination of less bulky alcohol species.

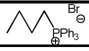
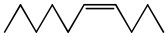
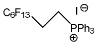
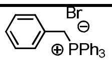
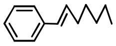
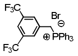
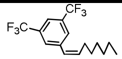
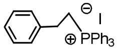
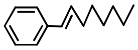
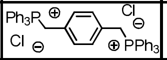
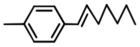
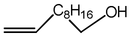
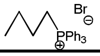
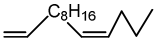
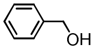
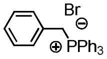
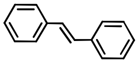
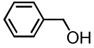
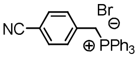
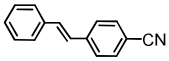
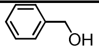
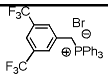
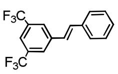
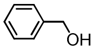
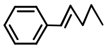
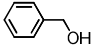
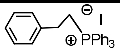
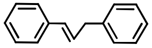
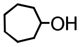
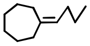
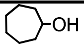
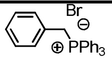
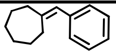
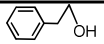
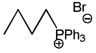
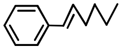
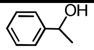
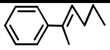
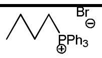
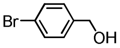
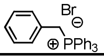
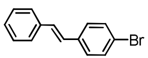
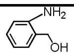
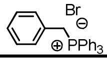
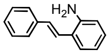
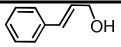
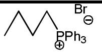
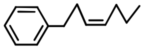
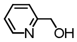
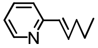
The power of the transformation is best demonstrated by entry 7, where a high isolated yield of the product olefin was obtained, with no hydrogenation of the terminal double bond or its migration to another position[14] (activated olefins are isomerized in entries 5,12,15)[15] during the reaction and the geometry of the inner bond is mostly *Z,* ruling out significant isomerization reactivity with the metal complex after the transformation. Notably, nitrile groups do not get hydrogenated under the reaction conditions (entry 9) as Ru complexes are known to be active in the hydrogenation of nitriles when a hydrogen source is present,[16] and amine moieties are tolerated (entries 17/19). Activated benzyl olefins give *E* stereochemistry, possibly via a catalyzed rearrangement after the initial reaction[15] as the products of Wittig reactions in the absence of lithium cation are overwhelmingly *Z*.[17] In Table 2, lower catalyst loadings led to higher amounts of the *Z* isomer (Table 2; entry 4), and at 1% loading the *Z* isomer is present after 1 hour, but cannot be detected after a 2 hour reaction time. Purely thermal rearrangement towards the more thermodynamically stable *E* isomer at the activated benzylic position and an initial higher preference for the *E* isomer in the case of benzylic substrates cannot be completely ruled out. In light of earlier reports of Ru catalyzed olefin isomerization,[15] it's notable that our catalyst's isomerization activity seems limited to activated benzylic double bonds, as the isomerisation reaction is undesirable when attempting to synthesize substrates such as those in entry 7. Minor products in the case of benzylic substrates included the 2-aryl-ene isomerisation product that may be accessed kinetically during the reaction. In all cases, these species are readily identifiable by NMR as the peaks shift upfield and the coupling pattern is altered dramatically, with the full product breakdown being reported in the SI.

In contrast with the above-mentioned isomerisation activity, the benzylic but electron poor bis-trifluoromethyl Wittig reagent of entry 4 shows good selectivity towards the *Z* product. A rearrangement towards the more stable benzylic conjugated double bond is seen in entries 5 and 15, while in entry 20 the activated benzylic double bond is completely hydrogenated and no trace of diene was observed; however, the resulting 3-heptene position is too isolated for subsequent rearrangement to the benzylic position. A more detailed discussion of most of the entries, including spectroscopic NMR evidence, isomer breakdown and isolation procedures, is available in the SI, where applicable.

With the above results in hand, we chose a reaction that appeared to be the most active, in order to test the limits of catalyst loading. Entry 9 in Table 1 consistently gave quantitative yields, but was prone to some hydrogenation of the double bond, leading us to try to optimize the outcome by lowering reaction temperature, and decreasing the catalyst loading (Table 2).

Lowering the reaction temperature with THF solvent leads to lower yield and rate, and more hydrogenated byproduct (entry 3). Stopping the reaction after one hour (entry 1), results in minimization of the undesired hydrogenation, indicating that the hydrogenation process is much slower than olefination. Significantly, lowering the catalyst loading to 0.02% results in quantitative yield of the products after 24 hrs, with only 1% of the alkane being formed and the rest being the desired olefin. The increasing percentage of the *E* isomer on going from entries 1 to 2 (Table 2) with increasing reaction time supports a mechanism where the *Z* isomer is primarily formed first, and is subsequently isomerized under the reaction conditions.

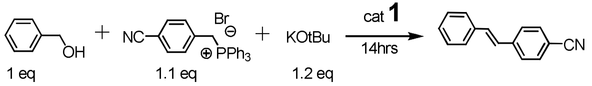
Table 1. Catalytic olefination of alcohols using Wittig reagents.

#	Alcohol	Wittig Salt	KO^{t}Bu eq	Conver-sion%	Product	Stereochem.	Yield[a] %
1			1.2	>99%		72%*Z*/28%*E*	>99
2			1.2	D	complex mixture	complex mixture	--
3			1.2	>99%		89%*E*/ 3 others (cis/aryl-2ene)[i]	>99[81]
4			1.2	82		86%*Z*/2 others (trans/aryl-2ene)[i]	82[37][b]
5			1.2	92		82%*Z*/2others (cis/aryl-2ene)[i]	92[33][b]
6			3.0	90		Mostly *E* (cis/aryl-2ene/dimer)[d,i]	90[32][b]
7			1.2	99		87%*Z*	99[84]
8			1.2	>99%		99%*E*/ <1%*Z*+H	>99[81]
9			1.2	>99%		86%*E*/ 14%H	>99[c]
10			1.2	>99%		97%*E*/ 3%H	>99[c]
11			1.2	89		91%*E*/2others (cis/aryl-2ene)[i]	89
12			1.2	77		95%*E*/ 5%*Z*	77
13			1.2	68		one isomer	68
14			1.2	54		3 isomers 90/6/4% (aryl-2-ene)[i]	54
15			1.7	74		88%*E*/2others (cis/aryl-2ene)[i]	74
16			1.7	25		60%*E*/40%*Z*	25
17			1.7	>99%		Large majority *Z*	99[32][e]
18			1.7	99		10%*Z* / 27%*E* (+debrominated)	37[f]
19			1.7	>99%		87%*E*/8%*Z*/7%H	60[g]
20			1.7	95		mostly Z (see SI)	95[71]
21			1.7	>99%		75%E/3others (cis/2aryl-2ene)[i]	85[h]

Conditions: alcohol 1eq.; Wittig salt 1.1eq; 14 hrs vigorous refluxing in dioxane; 1 mol% complex **1**. D=decomposition *Z*=cis *E*=trans H=hydrogenated, Quantitative yield indicated as >99% [a] Yield determined via GC/FID, corresponds to conversion unless noted, and refers to all olefin and minor hydrogenated products unless noted. Isolated yield in brackets is after extraction, column chromatography, vacuum concentration, unless noted. [b] 200 eq. of alcohol used for entry 6. Low isolated yields due to separation from large amounts of PPh_3. [c] yield determined after extraction in Et_2O, via NMR of crude with 10% cyclooctene internal standard [d] mixture of mono (major) and doubly hexylated products; [see SI] [e] product was isolated via acid/base extraction; [see SI] [f] the rest of the products are debrominated stilbenes 18%Z and 45%E [g] 40% byproduct, [see SI] [h] 15% oxygenated product, cis and 2-butene isomers, [see SI]. [i] Other isomers are the *Z* isomer and 2-aryl-ene rearrangement products; [see SI]

Compared to our earlier reported alcohol and amine coupling chemistry,[7-9] where esters and amides are formed with hydrogen liberation, this reactivity is not observed, and amide is a minor byproduct in the case of Entry 19 in Table 1 while a tertiary amine is understandably completely inactive for amide formation (Entry 17 Table 1). Based on our earlier results, it is clear that ester should be formed from the alcohol in an open system where the hydrogen is driven off. The catalytic reactivity of the alcohol with the ylide is more comparable to the earlier reported synthesis of carboxylic acid salts,[10] where water or hydroxide ion intercepts the aldehyde intermediate and ester formation is suppressed.

Table 2. Optimization of entry 9 (Table 1) reaction between benzyl alcohol and 4-cyano benzyl Wittig salt.



Entry	Time hrs	Catalyst Loading	Solvent bath T^{o}C	Yield[a]	Stereo-chemistry
1	1	1%	Dioxane 110^{o}C	>99%	4%*Z* 4%H 92%*E*
2	2	1%	Dioxane 110^{o}C	>99%	13%H 87%*E*
3	24	1%	THF 72^{o}C	78	21%H 79%*E*
4	24	0.02%	Dioxane 110^{o}C	>99%[b]	7%*Z* 1%H 92%*E*

Q=quantitative *Z*=cis *E*=trans H=hydrogenated. Yield determined by GC/FID except for last entry. [a] Yield is the same as conversion for this reaction. [b] yield determined after extraction by ether, a quick silica gel column in ether (to remove $OPPh_3$), vacuum concentration and an NMR spectrum of the resulting crude mixture; 10% cyclooctene internal standard.

In conclusion, we have presented a direct, catalytic olefination reaction of alcohols using Wittig reagents that liberates H_2 gas, does not require an oxidant, and is compatible with both aliphatic and aromatic alcohols. A number of alcohol substrates were tested and showed selective transformation to the desired olefin. This type of reaction may be attractive for industrial processes and fine chemicals as it allows to skip an oxidation step, often saving time and reagents and avoiding the use of stoichiometric amounts of potentially toxic oxidants. Another attractive feature is that the use of non-stabilized ylides is enabled via this protocol, increasing the diversity of products that can be generated.

The reaction proceeds via dehydrogenation of the alcohol by the catalyst and subsequent release of H_2, which is then released from the system under vigorous reflux. The ylide captures a putative aldehyde intermediate before it can be transformed to the ester product. The transformation is tolerant of a number of functional groups, requires low catalyst loading, results mostly in the *Z* isomer (and *E* for benzylic positions), forms only traces of the alkane, and is carried out under mild conditions. We are currently examining the full substrate scope of this transformation.

Notes and references

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