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Room temperature hydrophosphination using a simple iron salen pre-catalyst

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K. J. Gallagher and R. L. Webster*

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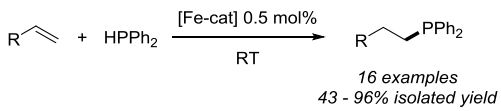
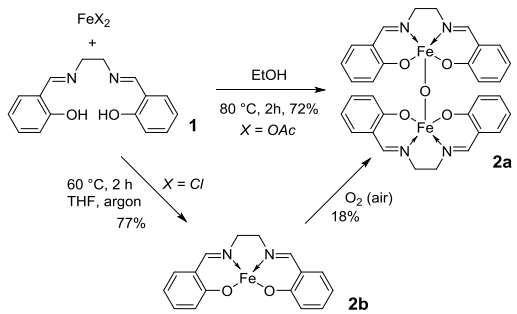
Phosphines are fundamentally important to the fine chemicals, pharmaceutical and agrochemical industries and most notably for their use as ligands in catalysis. Herein, we report the first example of the preparation of tertiary phosphines *via* alkene hydrophosphination utilizing a designed iron pre-catalyst. This facile transformation yields anti-Markovnikov products in high yield using only 0.5 mol% of an iron salen pre-catalyst at room temperature. The resulting phosphine products are shown to be excellent pro-ligands for Fe-catalyzed Negishi cross-coupling.

The synthesis of phosphorus-containing motifs is of fundamental importance in terms of the preparation of ligands for use in homogeneous catalysis,[1] organocatalysis[2] and as synthetic reagents in their own right.[3] Hydrophosphination (HP) offers the ideal P–C bond-forming process: the potential to be a 100% atom economic transformation with opportunities for regio- and stereocontrol, where molecular complexity can be rapidly accessed from simple, commercially available starting materials.[4,5] Whilst Platinum Group Metals (PGMs), early transition metals, lanthanides alkaline- and rare-earth metals have all[4] proved competent in catalyzing HP, it is of note that the use of base metals in this transformation is limited.[6,7] With this in mind, and driven by the major global efforts towards the development of sustainable chemical methodology, we sought to address these challenges through the use of iron, an appealing low cost, highly abundant, biocompatible and non-toxic alternative to the PGMs. Remarkably, despite the intense activity currently surrounding the development of iron catalysis, only simple Fe (II)/(III) chloride salts have been reported for the HP of electron deficient alkenes at a sub-stoichiometric loading of 0.3 eq.[8] Catalyst design presents a significant opportunity to tune the reactivity of such systems, moving to lower catalyst loadings and room temperature; herein we report the use of a simple Fe(III) salen pre-catalyst for HP. The reaction takes place at room temperature, with only 0.5 mol% catalyst loading and without the need for any additives (Scheme 1). Furthermore, we extend this methodology beyond simple synthesis by exploiting the products of HP as ligands in their own right, an often overlooked facet of HP. Through this expressed aim of developing this phosphine ligand motif for base metal catalysis, we present some preliminary results in Fe-catalyzed Negishi cross-coupling.



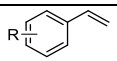
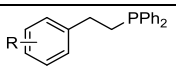
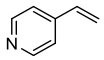
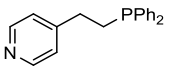
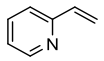
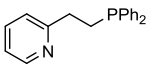
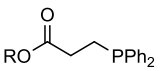
Scheme 1 Room temperature, anti-Markovnikov selective iron-catalyzed hydrophosphination.

We initiated our research program into Fe-catalyzed HP by synthesizing the simplest salen pro-ligand (**1**). [9] Ligation to $Fe(OAc)_2$ in EtOH gives a high yield of μ-oxo-bis(*N*,*N*'-ethylenebis(salicylideniminato)iron(III) complex, **2a** (Scheme 2), which is isolated as the analytically pure compound in good yield (see ESI).[10,11] The Fe(II) analogue, **2b**,[12] is a highly air sensitive solid, requiring preparation with rigorous air-sensitive handling techniques, however, we believe our route to **2b** is the simplest definitive method for its synthesis. Upon exposure of **2b** to air, O_2 activation takes place and **2a** is formed in modest yield (18%).[13]



Scheme 2 Synthesis of pre-catalysts **2a** and **2b**.

Table 1. HP substrate scope

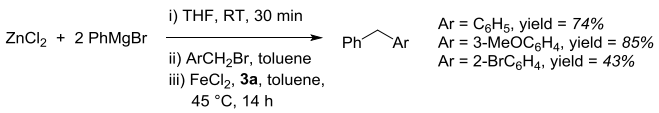
Entry	Alkene	Product		Yield[a] (Spec. Yield)[b]
				
1		R = H	**3a**	89 (100)[c]
2		R = 4-Me	**3b**	79 (96)
3		R = 4-OMe	**3c**	89 (97)
4		R = 4-Br	**3d**	65 (82)[c]
5		R = 4-Cl	**3e**	74 (100)[d]
6		R = 4-CN	**3f**	43 (93)
7		R = 4-CF_3	**3g**	83 (85)[e]
8		R = 4-Ph	**3h**	58 (85)[e]
9		R = 3-Me	**3i**	95 (100)[c]
10		R = 3-Br	**3j**	96 (98)[c]
11		R = 3,5-OMe	**3k**	89
12		R = 2-OMe	**3l**	62 (87)
13			**3m**	75 (80)[c,f]
14			**3n**	86 (92)[f]
				
15		R = Me	**3o**	69 (80)
16		R = ^{n}Bu	**3p**	76 (93)

Conditions: alkene (1.04 mmol, 1.82 eq), $HPPh_2$ (0.57 mmol, 1 eq), **2a** (1.8 mg, 0.5 mol% **2a** (1 mol% Fe-center)), MeCN (0.35 mL), RT, 24 h. [a]Isolated yield (%). [b]Spectroscopic yield (%), 1,2-DCE used as a standard. [c]Trace amounts of an unknown impurity co-elute with the product (see Ref 14). [d]114 h. [e]60 °C. [f]72 h.

With Fe(III) (**2a**) and Fe(II) (**2b**) pre-catalysts in hand, we began to investigate their use in HP. To our delight it was found that 0.5 mol% of **2a** catalyzes the reaction between styrene and diphenylphosphine at room temperature to give a quantitative spectroscopic yield of the anti-Markovnikov (AM) product, **3a**, cleanly. The reaction proceeds similarly in a range of solvents (THF, CH_2Cl_2, MeCN) and also under solvent-free conditions; however, considering both sustainability and ease of reaction monitoring, we proceeded with MeCN as the solvent of choice. In the absence of any source of Fe only a trace amount of AM product is observed at RT in MeCN.

With mild conditions in hand we began to explore the substrate scope and limitations of this system. Pleasingly, a wide range of electron deficient alkenes including styrenes, halo-styrenes and acrylates all undergo HP to give the AM product in high yield (Table 1). Heterocycles are well tolerated as evidenced by the phosphine product **3n** from 2-vinylpyridine (Entry 14), which is known to be an important pro-ligand for carbonylation reactions and Pd-catalyzed Suzuki-Miyaura cross-coupling.[15] We believe the need for extended reaction times (72 h) is due to competing coordination of **3n** to the Fe-center.

The power of hydrophosphination is highlighted through the facile synthesis of phosphinoester products **3o** and **3p** (Entries 15 and 16). The phosphinoester core is a key component in the synthesis of diazo compounds for use in chemical biology. This P–C bond formation requires four sequential steps when using traditional methods.[16] However, with HP the same key P–C bond forming process is undertaken in one step at room temperature in a 100% atom efficient manner with 0.5 mol% of **2a**. To further develop this HP transformation beyond proof of principal results and cultivate first row TM-catalyzed applications, we carried out a short investigation into the use of **3a** as a ligand in iron-catalyzed Negishi cross-coupling.[17] Surprisingly, very simple alkyl-aryl phosphines such as **3a** to **3l** have never before been used as ligands in TM catalysis. Meanwhile Fe(II)-catalyzed Negishi cross-coupling is an elegant transformation which demonstrates the potential of base metal catalysis, allowing the synthesis of unsymmetrically substituted diarylmethanes. To our delight these simple mono-phosphines prove to be excellent pro-ligands for the cross-coupling of diaryl zinc reagents and benzyl bromides (Scheme 3).[18,19] To the best of our knowledge this is the first reported use of these phosphines in a catalytic transformation and furthermore the first report of such a simple mono-phosphine facilitating a Negishi reaction of this type, with state-of-the-art examples often being undertaken with expensive bis-phosphines such as 1,2-bis(diphenylphosphino) benzene (dpbz). We also provide an example with 2-bromobenzyl bromide, which cannot be accessed by traditional Pd-catalyzed cross-coupling due to competing aryl-aryl bond formation. In the absence of **3a** only 16% diphenylmethane is observed from the reaction of benzyl bromide and diphenylzinc in the presence of 5 mol% $FeCl_2$.



Scheme 3 Iron catalyzed Negishi cross-coupling using **3a** as the pro-ligand.

We have initiated some preliminary mechanistic studies to further our understanding of this particular HP catalytic system. Unactivated substrates (*i.e.* 1-hexene, allylbenzene) only show trace amounts of the desired product. The reaction mediated by **2a** does not appear to be radical catalyzed since the addition of a radical trap is not detrimental to the reaction which still proceeds with good yields (94% **3a** with 3 mol% cumene, 87% **3a** with 3 mol% TEMPO). The presence of a vast excess of cumene has very little effect on the reaction (89% **3a** with 0.57 mmol cumene) and reaction monitoring shows very little difference in the reaction profile compared to the same reaction in the absence of cumene (the initial rate of conversion to **3a** is 0.0626 mmol s^{-1} for HP in the absence of cumene and 0.0616 mmol s^{-1} in the presence of 0.57 mmol cumene, see ESI). It is reasonable to invoke a key disproportionation of **2a** in order for the dimer to become active in catalysis[20] with homoleptic cleavage by $HPPh_2$ forming two equivalents of **2b** and diphenylphosphine oxide. In order to test this hypothesis, **2b** was employed as the pre-catalyst under the standard reaction conditions, however, to our surprise no reaction is observed as only starting material remains after 24 h. This was unexpected as we anticipated that an Fe(II) pre-catalyst would be highly active and suggests disproportionation of **2a** into **2b** does not occur. We hypothesized that proton abstraction from diphenylphosphine must be necessary for **2b** to become catalytically active. Addition of a base (2 mol% NaO^tBu) to the standard catalytic reaction with 1 mol% **2b** as the pre-catalyst gives 20% **3a**. Increasing the loading of NaO^tBu to 0.57 mmol (1 eq.) gives 66% **3a** while 0.57 mmol of base in the absence of **2b** gives only 12% **3a**.[21] We have extended our mechanistic investigations to include some kinetic studies of the synthesis of **3a** using **2a** (0.5

mol%). Many of these NMR studies are only possible due to the paramagnetic pre-catalyst **2a** being catalytically active at such low loadings. The turnover frequency for the formation of **3a** over the initial 30 minutes is 80 h^{-1}, slowing to 33 h^{-1} after 3 hours (at which point the reaction is 50% complete). The upper turnover number limit is 200 for this reaction (assuming **2a** acts as a dimer in the catalytic cycle). A Hammett plot of HP with **2a** shows that there is a change in rate limiting step (see ESI) and further investigation shows that the order in **2a** is 1.6, suggesting a far more complicated catalytic cycle than originally anticipated and, at these early stages of our mechanistic studies, we cannot fully rule out a Michael addition or a 1,2-insertion process.[4c] Therefore, a full mechanistic investigation is underway and will be reported in due course.

In summary, we have developed a simple, air stable iron pre-catalyst for the hydrophosphination of activated alkenes. The reaction proceeds with low catalyst loading and at room temperature. We have also shown that the reaction is unlikely to be radical mediated. Full mechanistic studies will be reported shortly and is being used to inform the design of pro-ligands and thus iron pre-catalysts which will utilize unactivated starting materials (unactivated alkenes, alkyl phosphines, internal alkenes). In addition, the obtained phosphine products have shown early promise as pro-ligands for the Fe-mediated Negishi cross-coupling of benzyl bromides and diaryl zinc reagents, demonstrating for the first time the synthetic application of mono-phosphines obtained from HP.

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Department of Chemistry, University of Bath, Claverton Down, Bath, UK BA2 7AY. r.l.webster@bath.ac.uk

† Electronic Supplementary Information (ESI) available: all experimental and analysis data. See DOI: 10.1039/b000000x/

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