Homogeneous Catalysis

International Edition: DOI: 10.1002/anie.201701051
German Edition: DOI: 10.1002/ange.201701051

Iron(II)-Catalyzed Hydrophosphination of Isocyanates

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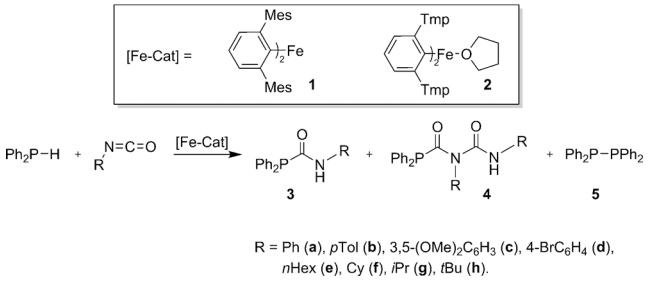
Abstract: *The first transition metal catalyzed hydrophosphination of isocyanates is presented. The use of low-coordinate iron(II) precatalysts leads to an unprecedented catalytic double insertion of isocyanates into the P–H bond of diphenylphosphine to yield phosphinodicarboxamides [$Ph_2PC(=O)N(R)C(=O)N(H)R$], a new family of derivatized organophosphorus compounds. This remarkable result can be attributed to the low-coordinate nature of the iron(II) centers whose inherent electron deficiency enables a Lewis-acid mechanism in which a combination of the steric pocket of the metal center and substrate size determines the reaction products and regioselectivity.*

Organophosphorus compounds are a vital class of chemicals with extensive commercial applications.[1] Classic synthetic methodologies for phosphine preparation have major drawbacks, including poor functional-group tolerance, side-product formation, the use of protecting groups and stoichiometric amounts of additives, which is a significant disadvantage for atom economy.[2] Therefore, there is growing demand to develop atom-economical routes for the preparation of functionalized phosphines. In particular, hydrophosphination is an attractive synthetic route to phosphine products, proceeding by P–H bond addition across a C–C/X (X = O, N, S) multiple bond.[3] However, this reaction can be synthetically challenging as a result of the coordination capability of both the phosphine substrates and products which can poison the metal catalyst.

The hydrophosphination of olefins and alkynes has received much attention in the last decade,[4] but the use of heterocumulene substrates has been less explored, with examples of precatalysts for these reactions being limited to rare-earth,[5] alkali-metal,[6] and group 2 complexes.[7] The hydrophosphination of organic isocyanates, yielding phosphinocarboxamide products, is limited to a few recent examples, all of which are catalyzed by f-block complexes.[5a–c,e] A significant issue with the hydrophosphination of isocyanates is the competing side reactions, such as the cyclotrimerization of isocyanates to isocyanurates, and catalyst incompatibility towards heteroatom-containing substrates. This catalyst incompatibility has been documented for the hydrophosphination of aromatic isocyanate substrates using $LY[N(SiMe_3)_2]_2$ (L = [4-CH_3-2-{(CH_3)CH-[$N(CH)_2CN$]}-$C_6H_3]_2N$).[5c]

Herein, we report the first transition metal catalyzed hydrophosphination of isocyanates, which affords phosphinodicarboxamides by an unprecedented catalytic double insertion of isocyanates into the P–H bond of the phosphine. The reaction between organic isocyanates and diphenylphosphine in the presence of catalytic amounts of $(2,6\text{-}Mes_2C_6H_3)_2Fe$[8] (**1**; Mes = 2,4,6-$Me_3C_6H_2$) or $(2,6\text{-}Tmp_2C_6H_3)_2Fe(THF)$[9] (**2**; Tmp = 2,4,5-$Me_3C_6H_2$) produces the mono- (**3**) and/or di-insertion (**4**) products, where one and two isocyanate units, respectively, have inserted into the P–H bond (Scheme 1). This result is remarkable since diinsertion processes are incredibly rare.[10] Significantly, the compounds **4** are a new family of derivatized phosphinodicarboxamides, and have potential applications in coordination chemistry,[11] supramolecular and self-assembled arrays,[12] biomedicine,[13] and enantioselective catalysis.[14]



Scheme 1. Hydrophosphination of isocyanates with Ph_2PH catalyzed by **1** and **2**.

Initially, Ph_2PH was treated with one equivalent of PhNCO using 5 mol% of **1** as the precatalyst (Table 1, entry 1). After 16 hours at room temperature, the solution underwent a color change from yellow to dark red, with concomitant formation of two phosphorus-containing products, as observed by ^1H and $^{31}P\{^1H\}$ NMR spectroscopy, in a relative ratio of 59:41 (98% conversion). Further analysis revealed that the major product was [$Ph_2PC(=O)N(H)Ph$] (**3a**), while the second product was [$Ph_2C(=O)N(Ph)C(=O)N(H)Ph$] (**4a**), resulting from the insertion of two isocyanate molecules into the P–H bond of Ph_2PH. To optimize the formation of **4a** the ratio of PhNCO/Ph_2PH was changed from 1:1 to 2:1 (entry 2), resulting in an increase in the ratio of **4a** (67%) with respect to **3a** (33%). The three-coordinate complex **2** shows a higher activity than **1**, and high conversion is achieved in a significantly shorter time with a similar product distribution (entry 3). Very similar behavior is observed for *p*TolNCO (entries 4 and 5). When 3,5-$(OMe)_2C_6H_3NCO$ is used the hydrophosphination proceeds

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Supporting information (full experimental details for the hydrophosphination reactions, reaction monitoring by NMR spectroscopy, crystallographic data) and the ORCID identification number(s) for the author(s) of this article can be found under: http://dx.doi.org/10.1002/anie.201701051.

Table 1: Catalytic hydrophosphination of isocyanates mediated by **1** and **2**.[a]

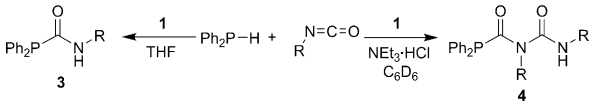
Entry	RNCO	Cat.	RNCO/Ph_2PH	*t* [h]	Conv. [%][b]	**3**/**4**/**5** [%][c]
1	Ph	**1**	1:1	16	98	59:41:0
2	Ph	**1**	2:1	15	95	33:67:0
3	Ph	**2**	2:1	6	96	35:65:0
4	*p*Tol	**1**	2:1	16.5	95	27:72:1
5	*p*Tol	**2**	2:1	4.8	94	36:63:1
6	$(OMe)_2C_6H_3$	**1**	2:1	12	95	43:57:0
7	$(OMe)_2C_6H_3$	**2**	2:1	3	99	46:54:0
8	4-BrC_6H_4	**1**	2:1	15	99	30:70:0
9	4-BrC_6H_4	**2**	2:1	4	99	27:71:2
10	*n*Hex	**1**	1:1	15	99	13:26:5:56[d]
11	*n*Hex	**1**	2:1	15	99	8:39:3:49[d]
12	*n*Hex	**2**	2:1	15	99	12:36:7:46[d]
13	Cy	**1**	1:1	16	90	93:0:6[e]
14	Cy	**2**	1:1	8	89	95:0:5
15	*i*Pr	**1**	1:1	16	55	91:5:4
16	*i*Pr	**1**[f]	1:1	1.6	89	96:0:4
17	*i*Pr	**2**[f]	1:1	1	92	97:0:3
18	*t*Bu	**1**[f]	1:1	16	70	91:0:9
19	*t*Bu	**2**[f]	1:1	16	77	86:0:14

[a] Reaction conditions: 10 mg cat. (5 mol%), 0.6 mL of C_6D_6, 25 °C. [b] Determined by ^1H NMR and $^{31}P\{^1H\}$ NMR spectroscopy. [c] Ratio by ^1H NMR and $^{31}P\{^1H\}$ NMR spectroscopy. [d] Cyclotrimer ratio. [e] 1% unidentified $^{31}P\{^1H\}$ peak. [f] Catalysis performed at 60 °C.

with a higher reaction rate and a small decrease in the amount of the diinsertion product (entries 6 and 7). Reactions with isocyanates featuring functional groups proceed in a similar manner, with excellent conversions for substrates which bear either electron-donating or electron-withdrawing groups (entries 6–9).

To explore the scope of the reaction, aliphatic isocyanates were tested. When the reaction was performed with *n*HexNCO, the hydrophosphination competed with the cyclotrimerization reaction, leading to a mixture of $[n\text{HexNCO}]_3$,[9] $[Ph_2PC(=O)N(H)n\text{Hex}]$ (**3e**), and $[Ph_2PC(=O)N(n\text{Hex})C(=O)N(H)n\text{Hex}]$ (**4e**) (Table 1, entries 10–12). Meanwhile, reactions with more sterically encumbered secondary and tertiary isocyanates (CyNCO, *i*PrNCO, and *t*BuNCO) afforded, almost exclusively, the monoinsertion products (**3f–h**; entries 13–19). For *i*PrNCO and *t*BuNCO the temperature was raised to 60 °C to reach reasonable conversions, within 16 hours (entries 15–19), of around 90% for **3g** and greater than 70% for **3h**. Previous attempts by others to catalyze the hydrophosphination of *t*BuNCO with Ph_2PH were low yielding (<20%).[5e] Collectively, these results indicate that the observed selectivity between the catalysis of the mono- and diinsertion of isocyanates into Ph_2PH may be governed by steric factors, preferentially obtaining the diinsertion product for less bulky isocyanates and the monoinsertion product for secondary and tertiary aliphatic isocyanates.

Changing the solvent from C_6D_6 to THF resulted in a significant change in the selectivity (Scheme 2; see Table S1 in the Supporting Information), affording the monoinsertion product almost exclusively. A decrease in catalyst activity was also observed, and the reactions required heating to 60 °C to obtain moderate conversions (see Table S1, entries 1–4).



Scheme 2. Hydrophosphination products obtained when using either THF (left) or $NEt_3{\cdot}HCl$ in C_6D_6 (right) and 5 mol% of the catalyst **1**. THF = tetrahydrofuran.

To investigate the faster rates for the precatalyst **2** compared to **1**, the hydrophosphination catalysis was monitored using ^1H and $^{31}P\{^1H\}$ NMR spectroscopy. When using **1**, an induction period of around 2 hours was observed (Figure 1; see the Supporting Information), indicating that **1** is not the true catalyst and that a transformation takes place before the catalysis begins. No induction period is observed for **2**, where the catalysis starts immediately after substrate addition. It is likely that the same initial reaction takes place for **2** but the labile THF ligand is easily displaced, thus making this step considerably faster. Surprisingly, when **1** was reacted separately with either Ph_2PH or CyNCO no reaction was observed after 48 hours at room temperature, either by NMR or IR spectroscopy. As soon as the other substrate is added the formation of **3f** is observed. Stoichiometric studies were not conclusive as IR spectroscopy shows several peaks in the amide region, but indicate that the active catalyst is an iron amidate complex (**A**; Scheme 3). The formation of this species could be in equilibrium, therefore both Ph_2PH and CyNCO are needed to drive the reaction to **A**. However, the possibility that both substrates are required for precatalyst activation cannot be ruled out.

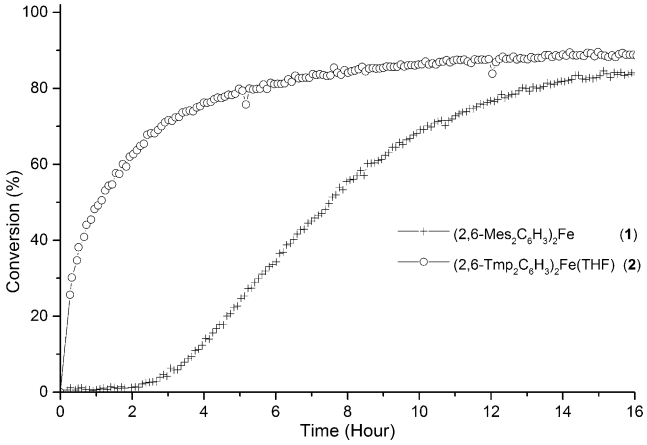
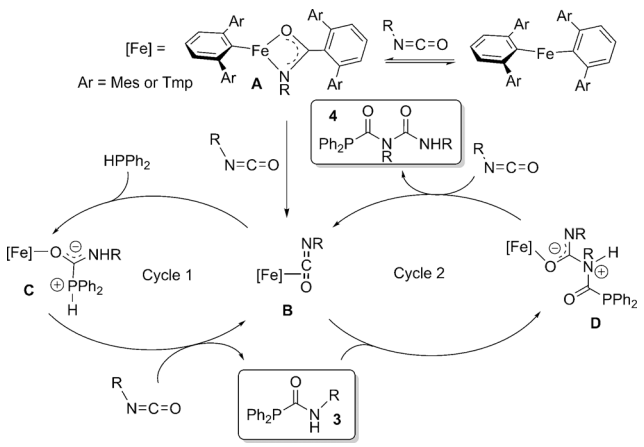


Figure 1. Conversion [%] versus time [h] for the hydrophosphination of CyNCO with 5 mol% cat. **1** (+) and **2** (○) in C_6D_6 at 25 °C.

Sigmoidal reaction kinetics have been used as evidence for a heterogeneous mechanism where the catalyst may be bulk iron metal or trace iron nanoclusters.[15] To distinguish the true nature of the catalyst, poisoning experiments with Hg and CS_2 were performed (see the Supporting Information). No change was observed in either the reaction rate or catalyst selectivity, suggesting that the reaction most likely occurs



Scheme 3. Proposed mechanism for the mono- and diinsertion of isocyanates into the P–H bond of Ph_2PH.

through a homogenous mechanism. Moreover, the reaction does not appear to be catalyzed by radicals since the presence of excess cumene does not affect the rate of the reaction (see the Supporting Information).[16] No significant changes were observed when triethylamine was added to the reaction mixture (see Table S2, entry 1). The addition of a weak acid (NEt_3·HCl) favors the double insertion product, affording **4a** and **4c** almost exclusively (see Table S2, entries 2 and 4; Scheme 2), and highlights the mechanistic differences between our catalytic system and traditional palladium catalysts.[17]

With these mechanistic considerations in mind the proposed catalytic cycle is shown in Scheme 3. Because of the relatively high oxidation state of the iron(II) and its coordinative unsaturation, it is conceivable to envisage the metal center acting as a Lewis acid.[4e,18] Therefore, a likely first step is the coordination of an isocyanate molecule leading to the intermediate **B**. Nucleophilic attack of free Ph_2PH on the coordinated isocyanate leads to P–C bond formation and the transient species **C**. Similar substrate coordination followed by outer-sphere attack of a phosphine have been proposed.[4e,19] A 1,3-proton shift, followed by addition of a new molecule of isocyanate regenerates the active species **B** with displacement of **3**. When the phosphinocarboxamide (**3**) produced in Cycle 1 contains a smaller R group it is also possible to proceed into Cycle 2 by a nucleophilic attack on **B** with the subsequent formation of **D**. Proton transfer followed by displacement of the phosphinodicarboxamide (**4**) by an incoming isocyanate molecule results in the regeneration of **B**. When coordinating solvents such as THF are used, solvation of **B** can occur, thus blocking the approach of a phosphinocarboxamide molecule, and enforcing the monoinsertion pathway. The weak acid will likely aid the protonolysis step in Cycle 2, a rate-limiting step for hydroamination reactions.[20] Indeed, when a mixture of PhNCO and CyNCO is reacted with diphenylphosphine (1:1:1) a combination of four products **3a**/**3f**/**4a**/**4i** is obtained (see Scheme S1). The diinsertion product **4i** [$Ph_2PC(=O)N(Ph)C(=O)NH(Cy)$] results from the coordination of CyNCO with nucleophilic attack of [$Ph_2PC(=O)N(H)Ph$] (**3a**), and is in agreement with our proposed mechanism.

An alternate mechanism, similar to those reported for rare-earth precatalysts[5a,b,e] where the Ph_2PH attacks the metal center first, through protolytic cleavage of the amide ligand, has been dismissed because of the lack of evidence for the formation of (2,6-$MesC_6H_3$)C(=O)NH(R) as determined by either ^{1}H NMR or IR spectroscopy.

Reactions were scaled up successfully, leading to good yields of isolated products for the diinsertion products (**4a–d**) and for monoinsertion products (**3a,c–d,f–h**; see the Supporting Information for full procedures).

In summary, the catalytic hydrophosphination of isocyanates under mild reaction conditions has been demonstrated using the iron precatalysts **1** and **2**, which display remarkable reactivity because of their low coordination number and the unique steric pocket created by the bulky *m*-terphenyl ligands. Simple modification of the reaction conditions can control the synthetic outcome yielding either mono- or diinsertion products with high selectivity.

Acknowledgments

We gratefully acknowledge the support of the University of Nottingham, the EPSRC and Leverhulme Trust. We also thank Dr. Ross Denton, University of Nottingham for mechanistic discussions, Dr. Huw Williams, University of Nottingham for helpful NMR discussions, Dr. Mick Cooper at the University of Nottingham for mass spectrometry and Stephen Boyer (London Metropolitan University) for elemental analyses.

Conflict of interest

The authors declare no conflict of interest.

Keywords: homogeneous catalysis · hydrophosphination · iron · ligand design · reaction mechanisms

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Manuscript received: January 30, 2017
Revised: March 1, 2017
Final Article published: ■■ ■■, ■■■■

Communications

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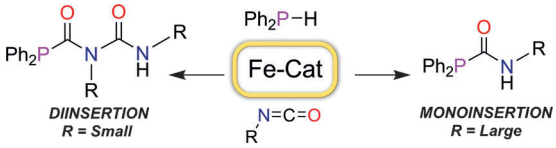
Iron(II)-Catalyzed Hydrophosphination of Isocyanates



Seeing double: Low-coordinate iron(II) complexes have been used in the hydrophosphination of isocyanates to produce mono- and/or diinsertion products yielding phosphinodicarboxamides, a new family of derivatized organophosphorus compounds. Small changes in reaction conditions drastically alter the product selectivity.