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Iron(II)-Catalyzed Hydroamination of Isocyanates

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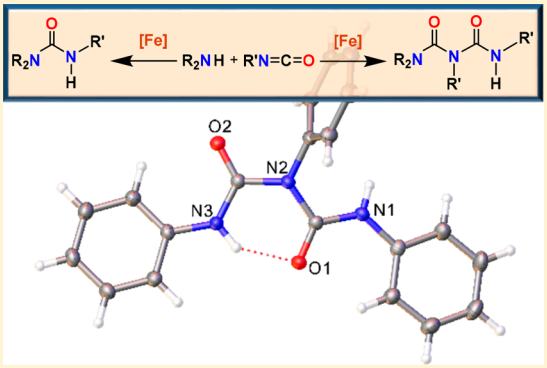
Supporting Information

ABSTRACT: A two-coordinate Fe(II) *m*-terphenyl complex acts as a precatalyst for the hydroamination of isocyanates, affording urea and biuret derivatives, with product selectivity accomplished via modification of the reaction conditions. Using a more nucleophilic amine facilitates the insertion of up to four isocyanates into the N−H bond, affording triuret and tetrauret derivatives.



Urea derivatives are essential in a wide range of biological systems[1] and are fundamental building blocks in the chemical industry and academia with a wide range of applications in pharmaceuticals,[2] agriculture,[3] material,[4] supramolecular,[5] and synthetic chemistry.[6] Despite their importance, there are few methods for the synthesis of urea derivatives. Most synthetic routes require the use of expensive noble metal catalysts, for example, via oxidative catalytic carbonylation reactions of amines,[7] catalytic reduction of nitro compounds with carbon monoxide,[8] and the cross-coupling of aryl chlorides with sodium cyanate,[9] or they include stoichiometric amounts of other reagents.[10] More recently, ureas have been synthesized through the coupling of silylamines and carbon dioxide using an indium precatalyst[11] and an iron-catalyzed dehydrogenative coupling of methanol and amines.[12]

Hydroamination is an atom-economical alternative to the above routes, in which an N−H bond is added across an unsaturated organic bond, affording C−N bonds without the need for dehydrating/activating agents.[13] The catalytic hydroamination of alkenes, alkynes, and carbodiimides to form C−N bonds has been widely studied.[14] However, there are few reported examples for the catalytic hydroamination of isocyanates leading to urea derivatives; with examples limited to group 2,[15] titanium,[16] zinc,[17] and actinide complexes.[18] Although some hydroamination reactions of isocyanates can occur without a catalyst, these generally require long reaction times and high temperatures and are limited to nucleophilic amines.[19]

The synthesis of biuret and triuret derivatives is especially challenging, as ureas are significantly less nucleophilic than secondary amines[20] due to the electron-withdrawing effect of the carbonyl group. As a result, there are very few examples of these compounds being formed catalytically. Early studies report the synthesis of biurets from the pyrolysis of ureas or their catalytic formation from substituted ureas using organotin compounds.[21] A more recent study tested several catalysts such as $SOCl_2$ and $ClSO_2OH$ for the transformation of urea to biuret. This method gave higher yields than the pyrolytic decomposition, although the synthesis required high temperatures (145 °C).[22] To our knowledge, there are no reports of the direct transformation of secondary amines to biuret derivatives. The absence of direct catalytic routes is surprising considering the significance of molecules with multiple urea moieties, as such species have a high capacity for hydrogen bonding, which is valuable in the design of foldamers,[23] self-assembly,[24] and molecular recognition.[25]

We have previously reported the hydrophosphination of isocyanates mediated by low-coordinate Fe(II) precatalysts.[26] We present here an expansion of this work, using the iron precatalyst $(2,6\text{-}Mes_2C_6H_3)_2Fe$[27] (**1**; Mes = 2,4,6-$Me_3C_6H_2$) for the hydroamination of isocyanates to afford urea and biuret derivatives, the latter being achieved via a unique diinsertion reaction. Triuret and tetrauret compounds are obtained from more nucleophilic amines via unusual tri- and tetrainsertion pathways.

Initial efforts focused on the reaction between Ph_2NH and PhNCO (Scheme 1), allowing for a direct comparison with the analogous hydrophosphination reaction with Ph_2PH.[26] Monitoring the reaction between Ph_2NH and PhNCO (1:1 substrate ratio, C_6D_6, 25 °C, 5 mol % **1**) by ^1H NMR

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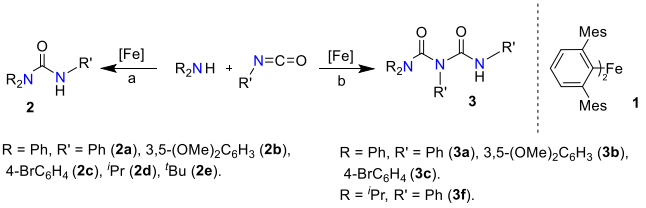
Scheme 1. Hydroamination of Isocyanates with R_2NH Catalyzed by 1[a]



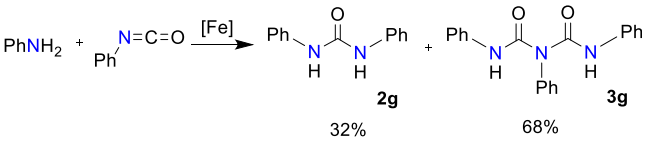
[a]Reaction conditions: (a) 5 mol % **1**; Ph_2NH/RNCO (1:1) in THF at 60 °C (**2a**–**2e**). (b) 5 mol % **1**; Ph_2NH/RNCO ratio (1:5) in C_6D_6 at 25 or 60 °C (**3a**–**3c**) and $^iPr_2NH$/PhNCO (1:2) in C_6D_6 at 25 °C (**3f**).

spectroscopy revealed 93% conversion after 20 h. Two products are obtained in a relative ratio of 88:12 (Table 1, entry 1) with the major product being urea **2a** [$Ph_2NC(=O)N(H)Ph$] and the minor product being biuret **3a** [$Ph_2NC(=O)N(Ph)C(=O)N(H)Ph$]. The presence of excess PhNCO increases the yield of **3a**, with a Ph_2NH/PhNCO ratio of 1:2 giving a 44% NMR yield, while a 1:5 ratio of Ph_2NH/PhNCO affords **3a** as the major product (71%, Table 1, entries 2 and 3) with excellent conversions in both cases. At 60 °C, the reaction time is reduced to 4 h, and the selectivity for **3a** increases (90%, Table 1, entry 4). Control experiments between Ph_2NH and isocyanates in the absence of **1** revealed either no hydroamination reaction or very low conversions in all cases (Table S1 and Supporting Information section S2.4).

Precatalyst **1** was found to be effective for a range of isocyanates, including both electron-rich and -poor species (Table 1, entries 5–10). When 4-BrC_6H_4NCO was used, the reaction was significantly slower at 25 °C (Table 1, entry 8); however, full conversion was achieved after 4 h at 60 °C (Table 1, entry 9). As with PhNCO, reactions with both 3,5-$(MeO)_2C_6H_3NCO$ and 4-BrC_6H_4NCO in a 1:5 ratio of Ph_2NH/R′NCO showed excellent selectivity for diinsertion products **3b** (100%) and **3c** (98%), respectively (Table 1, entries 7 and 10). For primary aliphatic isocyanate substrates, a competing cyclotrimerization of the isocyanate affording isocyanurates is observed.[28] It is worth noting that when secondary and tertiary aliphatic isocyanates (R′ = ^{i}Pr and ^{t}Bu) are used the reaction exclusively affords monoinsertion products **2d** and **2e**, respectively (Table 1, entries 11 and 12). When reactions containing excess isocyanate were left over several days, cyclotrimerization of the unreacted isocyanates to isocyanurates was observed. This cyclotrimerization reaction has been previously reported to be catalyzed by Lewis bases,[29] and it is therefore presumably catalyzed by either the Ph_2NH substrate or the resulting urea products. Similar to the hydrophosphination of isocyanates with precatalyst **1**,[26] changing the solvent from C_6D_6 to THF results in the exclusive formation of monoinsertion products **2a**–**2c** (Scheme 1).

The hydroamination of aniline to afford urea **2g** occurs without a catalyst (Table S1), but the presence of **1** affords biuret **3g** (Scheme 2 and Supporting Information section S3.1)

Scheme 2. Hydroamination of Phenyl Isocyanate with $PhNH_2$ Catalyzed by 1 Leads to the formation of 2g and 3g[a]



[a]Reaction conditions: 5 mol % **1**, 1:5 $PhNH_2$/PhNCO ratio in C_6D_6 at 25 °C.

as the major product. The molecular structure of **3g** was determined by X-ray crystallography (Figures 1 and S23) and features both intermolecular and intramolecular hydrogen bonds. O2 features a H-bond to H1 [O···N 2.8809(13) Å, O···H 2.054(17) Å] in a neighboring molecule (Figures 1 and S23), while the amide oxygen O1 displays two intramolecular H-bonds to H2 [O···C 2.8208(16) Å, O···H 2.2134(10) Å] and H3 [O···N 2.5881(14) Å, O···H 1.831(18) Å].

The catalysis was conducted in the presence of different additives (Table 2). In contrast to the hydrophosphination of isocyanates by the same precatalyst, **1**,[26] addition of a weak acid (NEt_3·HCl) has only a minor effect on the product distribution (Table 2, entry 1).

In order to determine whether the catalysis was heterogeneous or homogeneous, poisoning experiments[30] were carried

Table 1. Catalytic Hydroamination of Isocyanates Mediated by 1[a]

entry	R_2NH	R′NCO	R_2NH/R′NCO	T (°C)	t (h)	conv. (%)[b]	**2**/**3**(%)[b]
1	Ph	Ph	1:1	25	20	93	88/12
2	Ph	Ph	1:2	25	20	100	56/44
3	Ph	Ph	1:5	25	20	100	29/71
4	Ph	Ph	1:5	60	4	100	10/90
5	Ph	$(MeO)_2C_6H_3$	1:1	25	24	92	100/0
6	Ph	$(MeO)_2C_6H_3$	1:2	60	17	100	41/59
7	Ph	$(MeO)_2C_6H_3$	1:5	25	2	80	0/100
8	Ph	4-BrC_6H_4	1:1	25	96	80	100/0
9	Ph	4-BrC_6H_4	1:2	60	4	100	57/43
10	Ph	4-BrC_6H_4	1:5	60	4	100	2/98
11	Ph	^{i}Pr	1:1	60	4	96	100/0
12	Ph	^{t}Bu	1:1	25	3	92	100/0
13	^{i}Pr	Ph	1:2	25	0.1	100	0/87/13[c]
14	^{i}Pr	Ph	1:5	25	0.1	100	0/25/54[c]/21[d]

[a]Reaction conditions: 10 mg of **1** (5 mol %), 0.6 mL of C_6D_6. [b]Determined by ^{1}H NMR spectroscopy using either trimethoxybenzene or TMS as an internal standard. [c]Triinsertion product (**4f**). [d]Tetrainsertion product (**5f**).

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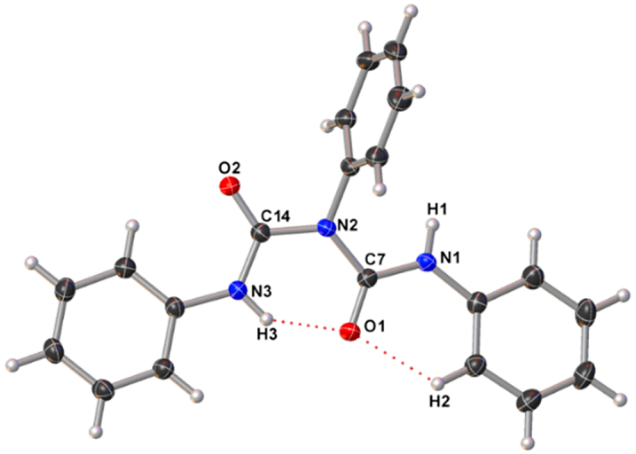

Figure 1. Molecular structure of **3g** with anisotropic displacement ellipsoids set at 50% probability. Selected bond lengths (Å) and angles (deg):N1−C7 1.3534(16), C7−N2 1.4159(15), C7−O1 1.2268(15), N2−C14 1.4260(16), C14−O2 1.2199(15), C14−N3 1.3474(16), O1···H3 1.831(18), O1···H2 2.2134(10), N3−C14−N2 115.98(10), N2−C7−N1 114.15(10), C7−N2−C14 124.20(10).

Table 2. Catalytic Hydroamination of Isocyanates Mediated by 1 in the Presence of Additives[a]

entry	R_2NH	R′NCO	additive	T (°C)	t (h)	conv. (%)[b]	**2**/**3**(%)[b]
1	Ph	Ph	NEt_3·HCl	25	16	83	80/20
2	Ph	Ph	Hg	25	20	85	90/10
3	Ph	^{t}Bu	CS_2	25	5	90	100/0
4	Ph	^{t}Bu	PPh_3	40	2	90	100/0
5	Ph	^{t}Bu	$PPhMe_2$	25	3	93	100/0

[a]Reaction conditions: 10 mg of **1** (5 mol %), 0.6 mL of C_6D_6, 1:1 R_2NH/R′NCO. [b]Determined by ^{1}H NMR spectroscopy.

out using Hg(0)[31] as well as CS_2, PPh_3, and $PPhMe_2$.[32] In all cases, the reaction reached conversions similar to those without the additive, which suggests that the catalysis is proceeding through a homogeneous pathway (Table 2, entry 2−5). Moreover, no metal precipitate or darkening of the solutions was observed during the reaction, lending further support for a homogeneous mechanism. The catalysis was also performed in the presence of cumene, which can act as a radical trap.[33] This did not inhibit the catalysis, suggesting that the reaction does not proceed via a radical mechanism.

A stoichiometric reaction between **1**, Ph_2NH, and PhNCO resulted in a color change from bright to pale yellow. In the ^{1}H NMR spectrum, the paramagnetically shifted peaks for **1** were no longer present, and new peaks were observed (Supporting Information section S7.1), indicating that **1** had transformed into a new paramagnetic species, possibly the active catalyst. This change is not observed when either Ph_2NH or PhNCO alone is added to **1**. This stoichiometric reaction was also analyzed by UV/vis spectroscopy, mass spectrometry, and infrared spectroscopy. UV/vis spectroscopy revealed no significant change compared to the spectrum of precatalyst **1**,[27] likely because the UV/vis transitions are dominated by the aromatic terphenyl ligands (Supporting Information section S7.2). Mass spectrometry of the reaction mixture showed the presence of diphenylamine and protonated terphenyl ligand (ArH species are common decomposition artifacts of the EI mass spectrometry measurements of these transition metal terphenyl complexes due to their high air- and moisture-sensitivity), but no iron-containing products were identified (Supporting Information section S7.3). Infrared spectroscopy of the stoichiometric reaction in benzene revealed complete consumption of the substrates, with the disappearance of the characteristic N−H and N═C═O stretching bands (Supporting Information section S7.4 and Figure S22). However, the lack of bands between 1600−1700 cm^{-1} and 3200−3500 cm^{-1} indicate that the stoichiometric reaction has not formed urea product **2a**. We therefore conclude that this reaction affords some unknown species, possibly the active catalyst, and that this does not contain any N−H or C═O functionalities.

Stoichiometric reactions with **1**, aniline, and PhNCO again resulted in transformation of **1** into a new paramagnetic species (Supporting Information section S7.1). It is conceivable that the Fe(II) center will behave as a Lewis acid, similar to other low-coordinate transition metal aryl precatalysts.[14f,26,28,34] Deprotonation of the amine by the terphenyl ligand to afford an iron amide was discounted, as formation of the free ligand is not observed by ^{1}H NMR spectroscopy in either the stoichiometric or catalytic reactions even when an excess of amine is used.

Kinetic experiments were undertaken to investigate the mechanism of this reaction (Supporting Information section S6). The reaction between Ph_2NH and ^{t}BuNCO in the presence of **1** was chosen, as it cleanly affords a single product (**2d**), and the ^{t}Bu group gives clear distinct singlets for both product and reagent in the ^{1}H NMR spectrum. Three samples were prepared with an equimolar amount of Ph_2NH, ^{t}BuNCO, trimethoxybenzene, and 5 mol % of **1**. After monitoring the reaction for each of these 3 samples by ^{1}H NMR spectroscopy, the data showed poor reproducibility, with rate versus [^{t}BuNCO] plots giving a different curve for each run (Figure S16). In one of these kinetic runs, a sigmoidal curve was observed in the plot of [^{t}BuNCO] versus time (Figure S15). This suggests the reaction has an activation step, likely corresponding to the conversion of precatalyst **1** to the active species.

The inconsistency in the observed rates may be due to differences in the amount of active species generated in the time between sample preparation and transfer to the NMR spectrometer. Although samples were frozen at −78 °C as soon as possible after preparation and remained frozen until they could be measured, it was not possible to prevent this initiation reaction occurring to different degrees in each sample. As such, we could not obtain meaningful kinetic data via this method.

The substrate scope has been broadened to a more nucleophilic amine, ^{i}Pr$_2$NH (Scheme 3). In the absence of a catalyst, the reaction with PhNCO affords urea **2f** at 25 °C (Scheme 3, Table S1). However, in the presence of 5 mol % **1**, **2f** is not observed. Instead, diinsertion product **3f** is the major product (Table 1, entry 13), with small amounts of triinsertion product **4f**. When the ratio of ^{i}Pr$_2$NH/PhNCO ratio is increased to 1:5 the tetrainsertion product (**5f**) is also observed (Table 1, entry 14). These products were identified by ^{1}H, ^{13}C{^{1}H} and DOSY NMR spectroscopy and mass spectrometry (Figure S13 and Table S2). When the reaction is performed using the urea ^{i}Pr$_2$NC(O)NHPh (**2f**) as the substrate, complete conversion to the polyinsertion products is accomplished in 10 min at 25 °C (5 mol % of **1**, ^{i}Pr$_2$NC(O)NHPh/PhNCO ratio of 1:4), with a similar product distribution. Although **4f** and **5f** are obtained as mixtures (**3f** 25%, **4f** 54%, and **5f** 21%), it should be noted that

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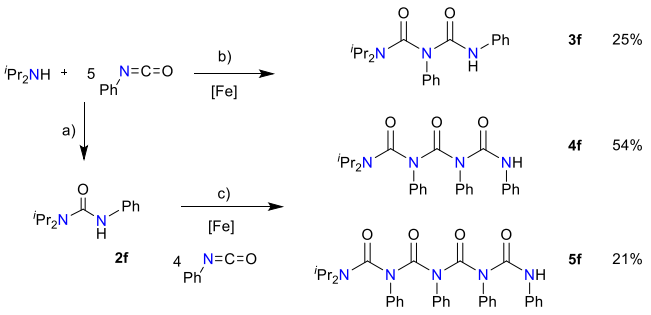
Scheme 3. Hydroamination of PhNCO with $^{i}Pr_2NH$[a]



[a]Reaction conditions: (a) without catalyst, ratio $^{i}Pr_2NH$/PhNCO 1:1, 1 h at 25 °C in C_6D_6. (b) 5 mol % **1**, ratio $^{i}Pr_2NH$/PhNCO 1:5, 10 min at 25 °C in C_6D_6. (c) 5 mol % **1**, ratio $^{i}Pr_2NC(=O)NH(Ph)$/PhNCO 1:4, 10 min at 25 °C in C_6D_6.

there are very few reported synthetic routes to these compounds in the literature.[35] Given the importance of species with multiple amide functionalities in natural products,[36] drugs,[37] and polymers,[38] the synthesis of these molecules under such mild conditions is promising for future development.

In conclusion, the two-coordinate Fe(II) complex $(2,6\text{-}Mes_2C_6H_3)_2Fe$ is an effective precatalyst for the mono- and diinsertion of isocyanates into N−H bonds in primary and secondary amines. Modification of the reaction conditions can alter the product distribution, allowing for the selective formation of ureas or enhanced selectivity of biuret products. Using a more nucleophilic amine produces triuret and tetrauret derivatives which are difficult to obtain by other synthetic routes.

Experiments to understand this catalytic process have indicated that it is likely complex in nature, but they have shown that a new paramagnetic active species is formed during the reaction and have allowed us to rule out activation mechanisms such as amine deprotonation. Future experiments to compare the behavior of **1** against other two-coordinate iron complexes may help shed further light on this mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.9b00393.

Experimental procedures, NMR spectra, and crystallographic data (PDF)

Accession Codes

CCDC 1850900 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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