



# The efficient synthesis of carbodiimides using a titanium imido complex

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## ABSTRACT

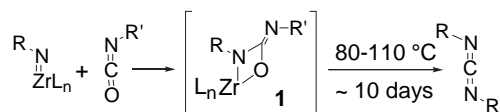
An efficient rt synthesis of carbodiimides or ureas from the combination of a titanium imido complex **2** and a range of 12 aryl and aliphatic isocyanates is described. Control experiments suggest that carbodiimide formation is via heterocumulene metathesis through a transient intermediate  $\eta^2$ -ureato-*N,O* metallacycle **8**.

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## 1. Introduction

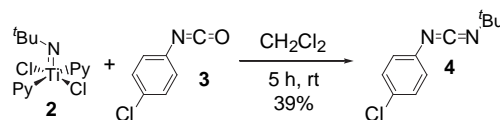
Although carbodiimides are rare subunits in natural products, they are precursors for many common and biologically active motifs, making them valuable functional groups for synthetic chemistry. The reactive carbodiimide group has been used in polymer chemistry<sup>1</sup> and can be readily converted into ureas,<sup>2</sup> imido carbonates,<sup>3</sup> imido amides,<sup>4</sup> guanidines,<sup>5</sup> oxazolidinone derivatives<sup>6</sup> and aromatic and non aromatic heterocycles.<sup>7</sup> Traditional methods of preparation have involved the removal of H<sub>2</sub>X from urea and its derivatives (X=O, S, Se), but this requires harsh conditions and reagents.<sup>8</sup> Stoichiometric metal and metal catalysed processes include the combination of potentially explosive alkyl azides and isonitriles using catalytic Fe(CO)<sub>5</sub>.<sup>9</sup> This was improved by using PdCl<sub>2</sub> as the catalyst for the addition of an amine to an isonitrile, but required an extra oxidation to give a carbodiimide.<sup>10,11</sup> Other well known methods involve the treatment of isocyanates with catalytic phosphine oxide.<sup>12</sup> This two-step process generates an imidophosphine with CO<sub>2</sub> as a byproduct, followed by metathesis with the remaining isocyanate to generate a symmetrical carbodiimide and phosphine oxide as byproduct. This method can be used for the synthesis of unsymmetrical carbodiimides by prior formation of the imidophosphine, from Staudinger reduction of azides or similarly high energy intermediates<sup>5b</sup> and reaction with a different isocyanate. More recently transition metal complexes

have been used to generate carbodiimides via heterocumulene metathesis. The reaction of stoichiometric zirconium imido complexes with isocyanates in sealed NMR tubes gave carbodiimides, but only under high temperatures and long reaction times (Scheme 1).<sup>13</sup> The intermediate  $\eta^2$ -ureato-*N,O* metallacycle **1** has been characterized by single crystal X-ray crystallography.<sup>13b</sup>



Scheme 1.

There have been many other studies investigating the heterocumulene metathesis of imido complexes,<sup>14</sup> but none to give isocyanates by treatment with carbodiimide. As part of a research programme investigating the synthetically useful reactivity of metal oxo and imido complexes with heterocumulenes<sup>15</sup> we found that treatment of Mountford's easily prepared titanium imido complex **2**<sup>16</sup> with 4-chlorophenyl isocyanate **3** gave carbodiimide **4** in an unoptimised 39% isolated yield (Scheme 2). In this paper we



Scheme 2.

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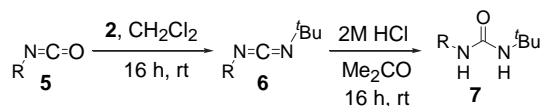
describe the optimisation of this process for the efficient synthesis of carbodiimides and control experiments, which suggest the intermediacy of a  $\eta^2$ -ureato-*N,O* metallacycle complex.

## 2. Results and discussion

Optimisation studies determined that a homogeneous reaction, such as that observed with  $\text{CH}_2\text{Cl}_2$ , gave the highest yields. The only other useful solvent found was THF, which gave an identical yield.<sup>17</sup> Higher reaction temperatures led to increased byproducts. At lower temperatures the reaction was slow and longer reaction times resulted in lower yields. The use of 0.5 and 2 M equiv of isocyanate did not affect the yield of the reaction. Due to concerns that isolation of the carbodiimide was complicated by hydrolysis to the urea, <sup>1</sup>H NMR experiments were conducted on a 1:1 mixture of isocyanate and titanium imido complex in  $\text{CDCl}_3$  at rt in a sealed tube, in order to ascertain the optimum reaction time. In less than 5 min all starting materials were consumed and a major intermediate (85%) and carbodiimide (15%) were observed. From these experiments it was determined that the optimum time for reaction was 16 h, by which time the majority of signals were due to carbodiimide. Leaving the reaction for 24 h or longer resulted in unknown byproduct formation at the expense of product formation. From these experiments and those of others (Table 1) the consumption of starting material was very fast, presumably to an imido-carbamate metallocycle (like **7** vide infra). Collapse of the intermediate by a retro-cycloaddition was much slower and presumably represents the rate determining step of this transformation.

**Table 1**

Preparation of carbodiimides and ureas from titanium imido complex and isocyanates



R	Yield <b>6</b> %	Yield <b>7</b> %	Yield <b>7</b> % (two steps)	Yield <b>7</b> % (one-pot)
4-ClPh	46	93	43	63
4-EtO <sub>2</sub> CPh	49	94	46	93
4-O <sub>2</sub> NPh	64	98	63	85
4-MeOPh	80	65	52	77
4-Me <sub>2</sub> NPh	— <sup>a</sup>	— <sup>a</sup>	—	— <sup>a</sup>
Bn	76	89	68	82
Ph(CH <sub>2</sub> ) <sub>2</sub>	68	76	52	67
4-MePh	38	89	34	78
Cy	85	98	83	87
2,6-Me <sub>2</sub> Ph	— <sup>b</sup>	61 <sup>c</sup>	61	60
2,6- <sup>i</sup> Pr <sub>2</sub> Ph	— <sup>b</sup>	20 <sup>c</sup>	20	35
<sup>t</sup> Bu	— <sup>b</sup>	16	16	— <sup>a</sup>

<sup>a</sup> Not isolated or detected.

<sup>b</sup> Impure urea was isolated.

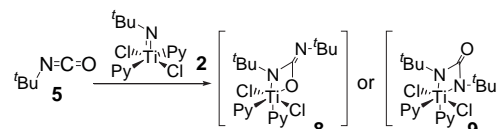
<sup>c</sup> Obtained directly.

A series of isocyanates were then surveyed under these optimized conditions to delineate the scope of the reaction (Table 1). After isolation of the carbodiimides **6** they were hydrolysed to the corresponding ureas **7** by treatment with 2 M aqueous HCl in an equal volume of acetone at rt.

The isolated yield of the carbodiimide varied from moderate to good, with higher yields obtained for aliphatic isocyanates. The exception was for the most hindered aliphatic substituent R=<sup>t</sup>Bu and we believe the low yield is due to isolation problems rather than any severe steric interaction. For the very sterically hindered substrates R=2,6-Me<sub>2</sub>Ph and 2,6-<sup>i</sup>Pr<sub>2</sub>Ph, carbodiimide could not be isolated. Instead the corresponding ureas were obtained directly.

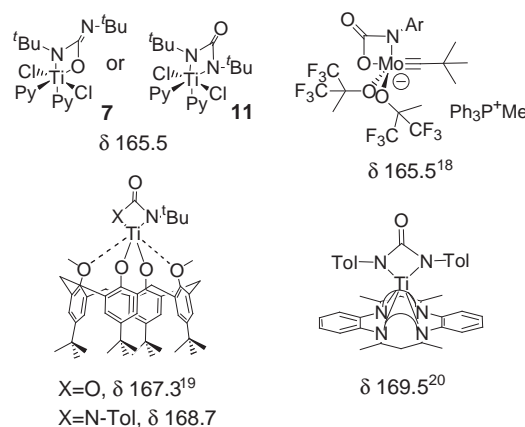
Assuming these ureas were derived from the corresponding carbodiimides, their higher reactivity towards hydrolysis may be explained by the release of steric strain upon protonation and formation of the linear nitrilium ion. Acidic hydrolysis of the carbodiimides **6** to ureas **7** was generally a high yielding process, with the exception of R=Me<sub>2</sub>NPh, which was not isolated. During the isolation of the carbodiimides **6** some product was inevitably lost in the solvent extraction and some hydrolysis to urea could occur during isolation and purification. To improve the overall yield of urea formation a one pot reaction between titanium imido complex **2** and isocyanate **5** was quenched after 16 h with the same 2 M HCl acetone mixture. This led to a much higher isolated yield of urea **7** in most cases. The yields for the 4-substituted phenyl derivatives suggest that electron deficient aromatic isocyanates reacted with higher yields than electron rich ones. The aliphatic isocyanates gave a similar yield and additional steric hindrance gave lower yields, with <sup>t</sup>Bu isocyanate not giving any product under this one pot protocol.

Observing the reaction with *tert*-butyl isocyanate (**5** R=<sup>t</sup>Bu) in a <sup>1</sup>H NMR experiment showed only a constant ~1:1 mixture of an intermediate and carbodiimide product over 16 h with no impurities [Scheme 3, intermediate (30%): **2** (43%): bis-*N,N'*-*tert*-butyl carbodiimide (23%): corresponding oxo complex of **2** (3%)]. The <sup>13</sup>C NMR spectrum showed the presence of a quaternary carbon at  $\delta$  165.5 ppm, which we have tentatively assigned to the quaternary imine carbon of the intermediate  $\eta^2$ -ureato-*N,O* metallacycle **8**. We were unable to isolate this sensitive intermediate from the NMR experiment in attempts to obtain single crystals for X-ray analysis.



**Scheme 3.**

Few similar compounds have been detected in the literature, but some examples of carbamate and urea containing metallocycles have been reported (Fig. 1). The chemical shift of the quaternary carbon atoms are similar to that observed in our intermediate. It is possible that the intermediate we observe for the *tert*-butyl isocyanate experiment is the urea metallocycle **9** and that carbodiimide formation is fast from a transient **8**.



**Fig. 1.** <sup>13</sup>C NMR chemical shifts for known carbamate and urea metallocycles.<sup>18–20</sup>

The higher yields from the one pot experiment supported our notion that we were losing carbodiimide during the isolation

procedure. However hydrolysis of the postulated intermediate like **8** would also provide a higher yield of urea.

### 3. Conclusion

We have shown that the readily available titanium imido complex **2** can form isolable carbodiimides when combined with an equimolar amount of isocyanate at rt. Most aryl and aliphatic isocyanates react efficiently with **2**, except for the most sterically hindered 2,6-*i*-Pr<sub>2</sub>Ph isocyanate and the basic dimethylaniline isocyanate. Control experiments suggest that carbodiimide formation is via heterocumulene metathesis through a transient intermediate  $\eta^2$ -ureato-*N,O* metalocycle **8**. A practical and high yielding one pot synthesis of ureas from **2** and isocyanates has been devised. Further work is exploring the synthesis of other imido complexes to be used in this transformation towards a catalytic synthesis of carbodiimides from amines and CO<sub>2</sub>.

### 4. Experimental

#### 4.1. General

All experimental procedures unless otherwise stated were carried out under an atmosphere of dry, oxygen free nitrogen. Those involving metal complexes were performed using standard Schlenk techniques. All glassware was rigorously flame-dried prior to use and a nitrogen atmosphere was maintained throughout the process. Degassed solutions and solvents were prepared by repeating a cycle of solidifying with a liquid nitrogen bath, applying vacuum (30 s) and melting three times. NMR experiments were prepared using a glove box and pre-dried Young's Tap NMR tubes. Reactions at rt imply temperatures in the range 20–25 °C. Reaction solvents were purchased as HPLC grade and dried by passing them through activated alumina towers (dichloromethane, hexanes and toluene) or activated alumina and CaO towers (THF and Et<sub>2</sub>O). All reagents were purchased and used without further purification unless otherwise stated. All amines, anilines, pyridines and phenols were redistilled or recrystallised according to literature procedures.<sup>21</sup> Column chromatography was performed using BDH 60 silica gel in the indicated solvent. Chromatography solvents were used as supplied without further purification. Column chromatography was monitored by thin layer chromatography (TLC) performed on Polgram SIL G/UV<sub>254</sub> plastic backed plates in the indicated solvent and were visualised by combination of ultraviolet light (254 nm) and a visualising dip of potassium permanganate. Melting points are uncorrected. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded at 298 K in CDCl<sub>3</sub>, unless otherwise stated.

#### 4.2. General procedure for the synthesis of carbodiimides (**6**) from titanium imido complex **2** and isocyanates (**5**)

To a clear bright orange solution of dichloro *tert*-butylimido bispyridine titanium(IV) (**2**, 1 mmol) in dry dichloromethane (15 mL) at rt under a N<sub>2</sub> atmosphere, a solution of freshly prepared isocyanate (**5**, 1 mmol) in dry dichloromethane (5 mL) was added dropwise over approximately 30 s. The bright orange solution immediately turned to a black mixture. After stirring for 16 h the solvent was reduced to approximately 3 mL in vacuo and triturated with dry toluene (20 mL). The solvent was again reduced to approximately 3 mL and triturated with dry hexanes (20 mL). All volatiles were removed in vacuo to leave crude carbodiimide as a yellow oil. Purification by flash column chromatography produced pure carbodiimide **6**. To minimise degradation of the carbodiimide to urea due to the acidity of silica gel, chromatography was performed quickly using a short column of silica.

NB MS data could not be obtained.

**4.2.1. *N'*-*tert*-Butyl-*N*-4-chlorophenyl carbodiimide.** 4-Chlorophenyl isocyanate (133 mg, 1.00 mmol) gave crude carbodiimide, which was purified by flash column chromatography (hexanes, 10% Et<sub>2</sub>O/hexanes) to give pure carbodiimide (117 mg, 46%) as a yellow oil. *R*<sub>f</sub> 0.80 (50%, Et<sub>2</sub>O/hexanes); IR  $\nu_{\max}$  (solution in CHCl<sub>3</sub>) 2965, 2930, 2857, 2130 (N=C=N), 1498, 1264 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  1.41 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 7.02 (2H, m, *m*-CH), 7.25 (2H, m, *o*-CH); <sup>13</sup>C NMR  $\delta$  31.6 (C(CH<sub>3</sub>)<sub>3</sub>), 57.7 (C(CH<sub>3</sub>)<sub>3</sub>), 124.3 (*m*-CH), 129.4 (*o*-CH), 129.7 (C), 135.7 (C), 139.7 (C).

**4.2.2. *N'*-*tert*-Butyl-*N*-4-ethoxycarbonylphenyl carbodiimide.** 4-Ethoxycarbonylphenyl isocyanate (191 mg, 1.00 mmol) gave crude carbodiimide, which was purified by flash column chromatography (hexanes, 10% Et<sub>2</sub>O/hexanes) to give pure carbodiimide (121 mg, 49%) as a white semi-solid. *R*<sub>f</sub> 0.75 (50%, Et<sub>2</sub>O/hexanes); IR  $\nu_{\max}$  (solution in CHCl<sub>3</sub>) 2979, 2932, 2128 (N=C=N), 1709, 1602, 1278 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  1.38 (3H, t, *J*=7.2, CH<sub>3</sub>CH<sub>2</sub>), 1.43 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 4.36 (2H, q, *J*=7.2, CH<sub>3</sub>CH<sub>2</sub>O), 7.10 (2H, d, *J*=8.4, *o*-CH), 7.97 (2H, d, *J*=8.4, *m*-CH); <sup>13</sup>C NMR  $\delta$  14.3 (CH<sub>3</sub>CH<sub>2</sub>O), 31.6 (C(CH<sub>3</sub>)<sub>3</sub>), 58.0 (C(CH<sub>3</sub>)<sub>3</sub>), 60.9 (CH<sub>3</sub>CH<sub>2</sub>O), 123.0 (CH<sub>Ar</sub>), 126.5 (C<sub>Ar</sub>), 131.1 (CH<sub>Ar</sub>), 134.5 (C), 146.0 (C), 166.2 (C=O). Anal. calcd for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: C 68.5, H 7.5, N 11.1, found C 68.3, H 7.4, N 11.4%.

**4.2.3. *N'*-*tert*-Butyl-*N*-4-nitrophenyl carbodiimide.** 4-Nitrophenyl isocyanate (164 mg, 1.00 mmol) gave crude carbodiimide, which was purified by flash column chromatography (hexanes, 10% Et<sub>2</sub>O/hexanes) to give pure carbodiimide (140 mg, 64%) as a pale brown semi-solid. *R*<sub>f</sub> 0.81 (50%, Et<sub>2</sub>O/hexanes); IR  $\nu_{\max}$  (solution in CHCl<sub>3</sub>) 2964, 2928, 2860, 2132 (N=C=N), 1602, 1516, 1342, 1261 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  1.46 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 7.15 (2H, m, *o*-CH), 8.17 (2H, m, *m*-CH); <sup>13</sup>C NMR  $\delta$  31.6 (C(CH<sub>3</sub>)<sub>3</sub>), 58.6 (C(CH<sub>3</sub>)<sub>3</sub>), 123.5 (*o*-CH), 125.3 (*m*-CH), 148.8 (C), 191.8 (C), missing quaternary carbon.

**4.2.4. *N'*-*tert*-Butyl-*N*-4-methoxyphenyl carbodiimide.** 4-Methoxyphenyl isocyanate (149 mg, 1.00 mmol) gave crude carbodiimide, which was purified by flash column chromatography (hexanes, 10% Et<sub>2</sub>O/hexanes) to give pure carbodiimide (163 mg, 80%) as a yellow semi-solid. *R*<sub>f</sub> 0.73 (50%, Et<sub>2</sub>O/hexanes). <sup>1</sup>H NMR  $\delta$  1.40 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 3.79 (3H, s, OCH<sub>3</sub>), 6.83 (2H, d, *J*=8.9, *o*-CH), 7.03 (2H, d, *J*=8.9, *m*-CH). All other spectroscopic data were in agreement with that previously reported.<sup>22</sup>

**4.2.5. *N'*-*tert*-Butyl-*N*-4-(*N''*-dimethylamino)phenyl carbodiimide.** 4-(*N''*-Dimethylamino)phenyl isocyanate (162 mg, 1.00 mmol) gave crude carbodiimide, which was purified by flash column chromatography (hexanes, 10% Et<sub>2</sub>O/hexanes) to give pure carbodiimide (104 mg, 48%) as a yellow semi-solid. *R*<sub>f</sub> 0.51 (66%, Et<sub>2</sub>O/hexanes); IR  $\nu_{\max}$  (solution in CHCl<sub>3</sub>) 2974, 2361, 2113 (N=C=N), 1603, 1519, 1367, 1261, 1192, 1098 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  1.39 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.93 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>), 6.68 (2H, m, *m*-CH), 7.01 (2H, m, *o*-CH); <sup>13</sup>C NMR  $\delta$  31.6 (C(CH<sub>3</sub>)<sub>3</sub>), 41.0 (N(CH<sub>3</sub>)<sub>2</sub>), 57.0 (C(CH<sub>3</sub>)<sub>3</sub>), 113.6 (*m*-CH), 123.9 (*o*-CH), 129.4 (*ipso*-C), 138.2 (N=C=N), 148.3 (*p*-C).

**4.2.6. *N*-Benzyl-*N'*-*tert*-butyl carbodiimide.** Benzyl isocyanate (133 mg, 1.00 mmol) gave crude carbodiimide, which was purified by flash column chromatography (hexanes, 10% Et<sub>2</sub>O/hexanes) to give pure carbodiimide (143 mg, 76%) as a yellow oil. *R*<sub>f</sub> 0.87 (50%, Et<sub>2</sub>O/hexanes). <sup>1</sup>H NMR  $\delta$  1.16 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 4.35 (2H, s, CH<sub>2</sub>Ph), 7.28–7.41 (5H, m, CH<sub>Ar</sub>). All other spectroscopic data were in agreement with that previously reported.<sup>2b</sup>

**4.2.7. *N'*-*tert*-Butyl-*N*-2-phenylethyl carbodiimide.** 2-Phenylethyl isocyanate (147 mg, 1.00 mmol) gave crude carbodiimide, which was purified by flash column chromatography (hexanes, 10% Et<sub>2</sub>O/hexanes) to give pure carbodiimide (138 mg, 68%) as a colourless oil. *R*<sub>f</sub> 0.83 (50%, Et<sub>2</sub>O/hexanes); IR  $\nu_{\max}$  (solution in CHCl<sub>3</sub>) 2927,

2870, 2108 (N=C=N), 1679, 1366, 1185, 1083, 1032  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  1.21 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.89 (2H, t,  $J=7.3$ ,  $\text{CH}_2\text{Ph}$ ), 3.47 (2H, t,  $J=7.3$ ,  $\text{CH}_2\text{N}$ ), 7.20–7.34 (5H, m,  $\text{CH}_{\text{Ar}}$ );  $^{13}\text{C}$  NMR  $\delta$  31.2 ( $\text{C}(\text{CH}_3)_3$ ), 37.8 ( $\text{CH}_2\text{Ph}$ ), 48.2 ( $\text{CH}_2\text{N}$ ), 55.1 ( $\text{C}(\text{CH}_3)_3$ ), 126.5 ( $\text{CH}_{\text{Ar}}$ ), 128.5 ( $\text{CH}_{\text{Ar}}$ ), 128.8 ( $\text{CH}_{\text{Ar}}$ ), 138.9 (*ipso*- $\text{C}_{\text{Ar}}$ ), 139.9 (N=C=N). Anal. calcd for  $\text{C}_{12}\text{H}_{18}\text{N}_2$ : C 77.2, H 9.0, N 13.8, found C 76.9, H 9.0, N 13.4%.

**4.2.8. *N'*-tert-Butyl-*N*-4-methylphenyl carbodiimide.** 4-Methylphenyl isocyanate (133 mg, 1.00 mmol) gave crude carbodiimide, which was purified by flash column chromatography (hexanes, 10%  $\text{Et}_2\text{O}$ /hexanes) to give pure carbodiimide (71 mg, 68%) as a yellow oil.  $R_f$  0.84 (50%,  $\text{Et}_2\text{O}$ /hexanes).  $^1\text{H}$  NMR  $\delta$  1.40 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.32 (3H, s,  $\text{CH}_3\text{Ph}$ ), 6.99 (2H, dm,  $J=8.3$ , *o*-CH), 7.10 (2H, dm,  $J=8.3$ , *m*-CH). All other spectroscopic data were in agreement with that previously reported.<sup>8c</sup>

**4.2.9. *N'*-tert-Butyl-*N*-cyclohexyl carbodiimide.** Cyclohexyl isocyanate (125 mg, 1.00 mmol) gave crude carbodiimide, which was purified by flash column chromatography (hexanes, 10%  $\text{Et}_2\text{O}$ /hexanes) to give pure carbodiimide (153 mg, 80%) as a yellow oil.  $R_f$  0.83 (50%,  $\text{Et}_2\text{O}$ /hexanes).  $^1\text{H}$  NMR  $\delta$  1.19–1.40 (16H, m,  $\text{CH}_3$ ,  $\text{CH}_2$ ), 1.54–1.62 (2H, m,  $\text{CH}_2$ ), 1.70–1.76 (2H, m,  $\text{CH}_2$ ), 1.90–1.98 (2H, m,  $\text{CH}_2$ ), 3.15–3.42 (1H, m, CHN). All other spectroscopic data were in agreement with that previously reported.<sup>23</sup>

### 4.3. General procedure for the hydrolysis of carbodiimides 6 to ureas 7

To a colourless solution of carbodiimide **6** (from above) in dichloromethane (20 mL) and acetone (20 mL), 2 M HCl (aq) (20 mL) was added. The clear biphasic mixture was stirred vigorously for other 16 h before being neutralised with  $\text{NaHCO}_3$ . The two phases were separated and the aqueous layer was extracted with dichloromethane (2  $\times$  20 mL). The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated in vacuo. Purification by flash column chromatography produced pure urea **7**.

**4.3.1. *N'*-tert-Butyl-*N*-4-chlorophenyl urea.** 4-Chlorophenyl carbodiimide (76 mg, 0.35 mmol) gave crude urea, which was purified by flash column chromatography ( $\text{Et}_2\text{O}$ /hexanes, 10–20% to 50%) to give pure urea (76 mg, 93%) as a white solid mp 190–193  $^\circ\text{C}$  (lit.<sup>24</sup>);  $R_f$  0.28 (50%,  $\text{Et}_2\text{O}$ /hexanes).  $^1\text{H}$  NMR  $\delta$  1.38 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 4.60 (0.9H, br s, NH), 6.22 (0.9H, br s, NH), 7.24 (4H, s,  $\text{CH}_{\text{Ar}}$ ). All other spectroscopic data were in agreement with that previously reported.<sup>24</sup>

**4.3.2. *N'*-tert-Butyl-*N*-4-ethoxycarbonylphenyl urea.** 4-Ethoxycarbonylphenyl carbodiimide (117 mg, 0.48 mmol) gave crude urea, which was purified by flash column chromatography ( $\text{Et}_2\text{O}$ /hexanes, 20–50%) to give pure urea (121 mg, 94%) as a white solid mp 134–136  $^\circ\text{C}$ ;  $R_f$  0.10 (50%,  $\text{Et}_2\text{O}$ /hexanes); IR  $\nu_{\text{max}}$  (solution in  $\text{CHCl}_3$ ) 3440, 3013, 2970, 1708 (C=O), 1506, 1283, 1176  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  1.35 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.37 (3H, t,  $J=7.1$ ,  $\text{CH}_3\text{CH}_2\text{O}$ ), 4.34 (2H, q,  $J=7.1$ ,  $\text{CH}_3\text{CH}_2\text{O}$ ), 5.47 (1H, br s, NH), 7.37 (2H, m, *o*-CH), 7.58 (1H, br s, NH), 7.90 (2H, m, *m*-CH);  $^{13}\text{C}$  NMR  $\delta$  14.4 ( $\text{CH}_3\text{CH}_2\text{O}$ ), 29.3 ( $\text{C}(\text{CH}_3)_3$ ), 50.8 ( $\text{C}(\text{CH}_3)_3$ ), 60.9 ( $\text{CH}_3\text{CH}_2\text{O}$ ), 117.8 (*o*-CH), 123.6 (*ipso*-C), 130.9 (*m*-CH), 144.1 (*p*-C), 154.6 (C=O, urea), 166.9 (C=O, ester); ESI/MS:  $m/z$  265.1547 (M+H, 4%), 287.1357 (M+Na, 100%); HRMS: found (calcd for  $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_3$ )  $m/z$  265.1547 (265.1547). Anal. calcd for  $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3$ : C 63.6, H 7.6, N 10.6, found C 63.2, H 7.7, N 10.2%.

**4.3.3. *N'*-tert-Butyl-*N*-4-nitrophenyl urea.** 4-Nitrophenyl carbodiimide (48 mg, 0.22 mmol) gave crude urea, which was purified by flash column chromatography ( $\text{Et}_2\text{O}$ /hexanes, 20–50%) to give pure urea (51 mg, 98%) as a white solid mp 142–143  $^\circ\text{C}$  (lit.<sup>24</sup>);  $R_f$  0.10 (50%,  $\text{Et}_2\text{O}$ /hexanes).  $^1\text{H}$  NMR  $\delta$  1.41 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 4.78 (0.98H, br s, NH), 6.73 (0.97H, br s, NH), 7.50 (2H, dm,  $J=9.2$ , *o*-CH), 8.16 (2H,

dm,  $J=9.2$ , *m*-CH). All other spectroscopic data were in agreement with that previously reported.<sup>25</sup>

**4.3.4. *N'*-tert-Butyl-*N*-4-methoxyphenyl urea.** 4-methoxyphenyl carbodiimide (100 mg, 0.49 mmol) gave crude urea, which was purified by flash column chromatography ( $\text{Et}_2\text{O}$ /hexanes, 20–50%) to give pure urea (70 mg, 65%) as a white solid mp 140–143  $^\circ\text{C}$  (lit.<sup>22</sup> 142–145  $^\circ\text{C}$ );  $R_f$  0.40 (66%,  $\text{Et}_2\text{O}$ /hexanes).  $^1\text{H}$  NMR  $\delta$  1.34 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 3.77 (3H, s,  $\text{OCH}_3$ ), 4.88 (1H, br s, NH), 6.53 (1H, br s, NH), 6.83 (2H, dm,  $J=6.8$ , *o*-CH), 7.17 (2H, dm,  $J=6.8$ , *m*-CH). All other spectroscopic data were in agreement with that previously reported.<sup>22</sup>

**4.3.5. *N*-Benzyl-*N'*-tert-butyl urea.** 4-Benzyl carbodiimide (74 mg, 0.39 mmol) gave crude urea, which was purified by flash column chromatography ( $\text{Et}_2\text{O}$ /hexanes, 20–50%) to give pure urea (78 mg, 89%) as a white solid mp 109–112  $^\circ\text{C}$  (lit.<sup>26</sup> 110–112  $^\circ\text{C}$ );  $R_f$  0.25 (66%,  $\text{Et}_2\text{O}$ /hexanes).  $^1\text{H}$  NMR  $\delta$  1.33 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 4.30 (2H, d,  $J=5.6$ ,  $\text{CH}_2\text{Ph}$ ), 4.45 (0.96H, br s, NH), 4.73 (0.94H, m, NH), 7.23–7.36 (5H, m,  $\text{CH}_{\text{Ar}}$ ). All other spectroscopic data were in agreement with that previously reported.<sup>26</sup>

**4.3.6. *N'*-tert-Butyl-*N*-2-phenylethyl urea.** 2-Phenylethyl carbodiimide (80 mg, 0.40 mmol) gave crude urea, which was purified by flash column chromatography ( $\text{Et}_2\text{O}$ /hexanes, 20–50%) to give pure urea (67 mg, 76%) as a white solid mp 73–74  $^\circ\text{C}$  (lit.<sup>27</sup> 70–71  $^\circ\text{C}$ );  $R_f$  0.20 (66%,  $\text{Et}_2\text{O}$ /hexanes).  $^1\text{H}$  NMR  $\delta$  1.33 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.82 (2H, t,  $J=6.9$ ,  $\text{CH}_2\text{Ph}$ ), 3.41 (2H, q,  $J=6.9$ ,  $\text{CH}_2\text{N}$ ), 4.30 (0.94H, br s, NH), 4.37 (0.94H, br s, NH), 7.19–7.36 (5H, m,  $\text{CH}_{\text{Ar}}$ ). All other spectroscopic data were in agreement with that previously reported.<sup>27</sup>

**4.3.7. *N'*-tert-Butyl-*N*-4-methylphenyl urea.** 4-Methylphenyl carbodiimide (55 mg, 0.29 mmol) gave crude urea, which was purified by flash column chromatography ( $\text{Et}_2\text{O}$ /hexanes, 20–50%) to give pure urea (53 mg, 89%) as a white solid mp 184–186  $^\circ\text{C}$ ;  $R_f$  0.20 (66%,  $\text{Et}_2\text{O}$ /hexanes); IR  $\nu_{\text{max}}$  (solution in  $\text{CHCl}_3$ ) 3429, 3011, 1669 (C=O), 1514, 1453, 1393, 1311  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  1.36 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.31 (3H, s,  $\text{CH}_3\text{Ph}$ ), 4.74 (1H, br s, NH), 6.25 (1H, br s, NH), 7.08–7.16 (4H, m,  $\text{CH}_{\text{Ar}}$ );  $^{13}\text{C}$  NMR  $\delta$  20.8 ( $\text{PhCH}_3$ ), 29.4 ( $\text{C}(\text{CH}_3)_3$ ), 50.7 ( $\text{C}(\text{CH}_3)_3$ ), 121.7 (*m*-CH), 129.9 (*o*-CH), 133.6 (*p*-CH), 136.1 (*ipso*-C), 155.2 (C=O); ESI/MS:  $m/z$  229.1316 (M+Na, 11%); HRMS: found (calcd for  $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}$ )  $m/z$  229.1316 (229.1311). Anal. calcd for  $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}$ : C 69.8, H 8.8, N 13.6, found C 69.4, H 8.8, N 13.4%.

**4.3.8. *N'*-tert-Butyl-*N*-cyclohexyl urea.** Cyclohexyl carbodiimide (50 mg, 0.28 mmol) gave crude urea, which was purified by flash column chromatography ( $\text{Et}_2\text{O}$ /hexanes, 20–50%) to give pure urea (55 mg, 98%) as a white solid mp 223–224  $^\circ\text{C}$  (lit.<sup>28</sup> 226  $^\circ\text{C}$ );  $R_f$  0.33 (66%,  $\text{Et}_2\text{O}$ /hexanes).  $^1\text{H}$  NMR  $\delta$  1.00–1.50 (16H, m), 1.55–1.61 (1H, m, CH), 1.65–1.72 (2H, m,  $\text{CH}_2$ ), 1.87–1.96 (2H, m,  $\text{CH}_2$ ), 3.40–3.53 (1H, m, NCH), 4.30 (2H, br s, NH). All other spectroscopic data were in agreement with that previously reported.<sup>28</sup>

**4.3.9. *N'*-tert-Butyl-*N*-2,6-dimethylphenyl urea.** 2,6-Dimethylphenyl isocyanate (147 mg, 1.00 mmol) gave crude urea, which was purified by flash column chromatography ( $\text{Et}_2\text{O}$ /hexanes, 20–50%) to give pure urea (133 mg, 61%) as a white solid mp 169–171  $^\circ\text{C}$ ;  $R_f$  0.13 (50%,  $\text{Et}_2\text{O}$ /hexanes); IR  $\nu_{\text{max}}$  (solution in  $\text{CHCl}_3$ ) 3344, 3289, 2963, 2922, 1635 (C=O), 1557, 1450, 1362, 1278, 1215, 767  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  1.29 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.30 (6H, s,  $\text{CH}_3\text{Ph}$ ), 4.08 (1H, br s, NH), 5.45 (1H, br s, NH), 7.09–7.14 (3H, m,  $\text{CH}_{\text{Ar}}$ );  $^{13}\text{C}$  NMR  $\delta$  18.3 ( $\text{CH}_3\text{Ph}$ ), 29.3 ( $\text{C}(\text{CH}_3)_3$ ), 50.4 ( $\text{C}(\text{CH}_3)_3$ ), 127.7 (*p*-CH), 128.8 (*m*-CH), 134.3 (*ipso*-C), 137.1 (*o*-C), 155.8 (C=O); ESI/MS:  $m/z$  221.1667 (M+H, 7%), 243.1480 (M+Na, 50%); HRMS: found (calcd for  $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}$ )  $m/z$



221.1667 (221.1648); HRMS: found (calcd for  $C_{13}H_{20}N_2O_Na$ )  $m/z$  243.1480 (243.1468).

**4.3.10. *N'*-tert-Butyl-*N*-2,6-diisopropylphenyl urea.** 2,6-Diisopropylphenyl isocyanate (203 mg, 1.00 mmol) gave crude urea, which was purified by flash column chromatography ( $Et_2O$ /hexanes, 20–50%) to give pure urea (55 mg, 35%) as a white solid mp 178–179 °C;  $R_f$  0.39 (50%,  $Et_2O$ /hexanes).  $^1H$  NMR  $\delta$  1.15–1.25 (12H, br s,  $CH(CH_3)_2$ ), 1.27 (9H, s,  $C(CH_3)_3$ ), 3.32 (2H, sept,  $J=6.9$ ,  $CHMe_2$ ), 7.20 (2H, d,  $J=7.7$ , *m*-CH), 7.33 (1H, t,  $J=7.7$ , *o*-CH). All other spectroscopic data were in agreement with that previously reported.<sup>29</sup>

**4.3.11. Bis-*N,N'*-tert-butyl urea.** *tert*-Butyl isocyanate (99 mg, 1.00 mmol) gave crude urea, which was purified by flash column chromatography ( $Et_2O$ /hexanes, 20–50%) to give pure urea (27 mg, 16%) as a white solid mp 238–240 °C (lit.<sup>30</sup> 238–239 °C);  $R_f$  0.14 (50%,  $Et_2O$ /hexanes).  $^1H$  NMR  $\delta$  1.32 (9H, s,  $C(CH_3)_3$ ), 4.05 (1H, br s, NH). All other spectroscopic data were in agreement with that previously reported.<sup>30</sup>

#### 4.4. General procedure for the synthesis of ureas (7) from titanium imido complex 1 and isocyanates (6)

To a clear bright orange solution of dichloro *tert*-butylimido bispyridine titanium(IV) (**2**, 350 mg, 1 mmol) in dry dichloromethane (15 mL) at rt under a  $N_2$  atmosphere, a solution of freshly prepared isocyanate (1 mmol) in dry dichloromethane (5 mL) was added dropwise over approximately 30 s. The bright orange solution turned immediately to a black mixture. After stirring the black mixture for 16 h, 2 M HCl (aq) (20 mL) and acetone (20 mL) were added. The clear biphasic mixture was stirred vigorously for other 16 h before being neutralised with  $NaHCO_3$ . The two phases were separated and the aqueous layer was extracted with dichloromethane (2×20 mL). The combined organic layers were dried over  $MgSO_4$  and concentrated in vacuo. Purification by flash column chromatography produced pure ureas as previously described.

**4.4.1. Reaction of titanium imido complex 2 with *tert*-butyl isocyanate (5,  $R=^tBu$ ).** To a clear bright orange solution of *tert*-butylimido dichloro bispyridine titanium(IV) (**2**, 25.0 mg, 0.0072 mmol) in  $CDCl_3$  (0.4 mL) in a Young's Tap NMR tube was added a solution of *tert*-butyl isocyanate (**5**,  $R=^tBu$ ) (7.00 mg, 0.007 mmol) in  $CDCl_3$  (0.35 mL). The clear solution immediately turned to a black suspension and NMR spectra were recorded. A mixture of metalocycle **8** or **9** (30%): titanium imido complex **2** (43%): bis-*N,N'*-*tert*-butyl carbodiimide (23%): corresponding oxo complex of **2** (3%).  $^1H$  NMR data for metalocycle **8** or **9**:  $\delta$  1.44 (18H, s,  $C(CH_3)_3$ ), 7.40–7.47 (4H, m, 3-CH), 7.80–7.90 (2H, m, 4-CH), 9.07 (4H, app. dd,  $J=6.4$ , 1.6, 2-CH);  $^{13}C$  NMR  $\delta$  31.1 ( $C(CH_3)_3$ ), 62.9 ( $C(CH_3)_3$ ), 124.4 (3-CH), 139.5 (4-CH), 151.8 (2-CH), 165.5 ( $C=N$  or  $C=O$ ).

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