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# Transamidation of primary amides with amines catalyzed by zirconocene dichloride†

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Zirconocene dichloride ( $\text{Cp}_2\text{ZrCl}_2$ ) has been shown to be an effective catalyst for the transamidation of primary amides with amines in cyclohexane at 80 °C in 5-24 hours. For favourable substrates, the reaction can be performed at temperatures as low as 30 °C.

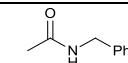
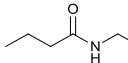
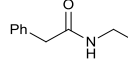
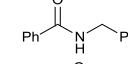
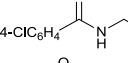
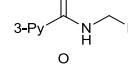
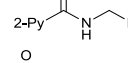
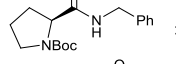
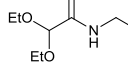
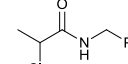
Amides are one of the most important functional groups, being widely found in natural products, pharmaceuticals and materials.<sup>1</sup> In order to avoid the use of stoichiometric activating agents, many catalytic methods for amide synthesis have been developed in recent years.<sup>2</sup> Amines can react directly with carboxylic acids, most often catalyzed by boronic acid derivatives,<sup>3</sup> although metal catalysts, including our own recent work using zirconocene dichloride, can also be used.<sup>4</sup> There have been several reports of the oxidative coupling of alcohols with amines to give amides,<sup>5</sup> along with metal-catalyzed rearrangement reactions of oximes which usually only give primary amides.<sup>6</sup>

Amides are relatively inert in comparison with other acyl donors and therefore uncatalyzed transamidation reactions require forcing reaction conditions.<sup>7</sup> The reaction has been catalyzed by imidazole,<sup>8</sup> at least for formamide synthesis and by hydroxylamine hydrochloride.<sup>9</sup> Other non-metal catalysts include boric acid<sup>10</sup> and related compounds.<sup>11</sup> Stahl and co-workers have identified several catalysts,<sup>12</sup> including zirconium<sup>13</sup> and aluminium-based<sup>14</sup> catalysts, where the main focus has been on achieving equilibration between amides. Other catalysts include cerium oxide<sup>15</sup> and Beller's recent report of the use of copper acetate.<sup>16</sup> All of the reported catalysts have some drawback; the need for high temperatures, reversibility or high catalyst loading. Myers has reported that transamidation can be achieved catalytically under mild conditions, but the protocol requires derivatization of the amide with a stoichiometric activating agent.<sup>17</sup>

Further to our report of hydroxylamine hydrochloride acting as a catalyst for transamidation, we chose to investigate the use of metal catalysts for this process, with the reaction of primary

amides **1** with benzylamine **2** to give secondary amides **3**. Using toluene as a solvent, many Lewis acids showed at least some catalytic activity,† although  $\text{Cp}_2\text{ZrCl}_2$  and  $\text{Cp}_2\text{HfCl}_2$  stood out as catalysts capable of achieving close to full conversion in only 5 hours at reflux.

**Table 1** Acylation of benzylamine with amides

Entry	Amide Product	Time (h)	Conversion <sup>a</sup> (%)	Isolated Yield (%)
1		5	100	83
2		5	100	88
3		8	96	84
4		18	100	93
5		18	89	76
6		18	100	84
7		18	100	86
8	 >99% ee	24	87	73
9		18	91	84
10		5	100	92

<sup>a</sup> Conversions were determined by analysis of the crude <sup>1</sup>H NMR spectra.

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† Electronic supplementary information (ESI) available: Full experimental details, product characterization and selected NMR spectra are provided. See DOI: 10.1039/b000000x/

A solvent screen† identified commercially available anhydrous cyclohexane as a particularly good solvent. The reagent grade solvent performed less well, indicating that the presence of

adventitious water is slightly detrimental to the reaction. Complete conversion was achieved when a small excess of amine **2** was used. The optimized reaction conditions allowed the reaction to be performed at only 80 °C in 5 hours.

Having established a viable catalytic transamidation under relatively mild conditions, we explored the reaction scope. We were pleased to find that benzylamine reacted with a range of primary amides at 80 °C (Table 1). Longer reaction times were required for less reactive amides such as benzamide and related aromatic amides (Table 1, entries 4-7). *N*-Boc prolinamide (Table 1, entry 8) was found to be less reactive, perhaps due to its chelating ability, but we were pleased to see that stereochemistry was fully retained in the secondary amide product.

**Table 2** Further transamidation reactions

Entry	Amide product	Time (h)/ Temp (°C)	Conversion <sup>a</sup> (%)	Isolated Yield (%)
1		5/80	100	78
2		5/80	100	81
3		5/80	100	69
4		18/80	95	86
5		5/80	100	91
6		5/80	100	89
7		8/80	100	90
8		18/100 <sup>b</sup>	81	54
9		18/100 <sup>b</sup>	80	68
10		5/30	100	88
11		5/30	100	95
12		5/30	100	90
13		5/30	100	89

<sup>a</sup> Conversions were determined by analysis of the crude <sup>1</sup>H NMR spectra.

<sup>b</sup> These reactions were performed in *n*-heptane.

A range of other amines was used successfully (Table 2). Most substrates underwent conversion into product at 80 °C

although the less nucleophilic amines, *p*-methoxyaniline and 2-aminothiazole (Table 2, entries 8 and 9) required a higher temperature. Remarkably, trifluoroacetamide underwent catalytic transamidation with (*S*)-(-)- $\alpha$ -methylbenzylamine at 30 °C and with retention of stereochemistry (Table 2, entry 10). Formamide

was also converted into the corresponding secondary and tertiary amides at the same temperature (Table 2, entries 11 – 13). Notable limitations<sup>†</sup> include the use of bulky amines (H<sub>2</sub>N<sup>t</sup>Bu with butyramide) and amides (<sup>t</sup>BuCONH<sub>2</sub> with benzylamine), which each gave less than 10% conversion into the desired secondary amides in their respective reactions. The transamidation of secondary amides and ureas, along with amidation of simple esters, were found to be less effective under the optimized reaction conditions.

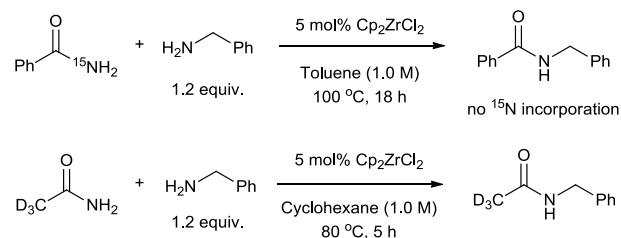
Carbamates, however, were found to be good substrates for conversion into the corresponding mono-substituted ureas – the most convenient substrate was ethyl carbamate and the reaction was successful with primary amines, anilines and with piperidine (Table 3). Heptane was used as solvent in order to accommodate the higher temperature required.

**Table 3** Reaction of amines with ethyl carbamate

Entry	Mono-substituted urea	Conversion <sup>a</sup> (%)	Isolated yield (%)
1		100	87
2		100	80
3		96	92
4		100	89
5		100	84

<sup>a</sup> Conversions were determined by analysis of the crude <sup>1</sup>H NMR spectra.

Although it seemed unlikely that the amide was attacking the amine, we confirmed this with an isotope labeling study. The reaction of <sup>15</sup>N-labeled benzamide with unlabeled benzylamine led to the exclusive formation of unlabeled secondary amide product (Scheme 1), indicating that the amine adds to the amide.



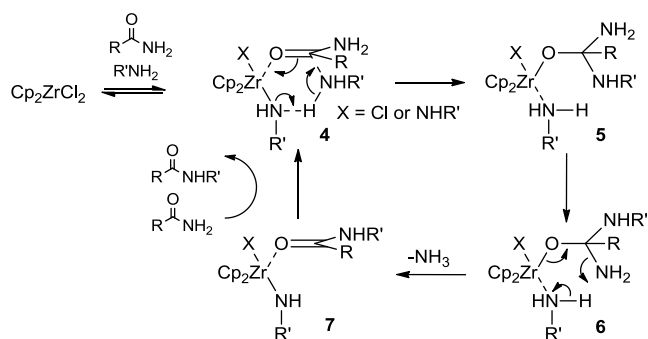
**Scheme 1** Mechanistic studies

In a second experiment, a small amount of H/D exchange was observed when acetamide-d<sub>3</sub> was converted into the secondary amide. It is unlikely that a ketene mechanism plays any significant role in the reaction, as this would be expected to lead to a greater level of H/D exchange (D/H ~ 67/33).

Analysis of the <sup>1</sup>H NMR spectra of Cp<sub>2</sub>ZrCl<sub>2</sub> in the presence of varying concentrations of either benzamide or benzylamine revealed that the cyclopentadienyl ligands were not displaced and that both substrates bound fairly weakly (K<sub>a</sub> = 0.4 M<sup>-1</sup> for benzylamine and 1.5 M<sup>-1</sup> for benzamide).

A kinetic analysis of the reaction established that the reaction was first order in both Cp<sub>2</sub>ZrCl<sub>2</sub> and benzamide. However, the reaction was found to be second order in benzylamine. One explanation for this might be that the amine is used as a base as well as a nucleophile in the reaction, but the reaction rate was found to be zero order with respect to tertiary amine when Pr<sub>2</sub>NEt was added (in fact the rate decreased slightly).

One possible mechanism which is consistent with the data is presented in Scheme 2. Reaction of the zirconium catalyst with the amine leads to formation of a zirconium amide (i.e. Zr-NHR). Complexation of the carboxamide to the catalyst would be followed by addition of the amine to the carboxamide as shown in Scheme 2, intermediate **4**. We speculate that this addition may be assisted by the zirconium amide (Zr-NHR), which would rationalize why the reaction is second order in amine. After loss of ammonia from intermediate **6**, secondary amide would be exchanged from intermediate **7** to complete the catalytic cycle.



**Scheme 2** Possible mechanism for transamidation

In summary, we have identified zirconocene dichloride as an effective catalyst for transamidation reactions of primary amides under milder conditions than previously reported.

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