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REDUCTIVE DEOXYGENATION BY Cp_2ZrHCl: SELECTIVE FORMATION OF IMINES VIA ZIRCONATION/HYDROZIRCONATION OF AMIDES

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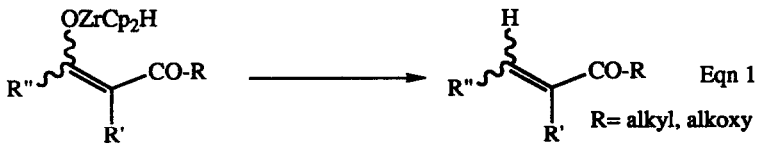
Abstract: A general new process is described by which zirconium (IV) salts of secondary amides and lactams are transformed by Cp_2ZrHCl directly into N–substituted imines in one step.

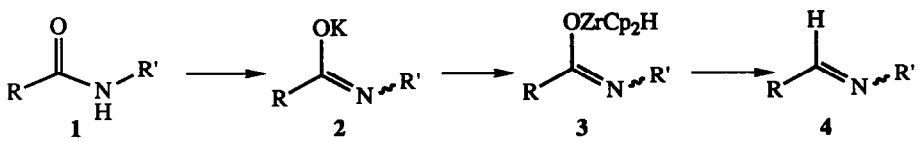
The hydrozirconation of alkenes, alkynes and simple carbonyl compounds by Cp_2ZrHCl and its congeners has been well documented.[1,2] With their coordinative unsaturation and high affinity for oxygen ligands, many zirconocene complexes also reduce and couple carbon monoxide to form zirconium (IV) methoxides and enediolates, respectively.[3,4] Recently we reported that Cp_2ZrH enolates of β-ketoesters and β-diketones, unlike the corresponding enolates of simple ketones,[5] were smoothly transformed to alkenes in good yield (Eqn 1).[6]



Eqn 1

R= alkyl, alkoxy

Consequently we decided to explore whether other electron-deficient enolates or electrophilic π-systems might undergo a similar reduction as zirconate complexes. Substituted zirconocenes such as **3**, which might be derived[7] from simple carboxamides as shown in Eqn 2, were particularly intriguing since hydride transfer reactions leading to **4** could be envisioned via metallacyclic or dinuclear complexes akin to those observed in carbonylation reactions.[3,4]



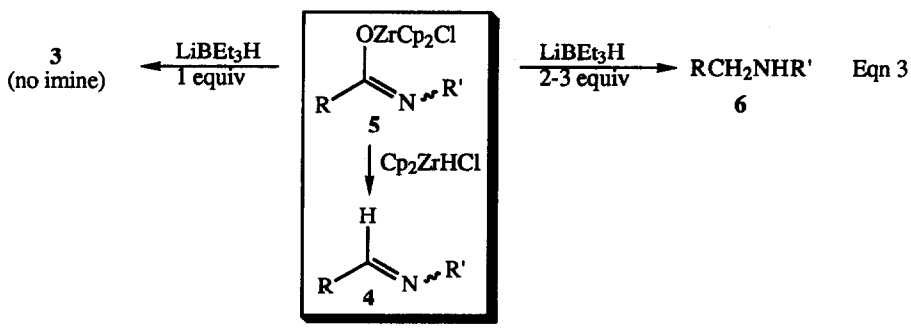
1 **2** **3** **4** Eqn 2

Here we report that zirconated amides [i.e. zirconium (IV) salts of amide anions] are transformed by Cp_2ZrHCl directly to N-substituted imines. The process is general, and efforts to elucidate the mechanism have implicated both hydrido and chlorozirconocene complexes as viable intermediates. To our knowledge, this method

represents the first controlled reduction of amides and lactams to the corresponding imines, a transformation which is otherwise very difficult to achieve, since imines are reduced very rapidly to amines by most metal hydride reagents.[8] Moreover, no products of reductive cleavage of the amides were observed.

To implement the sequence shown in Eqn 2, N-decylbenzamide **7** (Table) was kaliated (KH, THF, 0°C) and the resulting anion was transferred by syringe to a suspension of Cp_2ZrHCl (2.4 equiv) at -20°C.[9] After warming to rt, whereupon the reaction mixture became homogeneous, nonaqueous workup afforded benzaldehyde N-decyl imine **8** (86% yield) which was identified by comparison with an authentic sample prepared by a published method.[10] This procedure (Method A) was successfully applied to a number of representative amides, as shown in the Table.[9]

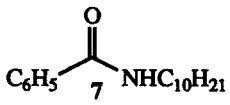
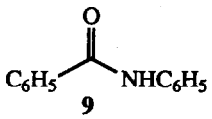
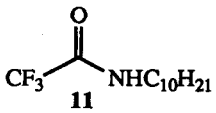
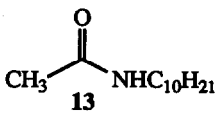
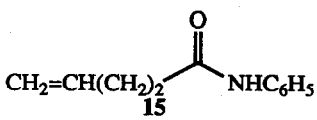
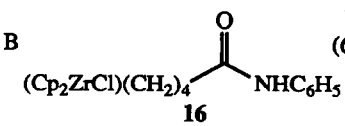
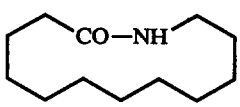
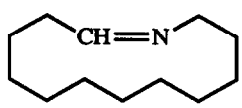
The fact that yields of **4** dropped precipitously using fewer than 2 equiv of Cp_2ZrHCl suggested that the intermediate hydridozirconocene complex **3** (Eqn 2) might not be capable by itself of forming imine. To test this hypothesis, **3** (R= C_6H_5, R'= $C_{10}H_{21}$) was synthesized independently by reacting **2** with Cp_2ZrCl_2 and reducing the intermediate chlorozirconocene complex **5** (Eqn 3) with one equiv of $LiBEt_3H$.[11] As anticipated, no imine was recovered in the hexanes extract, and only starting N-decylbenzamide was obtained by hydrolysis of the precipitated solids. Addition of 2-3 equiv of $LiBEt_3H$ to **5** produced amine **6**. However when 1 equiv of solid Cp_2ZrHCl was added to the suspension of **5** in THF, benzaldehyde N-decyl imine was obtained in 60% yield. This finding indicated that both hydrido and chlorozirconocene complexes of amide anions were selectively reduced to imines by Cp_2ZrHCl.



The unexpected reduction of **5** to **4** by Schwartz' reagent led us to discover that imines could also be produced directly from secondary amides or lactams using two equiv of Cp_2ZrHCl. Prior metalation by KH proved unnecessary for relatively acidic carboxamides.[12] Thus, H_2 evolution was observed when **7** was added to a suspension of Cp_2ZrHCl in THF.[13] Upon warming to rt, the reaction mixture became homogeneous. Addition of hexanes and filtration of the organic supernatant furnished imine **8** in 83% yield. Results on a variety of carboxamides using the simplified procedure (Method B) are summarized in the Table.[13]

Tertiary amides such as N-benzoylpiperidine are not reduced by Cp_2ZrHCl. Moreover results with unsaturated amide **15** (Entry 8) indicate that hydrozirconation of alkenes occurs much more rapidly than amide reduction. Although the mechanism of imine formation has not been elucidated, hydrido and chlorozirconocene

TABLE: *Reductive Deoxygenation of Carboxamides to Imines*

Entry	Reactant	Method[a]	Product (Yield)[b]	
1	 **7**	A	$C_6H_5CH{=}N\text{-}C_{10}H_{21}$ **8**	(86%)
2	**7**	B	**8**	(83%)
3	 **9**	A	$C_6H_5CH{=}N\text{-}C_6H_5$ **10**	(78%)
4	**9**	B	**10**	(76%)
5	 **11**	A	$CF_3CH{=}N\text{-}C_{10}H_{21}$ **12**	(61%)
6	**11**	B	**12**	(42%)
7	 **13**	A	$CH_3CH{=}N\text{-}C_{10}H_{21}$ **14**	(41%)
8	 **15**	B	 **16**	(68%)
9	 **17**	A	 **18**	(45%)
10	**17**	B	**18**	(25%)[c]

(a) Method A (see Ref 9); Method B (see Ref 13); (b) Products were identified by direct comparison with authentic samples; (c) Ca. 20% of starting lactam was also recovered.

imidates **3** and **5**, respectively, are likely intermediates. A good precedent for reduction of such imidates is the well-known conversion of O-alkyl iminoethers to amines by mild hydride donors such as $NaBH_4$.[14] However, Cp_2ZrHCl has no effect on the corresponding methyl iminoether of N-decylbenzamide, which is recovered in 96% yield after exposure to normal, amide-reducing reaction conditions.

With its demonstrated scope and generality, the selective reduction of amides to imines by Cp_2ZrHCl illustrates some of the yet-unrealized potential of early transition metal hydrides in synthesis. The method may prove to be a useful alternative to the partial reduction of amides, or to known reductive or hydrolytic deprotection procedures for amides, especially in situations where more drastic hydride reagents must be avoided.[15]

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9. *Representative Procedure for the Reduction of Amides by Method A:* To a suspension of KH (1 equiv; 25 mg in 1 mL THF, 0°C) was added a solution of **7** (153 mg in 2 mL THF) and after 10 min, the clear anion solution was transferred via syringe to a suspension of Cp_2ZrHCl (2.4 equiv; 368 mg in 0.5 mL THF, -20°C). After warming gradually to rt (2 h) the reaction was poured into ice-cold hexanes (10 mL) and filtered through Celite using more hexanes (10 mL). The pale yellow filtrate was concentrated in vacuo, resuspended in hexanes and the process repeated to afford imine **8** (124 mg, 86%).
10. Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178.
11. Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257.
12. N-Alkylacetamides and other relatively nonacidic amides were best reduced by Method A.
13. *Representative Procedure for the Reduction of Amides by Method B:* A solution of **7** (100 mg in 1 mL THF, -20°C) was added dropwise to Cp_2ZrHCl (2.4 equiv; 240 mg in 1 mL THF) and after 10 min the reaction mixture was gradually warmed to rt. After 4 h, the reaction mixture was worked up as described (Ref 9) to afford imine **8** (78 mg, 83%).
14. (a) Borch, R. F. *Tetrahedron* **1968**, 61; (b) Raucher, S.; Klein, S. *Tetrahedron Lett.* **1980**, *21*, 4061.

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