

Reaction Mechanisms

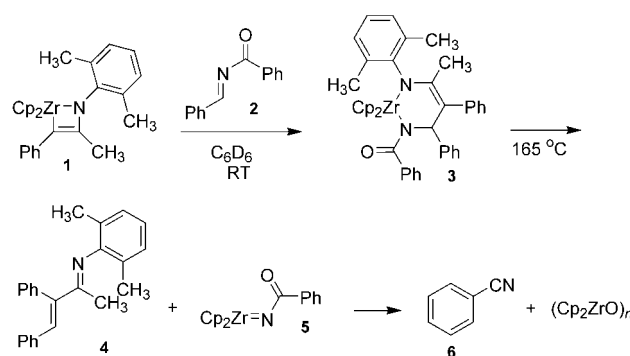
Zirconium-Mediated Conversion of Amides to Nitriles: A Surprising Additive Effect**

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The cyano ($\text{C}\equiv\text{N}$) functional group is useful for the introduction of nitrogen into organic molecules for the activation of adjacent C–H bonds and for efficient conversion into other functional groups, such as amines and ketones.^[1] The dehydration of primary amides to nitriles has long relied upon the use of strong dehydrating agents, such as P_2O_5 ^[2] or SOCl_2 .^[3] Such transformations often require high temperatures and lead to multiple by-products depending on the functional groups present in the starting amide. The lone early-transition-metal-mediated process reported for this dehydration involves the use of TiCl_4 and base at 0°C ;^[4] however, this method has largely been ignored in synthetic applications. Herein, we present a functionally simple method for preparing nitriles from primary amides that appears to proceed through the corresponding *N*-acylimidozirconocene complex. A detailed mechanistic study has been carried out that elucidates a remarkable additive effect on this reaction. Isotopic labeling and kinetic studies reveal an unprecedented reaction pathway in imidozirconium chemistry.

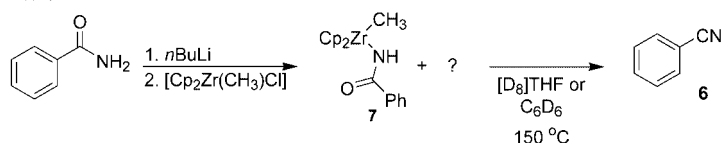
We recently reported that *N*-sulfonyl, sulfinyl, and phosphinyl imines insert into the metal–carbon–ring bond of azazirconacyclobutene **1** to generate new six-membered-ring zirconacycles **3** (see Scheme 1).^[5] Upon heating, these complexes undergo retro-[4+2] cycloadditions to generate α,β -unsaturated imines and inactive imidozirconocene complexes.^[5] *N*-Benzoyl benzaldimine (**2**)^[6] was also a competent substrate in this chemistry, but only the α,β -unsaturated imine product **4** (and not the new imidozirconium species) was detected by ^1H NMR spectroscopy. Instead, we identified the quantitative formation of benzonitrile (**6**), presumably formed by deoxygenation of the *N*-benzoylimidozirconocene complex **5** (Scheme 1; $\text{Cp} = \text{C}_5\text{H}_5$).

We subsequently prepared an alternative zirconium precursor to the imido compound **5** from the reaction between the lithium salt of benzamide and $[\text{Cp}_2\text{Zr}(\text{CH}_3)\text{Cl}]$ ^[7] (Method 1, Scheme 2). Heating this compound to 150°C in benzene or THF (reactions carried out in sealed tubes, for full experimental details see the Supporting Information) led to

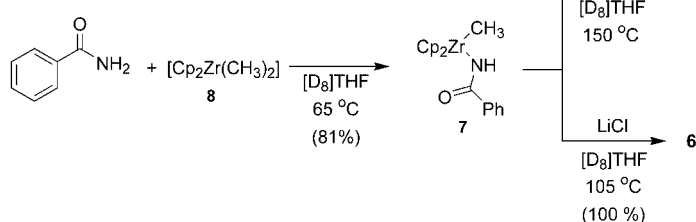


Scheme 1.

Method 1:



Method 2:



Scheme 2.

methane elimination and afforded benzonitrile in quantitative yield from the zirconium starting material, providing a two-step synthetic sequence for the clean and quantitative, albeit slow, conversion of primary amides to nitriles. Based on earlier precedent,^[8] we treated benzamide with $[\text{Cp}_2\text{Zr}(\text{CH}_3)_2]$ (**8**) at 65°C to generate the expected methylzirconium amide **7** (Scheme 2, Method 2).^[9] However, in contrast to our observations in Method 1, prolonged heating of **7** prepared by Method 2 at temperatures as high as 165°C failed to provide the expected nitrile and left **7** intact.

X-ray diffraction studies conducted on crystals of compound **7** prepared by Method 1 revealed that it was an 18-electron complex with the carbonyl oxygen atom coordinated to the zirconium center (Figure 1). The Zr–N and Zr–O bond lengths were identical at 2.30 \AA . Surprisingly, a chloride anion was located in the crystal lattice. This finding led us to suspect that residual LiCl by-product from the preparation of **7** by Method 1 may facilitate the desired nitrile formation, thereby accounting for the observed reactivity difference between **7** prepared by Methods 1 and 2. Indeed, heating compound **7** prepared by Method 2 in the presence of 0.2–2 equivalents of LiCl led to quantitative formation of benzonitrile (Scheme 2) and we were now able to carry out the reaction at 105°C in the presence of added LiCl. The reaction is catalytic in LiCl, but 0.5 equivalents were used for synthetic purposes.

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Supporting information (full experimental details) for this article is available on the WWW under <http://www.angewandte.org> or from the author.

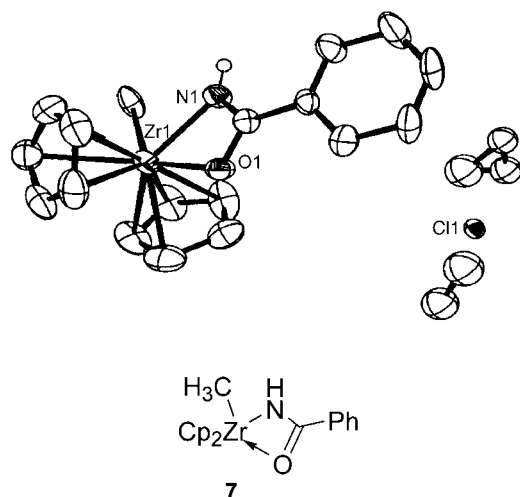


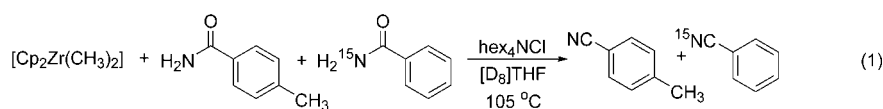
Figure 1. ORTEP diagram of methylzirconium benzamide complex **7** (thermal ellipsoids set at 50% probability). Also shown are the chloride ion and two benzene molecules found in the lattice. A line drawing is provided for clarity.

A variety of primary amides were competent substrates for this transformation, affording the corresponding nitrile compounds in excellent yields (Table 1). Intermediate methylzirconium amide complexes were detected by ^1H NMR spectroscopic monitoring of the transformation. In addition to the parent benzamide (entry 1), electron-rich (entries 2 and 3) and electron-poor (entries 4 and 5) aryl amides underwent this reaction efficiently. The reaction tolerated the increased steric hindrance of *o*-toluamide (entry 6). Primary alkyl amides with and without α -protons were also competent substrates, with hexanoamide (entry 7) and trimethylacetamide (entry 8) each providing the corresponding nitrile in excellent yield.

To study the mechanism of this transformation and elucidate the role of LiCl, a soluble additive capable of

catalyzing this chemistry was required. The possibility that traditional Lewis bases could effect this chemistry was ruled out since these reactions were conducted in neat THF, known to be an excellent ligand for zirconium. Other lithium salts,^[10] some soluble in THF, were screened in the decomposition reaction of complex **7**. However, all these Li^+ additives performed poorly relative to LiCl, requiring increased temperatures and/or reaction times. A series of tetraalkylammonium salts were also screened as additives; we were pleased to find that the soluble salt tetra-*n*-hexylammonium chloride (hex_4NCl) catalyzed the formation of benzonitrile from **7** with $t_{1/2} \approx 20$ min (versus $t_{1/2} \approx 80$ min with LiCl). These results suggest that interaction of chloride (rather than lithium) with zirconium compound **7** facilitates the generation of the imidozirconocene complex **5**. Consistent with this assessment is the observation that sodium isopropoxide and potassium *tert*-butoxide also catalyzed nitrile formation, albeit at diminished rates, probably because of the partial insolubility of the alkoxide additives. Further, based on the results of Scheme 1, conversion of the imidozirconocene **5** into benzonitrile does not require the presence of an added anion source.

With this soluble additive in hand, we could investigate the mechanism of the overall reaction and the surprising effect of added chloride ion. A crossover experiment was conducted, in which 2.2 equivalents of $[\text{Cp}_2\text{Zr}(\text{CH}_3)_2]$ were treated with one equivalent each of *p*-toluamide and ^{15}N -labelled benzamide in the presence of hex_4NCl [Eq. (1)]. No crossover was observed in this reaction: only unlabeled *p*-

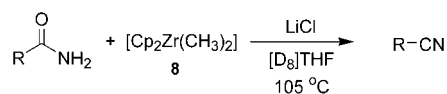


tolunitrile and ^{15}N -labeled benzonitrile were detected by ^{15}N NMR spectroscopy and GC/MS.^[11]

Kinetic studies were undertaken to determine the rate law for the reaction of complex **7** with hex_4NCl . Disappearance of **7** at a given $[\text{hex}_4\text{NCl}]$ was monitored by ^1H NMR spectroscopy. These data revealed a first-order dependence on **7** and provided the first-order rate constant, k , from the equation, $\ln[\mathbf{7}] = -kt$.^[12] Plotting values of k determined at different concentrations of hex_4NCl provided a linear correlation between the two variables and a first-order dependence on $[\text{hex}_4\text{NCl}]$ (Figure 2). The rate law for the decomposition of **7** was thus determined to be: $d[\mathbf{7}]/dt = -k[\text{hex}_4\text{NCl}][\mathbf{7}]$. Rates determined over the temperature range of 105–150 °C gave activation parameters $\Delta H^\ddagger = 18 \pm 2 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = -16 \pm 5 \text{ cal mol}^{-1} \text{ K}^{-1}$, consistent with a bimolecular rate-determining step.

Having established the rate law, we conducted a kinetic isotope effect (KIE) study using compound **7** and its N-D analogue. The deuterated analogue (**7-D**) was prepared by treatment of $[\text{Cp}_2\text{Zr}(\text{CH}_3)_2]$ with $[\text{D}_2]$ benzamide. Comparison of the decomposition rates for **7** and **7-D** enabled the measurement of a deuterium isotope effect of $k_{\text{H}}/k_{\text{D}} = 1.07$. This KIE very close to unity stands in stark contrast to the

Table 1:



Entry	Amide	Nitrile ^[a]	Yield [%] ^[b]
1	benzamide	benzonitrile	100
2	<i>p</i> -methoxybenzamide	<i>p</i> -methoxybenzonitrile	97
3	<i>p</i> -toluamide	<i>p</i> -tolunitrile	91
4	<i>p</i> -bromobenzamide	<i>p</i> -bromobenzonitrile	92 (83) ^[c]
5	<i>p</i> -trifluoromethyl-benzamide	<i>p</i> -trifluoromethyl-benzonitrile	93
6	<i>o</i> -toluamide	<i>o</i> -tolunitrile	98
7	hexanoamide	hexanenitrile	92
8	trimethylacetamide	trimethylacetoneitrile	96 ^[d]

[a] ^1H NMR spectra of all the nitrile products were correlated with authentic material. [b] Yield after 15 h relative to an internal standard by ^1H NMR spectroscopy; all starting amide had been consumed. [c] Value in parentheses is the yield of isolated product after chromatography. [d] Reaction required 48 h to proceed to completion.

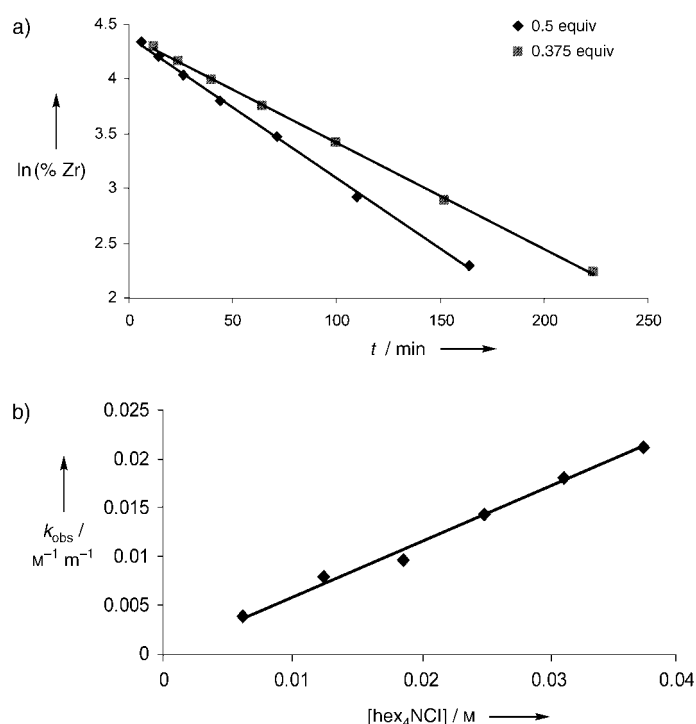


Figure 2. a) Graph for determining the order in [7] at two concentrations of hex_4NCl . b) Graph for determining the order in $[\text{hex}_4\text{NCl}]$.

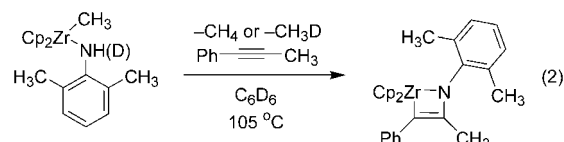
value of $k_{\text{H}}/k_{\text{D}} = 3.6$ determined for formation of a common *N*-arylimidozirconocene complex from the methylzirconium amide precursor.^[13] The collective data presented herein are most consistent with a mechanism in which rate-determining chloride-association takes place with displacement of the carbonyl oxygen atom from zirconium.^[14] The resulting intermediate, in a fast step, undergoes methane elimination to generate the *N*-acylimidozirconium species, which goes on to form the product nitrile. Presumably, chloride-assisted oxygen de-chelation is required for the complex to adopt the conformation necessary for reductive elimination.

In summary, we have developed a new method for the dimethylzirconocene-mediated conversion of primary amides to the corresponding nitriles in excellent yields. This transformation proceeds via the *N*-acylimidozirconocene complex, formation of which is dependent upon an unprecedented chloride-anion additive effect. Full experimental details can be found in the Supporting Information. A related paper describing catalytic imine insertions into azazirconacyclobutenes also appears in this issue.^[15]

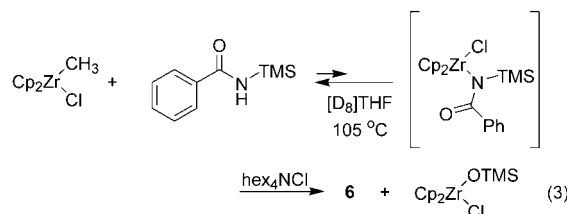
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- [11] A control experiment was conducted, in which ^{15}N -labeled benzonitrile and ^{15}N -labeled toluenitrile were shown to have distinct resonance signals in the ^{15}N NMR spectrum.
- [12] All reactions were conducted in the presence of catalytic concentrations of hex_4NCl .
- [13] The reaction used in KIE studies is shown in Equation (2). The reaction rate was shown to be independent of [alkyne] under the conditions employed.



- [14] Hydrogen bonding to the NH proton was ruled out as a possible mechanism because chloride can be used to accelerate the following reaction [Eq. (3)].



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