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Supporting Information

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

Rebecca T. Ruck and Robert G. Bergman*

[*] Prof. R. G. Bergman, R. T. Ruck
Department of Chemistry and
Center for New Directions in Organic Synthesis
University of California, Berkeley
Berkeley, CA 94720 (USA)
Fax: (+1) 510-642-2156
e-mail: bergman@cchem.berkeley.edu

General Procedures. Unless otherwise noted, reactions and manipulations were performed at ambient temperature in an inert atmosphere (N_2) glovebox, or using standard Schlenk and high vacuum line techniques. Glassware was dried overnight at 150 °C or flame-dried under vacuum immediately prior to use. All NMR spectra were obtained at ambient temperature using Bruker DRX-500, AVB-400 or AVQ-400 spectrometers. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual protiated solvent. ^{13}C NMR chemical

shifts (δ) are reported in ppm relative to the carbon resonance of the deuterated solvent. Infrared (IR) spectra were recorded as a thin film between NaCl plates. Elemental analyses were performed at the University of California, Berkeley Microanalytical facility on a Perkin Elmer 2400 Series II CHNO/S Analyzer. X-ray structural analyses were performed by Dr. Fred Hollander and Dr. Allen Oliver in the University of California, Berkeley CHEXRAY facility.

Materials. Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification. Tetrahydrofuran, pentane, hexanes and toluene (Fisher) were passed through a column of activated alumina (type A2, size 12 x 32, Purify Co.) under nitrogen pressure and sparged with N_2 prior to use. Azazirconacyclobutene **1**,[1] *N*-benzoylbenzaldimine (**2**),[2] ^{15}N-labelled benzamide[3] and methylzirconium 2,6-dimethylphenylamide[1] were prepared according to literature procedures. α,β-Unsaturated imine **4** is a known compound, whose spectral data was compared to literature values.[4]

Analytical scale conversion of amides to nitriles. In the glovebox, a medium-walled NMR tube was charged with LiCl (~2.5 mg, 0.05 mmol). To this tube was added 500 μL of

a THF-d_8 solution of amide (0.05 mmol), dimethylzirconocene (13.8 mg, 0.055 mmol) and hexamethylbenzene (1.5 mg) as internal standard. The NMR tube was fitted with a Cajon adaptor and removed from the glovebox. The tube was sealed and heated in 105 °C oil bath for 15 h (48 h for trimethylacetamide). A standard of the corresponding nitrile compound and hexamethylbenzene in THF-d_8 was prepared using known masses of the reagents. ^{1}H NMR spectra of the reaction and standard tubes were acquired and yield determined based on the amount of nitrile expected to be formed during the reaction.

Synthetic scale conversion of *p*-bromobenzamide to *p*-bromobenzonitrile. In the glovebox, a thick-walled reaction vessel with Teflon stopcock was charged with LiCl (~15 mg, 0.30 mmol). To this tube was added 3 mL of a THF solution of *p*-bromobenzamide (60.0 mg, 0.30 mmol) and dimethylzirconocene (82.8 mg, 0.33 mmol). The reaction vessel was fitted with the stopcock and removed from the glovebox. The vessel was cooled in a liquid nitrogen bath and evacuated and then heated at 105 °C for 15 h. After this time, the reaction mixture was cooled to room temperature, and THF was removed under vacuum. Silica gel chromatography (1:1 CH_2Cl_2: hexanes) afforded 4-bromobenzonitrile (45.1 mg, 83%).

$Cp_2Zr(CH_3)NHC(O)Ph$ (7). Dimethylzirconocene (502 mg, 2.00 mmol) and benzamide (242 mg, 2.00 mmol) were dissolved in THF (5 mL) in a scintillation vial. The solution was transferred to a glass reaction vessel equipped with a Teflon stopcock. The reaction vessel was removed from the glove box and the solution degassed with three freeze-pump-thaw cycles. The vessel was heated for three hours at 105 °C and then returned to the glove box. The solution was transferred to a scintillation vial and the solvent was removed under vacuum. Toluene (2 mL) was added to dissolve the product, and a layer of hexanes (5 mL) was placed on top of the toluene layer. The vial was placed in a freezer at −30 °C and allowed to stand overnight. White crystals were collected by vacuum filtration. Trituration (3x) with THF allowed for isolation of **7** as the adduct with approximately 0.5 bound molecules of THF determined by ^{1}H NMR (582 mg, 81%). ^{1}H NMR (C_6D_6, 400 MHz) δ 7.47 (d, *J* = 8.0 Hz, 2H, *o*-Ph*H*), 7.08 (m, 1H, *p*-Ph*H*), 7.01 (t, *J* = 7.2 Hz, 2H, *m*-PhH), 6.02 (br s, 1H, N*H*), 5.81 (s, 10H, Cp*H*), 3.56 and 1.40 (bound THF), 0.28 (s, 3H, C*H*$_3$) ppm. ^{13}C {^{1}H} NMR (C_6D_6, 100 MHz) δ 178.2 (*C*O), 132.8 (Ph*C*), 131.3 (Ph*C*), 128.1 (Ph*C*), 126.7 (Ph*C*) ppm. IR (NaCl): 1648 cm^{-1}. Anal. Calcd for $C_{18}H_{19}NOZr$: C, 60.63; H, 5.37; N, 3.93. Found: C, 60.51; H, 5.64; N, 3.61.

$Cp_2Zr(CH_3)NDC(O)Ph$ (7-*d*). This compound was prepared in analogous fashion to **7** from benzamide-d_2[5]. Spectral data were consistent except for the disappearance of the NH resonance and the appearance of a resonance in the ^2H spectrum. ^2H NMR (C_6H_6, C_6D_6, 77 MHz) δ 6.32 ppm.

Procedure for crossover experiment. A solution of dimethylzirconocene (27.6 mg, 0.110 mmol), ^{15}N-labelled benzamide (6.1 mg, 0.050 mmol), *p*-toluamide (6.7 mg, 0.050 mmol) and tetrahexylammonium chloride (9.8 mg, 0.025 mmol) in THF (500 μL) were added to a medium-walled NMR tube. The NMR tube was fitted with a Cajon adaptor and removed from the glovebox. The tube was sealed and heated at 105 °C for 5 h. ^{15}N NMR (THF-d_8, 40.6 MHz) δ 257.27 ppm. The ^1H NMR spectrum is shown in Figure 1a; the ^{15}N NMR spectrum is shown in Figure 2a.

An analogous experiment employing ^{15}N-labelled benzamide and ^{15}N-labelled *p*-toluamide[6] (13.5 mg, 0.050 mmol) was conducted to establish that ^{15}N-benzonitrile and ^{15}N-*p*-tolunitrile have distinct resonances in the ^{15}N NMR spectrum. ^{15}N NMR (THF-d_8, 40.6 MHz) δ 257.27 (^{15}N-benzonitrile), 256.39 (^{15}N-*p*-tolunitrile) ppm. The ^1H NMR spectrum is shown in Figure 1b; the ^{15}N NMR spectrum is shown in Figure 2b. Evidence for no crossover is

demonstrated in the identical ^{1}H NMR spectra in Figure 1 and the distinct ^{15}N NMR spectra in Figure 2.

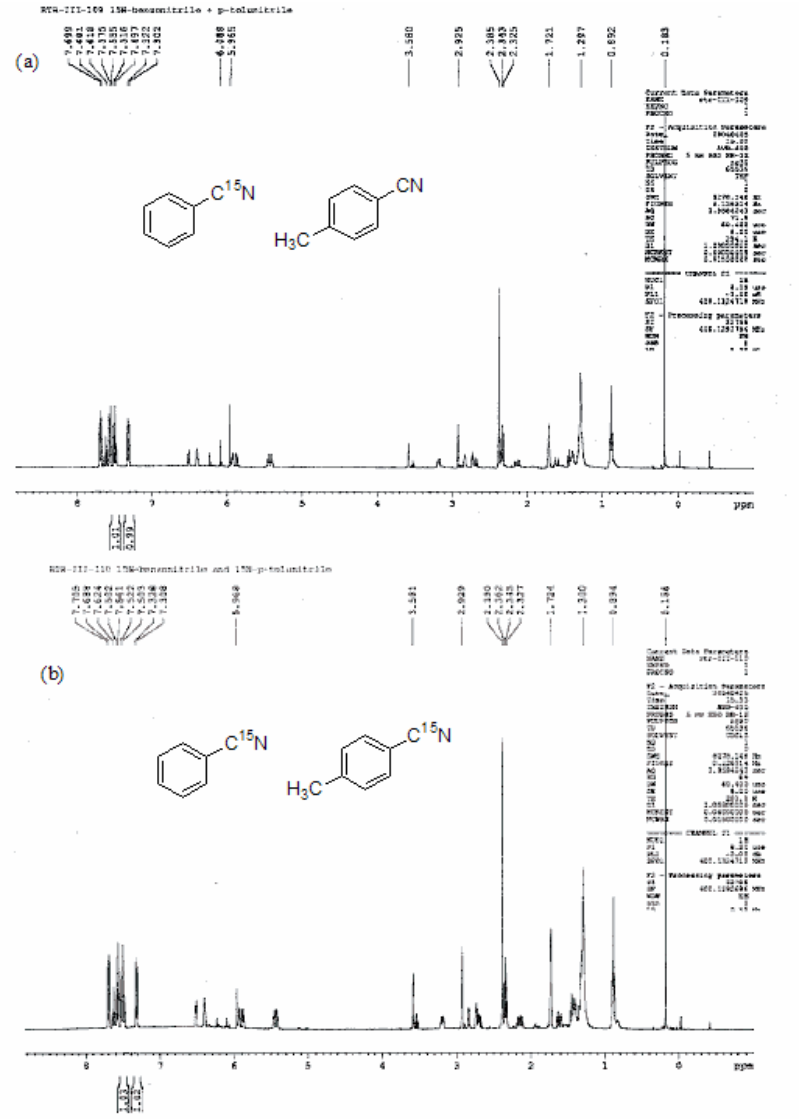


Figure 1. (a) ^{1}H NMR spectrum of reaction generating ^{15}N-benzonitrile and *p*-tolunitrile; (b) ^{1}H NMR spectrum of reaction generating ^{15}N-benzonitrile and ^{15}N-*p*-tolunitrile. These spectra are identical.

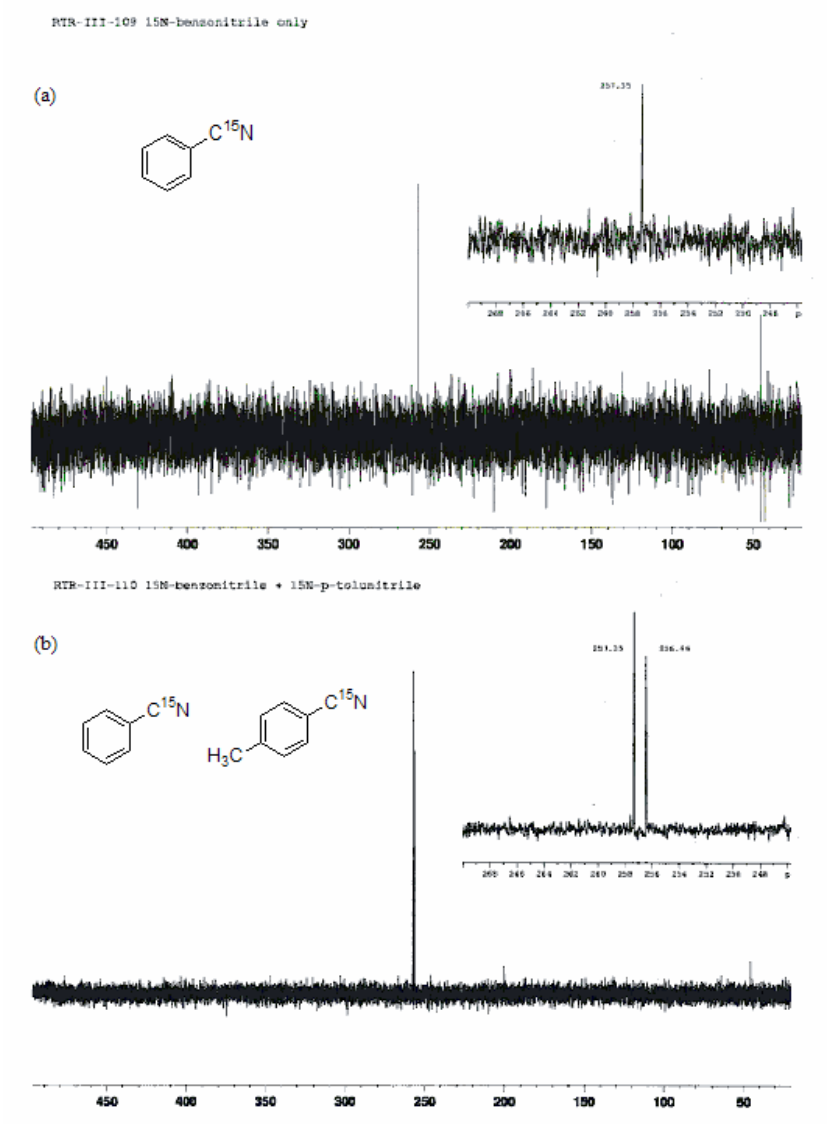
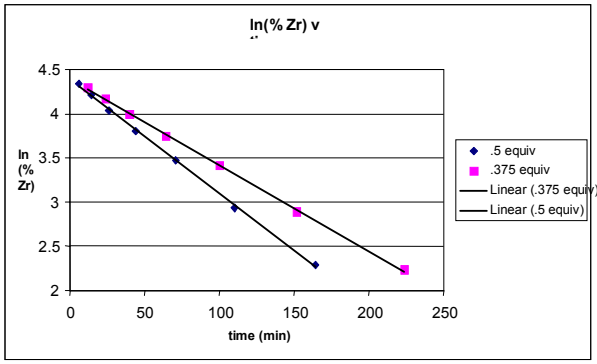


Figure 2. (a) ^{15}N NMR spectrum of reaction generating ^{15}N-benzonitrile and *p*-tolunitrile; (b) ^{15}N NMR spectrum of reaction generating ^{15}N-benzonitrile and ^{15}N-*p*-tolunitrile. These spectra are different.

Procedure for kinetic studies. A solution of compound **7** (8.9 mg, 0.025 mmol) and hex_4NCl (variable) in THF-d_8 (500 μL) was added to a medium-walled NMR tube. The tube was fitted with a Cajon adaptor, removed from the glovebox and sealed. The tube was heated in a 105 ± 0.2 °C constant temperature bath for an appropriate length of time, at which point it was removed from the bath into an ice-H_2O bath. A ^1H NMR spectrum was acquired and the ratio of **7** versus **7** + benzonitrile determined. This procedure was continued over the course of the reaction. The first two timepoints were disregarded, since, in the early stages of the reaction, reaction progress continued between removal from the oil bath and cooling in the ice bath. Conversion was plotted versus time and ln (% **7**) v time afforded a straight line, identifying the reaction as first order.

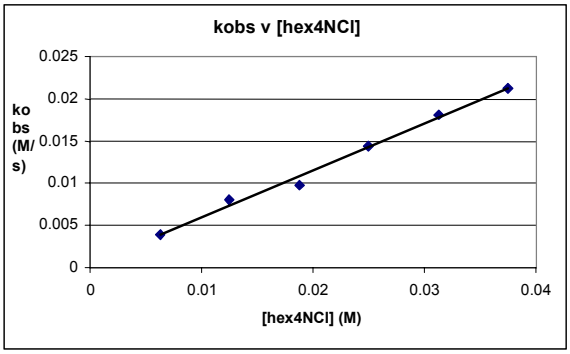
Sample graph for kinetic studies showing disappearance in [7] v time with 0.5 and 0.375 equiv hex_4NCl (Figure 3).



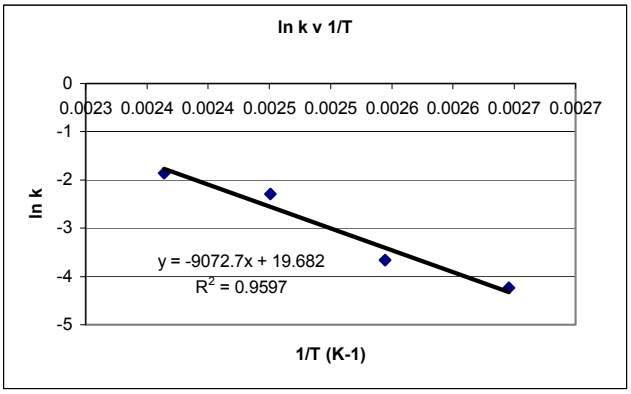
k(0.5 equiv) = 0.013±0.001

k(0.375 equiv) = 0.0097±0.001

Graph for k_{obs} versus $[hex_4NCl]$ (Figure 4).



Procedure for determination of activation parameters. Kinetic data were acquired as above at T = 105, 120, 135 and 150 °C. A graph of (ln k_{obs}) *v.* (1/T) provided the slope and intercept data necessary to determine that $\Delta H^{\ddagger}$ = 18 ± 2 kcal•mol^{-1} and $\Delta S^{\ddagger}$ = -16 ± 5 cal•mol^{-1}•K^{-1}.



Kinetic Isotope Effect study using 7 and 7-*d*. An identical procedure was employed for the KIE study as for the kinetic studies. 0.5 Equivalents hex_4NCl (4.9 mg, 0.0125 mmol) relative to Zr were used in this study. The rate constant was determined for each reaction (the plot is provided in **Figure 5**) to afford k_H/k_D = 1.07.

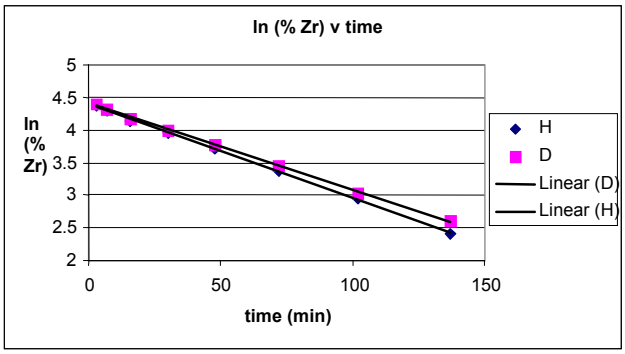
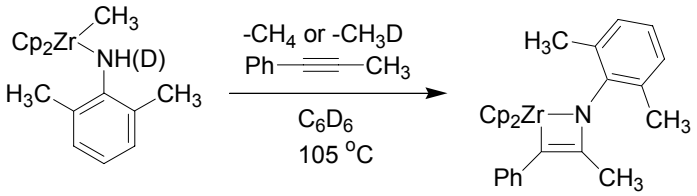


Figure 5.

k_H = 0.0144 ± 0.001

k_D = 0.0134 ± 0.001

Kinetic Isotope Effect study on methane elimination from methylzirconocene(2,6-dimethylphenyl)amide.



Methylzirconocene(2,6-dimethylphenyl)amide (8.9 mg, 0.025 mmol) and 1-phenyl-1-propyne (25, 50 or 75 μL, 0.2, 0.4 or 0.6 mmol) were combined in C_6D_6 (to total 525 μL) containing a small amount of 1,3,5-trimethoxybenzene. The solution was transferred to a medium-walled NMR tube, and the tube was fitted with a Cajon adaptor. The tube was removed from the glovebox and sealed. A timepoint for *t*=0 was acquired by ^{1}H NMR spectroscopy. The tube was then heated at 105 °C and NMR timepoints acquired over the course of the reaction. The reactions containing three different concentrations of 1-phenyl-1-propyne were shown to have the same rate constants within error (Figure 6).

The deuterated starting methylzirconocene(2,6-dimethylphenyl)amide was prepared from 2,6-dimethylaniline (87%-*d* by ^{1}H NMR). All spectra were consistent with the protiated sample; ^{2}H NMR (C_6H_6, C_6D_6, 77 MHz) δ 6.15 ppm. The elimination of CH_3D proceeded much more slowly than CH_4. As

such, full kinetics were not pursued; instead, we look at the initial rate over the first 12.5% conversion (Figure 7). Based on these data, k_H/k_D was determined to be 3.6 ± 0.5.

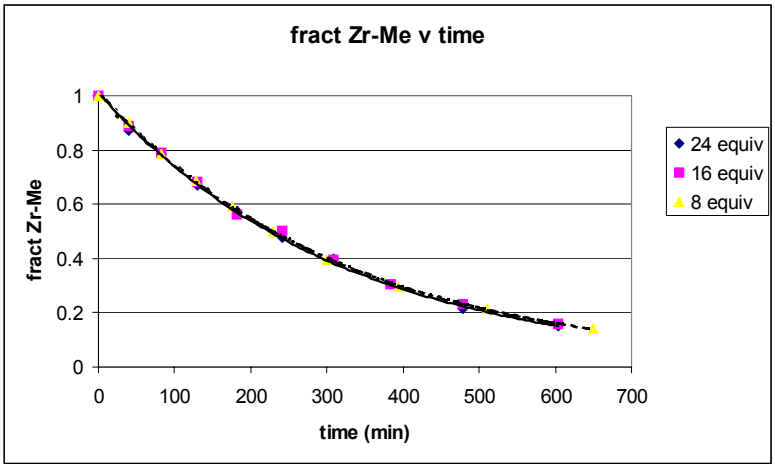


Figure 6. k_{24} = 0.00316 ± 0.00005; k_{16} = 0.00308 ± 0.00005; k_8 = 0.00305 ± 0.00005. k_H = 0.0031 ± 0.0001.

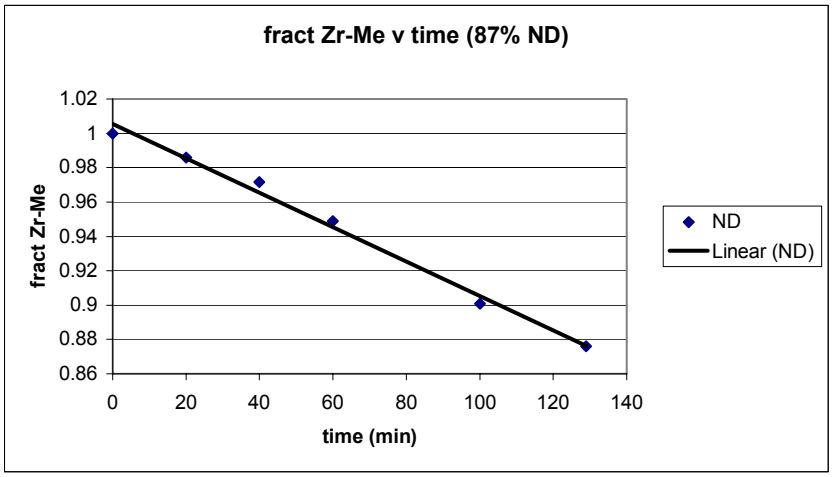


Figure 7. k_{8D} = 0.00100 ± 0.0001. Because the sample was only 87% deuterated, k_D = 0.00087 ± 0.0001.

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[5] M. Schuetz, *J. Org. Chem.* **1959**, *24*, 297.

[6] ^{15}N-Labelled *p*-toluamide was prepared analogously to ^{15}N-labelled benzamide: see ref. 3.