A General Method for the Preparation of Zirconocene Complexes of Substituted Benzynes: In Situ Generation, Coupling Reactions, and Use in the Synthesis of Polyfunctionalized Aromatic Compounds

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Abstract: A general method for the in situ production of zirconocene complexes of substituted benzynes is reported. These complexes can be trapped with nitriles to form good yields of metallacyclic compounds with extremely good regiochemical control. These compounds can be converted into ketones, α-iodo ketones, and isothiazoles by using experimentally simple procedures. In addition, generation of the benzyne complexes under 1 atm of ethylene produces metallacycles which can be readily converted into the corresponding benzocyclobutanes.

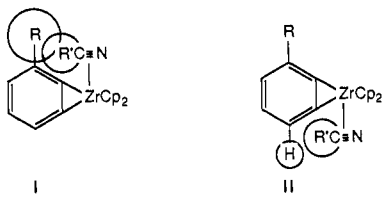
One important aspect of organic synthesis is the formation of carbon–carbon bonds. A particularly attractive means of achieving this goal is the metal-induced coupling of two readily accessible pieces into a more complex molecule with formation of a new carbon–carbon bond and a metal–carbon bond which can be readily converted into a variety of organic functional groups. Herein, we report on a general method for the in situ generation of substituted benzyne complexes of zirconocene,[1] their couplings with nitriles[1] and ethylene[2] to form metallacycles, and the subsequent conversion of these metallacycles into useful organic products.

Erker in his elegant study of the generation of zirconocene–aryne complexes from diaryl zirconocenes[3] describes an inability to prepare the di(*o*-tolyl)zirconocene precursor to the 3-methylbenzyne complex, presumably due to unfavorable steric interactions. We became interested in the generation of polysubstituted benzyne complexes and sought a method which did not require the use of 2 equiv of the substituted aromatic precursor. We reasoned that replacement of one aromatic group by a methyl group might solve both of the abovementioned problems.[4] Synthetically, the method requires only the readily prepared zirconocene (methyl) chloride and 1 equiv of a lithiated aromatic species, available by metal–halogen exchange of an appropriate haloaromatic compound.[5] We have applied this method to the preparation of a variety of substituted aromatic systems trapping the in situ generated benzyne complexes as detailed below.

As shown in Scheme I, thermolysis of **1** generates **2** at 70 °C in benzene or THF. In the presence of ca. 1.1 equiv of a nitrile, high yields of metallacycles **3** are produced. These metallacycles can be converted to useful organic products without isolation or purification. Our results, to date, are summarized in Table I. The overall result is to convert a haloaromatic precursor into a 1,2-dianion equivalent followed by protonation or iodination/hydrolysis. The iodo ketone products formed by this method (entries 5–10) are equivalent to having a positive and negative charge on contiguous carbons when linked to coupling reaction with use of palladium(0)[6] or organoboranes.[7] In the cases where neither X nor Y = H (entries 8 and 9), coupling with a nitrile followed by iodinolysis and hydrolytic workup gives the iodoimines in high yield, as shown in Table I. Presumably in these cases hydrolysis to the ketone is slowed due to steric hindrance of the imine carbon.[8]

The regiochemical outcome of these coupling reactions deserves some note. Starting with a 2-substituted phenyllithium, conversion to the benzyne complex, coupling, and hydrolysis gives almost exclusively the non-Friedel–Crafts isomer of the substituted phenone.[9] Since changing the substituent from methoxy to methyl has little effect on the product ratio, we surmise that the regiochemical preferences are steric in origin. In Chart I are shown what we believe to be the intermediate complexes just prior to insertion. It is clear that the R–R′ interaction in I is far worse than the R′–H interaction in II and that formation of the product via II would lead to a preponderance of the isomer in which the zirconocene moiety is ortho to R as is seen experimentally.

Chart I



Entries (11–14) show the conversion of the intermediate metallacycles to the corresponding isothiazoles upon treatment with S_2Cl_2 in THF. This represents a general entry to such compounds which have been little studied due to lack of convenient methods for their synthesis.[10] These heterocycles themselves should be useful precursors to a number of polysubstituted aromatic species.

In Scheme II is shown how these nascent benzyne complexes provide a useful method for the synthesis of aromatic-substituted benzocyclobutanes.[11] Generation of the benzyne complex under

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(4) (a) Buchwald, S. L.; Lum, R. T.; Dewan, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7441. (b) Buchwald, S. L.; Nielsen, R. B.; Dewan, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 1590.
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(8) For other examples of aromatic imines which resist hydrolysis cf. Culbertson (Culbertson, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 4818) and Geneste et al. (Geneste, P.; Durand, R.; Pioch, D. *Tetrahedron Lett.* **1979**, 4845).
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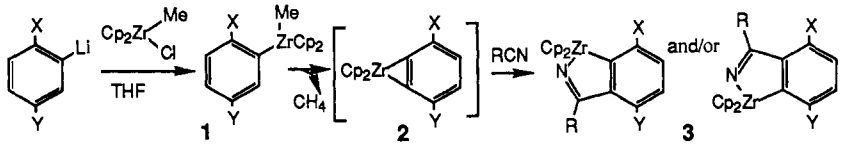
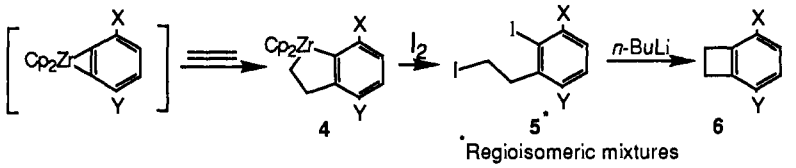
Scheme I



Scheme II



X	Y	Isolated Yield
OMe	H	50%
CH_3	OMe	69
OMe	OMe	70
Me	H	65*

*Estimated by ^1H NMR

an atmosphere of ethylene leads to metallacycle **4**.[2] Without isolation, **4** can be treated with an excess of iodine to give diiodide **5**[12] as shown in Scheme II. Treatment of **5** with 1 equiv of *n*-butyllithium[13] yields the desired benzocyclobutanes **6** in good overall yield.

In summary we have devised a general, experimentally simple method for the generation and trapping of substituted benzyne complexes of zirconocene. The initially formed metallacycles can be converted into useful and previously relatively inaccessible substituted aromatic and heterocyclic compounds. The fact that 17 of 22 organic compounds described in this paper have not previously been reported speaks for the utility of this method.

We are continuing work in this area to expand the scope of the synthetic transformations we are able to achieve. In addition, we are applying this and related methodology to the synthesis of quinone and anthraquinone natural products.

Experimental Section

All reactions were conducted under a nitrogen or argon atmosphere by using standard Schlenk techniques. Transfers and storage of air or moisture sensitive reagents were performed in a Vacuum Atmospheres Co. drybox. The sealable tubes used in the procedures were single-necked flasks with Teflon O-ring screw valves. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker WM-250, Varian XL-300, or Varian XL-400 Fourier transform spectrometers. Infrared (IR) spectra were recorded on an IBM IR/30S Fourier transform spectrometer. Gas chromatography analyses were performed on a Hewlett Packard Model 5890 GC with FID detector with use of a 25-m capillary column with cross-linked SE-30 as a stationary phase. Gas chromatography/mass spectrum analyses were obtained by using a Hewlett Packard System 5990A GCMS. Electron impact mass spectra and high resolution mass determinations (HRMS) were recorded on a Finnegan MAT System 8200.

Tetrahydrofuran, benzene, and diethyl ether were distilled from sodium/benzophenone ketyl. Hexane was deolefinated by stirring over H_2SO_4 before distillation from sodium/benzophenone ketyl. Cp_2ZrCl_2 was purchased from Boulder Scientific Inc., Mead, Co. $Cp_2Zr(Me)Cl$ was prepared by the published procedure.[14] Ethylene was purchased from Matheson Gas Products and was used without further purification. All aryl bromides are available from commercial sources and were purified before use by passage through a short column of neutral alumina (ICN Alumina N, Akt I). All other reagents were available from commercial sources and were used without further purification. Preparative flash chromatography was performed on E.M. Science Kieselgel 60 (230–400 mesh). Unless otherwise stated, yields refer to isolated yields of compounds of greater than 95% purity as determined by capillary GC and ^1H NMR.

A Typical Procedure for the Coupling of a Nitrile with a Substituted Benzyne Followed by Hydrolysis: The Preparation of 1-(3-Methoxyphenyl)ethanone (Table I, Entry 1A)[15a] and 1-(2-Methoxyphenyl)ethanone (Table I, Entry 1B).[15b] To a solution of 2-bromoanisole (0.187 g, 1.0 mmol) in 10 mL of THF at −50 °C under an argon atmosphere was added *n*-butyllithium (0.66 mL of a 1.67 M solution in hexane, 1.0 mmol), and the solution was allowed to stir at −50 °C for 30 min. This solution was added dropwise to a solution of zirconocene (methyl) chloride (0.326 g, 1.2 mmol) in 10 mL of THF at −50 °C, and the reaction mixture was allowed to stir for an additional 15 min. The reaction mixture was warmed to room temperature and transferred by cannula to a sealable tube. Acetonitrile (0.045 g, 1.1 mmol) was added, and the reaction mixture was heated to 80 °C for 24 h during which time a yellow solid precipitated. The reaction mixture was cooled to room temperature, 1 N HCl (2 mL) was added, and the mixture was allowed to stir for 4 h. The reaction mixture was diluted with ether (100 mL), washed with water and brine, and dried over $MgSO_4$. Flash chromatography (20% ether/hexane) afforded 0.129 g (86%) of a colorless liquid which was determined to be a mixture of 3-methoxy and 2-methoxy isomers in a 98:2 ratio. **1-(3-Methoxyphenyl)ethanone (Table I, Entry 1A)**: ^1H NMR (300 MHz, $CDCl_3$) δ 2.60 (s, 3 H), 3.86 (s, 3 H), 7.09–7.15 (m, 1 H), 7.20–7.40 (m, 1 H), 7.48 (s, 1 H), 7.50–7.58 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.76, 55.38, 112.21, 119.49, 120.99, 129.42, 138.29, 159.61, 197.72; IR (neat) (cm^{-1}) 3075, 3009, 2964, 2943, 2837, 1686, 1598, 1486, 1430, 1091.

1-(2-Methoxyphenyl)ethanone (Table I, Entry 1B). ^1H NMR (300 MHz, $CDCl_3$) δ 2.61 (s, 3 H), 3.90 (s, 3 H), 6.98 (m, 2 H), 7.45 (m, 1 H), 7.73 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.55, 55.17, 111.36, 120.21, 127.95, 129.97, 133.41, 158.66, 199.38; IR (neat) (cm^{-1}) 3074, 3004, 2970, 2945, 2840, 2722, 1681, 1599, 1487, 1438, 1359, 1249.

1-(3-Methylphenyl)ethanone (Table I, Entry 2A).[15c] ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 2.60 (s, 3 H), 7.36 (m, 2 H), 7.77 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.42, 26.76, 125.49, 128.31, 128.66, 133.73, 137.01, 138.23, 198.20; IR (neat) (cm^{-1}) 2924, 1685, 1604, 1588, 1485, 1426, 1358, 1194.

1-(4-Methoxyphenyl)ethanone (Table I, Entry 3A).[15d] ^1H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3 H), 3.87 (s, 3 H), 6.93 (d, J = 8.7 Hz, 2 H), 7.94 (d, J = 9.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.25, 55.41, 113.65, 130.36, 130.56, 163.46, 196.67; IR (neat) (cm^{-1}) 2962, 2843, 1670, 1602, 1577, 1454, 1438, 1417, 1312.

1-(2-Methoxy-5-methylphenyl)ethanone (Table I, Entry 4A). ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3 H), 2.60 (s, 3 H), 3.88 (s, 3 H), 6.86 (d, J = 8.0 Hz, 1 H), 7.25–7.30 (m, 1 H), 7.54 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.25, 31.85, 55.52, 111.45, 127.62, 130.41, 134.02, 138.48, 156.78, 199.83.

1-(3-Methoxy-6-methylphenyl)ethanone (Table I, Entry 4B). ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 2.57 (s, 3 H), 3.82 (s, 3 H), 6.90–6.97 (m, 1 H), 7.14 (m, 1 H), 7.20 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.71, 29.79, 55.51, 114.95, 116.19, 129.81, 132.38, 138.00,

(11) To our knowledge the only substituted examples of **6** to be reported are (a) with X = Y = OMe (Watabe, T.; Oda, M. *Chem. Lett.* **1984**, 1791) and (b) X = H, Y = Me (Riemann, J. M.; Trahanovsky, W. S. *Tetrahedron Lett.* **1977**, 1863).

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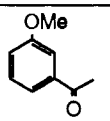
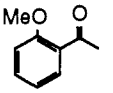
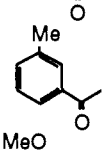
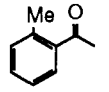
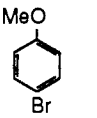
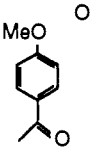
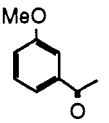
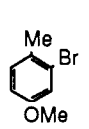
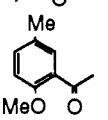
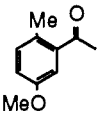
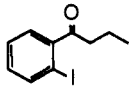
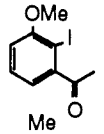
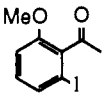
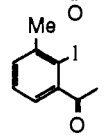
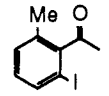
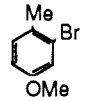
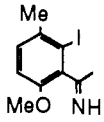
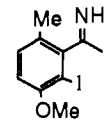
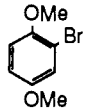
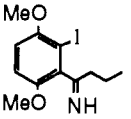
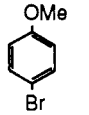
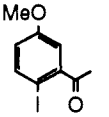
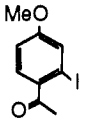
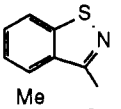
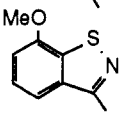
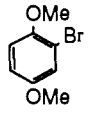
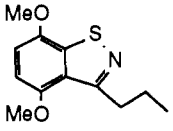
Table I

Entry	Precursor	E⁺1	E⁺2	Regioisomer A		Regioisomer B		Isolated Yield[a]
1		CH_3CN	H_3O^+		(98)		(2)	86%
2		CH_3CN	H_3O^+		(100)		(0)	62
3		CH_3CN	H_3O^+		(50)		(50)	74
4		CH_3CN	H_3O^+		(89)		(11)	47
5			I_2-->H_3O^+					70
6		CH_3CN	I_2-->H_3O^+		(100)		(0)	61
7		CH_3CN	I_2-->H_3O^+		(100)		(0)	67
8		CH_3CN	I_2-->H_3O^+		(89)		(11)	47
9			I_2-->H_3O^+					71
10		CH_3CN	I_2-->H_3O^+		(50)		(50)	74
11		CH_3CN	S_2Cl_2		(only isomer observed)			83
12		CH_3CN	S_2Cl_2		"			59
13		CH_3CN	S_2Cl_2		"			25
14			S_2Cl_2		"			52

[a] All yields are based on bromoaromatic precursor except for entry 5 (based on diphenyl zirconocene) and entry 11 (based on metallacycle).

157.14, 201.43; IR (mixture) (neat) (cm^{-1}) 2929, 2839, 1683, 1610, 1585, 1572, 1500, 1381, 1357.

1-(2-Iodophenyl)-1-butanone (Table I, Entry 5A). To a solution of diphenyl zirconocene[3] (0.375 g, 1.0 mmol) in 40 mL of THF in a sealable tube was added butyronitrile (0.069 g, 1.0 mmol). The reaction mixture was heated to 80 °C for 24 h during which time a yellow solid precipitated. The mixture was cooled to 60 °C, a solution of iodine (0.304 g, 1.2 mmol) in 10 mL of benzene was added, and the resulting mixture was stirred for an additional 15 min. The reaction mixture was cooled to room temperature, 1 N HCl (2 mL) was added, and the mixture was

stirred for 4 h. The reaction mixture was diluted with ether (100 mL), washed with 15% Na_2SO_3, water, and brine, and dried over $MgSO_4$. Flash chromatography (5% hexane/ether) afforded 0.198 g (70%) of a pale yellow liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3 H), 1.75 (6 lines, J = 7.3 Hz, 2 H), 2.87 (t, J = 7.4 Hz, 2 H), 7.12 (d of t, J = 1.8, 3.9 Hz, 2 H), 7.36 (m, 2 H), 7.89 (dd, J = 2.1, 1.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.75, 17.56, 43.96, 90.87, 127.58, 127.98, 131.34, 140.48, 144.99, 204.95; IR (neat) (cm^{-1}) 3059, 2963, 2932, 2874, 1699, 1581, 1560, 1358, 1280; HRMS calcd for $C_{10}H_{11}IO$ 273.9854, found 273.9854 ± 0.0004 amu.

A Typical Procedure for the Coupling of a Nitrile with a Substituted Benzyne Followed by Iodinolysis and Hydrolysis: The Preparation of 1-(2-Iodo-3-methoxyphenyl)ethanone (Table I, Entry 6A). To a solution of 2-bromoanisole (0.187 g, 1.0 mmol) in 10 mL of THF at −50 °C under an argon atmosphere was added *n*-butyllithium (0.66 mL of a 1.67 M solution in hexane, 1.0 mmol), and the solution was allowed to stir at −50 °C for 30 min. This solution was added dropwise to a solution of zirconocene (methyl) chloride (0.326 g, 1.2 mmol) in 10 mL of THF at −50 °C, and the reaction mixture was allowed to stir for an additional 15 min followed by warming to room temperature and transfer to a sealable tube via cannula. Acetonitrile (0.045 g, 1.1 mmol) was added, and the reaction mixture was heated to 80 °C for 24 h, during which time a yellow solid precipitated. The reaction mixture was cooled to 60 °C, a solution of iodine (0.634 g, 2.5 mmol) in 10 mL of benzene was added, and the reaction mixture was allowed to stir for 6 h. The mixture was cooled to room temperature, 1 N HCl (2 mL) was added and the mixture was allowed to stir for 4 h. The reaction mixture was diluted with ether (100 mL), washed with 15% Na_2SO_3, water, and brine, and dried over $MgSO_4$. Flash chromatography (30% ether/hexane) afforded 0.169 g (61%) of a pale yellow liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 2.60 (s, 3 H), 3.92 (s, 3 H), 6.85–6.93 (m, 2 H), 7.35 (t, J = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.14, 56.70, 111.86, 119.32, 129.57, 139.24, 147.81, 158.09, 203.14; IR (neat) (cm^{-1}) 3098, 3037, 2989, 2953, 1758, 1582, 1498, 1337, 1333; HRMS calcd for $C_9H_9IO_2$ 275.9647, found 275.9648 ± 0.0008 amu.

1-(2-Iodo-3-methylphenyl)ethanone (Table I, Entry 7A). ^1H NMR (300 MHz, $CDCl_3$) δ 2.49 (s, 3 H), 2.59 (s, 3 H), 7.07 (t, J = 6.0 Hz, 1 H), 7.28 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.07, 30.27, 96.77, 124.09, 127.94, 130.72, 142.87, 147.15, 203.93; IR (neat) (cm^{-1}) 3084, 2977, 1703, 1558, 1460, 1396, 1275; HRMS calcd for C_9H_9IO 259.96981, found 259.96984 ± 0.0008 amu.

α,3-Dimethyl-2-iodo-6-methoxybenzenemethanimine (Table I, Entry 8A), Major Product. ^1H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3 H), 2.41 (s, 3 H), 3.78 (s, 3 H), 6.80 (d, J = 8.4 Hz, 1 H), 7.17 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.77, 27.94, 55.77, 100.31, 110.42, 128.99, 133.75, 137.03, 152.98, 180.06; IR (mixture) (neat) (cm^{-1}) 3247, 2943, 2837, 1638, 1585, 1567, 1465, 1436, 1392, 1367, 1255, 1245; HRMS (mixture) calcd for $C_{10}H_{12}INO$ 288.9964, found 288.9962 ± 0.0007 amu.

α,6-Dimethyl-2-iodo-3-methoxybenzenemethanimine (Table I, Entry 8B), Minor Product. ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3 H), 2.34 (s, 3 H), 3.87 (s, 3 H), 6.69 (d, J = 10.0 Hz, 1 H), 7.14 (d, J = 10.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.28, 27.66, 56.42, 85.07, 109.50, 126.19, 131.04, 148.44, 156.11, 181.47.

3,6-Dimethoxy-2-iodo-α-propylbenzenemethanimine (Table I, Entry 9A). ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, J = 9.9 Hz, 3 H), 1.71 (m, 2 H), 2.54 (t, J = 7.8 Hz, 2 H), 3.75 (s, 3 H), 3.85 (s, 3 H), ab 6.75, 6.85 (Abq, J = 9.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.83, 18.24, 41.18, 56.33, 57.04, 87.47, 110.39, 111.55, 138.22, 149.94, 152.51, 181.72; IR (KBr) (cm^{-1}) 3239, 2997, 1639, 1589, 1469, 1432, 1262; HRMS calcd for $C_{12}H_{16}INO_2$ 333.02257, found 333.02256 ± 0.001amu.

1-(2-Iodo-5-methoxyphenyl)ethanone (Table I, Entry 10A). ^1H NMR (300 MHz, $CDCl_3$) δ 2.60 (s, 3 H), 3.81 (s, 3 H), 6.70 (dd, J = 3.0, 8.0 Hz, 1 H), 6.98 (d, J = 3.0 Hz, 1 H), 7.76 (d, J = 8.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.48, 55.49, 79.03, 114.37, 117.69, 141.28, 145.14, 159.63, 201.73; IR (neat) (cm^{-1}) 3065, 3003, 2962, 2937, 1701, 1696, 1586, 1560, 1466, 1388, 1354, 1280; HRMS calcd for $C_9H_9IO_2$ 275.9647, found 275.9647 ± 0.008 amu.

1-(2-Iodo-4-methoxyphenyl)ethanone (Table I, Entry 10B). ^1H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3 H), 3.83 (s, 3 H), 6.92 (dd, J = 7.8, 2.4 Hz, 1 H), 7.51 (d, J = 2.4 Hz, 1 H), 7.59 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.69, 55.63, 92.88, 113.44, 127.10, 130.88, 134.23, 161.49, 198.67; IR (neat) (cm^{-1}) 3005, 2966, 2938, 2838, 1684, 1588, 1557, 1486, 1438, 1394, 1355; HRMS calcd for $C_9H_9IO_2$ 275.9647, found 275.9647 ± 0.001 amu.

3-Methyl-1,2-benzisothiazole (Table I, Entry 11A).[10] To a suspension of the azametallacycle (derived from thermolysis of diphenylzirconocene in the presence of acetonitrile)[1b] (0.338 g, 1.0 mmol) in 15 mL of THF was added sulfur monochloride (0.202 g, 1.5 mmol), and the mixture was allowed to stir at room temperature for 9 h. The reaction mixture was diluted with ether (50 mL), washed with water and brine, and dried over $MgSO_4$. Flash chromatography (5% ether/hexane) afforded 0.124 g (85%) of a yellow liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 2.75 (s, 3 H), 7.42 (m, 2 H), 7.92 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.39, 119.49, 123.36, 124.44, 127.43, 135.03, 152.03, 162.80; IR (neat) (cm^{-1}) 3064, 2994, 2953, 2916, 2856, 1592, 1494, 1435, 1381, 1342, 1320, 759, 732; HRMS calcd for C_8H_7NS 149.0299, found 149.0299 ± 0.0005 amu.

3,7-Dimethyl-1,2-benzisothiazole (Table I, Entry 12A). ^1H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3 H), 2.75 (s, 3 H), 7.28 (d, J = 6.0 Hz, 1 H), 7.37 (t, J = 8.7 Hz, 1 H), 7.77 (d, J = 6.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.66, 20.32, 120.91, 125.26, 127.47, 130.14, 134.98, 152.68, 163.62; IR (KBr) (cm^{-1}) 3035, 2914, 2856, 1593, 1494, 1436, 1387, 1347, 1323; HRMS calcd for C_9H_9NS 163.04557, found 163.04556 ± 0.0006 amu.

7-Methoxy-3-methyl-1,2-benzisothiazole (Table I, Entry 13A). ^1H NMR (300 MHz, $CDCl_3$) δ 2.73 (s, 3 H), 4.00 (s, 3 H), 6.87 (d, J = 8.0 Hz, 1 H), 7.38 (t, J = 8.0 Hz, 1 H), 7.51 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.56, 55.68, 106.64, 115.46, 126.41, 137.08, 142.13, 153.01, 162.94; IR (neat) (cm^{-1}) 3248, 2942, 2837, 1638, 1585, 1496, 1465, 1279, 1257, 1246, 1029; HRMS calcd for C_9H_9NOS 179.0405, found 179.0405 ± 0.0004 amu.

A Typical Procedure for the Preparation of Substituted Isothiazoles: The Preparation of 4,7-Dimethoxy-3-propyl-1,2-benzisothiazole (Table I, Entry 14A). To a solution of 2,5-dimethoxybromobenzene (0.208 g, 0.96 mmol) in 10 mL of THF at −78 °C under an argon atmosphere was added *n*-butyllithium (0.66 mL of a 1.67 M solution in hexane, 1.0 mmol), and the solution was allowed to stir for 15 min. This solution was added to a solution of zirconocene (methyl) chloride (0.325 g, 1.2 mmol) in 10 mL of THF at −78 °C and was stirred for an additional 15 min before warming to room temperature. Butyronitrile (0.076 g, 1.1 mmol) was added, and the reaction mixture was transferred by cannula to a sealable tube and was heated to 80 °C for 16 h. The reaction mixture was cooled to room temperature, sulfur monochloride (0.141 g, 1.05 mmol) was added, and the mixture was allowed to stir at room temperature for 18 h. The reaction mixture was diluted with ether (40 mL), washed with water, aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. Flash chromatography (40% ether/hexane) afforded 0.107 g (52%) of a yellow solid: ^1H NMR (250 MHz, $CDCl_3$) δ 1.64 (t, J = 7.3 Hz, 3 H), 1.83 (m, 2 H), 3.21 (t, J = 7.5 Hz, 2 H), 3.92 (s, 3 H), 3.93 (s, 3 H), 6.75, 6.66 (Abq, J = 8.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.03, 21.91, 36.42, 55.70, 55.98, 104.98, 107.11, 126.81, 145.13, 146.62, 151.19, 167.45; IR (KBr) (cm^{-1}) 3006, 1598, 1499, 1464, 1436, 1265, 1046, 806, 714; HRMS calcd for $C_{12}H_{15}O_2NS$ 237.08234, found 237.08227 ± 0.0007 amu.

2-Methoxybicyclo[4.2.0]octa-1,3,5-triene (Scheme II, Entry 1). ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (t, J = 3.0 Hz, 2 H), 3.32 (t, J = 4.0 Hz, 2 H), 3.86 (s, 3 H), 6.66 (d, J = 6.0 Hz, 2 H), 7.12 (t, J = 6.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.41, 29.83, 56.06, 112.68, 115.30, 128.45, 128.56, 147.72, 153.48; IR (neat) (cm^{-1}) 3061, 3001, 2964, 2927, 2834, 1827, 1603, 1589, 1476, 1464, 1436, 1267; HRMS calcd for $C_9H_{10}O$ 134.0732, found 134.0731 ± 0.0004 amu.

A Typical Procedure for the Preparation of a Substituted Benzocyclobutane: The Preparation of 2-Methoxy-5-methylbicyclo[4.2.0]octa-1,3,5-triene (Scheme II, Entry 2). To a solution of 2-bromo-4-methylanisole (0.200 g, 1.0 mmol) in 10 mL of THF at −50 °C under an argon atmosphere was added *n*-butyllithium (0.66 mL of a 1.67 M solution in hexane, 1.0 mmol), and the solution was allowed to stir at −50 °C for 30 min. This solution was added dropwise to a solution of zirconocene (methyl) chloride (0.326 g, 1.2 mmol) in 10 mL of THF at −50 °C, and the resulting mixture was allowed to stir an additional 15 min. The reaction mixture was warmed to room temperature and transferred to a sealable tube via cannula. The reaction mixture was degassed by 1 freeze–pump–thaw cycle. At room temperature, the reaction mixture was placed under 1 atm of ethylene and was heated to 80 °C for 20 h. The resulting yellow solution was cooled to 60 °C, a solution of iodine (0.634 g, 2.5 mmol) in 10 mL of benzene was added, and the resulting mixture was stirred for 3 h. The mixture was cooled to room temperature, diluted with ether (100 mL), washed with 15% Na_2SO_3, water, and brine, and dried over $MgSO_4$, and the solvent was removed in vacuo. The crude material was diluted with 10 mL of hexane, filtered to remove any insoluble material, and then concentrated in vacuo. Ether (10 mL) was added to the resulting oil which was cooled to −50 °C. *n*-Butyllithium (0.66 mL of a 1.67 M solution in hexane, 1.0 mmol) was added, and the mixture was allowed to stir at −50 °C for 3 h. The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was diluted with ether (100 mL), washed with water and brine, and dried over $MgSO_4$. Flash chromatography (5% ether/hexane) afforded 0.103 g (69%) of a white solid, mp 54–55 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3 H), 3.08 (t, J = 4.0 Hz, 2 H), 3.27 (t, J = 4.0 Hz, 2 H), 3.85 (s, 3 H), 6.59 (d, J = 9.0 Hz, 1 H), 6.90 (d, J = 8.0 Hz, 1 H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 15.49, 28.56, 28.72, 56.26, 113.08, 124.77, 127.98, 128.92, 145.91, 151.58; IR (neat) (cm^{-1}) 3018, 2985, 2970, 2930, 1750, 1699, 1695, 1684, 1674, 1619, 1501, 1449, 1376; HRMS calcd for $C_{10}H_{12}O$ 148.0888, found 148.0888 ± 0.0006 amu.

2,5-Dimethoxybicyclo[4.2.0]octa-1,3,5-triene (Scheme II, Entry 3).[11a] ^1H NMR (300 MHz, $CDCl_3$) δ 3.29 (s, 4 H), 3.82 (s, 6 H), 6.61 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.28, 56.41, 113.84, 130.17, 148.05; IR (KBr) (cm^{-1}) 3023, 2999, 2971, 1593, 1492, 1456, 1440; HRMS calcd for $C_{10}H_{12}O_2$ 164.08372, found 164.08379 ± 0.0006 amu.

2-Methylbicyclo[4.2.0]octa-1,3,5-triene (Scheme II, Entry 4).[11b] ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3 H), 3.12 (s, 4 H), 6.87 (d, J = 6.9 Hz, 1 H), 6.97 (d, J = 8.2 Hz, 1 H), 7.10 (t, J = 6.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.49, 29.71, 119.79, 127.19, 127.41, 132.38, 144.53, 145.39; IR (neat) (cm^{-1}) 2924, 1611, 1591, 1457, 1340, 1260, 1100.

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Ammonia-Catalyzed Silylation Reactions of Cab-O-Sil with Methoxymethylsilanes

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Abstract: The reactions of methoxymethylsilanes with Cab-O-Sil in dry toluene medium in the presence of ammonia were investigated as a model system to understand the role of ammonia as a catalyst in the silylation of silica surfaces. Diffuse reflectance sampling technique and FTIR spectroscopy were used for this study. Ammonia was found to be a true catalyst under the reaction conditions used. It catalyzes the direct condensation reaction of unhydrolyzed methoxymethylsilanes with "dry" Cab-O-Sil permitting surface structural information to be inferred. High-temperature post-reaction curing is unnecessary for silylation to occur on either "wet" or "dry" Cab-O-Sil in the presence of ammonia. Monolayer or greater than monolayer surface converage is obtained for methoxymethylsilane reactions with Cab-O-Sil when ammonia is present and is about 12 times the surface coverage obtained in the absence of ammonia.

The utility of organosilane-modified surfaces has been demonstrated in a variety of fields ranging from their use as stationary phases for chromatography,[1] antimicrobials,[2] catalysts,[3] immobilized enzymes,[4] and fiber reinforced composites.[5] To better tailor surfaces with specific properties, it is necessary to understand how reaction conditions affect reaction mechanisms and surface structure. With this goal in mind, we have undertaken a detailed study of a model system consisting of Cab-O-Sil (a very pure, high surface area silica) modified with methoxymethylsilanes (the simplest alkoxyalkylsilanes) from dry toluene medium. We have found diffuse reflectance FTIR spectroscopy to be a useful quantitative tool[6,7] as well as an ideal sampling technique for these materials.[8] A previous report[9] addressed the role of surface-adsorbed water and post-reaction curing temperature on reaction mechanism and relative silane loading.

The use of an amine during silylation of silica surfaces with chlorosilanes from nonaqueous medium is recommended for the synthesis of reversed-phase chromatography packings.[10-12] The amine shifts the equilibrium by binding the acid formed in the reaction. The mechanistic aspects of similar reactions have been studied in homogeneous[13] medium. Kinkel and Unger[14] assumed the same mechanistic aspects to be applicable to reactions in a heterogeneous phase. The presence of a base is also known to increase the silane loading when alkoxysilanes are used. Few systematic studies have been done to understand the role played by a base in the silylation reaction with alkoxysilanes. As early as 1967, it was observed[15] that the addition of *n*-propylamine when treating silica with triethoxyethylsilane produces a more hydrophobic surface. Stark et al.[16] used radiochemical tracer techniques to investigate the specific roles of silane functional groups, condensation catalyst, and adsorbed water on adsorbate-adsorbent interactions. They reported that the addition of anhydrous ammonia prior to the vapor-phase adsorption of trimethylsilanol resulted in a 9-fold increase in the concentration of the bound silane. Kaas and Kardos[17] used infrared spectroscopy to show that the presence of *n*-propylamine at 1:1 mole ratio with ethyltriethoxysilane greatly enhanced the concentration of the silane bound to a Cab-O-Sil wafer. Although the concentration of *n*-propylamine was not varied, its presence was found to accelerate the surface reaction of other silanes. The amine func-

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