

Table I. Mixed Metal Reagent Deuteration of Ketones^a

compound	method	yield, %	major product	composition, %	minor product	%
benzophenone	A, I	84	diphenylmethane-1,1-d ₂	100	—	—
benzophenone	B, I	96	diphenylmethane-1,1-d ₂	100	—	—
3-bromoacetophenone	B, II	79	3-(1-hydroxyethyl-1-d ₁)-1-bromobenzene	94	3-(vinyl-1-d ₁)-1-bromobenzene	6
1-tetralone	A, III	87	tetralin-1,1-d ₂	85	1,2-dihydronaphthalene-1-d ₁	15
1-acetonaphthone	A, III	96	1-(ethyl-1,1-d ₂)naphthalene	93	1-(vinyl-1-d ₁)naphthalene	7
2-acetonaphthone ^{b,c}	A, III	86	2-(ethyl-1,1-d ₂)naphthalene	84	2-(vinyl-1-d ₁)naphthalene	10
3-acetylphenanthrene ^{b,d}	A, II	88	3-(ethyl-1,1-d ₂)phenanthrene	82	3-(vinyl-1-d ₁)phenanthrene	17

^aThe reactions were carried out for 30–45 min after the addition of the ketone. ^bThe reaction was carried out for 2–3 h. ^cThe crude product contained 6% of the alcohol. ^dApproximately 12% of the starting material and 1% of the alcohol were present in the crude product.

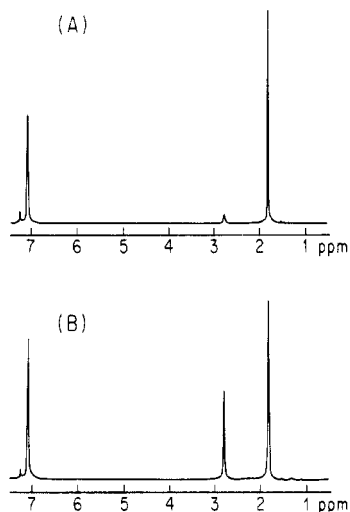


Figure 1. ¹H NMR (500 MHz) spectra of the reduction products of 1-tetralone using (A) palladium-catalyzed reduction with di-deuterium, and (B) with a mixed metal reagent reduction through aluminum chloride and lithium aluminum deuteride.

lyzed reaction is not surprising. Indeed, it was observed previously that the palladized carbon in the presence of dideuterium gas not only reduces the carbonyl group but also effects deuterium–hydrogen exchange in the 4-position.³ The mixed metal reagent cannot accomplish this exchange reaction.

Mechanistically, the mixed metal hydride reduction appears to follow the same path as the catalytic reduction.^{10–13} Both reactions proceed via an intermediate alcohol followed by hydrogenolysis to produce the hydrocarbon.

Experimental Section

All the starting materials including lithium aluminum deuteride (98% d) and heavy water (99.8%) were commercially available and were purified as necessary.

¹H NMR spectra were recorded at 500 MHz. The ²H NMR spectra were recorded at 400 MHz on solutions in dichloromethane. The deuterium content and isotopic purity were determined from mass spectroscopic data that were obtained with an HP GC–MS system.

Mixed Metal Deuteride Reduction Procedure. Method A. The reduction was effected via the approach of Nystrom and Berger.⁹ In a typical reaction, lithium aluminum deuteride (0.42 g, 10 mmol) in dry ether (10 mL) was stirred for 15 min under dinitrogen as aluminum chloride (1.4 g, 11 mmol) in dry ether

(10 mL) was slowly added. Five minutes after the addition, a mixture of benzophenone (1.7 g, 10 mmol) and aluminum chloride (1.4 g, 11 mmol) in dry ether (20 mL) was added to the solution of mixed metal hydride. The reaction mixture was vigorously stirred for 45 min under dinitrogen, and the reaction was quenched with heavy water (10–15 mL) followed by 6 N sulfuric acid (11 mL). The reaction mixture was further diluted with water (25 mL), and the aqueous layer was extracted with four portions of ether (4 × 30 mL). The combined organic layers were washed with water, 10% sodium bicarbonate solution, and again with water and dried. The solvent was removed under vacuum to recover the product (1.4 g, 84%).

Method B. The same procedure as described in method A was used except that the ketone was dissolved in ether (without the addition of aluminum chloride) and then added to the equimolar quantities of lithium aluminum deuteride and aluminum chloride.

The original products proved to be mixtures of the desired labeled compound contaminated with the starting material, the intermediate alcohol, and the alkene. Flash chromatography and vacuum distillation were used to isolate these materials in some experiments. Subsequent work revealed that column chromatography was more suitable, and the crude products were purified by this method to obtain the arylalkanes as noted in the table. In method I, the crude product was chromatographed on silica gel (60–200 mesh, 140A) with hexane as eluent; in method II, the alkene was separated by elution with hexane as described in I and the alcohol was eluted with ether; in method III, the crude product was chromatographed on silica gel (230–400 mesh, 60A) with hexane as eluent.

The alkanes were characterized by GC–MS and NMR spectroscopy. The deuterium content exceeded 96% of the expected value in every case with the d₁ compound as the principal contaminant.

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Ortho-Directed Lithiation in π -Deficient Diazinyl Heterocycles

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Over the past decade, the ortho-directed aromatic lithiation reaction has become a valuable and efficient synthetic method. While this reaction has been thoroughly studied with some heterocycles such as pyridine, very few ortho-lithiations of pyrazines, pyrimidines, or pyridazines have been reported, and none in high yield. 5-Bromo- and 5-methylpyrimidines are reported to lithiate at C-4^{1,2} and

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Table I

product	yields, ^b %				product	yields, ^b %			
	A E = TMS	B E = Me	C E = PhCHOH	D E = PhCO		A E = TMS	B E = Me	C E = PhCHOH	D E = PhCO
	85	86	82	<i>a</i>		99	92	95	91
	47	47	49	<i>a</i>		68	57	95	<i>a</i>
	68	83	98% (65 ^a)	<i>a</i>		57	92	79	<i>a</i>
	76	75	97	84					

^a Complex mixture, low yield of expected product. ^b All yields are of purified products.

Table II

compd	mp, °C, <i>R_f</i>	IR, cm ⁻¹	MS	NMR (300 MHz, CDCl ₃)	elemental analysis (calcd/found)
1A	oil, 0.41 ^a	754, 1370, 1460	213 (MH) ⁺ , 197 (MH - CH ₄) ⁺	0.20 (s, 9 H), 3.95 (s, 3 H), 3.96 (s, 3 H), 6.88 (s, 1 H)	C ₉ H ₁₆ N ₂ O ₂ Si·0.1H ₂ O C: 50.49/50.37 H: 7.63/7.49 N: 13.09/12.98
2A	oil, 0.10 ^a	758, 1288, 1394	183 (MH) ⁺ , 167 (MH - CH ₄) ⁺	0.28 (s, 9 H), 3.84 (s, 3 H), 8.17 (s, 1 P), 8.89 (s, 1 H)	C ₈ H ₁₄ N ₂ O ₃ Si C: 52.71/52.80 H: 7.74/7.70 N: 15.37/15.37
3A	oil, 0.43 ^a	1490, 1622, 1648	241 (M + C ₂ H ₅) ⁺ , 213 (MH) ⁺ , 197 (MH - CH ₄) ⁺	0.20 (s, 9 H), 3.92 (s, 3 H), 3.94 (s, 3 H), 8.12 (s, 1 H)	C ₉ H ₁₆ N ₂ O ₂ Si C: 50.91/51.44* H: 7.60/7.87 N: 13.19/12.66*
4A	oil, 0.69 ^a	758, 1396, 1560	213 (MH) ⁺ , 197 (MH - CH ₄) ⁺	0.22 (s, 9 H), 3.87 (s, 6 H), 8.38 (s, 1 H)	C ₉ H ₁₆ N ₂ O ₂ Si C: 50.91/50.95 H: 7.60/7.53 N: 13.19/13.04
5A	oil, 0.67 ^a	760, 1122, 1352	243 (MH) ⁺ , 227 (MH - CH ₄) ⁺	0.19 (s, 9 H), 3.88 (s, 6 H), 3.92 (s, 3 H)	C ₁₀ H ₁₈ N ₂ O ₃ Si C: 49.56/49.39 H: 7.49/7.56 N: 11.56/11.71
6A	oil, 0.71 ^a	758, 840, 1358	183 (MH) ⁺ , 167 (MH - CH ₄) ⁺	0.29 (s, 9 H), 3.90 (s, 3 H), 7.94 (d, 1 H, <i>J</i> = 2.7 Hz), 8.22 (d, 1 H, <i>J</i> = 2.7 Hz)	C ₈ H ₁₄ N ₂ O ₃ Si C: 52.71/52.60 H: 7.74/7.71 N: 15.37/15.24
7A	38-39, 0.59 ^a	838, 1244, 1340	213 (MH) ⁺ , 197 (MH - CH ₄) ⁺	0.27 (s, 9 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 7.96 (s, 1 H)	C ₉ H ₁₆ N ₂ O ₂ Si C: 50.91/50.65 H: 7.60/7.63 N: 13.20/13.13
1B	85-86, 0.26 ^b	1256, 1380, 1476	183 (M + C ₂ H ₅) ⁺ , 155 (MN) ⁺	2.15 (s, 3 H), 3.98 (s, 3 H), 4.02 (s, 3 H), 6.71 (s, 1 H)	C ₇ H ₁₀ N ₂ O ₂ C: 54.54/54.28 H: 6.54/6.50 N: 18.17/18.04
2B	oil, 0.12 ^b	570, 1302, 1408	153 (M + C ₂ H ₅) ⁺ , 125 (MH) ⁺	2.40 (s, 3 H), 3.86 (s, 3 H), 8.13 (s, 1 H), 8.64 (s, 1 H)	C ₈ H ₈ N ₂ O C: 58.05/57.91 H: 6.50/6.55 N: 22.57/22.20
3B	60-61, 0.28 ^b	1204, 1400, 1580	183 (M + C ₂ H ₅) ⁺ , 155 (MH) ⁺	2.02 (s, 3 H), 3.93 (s, 3 H), 3.96 (s, 3 H), 7.95 (s, 1 H)	C ₇ H ₁₀ N ₂ O ₂ C: 54.54/54.43 H: 6.54/6.54 N: 18.17/18.03
4B	90-91, 0.47 ^b	1142, 1468, 1586	183 (M + C ₂ H ₅) ⁺ , 155 (MH) ⁺	1.96 (s, 3 H), 3.94 (s, 6 H), 8.28 (s, 1 H)	C ₇ H ₁₀ N ₂ O ₂ ·0.03H ₂ O C: 54.35/53.95 H: 6.56/6.52 N: 18.11/17.70*
5B	99-100, 0.52 ^b	1148, 1376, 1592	213 (M + C ₂ H ₅) ⁺ , 185 (MH) ⁺	1.88 (s, 3 H), 3.91 (s, 3 H), 3.92 (s, 6 H)	C ₈ H ₁₂ N ₂ O ₃ C: 52.17/51.78 H: 6.57/6.58 N: 15.21/14.84
6B	oil, 0.40 ^b	1168, 1390, 1456	153 (M + C ₂ H ₅) ⁺ , 125 (MH) ⁺	2.38 (s, 3 H), 3.88 (s, 3 H), 7.84 (d, 1 H, <i>J</i> = 2.9 Hz), 7.90 (d, 1 H, <i>J</i> = 2.9 Hz)	C ₈ H ₈ N ₂ O·0.05H ₂ O C: 57.64/57.60 H: 6.53/6.58 N: 22.41/22.35
7B	oil, 0.53 ^b	1156, 1316, 1374	183 (M + C ₂ H ₅) ⁺ , 155 (MH) ⁺	2.31 (s, 3 H), 3.86 (s, 3 H), 3.89 (s, 3 H), 7.59 (s, 1 H)	C ₇ H ₁₀ N ₂ O ₂ C: 54.54/54.26 H: 6.54/6.47 N: 18.17/18.03
1C	99-101, 0.24 ^c	1122, 1576, 1668	247 (MH) ⁺ , 229 (MH - H ₂ O) ⁺	3.28 (s, 1 H), 3.94 (s, 3 H), 4.00 (s, 3 H), 5.82 (s, 1 H), 7.07 (s, 1 H), 7.22-7.32 (m, 5 H)	C ₁₃ H ₁₄ N ₂ O ₃ C: 63.40/63.54 H: 5.73/5.74 N: 11.38/11.34
2C	116-118, 0.10 ^c	1056, 1300, 1452	217 (MH) ⁺ , 199 (MH - H ₂ O) ⁺	3.84 (s, 3 H), 4.99 (d, 1 H, <i>J</i> = 7.5 Hz), 5.93 (d, 1 H, <i>J</i> = 4.5 Hz), 7.19-7.37 (m, 5 H), 8.24 (s, 1 H), 8.34 (s, 1 H)	C ₁₂ H ₁₂ N ₂ O ₂ C: 66.65/66.68 H: 5.59/5.62 N: 12.95/12.79
3C	oil, 0.18 ^c	1400, 1570, 1602	247 (MH) ⁺ , 229 (MH - H ₂ O) ⁺	3.09 (d, 1 H, <i>J</i> = 4.5 Hz), 3.92 (s, 3 H), 3.93 (s, 3 H), 5.85 (d, 1 H, <i>J</i> = 4.5 Hz), 7.21-7.34 (m, 5 H), 8.11 (s, 1 H)	C ₁₃ H ₁₄ N ₂ O ₄ C: 63.40/63.39 H: 5.73/5.79 N: 11.38/11.32
4C	oil, 0.38 ^c	758, 1110, 1578	247 (MH) ⁺ , 229 (MH - H ₂ O) ⁺	3.80 (d, 1 H, <i>J</i> = 11.4 Hz), 4.00 (s, 6 H), 6.10 (d, 1 H, <i>J</i> = 11.4 Hz), 7.20-7.34 (m, 5 H), 8.38 (s, 1 H)	C ₁₃ H ₁₄ N ₂ O ₃ H: 5.74/5.83 C: 63.41/63.51 N: 11.38/10.83*
5C	60-62, 0.32 ^c	1378, 1459, 1585	277 (MH) ⁺ , 259 (MH - H ₂ O) ⁺	3.60 (d, 1 H, <i>J</i> = 11.4 Hz), 3.94 (s, 3 H), 3.95 (s, 3 H), 6.03 (d, 1 H, <i>J</i> = 11.4 Hz), 7.18-7.34 (m, 5 H)	C ₁₄ H ₁₆ N ₂ O ₄ C: 60.86/60.86 H: 5.84/5.86 N: 10.14/10.19
6C	107-108, 0.34 ^c	1052, 1380, 1454	217 (MH) ⁺ , 199 (MH - H ₂ O) ⁺	3.90 (s, 3 H), 4.92 (d, 1 H, <i>J</i> = 7.1 Hz), 5.89 (d, 1 H, <i>J</i> = 7.1 Hz), 7.19-7.38 (m, 5 H), 8.02 (d, 1 H, <i>J</i> = 2.9 Hz), 8.09 (d, 1 H, <i>J</i> = 2.9 Hz)	C ₁₂ H ₁₂ N ₂ O ₂ C: 66.65/66.44 H: 5.59/5.60 N: 12.95/12.85
7C	99-100, 0.45 ^c	1170, 1374, 1456	247 (MH) ⁺ , 229 (MH - H ₂ O) ⁺	3.90 (s, 3 H), 3.91 (s, 3 H), 4.64 (d, 1 H, <i>J</i> = 7.5 Hz), 5.86 (d, 1 H, <i>J</i> = 7.5 Hz), 7.18-7.38 (m, 5 H), 7.74 (s, 1 H)	C ₁₃ H ₁₄ N ₂ O ₃ C: 63.40/63.45 H: 5.73/5.96 N: 11.38/11.39
4D	159-160, 0.59 ^c	1122, 1576, 1668	273 (M + C ₂ H ₅) ⁺ , 245 (MH) ⁺	3.90 (s, 6 H), 7.42-7.83 (m, 5 H), 8.51 (s, 1 H)	C ₁₃ H ₁₂ N ₂ O ₃ C: 63.93/63.94 H: 4.95/4.90 N: 11.47/11.35
5D	130-131, 0.54 ^c	1368, 1570, 1596	303 (M + C ₂ H ₅) ⁺ , 275 (MH) ⁺	3.88 (s, 6 H), 4.02 (s, 3 H), 7.39-7.82 (m, 5 H)	C ₁₄ H ₁₄ N ₂ O ₄ C: 61.31/61.32 H: 5.14/5.12 N: 10.21/10.13

^a 3% ethyl acetate in hexanes on silica gel. ^b 5% ethyl acetate in hexanes on silica gel. ^c 20% ethyl acetate in hexanes on silica gel.

2-chloro-4-methyl-, 4-methoxy-, and 2,4-dimethoxy-pyrimidine to lithiate at C-5.³ In the case of pyrazine, only the 2-chloro derivative has been lithiated at C-3,⁴ and this reaction fails entirely for both *N,N*-diethyl-⁵ and *N*-methylpyrazinamide.⁶ No directed lithiations of pyridazines have been reported. We now report that methoxy-pyridazines, -pyrimidines, and -pyrazines ortho-lithiate cleanly and incorporate electrophiles in high yields.

The methoxypyrazine, -pyrimidine, -pyridazine starting materials (1-7, E = H) were easily prepared from the corresponding chloro heterocycles by refluxing with sodium methoxide in methanol. These methoxy heterocycles were then lithiated under standard conditions using LiTMP in THF at -78 °C for 15 min. To evaluate the utility of this reaction, TMS-Cl, MeI, PhCHO, and PhCOCl were added to the lithiated heterocycles to give the results shown in Table I. All yields are of purified products having consistent NMR, IR, and elemental analyses (Table II). TMS-Cl, MeI, and PhCHO incorporated into all the heterocycles in good yields, giving products 1A-7A, 1B-7B, and 1C-7C, respectively. Some of the silylated systems, such as 3A and 6A, show somewhat lower yields, which may reflect the loss of these volatile products upon chromatography and Kügelrohr distillation. However, 5-methoxypyrimidine (2, E = H) gives lower yields with all the electrophiles, perhaps indicating some problem with the lithiation of this material. In contrast with the other electrophiles, benzoyl chloride incorporates well into only 4,6-dimethoxy- and 2,4,6-trimethoxypyrimidine, this electrophile giving complex mixtures and low yields of the expected products with the other lithiated heterocycles.

Further work is now underway to investigate the utility of other ortho-directing groups in these heterocyclic systems.

Experimental Section

The methoxydiazine starting materials were prepared from the corresponding chlorodiazines and were Kügelrohr distilled before use. All IR spectra were recorded on a Perkin-Elmer Model 1800 FT-IR spectrometer. The 300-MHz NMR spectra were determined on a Bruker AM300 spectrometer using deuteriochloroform with 2% (v/v) tetramethylsilane as the internal reference. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. All products were purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent. All yields given are of purified material, and all compounds had NMR, MS, and IR spectra consistent with the assigned structures and satisfactory elemental analyses ($\pm 0.4\%$, except as noted in Table II).

General Procedure. *n*-Butyllithium (5.2 mL of a 2.5 M solution in hexanes, 13 mmol) was added to a solution of freshly distilled tetramethylpiperidine (2.19 mL, 13 mmol) in 250 mL of anhydrous THF at 0 °C. After stirring at 0 °C for 30 min, the pale yellow solution was cooled to -78 °C, and the methoxy heterocycle (10 mmol dissolved in 15 mL of THF) was added dropwise over 3 min. The solution was stirred at -78 °C for 15 min, the electrophile (15 mmol) was added, and the solution was allowed to warm to room temperature overnight. The solvent was removed in vacuo, and the residue was partitioned between CH₂Cl₂ and water. The CH₂Cl₂ layer was separated, dried over Na₂SO₄, and concentrated in vacuo to give the crude product, which was purified by flash chromatography and Kügelrohr distillation.

Registry No. 1, 4603-59-2; 1A, 126327-65-9; 1B, 89943-29-3; 1C, 126327-66-0; 2, 31458-33-0; 2A, 126327-67-1; 2B, 19175-07-6;

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2C, 126327-68-2; 3, 3551-55-1; 3A, 62803-27-4; 3B, 5151-34-8; 3C, 110821-05-1; 4, 5270-94-0; 4A, 126327-69-3; 4B, 13566-63-7; 4C, 126327-70-6; 4D, 126327-71-7; 5, 13106-85-9; 5A, 126327-72-8; 5B, 96494-12-1; 5C, 126327-73-9; 5D, 126327-74-0; 6, 3149-28-8; 6A, 126327-75-1; 6B, 2847-30-5; 6C, 91392-53-9; 7, 4774-15-6; 7A, 126327-76-2; 7B, 90345-35-0; 7C, 126327-77-3.

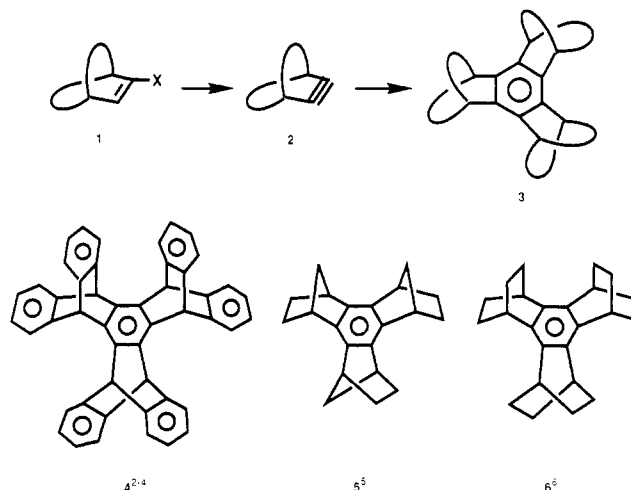
Extensions of Bicycloalkyne Trimerizations

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Bicyclic vinyl halides 1 can be "trimerized" to novel arenes 3 via bicycloalkyne intermediates 2. Specific examples of arenes that have been made in this way are 4-6.⁷



The mechanism by which 4 is formed is outlined in Scheme I.⁴ Each intermediate depicted in the scheme was identified through trapping.

Although the overall yield of trimers in these reactions is rather low ($\sim 20\%$), the products are easily isolated and identified because of their symmetry and may form a take-off point for further chemistry. The starting material for 4, the vinyl chloride 7, is readily available from anthracene. We describe here our first extensions of this chemistry to analogues of 4 starting with substituted anthracenes.

Reaction of 2,3,6,7-tetramethylantracene (12)⁸ with *trans*-1,2-dichloroethene gave a 70% yield of adduct 13,

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(7) Also known are syn-anti and all-syn bridgehead trimethyl-4⁴ and all-syn-5.⁵

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