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Selective Halogen–Lithium Exchange in 2,5-Dibromobenzenes and 2,5-Dibromopyridine[1]

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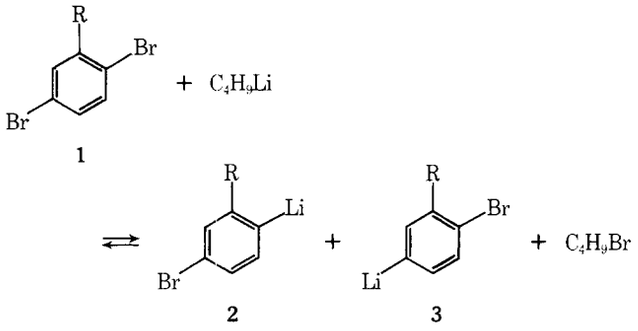
Reaction of a series of 2,5-dibromo-substituted aromatic systems with 1 equiv of *n*-butyllithium at −100 °C results in high selectivity of halogen–metal exchange when the substituent contains unshared electrons. The results suggest that product distribution at −100 °C is determined by thermodynamic rather than kinetic factors. Fair to excellent yields of derivatives of the monolithium intermediates have been obtained. Reaction of 2,5-dibromopyridine with 1 equiv of *n*-BuLi gives exclusively 2-bromo-5-lithiopyridine, which was converted in high yield into 2-bromo-5-deuteriopyridine. Reactions of 2- and 3-lithiopyridine, including their exchange with 2- and 3-bromopyridine, are described.

While selective metalation of substituted aromatic systems with alkyllithium generally occurs ortho to groups containing unshared electrons, an effect attributed to coordination of lithium with the attached functional group,[2] there has been little attention afforded[3] to selective halogen–lithium exchange in substituted dibromobenzenes (Scheme I). Extensive studies by Gilman and his co-workers[4] have established that halogen–metal exchange involves an equilibrium between reactants and products in which the lithium atom resides principally on the more electronegative carbon atom. Thus, one might anticipate that exchange in dibromobenzenes of type **1** would lead to a thermodynamically controlled mixture of **2** and **3**, possibly independent of kinetic factors which might influence the proportion of **2** and **3** formed initially.

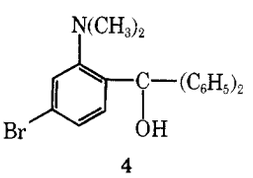
Scheme I



Since we were specifically interested in possible utilization of intermediates of type **2** and/or **3** for synthetic purposes, we have examined exchange in **1** with 1 equiv of *n*-C_4H_9Li in tetrahydrofuran (THF) at very low temperature (−100 °C). The course of reactions was determined by examining aliquots quenched with water, which were subsequently analyzed for starting material and the isomeric monobromobenzenes derived from **2** and **3** by GLC and/or NMR. With the exception of **1e**,[5] exchange was quite rapid and no appreciable change in ratio of products was observed after a few minutes. The results obtained are shown in Table I.

It is apparent that the product distribution shown in Table I does not correlate with Hammett σ functions (electrophilic substitution);[2b] however, with the possible exception of carboxylate,[7] the lithium atom in the product is preferentially located on the most electronegative carbon atom as judged by the inductive effect of the substituent. Whether this result is indeed a function of the inductive effect or a consequence of stabilization of the product by coordination of lithium with the substituent is not known; results with 2,5-dibromopyridine, discussed subsequently, suggest the latter and that the products are those determined by thermodynamic control.

In certain cases the aryllithium derivatives of **1** were elaborated by reaction with electrophiles. Warming the product derived from **1a** effected alkylation by *n*-C_4H_9Br, formed by exchange, to give a 70% yield of 5-bromo-2-*n*-butyltoluene and 2-bromo-5-*n*-butyltoluene in the approximate ratio of 3/7. Decomposition of the product from **1c** with water gave a 70% yield (isolated) of 3-bromo-*N*,*N*-dimethylaniline; reaction of the product from **1c** with benzophenone gave carbinol **4**, isolated pure in 34% yield. Treatment of the aryllithium obtained from **1d** with benzophenone gave 5-bromo-1,1-diphenylphthalide (**5**, pure 42% yield) while reaction of the product



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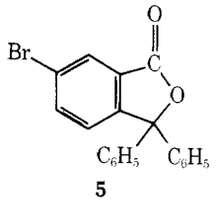

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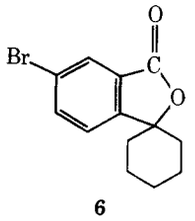

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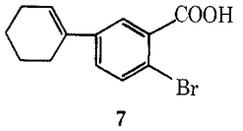

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from **1d** with cyclohexanone gave lactone **6** and the acid **7**, isolated pure in 45 and 5% yields, respectively. The structure of **7** was assigned by comparison of its NMR spectrum with those of methyl 2-bromobenzoate and methyl 3-bromobenzoate.[8]

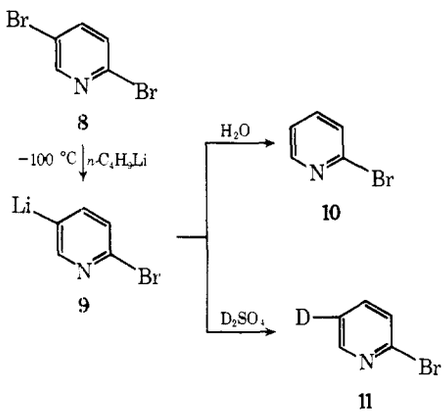
Reaction of 2,5-dibromopyridine (**8**) with 1 equiv of *n*-C_4H_9Li at −100 °C was rapid and complete and gave >99% 2-bromo-5-lithiopyridine (**9**, Scheme II). The product obtained by addition of water was essentially pure 2-bromopyridine (**10**); 3-bromopyridine was detectible (~1%) by GLC. Elaboration of **9** with D_2SO_4 gave a quantitative yield of 2-

Table I. Reactions of 1 with n-C_4H_9Li

Reactant 1	% exchange[a]	Ortho lithiation (ratio)	Meta lithiation (ratio)
1a (R = CH_3)	100	30[b]	70[b]
1b (R = NO_2)	100	100[c]	0[c]
1c [R = $N(CH_3)_2$]	100	95	5
1d (R = CO_2^-)	91[d]	90[d]	~10[d]
1e (R = NH^-)	10[e]	0[e]	100[e]

[a] Based on ratio of monobromobenzenes to **1** in aliquots as determined by GLC. [b] The ratio of monobromobenzenes was determined by NMR. The ratio of *o*-bromotoluene and *m*-bromotoluene did not change when excess dibromotoluene was added to the lithiated product. [c] Considerable by-products formed, thus it is probable that metalation also occurred at the meta position.[6] The only monobromobenzene detected, isolated (50% yield), was pure *m*-bromonitrobenzene. [d] Treatment of crude products with CH_2N_2 and analysis of esters by GLC; NMR of monobromides established nearly exclusive ortho lithiation. [e] Three equivalents of N-C_4H_9Li at −78 °C; products resulting from butylation by derived n-C_4H_9Br were observed and studies at higher temperature were not conducted. At −100 °C and with 3 equiv of n-C_4H_9Li no exchange was observed.

Scheme II

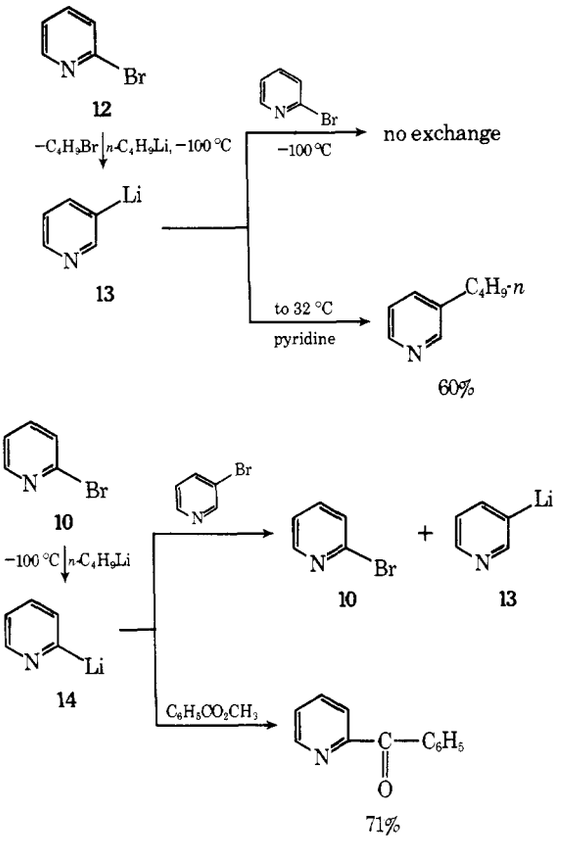


bromopyridine (**11**) which, by mass spectral analysis showed 85% incorporation of deuterium.

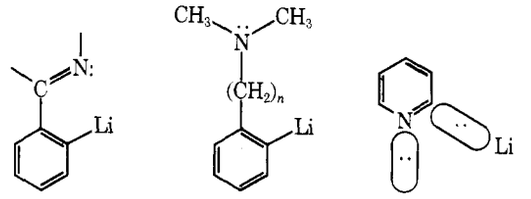
The high selectivity of lithium–halogen exchange at the 5 position of **8** was not expected since the 2 position in pyridine is more electron deficient (more electronegative) than the 5 position. Furthermore, if initial coordination of n-butyllithium with the heteroatom[2] is to play a role in determining initial exchange, then the 2 position would be favored. The above results are, however, consistent with the thermodynamic stability of the corresponding derived lithiopyridines (Scheme III). 3-Lithiopyridine (**13**), formed rapidly and nearly quantitatively at −100 °C from **12**, does not undergo exchange[9] with 2-bromopyridine (−100 °C, 50 min); recovered 2-bromopyridine (70%) contained only a trace of 3-bromopyridine which is thought to be a consequence of incomplete initial exchange from **12**. By contrast, 2-lithiopyridine (**14**), formed rapidly and in high yield at −100 °C from 2-bromopyridine (**10**), undergoes rapid exchange with 3-bromopyridine at −100 °C to give 2-bromopyridine and 3-lithiopyridine. The ratio of 2-bromopyridine and 3-bromopyridine (after water quench) was 79/21 after 20 min at −100 °C. That this ratio was not higher is thought to reflect the fact that 2-lithiopyridine is more reactive than 3-lithiopyridine and is partly consumed at −100 °C by 2-bromopyridine; consequently stoichiometry for complete exchange could not be maintained.

It is interesting to note that heteroatoms as shown in **15**,[2,10] and presumably as in **16**,[2] containing electrons which can be

Scheme III



orthogonal or noncoplanar to the plane containing lithium, can stabilize *o*-lithio derivatives by coordination while the heteroatom in **17**, in which the unshared electrons are coplanar with lithium, destabilize the aryllithium derivative.



The above results, coupled with those summarized in Table I, suggest that thermodynamic rather than kinetic effects determine the selectivity observed in halogen–metal exchange in dibromo aromatic systems. Such reactions are of synthetic use since selectivity is generally high and fair to good yields of elaborated products are obtained.

Some attempts were made, incidental to this study, to effect condensation of lithiopyridyls **13** and **14** with 2-bromo- and 3-bromopyridine to give bipyridyls; however, such reactions gave tarry mixtures. A convenient synthesis of 3-n-butylpyridine was developed and is shown in Scheme III. Other derivatives of **13** and **14** were prepared and are described in the Experimental Section.

Experimental Section

I. Bromine–Lithium Exchange of2,5-Dibromobenzenes. A. Reaction of 2,5-Dibromotoluene (1a). General Procedure. A solution of n-butyllithium (0.02 mol, 8.65 ml of 2.3 M solution in hexane) was added to a cold (−100 °C, liquid N_2–ether) solution, under N_2, containing 2,5-dibromotoluene (5.88 g, 0.02 mol) and dry (freshly distilled from $LiAlH_4$) THF (125 ml) while maintaining the mixture at −90 to −100 °C.

Aliquots (10 ml) were quenched with 50 ml of water. The resulting mixture was extracted with ether, dried ($MgSO_4$), concentrated, and

analyzed by GLC (6 ft × 0.25 in., 20% SE-30, 150 °C, 60 ml/min He) to determine the ratio of starting material (t_R 3.75 min) to monobromotoluenes (t_R 1.62 min). The residues were then analyzed by NMR to determine the ratio of *m*-bromotoluene (δ 2.11, $ArCH_3$) to *o*-bromotoluene (δ 2.26, $ArCH_3$). The first aliquot, taken after 30 min, showed no unchanged **1a**. The ratio of *o*-bromotoluene to *m*-bromotoluene (~70/30) did not change significantly over a period of 120 min.

B. Reaction of 1-Nitro-2,5-dibromobenzene (1b). Reaction was carried out as in IA. An aliquot (10 ml) was quenched with 10% hydrochloric acid and processed as in IA. Analysis by GLC (6 ft × 0.25 in., 20% Carbowax 20M on Chromosorb W, 140 °C, 45 ml/min He) showed *m*-bromonitrobenzene (t_R 3.25 min), no *o*-bromonitrobenzene (t_R 4.75 min), and a trace of 2,5-dibromonitrobenzene (t_R 12.00 min). The entire reaction was quenched in 10% HCl and worked up as in IA. The monobromobenzenes were collected by distillation (bp 88–95 °C, 1.0 Torr). No *m*-bromonitrobenzene could be detected by NMR (aromatic, comparison with authentic samples) or by GLC. The residue from distillation was tarry and contained no *m*-bromonitrobenzene or *o*-bromonitrobenzene as indicated by GLC. The isolated yield of pure *m*-bromonitrobenzene was 50%.

C. 2,5-Dibromo-*N,N*-dimethylaniline (1c) [prepared from 2,5-dibromoaniline (0.04 mol), methyl iodide (40 g, 0.28 mol), and NaH (0.10 mol) in THF; 77% yield, bp 90 °C (0.35 Torr); NMR ($CDCl_3$) δ 2.78 (s, 6) 7.2 (m, 3)].

Anal. Calcd for $C_8H_9Br_2N$: C, 34.44; H, 3.25; N, 5.02; Br, 57.29. Found: C, 34.69; H, 3.38; N, 4.86; Br, 57.41.

2-Bromo-*N,N*-dimethylaniline [bp 40 °C (0.25 Torr), lit.[11] bp 107–108 °C (14 Torr); NMR ($CDCl_3$) δ 2.75 (s, 6), 7.00 (m, 4)] and **3-bromo-*N,N*-dimethylaniline** [bp 70 °C (0.45 Torr), lit.[12] bp 100–104 °C (2 Torr); NMR ($CDCl_3$) δ 2.75 (s, 6), 6.8 (m, 4)] were prepared by the procedure of Borsch and Hassid.[13]

Reaction of **1c** was carried out as in IA.

Aliquots were quenched with water, extracted with ether, dried ($MgSO_4$), and concentrated. The first aliquot (1 h) showed by GLC (as in IA, 190 °C) no unchanged **1c** (t_R 9.25 min), 3-bromo-*N,N*-dimethylaniline (95% by peak height, t_R 6.00 min), and 2-bromo-*N,N*-dimethylaniline (<5%, t_R 3.75 min).

D. 2,5-Dibromobenzoic acid (1d) (mp 154–155 °C, lit.[14] 153 °C, from **1a**, $KMnO_4$, and water in *tert*-butyl alcohol, 73% yield) was treated with 2 equiv of *n*-C_4H_9Li as in IA. **Methyl 2,5-dibromobenzoate** (mp 43–45 °C, lit. 40–41 °C[15]), **methyl 2-bromobenzoate,** and **methyl 3-bromobenzoate** were prepared from the corresponding acids with diazomethane[15] and showed retention times of 2.62, 1.5, and 1.5 min, respectively (5 ft × 0.25 in., 3% SE-30, 190 °C, 30 ml/min He].

Aliquots (10 ml) were quenched with water and the aqueous solution was extracted with ether. The aqueous solution was acidified (concentrated HCl), extracted with ether, dried ($MgSO_4$), and concentrated. The crude residual acids were treated with excess ethereal CH_2N_2; acetic acid was employed to destroy excess CH_2N_2. The ether solution was extracted with aqueous bicarbonate, dried ($MgSO_4$), and concentrated. Analysis (GLC, see above, ID) showed 91% methyl monobromobenzoates (t_R 1.5 min) and 9% methyl 2,5-dibromobenzoate (t_R 2.62 min) (after 100 min). Analysis (NMR) of the methyl monobromobenzoates (collected by GLC) showed it to be nearly pure (>90%) *m*-bromobenzoate.

E. Reaction of 2,5-dibromoaniline (1e) was carried out as IA except that 2 equiv of *n*-C_4H_9Li was employed.

Aliquots were quenched with water, extracted with ether, dried ($MgSO_4$), and concentrated. Analysis was made by GLC (as in IA, 180 °C, 30 ml/min He). Retention times of authentic 2,5-dibromoaniline, *o*-bromoaniline, and *m*-bromoaniline were 11.37, 3.75, and 4.75 min, respectively. Essentially no exchange occurred at −100 °C. The ratio of **1e** to *o*-bromoaniline was 95/5 after 45 min at −78 °C and 90/10 after 135 min; no *m*-bromoaniline (exchange at ortho position) was detected. NMR analysis showed some butylation at −78 °C and considerable butylation when exchange was conducted at higher temperature.

Essentially identical results were obtained when 3 equiv of *n*-C_4H_9Li was employed.

II. Elaboration of 1. A. 2-Bromo-5-butyltoluene and 5-Bromo-2-*n*-butyltoluene. The mixture described in IA was allowed to warm to 32 °C and maintained at this temprature for 48 h. The mixture was processed essentially as described in IA to give a mixture of 2-bromo-5-*n*-butyltoluene and 5-bromo-2-*n*-butyltoluene [70% yield, bp 78–82 °C (1.0 Torr)].

Anal. Calcd for $C_{11}H_{15}Br$: C, 58.16; H, 6.65; Br, 35.18. Found: C, 58.32; H, 6.77; Br, 34.96.

The intensity of NMR signals at δ 2.28 and 2.13 showed that the ratio of the 2-bromo to the 5-bromo isomer was ~3/7.

B. 3-Bromo-*N,N*-dimethylaniline [70% yield from **1c**, see section IB for procedure, bp 75 °C (0.6 Torr), lit.[5b] bp 259 °C (760 Torr), pure by GLC (section IB)].

C. 4-Bromo-2-(*N,N*-dimethylamino)phenyldiphenylcarbinol (4). Reaction of **1c** (0.02 mol) was carried out as in IC; the reaction mixture was stirred for 30 min at −100 ° and benzophenone (0.0203 mol) in dry THF (30 ml) was added. The mixture was allowed to warm to 32 °C, THF was removed (rotary evaporation), and ether (100 ml) and cold 10% sulfuric acid (100 ml) were added. The ether extract was dried ($MgSO_4$) and concentrated to give 6.12 g of product which was recrystallized from petroleum ether (bp 30–60 °C) to give pure **4** [2.60 g, 34% yield, mp 113–114 °C; NMR ($CDCl_3$) δ 2.41 (6 H), 7.4 (18 H), 9.5 (1 H)].

Anal. Calcd for $C_{21}H_{20}BrNO$: C, 65.97; H, 5.27; Br, 20.90; N, 3.66. Found: C, 65.76; H, 5.41; Br, 21.18; N, 3.45.

D. 5-Bromo-1,1-diphenylphthalide (5). Reaction of 2,5-dibromobenzoic acid with *n*-C_4H_9Li was carried out as in section ID and the mixture was treated with benzophenone as described in section IIC. The mixture obtained subsequent to removal of THF was added to ether (100 ml) and water (100 ml). The aqueous layer was separated, made acidic with concentrated HCl, and warmed for 45 min on a steam cone to effect cyclization of the intermediate hydroxy acid to **5**. The acid solution was extracted with ether which was extracted with aqueous bicarbonate to remove acids. The ether extract was dried and concentrated to give 3.33 g of yellow oil which was recrystallized from ethanol to give 1.60 g (32% yield) of pure **5**, mp 118–120 °C.

Anal. Calcd for $C_{20}H_{13}BrO_2$: C, 65.77; H, 3.59; Br, 21.88. Found: C, 65.72; H, 3.52; Br, 21.96.

Chromatography (TLC, silica gel) of the mother liquor gave an additional 12% yield of pure **5**.

E. Spiro[5-bromoisobenzofuran-1(3*H*)-cyclohexan]-3-one (6) and **2-Bromo-5-(1-cyclohexenyl)benzoic acid (7).** Reaction of **1d** (0.014 mol) with 2 equiv of *n*-C_4H_9Li was carried out as in ID. The mixture was maintained at −100 °C for 45 min and cyclohexanone (0.0408 mol) in dry hexane (25 ml) was added. The mixture was processed essentially as described in section IID. The ether layer, obtained subsequent to treatment with hot aqueous acid, contained 1.81 g of product (mp 120–130 °C) which gave 1.73 g (45% yield) of pure **6** (mp 132–135 °C, from petroleum ether, bp 63–75 °C).

Anal. Calcd for $C_{13}H_{13}BrO_2$: C, 55.53; H, 4.66; Br, 28.42. Found: C, 55.62; H, 4.71; Br, 28.17.

Acidification of the bicarbonate solution gave 0.5 g of acid, mp 125–148 °C. Recrystallization of this product from acetone–water gave **7** [5% yield, mp 170–171 °C; NMR (Me_2SO-d_6) δ 1.6–2.5 (m, 8), 6.2 (s, 1), 7.4–7.8 (m, 4)].

Anal. Calcd for $C_{13}H_{13}BrO_2$: C, 55.53; H, 4.66; Br, 28.42. Found: C, 55.70; H, 4.73; Br, 28.15.

III. Lithium–Halogen Exchange in Bromopyridines. A. Reaction of 2,5-dibromopyridine (8, 0.01 mol) in THF (125 ml) with *n*-C_4H_9Li (0.011 mo) was carried out at −100 °C as described in IA.

Aliquots (10 ml, 20 and 55 min) were quenched in 50 ml of 10% HCl and the solution was extracted with ether. The acid solution was made strongly alkaline with 50% KOH and extracted with ether. The dried ($MgSO_4$) ether extract was concentrated to give residues analyzed by GLC (6 ft × 0.25 in., 20% Carbowax 20M on Chromosorb W, 120 °C, 30 ml/min He) which showed 2-bromopyridine (t_R 11.37 min, 99%) and less than 1% 3-bromopyridine (t_R 5.00 min). No 2,5-dibromopyridine (t_R 2.37 min at 200 °C) could be detected.

2-Bromo-5-deuteriopyridine. The cold solution, prepared from **8** (0.01 mol) and *n*-C_4H_9Li as described in IIIA, was aged for 30 min at −100 °C and then treated with 2 ml of D_2SO_4. The solution was allowed to warm to 32 °C, poured into dilute H_2SO_4 (200 ml), and extracted with ether. The acid solution was processed as in IIIA to give 1.93 g of crude amine which was analyzed by GLC (6 ft × 0.25 in., 20% Carbowax 20M on Chromosorb W, 150 °C, 30 ml/min He). Retention times of authentic samples follow: 3-bromopyridine, 1.00 min; 2-bromopyridine, 3.37 min; 3-bromopyridine (absent in the mixture) was used as internal added standard (same response as the 2 isomer). The product was essentially pure 2-bromopyridine (101% yield). Pure 2-bromopyridine was collected by GLC. Mass spectral analysis showed 85% incorporation of deuterium (by comparison of P and P − 1 peaks with undeuterated 2-bromopyridine).[16]

B. Reactions of 3-Bromopyridine (12). 1. 3-Lithiopyridine (**13**) was prepared from **12** (0.02 mol) and *n*-C_4H_9Li (0.02 mol) as described in section IA.

Aliquots (10 ml) were added to 10% HCl (100 ml) and THF was removed (rotary evaporator). The aqueous solution was extracted with ether and made strongly alkaline with 50% KOH. The solution was

extracted with ether, the dried extract was treated with ethereal HCl (100 ml), and ether was removed. The residue was treated with 15% aqueous NaOH and extracted with ether. The dried extract was concentrated and analyzed by GLC (20% Carbowax 20M, 150 °C, 30 ml/min He). Pyridine (98%, t_R 1.5 min) and 3-bromopyridine (2%, t_R 4.87 min) were detected.

2. 3-*n*-Butylpyridine. Pyridine (0.02 mol) was added at −100 °C to a solution of 3-lithiopyridine (0.02 mol), prepared as described above. The solution was allowed to warm to 32 °C, then processed essentially as described in the IIIB1 aliquot. Analysis (GLC, as shown above) showed 3-*n*-butylpyridine (t_R 2.25 min) and pyridine (t_R 1.5 min). Distillation of the crude product gave 1.62 g (60%) of pure 3-*n*-butylpyridine [bp 46–48 °C (1.5 Torr), lit.[17] bp 82–83 °C (10 Torr); NMR ($CDCl_3$) δ 0.9 (t, 3), 1.1–1.7 (m, 4), 2.5 (t, 2), 7.1–7.4 (m, 2), 8.4 (m, 2)].

3. 3-Pyridyldiphenylcarbinol. 3-Lithiopyridine (**13**, 0.022 mol) was treated at −100 °C with benzophenone (0.022 mol). The mixture was allowed to warm to 32 °C and THF was removed (rotary evaporator). Dilute H_2SO_4 (10 ml of 10%) was added and unreacted benzophenone (0.009 mol) was removed by filtration. The acid solution was made basic (KOH) and extracted with chloroform. The product (3.44 g) obtained from the dried chloroform was recrystallized from petroleum ether (bp 30–60 °C) to give 2.82 g (54% yield) of 3-pyridyldiphenylcarbinol (mp 111–114 °C, lit. 115 °C[18]).

4. Reaction of 3-Lithiopyridine (13) with 2-Bromopyridine at −100 °C. A mixture of **13** (0.02 mol), prepared as described above, and 2-bromopyridine (0.02 mol) was stirred at −100 °C for 40 min. The entire mixture was added to 10% HCl (200 ml) and processed essentially as described in IIIA aliquot. Analysis (GLC as in IIIA, 140 °C) showed the ratio of 2-bromopyridine (t_R 9.75 min) to 3-bromopyridine (t_R 6.00 min) to be 96/4. The yield of recovered 2-bromopyridine, determined by adding *o*-bromoanisole (t_R 10.75 min) and making corrections for the relative response factors of each, was 73%.

When the mixture of **13** and **10** was allowed to warm to 32 °C a black tar was obtained which was not processed.

C. Reactions of 2-Bromopyridine (10). 1. 2-Lithiopyridine (14) was prepared and analyzed as described for **13** in section IIIB. Analysis of aliquots (20 min, GLC, 130 °C) showed pyridine (t_R 2.12 min) and no unchanged 2-bromopyridine (t_R 5.62 min).

2. 2-Benzoylpyridine. A solution of **14** (0.0344 mol) was treated after 20 min with methyl benzoate (0.04 mol); the mixture was allowed to warm to room temperature, THF was removed (rotary evaporator), and the residue was partitioned between ether and water. The ether layer was distilled to give 4.46 g (71% yield) of 2-benzoylpyridine [bp 125–135 °C (0.3 Torr); picrate mp 129–130 °C, lit.[19] 124–127 °C].

3. Reaction of 2-lithiopyridine with 3-bromopyridine at −100 °C was carried out as in section IIIB4 (GLC, 6 ft × 0.25 in. 20% Carbowax 20M on Chromosorb W 30/60, 30 ml/min He). Aliquots taken at 20 and 60 min gave identical ratios of 2-bromopyridine (t_R 8.12 min) to 3-bromopyridine (t_R 4.37 min) of 79/21. Some condensation occurred as evidenced by the dark color of the crude product.

Registry No.—**1a**, 615-59-8; **1b**, 3460-18-2; **1c**, 60573-63-9; **1d**, 610-71-9; **1e**, 3638-73-1; **4**, 60573-64-0; **5**, 60573-65-1; **6**, 60573-66-2; **7**, 60573-67-3; **8**, 624-28-2; **10**, 109-04-6; **12**, 626-55-1; **13**, 60573-68-4; **14**, 17624-36-1; *n*-butyllithium, 109-72-8; 2-bromo-5-butyltoluene, 60573-69-5; 5-bromo-2-butyltoluene, 60573-70-8; benzophenone, 119-61-9; cyclohexanone, 108-94-1; 2-bromo-*N,N*-dimethylaniline, 698-00-0; 3-bromo-*N,N*-dimethylaniline, 16518-62-0; pyridine, 110-86-1; 3-*n*-butylpyridine, 539-32-2; methyl benzoate, 93-58-3; 2-benzoylpyridine, 91-02-1.

References and Notes

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(8) The aromatic proton (δ 8.2) ortho to both bromine and carbonyl in methyl *m*-bromobenzoate is deshielded to a greater extent than those adjacent to only bromine or carbonyl. There is no absorption at δ 8.2 in methyl *o*-bromobenzoate.
(9) A slow reaction occurs at −100 °C, expectedly more rapid at higher temperatures to give tarry condensation products.
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Reactions of Lithio Derivatives of Carboxylic Acids. 1. 3-Methyl-2-butenoic Acids[1]

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Halogen–metal exchange with 2-bromo-3-methyl-2-butenoic acid at −100 °C leads to a stable lithiovinyl intermediate which reacts with a variety of electrophiles to afford 2-alkylated derivatives in good yields. Reaction of 3-methyl-2-butenoic acid with *n*- and *tert*-butyllithium followed by protonation or alkylation is discussed.

Since 2-bromo-2-alkenoic acids are readily available from 2-alkenoic acids,[3] then possible reaction as shown in Scheme I (**1** → **2** → **3**) appeared attractive as a general method for synthesis of 2-substituted 2-alkenoic acids. The previous observation that salts of bromobenzoic acids[4a] and bromoarylalkanoic acids[4b] form stable lithium intermediates by halogen–metal exchange provided a firm precedent for this sequence; however, it remained to be established[3,5] whether proton removal from allylic (γ) positions (i.e., **1** → **6**) or lithium interchange (i.e., **2** ⇄ **4**) would impose a synthetically unacceptable limitation on such a sequence.

2-Bromo-3-methyl-2-butenoic acid (**1**)[3] was chosen as a model and halogen–metal exchange was conducted in tetrahydrofuran at −100 °C with *n*-butyllithium. The progress of