Sodium perchlorate monohydrate was Fischer Purified (98%+) and for the purpose of ionic strength calculation was assumed to be 99% pure.

N-Chloroacetanilide [mp 91.0–92.0 °C (lit.[10] mp 91.0 °C)] was prepared as previously described.[5]

All phenols were commercially available. *p*-Nitrophenol and *m*-nitrophenol were recrystallized from benzene. *m*-Nitrophenol: mp 96.0–98.0 °C (lit.[11] mp 97 °C). *p*-Nitrophenol: mp 112.0–114.0 °C (lit.[11] mp 114.9 °C). Phenol: mp 41.5–43.5 °C (lit.[11] mp 43 °C). All phenols showed only one peak by HPLC analysis under conditions identical with those used in kinetic runs.[12]

Kinetics were monitored under pseudo-first-order conditions with phenol in at least an 11-fold excess. All kinetic runs were monitored to greater than 85% reaction with 10–20 data points being obtained for each run. The pseudo-first-order rate constant, k_{obsd}, for each phenol was evaluated at several different pHs between 5.4 and 7.3. For each reaction two stock solutions were made, one that was 0.500 M in monobasic sodium phosphate and the other 0.500 M in dibasic sodium phosphate. The ionic strength of both buffers was maintained at 1.500 M by adding appropriate amounts of sodium perchlorate monohydrate. Two phenol stock solutions were accurately made of approximately 1.0 M and approximately 0.6 M in acetonitrile. Both phenol stock solutions contained nitrobenzene as an internal standard. The desired pH was obtained by mixing appropriate volumes of the stock buffer solutions. To 9.0 mL of a buffer solution was added 1.0 mL of the phenol solution. The test tube was covered, shaken, and placed in a constant-temperature bath at 39.36 ± 0.005 °C. After thermal equilibration approximately 0.01 g (6.0×10^{-3} mol) of solid *N*-chloroacetanilide was added to initiate the reaction. The test tube was sealed, shaken, and returned to the constant-temperature bath. Aliquots of the reaction mixture were withdrawn periodically and injected on to the HLPC in order to obtain the concentration of *N*-chloroacetanilide as a function of time. The pseudo-first-order rate constants, k_{obsd}, were obtained from the equation

$$\ln [H_0/(H_t - H_\infty)] = k_{obsd}$$

where H_0 = initial HPLC peak height of *N*-chloroacetanilide, H_t = peak height at time t, and H_∞ = peak height at t_∞.

The pK_a of substituted phenols at 39.36 °C under the reaction conditions was determined by adding a known volume of 0.0858 M sodium hydroxide in 10% aqueous acetonitrile at an ionic strength of 1.350 M (sodium perchlorate monohydrate added as necessary) to 2.0 mL of an accurately weighed phenol solution (approximately 0.1 M) dissolved in 10% aqueous acetonitrile of ionic strength 1.350 M. The sodium hydroxide was standardized according to accepted procedure by titration of standard-grade potassium acid phthalate.

The pH of the phenol solution was determined after each addition of sodium hydroxide. (The pH of a given solution when measured 5 times had an average error of ±0.06 pH unit.) The concentration of phenoxide and phenol were determined by knowing the total amount of phenol and the amount of sodium hydroxide added. The pK_a values were then determined by using the Henderson–Hasselbach equation. The pK_a was calculated from the average of at least five measurements determined at different phenoxide/phenol ratios. The phenoxide/phenol ratio was varied from approximately 0.2 to 2.0 for each phenol.

In order to examine the products from the reaction of phenol with *N*-chloroacetanilide the reaction was repeated on a larger scale by doubling all reagents. The reaction was allowed to proceed for at least 10 half-lifes. The reaction mixture was cooled to room temperature and acidified with 30% H_2SO_4 and extracted twice with ethyl ether (40 mL). The ether layer was washed twice with 10% NaOH to remove any phenols. The ether layer was dried ($MgSO_4$) and removed under reduced pressure. The residue was dissolved in 20 mL of methanol and injected on the HPLC by using conditions identical with those used in a kinetic experiment.[12] Only one peak could be detected corresponding to acetanilide.

The aqueous layer was acidified with 10% H_2SO_4 and extracted twice with ethyl ether (50 mL). The ether layer was dried ($MgSO_4$) and removed under reduced pressure. The solid residue was dissolved in 20 mL of methanol and injected on the HPLC under identical conditions with those used in a kinetic run.[12] One large peak was detected corresponding to phenol and two smaller peaks that corresponded to the ortho- and para-chlorinated phenols. Also two very small peaks were detected that were identified as the *o*- and *p*-hydroxyacetanilides. HPLC peaks were identified by comparison of retention times with authentic samples and by spiking the extracted samples with authentic samples.

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Registry No. *N*-Chloroacetanilide, 579-11-3; *p*-methyl phenoxide, 22113-51-5; phenoxide, 3229-70-7; *m*-chlorophenoxide, 18938-14-2; *m*-nitrophenoxide, 16554-54-4; *p*-nitrophenoxide, 14609-74-6.

Supplementary Material Available: Summary of the specific reaction conditions and pseudo-first-order rate constants, k_{obsd}, for the reaction of various substituted phenols with *N*-chloroacetanilide and a summary of the HPLC conditions used to monitor the reaction rates of various phenols with *N*-chloroacetanilide (2 pages). Ordering information can be found on any current masthead page.

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New Procedures for Preparation of Potassium 3-Aminopropylamide

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Potassium 3-aminopropylamide, KAPA, is well-known as an efficient reagent in isomerizing internal acetylenes to the terminal position.[1] KAPA has been used in the synthesis of pheromones[2] and fatty acids.[3] The reagent was first prepared by C. A. Brown,[1] from 1,3-propanediamine and potassium hydride. The main disadvantages of using potassium hydride are that it is hazardous,[4] is expensive, and has a short shelf stability. An alternative route was developed by Brandsma,[4] who reacted potassium amide made in liquid ammonia with 1,3-propanediamine at 80 °C. Since we frequently employ KAPA for synthesis of pheromone analogues, it was essential to develop an alternative route. We report herein a direct, safe, and cheap procedure.

In preliminary experiments it was found that no reaction took place when molten potassium was stirred in 1,3-propanediamine for 2 h at 80 °C, perhaps due to its lack of solubility in amines.[5] Since potassium does dissolve

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Table I. Isomerization of Internal Acetylenes by KAPA and NAPA to a Terminal Position

compd	product[a]	method	reagent	% yield[b]
$CH_3(CH_2)_4C{\equiv}C(CH_2)_3OH$	$HC{\equiv}C(CH_2)_8OH$	A	KAPA	80
$CH_3(CH_2)_3C{\equiv}C\ CH_2OH$	$HC{\equiv}C(CH_2)_5OH$	A	KAPA	90
$CH_3(CH_2)_4C{\equiv}C(CH_2)_4CH_3$	$HC{\equiv}C(CH_2)_9CH_3$	A	KAPA	97
$CH_3(CH_2)_4C{\equiv}C(CH_2)_4CH_3$	$HC{\equiv}C(CH_2)_9CH_3$	B	KAPA	79
$CH_3(CH_2)_3C{\equiv}C\ CH_2OH$	$HC{\equiv}C(CH_2)_5OH$	B	KAPA	97
$CH_3(CH_2)_3C{\equiv}C(CH_2)_3CH_3$	$HC{\equiv}C(CH_2)_7CH_3$	B	KAPA	80
$CH_3(CH_2)_3C{\equiv}C(CH_2)_{11}OH$	$HC{\equiv}C(CH_2)_{15}OH$	B	KAPA	98
$CH_3(CH_2)_4C{\equiv}C(CH_2)_4CH_3$	$HC{\equiv}C(CH_2)_9CH_3$	B	NAPA	63
$CH_3(CH_2)_3C{\equiv}C(CH_2)_{11}OH$	$HC{\equiv}C(CH_2)_{15}OH$	B	NAPA	65

[a] Products were identified by comparison with authentic samples and/or from spectra. [b] The ratio of product to starting material is >98:2 according to GC analysis.

in ammonia, ammonia gas was bubbled into a stirred mixture of molten potassium and 1,3-propanediamine at 80 °C. That KAPA was formed was demonstrated by isomerizing acetylenes (see Table I). We do not know whether ammonia plays a role only as solvent for potassium or whether it forms potassium amide at the first stage.

Recently it has been reported that ultrasound can dramatically increase the rate of heterogeneous reactions.[6] We have successfully applied this technique to the preparation of KAPA. Heating potassium, 1,3-propanediamine, and a trace of ferric nitrate at 90 °C in a round-bottom flask immersed in a common ultrasonic cleaning bath (125 W) gave the reagent in 10 min on a 25-mmol scale. That potassium is partially dissolved in 1,3-propanediamine under these conditions is shown by the deep blue color that forms when ferric ion is not used. Ferric ion increases the rate of KAPA formation, although it is not essential. Reagent prepared in this way was used for isomerization of acetylenes and was found to be as good as those obtained by other methods. The results are summarized in Table I.

Sodium 3-aminopropylamide, NAPA, is an alternative reagent to KAPA. It was prepared either from sodium amide[4] or sodium hydride[7] and 1,3-propanediamine at 80 °C. We found that NAPA can be made by reacting sodium metal at 90 °C with 1,3-propanediamine in an ultrasound bath. The NAPA thus prepared caused isomerization of acetylenes to the terminal position in comparable yields to those described in the literature. Employing ultrasound for the preparation of KAPA and NAPA directly from the corresponding metals and 1,3-propanediamine appears to be the method of choice, since it is a simple, safe, and cheap procedure.

Experimental Section

The instruments used were as follows: ^1H NMR, Varian T-60; ^{13}C NMR, Bruker WP-60; MS, Varian MAT-711; GLC, F + M 810, carrier helium, column 15% carbowax on Gas Chrom Q, 2 m; IR, Perkin-Elmer 257.

General Procedure for Preparation of KAPA and NAPA. Preparation of KAPA: Method A. Ammonia gas was bubbled into a stirred mixture of 235 mg (6 mmol) of potassium, 1,3-propanediamine (6 mL, dried over calcium hydride), and ferric nitrate (3 mg) at 80 °C. The molten potassium disappeared within 1 h and the green-brown solution of KAPA was cooled to 0 °C. Alkyne (2 mmol) dissolved in 1 ml of tetrahydrofuran was added at once and the reaction was stirred for 30 min. It was worked up as usual[1] to yield terminal alkyne.

Method B. A mixture of 1 g (25 mmol) of potassium, 1,3-propanediamine (25 mL), and ferric nitrate (5 mg) was heated to 90 °C in a round-bottom flask immersed in common ultrasound cleaning bath (125W Bransonic Model 220). Within 10–15 min the molten potassium disappeared and a green-brown solution was formed. The solution was cooled to 0 °C, and alkyne (8.5 mmol) or alkynol (4.2 mmol) dissolved in 2 mL of tetrahydrofuran was added at once and the solution stirred for 30 min. It was worked up as usual[1] to yield the isomerized product.

Preparation of NAPA. NAPA was prepared by method B from 1 g (43 mmol) of sodium, 1,3-propanediamine (25 mL), and ferric nitrate (5 mg).

Preparation of 12-Heptadecyn-1-ol. 11-Bromo-1-(1-ethoxyethoxy)undecane was prepared as described by Eaton[8] from 5 g (40 mmol) of 11-bromo-1-undecanol, ethyl vinyl ether (15 mL), and three drops of dichloroacetic acid to yield 6.2 g (38.5 mmol) of crude product: ^1H NMR (CCl_4) δ 4.6 (q, 1 H), 3.4 (m, 6 H), 1.4 (m, 18 H), 1.2 (d, 3 H), 1.03 (t, 3 H).

n-Butyllithium (7.3 mL, 1.5 M in hexane, 11 mmol) was added to a solution of 0.9 g of hexyne (11 mmol) in tetrahydrofuran (10 mL) and hexamethylphosphoramide (10 mL) at 0 °C. The solution was stirred for 30 min, 3.23 g (10 mmol) of crude 1-(1-ethoxyethoxy)-11-bromoundecane was added, and the reaction mixture was stirred for 5 h at room temperature. Brine (15 mL) was added, and the solvents were removed under reduced pressure. The product was extracted with hexane (3 × 25 mL) and dried over sodium carbonate. The solvent was removed to yield 2.6 g of 1-(1-ethoxyethoxy)-12-heptadecyne (8 mmol). The crude product was hydrolyzed without further purification as described by Brandsma[9] to yield after flash chromatography (silica gel; hexane:methylene chloride, 1:1) 1.7 g (6.75 mmol) of 12-heptadecyn-1-ol: IR ($CHCl_3$) 3630 (O–H), 2930 (C–H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6 (brt, 2 H), 3.4 (brs 1 H), 2.2 (m, 4 H), 1.35 (m, 22 H), 0.98 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 79.37, 61.63, 31.97, 30.93, 30.54, 28.86, 28.47, 28.08, 26.8, 25.1, 21.22, 17.98, 17.72, 12.80; MS, found for $C_{17}H_{32}O$ m/e 252.2494 (calcd m/e 252.2453).

Preparation of 16-Heptadecyn-1-ol. To a stirred solution of KAPA prepared by method B from 190 mg (4.8 mmol) of potassium in 1,3-propanediamine (5 mL) was added at 0 °C 190 mg (0.75 mmol) of 12-heptadecyn-1-ol dissolved in tetrahydrofuran (1 mL). The reaction mixture was stirred for 30 min at 0 °C and then poured into 125 mL of water and extracted with hexane (3 × 100 mL). The extract was washed with 100 mL of water and dried over magnesium sulfate. The solvent was removed to give 185 mg (0.735 mmol) of 16-heptadecyn-1-ol as a white solid in 98% yield: mp 41 °C (hexane); IR ($CHCl_3$) 3630 (O–H), 3315 (C≡C–H), 2930 (C–H), 2120 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6 (m, 2 H), 2.55 (m, 1 H), 2.1 (m, 3 H), 1.35 (m, 26 H); ^{13}C NMR δ 84.7, 68.12, 62.68, 32.76, 31.85, 29.65, 29.14, 28.75, 28.49, 27.58, 25.90, 18.39; MS, found for $C_{17}H_{32}O$ m/e 252.2503 (calcd m/e 252.2453).

Registry No. KAPA, 56038-00-7; NAPA, 75896-84-3; $CH(CH_2)_4C{\equiv}C(CH_2)_3OH$, 69222-06-6; $CH_3(CH_2)_3C{\equiv}CCH_2OH$, 1002-36-4; $CH_3(CH_2)_4C{\equiv}C(CH_2)_4CH_3$, 6975-99-1; $CH_3(CH_2)_3C{\equiv}C(CH_2)_3CH_3$, 1942-46-7; $CH_3(CH_2)_3C{\equiv}C(CH_2)_{11}OH$, 56554-76-8; $HC{\equiv}C(CH_2)_8OH$, 17643-36-6; $HC{\equiv}C(CH_2)_5OH$, 63478-76-2; $HC{\equiv}C(CH_2)_9CH_3$, 765-03-7; $HC{\equiv}C(CH_2)_7CH_3$, 764-93-2; $HC{\equiv}C(CH_2)_{15}OH$, 62873-30-7; 1,3-propanediamine, 109-76-2; potassium,

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7440-09-7; sodium, 7440-23-5; ammonia, 7664-41-7; ferric nitrate, 10421-48-4; 11-bromo-1-(1-ethoxyethoxy)undecane, 73010-84-1; 11-bromo-1-undecanol, 1611-56-9; ethyl vinyl ether, 109-92-2; 1-hexyne, 693-02-7; 1-(1-ethoxyethoxy)-12-heptadecyne, 89998-64-1.

Superimposed Lateral Control of Structure and Reactivity Exemplified by Enantiospecific Synthesis of (+)- and (-)-Gabaculine[1]

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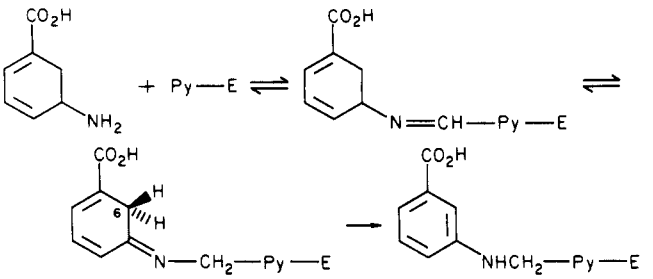
Gabaculine (**6**, R = H), a naturally occurring amino acid,[2] is a potent inhibitor of 4-aminobutyrate:2-oxoglutarate animotransferase (GABA-T), the major GABA catabolizing enzyme. Blocking of this enzyme leads to a buildup of GABA brain levels which may be useful in the treatment of certain diseases characterised by a deficiency of GABA function, e.g., Parkinsonism,[3] epilepsy and, Schizophrenia.[4] The synthesis of analogues for pharmacological examination is therefore desirable. The enzyme-activated mechanism of action of gabaculine has been studied[5] and is shown in Scheme I.

It might be expected that the hydrogen-removal step leading to the enzyme-bound *m*-anthranilic acid derivative would be specific for one of the two C-6 hydrogens. A suitably labeled gabaculine would probably give this information and complete the mechanistic details.

We report the synthesis, using tricarbonyl iron complexes, of gabaculine, in resolved form with known absolute configuration and of enantiospecifically labeled [6-^{2}H]gabaculine as a demonstration of the control features and capabilities of complexes of metal atoms in general and iron in particular.

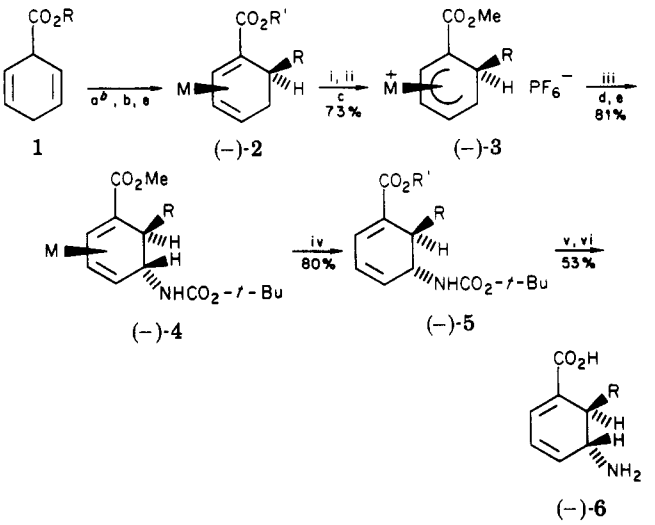
Lateral control as superimposed by π-complexed transition-metal atoms on olefinic bonds leads to new organic synthetic capabilities in bond formations, steric control, and a rational choice of simple precursors.[6,7] It contrasts with classical endogenous control of bond formation and stereochemistry by organic functional groups joined to the skeleton by σ-bonds. These groups in most cases need protection, modification, or removal, and they often do not permit complete steric, including chiral, control. In substituted complexes there is also an element of endogenous control of regiospecificity and reactivity (exemplified by the CO_2Me below in directing the position and rate of nucleophilic attack). However, the organic group is there as a desired structural unit, not primarily to permit formation of the new C–N bond which depends on the cationic nature of the $Fe(CO)_3$. Although the use in synthesis of complexed transition metals is widespread, the present example is one of the few where each major step of a synthetic sequence has been controlled by a different feature of the complexation as shown in Scheme II. Some of the initial steps have been described before but are included here in connection with the role of the complexing group.

Scheme I[a]



[a] Py-E = enzyme-bound pyridoxal phosphate.

Scheme II[a]



[a] Reagents: (i) CH_2N_2, Et_2O; (ii) $Ph_3C^+PF_6^-$, CH_2Cl_2; (iii) H_2NCO_2-*t*-Bu (2.2 equiv), Hunig's base, CH_2Cl_2, 0 °C, 5 min; (iv) Me_3NO, CH_3CONMe_2, −15 °C, 3 h, then 0 °C, 16 h; (v) NaOH, MeOH, H_2O (ref 5, 8, 9); (vi) 3 M HCl, MeOH, ion-exchange column (ref 8). M = $Fe(CO)_3$. [b] The letters a, b, etc., refer to subheadings in the main text.

The lateral control features are as follows.

(a) Catalysis of Formation and Structural Control of the (±) Precursor Comprising 2 (R = R′ = H) [Exemplified by Transformation 1 → 2]. Base-catalyzed conjugation of cyclohexa-2,5-dienoic ester **1** (R = Me) prepared from benzoic acid by Birch reduction,[10] followed by complexation with $Fe(CO)_5$ gives substantially pure 2-carbomethoxycyclohexadiene–$Fe(CO)_3$ complex. The presence of the metal permits acid-catalyzed isomerization entirely into the more stable 1-carbomethoxy complex.[11] The initial isomerization of the uncomplexed ester does not give the 1-CO_2Me derivative, although this is the more stable. With deutero acid the same control in the complex

(1) Taken in part from the Ph.D. Thesis of B.M.R.B., Research School of Chemistry, Canberra, 1977–1981. We thank the University of Peradenya for leave of absence (BMRB) and the Australian Research Grants Scheme for a Fellowship (L.F.K.).

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