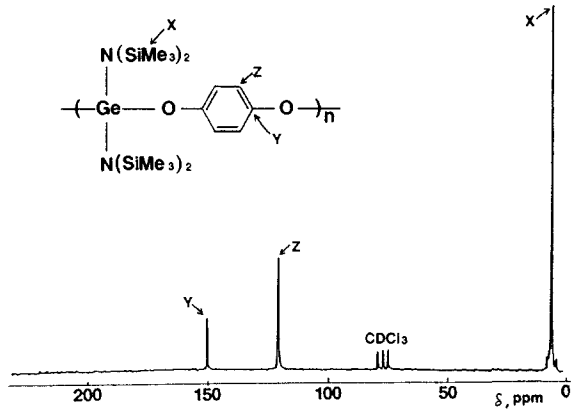
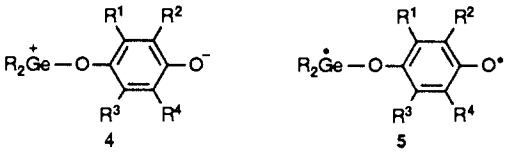


Figure 1. ^{13}C NMR spectrum of copolymer **3a** (entry 1) in $CDCl_3$.

The copolymerization took place smoothly at −78 °C in toluene without any added catalyst, to give the corresponding copolymer **3** in good yields (Table I). Under these conditions, the polymerization was completed within 1 h. The reaction proceeded readily even when sterically hindered *p*-benzoquinone derivatives (e.g., **2b** and **2d**) were used as oxidant monomers. These results indicate the high nucleophilicity of germylene **1** toward compounds having a carbon–oxygen double bond (similar reactivity is shown toward carbon–carbon double bonds in α,β-unsaturated carbonyl compounds[8]).

The resulting copolymers **3**[9] are white fine powders soluble in *n*-hexane, benzene, and chloroform and insoluble in acetone and acetonitrile. The copolymers have moderately high molecular weights ($M_w > 2.9 \times 10^4$); a copolymer of especially high molecular weight ($M_w = 3.6 \times 10^5$)[10] was obtained with 1,4-naphthoquinone as oxidant monomer (entry 7). Copolymer structures have been determined by ^1H and ^{13}C NMR as well as elemental analysis. The ^1H NMR spectrum of the copolymer obtained from **1** and **2a** in toluene (entry 1) exhibited signals at δ 0.25 ppm ascribable to the methyl protons of the trimethylsilyl group and at δ 6.92 ppm due to the aromatic protons of the *p*-hydroquinone unit, supporting structure **3a**. The ^{13}C NMR spectrum of copolymer **3a** shows three peaks at δ 5.5, 120.9, and 150.1 ppm, assignable to carbon atoms denoted as X, Z, and Y, respectively, in Figure 1. The elemental analysis of the copolymer also supported structure **3a**.[11]

The following reaction mechanism may be proposed for the oxidation–reduction copolymerization. The first step probably involves the formation of zwitterion **4** or diradical **5**.[12] Two molecules of **4** or **5** give a dimeric zwitterion or a dimeric diradical. Successive reactions between these intermediates lead to the alternating copolymer **3**.



(8) For example, the formation of a cyclic germanium(IV) enolate by the reaction of germylene **1** and α,β-unsaturated carbonyl compounds has been reported. Kobayashi, S.; Iwata, S.; Shoda, S. *Chem. Express* **1989**, *4*, 41.

(9) The resulting copolymers **3** are quite stable to the moisture. For example, no decrease of the molecular weight was observed by means of GPC after stirring an aqueous THF solution of **3b** for 24 h at room temperature. The product polymers are thermally stable and melt without decomposition. The glass transition and melt transition temperatures (T_g and T_m, respectively) were measured under air by means of differential scanning calorimetry (DSC), e.g., for copolymer **3a** (entry 3), $T_g = 75.6$ °C and $T_m = 234.7$ °C, and for copolymer **3e** (entry 8), $T_g = 46.1$ °C and $T_m = 234.9$ °C.

(10) Copolymer **3e** gave a film by casting from chloroform.

(11) Elemental analysis found for copolymer **3a** $(C_{18}H_{40}GeN_2O_2Si_4)_n$: C, 43.58; H, 8.24; N, 5.53. Calcd: C, 43.11; H, 8.04; N, 5.39.

(12) (a) Hall, H. K., Jr. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 440. (b) Brandt, M. W.; Mulvaney, J. E.; Hall, H. K., Jr. *Macromolecules* **1988**, *21*, 1553. (c) Lee, C.; Hall, H. K., Jr. *Macromolecules* **1989**, *22*, 21. (d) Iwatsuki, S.; Itoh, T.; Iwai, T.; Sawada, H. *Macromolecules* **1985**, *18*, 2726.

In conclusion, we have successfully synthesized new germanium(IV)-containing polymers **3** by a novel facile copolymerization of substituted germylene and *p*-benzoquinone derivatives. Further studies including physical properties of the resulting copolymers and the mechanism of the present copolymerization are now in progress.

Acknowledgment. This work was partly supported by a Grant-in-Aid for Scientific Research on Priority Area of "New Functionality Materials Design, Preparation, and Control" from the Ministry of Education, Science and Culture, Japan (No. 62604004 and 63604004).

Synthesis of Avermectin B_{1a} Aglycon

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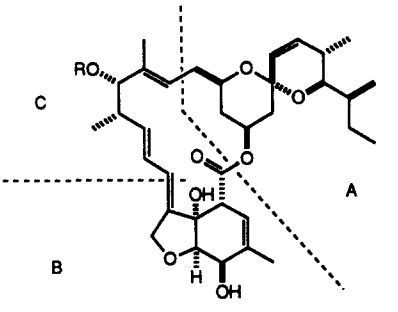
Received September 27, 1989

The emergence of avermectins as potent antiparasitic agents[1] with economic significance in animal health care[2] has elicited strong interest in their chemical properties and synthesis.[3] We previously reported routes to the spiroketal (A)[4] and oxahydrindene (B)[5] segments of avermectin B_{1a} (**1**) in anticipation that these would be linked to a third subunit (C) before closure to the macrolide. We now describe the concluding phase of this effort, culminating in a total synthesis of avermectin B_{1a} aglycon (**2**).[6]



1, R = L-Oleandrosyl-L-oleandrosyl

2, R = H

The linear segment C of **2** was elaborated from ethyl levulinate, which was converted in straightforward fashion to ketal **3**.[7] This ester was reduced to allylic alcohol **4**, and the latter was subjected to the catalytic version of the Sharpless epoxidation[8] to produce **5**. Opening of the epoxide with lithium dimethylcuprate proceeded with the expected regiospecificity[9] to yield **6**, and the primary alcohol was then selectively protected[10] as its pivalate **7**. The ketal

(1) Fisher, M. H.; Mrozik, H. *Macrolide Antibiotics*; Omura, A., Ed.; Academic Press: Orlando, 1985; p 553.

(2) Fisher, M. H. *Recent Advances in the Chemistry of Insect Control*; Janes, N. F., Ed.; Royal Society of Chemistry: London, 1985; p 53.

(3) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1989**, *111*, 2967 and references therein.

(4) Fox, C. M. J.; Hiner, R. N.; Warrier, U.; White, J. D. *Tetrahedron Lett.* **1988**, *29*, 2923.

(5) White, J. D.; Dantanarayana, A. *Tetrahedron Lett.* **1987**, *28*, 6417.

(6) For an account of the pioneering accomplishments of Hanessian in this area, which resulted in a synthesis of (+)-avermectin B_{1a} from a spiroketal segment obtained synthetically and an oxahydrindene subunit derived from degradation of **1**, see: Hanessian, S.; Ugolini, A.; Hodges, P. J.; Beaulieu, P.; Dubé, D.; Andrē, C. *Pure Appl. Chem.* **1987**, *59*, 299. Hanessian, S.; Ugolini, A.; Dubé, D.; Hodges, P. J.; Andrē, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776. Subsequently the oxahydrindene was prepared by synthesis from (−)-quinic acid (Dubé, D. Ph.D. Thesis, University of Montreal, 1988).

(7) Ethyl 4-oxo-2-pentenoate was prepared according to McMurry and Blaszczak (McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217) and ketalized under standard conditions (*p*-TsOH cat., benzene, reflux) with 2,2-dimethylpropane-1,3-diol.

(8) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(9) Kishi, Y.; Nagaoka, H. *Tetrahedron* **1981**, *37*, 3873.

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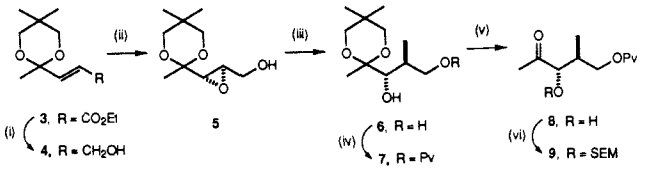
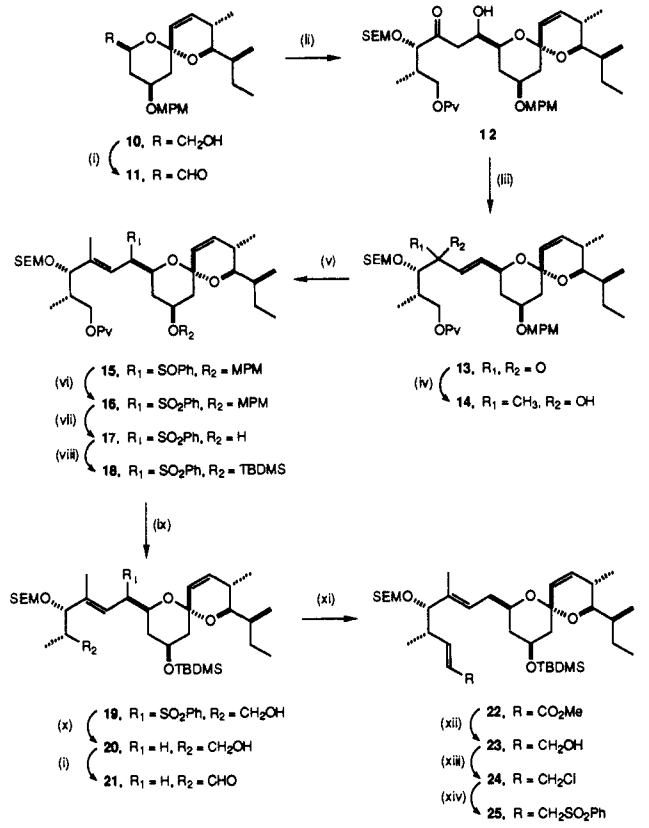
Scheme I[a]



[a] Reagents and conditions: (i) $(iBu)_2AlH$, toluene, −78 °C, 1 h, 74%; (ii) $PhCMe_2O_2H$, (−)-DIPT, $Ti(OiPr)_4$, CH_2Cl_2, 4-Å molecular sieves, −20 °C, 22 h, 90%; (iii) $LiCuMe_2$, Et_2O, 0 → 25 °C, 71%; (iv) Me_3CCOCl, py-DMAP-CH_2Cl_2, 25 °C, 2 h, 90%; (v) PPTS (cat.), THF-H_2O, 50 °C, 36 h, 86%; (vi) $Me_3SiCH_2CH_2OCH_2Cl$, $(iPr)_2NEt$, CH_2Cl_2, reflux, 4 h, 93%.

Scheme II[a]

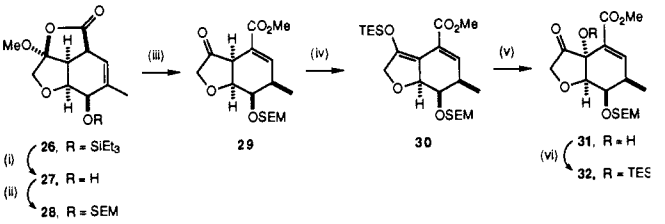


[a] Reagents and conditions: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 → 25 °C, 90%; (ii) **9**, LDA, THF, −78 °C, 0.5 h, 85%; (iii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 2 h, 25 °C, then DBU, 1 h, 25 °C, 87%; (iv) MeMgCl, THF, 0 °C, 1 h, 93%; (v) PhSCl, Et_3N, CH_2Cl_2, −78 → 25 °C, 87%; (vi) $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone), MeOH-H_2O, 25 °C, 48 h, 90%; (vii) $(NH_4)_2Ce(NO_3)_6$, MeCN-H_2O, 25 °C, 1 h, 92%; (viii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 82%; (ix) $LiAlH_4$, THF, 0 °C, 77%; (x) 2.5% Na(Hg), Na_2HPO_4, MeOH, 25 °C, 2 h, 35%; (xi) Ph_3PCHCO_2Me, toluene, reflux, 2 h, 98%; (xii) $(iBu)_2AlH$, toluene, −75 °C, 0.5 h, 94%; (xiii) N-chlorosuccinimide, Me_2S, CH_2Cl_2, 0 → 25 °C, 0.5 h, 93%; (xiv) $PhSO_2Na$, DMF, 25 °C, 48 h, 84%.

moiety of **7** was hydrolyzed, and the sterically hindered secondary alcohol of **8** was masked as 2-(trimethylsilyl)ethoxymethyl SEM ether **9** (Scheme I).

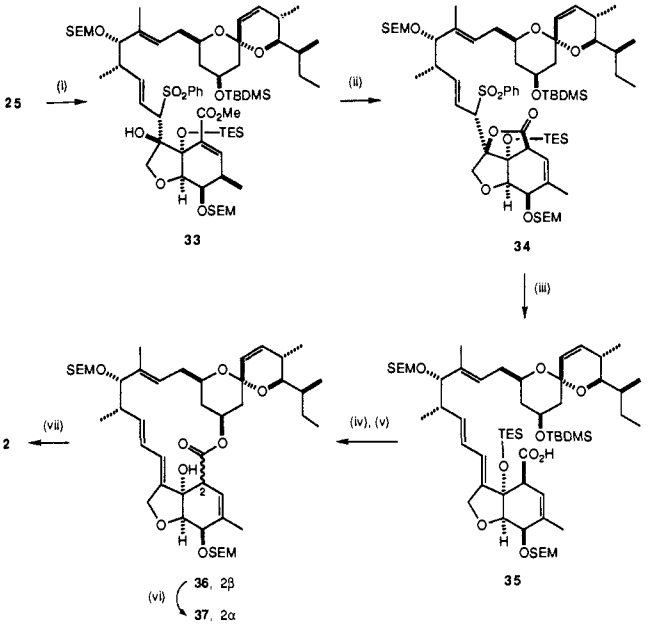
Condensation[11] of **11**, prepared by Swern oxidation of **10**,[4] with the enolate of **9** afforded the crossed aldol product **12** in high yield. β-Elimination of this hydroxy ketone, followed by reaction of **13** with methylmagnesium chloride, gave allylic carbinol **14**, which underwent smooth 1,3-transposition via its sulfenate[12] to sulfoxide

Scheme III[a]



[a] Reagents and conditions: (i) CF_3CO_2H, THF-H_2O, 55%; (ii) $Me_3SiCH_2CH_2OCH_2Cl$, $(iPr)_2NEt$, CH_2Cl_2, reflux, 2 h, 89%; (iii) K_2CO_3, MeOH, 25 °C, 1 h, 73%; (iv) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, 2 h, 84%; (v) MCPBA, CH_2Cl_2, 0 °C, 0.5 h, 57%; (vi) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, 3 h, 89%.

Scheme IV[a]



[a] Reagents and conditions: (i) *n*-BuLi, THF, −78 °C, 0.5 h, then **32**, 50%; (ii) NaOMe, Na_2HPO_4, MeOH, 0 °C, 0.5 h, 85%; (iii) 5% Na(Hg), Na_2HPO_4, MeOH, 0 °C, 3 h, 71%; (iv) TBAF, THF, 25 °C, 15 h; (v) 2-chloro-1-methylpyridinium iodide, Et_3N, MeCN, reflux, 2.5 h, 42% from **35**; (vi) imidazole, C_6H_6, reflux, 1.5 h, 43% (ref 17); (vii) 48% HF, MeCN, 25 °C, 48 h, 40%.

15. Oxidation of **15** to sulfone **16** and replacement of the *p*-methoxybenzyl protecting group (via **17**) by a *tert*-butyldimethylsilyl ether furnished **18**.[13] Removal of the pivalate from **18** gave **19**, and further reduction of this material with sodium amalgam resulted in **20**, accompanied by 38% of a 1,3-diene from elimination of the SEM ether. Wittig reaction of aldehyde **21** produced **22**, which was advanced to sulfone **25** via alcohol **23** and the corresponding allylic chloride **24** by employing standard methodology (Scheme II).

Before coupling **25** with the oxahydrindene component B, it was necessary to modify our previous approach[5] to this subunit in order to install the angular hydroxyl function. To this end, the silyl ether **26** was converted to a SEM ether via alcohol **27**, and lactone **28** was then opened to **29** with methoxide.[14] The accompanying migration of the C=C double bond into conjugation set the stage for introduction of the requisite hydroxyl substituent via epoxidation of silyl enol ether **30**. Finally, the tertiary alcohol of **31** was protected as silyl ether **32** for connection to **25** (Scheme III).

(10) Schuda, P. F.; Heimann, M. R. *Tetrahedron Lett.* **1983**, *24*, 4267.
(11) The favorable characteristic that endows this reaction with selectivity is believed to be the presence of α-oxygen substituents in both the aldehyde and ketone components (for a discussion of the directed aldol reaction, see: Mukaiyama, T. *Org. React.* (*N.Y.*) **1982**, *28*, 203).
(12) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.
(13) This interchange of protecting groups was effected in order to bring a synthetic intermediate into convergence with a substance obtained by degradation of natural **1**.
(14) The 4β configuration of the methyl substituent in **29** was established unambiguously by ^1H NMR spectroscopy.

The Julia coupling[15] of **25** with **32** proceeded in acceptable yield to give hydroxy sulfone **33**, but all attempts to effect olefin formation from this intermediate led instead to γ-lactone **34**, in which the $\Delta^{3,4}$ bond had reappeared (Scheme IV). Advantage was taken of this serendipitous event through a sodium amalgam reduction, which led cleanly to (*E,E*)-diene **35**. The silyl ether functions were unmasked, and subsequent macrolactonization[16] afforded **36**. Application to **36** of the epimerization conditions described by Hanessian for **1**[17] gave a **36**:**37** ratio of 34:50 together with 16% of the $\Delta^{2,3}$ isomer, which was removed by flash chromatography. Final cleavage of the SEM groups followed by chromatographic purification yielded **2** ($[\alpha]^{24}_D$ +126.1°), whose TLC properties and IR, ^{1}H NMR, and ^{13}C NMR spectra were identical with those of an authentic sample of avermectin B_{1a} aglycon ($[\alpha]^{24}_D$ +142.7°) derived from hydrolysis of natural **1**.[18] 2-Epiavermectin B_{1a} aglycon had $[\alpha]^{24}_D$ +264.0°.

Acknowledgment. We are grateful to Dr. Michael H. Fisher, Merck and Co., for a generous gift of avermectin B_{1a}, to Drs. Shen-chun Kuo and Anura Dantanarayana for preliminary studies on routes to **9**, and to Dr. Kazuhiko Sakuma for assistance with degradation studies. Financial support was provided by the National Institutes of Health through Grant AI 10964.

Supplementary Material Available: Spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, MS), optical rotations, and analytical data for **5–25**, **27–36**, **2**, and *epi*-**2** (12 pages). Ordering information is given on any current masthead page.

(15) Julia, M. *Pure Appl. Chem.* **1985**, *57*, 763.
(16) Mukaiyama, T.; Usui, M. *Chem. Lett.* **1976**, 49.
(17) Hanessian, S.; Dubé, D.; Hodges, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 7063.
(18) Mrozik, H.; Eskola, P.; Arison, B. H.; Albers-Schönberg, G.; Fisher, M. *J. Org. Chem.* **1982**, *47*, 489. These authors report $[\alpha]_D$ +65.6° for avermectin B_{1a} aglycon.

Activation of Amide N–H Bonds by Iron and Ruthenium Phosphine Complexes

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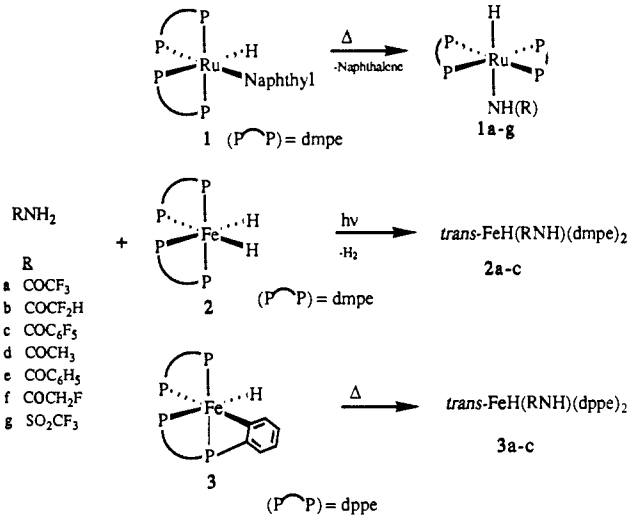
Activations of H–X bonds by transition-metal complexes are key steps in many catalytic functionalizations of C–C multiple bonds. Accordingly, N–H bond activation by metals[1] may play a key role in some catalytic olefin hydroamination[2] pathways. Here we report the facile activation of amide ($RCONH_2$) N–H bonds by iron and ruthenium phosphine complexes (**1–3**).

Reactions of *cis*-RuH(naphthyl)$(dmpe)_2$ (**1**),[3] *cis*-$FeH_2(dmpe)_2$ (**2**),[4] and $FeH(C_6H_4PPhCH_2CH_2PPh_2)$(dppe) (**3**),[5] either thermally (**1** and **3**) or photochemically (**2**), with 1.2 equiv of trifluoroacetamide[6] (a) lead to quantitative formation of products with the empirical formula M(trifluoroacetamide)$(diphosphine)_2$ (**1a**, **2a**, **3a**). Details of the spectroscopic characterizations are typified for RuH$(CF_3CONH)(dmpe)_2$ (**1a**) as follows:[7] the ^{31}P{^{1}H} spectrum of **1a** is a singlet (δ 48.6), which splits into a doublet ($J_{P-H} \cong 15$ Hz) when off-resonance (centered on the aliphatic region) ^{1}H decoupling is employed. The ^{1}H NMR spectrum of **1a** shows an upfield quintet (δ −18.8, J_{P-H} = 22 Hz, 1H), indicative of a hydride cis to four equivalent P atoms, and an N–H resonance (δ 4.0, 1 H) upfield from those of the free amide. The ^{19}F NMR spectrum shows a singlet (δ −70.2), and the positive ion fast atom bombardment (FAB) mass spectrum reveals a $[M]^+$ peak at m/z = 514 ± 1 (expect 515). The ruthenium–nitrogen connectivity is unambiguously identified by coupling of ^{15}N-a to both the hydride (J_{N-H} = 8.8 Hz) and the P (J_{N-P} = 3.0 Hz) nuclei; the N–H resonance of **1a** exhibits a lowered coupling (J_{N-H} = 68 Hz) vs free trifluoroacetamide (J_{N-H} = 91.8 anti, 90.8 syn). These spectroscopic features are consistent with the structure of **1a** shown herein, for which the disposition of the Ru–N bond may be syn or anti. Similar results are found for **1b–g**, **2a–c**, and **3a–c**[8] with the prominent exception that the iron complexes (**2a** and **3a**) yield no evidence of coupling between N and hydride or between N and P nuclei when ^{15}N-a is employed. Thus, metal–nitrogen connectivities for the iron complexes are not established.[9]



dmpe = 1,2-bis(dimethylphosphino)ethane
dppe = 1,2-bis(diphenylphosphino)ethane

Qualitatively, both the rates of formation and the stabilities of the products **1a–g**, **2a–c**, and **3a–c** depend on the natures of the metal, the amides, and the diphosphine ligand. For the ru-

(1) (a) Susa-Fink, G. *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **1980**, *35B*, 454. (b) Sappa, E.; Milone, L. *J. Organomet. Chem.* **1973**, *61*, 383. (c) Lin, Y.; Mayr, A.; Knobler, C. B.; Kaesz, H. C. *J. Organomet. Chem.* **1984**, *272*, 207. (d) Johnson, B. F. G.; Lewis, J.; Odiaka, T.; Raithby, P. R. *J. Organomet. Chem.* **1981**, *216*, C56. (e) Johnson, B. F. G.; Lewis, J. *J. Chem. Soc., Dalton Trans.* **1977**, 1328. (f) Hadden, D.; Roundhill, D. M.; Fultz, W. C.; Rheingold, A. L. *J. Am. Chem. Soc.* **1984**, *106*, 5014. (g) Roundhill, D. M. *Inorg. Chem.* **1970**, *9*, 254–258. (h) Park, S.; Hadden, D.; Roundhill, D. M. *Organometallics* **1986**, *5*, 2151. (i) Yamamoto, T.; Sano, K.; Yamamoto, A. *Chem. Lett.* **1982**, 907–910. (j) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *Inorg. Chem.* **1987**, *26*, 971. (k) Hillhouse, G. L.; Bercaw, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 5472. (l) Bercaw, J. E.; Davies, D. L.; Wolczanski, P. T. *Organometallics* **1986**, *5*, 443. (m) Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 8729.
(2) (a) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738. (b) Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108.
(3) Chatt, J.; Davidson, J. M. *J. Chem. Soc.* **1965**, 843.
(4) Obtained via reduction of *trans*-$FeCl_2(dmpe)_2$ (Chatt, J.; Hayter, F. G. *J. Chem. Soc.* **1961**, 5507) with $LiB(C_2H_5)_3H$.
(5) Azizian, H.; Morris, R. H. *Inorg. Chem.* **1983**, *22*, 6.
(6) Typical reaction conditions: trifluoroacetamide (a, 0.006 g, 0.052 mmol, 1.2 equiv) was added to a solution of **1** (0.024 g, 0.043 mmol, 1 equiv) in THF-d_8 (0.80 mL) in an NMR tube under a He atmosphere. After heating at 40 °C for 1 h, **1a** and naphthalene were produced quantitatively.
(7) Synthesis and characterization of **1a**: *cis*-RuH$(C_{10}H_7)(dmpe)_2$ (0.2 g, 0.38 mmol) and trifluoroacetamide (0.10 g, 0.88 mmol) were dissolved in THF (40 mL) and stirred at 55 °C for 2 h under an inert atmosphere. The solvent was removed in vacuo, and the free naphthalene and excess trifluoroacetamide were removed by sublimation. The tan solid was recrystallized by dissolution in THF (ca. 5 mL) followed by layering with hexane. Yield: 0.09 g (47%). Elemental analysis. Calcd: C, 32.69; H, 6.66; N, 2.72; Ru, 19.65. Found: C, 32.42; H, 6.33; N, 2.79; Ru, 19.40. FAB mass spectral data $[M]^+$ m/z = 514 ± 1 (expect 515). NMR data in THF-d_8. ^{31}P{^{1}H}: δ 48.6, s; ^{31}P{^{1}H off-resonance} δ 48.6, d, $J_{P-H} \cong 15$ Hz. ^{1}H: Ru*H*, δ −18.8, quintet, J_{H-P} = 22 Hz, 1 H; PC*H*$_3$, δ 1.0 and 1.2, 24 H; PC*H*$_2$, δ 1.32 and 1.42, 8 H; N*H*, δ 4.0, br s, 1 H. ^{19}F: δ −70.2, s. ^{15}N-**1a**. ^{1}H: Ru*H*, δ −18.8, quintet of doublets, J_{H-P} = 22 Hz, J_{H-N} = 8.8 Hz, 1 H; N*H*, δ 4.0, d, J_{H-N} = 68 Hz, 1 H. ^{31}P{^{1}H}: δ 48.6, d, J_{N-P} = 3.0 Hz.
(8) Full characterization data is provided in the supplementary material.
(9) Dynamic processes involving M–N bond rupture may prevent observation of ^{15}N–H and ^{15}N–^{31}P coupling. If such processes occur, at −60 °C they are not slowed sufficiently to permit observation.

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