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°.

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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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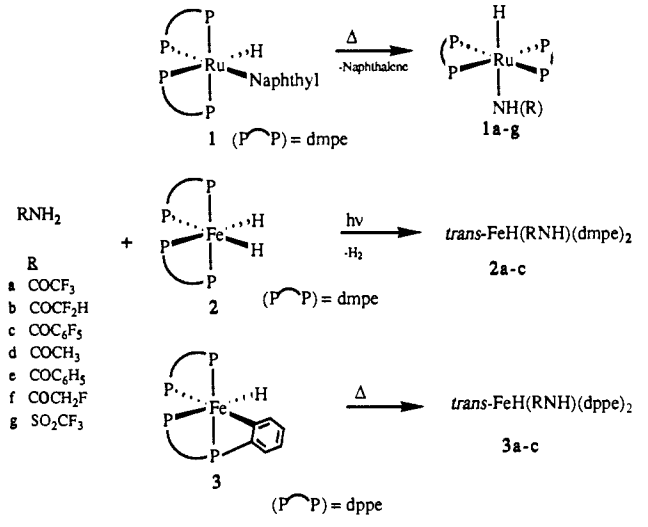
Activations of H–X bonds by transition-metal complexes are key steps in many catalytic functionalizations of C–C multiple bonds. Accordingly, N–H bond activation by metals[1] may play a key role in some catalytic olefin hydroamination[2] pathways. Here we report the facile activation of amide ($RCONH_2$) 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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thenium complex, **1**, products of N-H activation are observed for every amide tested whereas reactions are seen for the iron complexes, **2** and **3**, with amides a-c only. Increasing reaction times and temperatures for **1** are required as the acidities of the amides[10] are decreased: quantitative reaction with triflamide (g) occurs immediately at room temperature, trifluoroacetamide (a) requires heating at 50 °C for 40 min, difluoroacetamide (b) requires 20 h at 50 °C, and acetamide (d) requires heating at 50 °C for 36 h. The stabilities, also, of the products correlate with the amide acidity; quantitative yields of **1a** and free benzamide are obtained in the reaction of 2 equiv of trifluoroacetamide with **1e**. Although **1** and **2** are known to activate C-H bonds of arenes and alkanes to form stable products,[11] N-H activation products, only, are observed despite the high concentration of solvent (THF) C-H bonds and the presence of "activated" C-H bonds (e.g., the C-H bonds of acetamides b, d, and f).

The mechanism(s) of product (**1a-g**, **2a-c**, **3a-c**) formation is (are) unclear. Two possible limiting pathways (there are certainly other possibilities) for the reactions of **1**, **2**, and **3** with amides are (1) reductive elimination (photochemically driven for **2**[12]) to form zerovalent M(diphosphine)$_2$ followed by oxidative addition of the H-N bond and (2) bimolecular reaction (protonolysis) with amide. As the reaction of amides with **2** occurs with photochemical activation only, reductive elimination of H_2 is apparently required. However, intermediates resulting from C-H bond activation may be generated on the path to product formation. When an amide-d_2 (trifluoroacetamide or triflamide) is employed in the reaction with **1**, the product hydride resonance disappears and no deuterium is found in the elimination product, naphthalene.[13] This indicates that neither direct protonation of the M-C bond by the amide nor scrambling between amide N-H(D) and Ru-H bonds occurs. Furthermore, the rates at which **1** reacts with g and a ($t_{1/2}$ <2 and 20 min, respectively, at 25 °C) are much faster than the reported rate of naphthalene reductive elimination from **1** ($t_{1/2} \cong$ 300 min at 65 °C).[10b] These results lead us to favor a bimolecular reaction pathway consisting of a rate-determining, regiospecific protonation (possibly trans to the M-C bond) at the metal center followed by rapid arene elimination for the reactions of a and g with **1**. For the less acidic amides, pathways involving initial reductive elimination are kinetically competent and must be considered possible. When **1** reacts with excess g, dihydrogen (D_2 when g-d_2 is used) is evolved and a new product, tentatively identified as *cis*-Ru(dmpe)$_2$(NHSO$_2$CF$_3$)$_2$,[14] is produced.

The Ru(dmpe)$_2$(NHCOR)(H) products undergo rapid ($t_{1/2}$ < 3 min) exchange of amido groups but not through a reductive elimination/oxidative addition sequence. For example, reaction of **1a** with 1 equiv of ^{15}N-a immediately produces an equimolar mixture of ^{15}N-labeled and natural abundance ^{14}N **1a**, as shown by the coupling of the hydride and the N-H resonances in the ^{1}H NMR spectrum. Conversely, reaction of **1a** with an excess of a-d_2 over a 2-week period shows no exchange of deuterium for protium at the hydride resonance. Similar results are obtained when either ^{15}N- or D-labeled **1a** is equilibrated with unlabeled a. These results are consistent with a simple ligand-exchange process which may be associative or dissociative; due to the low dielectric constants of the solvents employed, the associative pathway seems most probable.

In summary, products of formal N-H bond activation result from the thermal reactions of amides with *cis*-RuH(naphthyl)-(dmpe)$_2$ and FeH(C$_6$H$_4$PPhCH$_2$CH$_2$PPh$_2$)(dppe) and from the photochemical reactions of *cis*-FeH$_2$(dmpe)$_2$ and amides. Alcohols, water, and simple amines do not undergo analogous reactions, suggesting that the design of late transition metal catalyzed hydroaminations may be achieved more readily by using amides as ammonia synthetic equivalents. Our current efforts are directed at clarification of the mechanistic aspects of amide N-H activation and at the exploitation of N-H activation in hydroamination catalysis.

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Supplementary Material Available: Experimental details of the isolation of compound **3a** and the attempted isolation of compound **2a** and NMR data for compounds **1b-g**, **2a-c**, and **3a-c** (4 pages). Ordering information is given on any current masthead page.

(10) Representative pK_a's: trifluoroacetamide (a), pK_a = 6.3 (water);[10a] trifluoromethanesulfonamide (g), pK_a = 6.3 (water);[10b] acetamide (d), pK_a = 25.5 (DMSO).[10a] (a) Bordwell, F. G. *Pure Appl. Chem.* **1977**, *49*, 963. (b) Trepka, R. D.; Harrington, J. K.; Belisle, J. W. *J. Org. Chem.* **1974**, *39*, 1094. We have not been able to find appropriate pK_a values in THF.

(11) (a) Baker, M. V.; Field, L. D. *J. Am. Chem. Soc.* **1987**, *109*, 2825. (b) Tolman, C. A.; Ittel, S. D.; English, A. D.; Jesson, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 4080.

(12) Bergamini, P.; Sostero, S.; Traverso, O. *J. Organomet. Chem.* **1986**, *299*, C11.

(13) Less than 5% C$_{10}$H$_7$D detected by GC/MS.

(14) NMR data. *cis*-Ru(CF$_3$SO$_2$NH)$_2$(dmpe)$_2$ in THF-d_8. ^{31}P{^{1}H}: δ 38.6, t, J_{P-P} = 24 Hz, 2 P; δ 54.1, t, J_{P-P} = 24 Hz, 2 P; ^{31}P{^{1}H off-resonance}: δ 38.6, t; δ 54.1, t. ^{19}F: δ -71.5, s. ^{1}H: PCH_3, δ 1.26 and 1.31, br, 24 H; PCH_2, δ 1.4, br, 8 H, no other peaks observed.

Endocyclic Restriction Test: Evaluation of Transition-Structure Geometry for an Aryl Bromide-Alkyllithium Exchange Reaction

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The endocyclic restriction test provides an approach for the evaluation of transition-structure geometry that is applicable to nonstereogenic atoms and thereby can provide information that can be used to distinguish between alternative mechanisms.[1-6] In this communication we report an investigation of this approach for a formal nucleophilic substitution at bromine and use our results to evaluate the mechanisms for the aryl bromide-alkyllithium exchange reaction. To the best of our knowledge, this is the first report of an experimental evaluation of transition-structure geometry for a formal substitution at bromine.

Treatment of *o*-bromophenethyl iodide **1** with 1.8 equiv of *tert*-butyllithium at -98 °C in tetrahydrofuran followed by addition of methanol gives the products **3-9** in the yields indicated along with 10% recovered **1**.[7] The products of interest, **3-5**, are considered to arise after initial conversion of **1** to (*o*-bromophenethyl)lithium (**2**). The *o*-bromoethylbenzene (**3**) is from protonation of **2** by methanol, the *o*-bromophenethyl bromide (**5**) from bromine-lithium exchange of **2**, and the phenethyl bromide (**4**) from intra- or intermolecular rearrangement of **2** to *o*-lithiophenethyl bromide (**10**) prior to protonation by methanol.[9]

An intermolecular pathway for a monomeric unit in the conversion of **2** to **10** was established by the double labeling exper-

(1) For substitution at carbon: Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2059.

(2) For substitution at sulfur: Hogg, D. R.; Vipand, P. W. *J. Chem. Soc. C* **1970**, 2142. Kampmeier, J. A. *ACS Symp. Ser.* **1978**, *No. 69*, 275. Andersen, K. K.; Malver, O. *J. Org. Chem.* **1983**, *48*, 4803. Andersen, K. K.; Chumpradit, S.; McIntyre, D. J. *J. Org. Chem.* **1988**, *53*, 4667. Beckwith, A. L. J.; Boate, D. R. *J. Chem. Soc., Chem. Commun.* **1986**, 189.

(3) For an early suggestion of this approach for iodine, see: Drury, R. F.; Kaplan, L. *J. Am. Chem. Soc.* **1972**, *94*, 3982.

(4) For substitution at nitrogen: Beak, P.; Basha, A.; Kokko, B. *J. Am. Chem. Soc.* **1984**, *106*, 1511. Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016.

(5) For substitution at oxygen: Beak, P.; Loo, D. *J. Am. Chem. Soc.* **1986**, *51*, 3834.

(6) For general discussion, see: Minkin, V. I.; Olekhnovich, L. P.; Zhdanov, Y. A. *Molecular Design of Tautomeric Compounds*; D. Reidel Publishing Co.: Dordrecht, Holland, 1988.

(7) Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847. Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785.

(8) Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1 and reference cited therein.

(9) An intramolecular reaction within a radical cage is also ruled out by these results. The possibility that electron transfer precedes formation of an ate complex or an S_N2 transition structure cannot be ruled out but is not necessary. The lack of bromide incorporation into **5** rules out formation of this product by bromide displacement on **1**.

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