Catalysis of the Aminomethylation Reaction. Enhanced Catalytic Activity with Mixed-Metal Catalysts. Applications of the Water-Gas Shift Reaction. 5[1]

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In recent papers we have described the use of several group 8 metal carbonyl complexes as catalyst precursors for catalysis of hydroformylation (eq 1) and hydrohydroxymethylation (eq 2) with H_2O as the source of hydrogen.[2] Moreover, in rhodium-catalyzed reactions of pyridine with CO and H_2O we found evidence that the aminomethylation reaction (eq 3) proceeds via a simple three-step mechanism shown in Scheme I.[1]

$$RCH{=}CH_2 + H_2O + 2CO \rightarrow RCH(CH_3)CHO \text{ or } RCH_2CH_2CHO + CO_2 \quad (1)$$

$$RCH{=}CH_2 + 2H_2O + 3CO \rightarrow RCH(CH_3)CH_2OH \text{ or } RCH_2CH_2CH_2OH + 2CO_2 \quad (2)$$

$$RCH{=}CH_2 + 3CO + H_2O + HNR'_2 \rightarrow R(CH_2)_3NR'_2 + 2CO_2 \quad (3)$$

Scheme I

$$RCH{=}CH_2 + 2CO + H_2O \rightarrow RCH_2CH_2CHO + CO_2$$

$$R(CH_2)_2CHO + HNR'_2 \rightleftharpoons RCH_2CH{=}CHNR'_2 + H_2O$$

$$RCH_2CH{=}CHNR'_2 + H_2O + CO \rightarrow R(CH_2)_3NR'_2 + CO_2$$

We describe here the results of some of our studies on the aminomethylation reaction using a variety of group 8 transition-metal carbonyl catalyst precursors, including the novel mixed-metal system ruthenium/iron.

Experimental Section

General Methods. Methanol used in kinetic runs was distilled from sodium methoxide or calcium hydride in a nitrogen atmosphere prior to use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under N_2 immediately prior to use. Ethoxyethanol and *n*-butyl ether were refluxed over $SnCl_2$ and distilled under N_2 prior to use. Piperidine was purchased from Aldrich and used as received. All metal carbonyl cluster complexes were purchased from Strem Chemical Co. and used as received. Hexanol was purchased from Aldrich.

Analytical Methods. Product analyses were performed with a Hewlett-Packard Model 5711 gas chromatograph equipped with an FID and using a 4.0 m × 0.328 cm column packed with 5% Carbowax on acid-washed Chromosorb G. Infrared spectra were obtained by using a Perkin-Elmer Model 281 infrared spectrometer.

Hydroformylation/Hydrohydroxymethylation Catalysis. A standard 0.5-h run requires mixing 4.72 g (6.0 mL) of methanol, 1.15 g (1.0 mL) of 3.0 N KOH, 2.53 g (4.0 mL, 36 mmol) of 1-pentene, and either 0.260 g (2.00 mmol) of *n*-butyl ether or 0.180 g (2.00 mmol) of ethoxyethanol as internal standard for chromatographic analysis in a quartz-lined, Parr, general-purpose bomb reactor. Also added is 0.1 mmol of catalyst precursor, or, where two catalyst precursors are added, 0.05 mmol of each is added unless otherwise noted (see Table I). The reactor, which contains the mixture and a magnetic stir bar, is sealed and degassed by three 800-psi pressurization/depressurization cycles with CO. The reactor is then charged to 800 psi of CO, heated with magnetic stirring at 150 °C for 0.5 h, cooled to 0 °C, and depressurized. The reactor is opened, and 3.0 mL of THF is added. The solution is stirred for 10 min and analyzed.

Aminomethylation Catalysis. A standard run is the same as described above with the exception that 1.0 mL (10 mmol) of piperidine is added to the reaction mixture as the limiting reactant. The activities of the various catalysts tested in this manner are listed in Table I in terms of turnover numbers (moles of product/mole of catalyst precursor(s)/0.5 h).[3]

Results and Discussion

Several important observations can be made from the data provided in Table I. The observations concern products and product selectivities, catalyst activities for hydroformylation vs. hydrogenation, and the catalysts themselves.

Products and Product Selectivities. Three products are formed during the course of aminomethylation catalysis. These products are C_6 aldehydes (hexanal and 2-methylpentanal), *N*-*n*-hexyl- and *N*-(2-methylpentyl)-piperidine, and piperidineformamide. The C_6 aldehydes are not observed because they rapidly react with piperidine to form enamines under the reaction conditions.[4] However, evidence for their formation is found in the product selectivities for ruthenium-catalyzed hydroformylation and aminomethylation which are identical (98% hexanal and 98% *N*-*n*-hexylpiperidine). Moreover, Watanabe has reported that aldehydes and amines can be reacted under conditions similar to those reported here to produce N-alkylated amines as would be expected according to the mechanism shown in Scheme I.[5]

In general, the product selectivities for *N*-*n*-hexylpiperidine are higher than those for hexanal for a given catalyst. The difference most likely stems from enamine formation/hydrogenation competing successfully with aldolization for hexanal. Hexanal is preferentially siphoned off during the aldolization.[2] Of interest are the product selectivities for the rhodium/iron aminomethylation catalyst which are significantly different from the simple $Rh_6(CO)_{16}$-based catalyst system. This evidence as well as the considerable rate increase on going to the rhodium/iron system indicates that the catalytic species involved are not the same.

Piperidineformamide formation is an unwanted side reaction that interferes with the usefulness of aminomethylation as a synthetic tool. Formamide synthesis readily competes with aminomethylation for starring amine and therefore lowers product yields. Moreover, formamide formation adds to the difficulty of purifying the product. Aminomethylation catalysis with CO and H_2O described here provides a means of reducing complications due to formamide. The presence of H_2O in the catalysis solution results in the hydrolysis of the formamide, thereby freeing the amine to participate in the aminomethylation reaction.

(1) Previous paper in this series: R. M. Laine, D. W. Thomas, L. W. Cary, *J. Org. Chem.*, **44**, 4964 (1979).
(2) (a) R. M. Laine, *Ann. N.Y. Acad. Sci.*, **333**, 124 (1979); (b) R. M. Laine, *J. Am. Chem. Soc.*, **100**, 6451 (1978).
(3) All of the catalysts can be reused following distillation (under CO pressure) of the products from the reaction solution. Additional base should be added to retain the same levels of activity. While catalyst lifetimes were not determined, previous work in this area suggests that the catalysts are quite stable over long periods of time (ref 2 and references therein).
(4) G. Stork, P. Rosen, and N. L. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961).
(5) Y. Watanabe, M. Yamamoto, T. Mitsudo, and Y. Takegami, *Tetrahedron Lett.*, 1289 (1978).

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Table I. Catalytic Activities[a] of Some Group 8 Metals for Hydroformylation, Hydrohydroxymethylation, Aminomethylation, and Formamide Formation

catalyst precursor	turnover rate: hydroformylation[b]	hydrohydroxymethylation[b]	aminomethylation[c]	formamide[c]
$Co_2(CO)_8$	nr	nr	nr	nr
$Os_3(CO)_{12}$	2 (86)			
$Ir_4(CO)_{12}$	17 (84)	1 (90)	12 (85)	12
$Fe_3(CO)_{12}$	19 (70)	2 (86)	8 (76)	14
$Ru_3(CO)_{12}$	20 (98)	1 (98)	20 (98)	12
$[(C_6H_5)_3P]$-Rh(CO)Cl	45 (75)		5 (88)	13
$Rh_6(CO)_{16}$	40 (63)	35 (88)	70 (83)	6
$Rh_6(CO)_{16}$[d]	40 (63)	27 (90)	60 (84)	5
$Rh_6(CO)_{16}$/ $Fe_3(CO)_{12}$	65 (65)	35 (82)	84 (78)	2
$Rh_6(CO)_{16}$/ $Fe_3(CO)_{12}$[e]			90 (78)	1
$Fe_3(CO)_{12}$/ $Ru_3(CO)_{12}$[f]			60 (94)	5
$Fe_3(CO)_{12}$/ $Ru_3(CO)_{12}$	110 (86)	5 (96)	70 (94)	3
$Fe_3(CO)_{12}$/ $Ru_3(CO)_{12}$[g]			70 (93)	4

[a] Activities are defined as turnover numbers/0.5 h (turnover rate). The numbers in parentheses are percentages of straight-chain products. [b] The turnover numbers in these columns are for the hydroformylation reaction run in the absence of piperidine. C_6 alcohols ($C_6H_{14}O$) are secondary products. [c] The turnover numbers in these columns are for the aminomethylation reaction. Catalysis of formamide ($C_6H_{11}NO$) formation is a side reaction of aminomethylation catalysis. [d] 0.05 mmol $Rh_6(CO)_{16}$. [e] 0.05 mmol $Rh_6(CO)_{16}$ and 0.10 mmol $Fe_3(CO)_{12}$. [f] 0.075 mmol $Ru_3(CO)_{12}$ and 0.025 mmol $Fe_3(CO)_{12}$. [g] 0.025 mmol $Ru_3(CO)_{12}$ and 0.075 mmol $Fe_3(CO)_{12}$.

Unfortunately, hydrolysis under the reaction conditions is slow. However, we have found that the use of the rhodium/iron or ruthenium/iron mixed-metal catalyst systems significantly reduces the side reaction that produces piperidineformamide as compared with the individual catalysts.[6]

Another primary goal of the present research was to enhance the activity of the highly selective ruthenium-catalyzed hydroformylation and aminomethylation reactions without loss of selectivity. This goal is attained through the use of ruthenium/iron mixed-metal catalysts (see Table I) that provide systems with 5.0 times the activity found with ruthenium alone and do not especially compromise the selectivity. We are presently investigating the use of the mixed-metal systems for the synthesis of primary and secondary amines.

Catalysts and Catalysis. There are two distinct catalytic reactions that occur during the course of the aminomethylation reaction. These are hydroformylation and reductive amination which involves catalytic hydrogenation of the enamine intermediate. Table I lists the results of our recent study on hydroformylation catalysis with CO and H_2O. Comparison of the hydroformylation activities with those found in aminomethylation catalysis indicates that, in general, the most active hydroformylation catalysts are also the most active hydrogenation catalysis. The specific exception to this observation is the $[(C_6H_5)_3P]_2$-Rh(CO)Cl catalyst system. The decrease in activity observed for this system may result from competition between aminomethylation catalysis and catalysis of formamide formation, with the formamide reaction predominating. Alternatively, piperidine or the hexylpiperidine products may bind strongly to the rhodium, thus obstructing approach of the alkene and preventing hydroformylation.

The most interesting catalyst systems are the mixed-metal rhodium/iron and ruthenium/iron catalysts. There are several reports in the literature of enhanced homogeneous catalysis through the use of mixed-metal catalysts, including Iqbal's work with rhodium/iron catalysis of aminomethylation.[6,7] However, to our knowledge the enhanced hydroformylation and aminomethylation catalysis activities obtained by using mixtures of ruthenium and iron rather than the individual metals as described here is without precedent. The enhanced catalytic activity of the mixed-metal systems is unusual, considering the fact that separately iron and ruthenium are only moderately active as hydroformylation catalysts and are relatively inefficient aminomethylation catalysts. As suggested above, the evidence indicates that the active catalytic intermediates in the mixed-metal catalysis reactions are different from those formed with the individual metals.

Unfortunately, characterization of the aminomethylation catalyst solutions by IR (ν_{CO}) is not possible at present because amines attack almost all types of IR cell window material.[8] Thus, evidence for mixed-metal reaction intermediates in aminomethylation catalysts must be by inference. That is, the rate enhancements must be the result of a mixed-metal interaction. A mixed-metal species is, of course, a cluster.

On the other hand, with the mixed-metal hydroformylation/hydrohydroxymethylation catalysis solutions it is possible to obtain IR data. For the brown equimolar rhodium/iron catalyst solutions ν_{CO} values are as follows: 2075 (vw), 2063 (sh), 2052 (sh), 2035 (s), 2024 (vs), 2006 (sh), 1988 (vs), 1980 (vs), 1885 (mw), 1865 (s), 1827 (m) cm^{-1}. By comparison, the purple rhodium catalysis solutions give ν_{CO} values as follows: 2088 (w), 2075 (sh), 2058 (m), 2035 (vs), 2013 (vs), 1875 (m), 1852 (sh), 1844 (ms), 1830 (m), 1787 (m), 1775 (ms) cm^{-1}. The $Fe_3(CO)_{12}$ solutions gave ν_{CO} values of 2021 (s) and 1999 (vs) cm^{-1}, indicative of $Fe(CO)_5$. The color of the catalyst solutions differ as do the IR spectra. The mixed-metal rhodium/iron systems IR spectra contain little evidence of $Fe(CO)_5$ or $HFe(CO)_4^-$, perhaps suggesting incorporation of the iron into a rhodium cluster system.[9] In the orange-brown equimolar ruthenium/iron systems the ν_{CO} values are as follows: 2072 (m), 2055 (sh), 2042 (sh), 2016 (vs), 2003 (s), 1999 (vs), 1964 (ms), 1919 (w) cm^{-1}. The related orange ruthenium catalyst solution has the following ν_{CO} values: 2088 (w), 2036 (sh), 2010 (vs), 1993 (s), 1974 (sh), 1964 (m, br) cm^{-1}. While some overlap exists between the spectra, there are sufficient differences to suggest that mixed-metal clusters do form.[7]

(6) (a) Rhodium oxide/$Fe(CO)_5$ mixed-metal catalysts have been used previously for the aminomethylaion reaction. A. F. M. Iqbal, *Helv. Chim. Acta* **54**, 1440 (1970), and references therein. (b) Aminomethylation using CO/H_2 has been reported: U.S. Patents 2422631 (1947), 2497310 (1950), 3234283 (1966), 3513200 (1970).

(7) (a) P. C. Ford, R. G. Ringer, R. M. Laine, C. Ungermann, V. Landis, and S. A. Moya, *J. Am. Chem. Soc.*, **100**, 4595 (1978). (b) *Adv. Chem. Ser.* **No. 173**, 81 (1979). (c) See also: U.S. Patent 4002677. (d) Related work in the heterogeneous phase with supported mixed-metal clusters is found in U.S. Patent 4144191.

(8) Kodak Irtran 1 has been found to be impervious to amines and will be used in future work to further characterize the metal carbonyl species in the aminomethylation catalysis reactions.

(9) (a) The mixed-metal catalyst solutions closely resemble solutions of $Rh_{12}(CO)_{30}^{2-}$; see ref 2a. (b) $HFe(CO)_4^-$ has ν_{CO} values of 2015 (w), 1937 m (sh), and 1897 (vs) cm^{-1}. W. F. Edgell, J. Huff, J. Thomas, H. Lehman, G. Angell, and C. Asato, *J. Am. Chem. Soc.*, **82**, 1254 (1960).

Thus, the combination of enhanced catalysis in the mixed-metal catalysis solutions, the change in selectivities, and the differences in IR spectra indicate that the rhodium/iron and ruthenium/iron catalyst solutions are novel forms of cluster catalysis. In light of recent proposals by Ugo[10] and Muetterties,[11] these cluster-catalyzed reactions may be of use in modeling heterogeneous catalysis.

(10) R. Ugo, *Catal. Rev.-Sci. Eng.*, 11, 225 (1975).
(11) E. L. Muetterties, *Science (Washington, DC)*, 196, 839 (1977).

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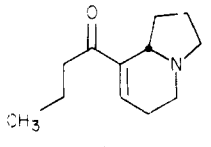
Registry No. Piperidine, 110-89-4; 1-pentene, 109-67-1; hexanal, 66-25-1; 2-methylpentanal, 123-15-9; *N*-hexylpiperidine, 7335-01-5; *N*-(2-methylpentyl)piperidine, 16627-38-6; piperidine formamide, 2158-03-4; $Co_2(CO)_8$, 10210-68-1; $Os_3(CO)_{12}$, 15696-40-9; $Ir_4(CO)_{12}$, 11065-24-0; $Fe_3(CO)_{12}$, 17685-52-8; $Ru_3(CO)_{12}$, 15243-33-1; $[(C_6H_5)_3P]Rh(CO)Cl$, 41988-66-3; $Rh_6(CO)_6$, 28407-51-4.

Communications

Total Synthesis of Elaeokanine A

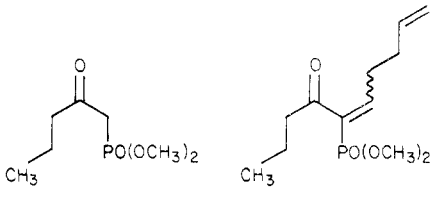
Summary: A new general approach to synthesis of *Elaeocarpus* alkaloids is discribed which utilizes the intramolecular imino Diels–Alder reaction as the key ring-forming step. The methodology has been applied to total synthesis of the alkaloid Elaeokanine A.

Sir: The *Elaeocarpus* alkaloids are a group of compounds isolated from the leaves of a few species of trees of the *Elaeocarpaceae* family, found mainly in tropical rain forests in several areas of the world.[1] We have developed a novel general strategy for construction of this class of natural products using the intramolecular imino Diels–Alder reaction as the pivotal step in formation of the bicyclic indolizidine ring system. Described below is the total synthesis of a typical *Elaeocarpus* alkaloid, elaeokanine A (**1**),[2] which exemplifies our new approach.[3]

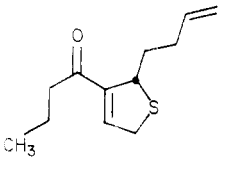


1

Keto phosphonate **2**[4] was condensed with 4-pentenal[5] with piperidine/acetic acid as catalyst[6] (benzene, reflux) to afford **3** in 76% yield as a 1:1 mixture of geometrical isomers which was used directly in the next step. Treatment of **3** with mercaptoacetaldehyde (generated in situ from its dimer, *p*-dithiane-2,5-diol) and triethylamine (CH_2Cl_2, reflux, 4–6 h) gave dihydrothiophene **4** in 56% yield.[7] Oxidation of **4** with excess *m*-CPBA in methylene chloride (room temperature, 24 h) afforded epoxy sulfone **5** (90%). Cleavage of the epoxide group of **5** to the carboxylic acid **6** was effected in a single step with a mixture of CrO_3/H_5IO_6 in aqueous acetone (room temperature, 3–4 h; 92%; IR (film) 3600–2800, 1710, 1680 cm^{-1}).[8] This carboxylic acid was converted to the corresponding amide **7** by treatment with ethyl chloroformate/triethylamine followed by anhydrous ammonia (58%; mp 76–78 °C; IR ($CHCl_3$) 3525, 3400, 1680, 1320, 1130 cm^{-1}; NMR ($CDCl_3$) δ 7.1 (1 H, br t), 6.2 (br s, NH_2)).



2 **3**



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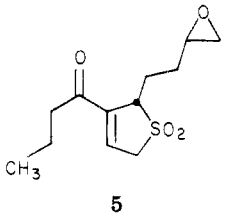

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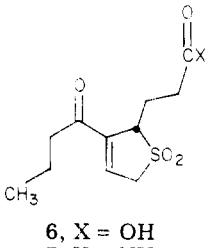
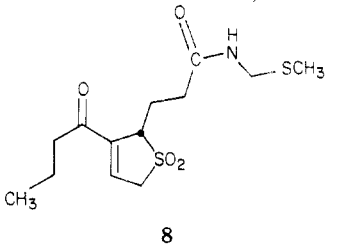


6, X = OH
7, X = NH_2



8

Several attempts were made to convert **7** into the derived *N*-(hydroxymethyl)amide with formaldehyde and

(1) Johns, S. R.; Lamberton, J. A. In "The Alkaloids"; Manske, R., Ed.; Academic Press: New York, 1973; Vol. 14, p 325.
(2) (a) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *J. Chem. Soc. D* **1971**, 360; (b) *Aust. J. Chem.* **1972**, *25*, 817.
(3) For previous synthetic approaches to the *Elaeocarpus* alkaloids, see: (a) ref 2b; (b) Onaka, T. *Tetrahedron Lett.* **1971**, 4395; (c) Tanaka, T.; Ijima, I. *Tetrahedron* **1973**, *29*, 1285; (d) Howard, A. S.; Meerholz, C. A.; Michael, J. P. *Tetrahedron Lett.* **1979**, 1339. (e) A total synthesis of elaeokanine A has just been reported: Tufariello, J. J.; Ali, Sk. A. *Ibid.* **1979**, 4445.
(4) Cf. Dauben, W. G.; Beasley, G. H.; Broadhurst, M. D.; Muller, B.; Peppard, D. J.; Pesnelle, P.; Suter, C. *J. Am. Chem. Soc.* **1975**, *97*, 4793.
(5) Montgomery, L. K.; Matt, J. W. *J. Am. Chem. Soc.* **1967**, *89*, 6556.
(6) McIntosh, J. M.; Sieler, R. A. *Can. J. Chem.* **1978**, *56*, 226.
(7) McIntosh, J. M.; Sieler, R. A. *J. Org. Chem.* **1978**, *43*, 4431.
(8) This combination of reagents has been used to cleave a 1,2-diol to the diacid: Perold, G. W.; Pachler, K. G. R. *J. Chem. Soc. C* **1966**, 1918. To our knowledge it has not previously been utilized for epoxide cleavage.

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