Communications

Chiral π-Complexes of Heterocycles with Transition Metals: A Versatile New Family of Nucleophilic Catalysts

J. Craig Ruble and Gregory C. Fu*

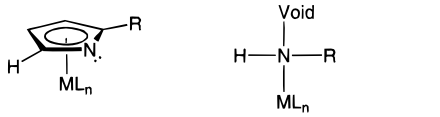
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received July 30, 1996

A wide array of reactions are subject to catalysis by nucleophiles, including the acylation of alcohols,[1] the cyanosilylation of aldehydes,[2] and the addition of alcohols to ketenes.[3] Although important progress has been made in the development of asymmetric variants of these processes,[4] the discovery of a catalyst that is both versatile and highly enantioselective remains elusive. This may be due in part to the fact that some of the most efficient nucleophilic catalysts for these reactions have planar structures (e.g., pyridine, 4-(dimethylamino)-pyridine (DMAP),[5] and imidazole), thereby requiring the design of an asymmetric environment in the vicinity of an sp^2-hybridized nucleophilic atom.[6]

We are exploring the possibility that π-complexation of a heterocycle to a transition metal may be an especially effective approach to the development of chiral analogues of planar nucleophilic catalysts such as DMAP and imidazole. When a 2-substituted heterocycle is π-bound to a metal, the resulting complex is chiral, and the asymmetry in the vicinity of the nucleophilic atom is well-pronounced, as illustrated in Figure 1. Viewing along the (lone pair)−(nitrogen atom) axis, increased differentiation of left from right (H vs R) and of top from bottom (a void vs ML_n) corresponds to a more asymmetric environment; if either left/right or top/bottom is not differentiated, then the compound is achiral. In this paper, we report the preparation of chiral π-complexes of heterocycles with transition metals and demonstrate that they serve as catalysts for an array of useful organic reactions. Furthermore, we establish the utility of one of the complexes as an asymmetric catalyst for the acylation of chiral secondary alcohols.

Our initial investigation has focused on the four previously unknown (π-heterocycle)FeCp* complexes depicted in Figure 2, three of which are chiral (**2**−**4**). We selected the FeCp* fragment as our ML_n because of its electron-rich nature, stability, and steric bulk,[7] and we



A A view along the (lone pair)-(nitrogen atom) axis of **A**

Figure 1. Chiral (π-heterocycle)ML_n complex.

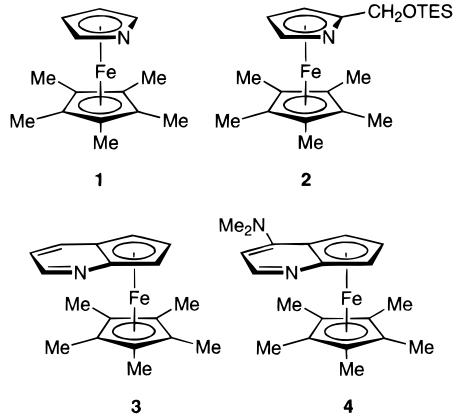


Figure 2. New (π-heterocycle)FeCp* catalysts.

chose azaferrocene derivatives **1** and **2**[8−10] and pyrindinyl complexes **3** and **4**[11] in order to explore the nucleophilicity of five- and six-membered π-bound heterocycles that have different steric and electronic characteristics. We have studied the catalytic activity of these complexes in the aforementioned reactions—the acylation of alcohols, the cyanosilylation of aldehydes, and the addition of alcohols to ketenes. In order to provide a clear comparison of the effectiveness of **1**−**4** as catalysts, we determined by ^{1}H NMR spectroscopy the half-life for each reaction in the presence of each complex.[12]

The development of new families of catalysts, both achiral and chiral, for the acylation of alcohols continues to be an important challenge in synthetic organic chemistry.[13,14] We have explored the reaction of 1-phenylethanol with diketene in the presence of complexes **1**−**4** (eq 1),[15] and we have established that azaferrocene derivatives **1** and **2**, as well as DMAP analogue **4**, serve

(1) (a) Pyridine: Verley, A.; Bölsing, F. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 3354−3358. (b) 4-(Dimethylamino)pyridine: Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981. See also: Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk SSSR, Ser. Khim.* **1967**, *176*, 97−100.

(2) (a) Evans, D. A.; Wong, R. Y. *J. Org. Chem.* **1977**, *42*, 350−352. (b) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537−540.

(3) Tidwell, T. T. *Ketenes*; Wiley: New York, 1995.

(4) (a) Acylation of alcohols: Wegler, R. *Liebigs Ann. Chem.* **1932**, *498*, 62−76. (b) Cyanosilylation of aldehydes: Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 541−544. (c) Addition of alcohols to ketenes: Pracejus, H. *Liebigs Ann. Chem.* **1960**, *634*, 9−22.

(5) (a) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129−161. (b) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069−2076. (c) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583.

(6) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809−1810.

(7) Leading references: Kerber, R. C. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier: Tarrytown, NY, 1995; Vol. 7, Chapter 2.

(8) (a) King, R. B.; Bisnette, M. B. *Inorg. Chem.* **1964**, *3*, 796−800. (b) Joshi, K. K.; Pauson, P. L.; Qazi, A. R.; Stubbs, W. H. *J. Organomet. Chem.* **1964**, *1*, 471−475. pK_a of azaferrocene (aqueous ethanol) = 4.5.

(9) Reviews that include overviews of azaferrocene chemistry: (a) Sadimenko, A. P.; Garnovskii, A. D.; Retta, N. *Coord. Chem. Rev.* **1993**, *126*, 237−318. (b) Zakrzewski, J. *Heterocycles* **1990**, *31*, 383−396. (c) Kuhn, N. *Bull. Soc. Chim. Belg.* **1990**, *99*, 707−715.

(10) (a) Report of *N*-alkylation of azaferrocene with methyl iodide: Ref. 8b. (b) Report of *N*-acylation of 2,3,4,5-tetramethylazaferrocene with acetyl chloride: Kuhn, N.; Schulten, M.; Zauder, E.; Augart, N.; Boese, R. *Chem. Ber.* **1989**, *122*, 1891−1896.

(11) We are aware of only one previous report of a pyrindinyl−metal complex: Ji, L.-N.; Kershner, D. L.; Rerek, M. E.; Basolo, F. *J. Organomet. Chem.* **1985**, *296*, 83−94.

(12) No intermediates were apparent in the ^{1}H NMR spectra of any of the four reactions.

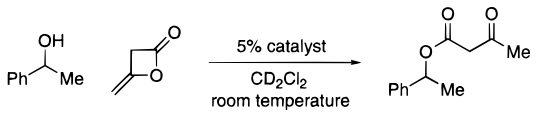
(13) Recent reports of achiral catalysts: (a) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358−3359. (b) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413−4414.

(14) Recent work on catalytic asymmetric acylation: Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430−431 and references therein.

(15) Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722−725.

S0022-3263(96)01433-8 CCC: $12.00

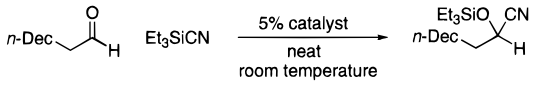
as effective catalysts for this acylation process (>10^2 rate enhancement).



(1)

complex	half-life (min)
1	16
2	810
3	~ 50,000
4	< 3
none	no reaction (3500 min)

π-Complexed heterocyclic nucleophiles also catalyze the cyanosilylation of aldehydes,[2,16] thereby generating synthetically useful cyanohydrins (eq 2).[17] The presence

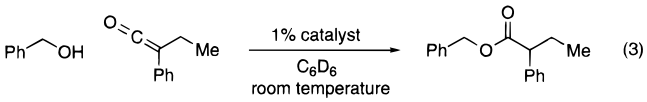


(2)

complex	half-life (min)
1	31
2	280
3	180
4	< 2
none	2300

of 5 mol % of complex **2** or **3** results in approximately 10-fold acceleration of the reaction, whereas **1** and **4** afford rate enhancements of ~2−3 orders of magnitude.

We have also explored the capacity of π-bound heterocycles **1**−**4** to catalyze the addition of an alcohol to a ketene.[3] In the addition of an alcohol to an unsymmetrical ketene, a new stereogenic center is formed in the product ester; the stereochemical issue for this reaction is therefore fundamentally different from the simple acylation process described earlier. A catalytic quantity of amine is known to significantly accelerate esterification, but the mechanism by which catalysis is achieved (nucleophilic or Bronsted base) is still under debate.[3] Heterocycles **1**−**4** have the potential to function either as nucleophiles or as Bronsted bases, and we have established that all four complexes do indeed serve as catalysts for the addition of benzyl alcohol to phenylethylketene (eq 3).

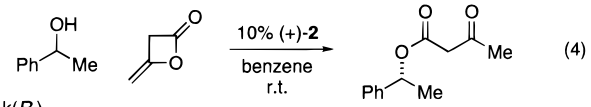


(3)

complex	half-life (min)
1	7
2	16
3	20
4	2
none	600

Thus, π-bound heterocyclic complexes **1**−**4** serve as catalysts, with varying degrees of effectiveness, for the acylation of alcohols, the cyanosilylation of aldehydes, and the addition of alcohols to ketenes (eqs 1−3).[18] Catalyst **4**, a chiral *ortho*-substituted derivative of DMAP, is the most effective, providing greater than 100-fold acceleration for each process.[19] The importance of the electronic activation afforded by the dimethylamino group is apparent from comparison of the catalytic activity of **4** with that of **3**.

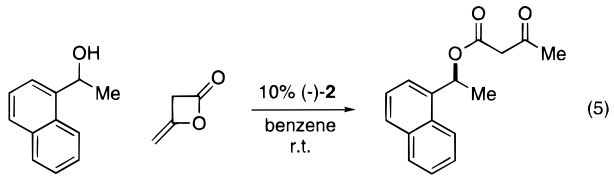
We have begun to explore the chemistry of optically active (π-heterocycle)−metal complexes.[20] In our initial studies, we have established that azaferrocene derivative **2** functions as an effective catalyst for the kinetic resolution of chiral secondary alcohols (eqs 4 and 5).[21] To the



(4)

$\frac{k(R)}{k(S)} = s = 3.7$

53% ee at 58% conversion



(5)

$\frac{k(S)}{k(R)} = s = 6.5$

87% ee at 67% conversion

best of our knowledge, these selectivity factors (s) are the highest that have been reported for the catalyzed, nonenzymatic acylation of these two substrates.[6,14]

In conclusion, we have demonstrated that chiral π-complexes of heterocycles with transition metals serve as catalysts for an array of important organic reactions. Furthermore, we have synthesized one such complex in enantiomerically pure form (**2**) and shown that it catalyzes the stereoselective acylation of alcohols. Current efforts are focused on additional studies of the utility of **2** as a chiral catalyst and on the synthesis of other optically active (π-heterocycle)−metal complexes.

Acknowledgment. We thank Pfizer for a generous donation of 6,7-dihydro-5*H*-1-pyrindine, Diego A. Hoic for aid with X-ray crystallography, Jack S. Liang for preliminary work on the cyanosilylation of aldehydes, Dr. Kenneth E. Stockman for helpful discussions, and the Buchwald group (MIT) for sharing their equipment. Support has been provided by the Camille and Henry Dreyfus Foundation, the National Science Foundation (predoctoral fellowship to J.C.R.; Young Investigator Award to G.C.F., with funding from DuPont, Hoechst Celanese, Merck, Pfizer, Procter & Gamble, Rohm & Haas, and Upjohn), and the American Cancer Society. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the ACS, for partial support of this research.

Supporting Information Available: A listing of experimental procedures and compound characterization data (18 pages).

JO961433G

(16) Review of nucleophile-catalyzed reactions of organosilicon compounds: Furin, G. G.; Vyazankina, O. A.; Gostevsky, B. A.; Vyazankin, N. S. *Tetrahedron* **1988**, *44*, 2675−2749.

(17) Recent reviews of asymmetric cyanohydrin synthesis: (a) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555−1564. (b) North, M. *Synlett* **1993**, 807−820.

(18) The half-life for each of these reactions (eqs 1−3) in the presence of catalytic DMAP was less than 2 min.

(19) When conducted on a 1 mmol scale in the presence of catalyst **4** (0.5−1 mol %), the three reactions afforded 89−98% isolated yields of the desired reaction products.

(20) Optically active 2-methylazaferrocene has been prepared through classical resolution, but the level of enantiomeric purity was not determined: Bauer, K.; Falk, H.; Schlögl, K. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 135.

(21) For the synthesis of enantiomerically pure 2, see the supporting information.