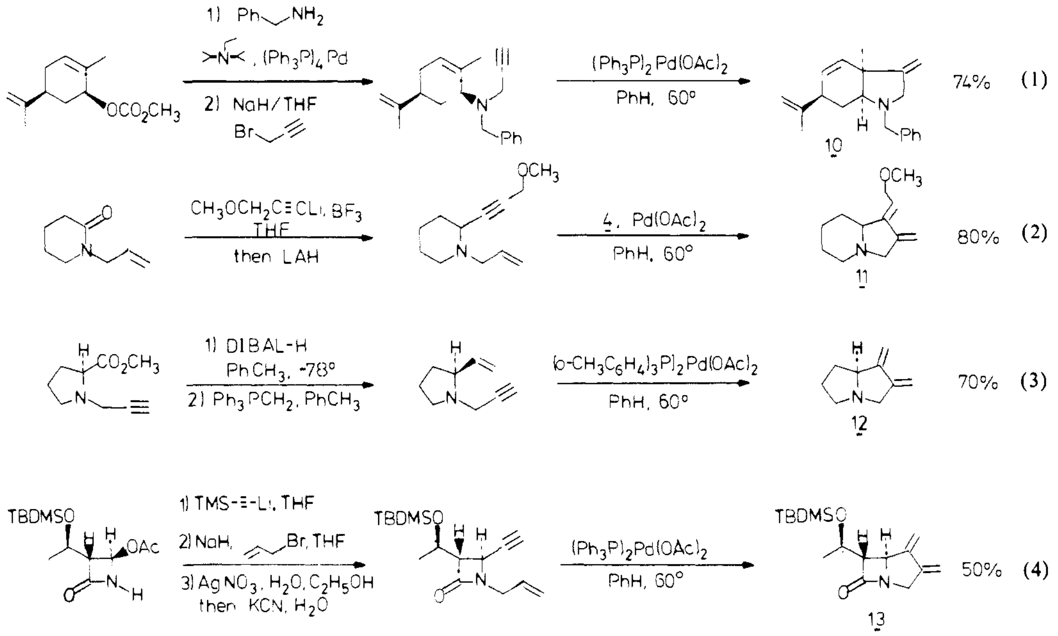
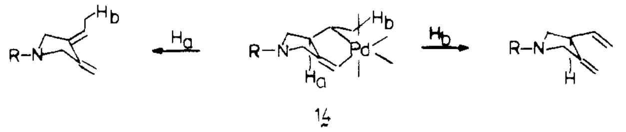
Scheme I



the bicyclic skeleton of 10[5] corresponds to the core ring of dendrobium alkaloids as represented by dendrobine itself.[9] The indolizidine skeleton of 11[5] may represent a bicyclic nucleus of diverse alkaloids.[10-13] The pyrrolizidine skeleton of 12 is the ring nucleus of many alkaloids of current interest.[1] The mildness of the reaction conditions is highlighted by the successful formation of the carbapenem nucleus of 13,[2] eq 4, by formation of the C(3)-C(4) bond.[2,14] This success is even more striking in light of a recent report where an attempt to form a similar carbapenem nucleus via a palladium-catalyzed addition of a vinyl bromide onto an olefin failed.[14]

While the mechanism of this reaction remains unknown, invoking a palladacycle such as 14 as an intermediate allows understanding of the origin of both the 1,3- and 1,4-dienes which control experiments establish as kinetic products.[4a,15,16] Whereas, the allylic hydrogen H_a in 14 represents the weakest bond and therefore the most likely bond for migration, steric hindrance in inserting into a tertiary hydrogen combined with the conformational restraints of the palladacyclopentene disfavor the process leading to the 1,3-diene in favor of inserting into H_b to give the 1,4-diene. The substantial amount of 1,3-diene formed in the case of 1 with phosphine ligands compared to the previously examined carbocycles may reflect more of the intrinsic electronic bias for H_a insertion as a result of greater conformational mobility and less steric hindrance in this heterocyclic system. Nevertheless, it could be controlled by ligand manipulation. As noted, the presence of an oxygen on the carbon bearing H_b as in 7 inhibits insertion into the C-H_b bond.[8] It appears that this electronic effect of oxygen on the regioselectivity is general and may be conveniently exploited as a regiochemical control element. The ability to generate nitrogen heterocycles under such mild conditions greatly expands the applicability of this cyclization to five-membered rings via palladium-catalyzed isomerization especially combined with Pd(0)-catalyzed alkylations to generate the requisite substrates.



14

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences, and the National Science Foundation for their generous support of our programs. We thank Drs. Burton Christensen and Frank DiNinno of Merck Sharp and Dohme Research Laboratories for a generous gift of the β-lactam starting material of eq 4.

---

(9) Yamamura, S.; Hirata, Y. *Tetrahedron Lett.* **1964**, 79. Inubushi, Y.; Sasaki, Y.; Tsuda, Y.; Nakano, J. *Ibid.* **1965**, 1519. Onaka, T.; Kamata, S.; Maeda, T.; Kawazoe, Y.; Natsume, M.; Okamoto, T.; Uchimaru, F.; Shimizu, M. *Chem. Pharm. Bull.* **1964**, *12*, 506.

(10) Clardy, J. C.; Wildman, W. C.; Hauser, F. M. *J. Am. Chem. Soc.* **1970**, *92*, 1781. Shiro, M.; Sato, T.; Koyama, H. *Chem. Ind.* (*London*) **1966**, 1229.

(11) Bick, I. R. C.; Hai, M. A. *Alkaloids* (*N.Y.*) **1985**, *24*, 113.

(12) Ripperger, H.; Schreiber, K. *Alkaloids* (*N.Y.*) **1981**, *19*, 81.

(13) Wall, M.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.

(14) For a recent example, see: Knight, J.; Parsons, P. J.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1986**, 78.

(15) Trost, B. M.; Lautens, M. *Tetrahedron Lett.* **1985**, *26*, 4887.

(16) For palladacyclopentanes, see: Diversi, P.; Ingrosso, G.; Luccherini, A.; Murtas, S. *J. Chem. Soc., Dalton Trans.* **1980**, 1633.

(17) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett* **1983**, *23*, 1719.

Asymmetric Synthesis of β-Lactams and the Carbapenem Antibiotic (+)-PS-5

David J. Hart*[†] and Chih-Shone Lee

Department of Chemistry, The Ohio State University
Columbus, Ohio 43210

William H. Pirkle, Myung Ho Hyon, and
Athanasios Tsipouras

School of Chemical Sciences, University of Illinois
Urbana, Illinois 61801

Received March 24, 1986

The condensation of ester enolates with aldimines is an effective method for preparing β-lactams.[1-8] Attempts to obtain optically

---

[†] Alfred P. Sloan Fellow, 1983-1987.

(1) Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* **1943**, *65*, 2255.

(2) Kagan, H. B.; Luche, J. L. *Bull. Soc. Chim. Fr.* **1969**, 3500.

(3) Dardoize, F.; Moreau, J.-L.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1973**, 1668.

(4) Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413.

(5) Hart, D. J.; Ha, D.-C.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4816. Hart, D. J.; Ha, D.-C. *Tetrahedron Lett.* **1985**, 5493. Georg, G. I. *Tetrahedron Lett.* **1984**, 3779. Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1984**, 1927. Cainelli, G.; Contento, M.; Gracomini, D.; Panunzio, M. *Tetrahedron Lett.* **1985**, 937.

(6) Overman, L. E.; Osawa, T. *J. Am. Chem. Soc.* **1985**, *107*, 1698.

Scheme I

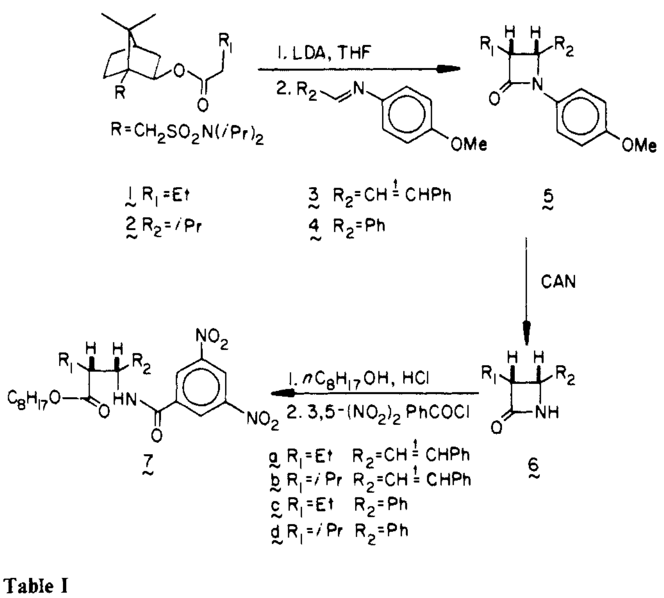


Table I

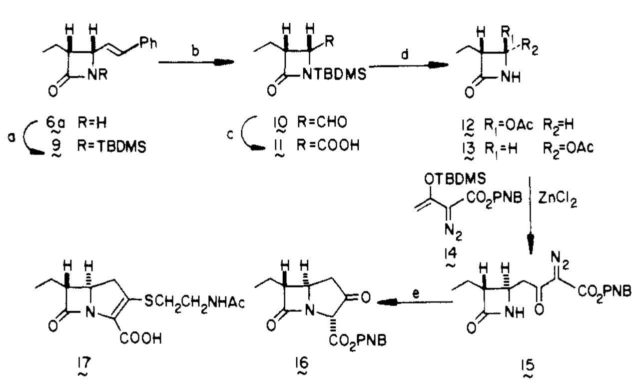
ester	imine	% yield **5**[a]	% yield **6**[b]	% ee
1	**3**	81 (10:1)	79	91[c]
2	**3**	80 (21:1)	80	82
1	**4**	88 (38:1)	85	92
2	**4**	70	86	56

[a] Combined yield of **5** and its trans diastereomer. The number in parentheses is the cis/trans ratio by ^{1}H NMR analysis. [b] Yield after chromatographic separation from trans diastereomer. [c] Average of four runs ranging from 89% to 92% ee.

active β-lactams by using menthyl esters in this process have not been extremely successful[2,4] and no asymmetric induction has been achieved by using homochiral esters of α-monosubstituted acetic acids.[9] This paper describes our initial efforts to induce asymmetry in the ester–imine condensation within the context of a synthesis of the carbapenem antibiotic (+)-PS-5 (**17**).[10]

We began by examining the reaction between the lithium enolate of butyrate **1** and cinnamaldimine **3**.[11] The choice of chiral auxilliary was based on Oppolzer's success in reactions of similar enolates with various electrophiles.[12] Treatment of **1** with lithium diisopropylamide in tetrahydrofuran followed by **3** (−70 → 25 °C, 1.5 h) gave β-lactam **5a** (81%) and isoborneol 10-diisopropylsulfonamide (95%).[13] The enantiomeric excess of **5a** could not be measured directly but was determined by a simple reaction sequence (Scheme I, Table I). Thus, ceric ammonium nitrate oxidation of **5a** and gave **6a** (79%).[14] Treatment of **6a** with 1-octanol and hydrochloric acid followed by 3,5-dinitrobenzoyl chloride gave a mixture of **7a** and its enantiomer which was analyzed chromatographically over chiral stationary phase **8**.[15,16] This analysis indicated that **7a** and, by extrapolation, **5a** and **6a** had been formed with 92% ee.

Scheme II[a]



[a] (a) *t*-BuMe$_2$SiCl, Et$_3$N, DMF; (b) O$_3$, CH$_2$Cl$_2$; Me$_2$S; (c) Jones; (d) Pb(OAc)$_4$, DMF, AcOH; (e) Rh$_2$(OAc)$_4$, PhH, Δ.

The absolute configuration of the major enantiomer was determined by completing a formal total synthesis (+)-PS-5 (**17**) as outlined in Scheme II. β-Lactam **6a** was converted to **9** (92%) by standard methodology.[17] Ozonolysis of **9** gave **10** (84%) and Jones oxidation afforded **11** (69%). Lead tetraacetate oxidation of **11** gave a 2:1 mixture of β-lactams **12** and **13** in 89% yield.[18] Treatment of the mixture of **12** and **13** with enol ether **14** and zinc chloride in dichloromethane[19,20] gave trans β-lactam **15** (63%) which had previously been prepared in configurationally pure form.[21,22] Further confirmation of absolute configuration was obtained by converting **15** to **16** (82%).[21,22] Since **16** has previously been converted to (+)-PS-5 (**17**), this constitutes the first total synthesis of this antibiotic which does not involve a resolution.[23]

The asymmetric induction observed above has some generality. Thus, esters **1** and **2**[11] react with imines **3** and **4** to give β-lactams **5a–d** with the chemical yields and percent ee's shown in Scheme I. The percent ee's for **5b–d** were obtained by the same procedure noted above for **5a**. In these cases, the assignment of absolute configuration is tentative and is based on the results obtained with **5a** and by analogy with the elution behavior of **7b–d** with the *N*-3,5-dinitrobenzoyl octyl esters derived from (*R*)- and (*S*)-4-phenyl-2-azetidinone over chiral stationary phase **8**.[15] The mechanistic details of the ester–imine condensation must be

---

(7) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 260.

(8) Ojima, I.; Inabe, S. *Tetrahedron Lett.* **1980**, 2081.

(9) Chiral imines have also been examined with modest to excellent results.[6-8] See also: Chillous, S. E. Ph.D. Thesis, The Ohio State University, 1984.

(10) Yamamoto, K.; Yoshioka, T.; Kato, Y.; Shibamoto, M.; Okamura, K.; Shimauchi, Y.; Ishikura, T. *J. Antibiot.* **1980**, *33*, 796.

(11) Esters **1** (mp 77–78 °C) and **2** (mp 85–87 °C) were prepared by sequential treatment of isoborneol 10-diisopropylsulfonamide[12] with methyl magnesium bromide and the appropriate anhydride in 90% and 84–98% yields, respectively.

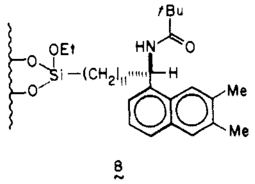
(12) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Tetrahedron Lett.* **1984**, 5885. Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212.

(13) This material was a 10:1 mixture of **5a** and the corresponding trans of β-lactam by integration of the C(4) protons which appeared at δ 4.71 (dd, J = 8.6, 5.8 Hz) and 4.28 (dd, J = 8.3, 2.3 Hz) for **5a** and its isomer, respectively.

(14) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765. β-Lactam **6a** was separated from the trans isomer at this stage by chromatography over silica gel.

(15) Pirkle, W. H.; Hyun, M. H.; Bank, B. *J. Chromatogr.* **1984**, *316*, 585. For details and generality of the analytical procedure, see: Pirkle, W. H.; Tsipouras, A.; Hyun, M. H.; Hart, D. J.; Lee, C.-S. *J. Chromatogr.* **1986**, *358*, 377.

(16) To avoid enantiomeric enrichment, no crystallizations were performed along this reaction pathway. Studies with a variety of β-lactams have shown that no cis–trans isomerization occurs during the conversion of **6** to **7**. In addition, the amido esters derived from the trans isomer of **6a** could easily be distinguished from **7** by using **8**.



8

(17) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(18) For racemic **12** and **13**, see: Kametani, T.; Honda, T.; Nakayama, A.; Sasakai, Y.; Mochizuki, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans 1* **1981**, 2228.

(19) Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, 2293.

(20) Veda, Y.; Roberge, G.; Vinet, V. *Can. J. Chem.* **1984**, *62*, 2936.

(21) Favara, D.; Omodei-Salé, A.; Consonni, P.; Depaoli, A. *Tetrahedron Lett.* **1982**, 3105.

(22) Using rotation data,[21] **15** and **16** were obtained in 80% ee and 85% ee, respectively. The decrease in % ee going from **6a** to these compounds may be the result of partial racemization in proceeding from **11** → **12** + **13** → **15**. Alternatively, small impurities in **15** and **16** (detected by NMR) may be responsible for the apparent decrease in percent ee.

(23) **Note Added in Proof**: An alternate enantioselective synthesis of **17** was reported after acceptance of this article: Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, 3119. For related studies see: Hsiao, C.-N.; Ashburn, S. P.; Miller, M. J. *Tetrahedron Lett.* **1985**, 4855.

clarified before a convincing rationale for the observed asymmetric induction can be offered.

In conclusion, an encouraging step toward incorporating asymmetry into ester-imine condensations has been achieved. This approach to optically active β-lactam is versatile in design and its utility has been demonstrated with a synthesis of (+)-PS-5 (**17**). Studies with other homochiral esters are in progress.

Acknowledgment. We thank the National Institutes of Health for their generous support (AI-21074) and Richard Weisenberger of The Ohio State University Campus Chemical Instrument Center for mass spectral analyses.

Direct Evidence for Spillover of Hydrogen from Ruthenium to Copper in Supported Cu–Ru/SiO$_2$ Catalysts: A Study by NMR of Chemisorbed Hydrogen

T. S. King and Xi Wu

Department of Chemical Engineering, Iowa State University
Ames Laboratory, Energy and Minerals Resources
Research Institute,[†] Ames, Iowa 50011

B. C. Gerstein*

Department of Chemistry and Ames Laboratory
Energy and Minerals Resources Research Institute[†]
Iowa State University, Ames, Iowa 50011

Received February 12, 1986

Bimetallic catalysts have received intense attention, both because of their industrial utility for catalytic reforming and the possibility of using them as model systems in fundamental investigations of catalytic phenomena.[1-5] Hydrogen chemisorption has been used to characterize these systems. Specifically, on supported Cu–Ru catalysts, the number of surface Ru atoms has been inferred from titration with hydrogen under the assumption that hydrogen does not dissociatively adsorb on copper. The bases for the use of this experiment lie both in experiment and theory: the activation energy for dissociative chemisorption of hydrogen on Cu has been found experimentally to be about 5 kcal mol^{-1}.[6] The activation energy for dissociative adsorption of hydrogen on Cu is a multivalued function of the orientation and vibrational–translational–rotational state of the hydrogen molecule as it approaches the surface and of the surface plane of the metal involved. Theoretical calculations have led to values both much less and much greater than that quoted above, depending upon the above-mentioned parameters, but having an average value of 5 kcal mol^{-1}.[7] Hydrogen does not dissociatively chemisorb on pure copper at room temperature.[8] Spillover of hydrogen from Ru to Cu would invalidate this method of quantifying surface Ru.[9,10]

Studying the (0001) surface of single-crystal Ru having varying amounts of Cu deposited on the surface, various researchers[11-17] have found that hydrogen does not spill over on Cu at temperatur below 150 K, but Goodman et al.[17] have found evidence f spillover of atomic H onto Cu in such a bimetallic single-cryst system at 230 K.

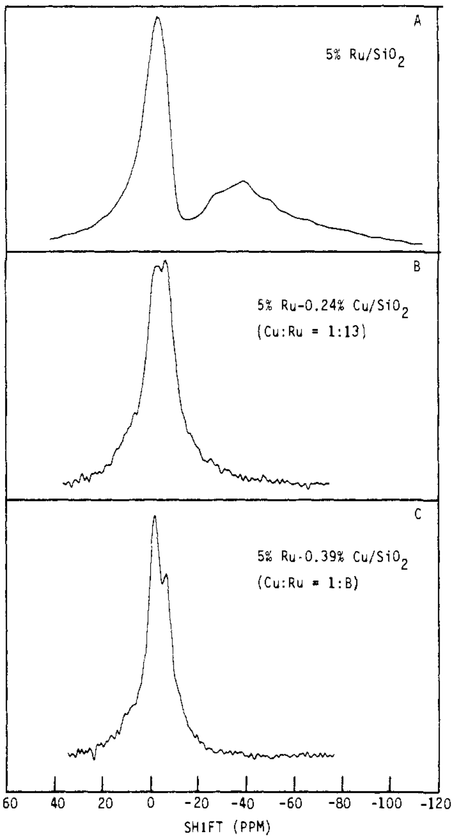


Figure 1. NMR of hydrogen under a single pulse excitation for hydrog on (a) 5% Ru/SiO$_2$, (b) 5% Ru–0.24% Cu/SiO$_2$, and (c) 5% Ru–0.39 Cu/SiO$_2$. Liquid water was used as reference and all spectra we normalized to the height of the highest peak.

Studies of supported Cu–Ru catalysts have not demonstrate spillover of hydrogen from Ru to Cu. The present work mak this demonstration for a number of Cu–Ru catalysts support on SiO$_2$, using nuclear magnetic resonance (NMR) of hydrog on the substrates. The NMR spectroscopy of chemisorbed h drogen on supported Ru has shown that the chemical shift of t hydrogen does not depend upon coverage and that the isotrop shift of hydrogen on Ru is found to be about 50 ppm upfield fro the proton resonance in Me$_4$Si.[18]

The home-built NMR spectrometer, similar to one previous described,[19] was operated at 220 MHz for proton resonance. Pro *Q*s were set between 50 and 200, depending upon the desir experimental response. A *Q* of 50, corresponding to a pro ringdown time of approximately $21Q/3f_0 = 1.8$ μs and having receiver dead time of 500 ns,[20] was used to determine that no li broader than 20 kHz was present in the samples under study. T 90° broadcast pulse at probe *Q* of 50 was 2.5 μs long, corr sponding to a broadcast bandwidth of 200 kHz at the 3-dB poir A Biomation 2805 transient recorder was used for digitizati of the NMR signal. The minimum dwell was 0.2 μs, which w used for initial experiments to determine the spectral width of t sample under investigation. A dwell of 5 μs and *Q* of 200 we used for experiments on hydrogen on the supported bimetal Cu–Ru catalyst, in which the signal-plus-noise to noise ratio w

---

[†] Operated for the U.S. Department of Energy by Iowa State University under Contract W-7405-Eng-82.

(1) Sinfelt, J. H. *Bimetallic Catalysts—Discoveries, Concepts, and Applications*; Wiley: New York, 1983.

(2) Biloen, P.; Heller, J. N.; Verbeek, H.; Dautzenberg, F. M.; Sachtler, W. M. H. *J. Catal.* **1980**, *63*, 112.

(3) Menon, P. G.; Froment, G. F. *J. Mol. Catal.* **1984**, *25*, 59.

(4) Sachtler, W. M. H. *J. Mol. Catal.* **1984**, *25*, 1.

(5) Christmann, K.; Ertl, G. *J. Mol. Catal.* **1984**, *25*, 31.

(6) Balooch, M.; Cardillo, M. J.; Miller, D. R.; Stickney, R. E. *Surf. Sci.* **1974**, *46*, 358.

(7) Lee, C.-Y.; Depristo, A. E. *J. Chem. Phys.* **1986**, *84*, 485.

(8) Greuter, F.; Plummer, E. W. *Solid State Commun.* **1983**, *48*, 37.

(9) Rouco, A. J.; Haller, G. L.; Oliver, O. J.; Kimball, C. *J. Catal.* **1983**, *84*, 297.

(10) Haller, G. L.; Reasasco, D. E.; Wang, J. *J. Catal.* **1983**, *84*, 477.

(11) Christmann, K.; Ertl, G.; Shimizu, H. *J. Catal.* **1980**, *61*, 397.

(12) Shimizu, H.; Christmann, K.; Ertl, G. *J. Catal.* **1980**, *61*, 412.

(13) Vickerman, J. C.; Christmann, K.; Ertl, G. *J. Catal.* **1981**, *71*, 175.

(14) Vickerman, J. C.; Christmann, K. *Surf. Sci.* **1982**, *120*, 1.

(15) Vickerman, J. C.; Christmann, K.; Ertl, G.; Heiman, P.; Himpsel, F. J.; Eastman, D. E. *Surf. Sci.* **1983**, *134*, 367.

(16) Yates, J. T. Jr.; Peden, C. H. F.; Goodman, D. W. *J. Catal.* **19** *94*, 576.

(17) Goodman, D. W.; Peden, C. H. F. *J. Catal.* **1985**, *95*, 321.

(18) Sheng, T.-C.; Gay, I. D. *J. Catal.* **1982**, *77*, 53.

(19) Cheung, T. T. P.; Worthington, L. E.; Murphy, P. D. B.; Gerste B. C. *J. Magn. Reson.* **1980**, *41*, 158.

(20) Stoll, M. E. *A Simple, Fast Recovery, Low-Noise Receiver-Amplif for Pulsed NMR Experiments*, Sandia Laboratories Report SAND80-87

0002-7863/86/1508-6056$01.50/0