

Microwave-Assisted Rapid and Simplified Hydrogenation^{1,†}Bimal K. Banik,[‡] Khaled J. Barakat,[§] Dilip R. Wagle,[⊥] Maghar S. Manhas, and Ajay K. Bose*

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Received July 30, 1998

Catalytic transfer hydrogenation has been conducted under microwave irradiation in open vessels using high-boiling solvents such as ethylene glycol (bp 198 °C) as the microwave energy transfer agent. Reduction of double bonds and hydrogenolysis of several functional groups were carried out safely and rapidly (3–5 min) at about 110–130 °C with 10% Pd/C as an efficient catalyst and ammonium formate as the hydrogen donor. Diverse types of β -lactam synthons were prepared by the reduction of ring substituents containing alkene and alkylidene groups or conjugated unsaturated esters. Cleavage of the β -lactam ring by hydrogenolysis of the N–C₄ bond of 4-aryl-2-azetidinones was a facile reaction with 10% Pd/C as the catalyst; but no ring scission occurred when Raney nickel catalyst was employed. Dehalogenation of aromatic compounds was also successful with ammonium formate and Pd/C catalyst. Hydrogenolysis of phenylhydrazones of methyl benzoylformate gave the methyl ester of phenylglycine in excellent yield. The techniques described here for microwave assisted hydrogenation are safe, rapid, and efficient and are suitable for research investigation as well as for undergraduate and high school laboratory exercises.

Introduction

Laboratory-scale catalytic hydrogenation² plays a key role in chemical research and the synthesis of organic intermediates. Any simplification of this operation is, therefore, potentially useful provided the total process is safe and ecologically friendly. Industrial-scale hydrogenation, which has special requirements, will not be considered here.

In most organic laboratories it is a common practice to conduct catalytic reduction or hydrogenolysis under 40 psi pressure in a commercially available apparatus. Pure hydrogen gas from a cylinder fitted with an appropriate valve system is required. The air in the hydrogenator has to be completely removed either by flushing the system for several minutes with hydrogen, or, by repeatedly pumping the system down to a low pressure and refilling with hydrogen. Laboratories in

remote locations may not have all of these facilities available at short notice. Many teaching laboratories are often not equipped with multiple units for frequent use by groups of students.

Some hydrogenation processes are more effective under higher pressure (1000 psi or more) and thus require more elaborate equipment. Considerable amounts of hydrogen are wasted during the flushing of such equipment. Hydrogen and air mixtures are potentially hazardous if flames or sparks are produced in the neighborhood of hydrogenators.

Results and Discussion

Catalytic Transfer Hydrogenation. In recent years a few laboratories have started to employ catalytic transfer hydrogenation (CTH).³ This is a safe and simple operation in which a catalyst and hydrogen gas are replaced with a catalyst and a hydrogen donor such as cyclohexane,⁴ hydrazine,⁵ formic acid,⁶ ammonium formate,⁷ cyclohexadiene,⁸ and phosphinic acid,⁹ sodium hypophosphite.¹⁰ This type of hydrogenation is usually conducted in flasks fitted with a magnetic stirrer and a reflux condenser. Ethyl alcohol is a widely used solvent for CTH.

[†] Dedicated to Prof. Sasanka C. Bhattacharyya on the occasion of his 80th birthday.

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Recently we¹¹ have demonstrated that catalytic transfer hydrogenation can be conducted very rapidly and in essentially quantitative yield inside an unmodified domestic microwave oven. We present here details of our technique and indicate the scope of reduction and hydrogenolysis achieved under microwave irradiation.

Microwave-Assisted Reactions. Two pioneering papers¹² appeared in 1986 on remarkable acceleration of many organic reactions upon irradiation with microwaves (2450 MHz). Since then, a number of laboratories, including our own, have been studying microwave-assisted chemical synthesis.¹³ Some research groups conduct their reactions in sealed tubes, which can withstand several atmospheres of pressures, but occasional explosions have been reported due to the high pressure from a rapid rise in temperature.

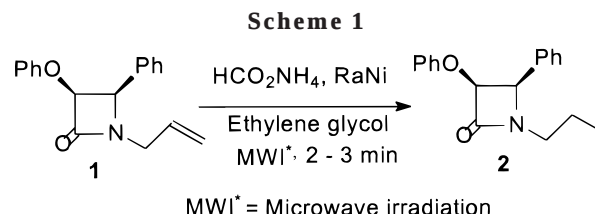
A few laboratories^{14a} avoid the risk of explosions by conducting microwave-assisted reactions at ambient pressure by irradiating reactants adsorbed on solid supports such as clay, alumina, or silica gel.

Special microwave ovens have been designed by some groups to prevent explosions caused by run away reactions.^{14b} We prefer to conduct experiments in open vessels in inexpensive, unmodified, domestic microwave ovens. A wide variety of compounds have been synthesized using our microwave-induced organic reaction enhancement (MORE) chemistry techniques.¹⁵

These techniques are also very convenient for rapid and safe catalytic transfer hydrogenation experiments.

MORE Chemistry Techniques. We have developed an unconventional experimental set up for conducting organic reactions to take advantage of the special nature of microwave energy.

Erlenmeyer flasks or beakers with loose covers are preferred reaction vessels for ambient pressure reactions in unmodified domestic microwave ovens. The upper parts of these vessels remain cool since glass is transpar-



ent to microwaves. The solvent (microwave energy transfer agent) should be polar and with a suitably high boiling point at least 20 or 30° higher than the projected reaction temperature.

Domestic microwave ovens produce 2450 MHz radiation at a rate that is controlled to a moderate degree by an "on-off" cycle. For finer control of the microwave energy input into small-scale reaction mixtures, it is convenient to use a "heat sink"—a beaker of water placed next to the reaction vessels inside the oven. This heat sink with appropriate amounts of water captures a significant amount of the microwave energy thereby reducing the energy supplied to the reaction mixture.

Since microwave energy is absorbed by all of the polar molecules and ions at the same time, no stirrer is required for reaction mixtures in shallow layers. Flasks with ground glass joints, heating mantles, and the other standard equipment of a conventional organic laboratory are not needed. Reflux condensers are unnecessary since liquids are maintained well below their boiling points when MORE chemistry techniques are used.

Microwave-Assisted CTH. Ethylene glycol (bp 198 °C) or more eco-friendly 1,3-propanediol, bp 210–212 °C, as the solvent and ammonium formate as the hydrogen donor form an excellent combination for catalytic transfer hydrogenation under microwave irradiation. Hydrazine hydrate was used as the hydrogen donor in a few cases but ammonium formate proved to be more convenient. Most of our studies on CTH reactions have been conducted with Pd/C (10%) catalyst. A few experiments were catalyzed with Ra/Ni catalyst. Since Pd/C catalyst is sometimes a pyrophoric powder, a specific protocol for CTH experiments was developed for ensuring safety (see the Experimental Section). Representative examples of CTH experiments are described below.

Reduction and Hydrogenolysis of β -Lactams. At the beginning of these studies, test runs with ammonium formate reduction in the presence of 10% Pd/C showed that oleic and linoleic acids (on a 1–2 g scale), were completely reduced to stearic acid in only 1–2 min at about 110–130 °C. We were, therefore, encouraged to undertake a detailed examination of CTH experiments of various types.

In the course of studies on substituted β -lactams as synthons for natural products, various β -lactams with unsaturated substituents were prepared. Some of these had been reduced in the past by conventional low-pressure hydrogenation in the presence of Raney nickel or Pd/C catalysts. Now the microwave-assisted CTH technique was applied to several of these compounds using commercially available Raney nickel catalyst when reduction products were obtained in about 80% yield or better in a few minutes. Thus, **1** with an N-allyl group was reduced to **2** with an N-propyl group (Scheme 1). The vinyl group at C-3 was converted to the ethyl group during the reduction of **3** to **4** (Scheme 2).

When 10% Pd/C was used as the catalyst the β -lactam **5** underwent selective hydrogenolysis of the O-benzyl

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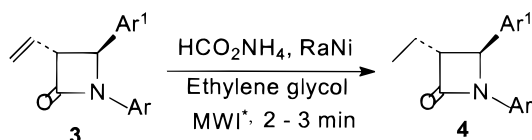
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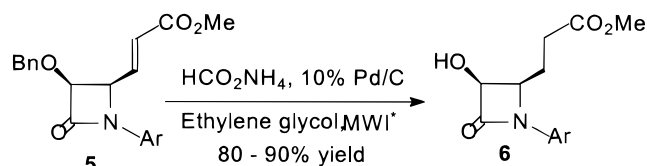
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Scheme 2



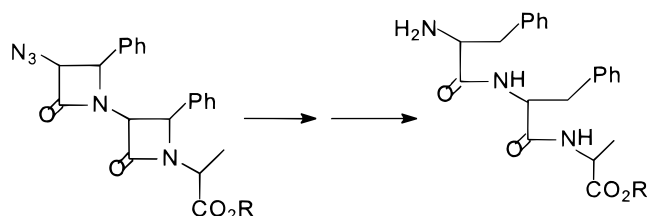
- a Ar = Ph, Ar¹ = Ph
 b Ar = PMP, Ar¹ = Ph
 c Ar = PMP, Ar¹ = 2-furyl
 PMP = *p*-methoxyphenyl

Scheme 3



- a Ar = PMP
 b Ar = Bn
 Bn = CH₂C₆H₅

Scheme 4

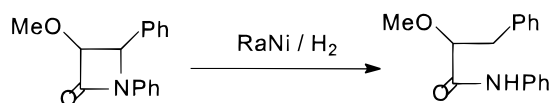


group and reduction of the unsaturated ester to a saturated ester side chain to give the β -lactam **6** which retained the *N*-benzyl group intact (Scheme 3).

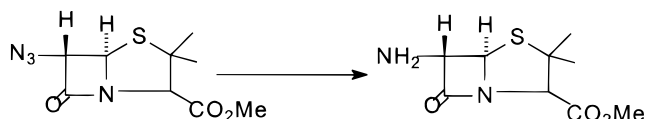
Using conventional catalytic hydrogenation (ambient pressure of hydrogen at 50 °C in methanol with Pd/C as the catalyst), Ojima et al.¹⁶ have cleaved *N*-C₄ bonds in 4-phenyl-2-azetidinones to produce phenylalanine derivatives (for example, see Scheme 4) in a convenient fashion and in high yield. We¹⁷ had observed earlier that, in the presence of a large excess of Raney nickel catalyst and hydrogen, 3-methoxy-1,4-diphenyl-2-azetidinone underwent β -lactam scission to provide a small amount of the anilide of α -methoxy- β -phenylpropionic acid (Scheme 5). However, under milder conditions, cleavage of the β -lactams ring does not occur. For several years now mild catalytic hydrogenation (5–10% Pd/C catalyst, room temperature) under conventional conditions have been the standard method in our laboratory for the reduction of α -azido- β -lactams to α -amino- β -lactams (for example, see Scheme 6).

Recently we¹¹ have studied microwave assisted catalytic transfer hydrogenolysis at 120–130 °C using 10% Pd/C as the catalyst. Rapid scission of 4-phenyl-2-azetidinones was observed in every case. The *N*-benzyl group of the β -lactam **9** was not hydrogenolyzed, but the *O*-Bn group at C-3 was converted to an OH group; alkenes (**11**, **13**, and **15**) were reduced to alkyl groups (Scheme 7). The reduction product was obtained in high

Scheme 5



Scheme 6



yield and in a few minutes. It is useful to note that under these conditions Ra-Ni did not cause cleavage of the β -lactam ring in **3** (See Scheme 2).

The hydrogenation of 4-styryl-2-azetidinones (**17** and **19**) showed an interesting pattern (Scheme 8): the alkene groups were reduced but there was only partial β -lactam ring scission under the conditions used with Pd/C catalyst. Thus, the two products (**18a,b**), namely, the saturated β -lactam and the open chain amide, were formed in approximately 6:4 ratio. It would appear that the vinylogous aryl group led to the scission of the C₄-N bond, but if the styryl group were reduced first, ring cleavage was of course no longer possible. The relative rates of reduction of the styryl group and hydrogenolysis of the β -lactam ring can therefore be expected to be influenced by the level of microwave irradiation.

Stereoselective Preparation of β -Lactam Synthons. A convenient procedure has been developed in our laboratory¹⁹ for resolving hydroxy- β -lactams (e.g., **23**) by the formation of two diastereomeric glycosides via the Ferrier reaction involving a glucal (e.g., **22**) (Scheme 9). The determination of the stereochemistry of the glycosidic linkages in these compounds was necessary. The problem appeared to have a reliable solution if the unsaturation could be easily removed, and the ¹H NMR spectra of the chair-shaped pyranosides could be studied. CTH reaction using 10% Pd/C was tested on **24a** and found to be successful: the unsaturation in the sugar moiety was removed without ring fission of the β -lactam to give **25a**. Allylic deacetoxylation also occurred to a limited extent and gave **25b**.

Microwave-assisted CTH reaction of **26** resulted in the formation of a reduced and deacetylated product **27**. The proton NMR spectrum of this compound was useful for assigning the stereochemistry of the glycosidic bond.

In the course of studies on carbapenem synthons, a series of monocyclic β -lactams were generated with an exo-alkene group at C-3.^{15b,20} These conjugated double bonds could be reduced easily under microwave-assisted CTH reaction (Scheme 10). Furthermore, because of the essentially planar shape of the β -lactam ring and the bulk of the substituent at C4, the hydrogenation was stereospecific: only *cis* β -lactams were obtained because the catalyst surface was always placed *trans* to the large substituent at C4. Such stereospecificity is of course highly desirable from the point of view of atom economy.

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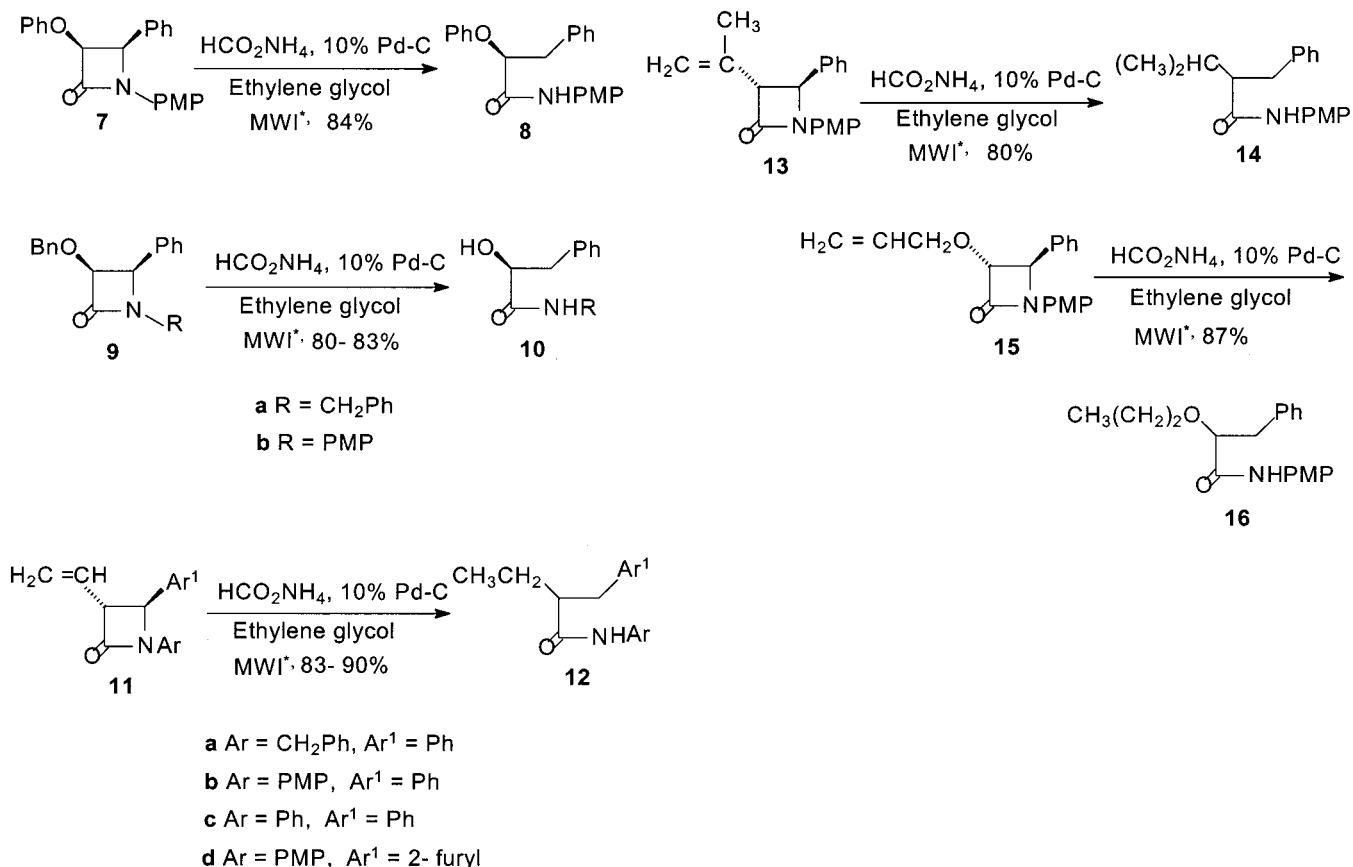
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Scheme 7



Dehalogenation Reaction. Rajagopal and Spatola²¹ have studied CTH methods for the dehalogenation of aromatic compounds. They have observed that the order of addition of reagents plays an important role in the dehalogenation process. According to them, the catalytic activity of the Pd/C catalyst is improved significantly when it is activated before the addition of the hydrogen acceptor. Thus, the dechlorination of 4-chlorotoluene is completed in 90 min at room temperature when ammonium formate is added to the catalyst after the introduction of the substrate. In contrast it required only 15 min for complete reduction if the sequence of the addition of the formate and the halo-compound were reversed.

We²² have observed, however, that when microwave-assisted CTH reactions are used for dehalogenation, the end products and the time for complete reduction are independent of the order of addition of the reactants. Several β -lactams (such as, **28** and **33**) and isoquinoline derivatives (e.g., **31** were smoothly dehalogenated (Scheme 11) in a few minutes.

During microwave-assisted dehalogenation of chlorobenzene and *p*-bromoanisole, the formation of biphenyls (Scheme 12) in about 10% yield was detected. No coupling to dimeric products was observed during the dehalogenation of 1-bromonaphthalene and 9-bromoanthracene.

Rajagopal and Spatola²³ studied the kinetics of the dehalogenation of *o*-chlorotoluene by HCO₂Na–EtOH–H₂O and DCO₂Na–EtOD–D₂O and noted a kinetic

isotope effect. On the basis of these findings they suggested that transfer of the formyl hydrogen of the donor to the catalyst surface is the rate-determining step. Wiener et al,²³ have observed a significant kinetic isotope effect in the decomposition of sodium formate (HCO₂Na–H₂O vs DCO₂Na–D₂O) catalyzed by 5% Pd/C at 35 °C. But, they²⁴ concluded from their study on the reduction of nitro-toluene with formate that there was no kinetic isotope effect.

Synthesis of Amines. Hydrazones are formed in excellent yield in minutes under microwave irradiation of ketones such as **35** and with hydrazine or phenylhydrazine in ethylene glycol solution. Such hydrazones can be converted to amines by microwave-assisted CTH reaction. Thus, methyl benzoylformate (**35**) gave the phenylhydrazone (**36**) in 90% yield in 6 min. Reduction of (**36**) during 4 min of microwave irradiation in the presence of ammonium formate and 10% Pd/C led to the amine (**37**) which was acetylated to give methyl *N*-acetyl phenylglycinate (**38**) in excellent yield (Scheme 13).²²

Summary and Outlook

In summary, we have devised safe, rapid, and efficient techniques for conducting catalytic hydrogenation and hydrogenolysis using just beakers and flasks and unmodified domestic microwave ovens. Runaway reactions under microwave irradiation leading to possible explosion are prevented by operating under ambient pressure in open systems. The source of hydrogen for this catalytic transfer hydrogenation method was ammonium

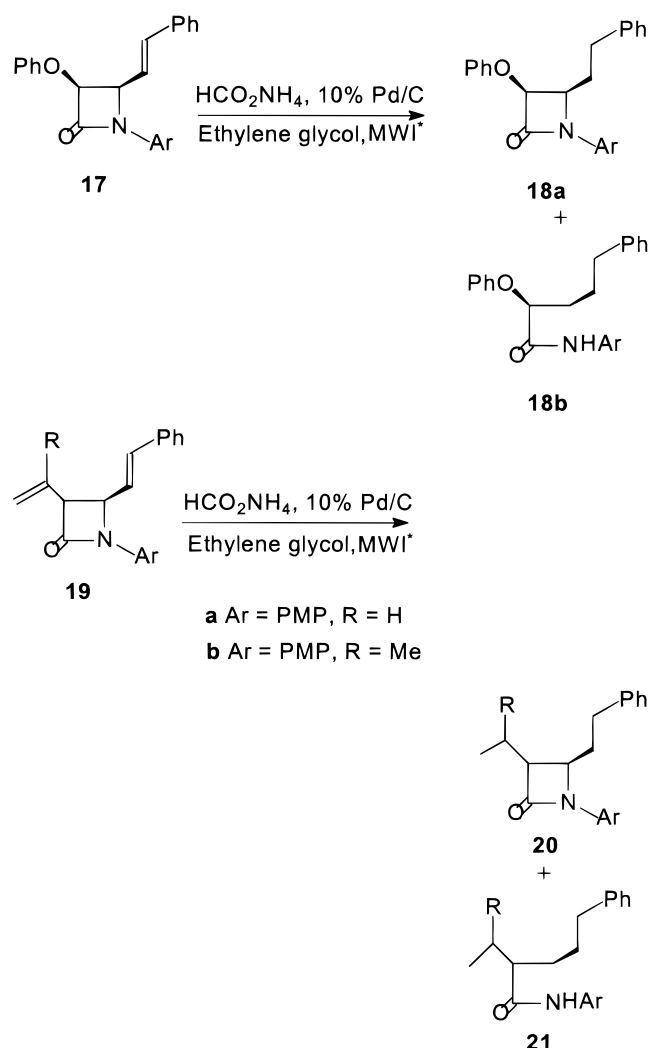
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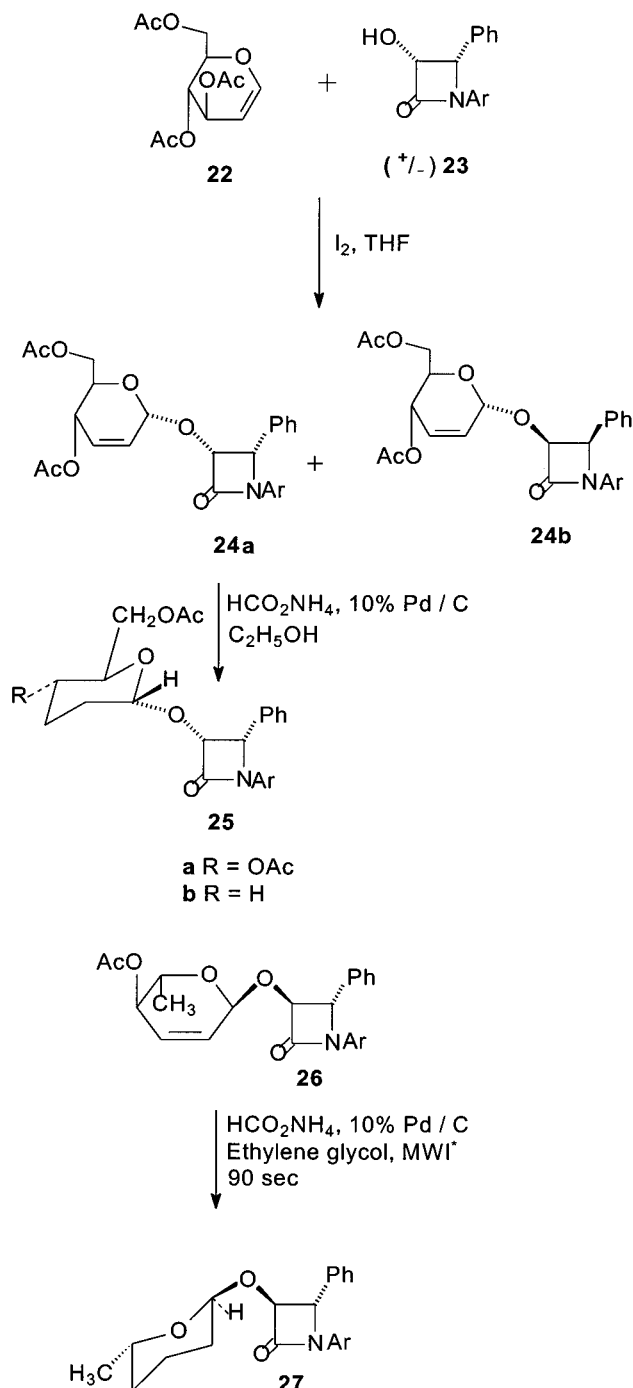
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Scheme 8



Scheme 9



formate, which is inexpensive and easy to store and transport—unlike pure hydrogen gas under pressure in cylinders.

Field tests at Stevens Institute of Technology and neighboring inner city high schools have shown that the microwave-assisted techniques described here for reduction and hydrogenolysis are safe and suitable for research investigations as well as laboratory exercises for college and pre-college students. With minor modifications these techniques could also be used for many industrial processes.

Recent publications show increasing use of catalytic transfer hydrogenation methods. Thus, Albanese et al.²⁵ have found these methods to be the best for the hydrogenolysis of 4-nitrobenzyl esters of cephalosporin antibiotics without isomerizing or reducing the conjugated double bond. Knochel and co-workers²⁶ have reported new efficient catalysts for enantioselective transfer hydrogenations. There is every reason to believe that these and other new developments²⁷ can be enhanced by the application of microwave-assisted techniques described by us here.

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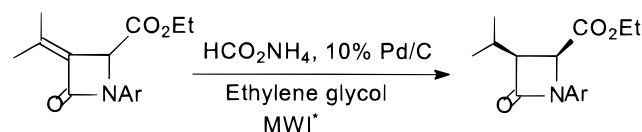
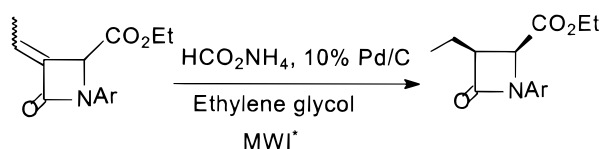
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Experimental Section

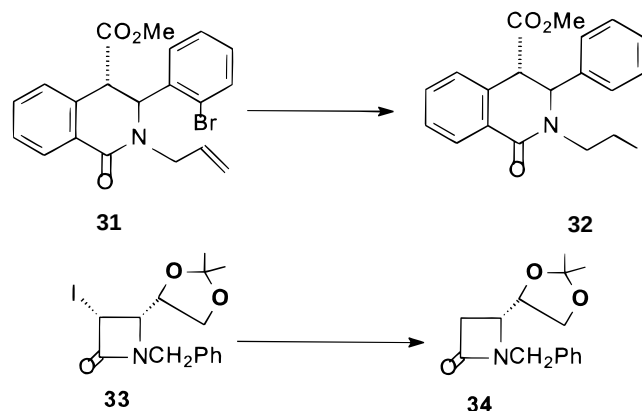
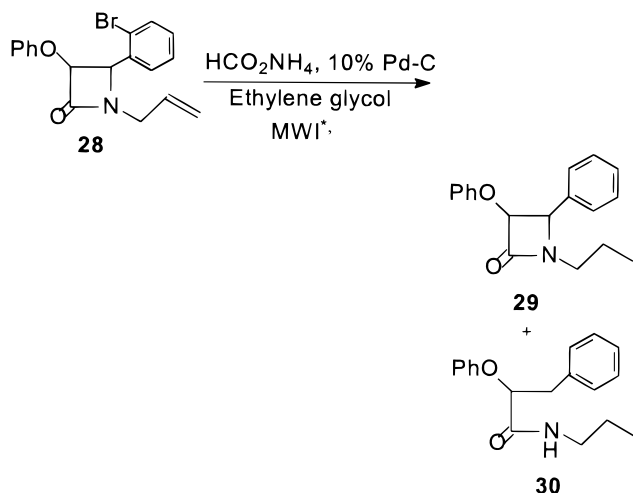
Melting points were determined with a Mel-temp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 1310 instrument. NMR spectra were recorded on a Bruker AC-20 spectrometer using TMS as an internal standard. Chemical ionization mass spectra were recorded on a Biospect. instrument using CH₄ as the reagent gas. Thin-layer chromatography was performed with Whatman plates, and the spots were detected by UV. Microanalyses were performed by Schwartzkopf Microanalytical Laboratory, NY. Compounds described here are racemates.

General Procedure for β -Lactams. The reaction of substituted acetyl chlorides with Schiff bases and tertiary amines (triethylamine for conventional experiments; *N*-methylmorpholine for reactions under microwave irradiation) was used for the synthesis of acetoxy-, benzyloxy-, methoxy-, and

Scheme 10



Scheme 11

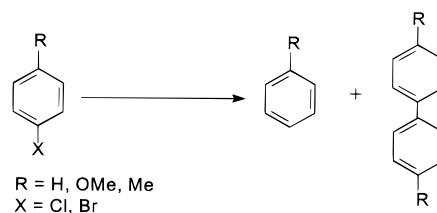


phenoxy-substituted β -lactams (for example, **1**, **5**, **17**, and **28**). For the preparation of α -vinyl- β -lactams (for example, **3** and **19**), α , β -unsaturated acid chlorides were substituted for acetyl chlorides and the reaction was conducted under microwave irradiation.²⁸

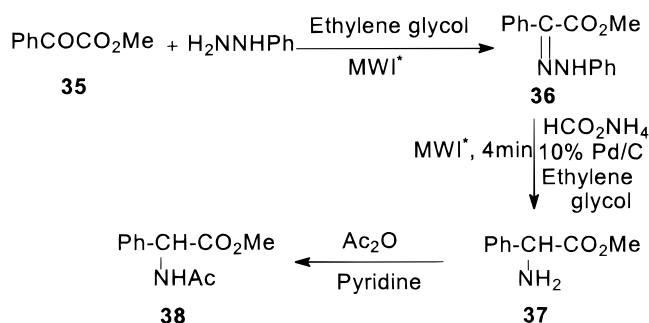
Schiff bases were prepared by the reaction of an aldehyde with an amine in methylene chloride solution in the presence of molecular sieves.²⁹

Almost all of the β -lactams used as starting material for this study are known compounds described in the literature. Many of these β -lactams have been reported in our earlier publications.³⁰

Scheme 12



Scheme 13



General Procedure for CTH Reaction. On the basis of several years of experience, we have found the following protocol to be safe for conducting catalytic transfer hydrogenation. Caution must be exercised, however, since some of the catalysts are pyrophoric; also mixtures of hydrogen and air can cause an explosion if ignited by a spark or a flame. An unmodified domestic microwave oven (600–1000 W) placed in a hood should be used. The reaction vessel should be a beaker or an Erlenmeyer flask of fairly large size. A beaker of water should be placed near this reaction vessel to serve as a “heat sink” to provide a finer control on the amount of microwave energy input into the hydrogenation mixture. Water absorbs microwave energy very efficiently and thereby reduces the amount of energy absorbed by the reaction mixture. The approximate amount of water to be used can be determined with a trial run involving only the solvent and without the catalyst.

The desired temperature of the solvent should rise to 110–120 °C in about 3 min. The catalyst should be quickly introduced into the reaction vessel and covered with the solvent (such as ethylene glycol, bp 198 °C) and made into a slurry by gentle swirling motion of the beaker or the conical flask. The compound to be reduced is dissolved in the solvent (ethylene glycol or 1,3-propanediol) and then added to the reaction vessel. The hydrogen donor (such as ammonium formate) is added now. Microwave irradiation for the pre-determined period of time to reach a temperature of 110–130 °C should be applied. The microwave oven door should be opened, and the temperature of the reaction mixture should be checked to be in the desired range.

The oven door should be closed and irradiation with microwave should be resumed for another 3–4 min. The microwave oven should be switched off, and the reaction vessel

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removed from the oven. Careful decantation of the reaction mixture after cooling followed by the addition of glycol to the reaction vessel would preserve the catalyst for the next experiment.

It is customary in our laboratory to place a beaker cover or a filter funnel on top of the reaction vessel to prevent any accidental spillage. Since glass is nearly transparent to microwaves, the upper parts of the beaker of flask serves as a condenser for any small amounts of vapors formed. After the hydrogenation the reaction mixture was cooled and then filtered. The filtrate was diluted with water and extracted with ethyl acetate, and the organic layer was washed with water. Evaporation of the solvent from the organic layer (dried over anhydrous Na_2SO_4) followed by crystallization gave the pure product in 80–90% yield. We have observed that the optimal ratio of the catalyst (10% Pd/C) to substrate is 0.3:1 by weight for each reducible group. Five equivalents of ammonium formate for each reducible group gave good results.

2: yield 75%; mp 108 °C; IR (CH_2Cl_2) 1740 cm^{-1} ; ^1H NMR 7.30–6.69 (m, 10H), 5.43 (d, $J = 4.30$ Hz, 1H), 4.93 (d, $J = 4.32$ Hz, 1H), 3.53–3.39 (m, 1H), 3.00–2.86 (m, 1H), 2.03–1.82 (m, 2H), 1.11 (t, $J = 7.37$ Hz, 3H); CIMS (CH_4 gas) m/z 282 ($\text{M} + \text{H}$) $^+$; Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_2$: C, 76.84; H, 6.80; N, 4.97. Found: C, 76.67; H, 6.67; N, 4.89.

4a: yield 80%; mp 118 °C; IR (CH_2Cl_2) 1740 cm^{-1} ; ^1H NMR 7.35–6.99 (m, 10H), 4.67 (d, $J = 2.34$ Hz), 3.10–3.01 (m, 1H), 2.03–1.82 (m, 1H), 1.11 (t, $J = 7.37$ Hz, 3H); CIMS (CH_4 gas) m/z 252 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}$: C, 81.24; H, 6.81; N, 5.57. Found: C, 80.99; H, 6.67; N, 4.89.

4b: yield 85%; mp 109 °C; IR (CH_2Cl_2) 1740 cm^{-1} ; ^1H NMR 7.32 (s, 5H), 7.15 (d, 2H), 6.69 (d, 2H), 4.54 (d, $J = 2.27$ Hz, 1H), 3.74 (s, 3H), 2.94–2.90 (m, 2H), 2.07–1.69 (m, 2H), 1.04 (t, 3H). Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_2$: C, 76.84; H, 6.80; N, 4.97. Found: C, 76.62; H, 6.92; N, 5.0.

4c: yield 85%, oil; IR (neat) 1740 cm^{-1} ; ^1H NMR 7.37 (brs, 1H), 7.25 (d, $J = 8.9$ Hz, 2H), 6.7 (d, $J = 8.9$ Hz, 2H), 6.38–6.29 (m, 2H), 4.66 (d, $J = 2.38$ Hz, 1H), 3.71 (s, 3H), 3.30–3.31 (m, 1H), 2.01–1.72 (m, 2H), 1.05 (t, $J = 7.41$ Hz, 3H); CIMS (CH_4 gas) m/z 272 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3$: C, 70.83; H, 6.31; N, 5.16. Found: C, 70.59; H, 6.11; N, 5.02.

6a: yield 90%; mp 109–110 °C; IR (Nujol) 3300, 1730 cm^{-1} ; ^1H NMR 7.41 (d, 2H), 6.92 (d, 2H), 5.04 (d, $J = 4.9$ Hz, 1H), 4.37 (m, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 2.61 (m, 2H), 2.12 (m, 2H); CIMS (NH_3 reagent gas) m/z 297 ($\text{M} + 18$) $^+$. Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_5$: C, 60.20; H, 6.10; N, 5.01. Found: C, 59.61; H, 6.26; N, 5.00.

6b: yield 85%; oil, IR (Nujol) 3350, 1730 cm^{-1} ; ^1H NMR 7.40 (s, 5H), 5.23 (m, 1H), 4.94 (t, 1H), 4.67 (d, $J = 15.4$ Hz, 1H), 4.20 (d, $J = 15.4$ Hz, 1H), 3.75 (s, 3H), 3.24 (m, 1H), 2.41 (m, 2H), 2.0 (m, 2H); CIMS (NH_3 reagent gas) m/z 281 ($\text{M} + 18$) $^+$.

8: yield 84%; mp 123–125 °C; IR (Nujol) 3300, 1640 cm^{-1} ; ^1H NMR 7.80 (brs, 1H), 7.00 (m, 14H), 4.93 (dd, $J_1 = J_2 = 3.91$ Hz, 1H), 3.8 (s, 3H), 3.33 (d, $J_1 = J_2 = 14.16$ Hz, 2H); ^{13}C NMR 168.80, 157.25, 136.40, 129.84, 128.32, 126.28, 122.42, 122.14, 115.82, 114.23, 80.16, 55.49, 38.97. Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{NO}_3$: C, 76.00; H, 6.05; N, 4.03. Found: C, 75.55; H, 6.12; N, 3.99.

10a: yield 83%; mp 89 °C; IR (Nujol) 3300, 1630 cm^{-1} ; ^1H NMR 7.25 (m, 10H), 4.23 (m, 2H), 3.40 (brs, 1H), 3.12 (dd, 2H), 2.64 (dd, 1H); CIMS (NH_3 reagent gas) m/z 273 ($\text{M} + 18$) $^+$. Anal. Calcd for $\text{C}_{26}\text{H}_{17}\text{NO}_2$: C, 75.29; H, 6.66; N, 5.49. Found: C, 75.13; H, 6.69; N, 5.58.

10b: yield 80%; mp 128 °C; IR (Nujol) 3300, 1640 cm^{-1} ; ^1H NMR 8.20 (brs, 1H), 7.51–6.80 (m, 9H), 4.4 (m, 1H), 3.85 (s, 3H), 3.42 (dd, $J_1 = 7.80$ Hz, $J_2 = 7.80$ Hz, 1H), 3.09 (dd, $J_1 = 8.30$ Hz, $J_2 = 14.10$ Hz, 1H), 2.63 (d, $J = 8.30$ Hz, 1H); CIMS (NH_3 reagent gas) m/z 289 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3$: C, 66.43; H, 6.51; N, 4.48. Found: C, 66.65; H, 5.84; N, 4.76.

12a: yield 83%; mp 113–115 °C; IR (Nujol) 1640 cm^{-1} ; ^1H NMR 7.10–6.65 (m, 9H), 3.73 (s, 3H), 2.82 (m, 2H), 2.21 (m, 1H), 1.75 (m, 2H), 0.90 (t, 3H); CIMS (NH_3 reagent gas) m/z 301 ($\text{M} + 18$) $^+$. Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_2$: C, 76.32; H, 7.42; N, 4.84. Found: C, 75.80; H, 7.79; N, 4.84.

12b: yield 80%; mp 107 °C; IR (CH_2Cl_2) 1640 cm^{-1} ; ^1H NMR 7.58 (s, 1H), 7.34–7.15 (m, 3H), 6.81 (d, $J = 6.61$ Hz, 2H), 6.25–6.22 (m, 1H), 6.02–6.01 (m, 1H), 3.73 (s, 3H), 3.05–2.68 (m, 2H), 2.58–2.44 (m, 1H), 1.87–1.43 (m, 2H), 0.97 (t, $J = 7.35$ Hz, 3H); CIMS (CH_4 gas) m/z 258 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.01; H, 7.38; N, 5.19.

14: yield 80%; IR (Nujol) 1650 cm^{-1} ; ^1H NMR 7.18–7.02 (m, H), 6.71–6.64 (m, 2H), 3.67 (s, 3H), 2.85 (d, $J = 6.81$ Hz, 1H), 2.06–1.93 (m, 2H), 1.03 (d, $J = 6.26$ Hz, 3H), 0.97 (d, $J = 6.18$ Hz, 3H); CIMS (CH_4 gas) m/z 258 ($\text{M} + \text{H}$) $^+$.

16: yield 87%; mp 69 °C; IR (Nujol) 3350, 1730 cm^{-1} ; ^1H NMR 8.30 (brs, 1H), 7.51–6.81 (m, 9H), 4.02 (dd, $J_1 = 3.5$ Hz, $J_2 = 7.59$ Hz, 1H), 3.85 (s, 3H), 3.42 (m, 2H), 3.03 (dd, $J_1 = 7.7$ Hz, $J_2 = 3.9$ Hz, 2H), 1.59 (m, 2H), 0.90 (t, 3H); CIMS (NH_3 reagent gas) m/z 314 ($\text{M} + \text{H}$) $^+$.

18a: yield 60%; mp 70 °C; IR (Nujol) 1740 cm^{-1} ; ^1H NMR 7.09 (m, 14H), 5.90 (d, $J = 4.9$ Hz, 1H), 4.72 (m, 1H), 3.84 (s, 3H), 2.63 (m, 2H), 1.81 (m, 2H); CIMS (NH_3 reagent gas) m/z 399 ($\text{M} + 18$) $^+$. Anal. Calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_3$: C, 77.21; H, 6.16; N, 3.75. Found: C, 76.39; H, 6.61; N, 3.81.

18b: yield 30% oil; IR (CH_2Cl_2) 3300, 1640 cm^{-1} ; ^1H NMR 7.42–7.16 (m, 13H), 6.84 (d, $J = 8.95$ Hz, 2H), 3.77 (s, 3H), 2.64 (t, $J = 7.19$ Hz, 1H), 2.33 (t, $J = 6.97$ Hz, 2H), 1.72 (m, 4H); CIMS (CH_4 reagent gas) m/z 376 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{24}\text{H}_{25}\text{NO}_3$: C, 76.76; H, 6.71; N, 3.73. Found: C, 76.51; H, 6.53; N, 3.81.

20a: yield 40%; mp 72 °C; IR (CH_2Cl_2) 1740 cm^{-1} ; ^1H NMR 7.36–7.17 (m, 7H), 6.86 (d, $J = 8.81$ Hz, 2H), 4.15–4.08 (m, 1H), 3.78 (s, 3H), 3.42–3.20 (m, 1H), 2.83–2.57 (m, 2H), 2.32–1.67 (m, 4H), 1.17 (t, $J = 7.43$ Hz, 3H); CIMS (CH_4 gas) m/z 326 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_3$: C, 77.64; H, 7.49; N, 4.52. Found: C, 77.76; H, 7.40; N, 4.57.

20b: yield 35%; mp 50 °C; IR (CH_2Cl_2) 1740 cm^{-1} ; ^1H NMR 7.36 (m, 7H), 6.85 (d, $J = 6.7$ Hz, 2H), 4.16 (dd, $J_1 = 5.54$ Hz, $J_2 = 11.23$ Hz, 1H), 3.84 (s, 3H), 3.08 (dd, $J_1 = 5.63$ Hz, $J_2 = 10.00$ Hz, 1H), 2.82–2.65 (m, 2H), 2.27–1.88 (m, 3H), 1.28 (d, $J = 6.54$ Hz, 3H), 1.06 (d, 6.39 Hz); CIMS (CH_4 gas) m/z 324 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.71; H, 7.64; N, 4.39.

21a: yield 40%; mp 87 °C; IR (CH_2Cl_2) 3320, 1640 cm^{-1} ; ^1H NMR 7.79 (s, 1H), 7.43 (d, $J = 8.9$ Hz, 2H), 7.32–7.15 (m, 5H), 6.85 (d, $J = 8.9$ Hz, 2H), 3.79 (s, 3H), 2.63 (t, $J = 6.78$ Hz, 2H), 2.08–2.06 (m, 1H), 1.79–1.50 (m, 6H), 0.94 (t, $J = 7.34$ Hz, 3H); CIMS (CH_4 gas) m/z 312 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_2$: C, 77.13; H, 8.09; N, 4.49. Found: C, 77.00; H, 8.37; N, 4.34.

21b: yield 35%; mp 121 °C; IR (CH_2Cl_2) 3350, 1650 cm^{-1} ; ^1H NMR 7.41 (d, $J = 8.77$ Hz, 2H), 7.35–7.14 (m, 6H), 6.83 (d, $J = 9$ Hz, 2H), 3.78 (s, 3H), 2.63 (t, $J = 7.07$ Hz, 2H), 1.91–1.51 (m, 6H), 0.98 (d, $J = 5.76$ Hz, 3H); CIMS (CH_4 gas) m/z 326 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_2$: C, 77.49; H, 8.36; N, 4.30. Found: C, 77.77; H, 8.35; N, 4.44.

29: mp 108 °C; IR (CH_2Cl_2) 1740 cm^{-1} ; ^1H NMR 7.30–6.60 (m, 10H), 5.43 (d, $J = 4.31$ Hz, 1H), 4.93 (d, $J = 4.32$ Hz, 1H), 3.53–3.39 (m, 1H), 3.00–2.86 (m, 1H), 1.57–1.46 (m, 2H), 0.89 (t, $J = 7.32$ Hz, 3H); CIMS (CH_4 gas) m/z 282 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_2$: C, 76.84; H, 6.80; N, 4.97. Found: C, 76.67; H, 6.67; N, 4.89.

30: IR (CH_2Cl_2) 1650 cm^{-1} ; ^1H NMR 7.40–6.51 (m, 11H), 4.83 (dd, $J_1 = 6.80$ Hz, $J_2 = 10.70$ Hz, 1H), 2.99–2.48 (m, 3H), 2.52–2.48 (m, 1H), 1.43–1.28 (m, 2H), 0.75 (t, $J = 7.42$ Hz, 3H).

32: IR (Nujol) 1660 cm^{-1} ; ^1H NMR 8.37–8.32 (m, 1H), 7.59–7.22 (m, 8H), 5.49 (brs, 1H), 4.36–4.19 (m, 1H), 4.12 (brs, 1H), 3.69 (s, 3H), 3.01–2.87 (m, 1H), 1.93–1.74 (m, 2H), 1.08 (t, $J = 7.33$ Hz, 3H). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_3$: C, 74.28; H 6.54; N, 4.33. Found: C, 74.39; H, 6.41; N, 4.38.

34: oil; IR (Nujol) 1750 cm^{-1} ; ^1H NMR 7.2 (s, 5H), 4.75 (d, $J = 16.0$ Hz, 1H), 4.20 (d, $J = 16.0$ Hz, 1H), 4.0 (m, 1H), 3.65–3.40 (m, 2H), 3.01 (dd, $J_1 = 5$ Hz, $J_2 = 16$ Hz, 1H), 2.55 (dd, $J_1 = 5$ Hz, $J_2 = 16$ Hz, 1H), 1.30 (s, 3H), 1.20 (s, 3H); CIMS (NH_3 reagent gas) m/z 279 ($\text{M} + 18$) $^+$.

Methyl Phenylglycinate (37). Methyl benzoyl formate (35) (6.1 mmol), phenyl hydrazine (7 mmol) and ethylene glycol

(5 mL) were placed in an Erlenmeyer flask (125 mL). The mixture was heated for 6 min at low power setting. The desired phenyl hydrazone (**36**) precipitated out on scratching under ice cold condition. It was filtered, washed with hexane, and dried (yield 90%, mp 86–88 °C).

Ammonium formate (200 mg) and 10% Pd/C (100 mg) were added to phenylhydrazone (**36**) (2 mmol) in ethylene glycol (5 mL). The mixture was irradiated for 4 min. After the usual workup, the amine (**37**) was isolated (92%): IR 1710 cm^{-1} ; ^1H NMR (CDCl_3) 7.40 (s, 5H), 4.6 (s, 1H), 3.61 (s, 3H), 2.0 (brs, 2H); ^{13}C NMR 174.19, 140.11, 128.56, 127.77, 126.69, 59.15, 52.11; CIMS (NH_3 reagent gas) m/z 183 ($M + 18$) $^+$. A portion of (**37**) was acetylated with acetic anhydride and pyridine to afford (**38**): mp 85–86 °C; IR (Nujol) 1700 cm^{-1} ; ^1H NMR 8.9 (brs, 1H), 7.31 (s, 5H), 5.60 (d, $J = 8.24$ Hz, 1H), 3.70 (s, 3H), 2.0 (s, 3H); ^{13}C NMR 168.79, 138.02, 128.83, 127.15, 119.98,

61.90, 56.56, 24.33; CIMS (NH_3 reagent gas) m/z 225 ($M + 18$) $^+$.

Acknowledgment. This research was supported by Stevens Institute of Technology (in part) and by the Howard Hughes Medical Institute [through a grant to our Chemical Biology Education Enhancement (CBEE) Program]. For technical help we thank Keiko Tabei and Raza Naqvi, undergraduate research participants Gregory Morriello, Kavita Mistry, and Madhumeeta Patel, and pre-college research trainees Ingrid Callejas and Varsha Valecha (supported by Project SEED of the American Chemical Society).

JO981516S