JOC*Article*

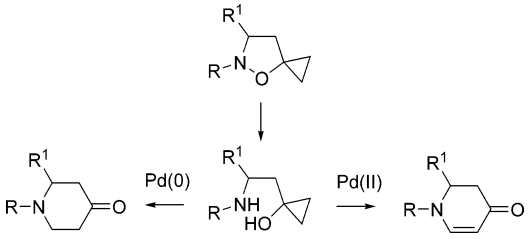
Two-Step Metal-Mediated Transformation of Isoxazolidine-5-spirocyclopropanes into Pyridone Derivatives†

Julia Revuelta, Stefano Cicchi, and Alberto Brandi*

Dipartimento di Chimica Organica "Ugo Schiff", Università di Firenze and ICCOM (Istituto per la Chimica dei Composti Organometallici), CNR, via della Lastruccia 13, 50019 Sesto Fiorentino (FI), Italy

alberto.brandi@unifi.it

Received April 1, 2005

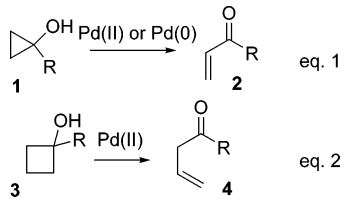


The two-step metal-catalyzed overall transformation of isoxazolidine-5-spirocyclopropanes into the corresponding dihydro- and tetrahydropyridones is described. The first step is the chemoselective reduction of the N−O bond of the isoxazolidine ring preserving the fragile cyclopropanol moiety while the second transformation is the Pd(II) or Pd(0) conversion of the β-aminocyclopropanol derivatives into the final compounds. The scope and limitations of this strategy are described.

Introduction

The reactivity of the cyclopropane ring, due to its high level of strain, has found many applications in synthetic organic chemistry, and it is so peculiar of this three-membered ring that it can be better considered as a real functional group rather than a simple structural unit.[1] Most of its chemistry concerns with ring-opening reactions mediated by a variety of reagents.[1] The presence of electron-donor substituents on the cyclopropane ring enhances its reactivity and allows a high control on the regioselectivity of the ring opening reaction.[2] Recently, several works dealing with the palladium-catalyzed ring cleavage of hydroxy substituted small cycles were published. $Pd(OAc)_2$ was reported to catalyze the ring cleavage of cyclopropanols **1**,[3] or cyclobutanols **3**, into α,β- and β,γ-unsaturated ketones **2** and **4**, respectively (Scheme 1).

SCHEME 1



This transformation can find interesting application onto substrates bearing other functionalities which are reactive toward the palladium intermediates formed in the reaction[4] or toward the double bond: for example, an intramolecular Michael reaction would afford cyclic compounds. Recently, we have started a research project aimed to the transformation of isoxazolidine-5-spirocyclopropanes mediated by transition metals, trying to conjugate the wide structural variability and easiness of assembly of isoxazolidines with the reactivity of the cyclopropane ring. These compounds have been studied thoroughly by our group, mainly for their thermal rearrangement into tetrahydropyridone derivatives **6** (Scheme 2, eq 1),[5] and this transformation has found wide ap-

† Dedicated to Professor Armin de Meijere on the occasion of his 65th birthday.

(1) (a) *Houben-Weyl, Methods of Organic Chemistry, Carbocyclic Three Membered Ring Compounds*; de Meijere, A., Ed.; Thieme: Stuttgart, 1997; Vol. E1. (b) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597−2632. (c) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165−198. (d) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, *74*, 605−623.

(2) (a) Ming, Y.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321−347. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151−1196. (c) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73−135.

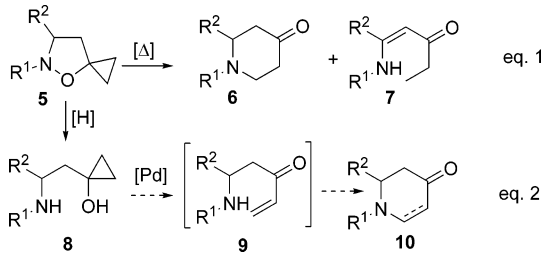
(3) (a) Park, S.-B.; Cha, J. K. *Org. Lett.* **2000**, *2*, 147−149. (b) Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* **2000**, 629−630.

(4) (a) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645−2646. (b) Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 1455−1465.

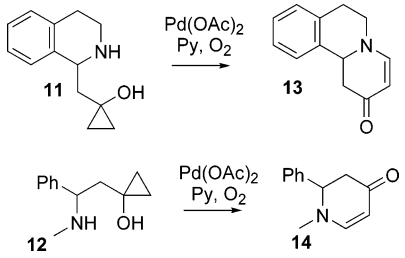
(5) Brandi, A.; Cordero, F. M.; De Sarlo, F.; Goti, A.; Guarna, A. *Synlett* **1993**, 1−8.

10.1021/jo050640q CCC: $30.25
Published on Web 06/16/2005

SCHEME 2



SCHEME 3



plication in the syntheses of several natural compounds and interesting heterocyclic structures.[6]

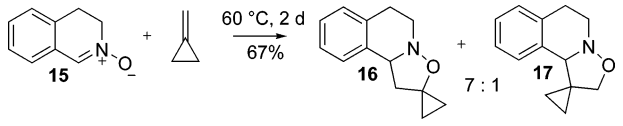
The remark that the simple reduction of the N−O bond of **5** affords the corresponding β-aminocyclopropanol **8** led us to explore the reactivity of this rather unknown class of cyclopropanols with the scope of building up a domino process affording pyridone derivatives **10** (Scheme 2, eq 2). The preliminary results obtained demonstrated that this domino process is possible and affords pyridone derivatives as expected, but with the added bonus of bringing about a new oxidative process leading, selectively, to dihydropyridones.[7] In fact, the complex $Pd(OAc)_2$/Py in combination with atmospheric oxygen as stoichiometric oxidant, as originally reported by Uemura[4] and Cha,[3] catalyzed the transformation of amino alcohols **11** and **12** to the corresponding dihydropyridone **13** and **14**, respectively (Scheme 3), and not to the expected saturated isomers.

Several issues remained to be addressed to make the overall process efficient and to give insight into the mechanistic aspects of this transformation. The reduction of the N−O bond of isoxazolidine-5-spirocyclopropanes was not a trivial task because of the known reactivity of the cyclopropane moiety under reducing conditions. It was then necessary to develop a new reliable procedure for this reduction. Finally, it was necessary to optimize the reaction conditions for the final transformation mediated by $Pd(OAc)_2$ and to demonstrate its generality and mechanistic implications.

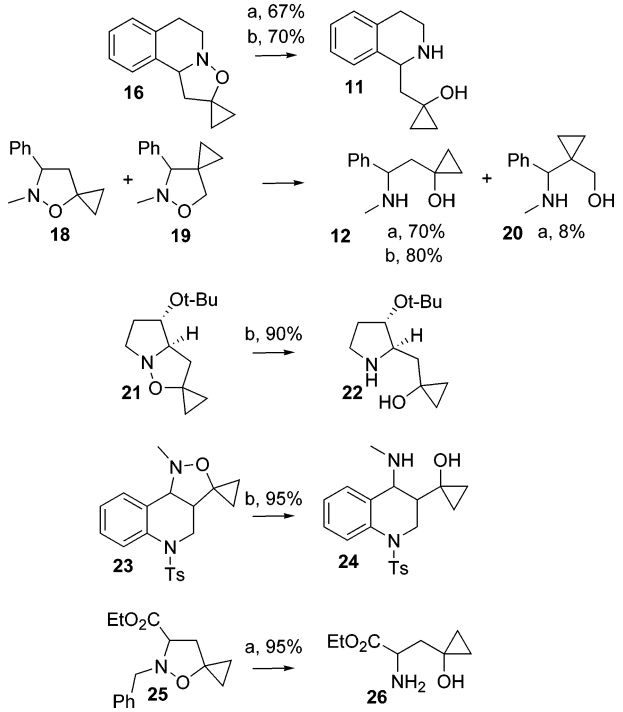
Results and Discussion

All isoxazolidine-5-spirocyclopropanes used as starting material in this work are obtained through 1,3-dipolar cycloaddition reactions of the proper nitrone to methylenecyclopropane and most of these reactions have been previously described. The isoxazolidine **16** is new and was obtained by cycloaddition of 3,4-dihydroisoquinoline 2-oxide (**15**) to methylenecyclopropane together with its 4-spirocyclopropane regioisomer **17** (Scheme 4).

SCHEME 4



SCHEME 5 [a]



[a] Key: (a) $Pd(OH)_2$/C, H_2; (b) SmI_2, 0.1 M THF solution.

The reduction of the N−O bond of simple isoxazolidines can be performed using a variety of different reagents;[8] however,the presence of a spirocyclopropane group α to the oxygen atom makes this reaction troublesome. $Mo(CO)_6$, for example, which was able to reduce 5-spirocyclopropane isoxazolines to cyclopropyl ketones,[9] failed to afford the analogous transformation for the corresponding isoxazolidine derivatives, although isoxazolidines are generally reduced by this reagent.[10] Several other reducing agents were tested, but always afforded complex mixtures of compounds. In two cases, for isoxazolidines **16** and **18**[11] (Scheme 5), $Pd(OH)_2$/C in the presence of H_2 atmosphere proved useful for the desired transformation. Due to the difficult separation of the two regioisomers, compound **18** was reduced in mixture with its 4-spirocyclopropane isomer **19** and the mixture of the two amino alcohols, **12** and **20**, respectively, was easily separated. Unfortunately, the extension of this procedure to other substrates was not possible.

(6) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213−1269.
(7) Cicchi, S.; Revuelta, J.; Zanobini, A.; Betti, M.; Brandi, A. *Synlett* **2003**, 2305−2308.
(8) Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J. Goti, A. *Org. Lett.* **2003**, *5*, 1773−1776 and references therein.
(9) Guarna, A.; Guidi, A.; Goti, A.; Brandi, A.; De Sarlo, F. *Synthesis* **1989**, 178.
(10) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351−3354.
(11) Brandi, A.; Garro, S.; Guarna, A.; Goti, A.; Cordero, F. M.; De Sarlo, F. *J. Org. Chem.* **1988**, *53*, 2434.

The known ability of SmI_2 to reductively cleave the N−O bond in several substrates[12] suggested the use of SmI_2 as reducing agent for these compounds. Treatment of isoxazolidines **16**, **18**, **21**[13] and **23**[14] with an excess of a commercial 0.1 M solution of SmI_2 allowed a smooth and efficient conversion to the corresponding amino-cyclopropanols (Scheme 5).[15]

The compared yields for the $Pd(OH)_2/C$ and the SmI_2 reduction of isoxazolidines **16** and **18** are reported in Scheme 5. In the case of isoxazolidines **21** and **23** the catalytic Pd hydrogenation was unsuccessful. The workup procedure needed for the reduction with SmI_2 caused partial hydrolysis of the ester group[15] and this made the procedure not useful for the reduction of isoxazolidine **25**. The amino alcohol **26**, however, was efficiently obtained by hydrogenolysis, although the complete deprotection of the amino group was achieved. The reduction with SmI_2, therefore, nicely complements the catalytic hydrogenolysis and even if the latter is an experimentally easier procedure, the use of SmI_2 allowed the transformation of more reactive isoxazolidine-5-spirocyclopropanes.

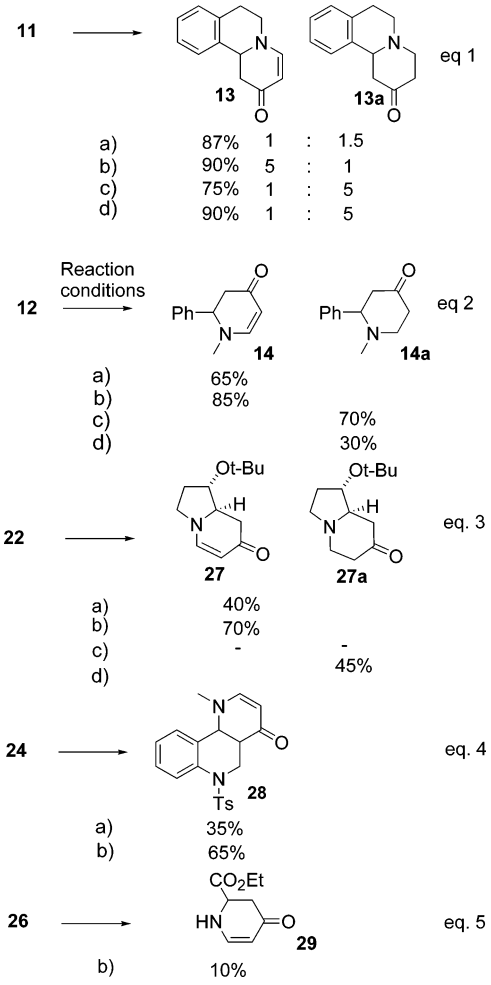
Subjecting amino alcohols **22**, **24**, and **26** to the conditions previously used provided dihydropyridones **27** and **28** in moderate yields (eqs 3 and 4, reaction conditions a, Scheme 6), confirming the same trend observed before. In contrast the primary amine **26** (eq 5, Scheme 6) did not cyclize under these conditions. Therefore, under $Pd(OAc)_2$/Py catalyzed conditions, secondary-amine-γ-cyclopropanols undergo a new process consisting of a rearrangement of the cyclopropanol followed by oxidative ring closure.

An elevated pressure of molecular oxygen to 0.5 MPa (Scheme 6, reaction conditions b), improved yields remarkably and even the primary amine **26** could be cyclized to compound **29**, albeit in low yields. Interestingly, in a singular case where a mixture of dihydro- and tetrahydropyridone was observed (eq 1, Scheme 6) the new conditions also increased the selectivity from (1:1.5) to (5: 1). The use of a pressure apparatus and a more complex experimental procedure of this variation therefore is justified by the higher efficiency of the transformations.

The structures of all compounds were easily assigned from their ^1H and ^{13}C spectra. The characteristic signals of the enaminone moiety also proved that the double bond is on the unsubstituted side of the piperidone ring.[7]

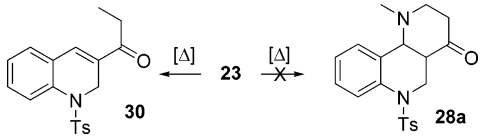
Other Pd(II) salts used in the process were less effective. $PdCl_2$ generally gave lower yields,[7] but interestingly transformed **11** cleanly to **13** (Scheme 6, eq 1) without concomitant formation of **13a**. In contrast PdI_2 was completely inactive[7] for both **11** and **12**. Pyridine as a base was superior to a hindered aliphatic amine, i.e., DIPEA.

SCHEME 6 [a]



[a] Reaction conditions: (a) $Pd(OAc)_2$ 10 mol %, Py, air, toluene, 80 °C; (b) Pd $(OAc)_2$ 10 mol %, Py, O_2 (5 atm); (c) Pd $(OAc)_2$ 10 mol %, LiOAc, $Cu(OAc)_2$; (d) $Pd_2(dba)_3$ 10 mol %.

SCHEME 7



As previously reported,[14] the thermal rearrangement of **23** peculiarly did not cyclize to **28a**, but afforded **30** as the main component of a complex mixture via cyclopropyl ring cleavage and elimination of methylamine (Scheme 7). In contrast, the process herein reported, afforded **28** in moderate to good yields, thus substantiating the first successful transformation of **23** into a hitherto unknown 4a,5,6,10b-tetrahydro-1*H*-benzo[*h*][1,6]naphthyridin-4-one tricyclic fused system (Scheme 6, eq 4).

Dihydropyridones with an unprotected nitrogen functionality could be obtained by thermal rearrangement of spirocyclopropane isoxazolines.[16] We now succeeded in

(12) Nitro compounds: Kende, S.; Mendoza, J. S. *Tetrahedron Lett*. **1991**, *32*, 1699−1702. Hydroxylamines and hydroxamic acids: Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995**, *36*, 7419−7422. 1,2-Oxazine: Pulz, R.; Al-Harrasi, A.; Reissig, H.-U. *Org. Lett.* **2002**, *4*, 2353−2355. Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995**, *36*, 7419−7422. Isoxazoles and isoxazolines: Natale, N. R. *Tetrahedron Lett.* **1982**, *23*, 5009−5012. Fan, X.; Zhang, Y. *Tetrahedron Lett.* **2002**, *43*, 7001−7003. Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 1587−1590. Jung, S. H.; Lee, J. E.; Koh, H. Y. *Bull. Korean Chem. Soc.* **1998**, *19*, 33−35.

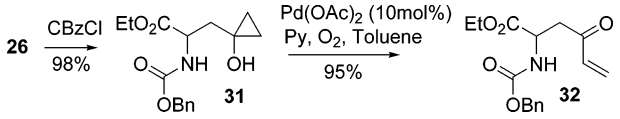
(13) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743−4748.

(14) Cordero, F. M.; Pisaneschi, F.; Goti, A.; Ollivier, J.; Salun, J.; Brandi, A. *J. Am. Chem. Soc.* **2000**, *122*, 8075−8076.

(15) Revuelta, J.; Cicchi, S.; Brandi, A. *Tetrahedron Lett*. **2004**, *45*, 8375−8377.

(16) Brandi, A.; Cordero, F. M.; de Sarlo, F.; Goti, A.; Guarna, A. *Synlett* **1993**, 1−8.

SCHEME 8



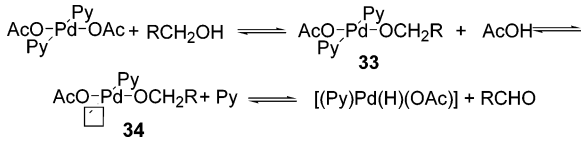
the direct synthesis of *N*-unprotected dihydropyridone **29** by cyclization of aminocyclopropanol **26**, albeit yields were low (eq 5, Scheme 6). Attempts to improve the yields, even by using stoichiometric amounts of $Pd(OAc)_2$ remained unsuccessful. To study the cyclization process, **26** was converted into the corresponding CBz derivatives **31** (Scheme 8).

Due to the lowered nucleophilicity of the nitrogen, the intermediate ketone **32** could be trapped almost quantitatively under the usual conditions. Subsequent cyclization would explain generation of a saturated tetrahydripyridone, as singularly observed in Scheme 6, eq 1, but not the formation of dihydropyridones being predominantly observed in all other reactions. Oxidation of a tetrahydropyridone to the corresponding dihydropyridone with IBX, $Hg(OAc)_2$, MCPBA or DDQ has been described,[17] but palladium catalysis was unsuccessful as reported by Murahashi.[18] Furthermore, this course would not explain the complete regioselectivity of the double bond formation. In fact, reacting **14** under the usual conditions gave no evidence for the formation of **14a**.

To further elucidate the course of the reaction, we attempted to replace molecular oxygen in this Wacker-like process[19] by other stoichiometric oxidants. Copper acetate has often been used as a stoichiometric oxidant in Pd(II) catalyzed reactions. Therefore, the same reactions were run using $Cu(OAc)_2$ (2 equivalents), LiOAc (3 equivalents) as base in the presence of 10 mol % of $Pd(OAc)_2$ in DMF (reaction conditions c, Scheme 6).[20] This variation fundamentally changed the outcome of the reaction. Transformation of amino alcohols **11** and **12** afforded the corresponding tetrahydropyridones **13a** and **14a** in good yields. Conversely, application of these reaction conditions to amino alcohols **22** and **24** resulted in complex mixtures from which neither the dihydro nor the tetrahydro derivatives could be isolated.

As recently demonstrated, Pd(0) also transforms cyclopropanols into the corresponding α,β-unsaturated ketones.[3b] Consequently, $Pd_2(dba)_3$ in CH_3CN at 50 °C was applied according to the literature (reaction condition d, Scheme 6). Again, the saturated derivatives **13a**, **14a**, and **27a**[13] (eqs 1−3, reaction condition d, Scheme 6) were obtained predominantly, if not exclusively. The reaction of amino alcohol **24** furnished a complex mixture with compound **30** as the main product (50% yield), as already observed with the thermal rearrangement of isoxazolidine **23** (vide supra). Compound **26**, with the primary amine group, failed to give any product under these conditions.

SCHEME 9



Based on our findings, we propose a mechanistic explanation for this novel Pd(II) catalyzed domino ring opening/cyclization/oxidation of γ-aminocyclopropanols. This hypothesis is strongly supported by a recent publication about the aerobic alcohol oxidation catalyzed by $Pd(OAc)_2$/pyridine,[21] including one example of an oxidative ring-cleavage of a *tert*-cyclobutanol to an β,γ-unsaturated ketone.[4]

This transformation is proposed to proceed through the formation of a Pd alcoholate species **33** which, upon elimination of a pyridine molecule, affords a coordinatively unsaturated species **34** that undergoes the β-hydride elimination providing the carbonyl compound and the reduced Pd species, that is subsequently reoxidated by molecular oxygen (Scheme 9).

Pyridine appears to play a key role in stabilizing the Pd(II) species and facilitates the reoxidation step after the reductive elimination. Although a full characterization of the reactive species has not been possible so far, also other authors postulated a Pd alcoholate species as key intermediate in the oxidative ring cleavage of tertiary cyclobutanols[4] and cyclopropanols.[3] A similar mechanism might be expected when applied to amino cyclopropanols, even if the primary or secondary amino functionality could participate in the complexation of the Pd nucleus (Scheme 10). In fact, when lowering the nucleophilicity of the amino nitrogen by a carbamate protective group, as demonstrated with **31** (Scheme 8), accordingly the corresponding α,β-unsaturated ketone **32** was obtained. A ^1H NMR analysis of the behavior of $Pd(OAc)_2$/Py complex upon the addition of increasing amount of amino alcohol **11** revealed the presence of more than one species in solution. The spectra were recorded in C_6D_6 at room temperature with a 4.5×10^{-2} M concentration of $Pd(OAc)_2$ in the presence of an excess of Py (10 equiv). In this conditions a precipitate of the $Pd(OAc)_2$/py complex was formed, which completely dissolves upon addition of two equivalents of the amino alcohol **11**. The singlet at 2.00 ppm, related to the two acetate group bonded to Pd,[21] decreased upon addition of **11**, but disappeared only after the addition of 2 equivalents of amino alcohol **11** to afford two separate singlets at 2.1 and at 1.9 ppm. A still intact cyclopropane ring at room temperature could be detected from only slightly modified signals at 1.5 to 0.5 ppm. The solution remained stable at least for 2 days, after which a black precipitate of colloidal Pd(0) was formed. The observation of more than one Pd complex may indicate a dynamic equilibrium in which the initial pyridine ligands are exchanged with the secondary amino group of the amino alcohol (Scheme 10). Consequently, we propose a mechanism, postulating a key Pd alcoholate intermediate, analogous to those reported by Stahl et al.[21] and Okumoto et al.[3b]

(17) *O*-Iodoxybenzoic acid: Nicolau, K. C.; Montagnon, T.; Baran, P. S.; *Angew. Chem., Int. Ed.* **2002**, *41*, 993−996. $Hg(OAc)_2$: Zhao, Z.; Dalvie, D.; Naiman, N.; Castagnoli, K.; Castagnoli, N., Jr. *J. Med. Chem.* **1992**, *35*, 4473−4478. *m*-Chloroperbenzoic acid: Kuehne, M. E.; Muth, R. S. *J. Org. Chem.* **1991**, *56*, 2701−2712. DDQ: Pfaendler, H. R.; Jenni, W. *Heterocycles* **1999**, *50*, 867−874.

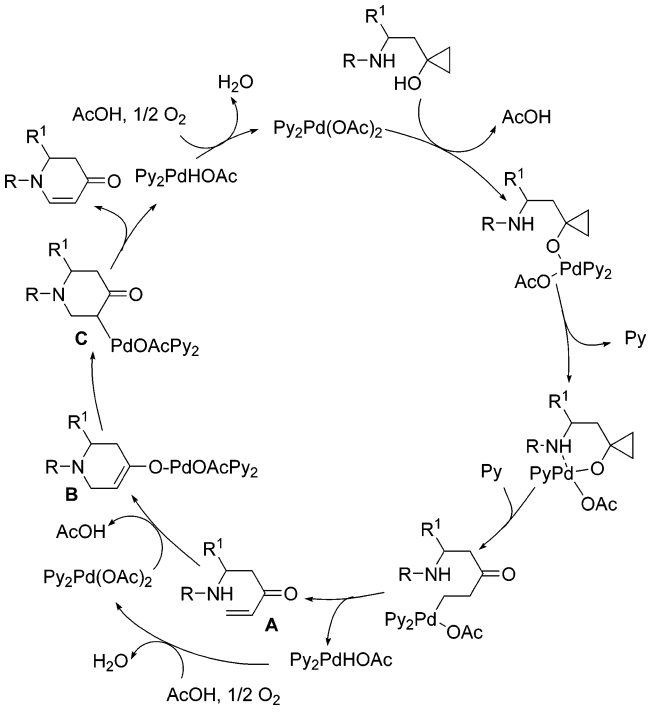
(18) Murahashi, S.-I.; Mitsue, Y.; Tsumiyama, T. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 3285−3288.

(19) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley and Sons: Chichester, 1995; Chapter 3.

(20) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A. *Org. Lett*. **2001**, *3*, 3313−3316.

(21) Steinhoff, B. A.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 11268−11278

SCHEME 10



Once that the α,β-unsaturated ketone **A** (Scheme 10) has been formed, subsequent aza-Michael addition of the amino group would lead to palladium enolate **B**, which is in equilibrium with the carbopalladated intermediate **C**. Ultimately a reductive elimination affords the dihydropyridone. It has been demonstrated that the aerobic oxidation can be accomplished in the absence of Py, but with a large excess of the acetate anions,[21] and so it might be argued that an excess of $Cu(OAc)_2$ could also promote oxidative ring cleavage. However, our experiments indicate that excessive Cu(II) forms a Cu enolate which competes with the Pd enolate **B**. Hydrolysis of the former, in contrast to reductive elimination of the latter, simply affords tetrahydropyridones at the end of the sequence.

With regard to the role of $Pd_2(dba)_3$, the outcome of the reactions (Scheme 6, reaction conditions d)) is in accordance with the inability to form enolates and with the expected reactivity of the intermediate α,β-unsaturated ketone.

In conclusion, we developed a new domino process to structurally diverse dihydropyridones by exploiting a combination of the synthetically versatile 1,3-dipolar cycloaddition of nitrones to methylenecyclopropane, an optimized reductive N−O bond cleavage, and subsequent Pd-catalyzed cyclization. In particular, this methodology allows regiospecific introduction of the enaminone double bond on the less substituted side of the dihydropyridone, thus complementing other common methods.[22] On the other hand, while the use of Pd(0) or Pd(II)/Cu(II) species does not yet represent a practical alternative to the thermal rearrangement of isoxazolidine-5-spirocyclopropanes, it appears mechanistically interesting to be able to control the oxidation level of the products by a simple change of the catalyst. The future developments of this strategy will aim for the synthetic exploitation of the structurally diverse dihydropyridones thus made accessible.

(22) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 2863−2866 and references therein.

Experimental Section

Compounds **18**, **21**, **23,** and **25** were synthesized following the reported procedures. See refs 11 and 14.

Cycloaddition of 3,4-Dihydroisoquinoline 2-Oxide to Methylenecyclopropane. Methylenecyclopropane (486 mg, 9.0 mmol) was added to a solution of 3,4-dihydroisoquinoline 2-oxide **15** (440 mg, 3.0 mmol) in toluene (4 mL), and the mixture was heated in a sealed vial at 60 °C for 2 d. The solvent was then removed under reduce pressure and the crude products were purified by chromatography on silica gel (eluent: AcOEt/petroleum ether = 1:10) to obtain **16** as a pale-yellow oil (356 mg, yield 59%) and **17** as a yellow oil (48 mg, yield 8%).

1′,5′,6′,10′b-Tetrahydrospiro[cyclopropane-1,2′-[2*H*]isoxazolo[3,2-*a*]isoquinoline] (16): R_f = 0.35 (AcOEt/petroleum ether 1:10); ^{1}H NMR δ 7.30−7.10 (m, 4H), 4.90 (t, J = 8.5, 1H), 3.42 (dd, J = 10.3, 4.4 Hz, 1H), 3.24 (dt, J = 10.3, 4.4 Hz, 1H), 3.10 (ddd, J = 16.1, 10.3, 4.4 Hz, 1H), 2.90 (dt, J = 16.1, 4.4 Hz, 1H), 2.81 (dd, J = 12.1, 8.4 Hz, 1H), 2.47 (dd, J = 12.1, 8.8 Hz, 1H), 1.13−0.94 (m, 2H), 0.81−0.64 (m, 2H); ^{13}C NMR 135.7 (s), 132.6 (s), 127.6 (d), 126.6 (d), 125.8 (d), 125.6 (d), 63.3 (d), 62.3 (s), 40.1 (t), 42.4 (t), 27.6 (t), 12.1 (t), 8.1 (t); MS (EI) *m/z* 201(18), 172 (49), 146 (41), 143 (53), 130 (100), 118 (29), 115 (78), 103 (44), 75 (15), 56 (35), 52 (27); IR ($CDCl_3$) 3081, 2858, 1607, 1583, 1492, 1455, 1013 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.61; H, 7.52; N, 6.95.

6′,10′b-Dihydrospiro[cyclopropane-1,1′(5′*H*)-[2*H*]isoxazolo[3,2-*a*]isoquinoline] (17): R_f = 0.13 (AcOEt/petroleum ether, 1:10); ^{1}H NMR δ 7.27−7.18 (m, 3H), 6.84 (m, 1H), 4.58 (s, 1H), 4.12 (system AB, 2H), 3.44−3.40 (m, 1H), 3.30−3.24 (m, 2H), 2.90−2.80 (m, 1H), 0.79−0.76 (m, 2H), 0.44 (m, 1H), 0.40 (m, 1H); ^{13}C NMR 131.2 (s), 134.4 (s), 127.7 (d), 126.4 (d), 125.3 (d), 125.2 (d), 73.7 (t), 65.0 (d), 47.7 (t), 28.6 (t), 27.9 (s), 10.7 (t), 3.6 (t); MS (EI) *m/z* 201 (28), 184 (33), 180 (36), 148 (52), 145 (38), 131 (60), 127 (42), 87 (55), 85 (94), 82 (100), 58 (79), 52 (51); IR ($CDCl_3$) 3072, 2874, 1495, 1455, 1119, 1022 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.54; H, 7.57; N, 6.90.

General Procedures for the Reduction of Isoxazolidines. Method A. $Pd(OH)_2$/C (20% in mass) was added to a solution of the isoxazolidine (0.33 mmol) in MeOH (7 mL). The reaction mixture was stirred under hydrogen at room temperature until the TLC showed consumption of the starting material. Palladium salts were then removed by filtering through a pad of Celite, and the solvent was then removed under reduce pressure. **Method B**. A 100 mL Schlenck flask charged with the isoxazolidine (0.5 mmol) was added, under nitrogen atmosphere, with 17.5 mL of a commercial 0.1 M THF solution of SmI_2 (3.5 equiv) at room temperature. The resulting blue solution was stirred for 2 h. A 1 M solution of NH_4OH in MeOH (8.5 mL) was added and left under stirring for 20 min. Finally, 17 mL of water was added, and the resulting solution was brought to pH 9 by addition of a 1 M solution of NaOH in water. The mixture was then saturated with $Na_2S_2O_3$ and extracted with diethyl ether (3 × 15 mL). The organic phase was then dried with Na_2SO_4, filtered, and concentrated to afford the crude product.

The crudes are sufficiently pure to be used directly for the following step. A short pad filtration over silica gel of an analytical sample affords the pure products for elemental analysis.

1-(1,2,3,4-Tetrahydroisoquinolin-1-ylmethyl)cyclopropanol (11): yellow solid; method A 67% yield, method B 70% yield; R_f = 0.17 (CH_2Cl_2/CH_3OH, 15:1 + 0.6% NH_4OH); mp = 85−86 °C; ^{1}H NMR δ 7.31−7.15 (m, 2H), 7.09−6.98 (m, 2H), 4.40 (dd, J = 11.4, 2.6 Hz, 1H), 3.36−3.12 (m, 2H), 2.83 (dd, J

= 7.0, 4.8 Hz, 2H), 2.54 (dd, J = 14.6, 11.4 Hz, 1H), 1.43 (dd, J = 14.6, 2.6 Hz, 1H), 0.89−0.77 (m, 2H), 0.58−0.46 (m, 2H); ^{13}C NMR 134.4 (s, 2C), 129.4 (d), 126.4 (d), 126.3 (d), 126.0 (d), 56.6 (s), 55.9 (d), 41.9 (t), 38.2 (t), 29.0 (t), 13.2 (t), 12.9 (t); MS (EI) *m/z* 203(8), 197 (41), 184 (50), 170 (42), 167 (60), 158 (50), 143 (54), 130 (100), 115 (88), 103 (68), 57 (41); IR ($CDCl_3$) 3650, 3300−3200, 3083−2949, 1489, 1433, 1305 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.95; H, 8.36; N, 6.80.

1-[2-(Methylamino)-2-phenylethyl]cyclopropanol (12): method A 70% yield; method B 80% yield; R_f = 0.18 (AcOEt/MeOH, 10:1); ^{1}H NMR δ 7.42−7.22 (m, 5H), 3.88 (dd, J = 10.5, 2.9 Hz, 1H), 2.38 (dd, J = 14.2, 10.5 Hz, 1H), 2.32 (s, 3H), 1.35 (dd, J = 14.2, 2.9 Hz, 1H), 0.84−0.72 (m, 2H), 0.52−0.27 (m, 2H); ^{13}C NMR 141.0 (s), 127.9 (s), 126.6 (d), 125.8 (d), 64.5 (d), 55.6 (s), 43.4 (t), 32.8 (q), 12.7 (t), 12.1(t); MS (EI) *m/z* 191 (0.5) 160 (2), 120 (100), 104 (22); IR ($CDCl_3$) 3650, 3500−3200, 3085, 2803, 1600, 1493, 1299, 1008 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.70; H, 8.81; N, 7.15.

Since the two regioisomeric isoxazolidine-5- and 4-spirocyclopropane are not easily separated, the reduction step can be performed on the crude mixture obtained from the cycloaddition.[11] From this reduction, the amino alcohol derived from the 4-spirocyclopropane derivative was also isolated.

{1-[(Methylamino)(phenyl)methyl]cyclopropyl}methanol (20): white solid; method A 8% yield; R_f = 0.14 (AcOEt/CH_3OH, 10:1); mp = 97−98 °C; ^{1}H NMR δ 7.52−7.20 (m, 5H), 5.80 (bs, 2H), 3.84 (part A system AB, J = 11.7 Hz, 1H), 3.54 (s, 1H), 3.08 (part B system AB, J = 11.7 Hz, 1H), 2.49 (s, 3H), 0.86−0.53 (m, 3H), 0.46−0.25 (m, 1H); ^{13}C NMR 136.8 (s), 128.7 (d), 128.1 (s), 127.4 (d), 71.8 (d), 68.0 (t), 34.3 (q), 25.6 (s), 12.1 (t), 7.9 (t); MS (EI) *m/z* 191 (1), 160 (2), 120 (100), 104 (3); IR ($CDCl_3$) 3648, 3400−3150, 2800, 1600, 1450, 1255, 1120 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO\cdot H_2O$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.75; H, 8.95; N, 6.87.

1-{[(3*S*)-3-*tert*-Butoxypyrrolidin-2-yl]methyl}cyclopropanol (22): pale yellow oil; method B, 90% yield; R_f = 0.15 (AcOEt/CH_3OH, 2:1 + 0.2% NH_4OH). $[\alpha]^{20}_D$ = +6.3 (CH_2Cl_2, 0.5); ^{1}H NMR δ 4.05 (bs, 2H), 3.76 (dt, J = 6.6, 3.6 Hz, 1H), 3.25 (dt, J = 10.2, 3.6 Hz, 1H), 3.07 (ddd, J = 11.7, 6.6, 5.6 Hz, 1H), 2.93 (ddd, J = 11.7, 8.0, 5.6 Hz, 1H), 2.04 (tt, J = 8.0, 6.6 Hz, 1H), 1.84 (dd, J = 13.2, 10.2 Hz, 1H), 1.63 (ddt, J = 13.0, 5.6, 3.6 Hz, 1H), 1.22 (m, 1H), 1.13 (m, 9H), 0.69−0.58 (m, 2H), 0.35−0.29 (m, 2H); ^{13}C NMR 73.6 (d), 68.8 (s), 65.9 (d), 55.7 (s), 44.1 (t), 37.9 (t), 34.6 (t), 28.5 (q, 3C), 12.9 (t), 12.5 (t); MS (EI) *m/z* (213 (3), 192 (17), 174 (19), 156 (15), 86 (17), 82 (10), 57 (100); IR ($CDCl_3$) 3669, 3300−3200, 3083, 2976, 1630, 1462, 1434, 1364. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.66; H, 10.48; N, 6.29.

1-{4-(Methylamino)-1-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroquinolin-3-yl}cyclopropanol (24): colorless oil; method B 95% yield; R_f = 0.1 (CH_2Cl_2/CH_3OH, 2:1); ^{1}H NMR δ 7.96 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.37−7.27 (m, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.15−7.07 (m, 1H), 7.07−6.97 (m, 2H), 4.01−3.89 (m, 2H), 3.50 (d, J = 3.0 Hz, 1H), 2.37 (s, 3H), 2.04 (s, 3H), 1.13 (ddd, J = 12.1, 7.1, 3.0 Hz, 1H), 0.83−0.68 (m, 2H), 0.40−0.22 (m, 2H); ^{13}C NMR 144.0 (s), 135.3 (s), 134.5 (s), 131.1 (s), 129.7 (d), 128.8 (d), 128.7 (d), 127.0 (d), 125.5 (d), 124.4 (d), 60.9 (s), 56.7 (d), 44.4 (q), 43.6 (q), 34.1 (d), 21.5 (t), 13.2 (t), 11.9 (t); MS (EI) *m/z* 373 (2), 289 (11), 239 (13), 217 (20), 208 (8), 198 (9), 196 (100), 167 (10); IR ($CDCl_3$) 3688, 3547, 2980, 2950, 1599, 1486, 1171 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_2O_2S$: C, 64.49; H, 6.49; N, 7.52. Found: C, 64.30; H, 6.38; N, 7.75.

Ethyl 3-(1-hydroxycyclopropyl)alaninate (26): colorless oil; method A 100% yield; R_f = 0.20 (AcOEt/petroleum ether, 1:5); ^{1}H NMR δ 4.14 (q, J = 7.1 Hz, 2H), 3.93−3.76 (m, 3H), 2.02 (dd, J = 14.0, 9.6 Hz, 1H), 1.69 (dd, J = 14.4, 3.3 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H), 0.79−0.61 (m, 2H), 0.49−0.31 (m, 2H); ^{13}C NMR 174.7 (s), 61.7 (t), 55.1 (s), 54.0 (d), 40.2 (t), 14.1 (q), 13.5 (t), 12.6 (t);. MS *m/e* (rel intensity) 174 (25), 102 (42), 100 (70), 74 (50), 57 (100); IR ($CDCl_3$) ν 3552, 3025, 2245, 1737, 1643, 1594, 1494, 1320, 1260. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.36; H, 8.88; N, 8.05.

Ethyl *N*-[(Benzyloxy)carbonyl]-3-(1-hydroxycyclopropyl)alaninate (31). To a well-stirred solution of **26** (130 mg, 0.75 mmol) in acetone (4 mL) and water (1 mL) were added $NaHCO_3$ (63 mg, 0.75 mmol) and CbzCl (190 mg, 1.12 mmol). The resulting solution was stirred under N_2 for 3 h. at 0 °C and concentrated. The solid residue was washed with CH_2Cl_2 and the resulting solution concentrated. The residue was purified by FCC to obtain pure **31** (225 mg, 98%) as a yellow oil: R_f = 0.4 (CH_2Cl_2/CH_3OH, 97:3); ^{1}H NMR δ 7.43−7.22 (m, 5H), 5.64 (d, J = 2.2 Hz, 1H), 5.17 (AB system, 2H), 4.65 (ddd, J = 8.5, 3.2, 2.2 Hz, 1H), 4.22 (q, J = 7.5 Hz, 2H), 2.43 (dd, J = 8.5, 3.2 Hz, 1H), 1.35 (m, 1H), 1.33 (t, J = 7.5 Hz, 3H), 0.83−0.75 (m, 1H), 0.53−0.47 (m, 1H), 0.43−0.38 (m, 2H); ^{13}C NMR 172.4 (s), 156.4 (s), 136.1 (s), 128.5 (d), 128.3 (d), 127.5 (d), 67.3 (t), 61.8 (t), 60.9 (s), 52.0(d), 41.7 (t), 14.2 (q), 12.6 (t), 11.6 (t); MS (EI) *m/z* 307 (1), 91 (100), 65 (12), 57 (12), 55 (12); IR ($CDCl_3$) 3428, 2984, 2960, 2249, 1784, 1704, 1513, 1455, 1380, 1346, 1297, 1215, 1185. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.36; H, 6.82; N, 4.50.

General Procedure for the Synthesis of Dihydropyridones. A suspension of the β-aminocyclopropanol (0.5 mmol), Pd(II) catalyst (0.05 mmol), base (1.0 mmol) in toluene (5 mL) was stirred and heated at 80 °C for 3 h in a reactor with pressure of O_2 (5 atm.). The suspension was then filtered and concentrated and the residue purified by flash chromatography.

1,6,7,11b-Tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (13): yellow oil; R_f = 0.18 (AcOEt/petroleum ether, 5:1); ^{1}H NMR δ 7.20−7.00 (m, 5H), 5.10 (d, J = 7.3 Hz, 1H), 4.79 (dd, J = 15.7, 4.0 Hz, 1H), 3.69−3.53 (m, 1H), 5.46 (td, J = 11.7, 3.3 Hz, 1H), 3.19 (td, J = 15.7, 5.1 Hz, 1H), 3.06−2.98 (m, 2H), 2.86 (dd, J = 15.7, 3.3 Hz, 1H); ^{13}C NMR 196.9 (s), 154.1 (d), 129.0 (d), 127.1 (d), 127.0 (d), 125.6 (d), 98.5 (d), 56.6 (d), 49.6 (t), 44.0 (t), 30.3 (t); MS (EI) *m/z* 122 (43), 170 (47), 147 (15), 118 (28), 90 (20) 83 (100); IR ($CDCl_3$) 3075, 3028, 2852, 1635, 1593, 1574, 1452, 1377, 1196 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.20; H, 6.72; N, 7.10.

1-Methyl-2-phenyl-2,3-dihydropyridin-4(1*H*)-one (14): orange oil; R_f = 0.13 (AcOEt); ^{1}H NMR δ 7.48−7.26 (m, 5H), 7.13 (d, J = 7.3 Hz, 1H), 5.04 (d, J = 7.3 Hz, 1H), 4.51 (dd, J = 9.5, 7.3 Hz, 1H), 2.87 (dd, J = 16.8, 7.3 Hz, 1H), 2.72 (dd, J = 16.8, 9.5 Hz, 1H), 2.87 (s, 3H); ^{13}C NMR 190.5 (s), 155.2 (d), 138.7 (s), 129.0 (d), 128.3 (d), 126.9 (d), 98.4 (d), 63.7 (d), 43.8 (q), 41.4 (t); MS (EI) *m/z* 187 (49), 159 (10), 144 (10), 104 (100), 82 (31), 77 (32), 55 (19); IR ($CDCl_3$) 3068, 2810, 1633, 1592, 1582, 1455, 1421 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.69; H, 7.29; N, 7.45.

(1*S*,8a*R*)-1-*tert*-Butoxy-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (27): colorless oil; R_f = 0.4 (CH_2Cl_2/CH_3OH, 1:1 + NH_4OH 0.5%); $[\alpha]^{20}_D$ = −28.3 (CH_2Cl_2, 0.5); ^{1}H NMR δ 7.07 (d, J = 7.0 Hz, 1H), 4.93 (d, J = 7.0 Hz, 1H), 3.96 (q, J = 7.3 Hz, 1H), 3.50 (m, 3H), 2.55 (dd, J = 16.2, 5.1 Hz, 1H), 2.31 (t, J = 16.2 Hz, 1H), 2.25 (m, 1H), 1.90 (m, 1H), 1.18 (s, 9H); ^{13}C NMR 191.8 (s), 150.2 (d), 97.6 (d), 76.6 (d), 74.0 (s), 62.1 (d), 47.3 (t), 39.5 (t), 33.3 (t), 28.4 (q); MS (EI) *m/z* 209 (24), 153 (11), 152 (72), 136 (12), 119 (19), 108 (100), 96 (11), 80 (11), 57 (41). IR ($CDCl_3$) 2977, 2879, 2242, 1632, 1576, 1478, 1459, 1411, 1392, 1363, 1347 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.57; H, 9.53; N, 6.42.

(4a*RS*,10b*RS*)-1-Methyl-6-[(4-methylphenyl)sulfonyl]-4a,5,6,10b-tetrahydrobenzo[*h*]-1,6-naphthyridin-4(1*H*)-one (28): yellow oil; R_f = 0.16 (AcOEt/petroleum ether, 5:1); ^{1}H NMR δ 7.79 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.40−7.30 (m, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.18−7.08 (m, 1H), 7.05−6.97 (m, 3H), 6.28 (d, J = 7.4 Hz, 1H), 4.92 (d, J = 7.4 Hz, 1H), 4.13−4.08 (m, 2H), 3.88 (dd, J = 12.8, 8.0 Hz, 1H), 2.81 (td, J = 12.8, 5.2 Hz, 1H), 2.63 (s, 3H), 2.41 (s, 3H);

^{13}C NMR: 189.7 (s), 153.0 (d), 143.9 (s), 137.4 (s), 136.1 (s), 129.7 (d, 2C), 129.4 (d), 128.1 (d), 127.2 (d, 2C), 125.4 (s), 124.7 (d), 124.5(d), 98.0 (d), 58.7 (d), 44.6 (q), 43.5 (t), 41.2 (d), 21.5 (q); MS (EI) *m/z* 368 (10), 213 (8), 215 (100), 195 (13), 156 (12), 130 (70), 128 (22), 91 (24), 85 (15), 84 (21), 83 (46), 77 (14), 65 (15); IR ($CDCl_3$) 3100, 2926, 1642, 1583, 1488, 1420, 1326, 1168 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60. Found: C, 65.35; H, 5.30; N, 7.65.

Ethyl 4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate (29): colorless oil; R_f = 0.20 (AcOEt/petroleum ether, 1:5); ^{1}H NMR δ 7.23 (d, J = 7.3 Hz, 1H), 5.09 (d, J = 7.3 Hz, 1H), 4.38 (dd, J = 6.6, 1.5 Hz, 1H), 4.27 (q, J = 7.3 Hz, 2H), 2.80−2.72 (m, 2H), 1.29 (t, J = 7.3 Hz, 3H); ^{13}C NMR 199.3 (s), 172.4 (s), 153.5 (d), 99.1 (d), 61.3 (t), 58.0 (d), 40.0 (t), 14.1 (q); MS (EI) *m/z* 169 (24), 97 (12), 96 (100), 86 (12), 84 (16), 68 (27), 55 (26); IR ($CDCl_3$) 3436, 2928, 2245, 1737, 1643, 1594, 1494, 1392, 1374, 1260 cm^{-1}. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.97; H, 6.43; N, 8.25.

Ethyl 2-{[(benzyloxy)carbonyl]amino}-4-oxohex-5-enoate (32): yellow oil; R_f = 0.70 (AcOEt/petroleum ether, 3:7); ^{1}H NMR δ 7.42−7.25 (m, 5H), 6.28 (m, 2H), 5.92 (dd, J = 8.8, 2.2 Hz, 1H), 5.8 (sd, J = 8.0 Hz, 1H), 5.11 (s, AB system, 2H), 4.62 (dt, J = 8.8, 4.2 Hz, 1H), 4.19 (q, J = 7.3 Hz, 2H), 3.38 (system ABX, part A), 3.15 (system ABX, part B), 1.23 (t, J = 7.3 Hz, 3H); ^{13}C NMR 207.9 (s), 171.1 (s), 151.4 (s), 136.5 (d), 129.6 (s), 128.6 (s), 128.5 (t), 128.3 (d), 128.0 (s), 67.0 (t), 61.9 (t), 49.8 (d), 41.5 (t), 14.2 (q); MS (EI) *m/z* 304 (M − 1) (0.2), 199 (2.25), 107 (4), 91 (100) 65 (16); IR ($CDCl_3$) 3435, 2984, 2961, 2257, 1785, 1720, 1682, 1615, 1507, 1465, 1296, 1209, 1035 cm^{-1}. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.37; H, 6.64; N, 8.53.

General Procedure for the Synthesis of Tetrahydropyridones Using Cu(OAc)$_2$ as Stoichiometric Oxidant. A suspension of the β-aminocyclopropanol (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), $Cu(OAc)_2$ (1.0 mmol), and LiOAc (1.5 mmol) in DMF (5 Ml) was stirred and heated at 100 °C for 3 h. The suspension was then filtered and concentrated and the residue purified by flash column chromatography.

General Procedure for the Synthesis of Tetrahydropyridones Using Pd(dba)$_2$. A solution of the β-aminocyclopropanol (0.5 mmol) and $Pd(dba)_2$ (0.05 mmol) in anhydrous CH_3CN was heated at 50 °C for 20 h. The solution was concentrated and purified by flash column chromatography.

1,3,4,6,7,11b-Hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (13a): white solid; R_f = 0.33 (AcOt/petroleum ether, 5:1); mp = 92 °C; ^{1}H NMR δ 7.23−7.03 (m, 4H), 3.59 (dd, J = 11.5, 4.4 Hz, 1H), 3.39−3.29 (m, 10H); ^{13}C NMR 208.6 (s), 136.7 (s), 134.0 (s), 129.0 (d), 126.6 (d), 126.2 (d), 124.8 (d), 61.2 (t), 54.8 (d), 50.4 (t), 47.3 (t), 41.1 (t), 29.7 (t); MS (EI) *m/z* 201 (59), 158 (29), 130 (65), 115 (18), 104 (10), 86 (35), 83 (100); IR ($CDCl_3$) 3053, 3020, 2952, 2930, 1708 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.19; H, 7.43; N, 6.61.

14a: see ref 11.

27a: see ref 13.

Acknowledgment. We are grateful to Ente Cassa di Risparmio di Firenze, Firenze, Italy, for granting a 400-MHz NMR spectrometer to the Department of Organic Chemistry. Mrs. Brunella Innocenti and Mr. Maurizio Passaponti are acknowledged for technical assistance.

Supporting Information Available: General experimental methods and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050640Q