Notes

An Investigation of the Palladium-Catalyzed, Formate-Mediated Hydroxycarbonylation of Optically Active 1-Arylethyl Esters†

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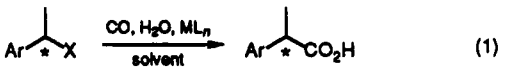
Received February 21, 1990

Introduction

The synthesis of 2-arylpropanoic acids has received considerable attention as a result of the analgesic and antiinflammatory properties of many of these compounds.[1] Markedly higher biological activity is often exhibited by one enantiomer, which renders those synthetic routes that provide the physiologically more active compound in optically pure form particularly advantageous.

One approach to the asymmetric synthesis of 2-arylpropanoic acids is the carbonylation of optically active 1-functionalized arylethanes with clean transfer of stereochemical information (eq 1). Attractive candidates for



(1)

such precursors include the 1-arylethanols (X = OH), which may be prepared in high optical purity by asymmetric reduction of arylmethyl ketones[2] or by enzymatic hydrolysis of racemic 1-arylethyl esters.[3] Direct transition-metal-catalyzed carbonylation of racemic 1-arylethanols to the corresponding racemic 2-arylpropanoic acids has been reported,[4] but no asymmetric variant of this transformation has appeared in the literature. Given the acidic medium required for this carbonylation, preservation of stereochemistry in the starting material is expected to be problematic. Alternatively, optically active 1-arylethanols can be converted to enantiomerically enriched 1-aryl-1-haloethanes (X = Cl or Br),[5] which Stille showed can undergo stereocontrolled stoichiometric palladium-mediated carbonylation.[6] While this method could probably be rendered catalytic,[7] such a process would be limited by the availability of optically pure 1-aryl-1-haloethanes, which are generally configurationally unstable.[8]

Another class of potential substrates for the stereoselective formation of 2-arylpropanoic acids is the optically active 1-arylethyl esters (X = O_2CR), which may be prepared directly from chiral 1-arylethanols or by enantioselective acylation of the racemic alcohols.[9] These esters are anticipated to be more chemically and configurationally stable than the corresponding 1-arylethyl halides. Catalytic carbonylation of benzylic esters has not, however, been described previously. We report herein that, under suitable conditions, selected chiral 1-arylethyl esters can be carbonylated directly to optically active 2-arylpropanoic acids, including the potent antiinflammatory agent naproxen (1).

Chart I

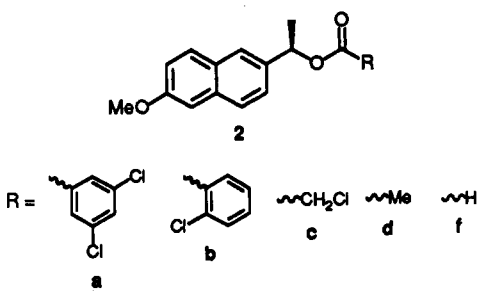
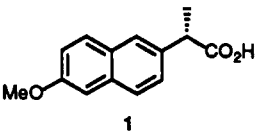


Table I. Variation of Leaving Group in the Formate-Mediated Hydroxycarbonylation of Chiral 1-(6-Methoxynaphth-2-yl)ethyl Esters (Ligand = PPh_3)[a]

substrate	t (h)	yield 1 + 4 (%)	iso/n	ee (%)
2a	141.7	70.7	>50:1	33.8 (*S*)
2a	40.4	20.1	>50:1	82.6 (*S*)
2b	88	42.9	>50:1	2.6 (*S*)
2b	23.3	19.9	>50:1	73 (*S*)
2c	62.5	11.2	>50:1	26.8 (*S*)
2d	43.5	trace		

[a] [Substrate] = 0.1 M, 1:1 DMF/toluene, 10 mol % of $PdCl_2$/3PPh_3, 120 °C, 100 psig CO.



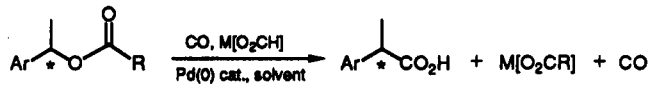
Results

Palladium(0)-catalyzed hydroxycarbonylation of certain optically active 1-arylethyl esters[10,11] to enantiomerically enriched 2-arylpropanoic acids can be achieved with net inversion of configuration under relatively mild conditions in the presence of 1 molar equiv of a formate salt (eq 2).

† Contribution no. 808.

(1) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.
(2) Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406.
(3) Schneider, M. P.; Laumen, K. *J. Chem. Soc., Chem. Commun.* **1988**, 598.
(4) (a) Mitsubishi Petrochemical Co., Ltd. JP 59 95,239, 1984; *Chem. Abstr.* **1984**, *101*, 170908y. (b) Hoechst-Celanese Co. EP 284-310-A, 1987.
(5) (a) Gerrard, W. *J. Chem. Soc.* **1945**, 848. (b) Hoffmann, H. M. R.; Hughes, E. D. *J. Chem. Soc.* **1964**, 1244.
(6) Lau, K. S. Y.; Wong, P. K.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 5832.
(7) (a) Arzoumanian, H.; Buono, G.; Choukrad, M.; Petrignani, J.-F. *Organometallics* **1988**, *7*, 59. (b) Alper, H.; Hashem, K.; Heveling, J. *Organometallics* **1982**, *1*, 775.
(8) (a) See ref 5. (b) Tsuno, Y.; Sawada, M.; Fujii, T.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3033.
(9) Laumen, K.; Breitgoff, D.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1459.
(10) (*R*)-1-Arylethyl esters were prepared by standard acylation of the corresponding (*R*)-1-arylethanols, which were in turn accessible in 84–99% ee via the asymmetric hydroboration of aryl methyl ketones according to the method of Corey et al.[11] See supplemental material.
(11) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

0022-3263/91/1956-1928$02.50/0



(2)

The 2-arylpropanoic acids can be isolated in up to 75% yield at 90–100% conversion, retaining at least some of the stereochemical information originally present in the substrate. The carbonylation is, however, extremely sensitive to the nature of the substrate, the catalyst precursor, and the reaction conditions (vide infra).

Our studies focused on the carbonylation of (*R*)-1-(6-methoxynaphth-2-yl)ethyl esters ((*R*)-**2a–d**, Chart I), possible precursors to naproxen. Evaluation of individual carbonylation runs focused on four issues: reactivity, chemoselectivity, regioselectivity, and stereoselectivity. The hydroxycarbonylation of esters **2a–d** catalyzed by the $Pd(PPh_3)_n$ system (Table I) proceeded slowly, typically requiring at least 60 h for complete consumption of starting material at 120 °C. Qualitatively, the reactivity of leaving groups decreased in the order 3,5-dichlorobenzoate > 2-chlorobenzoate > chloroacetate ≫ acetate. The catalytic activities of $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$–PPh_3, $PdCl_2$–$2PPh_3$, and $PdCl_2$–$3PPh_3$ as precursors to $Pd(PPh_3)_n$ were comparable, but $Pd(OAc)_2$–$3PPh_3$ was ineffective. The hydroxycarbonylation reaction could be conducted in polar aprotic solvents such as DMF, THF, DME, and CH_3CN but barely proceeded in toluene.

Unlike the formate-mediated hydroxycarbonylation of aryl halides reported by Pri-Bar,[12] very little formylation of **2a–d** to aldehyde **3** (<2%) was detected under any conditions. Major side products included the 3-arylpropanoic acid **4** (up to 50%), the vinylarene **5** (up to 20%), and the ethylarene **6** (<5%), as illustrated in Chart II. Formation of **5** increased with respect to the propanoic acids above 120 °C.

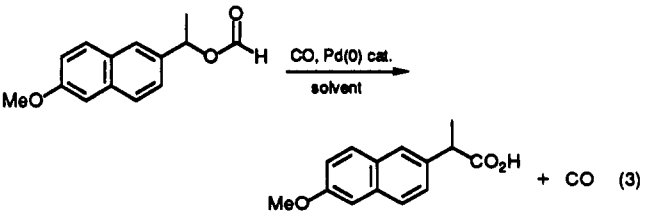
Reactions using the $Pd(PAr_3)_n$ catalyst system (Ar = Ph, *p*-tolyl) in 1:1 DMF/(benzene or toluene) proceeded with high regioselectivity for the 2-substituted acid at 100 psig, with iso/n ratios typically exceeding 50:1 (^1H NMR and HPLC). This ratio was independent of the extent of substrate conversion. The regioselectivity of carbonylation was, however, influenced by solvent; inferior iso/n ratios were obtained in neat DMF (1:2) or THF (3:4) at 100 psig. The choice of phosphine also affected the isomer ratio during hydroxycarbonylation; substitution of tris(*p*-methoxyphenyl)phosphine for PPh_3 in the $PdCl_2/3PAr_3$ system led to a 4:3 iso/n ratio. Poor regioselectivity at 100 psig was also observed when bidentate phosphine ligands were used (vide infra).

For all substrates examined, the optical purity of the isolated 2-arylpropanoic acid was highest at low substrate conversion and eroded gradually with increasing reaction time (Table I). Stereoselectivities corresponding to the full stereochemical information present in the alcohol employed to produce the substrate esters could be obtained at 20–30% conversion. For example, when **2a** derived from 1-arylethanol of 84.2% ee (*R*) was carbonylated at 100 °C for 40.4 h, a 20.1% yield of naproxen of 82.6% ee (*S*) was isolated. The stereoselectivity of hydroxycarbonylation was not strongly substrate dependent and did not vary consistently with catalyst precursor or solvent. Markedly lower stereoselectivity was observed, however, when the reaction was conducted above 120 °C.

Although the chlorobenzoate esters **2a–b** were effective substrates in the $Pd(PPh_3)_n$-catalyzed hydroxycarbonylation process, the coproduction of chlorobenzoic acids complicated extractive workup of the reaction mixture and the isolation of pure arylpropanoic acids. The corresponding acetate (**2d**) was viewed as an attractive alternative since the coproduced acetic acid could be easily removed by washing the crude product with water. This ester was, however, carbonylated extremely slowly under the conditions established for esters **2a–c**.

Use of the ligand 1,3-bis(diphenylphosphino)propane (dppp) in place of PPh_3 in palladium-catalyzed carbonylations has been reported to improve reaction rates and product yields.[13] When this ligand was employed in the hydroxycarbonylation of **2a** at 100 psig, a modest rate enhancement was observed, but an unsatisfactory 4:3 mixture of 2- and 3-arylpropanoic acids was isolated. Better selectivity for the branched isomer was observed at 650 psig, along with improved stereoselectivity (Table II). The $PdCl_2$/dppp catalyst system also permitted the carbonylation of acetate **2d** at rates competitive with the 3,5-dichlorobenzoate. As observed for **2a–c**, stereoselectivity at high substrate conversion was generally poor, but optical purities as high as 74.2% ee were attained for reactions taken to 10% conversion.

Utilization of the $PdCl_2$/dppp catalyst system also permitted the hydroxycarbonylation of formate ester **2e**. This substrate was of particular interest since the formate liberated during its carbonylation could in principle substitute for the stoichiometric formate salt required in the hydroxycarbonylation of other esters (eq 3). Indeed, when



(3)

ester **2e** was carbonylated in the presence of only 0.2 equiv of $Na[O_2CH]$, a 34.8% yield of propanoic acids (iso/n =

Chart II

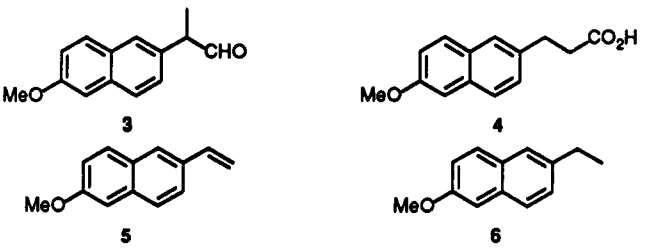


Table II. Variation of Leaving Group in the Formate-Mediated Hydroxycarbonylation of Chiral 1-(6-Methoxynaphth-2-yl)ethyl Esters (Ligand = dppp)[a]

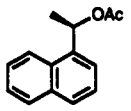
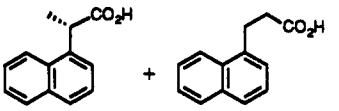
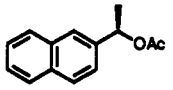
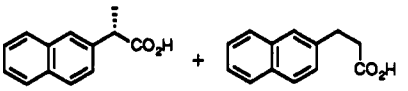
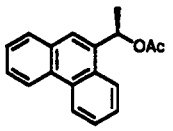
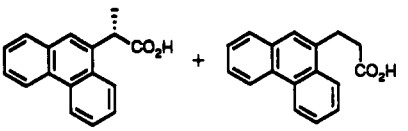
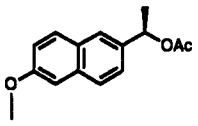
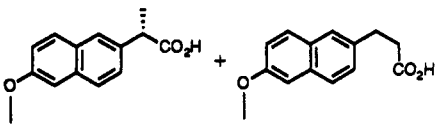
substrate	*t* (h)	yield 1 + 4 (%)	iso/n	ee (%)
2a	18	35.8	94:6	44.7 (*S*)
2a	16.7	36.1	9:1	91 (*S*)
2b	15.3	19.8	2:1	17.6 (*S*)
2c	65	59.8	18:13	8.6 (*S*)
2c	16.3	15.8	2:1	82.2 (*S*)
2d	50	74	83:17	7.8 (*S*)
2d	24	50	24:1	29.6 (*S*)
2d	16.9	49.5	9:1	33.8 (*S*)
2e	90.5	35	89:11	33.6 (*S*)
2e	48	42.6	>99:1	54 (*S*)

[a] [Substrate] = 0.1 M, 1:1 DMF/toluene, 10 mol % of $PdCl_2$/dppp, 120 °C, 650 psig CO.

(12) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1988**, *53*, 624.

(13) Dolle, R. E.; Schmidt, S. J.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1987**, 904.

Table III. Formate-Mediated Hydroxycarbonylation of 1-Arylethyl Acetates (Ligand = dppp)[a]

substrate	t (h)	acidic products	% yield	iso/n	ee (%)
 7	15.5	 8 + 9	24.1	93:7	15.2
 10	19.3	 11 + 12	56.9	84:16	7
10	22.0	11 + 12	6.5	97:3	71.8
 13	18.4	 14 + 15	36.1	24:1	45
 2d	16.9	 1 + 4	49.5	90:10	33.8

[a] [Substrate] = 0.1 M, 1:1 DMF/toluene, 10 mol % of $PdCl_2$/dppp, 120 °C, 650 psig CO.

4:1) was isolated. Better product yields and improved regio- and stereoselectivities were obtained, however, at higher formate salt loadings.[14]

The effect of aryl group variation was examined for a series of 1-arylethyl acetates (Ar = Ph, 4-FC_6H_4, 4-$iBuC_6H_4$, 4-$MeOC_6H_4$, 1-naphthyl, 2-naphthyl, and 9-phenanthryl). The most striking result from this study was the complete lack of reactivity of 1-phenylethyl acetates under conditions where hydroxycarbonylation of **2d** is facile. The unreacted acetate esters could be recovered unchanged from the hydroxycarbonylation mixtures. This lack of reactivity also extended to the 3,5-dichlorobenzoate ester of (*R*)-1-phenylethanol. Only 1-(4-methoxyphenyl)ethyl 3,5-dichlorobenzoate provided even traces of arylpropanoic acids under standard carbonylation conditions. In contrast to the 1-phenylethyl acetates, the polycyclic 1-arylethyl acetates **7**, **10**, and **13** were effective substrates in the formate-mediated hydroxycarbonylation reaction (Table III). These reactions were run to only partial conversion in an attempt to ensure non-zero optical purities for the product 2-arylpropanoic acids. Neither regioselectivity nor stereoselectivity correlated strongly with the nature of Ar.

Discussion

Mechanism of Hydroxycarbonylation. Key features of the formate-mediated, catalytic hydroxycarbonylation of chiral 1-arylethyl esters can be rationalized in terms of Scheme I. The active palladium(0) catalyst may be generated directly from a palladium(0) precursor complex by ligand dissociation or from palladium(II) precursors by formate reduction. The hydroxycarbonylation of chiral 1-arylethyl esters with net inversion of configuration at carbon is consistent with an oxidative addition process wherein carboxylate is displaced during backside attack by palladium(0).[15] The relative inertness of 1-phenylethyl esters in this reaction suggests, however, that the displacement process is not a simple S_N2-like substitution.

Scheme I

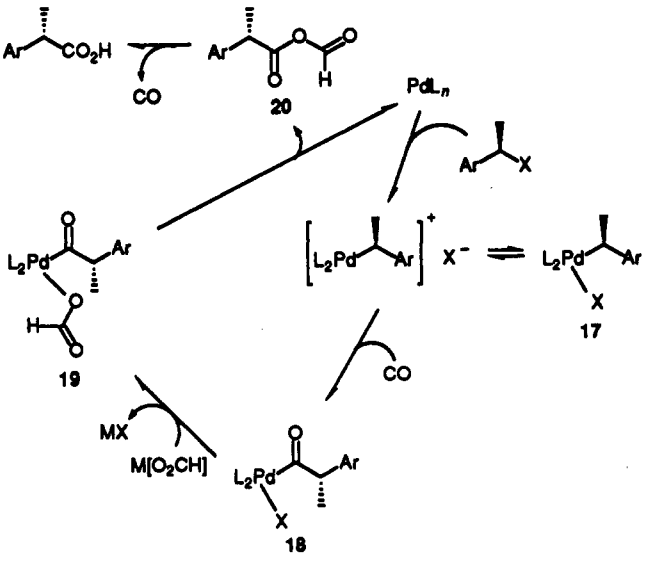
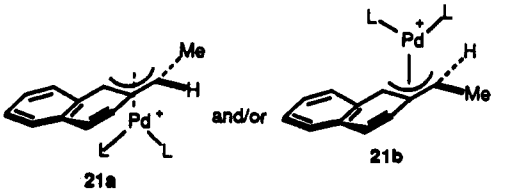


Chart III



We propose instead that the carboxylate displacement occurs stepwise, via initial alkene-like coordination of polycyclic arene to the Pd(0) center followed by metal-induced heterolysis of the carbon–oxygen linkage to give an intermediate π-allyl complex (e.g. **21a,b**, Chart III). A similar process has been invoked for the formation of cationic palladium(II) allylic intermediates during the alkylation of chiral allylic acetates.[16] Both cationic[17] and

(14) Employing 1.2 molar equiv of $Na[O_2CH]$, a 42.6% yield of propanoic acids having an iso/n ratio of 99:1 (54% ee) was obtained.
(15) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* 1977, *10*, 434.
(16) (a) Trost, B. M. *Pure Appl. Chem.* 1981, *53*, 2357. (b) Trost, B. M. *Acc. Chem. Res.* 1980, *13*, 385.

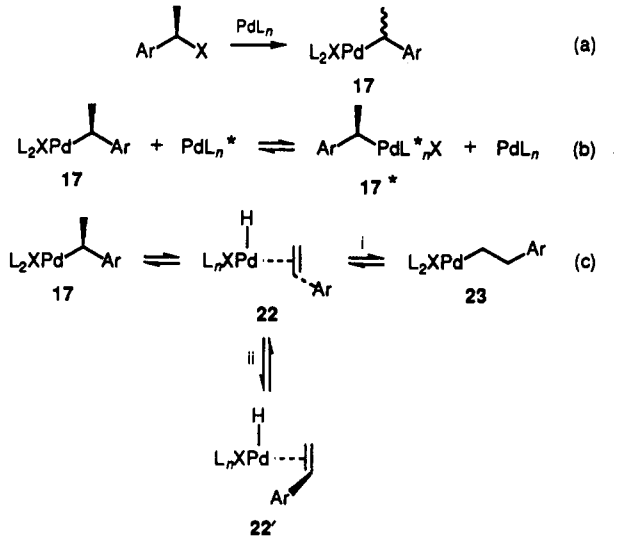
neutral[18] η^3-benzyl complexes of palladium(II) are known, and at least one example of η^3-benzyl carbonylation has been reported.[18a] In the present case, the disruption of aromaticity caused by π-allylic complexation is expected to be less severe for polycyclic than for simple phenyl derivatives. Subsequent migration of palladium to the benzylic position by η^3–η^1 interconversion generates secondary palladium(II) alkyl **17**.[19]

Several reaction pathways are available to the proposed palladium alkyl intermediate. In the productive cycle, interception of **17** by CO may lead to migratory insertion with retention of configuration at carbon, producing palladium(II) acyl **18**. Intermediate **18** may then be cleaved by formate, liberating a mixed formic anhydride (**19**) and regenerating the Pd(0) catalyst. Mixed formic anhydrides are thermally unstable, particularly in the presence of formate, and under the reaction conditions employed may spontaneously decarbonylate to provide the observed 2-arylpropanoic acids.[20] Such a process has previously been invoked in the formate-mediated hydroxycarbonylation of vinyl triflates[21] and aryl halides.[12] Alternatively, **17** may undergo β-hydride elimination to produce a transient olefin–hydride species from which vinylarene **5** may be displaced.[6] The olefin–hydride complex might also undergo nondegenerate β-hydride insertion to produce a primary palladium(II) alkyl. Subsequent carbonyl insertion and formate attack gives rise to a linear mixed anhydride and hence to the 3-arylpropanoic acid **4** by decarbonylation (vide supra). Finally, protonolysis of either primary or secondary alkyl may provide the observed traces of ethylarene **6**.

Within the context of the proposed reaction scheme, the regioselectivity of carbonylation depends upon the partitioning of **17** between **18** and the olefin hydride. Conditions that favor rapid interception of **17** by CO (e.g., high CO pressure) should allow regioselective formation of 2-arylpropanoic acids. Conversely, conditions that facilitate β-hydrogen elimination from **17** should skew the product distribution toward 3-arylpropanoic acid. The reported correlation of β-hydrogen elimination tendency with the electron-releasing character of ligands bound to the transition-metal center[22] is consistent with the low iso/n ratios encountered when ligands such as P(*p*-anisyl)$_3$ and dppp are substituted for PPh_3 in the hydroxycarbonylation reaction.

Racemization. Several pathways may be envisioned for the loss of stereochemical information originally present in the substrate[23] during carbonylation. The possibility that the catalyst promotes substrate racemization via reductive elimination of ester from intermediate **17**[24] was ruled out by isolation of acetate ester **2d** from a reaction taken to 20% conversion. Despite partial racemization of the product 2-arylpropanoic acid, no loss of optical purity in the substrate was observed. Loss of stereochemical information during catalysis may occur by at least three processes: (a) nonstereospecific oxidative addition, (b) exchange of secondary alkyl groups between palladium centers, and (c) reversible β-hydrogen elimination/readdition sequences (Scheme II). That stereoselectivity of hydroxycarbonylation is very high during the early stages of the reaction is inconsistent with an inherently nonstereoselective oxidative addition process. The insensitivity of the extent of racemization to initial catalyst loading argues against S_N2-like exchange of the alkyl group between palladium centers as a major racemization pathway.

Scheme II



Racemization via β-hydrogen elimination/readdition involving proposed intermediate **17** can take two forms: (i) reversible iso/n isomerization or (ii) olefin exchange. Stereochemical information originally present in **17** is lost upon formation of **23**. Reversal of the iso/n interconversion from **23** should provide racemic **17**. Attempts to probe the extent of such a racemization process using selectively deuterated acetate **2d** were inconclusive due to the large primary isotope effect associated with the hydrogen elimination step.[25] A second path by which stereochemical information may be lost during β-hydrogen elimination/readdition processes involves the reversible dissociation of olefin from intermediate **22**. Crossover experiments with 4-methylstyrene suggested that olefin exchange with **22** is possible,[26] but the extent to which this process influences the stereoselectivity of the carbonylation reaction is unknown.

Finally, stereochemical information may be lost by racemization of products released from the catalytic carbonylation cycle. In the present study, this could occur at either the mixed anhydride or acid stages. The thermal instability of the proposed mixed formic anhydride makes direct studies of its racemization difficult. When sodium acetate is employed in place of sodium formate in the carbonylation of acetate **2d**, acid **1** can once again be isolated from the reaction following aqueous workup. In these cases, however, the product is invariably racemic. This would suggest that the mixed acetic anhydride that would be anticipated to form[27] is configurationally unstable under

(17) (a) Stevens, R. R.; Shier, G. D. *J. Organomet. Chem.* **1970**, *21*, 495. (b) Becker, Y.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 845.
(18) (a) Roberts, J. S.; Klabunde, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 2509. (b) Sonoda, A.; Bailey, P. M.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1979**, 346.
(19) Becker, Y.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 845.
(20) Schijf, R.; Stevens, W. *Recl. Trav. Chim.* **1966**, *85*, 627.
(21) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
(22) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268.
(23) Control studies performed in the absence of palladium catalyst with **2a**, **2d**, and **2e** established that these substrates are configurationally stable in 1:1 DMF/toluene at 120 °C for at least 24 h.
(24) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, 2301.
(25) Use of (±)-d_3-**2d** with deuterium incorporation at the ethyl β-carbon led to a large increase in the iso/n ratio of the product mixture and no detectable scrambling of isotope in the 2-arylpropanoic acid.
(26) When 4-methylstyrene was included in the hydroxycarbonylation mixture containing acetate **2d** under conditions where iso/n isomerization is facile (120 °C, 100 psig CO), *p*-tolylpropanoic acids were produced together with naproxen and **4**, presumably by exchange of olefin ligands in intermediate **22**. In the absence of ester, only traces of the styrene carbonylation products were observed.

the reaction conditions. Indeed, when (S)-naproxen is heated to 120 °C in 1:1 DMF/toluene with 1 equiv of acetic anhydride (conditions similar to those reported to produce the mixed acetic anhydride[28]) for 24 h, the optical purity of the isolated acid drops by over 72%. This suggests that the isolation of optically active 2-arylpropanoic acids in the formate-mediated hydroxycarbonylation is at least partly a consequence of the instability of the formic anhydride, which decomposes before extensive racemization can occur.

As previously discussed, carbonylation reactions taken to low conversion generally provide 2-arylpropanoic acids with optical purities comparable to those of the secondary alcohols used to prepare the substrate esters. At high conversion (long reaction time), however, optical purities tend to be much lower or even zero. This implies that a process which racemizes the acid must be operative in this system. Although naproxen itself is quite configurationally stable in 1:1 DMF/toluene at 120 °C, its optical purity falls by ca. 37% in 24 h in the presence of the full carbonylation reagent mixture. By a process of elimination, it was concluded that sodium formate is the reagent responsible for racemization.[29] This racemization process was unaffected by the addition of water, and probably reflects slow enolization of the propanoic acid by formate. That formate, which appears to be essential for the stereoselective hydroxycarbonylation of chiral 1-arylethyl esters, is itself an agent that racemizes the product acid underscores a major limitation of this method.

Conclusions

Palladium(0)-catalyzed hydroxycarbonylation of 1-arylether esters to 2-arylpropanoic acids can be accomplished in the presence of 1 equiv of formate salt provided that the aryl substituent is a naphthyl or higher polycyclic ring system. Halobenzoate esters are carbonylated by using Pd(monodentate triarylphosphine)$_n$ precursors, but less reactive acetate and formate esters require use of the bidentate ligand 1,3-bis(diphenylphosphino)propane. Optically active 1-arylethyl esters can provide optically active 2-arylpropanoic acids with net inversion of configuration at carbon, but preservation of stereochemical information is highest at low substrate conversion (shorter reaction times). This observation is most easily accommodated by invoking racemization of either the penultimate carbonylation product (mixed formic anhydride) or the 2-arylpropanoic acid under the reaction conditions employed.

Experimental Section

Materials. Palladium dichloride, palladium acetate, triphenylphosphine, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, tris(*p*-tolyl)phosphine, tris(*p*-chlorophenyl)phosphine, and tris(*p*-anisyl)phosphine were purchased from Aldrich Chemical Co. and used as received. Tetrakis(triphenylphosphine)palladium,[30] bis(triphenylphosphine)palladium dichloride,[31] (1,3-bis(diphenylphosphino)propane)palladium dichloride,[32] and bis(dibenzylideneacetone)palladium[33] were prepared by literature procedures.

Acetonitrile, *N,N*-dimethylformamide (DMF), and toluene were dried over 4-Å molecular sieves, while tetrahydrofuran (THF) and 1,2-dimethoxyethane were distilled from sodium benzophenone ketyl before use. Sodium formate (Aldrich), calcium formate (Fluka), formic acid (Aldrich), and triethylamine (Mallinckrodt) were used without further purification. Carbon monoxide (Matheson, 99.5%) was used as received.

(*R*)- and (*S*)-1-phenylethyl alcohols ($[\alpha]^{22}_D$ +39.5° (neat) and −41.3° (neat), respectively, Aldrich), 4-fluoroacetophenone (Aldrich), 4-methoxyacetophenone (Aldrich), 4-isobutylacetophenone (Lancaster), 2-acetyl-6-methoxynaphthalene (Syntex Chemicals), 1-acetylnaphthalene (Aldrich), 2-acetylnaphthalene (Aldrich), and 9-acetylphenanthrene (Aldrich) were used without purification. The corresponding *R* alcohols were prepared by asymmetric hydroboration according to the method of Corey et al.[11] Physical data for these compounds, all of which have been previously reported, is available as supplementary material. The optically active carbonylation substrates were prepared by standard acylation techniques. Characterization data for these esters and for all previously reported carbonylation products is also available as supplementary material.

Physical Measurements. Proton NMR spectra were recorded on Varian EM-390 (90 MHz), Bruker WM-300 (300 MHz), or Bruker AM-500 (500 MHz) spectrometers and are reported in ppm (δ) downfield from an internal Me_4Si standard. Proton-decoupled ^{13}C NMR spectra were obtained on a Bruker AM-500 spectrometer operating at 125.8 MHz and are referenced to external Me_4Si using the carbon resonance of $CDCl_3$ at 77.0 ppm. Infrared spectra were recorded on a Nicolet Model 5PC FTIR spectrometer. Mass spectra were obtained from either a Varian MAT 311A or a Finnigen MAT 8230 instrument. Optical rotations were measured in $CHCl_3$ solution on a Jasco DIP-360 digital polarimeter. Combustion analyses were performed by the Analytical and Environmental Research Department of Syntex Research.

Gas chromatographic analyses were performed on a Varian 3400 chromatograph fitted with a 30-m Chirasil-Val capillary column (1-arylethanols) or a 30 m × 0.25 mm i.d. DB-5 capillary column (1-menthyl esters of 2-arylpropanoic acids). High performance liquid chromatography analyses were conducted on a Spectra-Physics SP8000 chromatograph equipped with either a 5μ 4.6 × 250 mm Regis Pirkle covalent D-naphthylalanine column ((3,5-dinitrophenyl)carbamates of 1-arylethanols) or a Spherisorb ODS II 5μ 4.6 mm × 250 mm column (l-methyltyrosine amides of 2-arylpropanoic acids). Enantiomer ratio determinations performed by both GC and HPLC methods typically agreed to within ±5%.

Apparatus. All carbonylation reactions were conducted in a magnetically stirred, glass-lined, 45-mL capacity Parr autoclave constructed of Hastelloy C.

Hydroxycarbonylation of Chiral 1-Arylethyl Benzoates. Typical Procedure. The 1-arylethyl ester (1.07 mmol), palladium dichloride (0.020 g, 0.11 mmol), triphenylphosphine (0.086 g, 0.33 mmol), and sodium formate (0.089 g, 1.31 mmol) were suspended in 10 mL of a degassed 1:1 DMF/toluene mixture within a 20-mL Pyrex sleeve under N_2. The reactor was then sealed and the bomb atmosphere replaced by CO by means of three pressurization (200 psig)/vent cycles. After pressurizing the reactor to 100 psig, the bomb was heated in an oil bath to 120 (± 10) °C for 23.3 h. The reactor was then cooled to ambient temperature and excess CO was released. Dilute HCl (2 mL of a 1 N solution) was added to the product suspension, and the resultant biphasic mixture was filtered through a 1-cm Celite pad with the aid of small portions of toluene (3 × 5 mL). The filtrate was washed with water (3 × 30 mL) to remove DMF and then extracted with 1 N Na_2CO_3 (3 × 25 mL). The combined extracts were acidified to pH 2 with concentrated HCl and the precipitated acids were extracted into CH_2Cl_2 (3 × 20 mL). After drying the CH_2Cl_2 solution over Na_2SO_4 (1 g), the product acids were then isolated by evaporation of solvent under reduced pressure.

Hydroxycarbonylation of Chiral 1-Arylethyl Acetates and Formates. Typical Procedure. The 1-arylethyl ester (1.23

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mmol), palladium dichloride (0.026 g, 0.14 mmol), 1,3-bis(diphenylphosphino)propane (0.055 g, 0.13 mmol), and anhydrous sodium formate (0.103 g, 1.52 mmol) were loaded into a 20-mL Pyrex sleeve under dry nitrogen. The mixture was then suspended in 10 mL of a degassed 1:1 DMF/toluene mixture, and the atmosphere above the suspension was replaced with CO by repetitively pressurizing the reactor with CO to 200 psig and then releasing pressure in a well-ventilated hood. The reaction vessel was pressurized to 650 psig with CO and heated in an oil bath to 120(± 10) °C for 50 h. After cooling the vessel to ambient temperature, excess CO was vented and 2 mL of 1 N HCl were added to the yellow-orange product mixture. The resultant biphasic mixture was filtered through a 1-cm pad of Celite to remove precipitated salts and palladium black, and the filter cake was rinsed with toluene (3 × 5 mL). The filtrate was washed with water (4 × 25 mL) to remove DMF and then extracted with 1 N KOH (4 × 25 mL). The combined extracts were rinsed with fresh toluene (1 × 10 mL) and then acidified to pH 1 with concentrated HCl. The precipitated acids were extracted into CH_2Cl_2 (3 × 20 mL), and the combined extracts were dried over anhydrous Na_2SO_4 (1 g). The CH_2Cl_2 solution was then filtered and the product acids were isolated by evaporation of solvent under reduced pressure.

Acknowledgment. We thank Professor E. J. Corey and Professor Jeffrey Schwartz for useful discussions and suggestions concerning this work.

Registry No. 1, 22204-53-1; **2a**, 129967-27-7; **2b**, 129967-28-8; **2c**, 129967-29-9; **2d**, 108781-66-4; **2e**, 129967-30-2; **4**, 3453-40-5; **7**, 84194-78-5; **8**, 26159-40-0; **9**, 3243-42-3; **10**, 84194-78-5; **11**, 26159-40-0; **12**, 21658-35-5; **13**, 129967-31-3; **14**, 130060-20-7.

Supplementary Material Available: Characterization data for optically active 1-arylethanols, optically active 1-arylethyl esters, and 2- and 3-arylpropanoic acids, table of aryl methyl ketone asymmetric hydroboration yields, and ^1H NMR spectra of 1-arylethanols (11 pages). Ordering information is given on any current masthead page.

Preparation of 3-Amino-4-(hydroxymethyl)azetidin-2-ones from the Reaction of Glycine Enolates with Imines of a Glycoaldehyde

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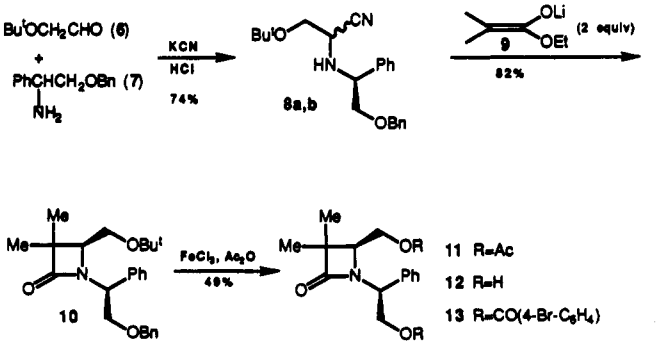
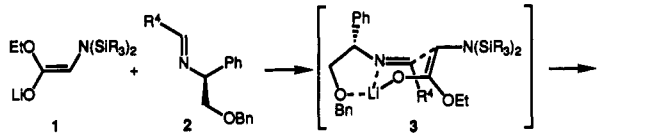
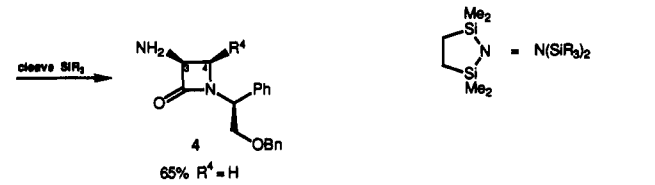
Received March 16, 1990

The preparation of β-lactams from the condensation of imines with metallo enolates (M = Al, B, Li, Mg, Sn, Zn, or Zr) has recently undergone a renaissance.[1] In an earlier disclosure from our laboratories, we reported that a wide variety of 4-unsubstituted β-lactams could be prepared in one step from the reaction of lithium ester enolates with formaldehyde imines, the latter intermediates being generated in situ from cyanomethyl amines.[2] Notably, 1,4-asymmetric induction in forming the C-3 stereogenic center was high (11:1) in condensations of the protected glycine enolate 1[3] with formaldehyde imines of phenylglycinol (e.g. 1, R^4 = H). Condensations of this type result in a useful asymmetric synthesis of 3-aminoazetidin-2-ones.[2] The stereoinduction observed in forming 4 (R^4 = H) was rationalized by a chelated closed transition state (3, R^4 = H).[2,4]

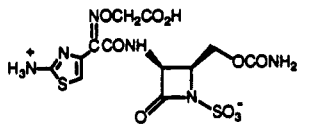
Scheme I







Stimulated by the clinical development of the monocyclic β-lactam carumonam (5),[5] we investigated the possibility of preparing 3-amino-4-(hydroxymethyl)azetidin-2-ones by related condensations of glycoaldehyde-derived imines (eq 1, R^4 = CH_2OR). If these condensations occurred in the sense suggested in transition-state model 3, the desired cis orientation of the β-lactam substituents at C-3 and C-4 would result. In this note we report the first examples of lithium ester enolate condensations of enolizable glycoaldehyde imines.[6,7]



carumonam (5)

Although a few examples of the successful addition of basic metallo ester enolates to enolizable imines have now

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