Catalytic Synthesis and Asymmetric Reduction of Pyridylglyoxylic Amides and Esters

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Abstract: The preparation of 2-pyridyl- and 4-pyridylglyoxylic esters and amides in moderate to high yields via palladium-catalyzed double carbonylation of 2-iodo- and 4-iodopyridines is reported. The effect of temperature, CO pressure, solvent, nature and concentration of nucleophile, nature of catalyst precursor, and substituents on iodopyridines has been investigated. The reduction of 4-pyridylglyoxylate esters into the corresponding α-hydroxy esters via ruthenium-catalyzed asymmetric hydrogenation or using alpine-borane proceeded in high yields but poor enantioselectivity. The results for the carbonylation and the hydrogenation catalytic processes are discussed in terms of electronic effects induced by the pyridyl ring.

Keywords: asymmetric hydrogenation; double carbonylation reactions; α-keto acid derivatives; palladium catalysts; pyridine

Introduction

Arylglyoxylic acid derivatives are versatile intermediates in organic synthesis for α-hydroxy acids, α-amino acids, and others;[1] they also play an important role in biological studies.[2] However, access to such compounds having an *N*-heteroaryl group, e. g., pyridylglyoxylic acid derivatives, remains very limited because the classical synthetic methods are unsatisfactory. Reported alternatives gave only poor yield or were effective with specific substrates and used harmful reagents: oxidation by SeO_2 of 3-acetylpyridine afforded 3-pyridylglyoxylic acid in ca. 70% yield but was totally ineffective for 2- and 4-acetylpyridine.[3] The coupling of 2-tributylstannylpyridine with ethyl chloroglyoxylate proceeded with loss of carbon monoxide giving useless amounts of ethyl 2-pyridylglyoxylate.[4] An amide derivative of the latter, *N*,*N*-diethyl-2-pyridylglyoxamide, was prepared in 80% yield through oxidation by SeO_2 of an appropriately 3-substituted [1,2,3]triazolo[1,5-*a*]pyridine with concomitant loss of nitrogen.[5]

In this study, we envisioned the double carbonylation of iodopyridines, which are readily attainable starting materials, as a practical, general preparation of pyridylglyoxylic acid derivatives. The palladium-catalyzed double carbonylation of aryl halides has been extensively studied.[6] This method provides an efficient route to convert a variety of functionalized aryl iodides and bromides into α-keto acids,[7] esters,[8] and amides,[1b, 9] by suitable choice of the nucleophile used. However, the rare attempts to apply it to *N*-heteroaryl halides suggested a poor efficiency for this class of substrates. In fact, carbonylation of 3-bromopyridine with diethylamine afforded the desired α-keto amide in 55% yield and selectivity,[10] and the 2-butyl α-keto ester of 2-iodoquinoline was formed in only 22% yield and selectivity.[11] We now describe that such a double carbonylation process does allow the preparation, in moderate to high yields, of different pyridylglyoxylic amides and esters, provided an adequate adjustment of the reactions parameters is undertaken.[12] Attempts to enantioselectively reduce 4-pyridylglyoxylate esters to form the corresponding chiral pyridyl α-hydroxy esters, an as yet unexplored but interesting class of compounds, are also discussed.

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Table 1. Palladium-catalyzed α-ketoamidocarbonylation of 4-iodopyridine (**1**) with $HNEt_2$.[a]

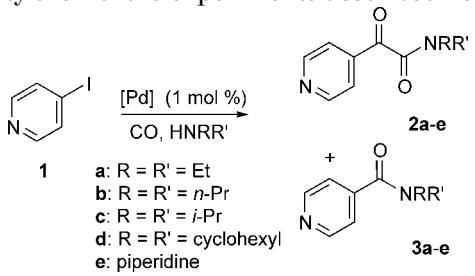
Entry	Catalyst precursor	Solvent	*P*(CO) (atm)	Time[b] (h)	Conversion of **1** (%)[c]	Selectivity for **2a** (%)[c]
1	$Pd(OAc)_2$	CH_2Cl_2	60	60	48	37
2	$Pd(OAc)_2$	Pyridine	60	60	97	30
3	$PdCl_2(PPh_3)_2$	CH_2Cl_2	60	5	100	50
4[d]	$PdCl_2(PPh_3)_2$	CH_2Cl_2	60	5.5	100	66
5[d]	$PdCl_2(PPh_3)_2$	acetone	60	6	100	28
6	$PdCl_2(PPh_3)_2$	$HNEt_2$	60	3.5	100	16
7	$PdCl_2(PPhMe_2)_2$	CH_2Cl_2	60	28	100	61
8	$Pd(OAc)_2$ + 3 PPh_2Me	CH_2Cl_2	20	90	85	78
9	$Pd(OAc)_2$ + 3 PPh_2Me	CH_2Cl_2	60	30	25	>99
10	$Pd(OAc)_2$ + 1.5 dppb	CH_2Cl_2	60	40	92	60
11	$Pd(OAc)_2$ + 3 [2-PyrPPh$_2$]	CH_2Cl_2	60	4	100	40
12	$Pd(OAc)_2$ + 3 PCy_3	CH_2Cl_2	10	60	90	84
13	$Pd(OAc)_2$ + 3 PCy_3	CH_2Cl_2	30	20	100	93
14	$Pd(OAc)_2$ + 3 PCy_3	CH_2Cl_2	60	6	100	95 (90)
15	$Pd(OAc)_2$ + 3 PCy_3	CH_2Cl_2	120	20	100	95
16[e]	$Pd(OAc)_2$ + 3 PCy_3	CH_2Cl_2	60	53[e]	100	86[e]
17	Pd(dba)(PCy_3)$_2$	CH_2Cl_2	60	6.5	100	93

[a] Unless stated otherwise, reactions were carried out at 50 °C using 2.45 mmol of **1**, 12 mmol of $HNEt_2$, and 0.0245 mmol of Pd in 30 mL of solvent.
[b] Reaction time was not necessarily optimized.
[c] Determined by quantitative GLC, figures in parentheses are yields of isolated, pure product. Compound **3a** accounts for the balance.
[d] 8.1 mmol of $HNEt_2$ and 45 mL of solvent were used.
[e] Pd = 0.00245 mmol (0.1% vs. **1**).

Results and Discussion

Synthesis of Pyridylglyoxamides

The yields of α-keto amides produced by double carbonylation are affected by various factors including the nature of the catalyst, substrate, amine, CO pressure, solvent, and temperature.[9] Appropriate conditions for the double carbonylation of iodopyridines were first sought by using 4-iodopyridine (**1**) as starting material. Based on previous results regarding the reactivity of non-heteroaryl halides,[9] diethylamine was selected as the most suitable secondary amine for obtaining α-keto amides. Table 1 summarizes the performance of various catalytic systems for this reaction. In all cases, the sole products observed were the expected *N,N*-diethyl-2-pyridylglyoxamide (**2a**) and *N,N*-diethyl-4-nicotinamide (**3a**), the monocarbonylation product (Scheme 1). Rigorous purification of the iodopyridines via column chromatography and subsequent recrystallization appears to be a prerequesite for high activity and selectivity as well as for reproducibility of all of the experiments described herein.



Scheme 1. α-Ketoamidocarbonylation of 4-iodopyridine.

Amidocarbonylation of **1** proceeds with such a simple catalyst precursor as palladium(II) acetate (entries 1–2). Nonetheless, the presence of tertiary phosphine ligands is required to develop catalytic activities and interesting selectivities for **2a**. Selectivity for α-keto amide formation was not high when a simple triphenylphosphine-coordinated complex was used (entries 3–6). Previous studies devoted to α-ketoaminocarbonylation have shown that best results are obtained with rather high basicity and bulky phosphines such as methyldiphenylphosphine and the chelating ligand diphenylphosphinobutane (dppb).[9] In the present case, virtually complete selectivity was indeed achieved when PPh_2Me was employed but the reaction rate was low (entry 9). Much more surprisingly, the catalyst system based on dppb proved to be inefficient (entry 10). The most satisfactory results regarding yield and selectivity were achieved using tricyclohexylphosphine-based catalysts (entries 12–17). Although Pd–PCy_3 catalysts have been extensively used for the synthesis of α-keto esters[8] (*vide infra*), their use in α-ketoaminocarbonylation remains largely unexplored.[9f] The combination of Pd(II) acetate with 3 equivalents of PCy_3 (entry 14), which is considered to generate catalytically active Pd(0) species under the reaction conditions,[13] showed nearly identical abilities as an equivalent preformed, zero-valent Pd–PCy_3 complex (entry 17); namely, at moderate reaction temperature of 50 °C and CO pressure of 60 atm, 1 mol % of these systems afforded α-keto amide **2a** in 93–95% yield. Under these conditions the substrate-to-catalyst ratio could be increased up to 1000

without affecting the turnover frequency but the selectivity was somewhat lower (entry 16).

The influence of the CO pressure is shown in entries 8–9 and 12–15. Higher pressure in the range 10 to 120 atm appears to be favorable for both the reaction rate and the selectivity although maximal selectivities are already reached under 60 atm. The influence of the reaction temperature with the Pd-PCy_3 catalytic system and upon using $PdCl_2(PPh_3)_2$ as the catalyst precursor is illustrated in Figure 1 and Figure 2, respectively. The same trend was found for both of the catalyst systems. As expected the reaction rate rapidly increased with temperature but the selectivity featured an optimum at ca. 50 °C; above this temperature, the selectivity markedly decreased. The solvent effect and the influence of the nucleophile concentration were briefly studied using $PdCl_2(PPh_3)_2$ as the catalyst precursor (entries 3–6). The results indicate that solvents of relatively low dielectric constants such as dichloromethane and a decrease in the nucleophile concentration favored the formation of α-keto amide. In particular, carrying out the reaction in neat diethylamine afforded a significantly lower yield of **2a**; this is in sharp contrast with previous results for double carbonylation of simple aryl halides, e. g., PhI and PhBr, where amines are used in large excess and are considered to serve as good solvents for promoting the formation of α-keto amides.[9b]

Amines used in the double carbonylation reaction have a considerable influence on the yields and selectivities as summarized in Table 2. Good yields for α-keto amides **2** are obtained with amines of high basicity and moderate steric demands. The bulkiest amine, *N*,*N*-dicyclohexylamine (**d**), was totally ineffective and *i*-Pr_2NH (**c**) gave almost exclusively amide **3c**. The selectivity decreases in the order Et_2NH (**a**) > *n*-Pr_2NH (**b**) ≅ piperidine (**e**) > *i*-Pr_2NH (**c**). A primary amine such as *n*-$BuNH_2$ (**f**) also serves as the reagent for the double carbonylation. However, this reagent further reacts with the α-keto group of the primary product to afford the Schiff's base of the α-keto amide (Scheme 2);[14] imine **4** was thus isolated in high yield, comparable to those for α-keto amides **2** produced from effective secondary amines.

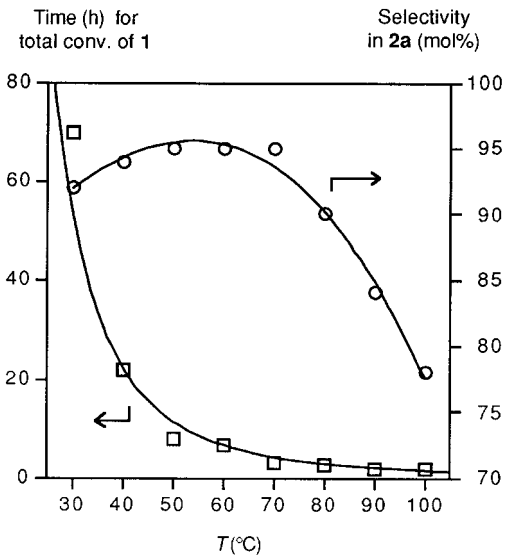


Figure 1. Temperature dependence of catalytic activity and selectivity for α-ketoamidocarbonylation of **1** using $Pd(dba)(PCy_3)_2$ as the catalyst precursor {P(CO) = 60 atm; [$HNEt_2$] = 0.39 M in CH_2Cl_2; **1**/Pd = 100}.

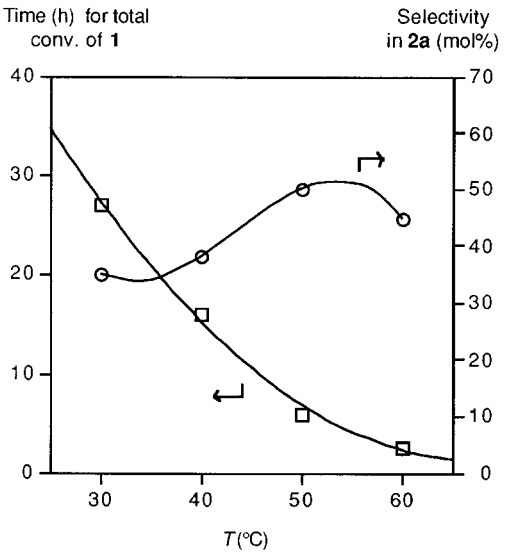


Figure 2. Temperature dependence of catalytic activity and selectivity for α-ketoamidocarbonylation of **1** using $PdCl_2(PPh_3)_2$ as the catalyst precursor {P(CO) = 60 atm; [$HNEt_2$] = 0.39 M in CH_2Cl_2; **1**/Pd = 100}.

Table 2. Palladium-catalyzed α-ketoamidocarbonylation of 4-iodopyridine (**1**) with various amines.[a]

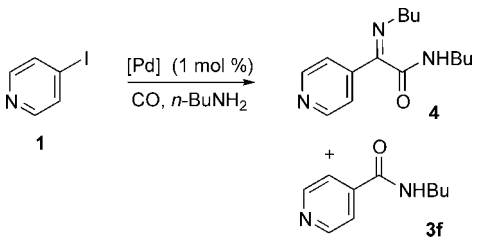
Entry	Amine	Time[b] (h)	Conversion of **1** (%)	Selectivity for **2**/**4** (%)[c]
18	*n*-Pr_2NH	41	100	90 (81)
19	*i*-Pr_2NH	90	10	10
20[d]	*i*-Pr_2NH	41	70	10
21	(cyclohexyl)$_2$NH	24	<<	–
22	Piperidine	23	100	90 (80)
23	*n*-$BuNH_2$	23	100	92 (81)

[a] P(CO) = 60 atm, T = 50 °C, 2.45 mmol of **1**, 12 mmol of amine, 0.0245 mmol of $Pd(OAc)_2$, 0.0735 mmol of PCy_3, 30 mL of CH_2Cl_2.
[b] Reaction time not necessarily optimized.
[c] GLC data; compounds **3b–f** account for the balance; figures in parentheses are yields of isolated, pure product.
[d] T = 70 °C.

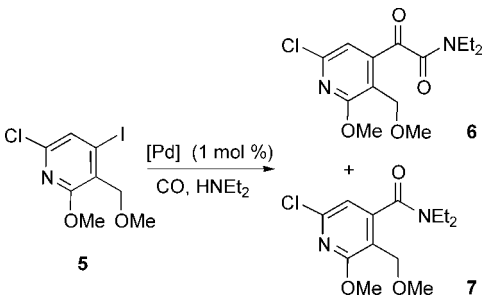
Table 3. Palladium-catalyzed α-ketoamidocarbonylation of iodopyridines **5** and **8** with $HNEt_2$.[a]

Entry	Substrate	Catalyst precursor	*T* (°C)	*P*(CO) (atm)	Time[b] (h)	Product[c]	Selectivity[c] (%)
24	**5**	$PdCl_2(PPh_3)_2$	40	90	31	**6**	75
25	**5**	$Pd(dba)(PCy_3)_2$	40	90	20	**6**	93 (82)
26	**8**	$PdCl_2(PPh_3)_2$	50	60	3	**9**	15
27	**8**	$Pd(dba)(PCy_3)_2$	50	60	3.5	**9**	58 (52)

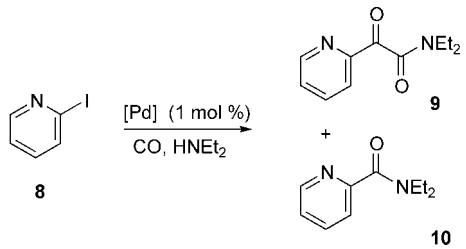
[a] 2.45 mmol of **5** or **8**, 12 mmol of $HNEt_2$, 30 mL of CH_2Cl_2, 0.0245 mmol of $Pd(dba)(PCy_3)_2$.
[b] Optimized reaction time for total conversion of iodopyridine.
[c] GLC data; compounds **7** and **10**, respectively, account for the balance; figures into parentheses are yields of isolated, pure product.



Scheme 2. *In situ* formation of Schiff's base via double carbonylation/enamination of 4-iodopyridine.



Scheme 3. α-Ketoamidocarbonylation of functional 4-iodopyridine **5**.



Scheme 4. α-Ketoamidocarbonylation of 2-iodopyridine.

Table 3 compares reactions of two other iodopyridines with CO in the presence of $HNEt_2$. The polyfunctional 4-iodopyridine **5** gave, under slightly modified reaction conditions, similar results to its non-substituted analogue **1** (entries 24–25) (Scheme 3). α-Keto amide **6**, which may serve as a useful building block for further synthesis,[15] was obtained in 93% yield with the Pd–PCy_3 catalyst system. This shows that introduction of substituents at the *meta*- as well as at the *ortho*-positions on the pyridine ring does not affect significantly the selectivity for double carbonylation. On the other hand, the reaction rates with both catalyst systems investigated seemed to be decreased to nearly the quarter of those for **1**, which evidently stems from a steric effect of the adjacent methoxymethyl group; a comparable drop in reactivity by introduction of methyl group(s) at the *ortho*-position(s) has been previously observed in ketoamidocarbonylation of phenyl bromides.[9b] In contrast, the reaction of 2-iodopyridine (**8**) led to a much lower selectivity for α-keto amide formation and somewhat higher reaction rates (entries 26–27) (Scheme 4). This reflects electronic effects due to the vicinity of the nitrogen atom and the possible involvement of the nitrogen lone pair in the reactivity of Pd intermediates toward the elementary steps (CO insertion, nucleophile attack, reductive elimination) of the catalytic cycle. Enhanced reactivity of the *ortho* C–X bond (X = Cl, Br) in 2,3- and 2,4-dihalopyridine compounds during palladium-catalyzed alkoxycarbonylation processes has been recently reported by us and others although the selectivity issue could not be addressed in these reactions.[16]

Synthesis of Pyridylglyoxylic Esters

Some α-keto amides may prove resistant to hydrolysis which could somewhat limit their interest as synthetic intermediates. It is thus sometimes desirable to perform the double carbonylation using alcohol to obtain α-keto esters. However, this catalytic process is known to proceed more slowly than the one performed in the presence of amines and, above all, the selectivities for α-keto esters are usually lower in spite of more severe experimental conditions.[8]

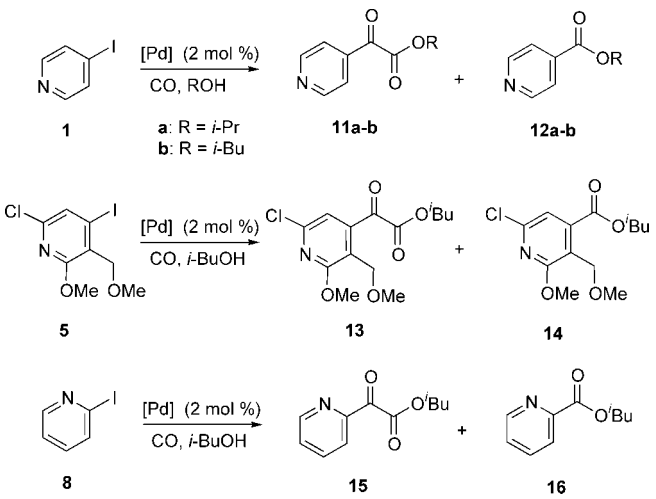
Table 4 summarizes the results obtained for the reactions of iodopyridines **1**, **5**, and **8** in the presence of 2-propanol or 2-butanol using triethylamine as the base (Scheme 5). The formation of α-keto esters **11a, b** from iodopyridine **1** was best achieved with a Pd-PCy_3 catalyst at 50 °C under 90 atm of CO. Tricyclohexylphosphine has often been claimed to be one of the most efficient ligands for α-keto ester synthesis.[8] In our studies, the divalent complex $PdCl_2(PCy_3)_2$ proved to be a sluggish, although selective, catalyst precursor (entry 29). Conversely, the

Table 4. Palladium-catalyzed α-ketoalkoxycarbonylation of iodopyridines **1**, **5**, and **8**.[a]

Entry	Substrate	Catalyst precursor	ROH	*T* (°C)	Time[b] (h)	Conversi on[b] (%)[c]	Product	Selectivity[c] (%)
28	**1**	$PdCl_2(PPh_3)_2$	2-PrOH	50	23	100	**11a**	45
29	**1**	$PdCl_2(PCy_3)_2$	2-PrOH	50	22	15	**11a**	75
30	**1**	$Pd(dba)(PCy_3)_2$ [d]	2-PrOH	40	25	95	**11a**	67
31	**1**	$Pd(dba)(PCy_3)_2$ [d]	2-PrOH	50	22	100	**11a**	70 (50)
32	**1**	$Pd(dba)(PCy_3)_2$ [d]	2-PrOH	60	23	100	**11a**	45
33	**1**	$Pd(dba)(PCy_3)_2$ [e]	2-PrOH	50	40	100	**11a**	75
34	**1**	$Pd(dba)(PCy_3)_2$ [d]	2-BuOH	50	48	100	**11b**	72 (55)
35	**1**	$Pd(dba)(P^tBu_3)_2$ [d]	2-PrOH	50	18[f]	100[f]	**11a**	12
36	**1**	$Pd(dba)(P(OMe)_3)_2$ [d]	2-PrOH	50	43	77	**11a**	24
37	**5**	$Pd(dba)(PCy_3)_2$ [d]	2-BuOH	50	22	100	**15**	31 (15)
38	**8**	$Pd(dba)(PCy_3)_2$ [d]	2-BuOH	50	140	100	**15**	16 (5)

[a] Reactions were carried out under 90 atm of CO in CH_2Cl_2 (25 mL) using 2.45 mmol of **1**, 30 mmol of ROH, 15 mmol of NEt_3, 0.049 mmol of Pd.
[b] Reaction time not necessarily optimized for the stated conversion of iodopyridine.
[c] Determined by quantitative GLC; figures into parentheses are yields of isolated, pure product. Compounds **12**, **14**, and **16** account for the balance, respectively.
[d] Prepared from $Pd_2(dba)_3$ and 2 equivalents (vs. Pd) of phosphine.
[e] 4 equivalents (vs. Pd) of phosphine were used.
[f] 60% conversion and 15% selectivity after 1.5 h.

preformed, zero-valent catalyst $Pd(dba)(PCy_3)_2$ allowed total conversions of **1** into **11a, b** in reasonably short reaction times (entries 30–34). With the latter system, addition of excess ligand (P/Pd = 4) caused a decrease in the reaction rate with a slight increase in the final selectivity (entry 33). Insignificant variations in the final selectivity for **11a, b** were observed upon varying the relative concentrations of **1**, NEt_3, and the secondary alcohol in a 2-fold range. Also, replacing 2-PrOH by 2-BuOH resulted in a noticeable decrease in the reaction rate but had no effect on the final yields which were in the range 70–75% (entry 34).



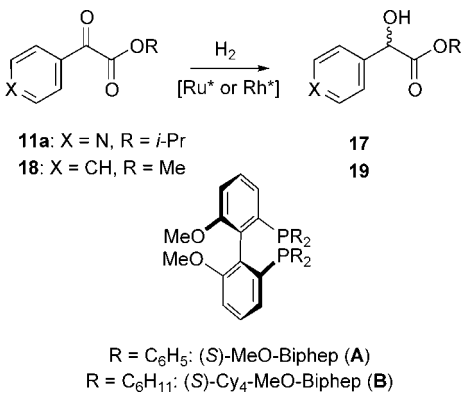
Scheme 5. α-Ketoalkoxycarbonylation of iodopyridines.

To our knowledge, these combined high activity and selectivity data are the best reported in the case of synthesis of α-keto esters. Formation of 2-butyl phenylglyoxylate from iodobenzene with a similar Pd-PCy_3 catalyst system proceeded in comparable selectivity but with a slower reaction rate.[8a] This suggests that the N atom in the 4-substituted heteroaryl ring does not affect selectivity but activates the catalytic process. It must be noted that, contrary to the formation of pyridylglyoxamides **2a-e**, a noticeable drop in selectivity with the progress of time was observed with all of the catalyst systems investigated. In a typical example (entry 34), the zero-valent Pd-PCy_3 system showed a high selectivity at the early stage of the reaction (ca. 99% selectivity for 5% conversion, 2.5 h), but the selectivity gradually decreased (90% selectivity for 17% conversion, 5 h; 82% selectivity for 67% conversion, 22 h) to reach 72% at total conversion. Another significant difference with the catalytic process carried out in the presence of amines is the much lower tolerance to substituents on the aryl ring. The polyfunctional 4-iodopyridine **5** and 2-iodopyridine **8** did not afford more than 31% and 16% selectivity into the corresponding 2-butyl α-keto esters, respectively. This clearly limits the practical interest of double carbonylation in the presence of alcohols to the production of non-substituted 4-pyridylglyoxylate esters.

Synthesis of 4-Pyridylglycolate Esters

α-Hydroxy acids, esters and amides are of great interest for many purposes, especially when they are optically active.[1e,1f] As for pyridylglyoxylic acid deriva-

tives, very few routes towards the pyridylglycolic acid derivatives $(C_5R_5N)CH(OH)CO_2R$ have been reported.[5,17] A typical synthesis involves cyanation of pyridine-carboxaldehyde and subsequent hydrolysis of the resulting cyanohydrin under acidic or esterification conditions.[17] As far as chirality is concerned, there is, to our knowledge, no report in the literature about optically active pyridylglycolic acid derivatives. Among the numerous asymmetric reduction techniques existing, the asymmetric hydrogenation of α-keto acid derivatives provides an elegant and efficient entry to chiral 2-hydroxyarylacetic compounds.[1c,1e,1f] In particular, some ruthenium-catalysts bearing atropisomeric bisphosphines, e.g., Binap, Bichep, and MeO-Biphep, reduce phenylglyoxylates to the corresponding mandelic esters in 80–99% ee.[18] We have thus investigated the performance of such catalysts in the asymmetric hydrogenation of 2-propyl 4-pyridylglyoxylate (**11a**) and of methyl phenylglyoxylate (**18**), respectively chosen as model pyridyl and reference substrates (Scheme 6).



Scheme 6. Ruthenium-catalyzed asymmetric hydrogenation of 4-pyridylglyoxylate **11a**.

Table 5 shows that $[RuBr_2\{(S)\text{-MeOBiphep}\}]$[18c] enables complete conversion of α-keto esters **18** and **11a** under relatively mild conditions in MeOH to give high yields of α-hydroxy esters **19** and **17**, respectively. In contrary to mandelates such as **19** which are completely air-stable, we observed that alcohol and chloroform solutions of pyridylglycolate **17** turned back to **11a** upon exposure to air at room temperature within a few days. Solutions of **17** were thus handled under inert atmosphere. However, hydrogenation of **11a** proceeded in much lower enantioselectivity than that of **18**. Low ee's for **17** were obtained on using other solvents and/or catalysts; e.g., the *in situ* combination $[Rh(COD)Cl]_2$/(*S*)-MeOBiphep in toluene afforded **17** in 94% yield (41 h) and ca. 0% ee. This unexpected drop in enantioselectivity stems possibly from a modification of the active catalyst species by coordination of the pyridyl function of the substrate onto the metal center. This hypothesis is supported by a control experiment that consisted in hydrogenating **18** in the presence of 1 equivalent of pyridine; in this case, methyl mandelate (**19**) was recovered in high yield but low enantioselectivity (entry 44), comparable to those observed for the reduction of **11a** in **17** (entries 39–42). To prevent this unfavorable interaction, several attempts aiming at protecting the pyridyl function were evaluated in the hydrogenation of **18**. The latter was almost completely inhibited when 1 equivalent (vs. **18**) of pyridine oxide was used. Conversely, the presence of 1 equivalent of a pyridinium salt $[C_5H_5NR][X]$ (R = H, X = Br, BF_4; R = Me, X = I) did not affect the catalytic activity and afforded ee's for **18** ca. 20 points lower than the reference value (compare entries 45–47 and 43); a better restoration of enantioselectivity was observed upon using an excess of HBF_4 although catalytic activity was somewhat decreased (entry 48). Nonetheless,

Table 5. Hydrogenation of methyl phenylglyoxylate (**18**) and 4-pyridylglyoxylate **11a**.[a]

Entry	Substrate	Catalyst	Additive (mol equiv. vs. **11a/18**)	Time[b] (h)	Conversion[b] (%)[c]	ee, configuration[d] (%)
39	**11a**	Ru–**A**	–	21	100	10 (+)
40	**11a**	Ru–**B**	–	17	93	5 (+)
41	**11a**	Ru–**A**	HBF_4 (1)	21	88	20 (+)
42	**11a**	Ru–**A**	$[C_5H_6N][Br]$ (1)	15	100	25 (+)
43	**18**	Ru–**A**	–	21	98	84 (*S*)
44	**18**	Ru–**A**	C_5H_5N (1)	21	100	20 (*S*)
45	**18**	Ru–**A**	$[C_5H_6N][Br]$ (1)	19	93	64 (*S*)
46	**18**	Ru–**A**	$[C_5H_5NMe][I]$ (1)	45	97	64 (*S*)
47	**18**	Ru–**A**	$[C_5H_6N][BF_4]$ (1)	40	100	66 (*S*)
48	**18**	Ru–**A**	$[C_5H_6N][BF_4]$ (1), HBF_4 (5)	70	100	74 (*S*)

[a] Reactions were carried out under 20 atm of H_2 in MeOH (20 mL) at 50 °C using 0.6 mmol of substrate and 0.012 mmol of Ru.
[b] Reaction time not necessarily optimized.
[c] Determined by quantitative GLC and ^1H NMR. Only desired hydrogenation products **17** and **19** were observed.
[d] Determined by chiral GLC.

the hydrogenation of **11a** in the presence of such additives proceeded in only 20–25% ee (entries 41–42).

In order to obtain pyridylglycolates with better enantioselectivities we also investigated the reduction of **11a** using a stoichiometric borane reagent; alpine-borane® was selected for this purpose due to its recognized ability to reduce enantioselectively arylglyoxylates.[19] The reaction of **11a** with 2.4 equivalents of (*R*)-alpine-borane® at room temperature in toluene for 2 days afforded **17** in virtually 100% yield but again in only 25% ee (+). No improvement of the enantioselectivity was noticed upon using a larger excess of (*R*)-alpine-borane®. An experiment conducted on a 1 : 1 mixture of **11a** and **18** with 3.8 equivalents of (*R*)-alpine-borane® afforded quantitatively both corresponding α-hydroxy esters **17** and **19** in 25% ee (+) and 93% ee (*R*), respectively.

These results show that the drop in enantioselectivity for the reduction of **11a** compared to that of **18** either by hydrogenation or using borane reagents does not only stem from the coordination of the pyridyl function of the substrate onto the active metal (Ru, B) center; it is likely that some electronic effects have to be taken into account. The presence of *para*-substituents with variable electronic properties on aryl rings of prochiral α-keto esters[18a] and benzophenones has been shown to affect dramatically the enantioselectivity of some ruthenium-catalyzed asymmetric hydrogenations.[20] It has been proposed that electronic influences affect the extent of coplanarity of the aryl ring with the C=O function in the transition state, thereby generating an asymmetric bias.[20a] The well-known electron-withdrawing effect induced by the nitrogen atom in the pyridyl ring at the 2- and 4- positions can be exemplified in different ways. We found electrochemical reduction potential (E^0), determined by cyclic voltammetry, to be a significant probe of this electron-withdrawing effect for our series of compounds; the first reversible one-electron transfer leading to the radical anion[21] for α-keto ester **11a** takes place at –1.63 V vs. ferrocene/ferrocenium, while that of **18** takes place at –1.86 V.

Conclusions

The double carbonylation of iodopyridines provides an efficient entry to pyridylglyoxamides and, to a lesser extent, to pyridylglyoxylates. The presence of the nitrogen atom in the aromatic ring influences significantly the course of the catalytic process, bringing some peculiarities with respect to previous studies on simple aryl halides. Due to the electron-withdrawing effect of the pyridyl ring at the 2- and 4-positions, the C–I bond is activated for oxidative addition to zero-valent palladium; this contributes to the activity of the palladium catalysts and allows complete conversions in reasonable times on using an acceptable palladium charge in the range 0.1–2 mol %. A readily available Pd-PCy_3 catalyst, so far forsaken for the synthesis of α-keto amides, affords high yields of 4-pyridylglyoxylic derivatives compatible with modern synthesis requirements. On the other hand, the conversion of 2-iodopyridine into double carbonylation products proceeds with lower selectivity, presumably because of the vicinity of the nitrogen lone pair. The latter and electronic effects within the pyridyl ring hamper even more the asymmetric reduction of 4-pyridylglyoxylates; ruthenium-catalyzed hydrogenation affords 4-pyridyl-α-hydroxy esters in high chemical yields but poor enantioselectivity. This point remains obviously the most challenging issue in our hands.

Experimental Section

General

Catalytic reactions and catalysts syntheses were performed under nitrogen using standard Schlenk techniques. Solvents and nucleophiles were freshly distilled with an appropriate drying agent (CH_2Cl_2, 2-propanol, 2-butanol: CaH_2; all amines: KOH) and degassed before use. GLC analyses were performed on Chrompack CP 9001 apparatuses equipped with a flame ionization detector and, respectively, a BPX5 (25 m × 0.32 mm, SGE) and a chiral Chirasil-DEX CB (25 m × 0.25 mm, Chrompack) column. ^1H and ^{13}C NMR spectra were recorded on a AC-300 Bruker spectrometer at 23 °C in $CDCl_3$; chemical shifts are reported in ppm downfield from TMS and were determined by reference to the residual ^1H ($\delta = 7.25$) and ^{13}C ($\delta = 77.0$) solvent peaks. All coupling constants are reported in Hz. MS and HR-MS were performed on a JMS-700 m Station mass spectrometer (JEOL) with either electron impact (70 eV) or chemical (CH_4) ionization mode. Microanalyses (C, H, N) were performed on a LECO-CHNS 932 apparatus. Optical rotations were measured on a Perkin Elmer 343 polarimeter at 25 °C in a 1 dm cell. IR spectra were recorded on a Nicolet 510 FTIR spectrophotometer in a KBr cell using CH_2Cl_2 solutions and are expressed by wave number (cm^{-1}). Melting points are uncorrected. Cyclic voltammograms were performed under nitrogen in dry THF containing $[NBu_4][PF_6]$ (0.2 M) on a Pt cathode with a voltage sweep rate of 50 mV s^{-1}.

Iodopyridines **1**,[22] **5**,[15a] and **8**[23] were prepared following reported procedures and strictly purified by column chromatography and subsequent recrystallization from pentane. Methyl phenylglyoxylate, (*R*)-alpine-borane® (0.5 M in THF), phosphines, and most of the palladium complexes were purchased from Aldrich and Strem Co., and used as received. Complexes $PdCl_2(PPhMe_2)_2$ and $PdCl_2(PPh_2Me)_2$ were prepared by reaction of Na_2PdCl_4 with the appropriate phosphine. Complex [$RuBr_2$\{(*S*)-MeOBiphep\}] was readily prepared by the reaction in acetone of [Ru(COD)(methylallyl)$_2$] with an equimolar amount of optically pure (*S*)-MeO-Biphep (Hoffman LaRoche) and 2.2 equivalents (vs. Ru) of HBr (0.3 m methanol solution).[18c]

General Procedure for Double Carbonylation of Iodopyridines

In a typical experiment (entry 14), a solution of **1** (0.50 g, 2.44 mmol), $HNEt_2$ (1.2 mL, 12 mmol), $Pd(OAc)_2$ (5.5 mg, 0.024 mmol), and PCy_3 (19.2 mg, 0.072 mmol) in CH_2Cl_2 (30 mL) was charged under nitrogen into a 60 mL-stainless steel autoclave equipped with a magnetic stirrer bar. After sealing, the reactor was pressurized to 60 bar with carbon monoxide and heated at 50 °C for 6 h. After cooling to room temperature, the solution was analyzed by GLC, which showed that *N,N*-diethyl-4-pyridylglyoxamide (**2a**) had been formed in 95% yield along with *N,N*-diethyl-4-nicotinamide (**3a**) in 5% yield. After concentration of the solution under vacuum, the crude product was chromatographed on silica using EtOH/AcOEt/heptane (2:2:1) as eluent, to give the analytically pure glyoxamide (0.45 g, 90% yield). Syntheses of other α-keto amides and α-keto esters were carried out in a similar manner by using the appropriate amine and alcohol, respectively.

***N,N*-Diethyl-4-pyridylglyoxamide (2a):** Yield: 0.45 g, 90%; brown oil; ^{1}H NMR: δ = 8.87 (dd, 2H, *J* = 4.0 and 1.6 Hz, H-2), 7.77 (dd, 2H, *J* = 4.0 and 1.6 Hz, H-3), 3.56 (q, 2H, *J* = 7.1 Hz, NCH_2), 3.32 (q, 2H, *J* = 7.1 Hz, NCH_2), 1.25 (t, 3H, *J* = 7.1 Hz, CH_3), 1.15 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR: δ = 191.6 (*C*O), 167.2 (*C*ON), 152.1 (C-2), 140.9 (C-4), 123.7 (C-3), 43.9 (NCH_2), 40.8 (NCH_2), 14.7 (CH_3), 13.3 (CH_3); IR: $\tilde{\nu}$ = 1695, 1638 cm^{-1}; MS (EI, relative intensity %): *m/z* = 206 (M^+, 48), 178 (M^+ – CO, 26), 106 (M^+ – $CONEt_2$, 12), 100 (M^+ – PyrCO, 88), 78 (Pyr^+, 28), 72 (Et_2N, 100), 51 (35); HR-MS: *m/z* calcd. for $C_{11}H_{15}N_2O_2$ $[M+H]^+$: 207.1134; found: 207.1127.

***N,N*-Di(*n*-propyl)-4-pyridylglyoxamide (2b):** Yield: 0.46 g, 81%; orange oil (AcOEt); ^{1}H NMR: δ = 8.77 (dd, 2H, *J* = 4.5 and 1.6 Hz, H-2), 7.66 (dd, 2H, *J* = 4.5 and 1.6 Hz, H-3), 3.65 (t, 2H, *J* = 7.6 Hz, NCH_2), 3.06 (t, 2H, *J* = 7.6 Hz, NCH_2), 1.63 (sext, 2H, *J* = 7.6 Hz, NCH_2CH_2), 1.50 (sext, 2H, *J* = 7.6 Hz, NCH_2CH_2), 0.91 (t, 3H, *J* = 7.6 Hz, CH_3), 0.71 (t, 3H, *J* = 7.6 Hz, CH_3); ^{13}C NMR: δ = 190.0 (*C*O), 165.7 (*C*ON), 151.1 (C-2), 139.2 (C-4), 122.0 (C-3), 49.2 (NCH_2), 46.1 (NCH_2), 21.9 (NCH_2CH_2), 20.5 (NCH_2CH_2), 11.3 (CH_3), 10.9 (CH_3). IR: $\tilde{\nu}$ = 1690, 1630 cm^{-1}; MS (EI): *m/z* = 234 (M^+, 2), 206 (M^+ – CO, 15), 128 (M^+ – PyrCO, 100), 106 ($PyrCO^+$, 54), 100 (2), 86 (90), 78 (Pyr^+, 58), 51 (45), 43 (96); HR-MS: *m/z* calcd. for $C_{15}H_{19}N_2O_2$ $[M+H]^+$: 235.1447; found: 235.1449. $C_{15}H_{18}N_2O_2$ (234.30) anal. calcd.: C 66.64, H 7.74, N 11.96; found: C 66.5, H 8.1, N 11.5.

***N,N*-Piperidinyl-4-pyridylglyoxamide (2e):** Yield: 0.43 g, 80%; brown oil (AcOEt/EtOH/heptane, 2:2:1); ^{1}H NMR: δ = 8.54 (d, 2H, *J* = 5.2 Hz, H-2), 7.42 (d, 2H, *J* = 5.2 Hz, H-3), 3.56 (t, 2H, *J* = 5.6 Hz, NCH_2), 3.15 (t, 2H, *J* = 5.4 Hz, NCH_2), 1.59 (m, 2H), 1.41 (m, 2H), 1.23 (m, 2H) (all CH_2); ^{13}C NMR: δ = 190.4 (*C*O), 163.7 (*C*ON), 150.9 (C-2), 138.8 (C-4), 121.7 (C-3), 46.8 (NCH_2), 44.3 (NCH_2), 23.9, 22.0, 18.2 (all CH_2); IR: $\tilde{\nu}$ = 1695, 1640 cm^{-1}; MS (EI): *m/z* = 218 (M^+, 2), 190 (M^+ – CO, 46), 112 ($COPip^+$, 100), 106 ($PyrCO^+$, 21), 84 (Pip^+, 11), 78 (Pyr^+, 57), 56 (40), 51 (61), 41 (81), 39 (11); HR-MS: *m/z* calcd. for $C_{12}H_{15}N_2O_2$ $[M+H]^+$: 219.1135; found: 219.1134.

***N,N*-Di(*n*-butyl)-(4-pyridyl)-2-butyliminoglyoxamide (4):** Yield: 0.52 g, 81%; yellow oil (AcOEt/EtOH/heptane, 2:2:1); ^{1}H NMR: δ = 8.50 (dd, 2H, *J* = 5.9 and 1.4 Hz, H-2), 6.97 (dd, 2H, *J* = 5.9 and 1.4 Hz, H-3), 3.20 (t, 2H, *J* = 7.2 Hz, NCH_2), 3.16 (t, 2H, *J* = 7.4 Hz, NCH_2), 1.56 (m, 2H, CH_2), 1.47 (m, 2H, CH_2), 1.24 (m, 2H, CH_2), 1.22 (m, 2H, CH_2), 0.82 (t, 3H, *J* = 7.2 Hz, CH_3), 0.78 (t, 3H, *J* = 7.4 Hz, CH_3); ^{13}C NMR: δ = 162.8, 160.1 (*C*ON and *C*=N), 149.9 (C-2), 141.0 (C-4), 122.6 (C-3), 53.3 (NCH_2), 39.1 (NCH_2), 32.5, 31.5, 20.4, 20.1 (all CH_2), 13.7 (CH_3), 13.6 (CH_3); IR: $\tilde{\nu}$ = 1705, 1630 cm^{-1}; MS (EI): *m/z* = 261 (M^+, 3), 218 ($M^+ - C_3H_7$, 71), 161 (62), 105 (100), 78 (Pyr^+, 24), 57 (Bu^+, 79), 41 (70); HR-MS: *m/z* calcd. for $C_{15}H_{24}N_3O$ $[M+H]^+$: 262.1918; found: 262.1919.

***N,N*-Diethylamino-2-chloro-5-methoxymethyl-6-methoxy-4-pyridylglyoxyamide (6):** Yield: 0.63 g, 82%; brown oil (AcOEt/heptane, 1:1); ^{1}H NMR: δ = 7.37 (s, 1H, H-3), 4.50 (s, 2H, CH_2OMe), 3.92 (s, 3H, $ArOCH_3$), 3.40 (2q, 2×2H, *J* = 7.0 Hz, 2 NCH_2), 3.23 (s, 3H, CH_2OCH_3), 1.25 (t, 3H, *J* = 7.0 Hz, CH_3), 1.17 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR: δ = 189.2 (*C*O), 163.6 (*C*ON), 160.9 (C-6), 147.9 (C-2), 147.6 (C-4), 117.9, 116.5 (C-3, C-5), 65.8 (CH_2OMe), 58.5 ($ArOCH_3$), 54.7 (CH_2OCH_3), 42.5 (NCH_2), 40.3 (NCH_2), 14.2 (CH_3), 12.4 (CH_3); IR: $\tilde{\nu}$ = 1701, 1631 cm^{-1}; MS (EI): *m/z* = 314 (M^+, 4), 214 (M^+ – $CONEt_2$, 61), 186 (M^+ – $COCONEt_2$, 18), 100 ($CONEt_2$, 100); HR-MS: *m/z* calcd. for $C_{14}H_{20}ClN_2O_4$ $[M+H]^+$ ^{35}Cl (^{37}Cl): 315.1112 (317.1087); found: 315.1109 (317.1082).

***N,N*-Diethyl-2-pyridylglyoxamide (9):**[5] Yield: 0.26 g, 52%; pale blue oil (AcOEt); ^{1}H NMR: δ = 8.61 (ddd, 1H, *J* = 4.2, 1.7 and 1.0 Hz, H-6), 7.97 (dt, 1H, *J* = 7.8 and 1.0 Hz, H-3), 7.79 (td, 1H, *J* = 7.8 and 1.7 Hz, H-4), 7.39 (ddd, 1H, *J* = 7.8, 4.2 and 1.0 Hz, H-5), 3.45 (q, 2H, *J* = 7.2 Hz, NCH_2), 3.13 (q, 2H, *J* = 7.1 Hz, NCH_2), 1.16 (t, 3H, *J* = 7.2 Hz, CH_3), 1.05 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR: δ = 191.8 (*C*O), 167.4 (*C*ON), 151.2 (C-6), 149.9 (C-2), 137.2 (C-4), 128.0 (C-3), 123.1 (C-5), 41.9 (NCH_2), 38.4 (NCH_2), 13.8 (CH_3), 12.7 (CH_3); IR: $\tilde{\nu}$ = 1695, 1638 cm^{-1}; MS (EI): *m/z* = 206 (M^+, 5), 178 (M^+ – CO, 1), 177 (32), 100 ($CONEt_2$, 96), 78 (Pyr^+, 71), 72 (NEt_2, 100), 52 (19), 51 (38), 44 (59); HR-MS: *m/z* calcd. for $C_{11}H_{15}N_2O_2$ $[M+H]^+$: 207.1134; found: 207.1137.

2-Propyl 4-pyridylglyoxylate (11a): Yield: 0.24 g, 50%, yellow solid (AcOEt/heptane, 2:3); mp: 127–128 °C; ^{1}H NMR: δ = 8.74 (dd, 2H, *J* = 4.4 and 1.6 Hz, H-2), 7.70 (dd, 2H, *J* = 4.4 and 1.6 Hz, H-3), 5.19 (sext, 1H, *J* = 6.3 Hz, O*CH*), 1.28 (d, 2×3H, *J* = 6.3 Hz, CH_3); ^{13}C NMR: δ = 185.3 (*C*O), 161.6 (*C*OO), 150.9 (C-2), 138.5 (C-4), 122.3 (C-3), 71.3 (O*C*H), 21.5 (CH_3); IR: $\tilde{\nu}$ = 1752, 1723 cm^{-1}; MS (EI): *m/z* = 193 (M^+, 13), 165 (M^+ – CO, 13), 150 ($M^+ - C_3H_7$, 15), 137 (30), 106 ($PyrCO^+$, 100), 87 (2), 78 (Pyr^+, 43), 51 (20); HR-MS: *m/z* calcd. for $C_{10}H_{12}NO_3$ $[M+H]^+$: 194.0811; found: 194.0817.

2-Butyl 4-pyridylglyoxylate (11b): Yield: 0.28 g, 55%; orange oil (AcOEt/petroleum ether, 1:3); ^{1}H NMR: δ = 8.77 (dd, 2H, *J* = 4.4 and 1.6 Hz, H-2), 7.74 (dd, 2H, *J* = 4.4 and 1.6 Hz, H-3), 5.07 (hept, 1H, *J* = 6.3 Hz, O*CH*), 1.62 (m, 2H, CH_2), 1.30 (d, 3H, *J* = 6.3 Hz, $CHCH_3$), 0.88 (t, 3H, *J* = 7.5 Hz, CH_2CH_3); ^{13}C NMR: δ = 185.4 (*C*O), 161.9 (*C*OO), 150.9 (C-2), 138.5 (C-4), 122.3 (C-3), 75.9 (O*C*H), 28.6 (CH_2), 19.3 (CH_3), 9.6 (CH_3); IR: $\tilde{\nu}$ = 1743, 1718 cm^{-1}; MS (EI): *m/z* = 207 (M^+, 1),

179 (M^+ – CO, 1), 150 (M^+ – Bu, 3), 124 (58), 106 ($PyrCO^+$, 100), 78 (Pyr^+, 42), 73 (3), 56 (31), 51 (34), 41 (21); HR-MS: *m/z* calcd. for $C_{11}H_{14}NO_3$ $[M + H]^+$: 208.0974; found: 208.0971.

2-Butyl 2-chloro-5-methoxymethyl-6-methoxy-4-pyridylglyoxylate (13): Yield: 0.12 g, 15%; orange oil (AcOEt/heptane, 1:3); ^{1}H NMR: δ = 6.9 (s, 1H, H-3), 4.98 (sext, 1H, *J* = 6.4 Hz, OC*H*), 4.49 (s, 2H, CH_2OCH_3), 3.98 (s, 3H, $ArOCH_3$), 3.26 (s, 3H, CH_2OCH_3), 1.64 (m, 2H, CH_2), 1.32 (d, 3H, *J* = 6.4 Hz, $CHCH_3$), 0.94 (t, 3H, *J* = 7.9 Hz, CH_2CH_3); ^{13}C NMR: δ = 185.3 (*C*O), 162.3 (*C*OO), 159.4 (C-6), 147.2 (C-2), 146.7 (C-4), 117.9 (C-5), 116.5 (C-3), 75.4 (O*C*H), 67.6 ($ArCH_2OCH_3$), 58.5 ($ArOCH_3$), 54.5 (CH_2OCH_3), 28.6 (CH_2), 19.1 ($CHCH_3$), 9.5 (CH_2CH_3); IR: $\tilde{\nu}$ = 1744, 1710 cm^{-1}; MS (EI): *m/z* = 315 (M^+, 2), 259 (24), 216 (77), 214 ($M^+ - CO_2i$Bu, 100), 186 ($M^+ - COCO_2i$Bu, 50), 184 (81), 126 (32), 92 (36), 78 (20), 57 (89), 51 (24), 41 (71); $C_{14}H_{18}ClNO_5$ (315.75): anal. calcd.: C 53.25, H 5.75, N 4.44; found. C 53.9, H 6.1, N 4.3; HR-MS: *m/z* calcd. for $C_{14}H_{19}ClNO_5$ $[M + H(^{35}Cl)]^+$: 316.0952; found: 316.0952.

2-Butyl 2-pyridylglyoxylate (15): Yield: 25 mg, 5%; yellow oil (AcOEt/heptane, 1:1); ^{1}H NMR: δ = 8.73 (ddd, 1H, *J* = 4.7, 1.6, and 1.0 Hz, H-6), 8.09 (dt, 1H, *J* = 7.7 and 1.0 Hz, H-3), 7.89 (dt, 1H, *J* = 7.7 and 1.6 Hz, H-4), 7.53 (ddd, 1H, *J* = 7.7, 4.7, and 1.0 Hz, H-5), 5.22 (sext, 1H, *J* = 6.3 Hz, OC*H*), 1.71 (m, 2H, CH_2), 1.37 (d, 3H, *J* = 6.3 Hz, $CHCH_3$), 0.99 (t, 3H, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR: δ = 188.0 (*C*O), 165.3 (*C*OO), 150.6 (C-6), 149.9 (C-2), 137.2 (C-4), 128.2 (C-3), 123.4 (C-5), 75.1 (O*C*H), 28.9 (CH_2), 19.5 ($CHCH_3$), 9.7 (CH_2CH_3); IR: $\tilde{\nu}$ = 1730, 1702 cm^{-1}; MS (EI): *m/z* = 207 (M^+, 1), 162 (4), 151 (13), 148 (21), 134 ($M^+ - Oi$Bu, 17), 108 (51), 106 ($PyrCO^+$, 98), 78 (Pyr^+, 100), 57 (*i*Bu, 90), 51 (78), 41 (80); HR-MS: *m/z* calcd. for $C_{11}H_{14}NO_3$ $[M + H]^+$: 208.0974; found: 208.0975.

Asymmetric Hydrogenation of 11a

In a typical experiment (Table 5, entry 39), a solution of **11a** (0.115 g, 0.6 mmol) in MeOH (10 mL) was degassed by two freeze-thaw cycles and then added under nitrogen to a solution of $RuBr_2$[(*S*)-MeO-Biphep] (10 mg, 0.012 mmol) in MeOH (10 mL). The resulting solution was transferred to a 100-mL stainless steel autoclave equipped with a magnetic stirrer bar. Hydrogen (99%, Air Liquide) was introduced (20 bar), the reactor was heated to 50 °C by circulating thermostated water in the double wall, and stirring was started. The reaction was monitored by quantitative and chiral GLC analysis (BPX5 and Chirasil-DEX CB columns) of some aliquots. After completion (21 h), the autoclave was cooled to room temperature, hydrogen was vented and the solution was concentrated under vacuum to give a gummy solid. Column chromatography using AcOEt as eluent afforded analytically pure 2-propyl 4-pyridylglycolate (**17**).

(+)-2-Propyl 4-pyridylglycolate (17): Yield: 0.11 g, 90%; off-white solid; ^{1}H NMR: δ = 8.56 (dd, 2H, *J* = 4.6 and 1.6 Hz, H-2), 7.40 (dd, 2H, *J* = 4.6 and 1.6 Hz, H-3), 5.13 (s, 1H, C*H*OH), 5.05 (sext, 1H, *J* = 6.3 Hz, OC*H*), 1.28 (d, 2×3H, *J* = 6.3 Hz, CH_3). ^{13}C NMR: δ = 171.8 (*C*OO), 149.8 (C-2), 147.5 (C-4), 121.2 (C-3), 71.6, 70.8 (O*C*H and *C*HOH), 21.7 (CH_3), 21.4 (CH_3); IR: $\tilde{\nu}$ = 3438, 1610 cm^{-1}; MS (EI): *m/z* = 195 (M^+, 3), 151 (22), 109 (82), 108 ($M^+ - CO_2i$Pr, 100), 80 (80), 78 (Pyr^+, 31), 53 (60), 51 (42), 43 (90), 41 (63), 39 (18); HR-MS: *m/z* calcd. for $C_{10}H_{13}NO_3$ $[M + H]^+$: 196.0974; found: 196.0979; $C_{10}H_{13}NO_3$ (195.22): anal. calcd.: C 61.53, H 6.71, N 7.21; found: C 61.3, H 6.6, N 7.4; $[\alpha]_D^{20}$: +3 (*c* 1.27, MeOH) (25% ee).

Supplementary Information Available: Cyclic voltammograms of α-keto esters **11a** and **18**.

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