Preparation and Utilization of Chiral Dihydropyridines. Synthesis of Chiral Indoloquinolizines and Benzoquinolizines

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An asymmetric synthesis of 3-formyl-1,4-dihydropyridines is described that entails the addition of organocopper reagents to activated 3-imidazolidinylpyridine, prepared with chiral diamines. The activator can be a chloroformate or an acid chloride. The methodology was used for the asymmetric syntheses of the indoloquinolizine and benzoquinolizine alkaloid frameworks.

Introduction

1,4-Dihydropyridines are important compounds in organic chemistry and biology. Their synthetic utility has been exploited in natural product synthesis, particularly in the field of alkaloids and pyridobenzoquinolizine systems. Among the methods available to prepare 1,4-dihydropyridines, one of the most widely used is the addition of nucleophiles to N-activated (generally *N*-alkyl or *N*-acyl) pyridines.[1] The regioselectivity of this reaction (1,4 versus 1,2 addition) has been shown to be dependent upon both the activating reagent and the nucleophile, as well as the nature and the position of the pyridine substituents.[1] In the case of *N*-acylpyridinium salts, the best 1,4 selectivity, with organometallic derivatives, was obtained by using organocopper reagents.[2] A very important point, for synthetic purposes, is the stability of the 1,4-dihydropyridines. It is well known that the more stable compounds are those with an *N*-acyl group or with an electron-withdrawing group in the 3-position.[1] Such 1,4-dihydropyridines can be conveniently isolated. There are few asymmetric syntheses of such compounds.[3] Meyers described the synthesis of chiral 3-formyl-1,4-dihydropyridines **1** (see **1a–n**, Scheme 3) by a regio- and stereoselective addition of organomagnesium or lithium derivatives to a chiral 3-oxazolinylpyridine, followed by trapping of the metal salt by methyl chloroformate.[4] It seemed obvious to us that such chiral aldehydes could be easily prepared from 3-formylpyridine (**2**) via the formation of chirals acetals **3**, oxazolidines **4**, or aminals **5**, **6** (Scheme 2). In addition, the possibility of using functionalized acyl chlorides opens interesting synthetic possibilities, particularly in the field of indole alkaloids.

Choice of Chiral Inductor. Given our experience with the use of chiral acetals,[5] and inspired by the work of Comins,[6] we first attempted to explore this particular possibility. Thus, 3-formylpyridine (**2**) was converted to acetal **3** with 2(*R*),4(*R*)-pentanediol in 70% yield (Scheme 1). Reaction of this acetal in THF with Et_2CuLi in the presence of methylchloroformate resulted exclusively in the C-4 adduct **7** in 90% yield (Scheme 2). However, the ^{13}C NMR spectrum of this compound showed four nearly equal lines for the acetalic carbon (two for each diastereomer, each in two conformers), indicating very poor diastereoselectivity.

The oxazolidine (Scheme 1) route was also briefly explored. (+)-Ephedrine reacted smoothly with 3-formylpyridine to produce the oxazolidine **4** as a 93:7 mixture of two diastereomers.[7] Reaction of this mixture with Et_2CuLi and $ClCO_2CH_3$ in THF gave a plethora of products, as judged by TLC. Acidic hydrolysis of the possible unstable oxazolidine adduct **8** (Scheme 2) gave no trace of the expected dihydropyridine. It seems that the oxazolidine ring is too sensitive to the reaction conditions and is probably attacked by the organometallic reagent. The third route was the use of chiral aminals, which have found many applications in our laboratories.[8] Two diamines **9** and **10** were examined (Scheme 1). Both reacted readily with 3-formylpyridine by mixing in ether, at room temperature, in the presence of 4-Å molecular sieves to afford the corresponding aminals **5** and **6** in good yields. Reaction of these aminals with Et_2CuLi and $ClCO_2CH_3$ in THF gave, regioselectively, the corresponding C-4 adducts **11** (not isolated) and **12b** (Schemes 2 and 3 and Table 1). Due to the instability of the aminal function, the adduct **11** was directly hydrolyzed under acidic conditions (HCl 5%) to afford the corresponding aldehyde **1b** as a racemic compound ($[\alpha]^{25}_D = 0$). In contrast, the 1,4 adduct **12b** was very stable and was chromatographed without any difficulty. The diasteromeric excess (de) was determined by ^1H NMR spectrocopy.[9] However, the NMR spectra of such compounds require very careful examination. Ro-

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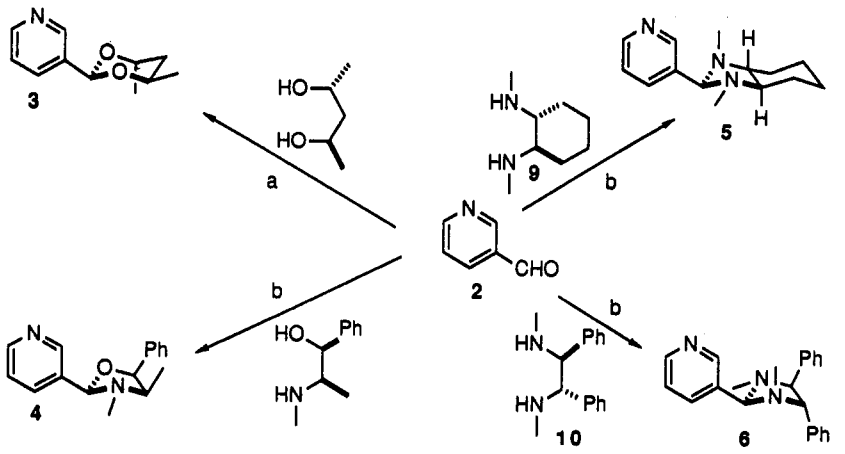
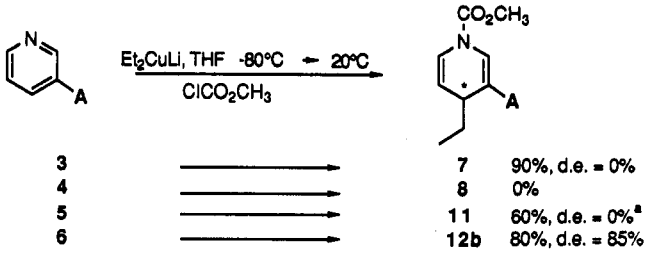
Scheme 1[a]



[a] Key: (a) *p*-TsOH, toluene, Dean Stark, 6 h, 70%; (b) Et_2O, molecular sieves 4Å.

Scheme 2[a]



3	⟶	7	90%, d.e. = 0%
4	⟶	8	0%
5	⟶	11	60%, d.e. = 0%[a]
6	⟶	12b	80%, d.e. = 85%

[a] The crude aminal 11 was directly hydrolyzed into aldehyde **1b**

tation around an amide bond can be slow, and generally, two sets of signals appeared in the NMR spectra of the adducts.[10] In order to distinguish conformers and diastereomers, the adduct **12b** was smoothly hydrolyzed under acidic conditions (Scheme 3) to give the corresponding aldehyde **1b**. Treatment of this aldehyde by diamine **10** of a reverse stereochemistry was a difficult reaction leading to low yields of diastereomeric aminal. Nevertheless, it was then possible to compare the NMR spectra and confirm the postulated de which was found to be high (85%). Moreover, the ^1H NMR spectrum of the adduct **12b** was recorded at 60 °C. The multiplicity of peaks coalesced into a single set of absorptions corroborating our expectations.

Therefore, we decided to focus our attention on aminal **6**. We report herein the details of our studies.[11]

Optimization Studies. Our preparation of 1,4-dihydropyridines from aminal **6** involves the addition of an organometallic reagent to an activated form of the pyridine ring. In order to obtain the best 1,4 selectivity with good stereocontrol, the influence of several factors had to be studied: the nature of the organometallic reagent (R^1M), the activating reagent (AX), and the reaction conditions. Our results are summarized in Table 1. For this study, only methyl or ethyl organometallic derivatives were used.

Acylpyridinium Salts. When the activated form of the pyridine was an acylpyridinium salt (AX = MeOCOCl or MeCOCl), it was not necessary to preform the salt. Acylation of the pyridine is a very fast reaction even at low temperature and occurs before reaction of the organometallic reagent with the chloroformate or acyl chloride.[1] Furthermore, at low temperature, the aminal ring does not react with methyl chloroformate or acetyl chloride.[12] Therefore, by a very simple procedure, the acylating reagent was added to a mixture of pyridine aminal **6** and the organometallic reagent in the appropriate solvent at −70 °C. Generally, the reaction was complete below −30 °C, as indicated by TLC. In every case, the NMR spectrum of the crude product was recorded in order to determine the regio and diastereoselectivity. When a mixture of dihydropyridines resulting from a 1,4 addition (C-4 adducts **12** or **13**) and 1,2 addition (C-6 adducts **14** or **15**) was obtained (Scheme 3), due to the complexity of the NMR spectra (presence of conformers), the diastereomeric purity of each adduct was determined after purification. In the case of 1,4 addition, this measure was confirmed by GC analysis, by which the two diastereomers were base line separated. The diastereomeric purity of the C-6 adducts was also confirmed by a partial separation of diastereomers **14a** by column chromatography.

As shown in Table 1, dihydropyridines resulting from an addition at position 2 were never observed. The presence of a bulky group in position 3 may block this position against nucleophilic attack.[1e] Moreover, no product resulting from aminal ring opening was detected.

As expected, the regioselectivity (addition at C-4 versus C-6) was dependent on the nature of the organometallic reagent; the use of organocopper derivatives is essential for 1,4 selectivity. When MeMgBr was used, associated with methyl chloroformate (entry 1), a 14/86 mixture of C-4 adduct **12a** (de = 93%) and C-6 adduct **14a** (de = 47%) was isolated in 71% overall yield. When organocopper reagents were used, except for Me_2CuLi (entries 2 and 3), more than the nature of the organometallic reagent, the presence of THF seems to be essential in order to obtain the C-4 adduct with good diastereoselectivity. In this solvent, with methyl chloroformate, good de were obtained, and excellent de was observed with acetyl chloride (compare, for example, entries 7 and 10).

Furthermore, the best results were obtained with a copper reagent prepared with an excess of soluble copper

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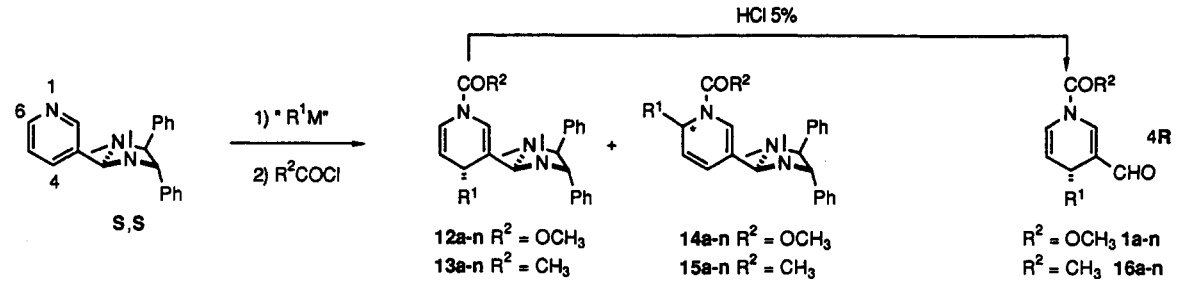
(12) We have observed that an aminal of crotonaldehyde reacts with phenyl copper reagents associated with methyl chloroformate or acetyl-chloride by a S_N2' process with concomittent opening of the imidazolidine ring.

Scheme 3



Substituents R^1 for adducts **12**, **13**, **14**, **15** (For **12n** and **14n** $R^1M = P(OEt)_3$):

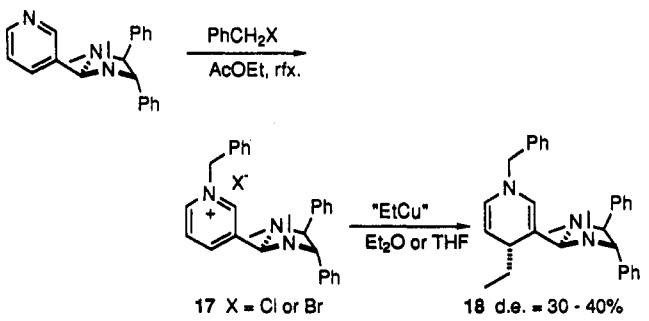
R^1 =	Me	Et	Bu	vinyl	Ph	iPr	tBu	Me_3Si—≡	allyl	EtO_2CCH_2	$MeO_2C(CH_2)_3$	$(MeO_2C)_2CH$	indolyl	$OP(OEt)_2$
a-n =	a	b	c	d	e	f	g	h	i	j	k	l	m	n

Table 1. Optimization Studies on Animal 6

entry	AX	R^1M	solvent	C-4/C-6	yield[a] (%)	C-4 adducts de[b] (%)	C-6 adducts de[b] (%)
1	CH_3OCOCl	MeMgBr	THF	14/86	71	**12a** (93)	**14a** (47)
2	CH_3OCOCl	Me_2CuLi	Et_2O	70/30	80	**12a** (95)	**14a** (0)
3	CH_3OCOCl	Me_2CuLi	THF	100/0	90	**12a** (41)	
4	CH_3OCOCl	$Me_2CuMgBr$	THF	100/0	90	**12a** (95)	
5	CH_3OCOCl	Et_2CuLi	Et_2O	81/19	79	**12b** (32)	**14b** (0)
6	CH_3OCOCl	$Et_2CuMgBr$	THF	100/0	90	**12b** (82)	
7	CH_3OCOCl	Et_2CuLi	THF	100/0	90	**12b** (85)	
8	CH_3COCl	$Me_2CuMgBr$	THF	100/0	90	**13a** (>95)	
9	CH_3COCl	MeCu[c]	THF	100/0	95	**13a** (>95)	
10	CH_3COCl	Et_2CuLi	THF	100/0	70	**13b** (>95)	
11	$PhCH_2Br$	EtCu	THF		0		
12	$PhCH_2Br$	Et_2CuLi	THF	100/0	95	18 (40)	

[a] Yield of C-4 + C-6 adduct. [b] The de was measured by ^1H NMR or by capillary GC. [c] Prepared from 1 MeLi + 2 CuBr, Me_2S, 4 LiBr.

Scheme 4



salt (CuBr, Me_2S, 2LiBr) (entry 9).[13] The aldehydes **1a,b** and **16a,b** were obtained by acidic hydrolysis (HCl 5%) of the aminals **12a,b** and **13a,b** with complete recovery of the starting diamine. The optical rotation of the aldehyde **1a** was compared with the value reported by Meyers.[4] The configuration of the newly formed stereogenic center was thereby shown to be *R*, starting from (*S,S*) diamine **10** (Scheme 3).

Alkylpyridinium Salts. When the activated form of the pyridine is an alkylpyridinium salt, it is necessary to preform this salt. Benzylpyridinium salts **17** were prepared by refluxing aminal **6** with benzyl chloride or bromide in ethyl acetate (Scheme 4).[14] The crude pyridinium salt was then added to the copper reagent in THF at −70 °C.

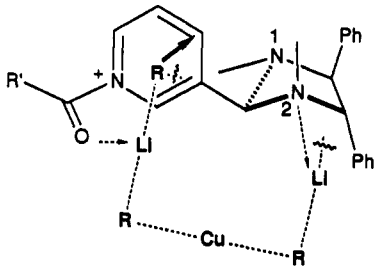


Figure 1. Hypothetic transition state.

No addition was observed with EtCu reagent. Clearly an alkylpyridinium salt is less reactive than an acylpyridinium salt. With the more active *ate* complex, Et_2CuLi, the reaction in THF (or in Et_2O) affords, regioselectively, the C-4 adduct **18** as the sole product. This *N*-benzyldihydropyridine was found to be surprisingly stable (several days in a refrigerator under N_2 atmosphere). The diastereomeric purity was cleanly measured by ^1H NMR[9] and found to be low. All parameters of the reaction were studied: solvent (THF, ether) and nature of the copper salt (CuBr, CuI), of the cuprate (prepared from EtMgBr or EtLi) and of the counterion of the pyridinium salt (Cl^- or Br^-). In every case, the obtained de was low (30–40%). The presence of a carbonyl function in the activating reagent seems to be essential for good diastereocontrol. Therefore, in order to explain the observed stereochemistry, when organocopper reagent is associated with acetyl chloride or methyl chloroformate, we propose a transition state as shown in Figure 1. From X-ray studies,[15] we know that the *N*-methyl substituents of the imidazolidine ring are in a trans relationship with the α-phenyl groups. This conformation creates a steric difference between the two

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Table 2. Preparation of Dihydropyridines

entry	R¹M	AX	C-4/C-6	yield[a] (%) 12 + 14 or 13 + 15	adducts 12 or 13 de[b] (%)	adducts 14 or 15 de[b] (%)
13	Bu_2CuLi	CH_3OCOCl	100/0	90	**12c** (95)	
14	$(CH_2{=}CH)_2CuMgCl$	CH_3OCOCl	100/0	90	**12d** (95)	
15	$Ph_2CuMgCl$	CH_3OCOCl	100/0	90	**12e** (95)	
16	Ph_2CuLi[c]	CH_3COCl	-	20	**13e**	**15e**
17	PhCu[d]	CH_3COCl	100/0	90	**13e** (>95)	
18	$iPr_2CuMgCl$	CH_3OCOCl	100/0	90	**12f** (77)	
19	$iPr_2CuMgCl$	CH_3COCl	100/0	90	**13f** (85)	
20	$tBu_2CuMgCl$	CH_3OCOCl	50/50	90	**12g** (0)	**14g** (0)
21	tBuCu[d]	CH_3COCl	45/55	60	**13g** (85)	**15g** (0)
22	$(Me_3SiC{\equiv}C)_2CuLi$	CH_3OCOCl	0/100	90		**14h** (0)
23	$CH_2{=}CH{-}CH_2Cu$	CH_3OCOCl	0/100	48		**14i** (75)
24	EtO_2CCH_2Cu	CH_3OCOCl	0/100	30		**14j** (25)
25	EtO_2CCH_2Cu	tBuCOCl	0/100	25		**15j** (20)
26	$CH_3O_2C(CH_2)_3Cu$[e]	CH_3OCOCl	100/0	80	**12k** (95)	
27	$(CH_3O_2C)_2CHNa$	CH_3OCOCl	0/100	30		**14l** (0)
28	$(indolyl)_2CuLi$	CH_3OCOCl	100/0	50	**12m** (95)	
29	$P(OEt)_3$	CH_3OCOCl	40/60	90	**12n** (84)	**14n** (56)

[a] Yield of isolated products, not optimized. [b] The de was measured by ^1H NMR or by capillary GC. [c] Due to the complexity of the reaction mixture, de and C-4/C-6 ratio were not measured. [d] Prepared from 1 RLi + 2 CuBr, Me_2S, 4 LiBr. [e] Prepared according to ref 24.

faces of the pyridinium ring. An examination of the molecular models shows that this differentiation is more efficient when the pyridinium aminal adopts the conformation shown in Figure 1. It may be *hypothesized* that this conformation is locked by a chelation of the square planar dimeric cuprate[16] with the lone pair of the N2–CH_3 (the more accessible one) and the oxygen of the carbamate or amide function.[17] Under these conditions the cuprate attacks the *Re* face of the pyridine ring (starting from a (*S*,*S*) diamine).

To summarize, chiral 1,4-dihydropyridines are readily available, from aminal **6**, by addition of organocopper reagents in the presence of an acylating reagent (methyl chloroformate or acetyl chloride).

Generalization. In order to assess the scope of this reaction, we have tried to generalize our results. This study is summarized in Table 2. Complete C-4 regioselectivity and good to excellent diastereoselectivity were obtained when "simple" (nonfunctionalized) alkyl-, vinyl- and arylcopper reagents were used (entries 13–19). An exception is the tBu group, which was nonselective (entry 20). As was observed in the optimization study, the use of acetyl chloride increases the diastereoselectivity (compare entries 18 and 19).

With an alkynyl derivative, a regioselective addition led exclusively to the C-6 adduct **14h**, which was obtained with no diastereoselectivity (entry 22). The observed regioselectivity was not unexpected on the basis of the known propensity of such reagents to undergo 1,2 rather than 1,4 addition.[18] The allylcopper reagent (entry 23), prepared according to Lipshutz,[19] also gave only the C-6 adduct **14i**.[20] The de was surprisingly high (75%) when one considers the distance between the chiral auxiliary and the prochiral center.

The copper reagent derived from ethyl acetate was also tried (entry 24). This reagent is known to effect a S_N2 displacement with allyl halides and to open, in a $S_{N'}2$ process, a cyclic allylic epoxide.[21] In our case, whatever the copper salt used (CuCN or CuBr, Me_2S), only C-6 adduct **14j** was obtained with poor yield and poor diastereoselectivity. The same result was obtained with bulky pivaloyl chloride[22] (entry 25). C-6 regioselectivity was also obtained with the sodium salt of methyl malonate without any diastereoselectivity (adduct **14l**, entry 27). Clearly, in the presence of an enolate type functionality, the C-6 addition is preferred.[23] However, it was possible to introduce a remote ester functionality by using a zinc organocopper reagent.[24] These reagents, which are compatible with the presence of such functionality, are known to effect a conjugate addition on acylpyridinium salts.[25] Therefore, we have prepared a zinc organocopper reagent from methyl 4-iodobutyrate. With this organometallic derivative, complete C-4 selectivity was obtained affording adduct **12k** with an excellent chemical yield and excellent diastereoselectivity (entry 26).

The diindolylcopper reagent (entry 28) was also used. This reagent has previously been added to pyridinium *N*-oxide with C-2 selectivity and very poor chemical yield.[26] Under our conditions, with aminal **6**, the C-4 adduct **12m**

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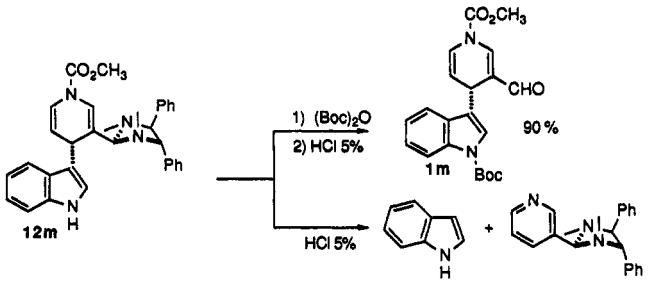
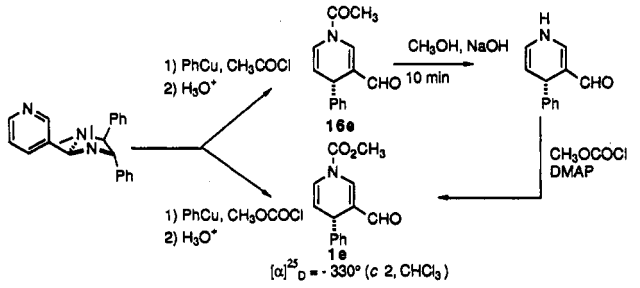
Scheme 5



Scheme 6



was obtained with a moderate chemical yield but very good diastereoselectivity. The use of a metallic derivative is necessary. Indeed, in our case, with indole itself,[26d] no reaction was observed.

Finally, triethyl phosphite, a nonorganometallic nucleophile, was tested (entry 29). Addition of trialkyl phosphites to *N*-acylpyridinium salts has already been described. The regioselectivity of this reaction was found to be dependent on steric factors.[27] In our case, a nonregioselective addition was observed affording a mixture of C-4 and C-6 phosphonates **12n** (de = 84%) and **14n** (de = 56%) in a 4/6 ratio.

All adducts **12** and **13** were hydrolyzed in good yields to the corresponding aldehydes (Scheme 3) with a complete recovery of the starting diamine **10**. The only exception was observed for the indolyl adduct **12m**. In this case, acidic treatment returned the starting materials (**6** and indole) by a retroaddition process. This reaction was avoided by protection of the indolyl function as a Boc derivative. With this compound, the aminal protective group was hydrolyzed, without any difficulty, to the aldehyde **1m** (Scheme 5).

In order to complete our study, we have confirmed that the stereochemistry of the reaction using acetyl chloride as activator is the same as that observed in the case of methyl chloroformate. The aldehyde **16e**, obtained by action of phenylcopper reagent with acetyl chloride followed by acidic hydrolysis, was submitted to alkaline methanolysis.[28] The "free" dihydropyridine, so obtained, was a very stable product. Treatment of this compound with methyl chloroformate in the presence of (dimethylamino)pyridine afforded the same aldehyde **1e** obtained by action of phenylcopper with methyl chloroformate followed by acidic hydrolysis (Scheme 6).

Synthetic Applications. Since chiral 3-formyl-1,4-dihydropyridines are available from **6**, by reaction of organocopper reagents associated with an acyl chloride, we explored the use of a functionalized acyl chloride. Indeed, if the acylating reagent (AX) could allow cyclization reactions with the dihydropyridine, it would be possible then to prepare, by a very short procedure, chiral dehydropiperidines which are very close precursors of natural alkaloids. Thus, with indolylacetyl chloride,[29] the addition of lithium diethylcuprate reagent to aminal **6** afforded, via the acylpyridinium **19**, the C-4 adduct **20** with excellent diastereoselectivity, albeit in a poor chemical yield (Scheme 7, Table 3). The de was measured by ^{1}H NMR and was confirmed by treatment of the corresponding aldehyde **21**, easily obtained by acidic hydrolysis, with diamine **10** of the reverse stereochemistry. By using the much less basic reagent EtCu, prepared with an excess of soluble copper salt, an excellent chemical yield of adduct **20** was obtained (Table 3), again as a single diastereomer, the same one as above.

Scheme 7

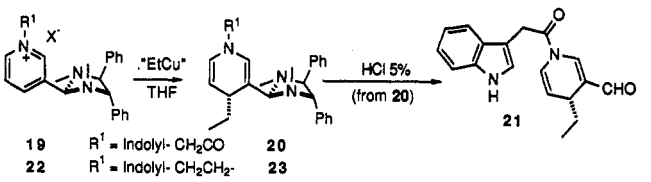


Table 3. Preparation of Dihydropyridines 20 and 23 by Activation with Tryptophyl Bromide or Indolylacetyl Chloride

pyridinium salt	EtCu	yield (%)	adduct	de[a] (%)
19	Et_2CuLi	20	**20**	95
19	EtCu, 1CuBr, 4LiBr	80	**20**	95
22	Et_2CuLi	100[b]	**23**	40
22	$Et_2CuMgBr$	100[b]	**23**	

[a] The de was measured by ^{1}H NMR. [b] Crude product.

The easy preparation of chiral indolodihydropyridine **21**, without any protection of the indole ring, prompted us to explore the synthesis of chiral indoloquinolizines as models for the enantioselective synthesis of indole alkaloids. Despite the result obtained with the alkylpyridinium salt during the optimization studies (entry 12, Table 1), we have tried to use as starting material the indolylpyridinium salt **22**, obtained from aminal **6** by treatment with tryptophyl bromide.[29] The use of organocopper reagent as described by Wenkert[30] would then lead, after cyclization in acidic medium (without any purification of the unstable 1,4-dihydropyridine **23**), to an indoloquinolizine **24** of the vallesiachotamine type (trans relationship between C2-H and C12b-H).[31,32] Indeed, we have observed that addition of diethylcuprate occurred affording 1,4-dihydropyridine **23** (Table 3) with a low de (40%), corroborating our previous results. We then used as precursors, the amide **20**, prepared with excellent diastereoselectivity (de = 95%). This compound was cleanly reduced by $LiAlH_4$ in ether to afford the dihydropyridine **23** without any racemization (Scheme 8). The use of THF

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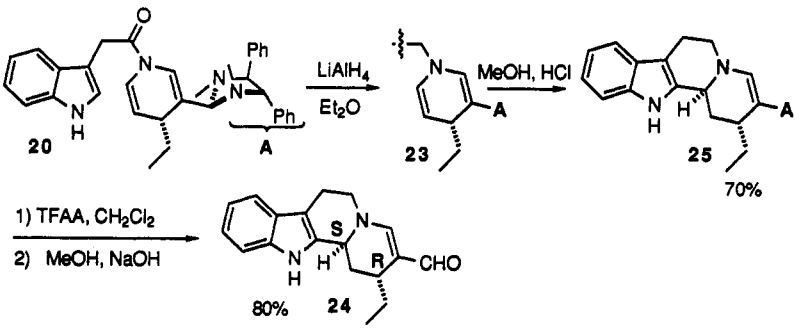
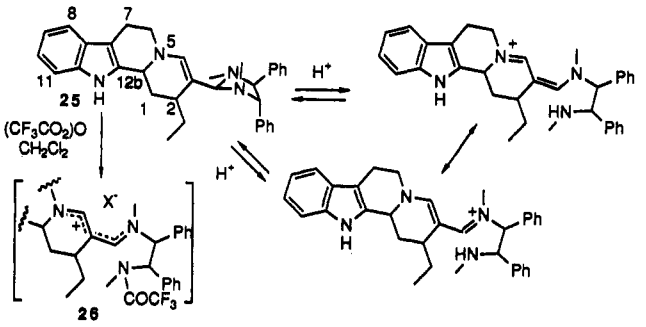
Scheme 8



Scheme 9



as solvent led to a mixture of the desired product and compounds resulting from cleavage of the amide bond.[33] The crude dihydropyridine **23** was then treated with a solution of methanol saturated with HCl[34] to yield the indoloquinolizine **25** (70% overall yield of isolated material) (Scheme 8). Only one diastereomer was detected by ^{1}H NMR. Since the chiral aminal functionality is still present in this compound, and since the formation of diastereomeric aminals has been shown to be an excellent way to determine the enantiomeric purity of chiral aldehydes,[9] we can assume that the cyclization occurs without racemization.

The trans relationship between C12b-H and C2-H, postulated by Lounasmaa and Wenkert for such cyclizations, was confirmed by the NMR spectra.[34] The formation of the trans isomer may reflect a kinetic intramolecular cyclization of the indolyl group to the iminium base from the less hindered β side.[35] Since we had assigned the *R* configuration to the C2 (starting from the (*S,S*) diamine **10**), the configuration of the C12b was postulated to be S.

The last step was the deprotection of the aldehyde function. This is routinely accomplished by aqueous acidic hydrolysis. In the present case, these conditions were completely ineffective. The starting material was always recovered even with a "diamine acceptor" such as formaldehyde or glyoxal. The use of Conia's procedure[36] was also inefficient. This result suggests that participation of the N5 atom stabilizes the iminium ion obtained by the opening of the aminal ring (Scheme 9). Our idea was to block the iminium species by using trifluoroacetic anhydride (TFAA). Indeed, treatment of aminal **25** with 2 equiv of TFAA led to a very polar compound (probably **26**, Scheme 9) which was not isolated. This compound was cleanly converted into the desired aldehyde **24** using alkaline conditions, in 80% yield (Scheme 8).

The same strategy was applied to an asymmetric synthesis of the benzoquinolizine framework.[37] Thus, aminal **6** was treated with methylcopper (or ethylcopper) in the presence of the (3,4-dimethoxyphenyl)acetyl chloride (Scheme 10) to give dihydropyridines **27a** or **27b** in excellent yield and de. Acidic hydrolysis of aminal **27b** afforded aldehyde **28**. On the other hand, reduction of **27a** or **27b** with $LiAlH_4$ in ether gave the corresponding dihydropyridines **29a** and **29b** which were cyclized without purification in trifluoroacetic acid at 0 °C.[38] The crude products were then treated as aminal **25** to give the aldehydes **30a** or **30b** as a mixture of two diastereomers (de = 65% for **30a** and 81% for **30b**). By analogy with our previous results, we have assigned the *S* configuration to the C11b atom of the major diastereomer (starting from **27a** or **27b** of *R* configuration). This relative configuration was confirmed by observation of a NOE effect in the ^{1}H NMR spectrum, between the C11b-H and one of the hydrogen atoms on C12.

We have checked the possible influence of the aminal on the diastereoselectivity of the ring closure of the dihydropyridines **23** and **29a**. Thus, the aldehydes **31** and **32**, readily obtained in good yield from **23** and **29a** (Scheme 11), were submitted to the cyclization reaction under the conditions used for the corresponding aminals. The cyclized products were indeed obtained, but surprisingly with a lower diastereoselectivity (respectively 55% for **24** and 40% for **30a**). It appears therefore that the presence of the chiral aminal increases the selectivity of the ring closure.

Conclusion

In this paper, we have described a very short and efficient synthesis of chiral 3-formyl-1,4-dihydropyridines. The starting aminal is prepared, in one step, from 3-formylpyridine and a chiral diamine of C_2 symmetry, which is totally recovered at the end of the synthesis of dihydropyridines. The possibility of varying either the nucleophile or the activator enhances the synthetic versatility of this methodology. The enantioselective syntheses of the indoloquinolizine and benzoquinolizine frameworks open a very short and efficient access to various natural products. Such synthetic applications are in progress in our laboratory.

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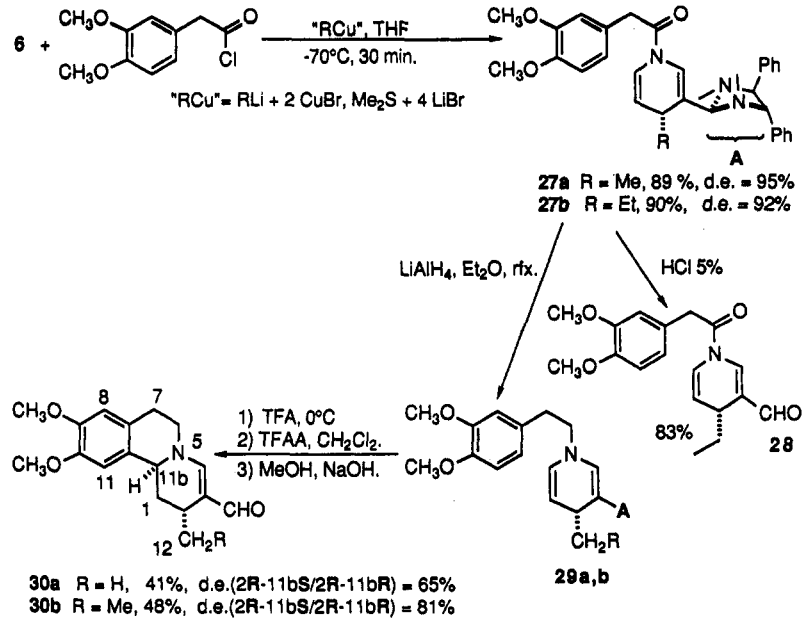
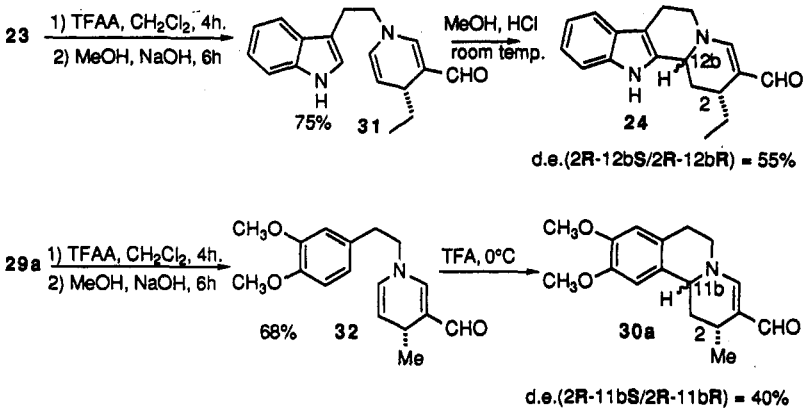
Scheme 10



Scheme 11



Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 400 or 200 MHz with tetramethylsilane (0.00 ppm) as an internal reference in $CDCl_3$ solutions. ^{13}C NMR were recorded at 100 or 50 MHz in $CDCl_3$ with tetramethylsilane (0.00 ppm) as the internal reference. Chemical shifts are given in ppm (δ); coupling constants, J, are reported in Hz. Due to the presence of conformers, often the signals are split. When there is a mixture of diastereomers, signals ascribed to the minor diastereomer are italic. Infrared spectra (IR) were obtained on a Perkin-Elmer 1420 infrared spectrometer. Peaks are reported in cm^{-1}. GC analyses were performed on a capillary quartz column (SE 20, 25 m, Φ 0.32 mm) with H_2 as gas vector. All solvents used in reactions were distilled from appropriate drying agents before use. All reactions were performed under an atmosphere of dry nitrogen. Organomagnesium and organolithium reagents were titrated before use. Organocopper reagents were prepared by using a CuBr·Me_2S complex. In all reactions involving 3-(1,3-dimethyl-4(*S*),5(*S*)-diphenylimidazolidin-2-yl)pyridine (**6**) the diamine **10** used had a 1*S*,2*S* configuration.

Acetal 3. A solution of 3-formylpyridine (1.92 g, 18.2 mmol) with 2(*R*),4(*R*)-pentanediol (2 g, 19.2 mmol) and *p*-TsOH (100 mg) in toluene was refluxed in a Dean Stark apparatus for 6 h. The solution was then poured in a saturated aqueous Na_2CO_3 solution. The organic layer was dried over Na_2CO_3 and concentrated in vacuo. Vacuum distillation afforded **3** (2.4 g, 70%): bp 100 °C (0.3 mmHg); $[\alpha]^{25}_D$ = 21° (*c* = 2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.7 (d, *J* = 2.1 Hz, 1H), 8.55 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.8 (m, 1H), 7.3 (m, 1H), 5.85 (s, 1H), 4.45 (m, 1H), 4.15 (m, 1H), 1.95 (m, 1H), 1.42 (m, 4H), 1.25 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 149.2, 147.8, 134.1, 133.3, 122.4, 91.9, 68.4, 67.5, 36.2, 21.7, 16.6. Anal. Calcd for $C_{11}H_{15}NO_2$ (193.25): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.35; H, 7.85; N, 7.23.

Oxazolidine 4. To a solution of 3-formylpyridine (1.92 g, 18.2 mmol) in ether was added 1(*S*),2(*R*)-ephedrine (3 g, 18.2 mmol). The resulting solution was stirred for 20 min in the presence of molecular sieves (4 Å) and then concentrated to give the corresponding oxazolidine as a clean mixture of two diastereomers (de = 86%): $[\alpha]^{25}_D$ = −50° (*c* = 5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.7 (d, *J* = 2.1 Hz, 1H), 8.55 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.0 (m, 1H), 7.3 (m, 6H), *5.6* and 5.2 (2d, *J* = 8 Hz, 1H), *5.3* and 4.7 (2s, 1H), *3.7* and 3 (2m, 1H), *2.25* and 2.2 (2s, 3H), 0.8 and *0.7* (2d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 150.6, 150.2, 139.5, 136.0, 134.0, 128.0, 123.7, 96.7, *93.4*, 82.8, *82.4*, 64.5, *61.5*, 35.7, *33.4*, 15.1, *8.9*. Anal. Calcd for $C_{16}H_{18}N_2O$ (254.33): C, 75.56; H, 7.13; N, 11.01. Found: C, 75.72; H, 7.09; N, 11.10.

Imidazolidine 5. To a solution of 3-formylpyridine (2.7 g, 25.5 mmol) in ether was added *N*,*N*′-dimethylcyclohexane-1(*R*),2-(*R*)-diamine (3.6 g, 25.5 mmol). The resulting solution was stirred for 20 min in the presence of molecular sieves (4 Å) and then, after filtration, concentrated to give the corresponding crude aminal. Vacuum distillation afforded **5** (4.7 g, 80%): bp 106 °C (0.1 mmHg); $[\alpha]^{25}_D$ = −14.7° (*c* = 5, $CHCl_3$); ^{1}H NMR ($CDCl$, 200 MHz) δ 8.6 (d, *J* = 2 Hz, 1H), 8.55 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.75 (m, 1H), 7.3 (m, 1H), 4.25 (s, 1H), 2.2 (s, 3H), 2.0 (s, 3H), 2.7–1.1 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 150.8, 149.5, 136.7, 135.8, 123.0, 87.7, 69.3, 68.2, 37.4, 35.7, 29.0, 28.8, 24.5, 24.3. Anal. Calcd

for $C_{14}H_{21}N_3$ (231.34): C, 72.69; H, 9.15; N, 18.16. Found: C, 72.65; H, 9.18; N, 18.13.

3-(1,3-Dimethyl-4(*S*),5(*S*)-diphenylimidazolidin-2-yl)pyridine (6). To a solution of 3-formylpyridine (1.07 g, 10 mmol) in ether was added 1,2-bis-N-(methylamino)-1(*S*),2(*S*)-diphenylethane (2.4 g, 10 mmol). The resulting solution was stirred for 20 min in the presence of molecular sieves (4 Å) and then concentrated to give a white crystalline solid which was recrystallized in ether (3.1 g, 95%): mp 106 °C; $[\alpha]^{25}_D = -56°$ (c = 3, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 8.9 (s, 1H), 8.6 (m, 1H), 7.95 (m, 1H), 7.35 (m, 1H), 7.1–7.3 (m, 10H), 4.85 (s, 1H), 3.9 (d, J = 8.1 Hz, 1H), 3.6 (d, J = 8.1 Hz, 1H), 2.15 (s, 3H), 1.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 150.7, 149.5, 138.8, 139.1, 136.4, 135.9, 127.9, 127.8, 127.5, 127.3, 127.2, 122.9, 85.9, 77.4, 76.6, 37.0, 35.3; IR (film) 3080, 3040, 2975, 2940, 2795 cm^{-1}. Anal. Calcd for $C_{22}H_{23}N_3$ (329.45): C, 80.21; H, 7.04; N, 12.75. Found: C, 80.20; H, 7.05; N, 12.74.

General Procedure for the Addition of Organometallic Reagents on Pyridines 3–6. To a solution of the appropriate organometallic reagent (RMgX, RCu, R_2CuX) (1.5 equiv) in THF or ether (30 mL for 1 mmol) was added a solution of pyridine **3**, **4**, **5**, or **6** (1 equiv) in THF or ether (10 mL for 1 mmol). The resulting mixture was cooled to −70 °C, and then the acylating reagent (methyl chloroformate or acetyl chloride) (1.5 equiv) was slowly added. The mixture was stirred for 6 h at −60 °C (TLC) and warmed to room temperature. The reaction was then quenched by addition of an aqueous solution of NH_4OH/NH_4Cl (1/1). The mixture was diluted with Et_2O and washed with an aqueous solution of NH_4Cl. The organic layer was dried (Na_2CO_3) and concentrated in vacuo to afford a yellow oil which was checked by ^1H NMR and then purified by column chromatography (SiO_2, cyclohexane/ether = 70/30).

4-Ethyl-3-(4,6-dimethyldioxolan-2-yl)-1,4-dihydropyridine-1-carboxylic acid methyl ester (7) (90% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.15 (br s, 0.5H), 7.05 (br s, 0.5H), 6.85 (m, 0.5H), 6.7 (m, 0.5H), 5.3 (br s, 1H), 4.8 (m, 1H), 4.35 (m, 1H), 4.0 (m, 1H), 3.8 (s, 3H), 3.15 (m, 1H), 1.9 (m, 1H), 1.5 (m, 1H), 1.4 (m, 5H), 1.2 (m, 3H), 0.85 (t, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.0, 151.8, 122.8, 122.7, 122.4, 122.3, 122.1, 122.0, 121.8, 118.4, 118.2, 118.0, 117.7, 92.9, 92.4, 92.2, 92.0, 68.1, 68.0, 67.8, 67.7, 67.6, 53.1, 36.7, 33.4, 33.2, 33.1, 21.7, 17.03, 16.8, 9.1. Anal. Calcd for $C_{15}H_{23}NO_4$ (281.35): C, 64.04; H, 8.24; N, 4.98. Found: C, 64.07; H, 8.27; N, 4.95.

3-(1,3-Dimethyl-4,5-diphenylimidazolidin-2-yl)-4-substituted-1,4-dihydropyridine-1-carboxylic Acid Methyl Esters (12a–g,k).

12a (R^1 = Me) (yields and de are reported in Table 1): ^1H NMR ($CDCl_3$, 400 MHz) δ 7–7.4 (m, 11H), 6.9 (br d, J = 7.8 Hz, 0.5H), 6.75 (br d, J = 7.8 Hz, 0.5H), 5.0 (m, 1H), 4.2 (br s, 1H), 3.8 (s, 3H), 3.85 (d, J = 7.7 Hz, 1H), 3.55 (d, J = 7.7 Hz, 1H), 3.25 and *3.06* (2m, 1H), 2.2 (s, 3H), 2.1 (s, 3H), 1.3 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 152.2, 140.6, 140.4, 128.8, 128.3, 128.2, 127.8, 127.4, 123.6, 121.8, 120.0, 113.2, 87.5, 77.9, 75.9, 53.5, 37.6, 35.0, 29.8, 22.5; IR (film) 2920, 2850, 1715, 1690 cm^{-1}. Anal. Calcd for $C_{25}H_{29}N_3O_2$ (403.53): C, 74.41; H, 7.24; N, 10.41. Found: C, 74.41; H, 7.28; N, 10.39.

12b (R^1 = Et) (yields and de are reported in Table 1): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.4–7 (m, 11H), 6.9 (br d, J = 7.8 Hz, 0.5H), 6.75 (br d, J = 7.8 Hz, 0.5H), 5.0 (m, 1H), 4.15 (s, 1H), 3.9–3.5 (m, 5H), 3.15 and *3.05* (2m, 1H), 2.3 (s, 3H), 2.2 (s, 3H), 1.6 (m, 2H), 0.9 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.3, 140.5, 140.3, 128.7, 128.5, 128.3, 128.2, 127.9, 127.5, 124.3, 123.1, 119.4, 111.0, 110.4, 89.5, 86.7, 77.7, 76.3, 53.5, 37.7, 35.7, 35.5, 28.1, 9.7; IR (film) 2920, 2850, 1715, 1690, 1340, 1320 cm^{-1}. Anal. Calcd for $C_{26}H_{31}N_3O_2$ (417.56); C, 74.79; H, 7.48; N, 10.06. Found: C, 74.75; H, 7.50; N, 10.01.

12c (R^1 = Bu) (90%, de = 95%): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.1 (m, 11H), 6.95 (d, J = 7.8 Hz, 0.5H), 6.8 (d, J = 7.8 Hz, 0.5H), 5.05 (m, 1H), 4.2 (s, 1H), 3.9 (s, 3H), 3.8 (d, J = 8.1 Hz, 1H), 3.5 (d, J = 8.1 Hz, 1H), 3.15 and *3.0* (2m, 1H), 2.25 (s, 3H), 2.0 (s, 3H), 1.7–1.2 (m, 6H), 0.9 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.5, 140.5, 140.3, 128.7, 128.3, 128.2, 127.7, 127.5, 124.5, 123.1, 119.8, 110.9, 86.7, 76.2, 77.7, 53.1, 37.7, 35.1, 34.6, 30.1, 23.0, 22.8, 13.9; IR (film) 2920, 2860, 2795, 1715, 1690 cm^{-1}. Anal. Calcd for $C_{28}H_{35}N_3O_2$ (445.61): C, 75.47; H, 7.92; N, 9.43. Found: C, 75.49; H, 8.02; N, 9.36.

12d (R^1 = vinyl) (90%, de = 95%): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.4–7.1 (m, 11H), 7.0 (d, J = 8 Hz, 0.5H), 6.8 (d, J = 8 Hz, 0.5H), 6.2 (m, 0.5H), 5.9 (m, 0.5H), 5.1 (m, 3H), 3.7 (m, 6H), 2.2 (s, 3H), 2.1 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.3, 140.5, 140.1, 128.8, 128.4, 128.3, 128.0, 127.5, 123.7, 122.9, 119.3, 114.4, 109.6, 87.0, 77.9, 75.9, 53.6, 38.8, 37.7, 35.0; IR (film) 2940, 2840, 2795, 1725, 1695, 1640 cm^{-1}. Anal. Calcd for $C_{28}H_{29}N_3O_2$ (415.54): C, 75.25; H, 7.03; N, 10.11. Found: C, 75.25; H, 7.11; N, 10.06.

12e (R^1 = phenyl) (yields and de are reported in Table 2): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.5–6.9 (m, 17H), 5.1 (m, 1H), 4.3 (d, J = 4.5 Hz, 0.5H), 4.15 (d, J = 4.5 Hz, 0.5H), 4.0 (s, 1H), 3.9 (s, 3H), 3.6 (d, J = 8.3 Hz, 1H), 3.45 (d, J = 8.3 Hz, 1H), 2.0 (s, 3H), 1.9 (s, 3H); ^{13} NMR ($CDCl_3$, 100 MHz) δ 152.4, 145.1, 140.3, 140.1, 129.6, 128.8, 128.6, 128.5, 128.4, 128.2, 128.0, 127.5, 127.4, 126.9, 123.5, 121.8, 119.0, 112.2, 86.0, 77.8, 76.0, 53.7, 41.9, 37.4, 35.2; IR (film) 2940, 2850, 2790, 1760, 1720, 1690, 1640 cm^{-1}. Anal. Calcd for $C_{30}H_{31}N_3O_2$ (465.60): C, 77.39; H, 6.71; N, 9.03. Found: C, 77.75; H, 6.75; N, 9.01.

12f (R^1 = iPr) (90%, de = 77%): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.5–7.1 (m, 11H), 7.05 (d, J = 7.9 Hz, 0.5H), 6.9 (d, J = 7.9 Hz 0.5H), 5.0 (m, 1H), 4.2 (s, 1H), 3.86 (s, 3H), 3.7 (d, J = 7.9 Hz, 1H), 3.5 (d, J = 7.9 Hz, 1H), 3.15 and *3.0* (2m, 1H), 2.19 (s, 3H), 2.15 (m, 4H), 0.9 (d, J = 6.8 Hz, 6H), 0.82 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.3, 140.5, 140.3, 128.7, 128.3, 128.2, 127.7, 127.5, 124.7, 124.6, 118.5, 106.7, 86.4, 77.6, 77.5, 53.5, 40.9, 37.7, 35.6, 30.9, 20.0, 16.9; IR (film) 3020, 2950, 2860, 2790, 1730, 1690 cm^{-1}. Anal. Calcd for $C_{27}H_{33}N_3O_2$ (431.59): C, 75.14; H, 7.70; N, 9.74. Found: C, 75.14; H, 7.75; N, 9.69.

12g (R^1 = tBu) (45%, de = 0%): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.4–6.6 (m, 12H), 5.15 (m, 1H), 3.8 (m, 5H), 3.2 and *2.6* (2d, J = 5 Hz, 1H), 2.4 (s, 3H), 2.1 (s, 3H), 1.0 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 153.1, 142.2, 140.0, 129.1, 128.8, 128.3, 128.1, 127.5, 127.3, 127.2, 126.5, 125.1, 124.3, 119.4, 118.0, 113.8, 110.2, 90.1, 78.7, 73.5, 72.1, 53.6, 48.0, 38.1, 37.7, 37.3, 27.3, 27.0, 25.7. Anal. Calcd for $C_{28}H_{35}N_3O_2$ (445.60): C, 75.47; H, 7.92; N, 9.43. Found: C, 75.62; H, 7.76; N, 9.25.

12k (R^1 = $(CH_2)_3CO_2CH_3$) (copper derivative was prepared according ref 24 (80%, de = 95%)): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.35–7.1 (m, 11H), 6.95 (d, J = 8 Hz, 0.5H), 6.8 (d, J = 8 Hz, 0.5H), 5.03 (m, 1H), 3.86 (br s, 3H), 3.62 (d, J = 8 Hz, 1H), 3.65 (s, 3H), 3.55 (d, J = 8 Hz, 1H), 3.26 and *3.22* (2m, 1H), 2.32 (m, 2H), 2.18 (s, 3H), 2.11 (s, 3H), 1.69 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.9, 152.0, 140.3, 139.9, 128.7, 128.2, 128.0, 127.6, 127.3, 124.4, 123.0, 119.1, 110.2, 87.3, 77.4, 75.7, 51.4, 37.5, 35.2, 35.0, 34.2, 33.6, 21; IR (film) 2940, 1730, 1450, 1335 cm^{-1}. Anal. Calcd for $C_{29}H_{35}N_3O_4$ (489.61): C, 71.13; H, 7.21; N, 8.59. Found: C, 71.14; H, 7.15; N, 8.57.

3-(1,3-Dimethyl-4,5-diphenylimidazolidin-2-yl)-6-substituted-1,6-dihydropyridine-1-carboxylic Acid Methyl esters (14a,b, 14g–j). 14a (R^1 = Me) (for yield and de see Table 1): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.3–7.05 (m, 10H), 6.9 and *6.95* (2s, 1H), 6.7 and *6.75* (2s, 1H), 6.45 and *6.2* (2br d, J = 9.6 Hz, 1H), 5.7 (m, 1H), 4.95 (m, 0.5H), 4.85 (m, 0.5H), 4.2 (s, 0.5H), 4.15 (s, 0.5H), 3.7–3.55 (m, 5H), 2.2 (s, 6H), 1.2 (d, J = 5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.6, 153.5, 140 (br signal), 128.0, 127.9, 127.7, 127.6, 127.3, 124.0 (br signal), 122 (br signal), 118.0, 86.3, 53.1, 49.0 (br signal), 37.3, 36.9, 29.6, 19.5 (br signal). Anal. Calcd for $C_{25}H_{29}N_3O_2$ (403.53): C, 74.41; H, 7.24; N, 10.41. Found: C, 74.39; H, 7.26; N, 10.38.

14b (R^1 = Et) (for yield and de, see Table 1): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.3–7.05 (m, 10H), 6.8 (m, 1H), 6.5 and *6.25* (2m, 1H), 5.7 (m, 1H), 4.9 (m, 1H), 4.2 (2s, 1H), 3.8–3.55 (m, 5H), 2.3–2.05 (m, 6H), 1.75 (m, 2H), 0.9 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.1, 154.8, 139.9, 128.3, 128.0, 127.8, 127.4, 125.7, 124.9, 122.3, 118.0 (br signal), 53.1, 37.2, 34.8, 26.9, 8.9. Anal. Calcd for $C_{26}H_{31}N_3O_2$ (417.55): C, 74.79; H, 7.48; N, 10.06. Found: C, 74.76; H, 7.52; N, 10.02.

14g (R^1 = tBu) (for yield and de see Table 2): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.3–6.72 (m, 11H), 6.7 (m, 1H), 6.55 and *6.35* (2d, J = 9.5 Hz, 1H), 4.7 (m, 1H), 4.1 (m, 1H), 3.7 (m, 3H), 3.5 (m, 2H), 2.17 (m, 6H), 0.95 (m, 9H).

14h (R^1 = (trimethylsilyl)ethynyl): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.25–7.1 (m, 10H), 7.05 and *6.9* (2br s, 0.5H), 6.95 and *6.75* (2br s, 0.5H), 6.55 and *6.35* (2br d, J = 9.6 Hz, 1H), 5.75 (m,

1H), 5.7 and *5.6* (2d, J = 7 Hz, 0.5H), 5.5 and *5.45* (2d, J = 7 Hz, 0.5H), 4.3 and *4.2* (2m, 1H), 3.9 and *3.85* (2s, 3H), 3.8 and *3.75* (2d, J = 7.7 Hz, 1H), 3.6 and *3.55* (2d, J = 7.7 Hz, 1H), 2.15 (br s, 6H), 0.1 and *0.07* (s, 9H). Anal. Calcd for $C_{29}H_{35}N_3O_2Si$ (485.70): C, 71.71; H, 7.26; N, 8.65. Found: C, 71.86; H, 7.17; N, 8.45.

14i (R^1 = allyl) (copper derivative was prepared according ref 19): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2 (m, 10H), *6.95* and 6.9 (2s, 1H), *6.8* and 6.75 (2s, 1H), 6.5 and *6.2* (2m, 1H), 5.75 (m, 2H), 5.05 (m, 2H), 4.9 (m, 1H), 4.13 (br s, 1H), 3.8 (m, 4H), 3.5 (d, J = 8 Hz, 1H), 2.25 (m, 2H), 2.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.9, 139.9, 133.7, 133.2, 128.9, 128.4, 128.2, 128.1, 127.9, 127.5, 125.6, 124.8, 123.3, 122.1, 118.8, 118.0, 86.5, 77.4, 77.1, 53.3, 43.8, 38.8, 37.2, 37.0, 35.0, 27.0. Anal. Calcd for $C_{27}H_{31}N_3O_2$ (429.56): C, 75.49; H, 7.27; N, 9.78. Found: C, 75.45; H, 7.30; N, 9.76.

14j (R^1 = CH_2CO_2Et) (copper derivative was prepared according ref 21a (yield = 30%)): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.1–7.4 (m, 10H), *6.95* and 6.9 (2s, 0.5H), *6.8* and 6.75 (2s, 0.5H), 6.5 and *6.3* (2m, 1H), 5.8 (m, 1H), 5.3 (m, 0.5H), 5.2 (m, 0.5H), 4.1 (m, 3H), 3.8 (m, 4H), 3.55 (m, 1H), 2.55 (m, 2H), 2.15 (m, 6H), 1.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 153.7, 139.8, 139.6, 128.8, 128.3, 128.2, 128.1, 127.9, 127.8, 127.5, 125.2, 124.6, 124.0, 123.8, 121.4, 121.2, 119.5, 118.3, 86.3, 77.4, 77.0, 60.7, 53.4, 50.0, 49.9, 37.2, 35.0, 14.2. Anal. Calcd for $C_{28}H_{33}N_3O_4$ (475.59): C, 70.71; H, 6.99; N, 8.84. Found: C, 75.85; H, 6.70; N, 8.71.

1-Acetyl-3-(1,3-dimethyl-4,5-diphenylimidazolidin-2-yl)-4-substituted-1,4-dihydropyridines (13a,b,e–g). 13a (R^1 = Me) (for yield and de see Table 1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (s, 0.5H), 7.35–7.1 (m, 10.5H), 7.0 (s, 0.5H), 6.5 (d, J = 8.1 Hz, 0.5H), 5.1 (2dd, J = 8.1, 4.8 Hz, 1H), 4.2 (s, 1H), 3.8 (d, J = 8 Hz, 1H), 3.55 (d, J = 8 Hz, 1H), 3.25 (m, 1H), 2.2 (m, 9H), 1.3 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.2, 140.8, 140.4, 140.3, 140.1, 128.9, 128.7, 128.4, 128.2, 127.8, 127.5, 124.2, 123.3, 122.6, 121.0, 114.7, 88.1, 86.9, 77.9, 76.0, 75.7, 37.6, 35.0, 34.6, 29.8, 23.0, 22.6, 21.6; IR (film) 2940, 2860, 2695, 1665, 1630 cm^{-1}. Anal. Calcd for $C_{25}H_{29}N_3O$ (387.53): C, 77.49; H, 7.54; N, 10.85. Found: C, 77.46; H, 7.6; N, 10.75.

13b (R^1 = Et) (for yield and de see Table 1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.6 (s, 0.5H), 7.4–7.05 (m, 11H), 6.6 (d, J = 8.1 Hz, 0.5H), 5.12 (m, 1H), 4.2 (s, 0.5H), 4.1 (s, 0.5H), 3.8 (d, J = 8 Hz, 0.5H), 3.7 (d, J = 8 Hz, 0.5H), 3.55 (d, J = 8 Hz, 1H), 3.2 (m, 1H), 2.25 (m, 9H), 1.6 (m, 2H), 0.9 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 140.7, 140.4, 140.2, 140.1, 128.9, 128.7, 128.4, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 127.3, 125.0, 124.0, 123.5, 122.4, 121.4, 120.7, 112.07, 87.5, 86.1, 77.9, 76.3, 76.1, 37.8, 37.7, 36.3, 35.7, 35.5, 35.4, 30.5, 28.2, 28.0, 9.9; IR (film) 2940, 2860, 2695, 1665, 1630 cm^{-1}. Anal. Calcd for $C_{26}H_{31}N_3O$ (401.56): C, 77.77; H, 7.78; N, 10.46. Found: C, 77.70; H, 7.80; N, 10.42.

13e (R^1 = Ph) (for yield and de see Table 2): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.8 (s, 0.5H), 7.4–7.0 (m, 16H), 6.7 (m, 0.5H), 5.75 (dd, J = 8.5, 5 Hz, 0.5H), 5.65 (2dd, J = 8.5, 5 Hz, 0.5H), 3.85 and 3.8 (2d, J = 5 Hz, 1H), 4.10 (br s, 1H), 3.6 (2d, J = 7.8 Hz, 1H), 3.4 (2d, J = 7.8 Hz, 1H), 2.84–1.85 (m, 9H). Anal. Calcd for $C_{30}H_{31}N_3O$ (449.60): C, 80.15; H, 6.95; N, 9.35. Found: C, 80.30; H, 7.02; N, 9.19.

13f (R^1 = iPr) (for yield and de see Table 2): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (s, 0.5H), 7.4–7.1 (m, 11H), 6.7 (d, J = 8.2 Hz, 0.5H), 5.10 (2dd, J = 8.2, 5 Hz, 1H), 4.3 (s, 0.5H), 4.2 (s, 0.5H). *3.95* and 3.85 (2d, J = 7.8 Hz, 0.5H), 3.75 (d, J = 7.8 Hz, 0.5H), 3.55 (d, J = 7.8 Hz, 1H), 3.2 (dd, J = 5, 3.1 Hz, 0.5H), 3.1 (dd, J = 5, 3.1 Hz, 0.5H), 2.27 (m, 10H), 1.0 (d, J = 7 Hz, 3H), 0.8 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4; 140.7, 140.4, 140.3, 140.1, 128.9, 128.7, 128.4, 128.3, 128.0, 127.9, 127.6, 127.5, 125.3, 125.2, 123.8, 123.9, 121.1, 120.5, 108.5, 108.4, 87.3, 85.9, 77.5, 76.6, 41.9, 41.2, 37.8, 37.7, 35.6, 31.1, 30.6, 21.8, 20.3, 20.1, 16.9; IR (film) 3020, 2950, 2860, 2790, 1640, 1630 cm^{-1}. Anal. Calcd for $C_{27}H_{33}N_3O$ (415.528): C, 78.04; H, 8.01; N, 10.11. Found: C, 78.08; H, 7.95; N, 10.01.

13g (R^1 = tBu) (for yield and de see Table 2, the diastereomeric ratio was determined by GC): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (s, 0.5H), 7.4–7.05 (m, 11H), 6.7 (m, 0.5H), 5.75 (m, 1H), 4.65 (br s, 0.5H), 3.95 (m, 1.5H), 3.4 (m, 1.5H), 2.7 (m, 1H), 2.22 (m, 9H), 0.92 (m, 9H).

1-Acetyl-3-(1,3-dimethyl-4,5-diphenylimidazolidin-2-yl)-6-substituted-1,6-dihydropyridines (15g and 15f). 15g (R^1 = tBu) (for yield and de see Table 2): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.05–7.4 (m, 10H), 6.65 and *6.64* (2 s, 1H), 6.5 (d, J = 9.9 Hz, 0.5H), 6.4 (d, J = 5.7 Hz, 0.5H), 5.8 (dd, J = 9.9, 5.7 Hz, 1H), 5.1 (m, 1H), 4.2 (s, 0.5H), 4.1 (s, 0.5H), 3.85 (2d, J = 8.3 Hz, 1H), 3.55 (2d, J = 8.3 Hz, 1H), 2.2 (m, 6H), 0.9 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 170.5, 139.8, 139.6, 128.4, 128.2, 127.8, 127.6, 127.3, 127.1, 124.1, 123.4, 123.0, 122.9, 122.4, 121.6, 87.2, 86.4, 77.5, 77.32, 77.0, 58.5, 57.9, 39.4, 39.2, 37.3, 37.2, 35.3, 34.6, 30.3, 29.8, 27.0, 26.0, 25.9 22.3.

15j (R^1 = CH_2CO_2Et, AX = tBuCOCl) (same procedure as for **14j** (yield 25%)): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.1–7.4 (m, 10H), 6.95 (s, 1H), *6.5* and 6.2 (2d, J = 6.5 Hz, 1H), 6.9 (m, 1H), 5.5 (m, 1H), 4.0 (m, 3H), 3.9 (m, 1H), 3.7 (m, 1H), 2.55 (m, 2H), 2.1 (br s, 6H), 1.4 (br s, 9H), 1.2 (m, 3H).

Addition of the Sodium Salt of Methyl Malonate. Preparation of 14l. Methyl malonate (0.7 mL, 6 mmol) was added to a suspension of NaH (320 mg, 6.08 mmol) in THF (20 mL) at room temperature. The mixture was stirred for 45 min. A solution of pyridine **6** (200 mg, 0.6 mmol) in THF (100 mL) and then a solution of methyl chloroformate (0.095 mL, 1.2 mmol) in THF (10 mL) were added. The reaction mixture was stirred at room temperature for 3 h and then diluted with an aqueous solution of NH_4Cl, extracted with ether, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, cyclohexane/ether = 70/30) to give 108 mg (30%, de = 0%) of **14l**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.4–7.1 (m, 10H), 7.0 and *6.95* (2s, 0.5H), 6.9 and *6.85* (2s, 0.5H), 6.5 and *6.4* (2m, 1H), 5.85 (m, 1H), 5.6 (m, 1H), 4.8–3.25 (m, 12H), 2.15 (m, 6H).

Addition of Diindolylcopper Reagent. Preparation of 12m. A solution of *n*-BuLi in hexane (1.52 mmol) was added to a solution of indole (178 mg, 1.52 mmol) in THF at −80 °C. The mixture was stirred for 30 min and the temperature allowed to warm to −40 °C and then cooled to −60 °C. CuI (145 mg, 0.76 mmol) was added and the reaction mixture stirred for 1 h at −40 °C and then cooled to −80 °C. During this time, the reaction mixture became a deep blue solution. Pyridine **6** (100 mg, 0.3 mmol) in THF (10 mL) and methyl chloroformate (0.12 mL, 1.52 mmol) were added, and the reaction mixture was stirred for 12 h and then allowed to warm to room temperature. The reaction was quenched by addition of an aqueous solution of NH_4OH/NH_4Cl (1/1). The mixture was diluted with Et_2O and washed with NH_4Cl aqueous solution. The organic layer was dried (Na_2CO_3) and concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO_2, cyclohexane/dichloromethane/ether = 70/10/20) to give 76 mg (50%, de = 95%) of pure **12m**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8 (s, 1H), 7.72 (m, 1H), 7.4–6.5 (m, 16H), 5.3 (m, 1H), 4.5 (d, J = 5.5 Hz, 1H), 4.1 (m, 1H), 3.9 (m, 4H), 3.35 (d, J = 8.1 Hz, 1H), 2.2 (s, 3H), 1.8 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 128.7, 127.9, 127.6, 127.5, 127.2, 126.7, 126.4, 124.4, 124, 121.4, 121.1, 120.2, 119.3, 119.1, 111.9, 111.1, 89.6, 89.4, 77.5, 77.3, 53.5, 37.1, 34.2, 31.1, 30.9, 30.2, 30.1. Anal. Calcd for $C_{32}H_{32}N_4O_2$ (504.63): C, 76.15; H, 6.40; N, 11.11. Found: C, 76.14; H, 6.45; N, 11.10.

3-(1,3-Dimethyl-4,5-diphenylimidazolidin-2-yl)-4-(diethylphosphonyl)-1,4-dihydropyridine-1-carboxylic Acid Methyl ester (12n) and 3-(1,3-Dimethyl-4,5-diphenylimidazolidin-2-yl)-6-(diethylphosphonyl)-1,6-dihydropyridine-1-carboxylic Acid Methyl Esters (14n). A solution of methyl chloroform (0.094 mL, 1.2 mmol) in dichloromethane (10 mL) was added to a solution of pyridine **6** (200 mg, 0.6 mmol) in dichloromethane (30 mL) at −20 °C. Then triethyl phosphite (0.514 mL, 3 mmol) was added and the reaction mixture stirred for 2 h. The temperature was allowed to warm to room temperature. The reaction mixture was concentrated in vacuo and then purified by column chromatography (SiO_2, cyclohexane/ether = 50/50) to give 170 mg of **12n** and 113 mg of **14n** (90%).

12n (de = 84%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.64 (m, 0.5H), 7.52 (s, 0.5H), 7.1–7.3 (m, 10H), 7.04 (s, 0.5H), 6.9 (s, 0.5H), 5.1 (m, 1H), 4.64 (s, 1H), 4.16 (m, 4H), 3.9 (m, 4H), 3.56 (m, 1H), 2.28 (s, 3H), 1.3 (t, J = 7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 152.3, 139.8, 140.0, 128.3, 128.2, 128.1, 127.9, 127.4, 126.0, 113.0, 102.5, 84.0, 77.4, 77.1, 62.6, 62.5, 53.7, 40–35 (br signal), 16.6, 16.5; ^{31}P NMR ($CDCl_3$, 36.22 MHz) δ *22.6*, *22.5*, 21.6, 21.5.

14n (de = 56%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.1–7.4 (m, 10H), *6.96* and 6.93 (2s, 0.5H), *6.82* and 6.75 (2s, 0.5H), 6.55 (m, 1H), 5.75 (m, 1H), 5.52 and *5.38* (2d, J = 7.6 Hz, 0.5H), 5.48 and *5.33* (2d, J = 7.6 Hz, 0.5H), 4.15 (m, 5H), 3.85 (s, 3H), 3.82 (m, 1H), 3.55 (d, J = 9.4 Hz, 1H), 2.23 (s, 3H), 2.17 (s, 3H), 1.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 153.7, 139.8, 139.7, 128.3, 128.2, 128.1, 127.8, 127.5, 125.2, 119.8, 115.8, 115.4, 86.5, 86.2, 77.4, 77.1, 62.8, 53.7, 37.2, 34.9 16.5; ^{31}P NMR ($CDCl_3$, 36.22 MHz) δ 22.6, 22.5, 21.6, 21.5.

Hydrolysis of Dihydropyridines 12a–n and 13a–n. Preparation of Aldehydes 1a–n and 16a–n: General Procedure. To a solution of dihydropyridines **12a–n** or **13a–n** (0.5 mmol) in 20 mL of Et_2O was added, at room temperature, 10 mL of HCl 5%. The yellow solution was stirred for 1 h, poured into Et_2O (50 mL), and washed with NH_4Cl aqueous solution and then Na_2CO_3 aqueous solution. The organic layer was dried (Na_2CO_3) and concentrated in vacuo to afford a yellow oil. Purification by column chromatography (SiO_2, cyclohexane/ether = 1/1) afforded the pure aldehydes **1a–n** or **16a–n**.

3-Formyl-4-substituted-1,4-dihydropyridine-1-carboxylic Acid Methyl Esters (1a–g,k,m,n). 1a (R^1 = Me) (yield = 85%): $[\alpha]^{25}_D$ = −267° (c = 6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.35 (s, 1H), 7.6 (br s, 1H), 6.7 (br d, J = 8.1 Hz, 1H), 5.1 (dd, J = 8.1, 5.1 Hz, 1H), 3.9 (s, 3H), 3.35 (m, 1H), 1.15 (d, J = 8.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.0, 151.9, 141.0, 125.1, 121.0, 115.2, 54.5, 26.0, 23.0; IR (film) 1740, 1670 cm^{-1}. Anal. Calcd for $C_9H_{11}NO_3$ (181.19): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.64; H, 6.13; N, 7.71.

1b (R^1 = Et) (yield = 82%): $[\alpha[^{25}_D$ = −276° (c = 4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.37 (s, 1H), 7.7 (br s, 1H), 6.8 (br d, J = 8.3 Hz, 1H), 5.1 (dd, J = 8.3, 4.8 Hz, 1H), 3.9 (s, 3H), 3.4 (m, 1H), 1.65 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.9, 151.3, 141.9, 123.0, 122.0, 112.9, 54.4, 31.6, 27.7, 9.3; IR (film) 2920, 2845, 1740, 1670, 1610 cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO_3$ (195.22): C, 61.52; H, 6.71; N, 7.17. Found: C, 61.72; H, 6.70; N, 7.10.

1c (R^1 = Bu) (yield = 88%): $[\alpha]^{25}_D$ = −154° (c = 2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.35 (s, 1H), 7.65 (br s, 1H), 6.8 (br d, J = 7.3 Hz, 1H), 5.7 (dd, J = 7.3, 4.5 Hz, 1H), 3.85 (s, 3H), 3.35 (m, 1H), 1.6–1.2 (m, 6H), 0.9 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 191.0, 151.5, 141.7, 123.8, 121.9, 113.5, 54.4, 35.4, 30.7, 27.6, 23.2, 14.1; IR (film) 1740, 1670, 1610, 1345, 1320 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_3$ (223.77): C, 64.55; H, 7.67; N, 6.27. Found: C, 64.58; H, 7.70; N, 6.23.

1d (R^1 = vinyl) (yield = 81%): $[\alpha]^{25}_D$ = −160° (c = 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.4 (s, 1H), 7.7 (br s, 1H), 6.85 (br d, J = 8.1 Hz, 1H), 5.9 (ddd, J = 17.1, 10.2, 6.3 Hz, 1H), 5.1 (m, 3H), 3.95 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.4, 151.4, 140.6, 139.2, 122.6, 122.0, 115.9, 114.4, 54.6, 34.2; IR (film) 1740, 1660, 1612, 1348, 1313 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO_3$ (193.21): C, 62.17; H, 5.74; N, 7.25. Found: C, 62.18; H, 5.74; N, 7.27.

1e (R^1 = Phenyl) (yield = 80%): $[\alpha]^{25}_D$ = −330° (c = 2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.35 (s, 1H), 7.8 (br s, 1H), 7.2 (m, 6H), 6.9 (br d, J = 8.1 Hz, 1H), 5.26 (dd, J = 8.1, 4.3 Hz, 1H), 4.5 (d, J = 4.3 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.2, 151.5, 143.9, 140.1, 127.1, 128.3, 128.7, 123.2, 121.1, 113.3, 54.6, 37.0; IR (film) 1740, 1675, 1612, 1348, 1313 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_3$ (243.26): C, 69.12; H, 5.39; N, 5.76. Found: C, 68.98; H, 5.41; N, 5.75.

1f (R^1 = iPr) (yield = 80%): $[\alpha]^{25}_D$ = −304° (c = 4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.4 (s, 1H), 7.7 (s, 1H), 6.85 (d, J = 8.3 Hz, 1H), 5.1 (dd, J = 8.3, 4.8 Hz, 1H), 3.9 (s, 3H), 3.35 (m, 1H), 2.0 (m, 1H), 0.95 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.0, 152.3, 142.1, 123.0, 109.7, 54.4, 36.07, 31.01, 9.32; IR (film) 1735, 1670, 1610, 1350, 1320 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_3$ (209.25): C, 63.14; H, 7.22; N, 6.71. Found: C, 63.18; H, 7.29; N, 6.68.

1g (R^1 = tBu) (yield = 81%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.5 (s, 1H), 8.0 (m, 0.5H), 7.4 (m, 0.5H), 7.25 (m, 0.5H), 6.75 (m, 0.5H), 5.35 (m, 1H), 3.25 (d, J = 5.7 Hz, 1H), 2.4 (s, 3H), 0.85 (s, 9H). Anal. Calcd for $C_{12}H_{17}NO_3$ (223.27): C, 64.55; H, 7.67; N, 6.27. Found: C, 64.72; H, 7.75; N, 6.17.

1k (R^1 = $(CH_2)_3CO_2Me$) (yield = 89%): $[\alpha]^{25}_D$ = −176° (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (s, 1H), 7.68 (br s, 1H), 6.82 (br s, 1H), 5.15 (m, 1H), 3.93 (s, 3H), 3.68 (s, 3H), 3.43 (m, 1H), 2.29 (m, 2H), 1.6 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 190.7, 173.8, 151.1, 141.8; 122.4, 121.9, 112.5, 54.3, 51.4, 34.21, 33.8, 30.1, 20.5; IR (film) 2940, 2840, 1730, 1670, 1610 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_5$ (267.28): C, 58.42; H, 6.41; N, 5.24. Found: C, 58.45; H, 6.43; N, 5.22.

1m (R^1 = Indolyl, Boc Derivative). Triethylamine (0.077 mL, 0.55 mmol) was added to a mixture of **12m** (277 mg, 0.55 mmol), Boc anhydride (205 mg, 1.1 mmol), and DMAP (67 mg, 0.55 mmol) in dichloromethane (50 mL). The reaction mixture was stirred for 12 h at room temperature, diluted with ether (100 mL), and then poured into 20 mL of HCl 5%. The yellow solution was stirred for 1 h, poured into Et_2O (50 mL), and washed with NH_4Cl aqueous solution and then Na_2CO_3 aqueous solution. The organic layer was dried (Na_2CO_3) and concentrated in vacuo to afford a yellow oil. Purification by column chromatography (SiO_2, cyclohexane/ether = 1/1) afforded 189 mg (90%) of aldehyde **1m**: $[\alpha]^{25}_D$ = 62° (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.4 (s, 1H), 8.1 (d, J = 7.8 Hz, 1H), 7.85 (s, 1H), 7.59 (d, J =7.8 Hz, 1H), 7.25 (m, 3H), 6.95 (m, 1H), 4.76 (d, J = 4.5 Hz, 1H), 4.0 (s, 3H), 1.65 (s, 9H); IR (film) 2940, 1724, 1685, 1630, 1600 cm^{-1}. Anal. Calcd for $C_{21}H_{22}N_2O_5$ (382.42): C, 65.96; H, 5.8; N, 7.33. Found: C, 65.97; H, 5.85; N, 7.30.

1n (R^1 = OP(OEt)$_2$) (yield = 95%): $[\alpha]^{25}_D$ = −167° (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.4 (s, 1H), 7.72 (br s, 1H), 6.9 (m, 1H), 5.25 (m, 1H), 4.09 (q, J = 7.2 Hz, 4H), 3.9 (m, 1H), 3.89 (s, 3H), 1.25 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 188.5, 156.9, 142.2, 124.2, 116.1, 105.0, 62.7, 62.6, 54.5, 31.9, 30.4, 16.3; IR (film) 2960, 1740, 1670, 1600 cm^{-1}.

1-Acetyl-3-formyl-4-substituted-1,4-dihydropyridines (16a,b,e–g). 16a (R^1 = Me) (yield = 87%): $[\alpha]^{25}_D$ = −265° (c = 2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.4 (s, 1H), 7.9 and 7.3 (2m, 1H), 7.1 (m, 1H), 6.5 (m, 1H), 5.2 (m, 1H), 3.4 (m, 1H), 2.3 (s, 3H), 1.15 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 191.5, 166.8, 138.7, 121.2, 119.3, 115.5, 25.7, 22.2, 21.1; IR (film) 2930, 1710, 1670, 1610, 1370 cm^{-1}. Anal. Calcd for $C_9H_{11}NO_2$ (165.19): C, 65.43; H, 6.71; N, 8.47. Found: C, 65.40; H, 6.73; N, 8.46.

16b (R^1 = Et) (yield = 84%): $[\alpha]^{25}_D$ = −113° (C = 4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.45 (s, 1H), 8.0 (br s, 1H), 7.35 (br s, 1H), 7.2 (br s, 1H), 6.65 (br s, 1H), 5.2 (br s, 1H), 3.4 (m, 1H), 2.35 (s, 3H), 1.5 (m, 2H), 0.8 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.2, 166.8, 141.0, 125.7, 124.0, 122.5, 114.1, 32.2, 29.9, 30.6, 21.6, 9.5; IR (film) 2930, 1710, 1670, 1610, 1370 cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO_2$ (179.22): C, 67.02; H, 7.31; N, 7.82. Found: C, 67.02; H, 7.29; N, 7.79.

16e (R^1 = Ph) (yield = 81%): $[\alpha]^{25}_D$ = −137° (c = 3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.4 (s, 1H), 8.2 (br s, 1H), 7.3 (m, 5H), 6.6 (br s, 1H), 5.25 (br s, 1H), 4.42 (s, 1H), 2.4 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.0, 161.1, 143.2, 138.1, 128.6, 128.0, 127.0, 121.0, 113.0, 37.2, 21.6; IR (film) 1710, 1660, 1600, 1170 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_2$ (227.26): C, 73.99; H, 5.77; N, 6.16. Found: C, 74.11; H, 5.84; N, 6.01.

16f (R^1 = iPr) (yield = 89%): $[\alpha]^{25}_D$ = −298° (c = 3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.45 (s, 1H), 8.0 (br s, 0.5H), 7.4 (br s, 0.5H), 7.2 (br s, 0.5H), 6.7 (br s, 0.5H), 5.2 (m, 1H), 3.35 (m, 1H), 2.4 (s, 3H), 2.0 (s, 1H), 0.95 (d, J = 7.0 Hz, 6H), 0.75 (d, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.2, 166.9, 140.9, 125.7, 123.9, 123.2, 37.3, 31.3, 30.6, 21.7, 19.5, 17.3; IR (film) 1705, 1670, 1610 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_2$ (193.25): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.52; H, 7.89; N, 7.08.

16g (R^1 = tBu) (yield = 82%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.5 (s, 1H), 8.0 (m, 0.5H), 7.4 (m, 0.5H), 7.25 (m, 0.5H), 6.75 (m, 0.5H), 5.35 (m, 1H), 3.25 (d, J = 5.7 Hz, 1H), 2.4 (s, 3H), 0.85 (s, 9H).

Preparation of 1e from 16e (Scheme 6). To a stirred solution of dihydropyridine **16e** (40 mg, 0.25 mmol) in CH_3OH (15 mL) was added 15 mL of an aqueous solution of NaOH (5%). The solution was stirred for 30 min and then poured into CH_2Cl_2. The aqueous layer was decanted. The organic layer was washed with H_2O, dried over Na_2CO_3, and then concentrated in vacuo to afford the crude NH dihydropyridine which was used without purification: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.1 (s, 1H), 7.2 (m, 5H), 6.8 (s, 1H), 5.95 (d, J = 7.1 Hz, 1H), 4.85 (dd, J = 7.1, 4.4 Hz, 1H), 3.85 (d, J = 4.4 Hz, 1H). The crude dihydropyridine was dissolved in Et_2O (10 mL), and (dimethylamino)pyridine

(10 mg) and then methyl chloroformate (1 mL) were added into the solution. The solution was stirred at room temperature for 1 h. Methanol (5 mL) was added to the reaction mixture, and the solution was stirred for 30 min and then poured into saturated aqueous Na_2CO_3 solution. The organic layer was decanted and the aqueous layer extracted with Et_2O. The combined organic extracts were dried over Na_2CO_3 and concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO_2, cyclohexane/ether = 80/20) to give 30 mg (50%) of pure **1e**.

4-Ethyl-1-[1(*H*)-indol-3-ylacetyl]-3-(1,3-dimethyl-4,5-diphenylimidazolidin-2-yl)-1,4-dihydropyridine (20). For the experimental procedure see the general procedure for the addition of organometallic reagents on pyridines **3–6** (for yield and de see Table 3): $[\alpha]^{25}_D = -40°$ (c = 3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.2 (s, 1H), 7.65 (m, 2H), 7.4–6.95 (m, 14.5H), 6.8 (d, J = 7.6 Hz, 0.5H), 5.15 (m, 1H), 5.05 (m, 1H), 4.1 (s, 1H), 4.0 (s, 1H), 3.75–3.45 (m, 2H), 3.2 (m, 0.5H), 3.1 (m, 0.5H), 2.05 (m, 6H), 1.5 (m, 2H), 0.85 (m, 3H); ^{13}C NMR δ 170.1, 169.6, 139.7, 139.6, 139.4, 139.2, 135.9, 128.9, 128.7, 128.6, 128.3, 128.1, 128.0, 127.8, 127.6, 127.5, 127.2, 127.0, 125.1, 122.6, 122.4, 122.2, 121.0, 119.7, 118.5, 113.6, 113.3, 112.0, 111.8, 111.2, 108.1, 107.9, 86.6, 85.1, 77.5, 76.5, 37.6, 37.4, 35.3, 36.1, 35, 31.5, 30.8, 27.5, 27.2, 9.2, 9.0; IR (film) 3420, 3050, 2950, 2880, 1715, 1680 cm^{-1}. Anal. Calcd for $C_{34}H_{36}N_4O$ (516.69): C, 79.03; H, 7.02; N, 10.84. Found: C, 78.99; H, 7.04; N, 10.85.

4-Ethyl-3-formyl-1-[1(*H*)-indol-3-ylacetyl]-1,4-dihydropyridine (21). For the experimental procedure see the general procedure for the hydrolysis of dihydropyridines **12a–n** and **13a–n** (yield = 70%): $[\alpha]^{25}_D = -160°$ (c = 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.4 (br s, 1H), 8.6 (br s, 1H), 7.9 (br s, 1H), 7.55 (d, J = 7 Hz, 1H), 7.3 (d, J = 7 Hz, 1H), 7.2 (m, 2H), 6.95 (s, 1H), 6.8 (br s, 1H), 5.1 (br s, 1H), 4.0 (s, 2H), 3.3 (m, 1H), 1.6 (m, 2H), 0.75 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.0, 167.7, 141.0, 136.2, 126.7, 123.0, 122.7, 120.1, 118.3, 113.8, 111.4, 107.0, 31.9, 31.4, 27.4, 9.2; IR (film) 3300, 2880, 2850, 2800, 1670, 1620 cm^{-1}. Anal. Calcd for $C_{18}H_{18}N_2O_2$ (294.36): C, 73.44; H, 6.16; N, 9.52. Found: C, 73.47; H, 6.17; N, 9.49.

***N*-Benzylpyridinium Salt 17.** A solution of benzylbromide or chloride (1.1 mmol) and pyridine **6** (329 mg, 1 mmol) in AcOEt (30 mL) was refluxed for 12 h and then concentrated in vacuo. The crude salt was washed with ether (50 mL) to give 387 mg (85%) of **17** as a yellow powder: ^1H NMR ($CDCl_3$, 200 MHz) δ 9.85 (d, 1H), 9.7 (s, 1H), 8.75 (d, 1H), 8.75 (d, 1H), 8.15 (m, 1H), 7.8–7 (m, 15H), 6.5 (s, 2H), 5.05 (s, 1H), 3.85 (d, 1H), 3.75 (d, 1H), 2.2 (s, 3H), 1.8 (s, 3H).

1-Benzyl-4-ethyl-3-(1,3-dimethyl-4,5-diphenylimidazolidin-2-yl)-1,4-dihydropyridine (18). To a solution of Et_2CuX (X = Li or MgBr, 0.9 mmol) in THF (30 mL) at −80 °C was added a solution of the pyridinium salt **17** (0.18 mmol) in THF (10 mL). The solution was stirred for 1 h at −70 °C and then quenched by an aqueous solution of NH_4OH/NH_4Cl. The organic layer was washed with the aqueous solution of NH_4OH/NH_4Cl until the disappearance of the blue color in the aqueous solution. The organic layer was dried over Na_2CO_3 and then concentrated in vacuo. The crude product was analyzed by NMR without any purification: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.5–7.1 (m, 15H), *6.4* and 6.1 (2s, 1H), *6.05* and 5.95 (2d, J = 8.4 Hz, 1H), *4.65* and 4.55 (2dd, J 8.4, 5.7 Hz, 1H), 4.35 (m, 2H), 4.15 and *4.10* (2s, 1H), *3.85* and 3.60 (2d, J = 8.1 Hz, 1H), 3.4 (m, 1H), 3.15 and *2.95* (2m, 1H), 2.15 (m, 6H), 1.45 (m, 2H), 0.9 (m, 3H).

Pyridinium Salt 22. A mixture of tryptophyl bromide (246 mg, 1.1 mmol) and pyridine **6** (329 mg, 1 mmol) were heated, without solvent, under a nitrogen atmosphere at 110 °C during 1 h and then cooled to room temperature. The mixture was dissolved in CH_2Cl_2, and then Et_2O was added in order to precipitate the pyridinium salt which was filtered to give 579 mg (95%) of **22** as a yellow powder: ^1H NMR ($CDCl_3$, 200 MHz) δ 10.3 (s, 1H), 9.2 (m, 1H), 8.7 (s, 1H), 8.3 (m, 1H), 7.8 (m, 1H), 7.4–6.8 (m, 15H), 5.1 (m, 1H), 4.6 (s, 1H), 3.5 (m, 2H), 3.4 (m, 2H), 1.9 (s, 3H), 1.5 (s, 3H).

4-Ethyl-1-[2-(1(*H*)-indol-3-yl)-ethyl]-3-(1,3-dimethyl-4,5-diphenylimidazolidin-2-yl)-1,4-dihydropyridine (23) by Addition of Diethylcuprate to the Pyridinium Salt 22. To a solution of diethylcuprate (Li or MgBr, 0.9 mmol) in THF (30 mL) at −80 °C was added a suspension of the pyridinium salt **22** (100 mg, 0.18 mmol) in THF (10 mL). The solution was stirred for 1 h at −70 °C and then quenched by an aqueous solution of NH_4OH/NH_4Cl. The organic layer was washed with the aqueous solution of NH_4OH/NH_4Cl until the blue color disappeared in the aqueous solution. The organic layer was dried over Na_2CO_3 and then concentrated in vacuo. The crude product was analyzed by NMR without any purification.

Preparation of 23 by $LiAlH_4$ reduction of the Dihydropyridine 20. To a solution of the 1,4-dihydropyridine **20** (150 mg, 0.3 mmol) in Et_2O (30 mL) at room temperature was added a solution of $LiAlH_4$ in Et_2O (1 mmol). The mixture was refluxed for 2 h and then cooled to room temperature. AcOEt (5 mL) was carefully added followed by an aqueous solution saturated with NH_4Cl (20 mL). The organic layer was washed with water, dried over Na_2CO_3, and then concentrated in vacuo. The crude product **23** was analyzed by NMR and used for the further transformation without purification: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.0 (s, 1H), 7.6–7.0 (m, 16H), 6.3 and *6.05* (2s, 1H), *6.0* and 5.95 (2d, J = 8.3 Hz, 1H), *4.6* and 4.45 (2dd, J = 8.3, 5.6 Hz, 1H), 4.1 and *4.05* (2s, 1H), *3.85* and 3.75 (2m, 2H), 3.55 (d, J = 8.1 Hz, 1H), 3.4 (m, 2H), 3.1 (m, 1H), 3.0 and *2.95* (2m, 1H), 2.2 (s, 3H), 2.0 (s, 3H), 1.4 (m, 2H), 0.9 (m, 3H).

Indoloquinolizine 25. A solution of **23** (100 mg, 0.2 mmol) in MeOH (15 mL) was saturated with gazeous HCl for 4 h. The red solution was stirred for 12 h at room temperature and then poured on a suspension of Na_2CO_3 in CH_2Cl_2. The suspension was stirred 1 h and then filtered. The yellow solution was concentrated in vacuo and the crude product purified by flash chromatography (basic Al_2O_3, cyclohexane/EtOAc = 70/30) to afford 71 mg (70%) of the indoloquinolizine **25**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.85 (s, 1H), 7.5 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.3–7.05 (m, 12H), 6.45 (s, 1H), 4.2 (d, J = 12.8 Hz, 1H), 4.05 (s, 1H), 3.75 (d, J = 8.0 Hz, 1H), 3.5 (m, 2H), 3.3 (m, 1H), 2.95 (m, 1H), 2.7 (m, 1H), 2.35 (m, 1H), 2.25 (m, 1H), 2.2–1.95 (m, 7H), 1.8 (m, 1H), 1.3 (m, 1H), 1.1 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.1, 139.8, 136.7, 135.8, 134.8, 128.9, 128.5, 128.3, 128.1, 127.9, 127.4, 126.9, 126.7, 121.6, 119.5, 110.9, 108.8, 108.2, 88.2, 77.3, 76.2, 50.3, 49.1, 37.6, 35.7, 34.6, 30.5, 21.9, 12.1. Anal. Calcd for $C_{34}H_{38}N_4$ (502.71): C, 81.23; H, 7.62; N, 11.15. Found: C, 81.20; H, 7.64; N, 11.12.

Indoloquinolizine 24. To a solution of 50 mg of indoloquinolizine **25** (0.1 mmol) in CH_2Cl_2 (10 mL) at room temperature was added trifluoroacetic anhydride (0.03 mL, 0.2 mmol). The solution was stirred for 4 h and then concentrated in vacuo to afford a very polar product. To this compound was added 20 mL of an aqueous solution of NaOH in MeOH (CH_3OH/NaOH (15%) = 50/50). The solution was stirred for 6 h and then diluted with CH_2Cl_2 (30 mL). The aqueous layer was decanted. The organic layer was washed with H_2O until neutral pH, dried over Na_2CO_3, and then concentrated in vacuo to afford a yellow oil which was purified by column chromatography (SiO_2, AcOEt) to afford 19 mg (80%) of indoloquinolizine **24**: mp 232 °C (MeOH); $[\alpha]^{20}_D = -110°$ (c = 2, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.95 (s, 1H), 8.8 (s, 1H), 7.49 (d, J = 7 Hz, 1H), 7.35 (d, J = 7 Hz, 1H), 7.18 (dd, J = 7, 7 Hz, 1H), 7.12 (dd, J = 7, 7 Hz, 1H), 7.03 (s, 1H), 4.7 (d, J = 12 Hz, 1H), 3.75 (m, 2H), 2.9 (m, 3H), 2.41 (dd, J = 12, 2 Hz, 1H), 1.6 (m, 1H), 1.75 (m, 1H), 1.3 (m, 1H), 1.03 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.0, 155.7, 132.6, 126.8, 122.2, 119.5, 118.0, 115.7, 112.2, 108.1, 51.7, 49.2, 31.2, 30.4, 28.2, 22.0, 12.0; IR (film) 3300, 1600, 1580, 1430 cm^{-1}; UV (λ max, EtOH) 215, 240, 285; MS m/e 280, 251, 149, 121, 119, 85, 83. Anal. Calcd for $C_{18}H_{20}N_2O$ (280.38): C, 77.11; H, 7.19; N, 9.99. Found: C, 77.13; H, 7.22; N, 9.95.

3-(1,3-Dimethyl-4,5-diphenylimidazolidin-2-yl)-4-methyl-(or ethyl)-1-[(3,4-dimethoxyphenyl)acetyl]-1,4-dihydropyridine (27a and 27b). For the experimental procedure see the general procedure for the addition of organometallic reagents on pyridines **3–6**. RCu was prepared with 1RLi + 2 CuBr, Me_2S + 4 LiBr.

27a (yield = 89%, de = 95%): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58 (s, 0.5H), 7.4–7.1 (m, 10.5H), 6.8 (m, 3.5H), 6.65 (d, J = 5 Hz, 0.5H), 5.2 (m, 0.5H), 5.05 (m, 0.5H), 4.2 (s, 1H), 3.9–3.4 (m, 10H), 3.25 (m, 0.5H), 3.07 (m, 0.5H), 2.17 (s, 1.5H), 2.12 (s, 1.5H), 2.08 (s, 1.5H), 2.05 (s, 1.5H), 1.22 (d, J = 5 Hz, 1.5H), 1.2 (d, J

= 5 Hz, 1.5H). Anal. Calcd for $C_{33}H_{37}N_3O_3$ (523.67): C, 75.69; H, 7.12; N, 8.02. Found: C, 75.84; H, 7.23; N, 7.81.

27b (yield = 90%, de = 92%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.68 (s, 0.5H), 7.4–7.1 (m, 10.5H), 6.8 (m, 4H), 5.17 (m, 0.5H), 5.07 (m, 0.5H), 4.18 (br s, 1H), 4.0–3.4 (m, 10H), 3.21 (m, 0.5H), 3.1 (m, 1H), 2.17 (s, 1.5H), 2.1 (s, 1.5H), 2.12 (s, 1.5H), 2.06 (s, 1.5H), 2.03 (s, 1.5H), 1.6 (m, 2H), 0.9 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 166.9, 149.1, 149.0, 140 (br signal), 128 (br signal), 126.8, 124.5, 123.3, 122.5, 121 (br signal), 120.7, 112 (br signal), 111.9, 86.6, 84.9, 77 (br signal), 55.7, 49.2, 40.8, 40.2, 37.4, 36.1, 35 (br signal), 27.6, 27.2, 9.4, 9.1. Anal. Calcd for $C_{34}H_{39}N_3O_3$ (537.70): C, 75.95; H, 7.31; H, 7.81. Found: C, 76.02; H, 7.41; N, 7.70.

4-Ethyl-3-formyl-1-[(3,4-dimethoxyphenyl)acetyl]-1,4-dihydropyridine (28). For the experimental procedure see the general procedure for hydrolysis of dihydropyridines **1a–n** and **16a–n** (yield = 83%): $[\alpha]^{25}_D$ = −129° (*c* = 2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.4 (s, 1H), 7.9 (br s, 1H), 6.7 (m, 3H), 5.6 (br s, 1H), 3.8 (m, 8H), 3.3 (m, 1H), 1.6 (m, 2H), 0.7 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 191, 167.5, 149.5, 148.6, 140.9, 124.9, 121.8, 121.0, 114.1, 111.8, 111.6, 55.6, 40.4, 31.9, 30.9, 27.4, 9.2; IR (film) 3300, 2880, 2850, 1700, 1670, 1610 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_4$ (315.37): C, 68.55; H, 6.71; N, 4.44. Found: C, 68.55; H, 6.75; N, 4.42.

Benzoquinolizines (30a and 30b). The dihydropyridines **27a** or **27b** were reduced by $LiAlH_4$ by the same procedure used for the preparation of **23**.

29a: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.2 (m, 10H), 6.8 (m, 3H), 6.1 (s, 1H), 5.8 (d, *J* = 7.7 Hz, 1H), 4.46 (dd, *J* = 7.7, 4.4 Hz, 1H), 4.1 (s, 1H), 3.9 (s, 3H), 3.8 (s, 3H), 3.6 (d, *J* = 8 Hz, 1H), 3.42 (d, *J* = 8 Hz, 1H), 3.36 (m, 2H), 3.2 (m, 1H), 2.8 (m, 2H), 2.15 (s, 3H), 2.1 (s, 3H), 1.1 (d, *J* = 7 Hz, 3H).

29b: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.2 (m, 10H), 6.8 (m, 3H), 6.2 (s, 1H), 5.8 (dd, *J* = 6, 1.4 Hz, 1H), 4.5 (dd, *J* = 7.5, 4.7 Hz, 1H), 4.1 (s, 1H), 3.9 (s, 3H), 3.8 (s, 3H), 3.6 (d, *J* = 7.9 Hz, 1H), 3.4 (d, *J* = 7.9 Hz, 1H), 3.3 (t, *J* = 7 Hz, 2H), 3.1 (m, 1H), 2.8 (t, *J* = 7.9 Hz, 1H), 2.2 (s, 3H), 2.1 (s, 3H), 1.45 (m, 2H), 0.9 (t, *J* = 7 Hz, 3H).

The crude product was then diluted, at 0 °C, with trifluoroacetic acid (10 mL for 1 mmol). The deep red solution was stirred, at 0 °C, for 12 h and then concentrated in vacuo. The crude product was diluted with dichloromethane (20 mL). Trifluoroacetic anhydride (0.56 mL, 4 mmol) was added and the reaction mixture stirred at room temperature for 4 h, concentrated in vacuo, and then diluted with 40 mL of an aqueous solution of NaOH in MeOH (CH_3OH/NaOH (15%) = 50/50). The reaction mixture was stirred at room temperature for 6 h and then diluted with CH_2Cl_2 (30 mL). The aqueous layer was decanted. The organic layer was washed with H_2O until neutral pH, dried over Na_2CO_3, and then concentrated in vacuo to afford to a yellow oil which was purified by column chromatography (SiO_2, AcOEt) to afford **30a** (yield 41%, de = 65%) or **30b** (yield = 48%, de = 81%).

30a: ^{1}H NMR (C_6D_6, 400 MHz) δ 9.0 (s, 1H), 6.14 (s, 1H), 6.07 (s, 1H), 6.02 (s, 1H), 3.85 and *3.61* (2d, *J* = 11.5 Hz, 1H), 3.13 (s, 3H), 3.11 (s, 3H), 2.93 (m, 1H), 2.57 (m, 1H), 2.41 (m, 1H), 2.21 (m, 1H), 1.78 (d, *J* = 15.4 Hz, 1H), 1.4 and *1.31* (2d, *J* = 13 Hz, 1H), 1.15 (m, 1H), 1.02 (d, *J* = 7 Hz, 3H). Anal. Calcd for $C_{17}H_{21}NO_3$ (287.36): C, 71.06; H, 7.37; N, 4.87. Found: C, 71.15; H, 7.46; N, 4.78.

30b: $[\alpha]^{20}_D$ = −112° (*c* = 2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.88 (s, 1H), 6.87 (s, 1H), 6.62 (s, 1H), 6.61 (s, 1H), 4.44 and *4.4* (2d, *J* = 11.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.61 (m, 2H), 3.0 (m, 1H), 2.68 (m, 1H), 2.64 (m, 1H), 2.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 186.8. 154.7, 148.1, 147.9, 127.7, 125.9, 115.7, 111.6, 108.9, 56.1, 55.9, 51.9, 50.9, 33.6, 30.7, 29.6, 28.1, 11.7; FAB MS *m/e* 302 (25%). Anal. Calcd for $C_{18}H_{23}NO_3$ (301.38): C, 71.73; H, 7.69; N, 4.65. Found: C, 71.75; H, 7.75; N, 4.56.

3-Formyl-1,4-dihydropyridines (31 and 32). Same procedure as for hydrolysis of indoloquinolizine **25** starting from **23** or **29a**.

31 (yield = 75%): $[\alpha]^{20}_D$ = −239° (*c* = 4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.84 (s, 1H), 8.49 (s, 1H), 7.56 (d, *J* = 8 Hz, 1H), 7.38 (m, 1H), 7.25 (m, 1H), 7.23 (m, 1H), 6.98 (s, 1H), 6.38 (s, 1H), 5.86 (d, *J* = 7.7 Hz, 1H), 4.9 (dd, *J* = 7.7, 5 Hz), 3.52 (t, *J* = 7 Hz, 2H), 3.45 (m, 1H), 3.03 (t, *J* = 7 Hz, 2H), 2.5 (m, 1H), 2.39 (m, 1H), 0.8 (t, *J* = 7 Hz, 3H). Anal. Calcd for $C_{18}H_{20}N_2O$ (280.37) C, 77.11; H, 7.19; N, 9.99. Found: C, 77.23; H, 7.31; N, 9.84.

32 (yield = 68%): $[\alpha]^{20}_D$ = −210° (*c* = 3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.80 (s, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.7 (m, 2H), 6.38 (s, 1H), 5.6 (d, *J* = 6 Hz, 1H), 4.8 (dd, *J* = 6, 5 Hz, 1H), 3.84 (s, 6H), 3.42 (m, 3H), 2.81 (t, *J* = 7 Hz, 2H), 1.1 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.7, 149.4, 148.7, 147.7, 129.7, 126.2, 120.8, 116.4, 112.6, 111.9, 111.2, 56, 55.6, 35.6, 25.1, 23.8; IR (film) 2950, 1652, 1640, 1570, 1460 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_3$ (287.36): C, 71.06; H, 7.37; N, 4.87. Found: C, 71.17; H, 7.42; N, 4.79.

Supplementary Material Available: ^{1}H NMR spectra of most compounds (51 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.