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Regio- and stereoselective synthesis of 1,4-dihydropyridines by way of an intramolecular interaction of a thiocarbonyl or carbonyl with a pyridinium nucleus

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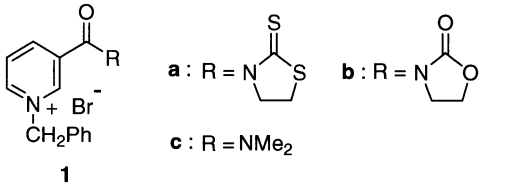
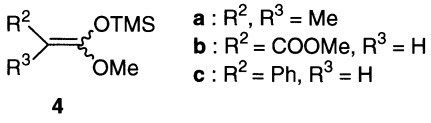
Abstract—Chiral 1,4-dihydropyridines were prepared by the regio- and stereoselective addition of ketene silyl acetals and organometallic reagents to pyridinium salts. In the addition reaction, an intramolecular interaction between the thiocarbonyl or carbonyl with the pyridinium nucleus plays an important role in bringing about the selectivities. The absolute configuration of the newly produced stereogenic center of the 1,4-dihydropyridines was determined by X-ray analysis and CD Cotton effects after conversion into the appropriate derivatives. The working model for the stereoselectivity was proposed based on the ab initio calculations at the RHF/3-21G* level.

1. Introduction

Chiral 1,4-dihydropyridines[1] have been employed as the synthetic intermediates for a wide variety of compounds such as natural products,[2,3] calcium channel blockers,[4] and NADH models.[5] Moreover, they have potential utility for obtaining various nitrogen containing chiral 6-membered heterocycles.[6,7] Among various methods for the preparation of chiral 1,4-dihydropyridines, faceselective nucleophilic addition to the pyridinium nucleus is an attractive method because of its synthetic convenience. Several types of pyridinium salts having a chiral oxazoline,[8] an aminal,[9] or an iron acyl[10] moiety at the 3-position have been utilized for the synthesis of them. In addition, 2,3-fused bicyclic pyridinium salts possessing a carbonyl group in the ring[11] and a bridged pyridinium[12] are also proved to be good precursors for chiral 1,4-dihydropyridines.

Recently, Comins and his coworkers have attained face-selective 1,2-addition by way of an intramolecular interaction between a pyridinium and a phenyl group to hinder one of the pyridinium faces.[13] We report here a new entry for the stereoselective synthesis of 1,4-dihydropyridines by regio- and stereoselective nucleophilic addition to the pyridinium salts having a 1,3-thiazolidine-2-thione[14] or a 1,3-oxazolidine-2-one moiety, where an intramolecular interaction of the thiocarbonyl or carbonyl group of the chiral auxiliary with the pyridinium nucleus[15] plays a critical role in the regio- and stereoselectivities.





2. Results and discussion

As substrates we employed *N*-benzylnicotinium salts **1a**–**1c**, and nicotinic amides **2a**–**2d** and **3a**–**3c**. First, we studied the regioselectivity in the addition of ketene silyl acetal **4a** to *N*-benzylnicotinic amides **1a**–**1c** because an intramolecular interaction between the thiocarbonyl and the pyridinium ring in **1a** was predicted by ^{1}H NMR studies and X-ray analysis.[15] The reaction of the pyridinium salts **1a** and **1b** with 1.5 equiv. of ketene silyl acetal **4a** was

Keywords: pyridinium salts; stereoselection; addition reaction; thiocarbonyl compounds; oxazolidinones; neighbouring group effects.

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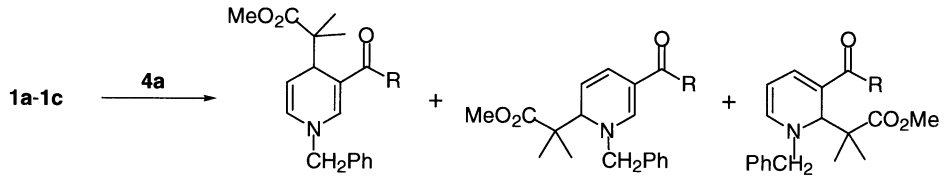
Table 1. Reaction of pyridinium salts **1a**–**1c** with a ketene silyl acetal



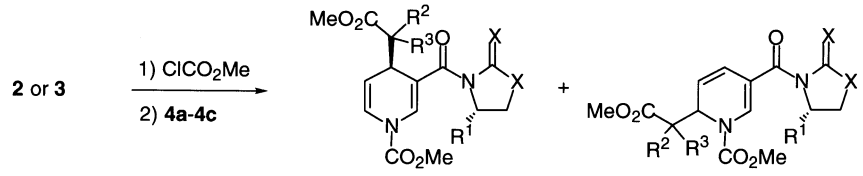
5 **6** **7**

Salts	Solvents	Time (h)	Yield (%)	Ratio (**5**:**6**:**7**)
1a	CD_3CN	4	77	96:4:0
1b	CD_3CN	3	93	94:6:0
1c	CD_3CN	4	73	35:56:9
1a	DMSO-d_6	2	79	51:49:0
1b	DMSO-d_6	2.5	97	57:43:0
1c	DMSO-d_6	2.5	83	38:54:8

conducted at 0°C for 2–4 h in CD_3CN or DMSO-d_6. The results are summarized in Table 1. In CD_3CN, the addition to **1a** and **1b** gave 1,4-adducts **5** as a major product with a small amount of 1,6-adduct **6**. The regioselectivity is much higher than that reported for similar reactions with ketene silyl acetals.[16] In contrast, the addition to standard **1c** provided 1,6-adduct **6** as a major product accompanied with 1,4-adduct **5** and a small amount of 1,2-adduct **7**. The isomer ratio was readily determined by ^{1}H NMR analysis based on the chemical shifts of the dihydropyridine moiety; 4H, 5H and 6H of **5b** in CD_3CN appeared at δ 4.01 (d, J=5.5 Hz), 4.77 (dd, J=5.5, 7.6 Hz), and 6.03 (dd, J=1.2, 7.6 Hz), respectively, whereas those of **6b** appeared at δ 6.63 (d, J=9.6 Hz), 4.96 (dd, J=5.6, 9.6 Hz) and 4.59 (d, J=5.6 Hz), respectively. It is remarkable that the selectivity was significantly dependent on the solvent employed; when the reaction was conducted in DMSO-d_6, the selectivities for **1a** and **1b** significantly decreased, whereas that for **1c** scarcely changed. Since the existence of an intramolecular interaction between the thiocarbonyl and the pyridinium ring of **1a** has been clarified by ^{1}H NMR studies and X-ray analyses,[15] this significant substituent dependence in the amido moiety on the regioselectivity would be attributable to the intramolecular C═S···Py$^+$ interaction. The remarkable solvent effect can be explained by the difference in the coordinating property of the solvents employed; since DMSO has a stronger coordinating property than CD_3CN, it may effectively disturb the intramolecular interactions by solvation of the pyridinium ring.

Next, we investigated the stereoselectivity in the addition of various ketene silyl acetals to the pyridinium salts possessing chiral thiazolidine-2-thiones or oxazolidine-2-ones. Chiral nicotinic amides **2b**–**2d** were readily prepared from (*S*)-4-phenyl-, (*S*)-4-benzyl[17]-, and (*S*)-4-*tert*-butyl[18]-1,3-thiazolidine-2-thiones with nicotinoyl chloride in the presence of Et_3N. On the other hand, **3b** and **3c** were successfully prepared by the reaction of (*S*)-4-phenyl- and (*S*)-4-benzyl-1,3-oxazolidine-2-ones with nicotinic pivalic anhydride, respectively. Since most faceselective nucleophilic 1,4-additions to pyridinium salts have been performed under chelation controlled conditions,[8–11] ketene silyl acetals have scarcely been employed for such reactions. The addition of ketene silyl acetal **4a** to the intermediary pyridinium salts formed by the reaction of **2b**–**2d** with methyl chloroformate gave 1,4-adduct **8a**–**8c** as major

Table 2. Reaction of pyridinium salts of **2** and **3** with ketene silyl acetals **4a**–**4c**

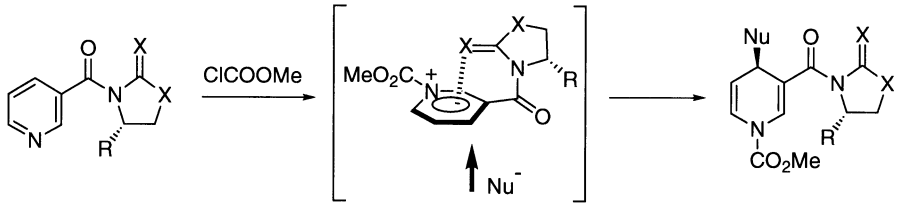


8 : X = S
10 : X = O

9 : X = S
11 : X = O

Entry	Amide	Nucleophile	Solvents	Time (h)	Products	Yield (%)[a]	(**8**:**9**) or (**10**:**11**)	dr of **8** or **10**
1	**2b**	**4a**	CH_3CN	1.5	**8a**, **9a**	89	67:33	86:14
2	**2b**	**4a**	Toluene	46	**8a**, **9a**	44	47:53	45:55
3	**2c**	**4a**	CH_3CN	1.0	**8b**, **9b**	91	78:22	92:8
4	**2d**	**4a**	CH_3CN	1.0	**8c**, **9c**	91	57:43	56:44
5	**3b**	**4a**	CH_3CN	2.0	**10a**, **11a**	91	86:14	87:13
6	**3c**	**4a**	CH_3CN	1.5	**10b**, **11b**	91	84:16	73:27
7	**2c**	**4b**	CH_2Cl_2	2.5	**8d**, **9d**	99	47:53	84:16
8	**2c**	**4c**	CH_3CN	3.5	**8e**, **9e**	67(98)[b]	96:4	97:3[c]

[a] Isolated yield.
[b] Conversion yield.
[c] No *syn*–*anti* isomers was observed.



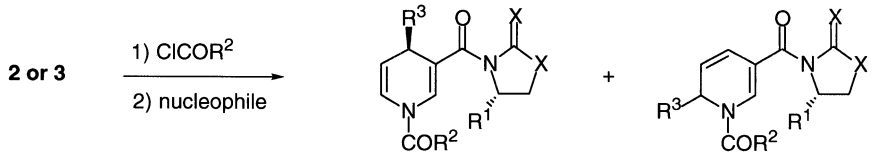
Scheme 1.

products and minor 1,6-adducts **9a**–**9c** (Table 2, entries 1–4). The relatively lower regioselectivity compared to the case of the *N*-benzylpyridinium salts described above is unclear, but the difference in the steric and electronic effects of the N-substituents may affect the regioselectivity. The diastereomer ratios for the major products were determined based on ^{1}H NMR chemical shifts of 2H, 5H and 6H of dihydropyridine moiety. The absolute configuration at C4 was determined to be *R* based on CD Cotton effects as described later. The stereoselectivity was dependent on the chiral auxiliary; among **2b**–**2d**, amide **2c** was the most effective (entry 3), whereas amide **2d** having the bulkiest substituent was the least effective (entry 4). The reactions with amides **3b** and **3c** also gave similar results to the case of amide **2** (entries 5 and 6). The other ketene silyl acetals **4b** and **4c** also acted as faceselective nucleophiles (entries 7 and 8). The addition of **4b** also proceeded in good stereoselectivity albeit with insufficient regioselectivity. Excellent regio- and stereoselectivities were obtained when using **4c** as a nucleophile. The diastereomer ratio with respect to the C4 of 1,4-adducts **8e** is 97:3 and no *syn*–*anti* isomers based on the another chiral center next to C4 was observed. Interestingly, use of toluene as a solvent resulted in significant slower reaction rate, and both the regio- and stereoselectivities were reversed (entry 2). This may be due to intermolecular cation–π interaction;[19] toluene would face the pyridinium plane and disturb the attack of a nucleophile.

The fact that the reaction with ketene silyl acetals yielded high stereoselectivity indicates that the reaction proceeded under non-chelation control. Thus, these stereoselectivities can be attributable to intramolecular C═S···Py$^+$ or C═O···Py$^+$ interaction. If the interaction occurs faceselectively, the nucleophile will attack the complex from the opposite side of the thiocarbonyl or carbonyl group, which would result in good stereoselectivity (Scheme 1). The faceselective complexation is indeed predicted by ab initio calculations as described later. The importance of the neighboring thiocarbonyl group in the stereoselectivity in various reactions containing carbocation intermediates is known.[20–22] However, since in the present system, no bonding between the sulfur atom of the thiocarbonyl and the pyridinium carbon was detected by ^{1}H and ^{13}C NMR spectroscopies, the interaction between the thiocarbonyl and the pyridinium may be a through-space electrostatic interaction such as a cation–π interaction.[19]

Organometallic reagents also worked as stereoselective nucleophiles. After the amides **2** and **3** were converted in situ into the corresponding pyridinium salts with acid chlorides or chloroformates, the addition of nucleophiles to the pyridinium salts was carried out. The results are shown in Table 3. The reaction of the pyridinium salts of **2b** with MeCu[23] gave a 93:7 mixture of **12a** and **13a**. The diastereomer ratio of **12a** was 67:33 (entry 1). This preference in the 1,4-addition of organocopper reagents is in agreement with reported observations.[24] Addition of PhCu to the pyridinium salts proceeded with higher stereoselectivity than that of MeCu (entry 2). Use of benzoyl chloride instead of methyl chloroformate to make an intermediary pyridinium salt improved both regio- and stereoselectivities in the addition reaction (entries 3–5), indicating

Table 3. Reaction of the pyridinium salts of **2** and **3** with organometallic reagents



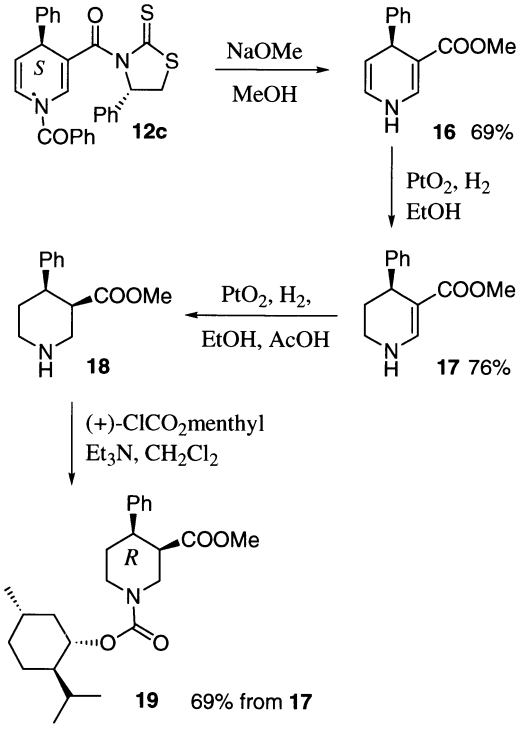
Entry	Amide	R^2	Nucleophile[a]	Yield (%)[b]	Products	(**12**:**13**)[c] or (**14**:**15**)	dr[c] of **12** or **14**
1	**2b**	OMe	MeCu	68(61)	**12a**, **13a**	93:7	67:33
2	**2b**	OMe	PhCu	70(46)	**12b**, **13b**	95:5	84:16
3	**2b**	Ph	PhCu	76(59)	**12c**, **13c**	100:0	88:12
4	**2c**	Ph	PhCu	59(48)	**12d**, **13d**	100:0	88:12
5	**2d**	Ph	PhCu	85(68)	**12e**, **13e**	100:0	91:9
6	**2b**	OMe	$BnSnMe_3$	72	**12f**, **13f**	100:0	80:20
7	**3b**	OMe	PhCu	70(47)	**14a**, **15a**	72:28	60:40
8	**3b**	OMe	$BnSnMe_3$	51	**14b**, **15b**	100:0	64:36

[a] 1.1 equiv. of reagent was used.
[b] Conversion yield. Isolated yield is shown in parentheses.
[c] Determined by ^{1}H NMR spectroscopy.

that the bulky substituent around the N-atom enhances the 1,4-selectivity by hindering the addition to C6. The difference in the substituents at the chiral center of the thiazolidine-2-thione moiety did not have a significant effect on the stereoselectivity (entries 3–5). This is in contrast to the addition of ketene silyl acetals as described above, where the substituents of the chiral auxiliary affect the stereoselectivity. This nucleophile-dependent stereoselectivity is unclear, but the difference in the coordination effect to substrates between ketene silyl acetals and organocopper reagents may be one reason. Trimethylbenzyltin also worked as a 1,4-selective nucleophile similar to the literature[25] to give **12f** in good regio- and stereoselectivities (entry 6). Amide **3b** having an oxazolidinone moiety as a chiral auxiliary also reacts with organocopper and organotin reagents to give the corresponding **14a** and **14b** similar to the reaction of amide **2b** (entries 7 and 8). However, the stereoselectivities are much lower than those obtained in the corresponding reactions of **2b** (entry 2 vs 7 and entry 6 vs 8). This would be ascribed to the difference in the coordinating ability of the carbonyl of **3b** and the thiocarbonyl of **2b** to organometallic reagents; the coordination will disturb the intramolecular C═O···Py^+ interaction.

The absolute configuration of the newly-produced stereogenic center for the major product of **12c** was determined by X-ray analysis after conversion of **12c** (R^1=Ph, R^2=Ph) into **19** (Scheme 2). The chiral auxiliary of **12c** (an 88:12 diastereomeric mixture) was removed by treatment with NaOMe to produce a methyl ester **16**. Catalytic hydrogenation of **16** with PtO_2 in EtOH resulted in partially reduced tetrahydropiperidine **17**. Further reduction was carried out in the presence of acetic acid to give a 9:1 *cis* and *trans* mixture of **18**, the ratio of which was determined by ^{1}H NMR spectroscopy based on the methyl protons. After conversion of **18** into crystalline menthyloxycarbamates **19**, several recrystallizations provided a single crystal for X-ray analysis.[26] The X-ray structure of **19** was given in Fig. 1, which unequivocally showed that the 4-position possesses *R* configuration, and the phenyl and the methoxycarbonyl groups have *cis* orientation; therefore, the absolute configuration at the 4-position of dihydropyridine **12c** was determined to be *S*. Comparison of the signs of specific rotation of **16** derived from **12d**, **12e** and **14a** with that of **16** obtained from **12c** described above clearly showed that **12d**, **12e** and **14a** possess the same configuration with **12c**.

Determination of the absolute configuration at C4 of **8b** and **12f**, which are the adducts of a ketene silyl acetal and trimethylbenzyltin, respectively, was performed based on their CD Cotton effects. The chiral center at C4 will govern the directionality of the rotation about the C3–C(O) bond, which is important in the sign of the CD Cotton effect. The chiral auxiliaries of **8b**, **12c**, and **12f** were readily removed by the reaction with dimethylamine[27] to afford the corresponding dimethylamides **20a**–**20c** in good yields (Scheme 3). The CD spectrum of **20b** derived from **12c** having *S* configuration showed a negative Cotton effect based on π–π^* absorption at 244 nm as shown in Fig. 2. A similar negative Cotton effect was observed for **20a** and **20c** at 245 and 242 nm, suggesting that their absolute configuration is *R*.[28]



Scheme 2.

To gain insight into the working model for the stereoselectivity, geometrical optimization of the intermediary pyridinium salt generated from **2b** with methyl chloroformate was carried out by semiempirical AM1 methods for each structure obtained from MMFF calculations in conjunction with Monte Carlo searching. Four typical conformers **A**–**D** obtained were further optimized by ab initio calculations at RHF/3-21G* level. Their structures and the relative energies based on the most stable conformer **A** are shown in Fig. 3. Each conformer has a helical structure about the C4–C3–CO–N–C═S moiety. The thiocarbonyl groups of **A** and **B** are close to C2 of the pyridinium nucleus, whereas those of **C** and **D** are close to the corresponding C4. The geometries of **C** and **D** are very similar to the X-ray structure of **1a**.[15] Both interatomic distances between the S atom of the thiocarbonyl and C4

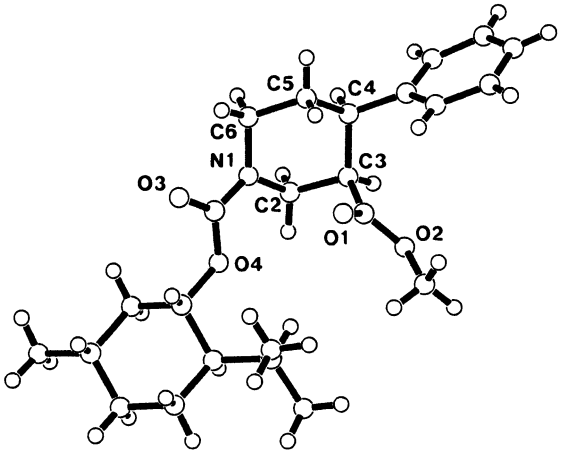
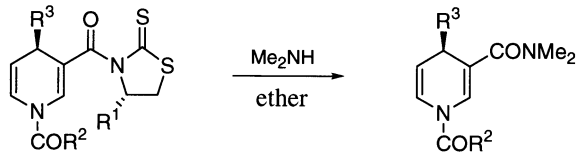


Figure 1. X-Ray structure of **19**.



8b : R^1 = Bn, R^2 = OMe, R^3 = $C(CH_3)_2CO_2Me$ **20a**
12c : R^1 = Ph, R^2 = Ph, R^3 = Ph **20b**
12f : R^1 = Bn, R^2 = OMe, R^3 = Bn **20c**

Scheme 3.

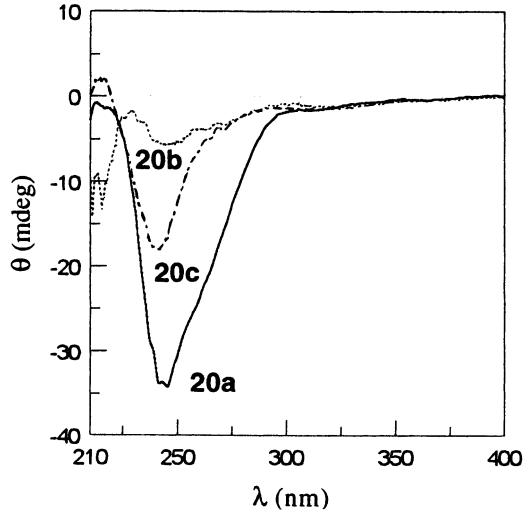


Figure 2. The CD spectra of dihydropyridines **20a** (—), **20b**(- - -), and **20c** (-·-·-) in EtOH.

(3.153 and 3.195 Å, respectively), are significantly shorter than the sum of van der Waals radii of the carbon and sulfur atoms,[29] suggesting the intramolecular interaction between the thiocarbonyl and the pyridinium nucleus.

Conformers **A** and **B** have less preferable geometries for nucleophilic attack to C4 because both the pyridinium faces around **C4** are blocked by a carbonyl or a thiocarbonyl group. Similarly, the carbonyl, thiocarbonyl and phenyl groups of conformer **D** also hinder both faces of the pyridinium ring. As a result, conformer **C**, one of the pyridinium faces of which is not hindered, would be a key intermediate for the addition reaction. Therefore, the following working model for the stereoselectivity can be proposed; the intramolecular C═S···Py^+ or C═O···Py^+ interaction restricts the conformation of the intermediary quarternary pyridinium salts, which enables nucleophiles to attack conformer **C** having the most unhindered pyridinium face from the opposite side of the thiocarbonyl group as shown in Scheme 1. The configuration predicted by this working model is consistent with those determined by X-ray analysis and CD spectra.

3. Conclusion

Addition of ketene silyl acetals and organocopper and organotin reagents to quarternary pyridinium salts possessing 1,3-thiazolidine-2-thione or 1,3-oxazolidine-2-one proceeded regio- and stereoselectively to give chiral 1,4-dihydropyridines. In the nucleophilic addition reactions, the intramolecular C═S···Py^+ or C═O···Py^+ interaction plays key roles to bring about the regio- and stereoselectivities. Thus, the intramolecular interaction restricts the molecular motion and hinders one of the pyridinium faces, in addition, the interaction would change the electronic properties of the pyridinium nucleus, which will enable nucleophiles to attack at C4 faceselectively. Since the reaction proceeds under non-chelation controlling conditions, the present method is complimentary to the published ones for the synthesis of chiral 1,4-dihydropyridines.

4. Experimental

4.1. General

Melting points are uncollected. Column chromatography

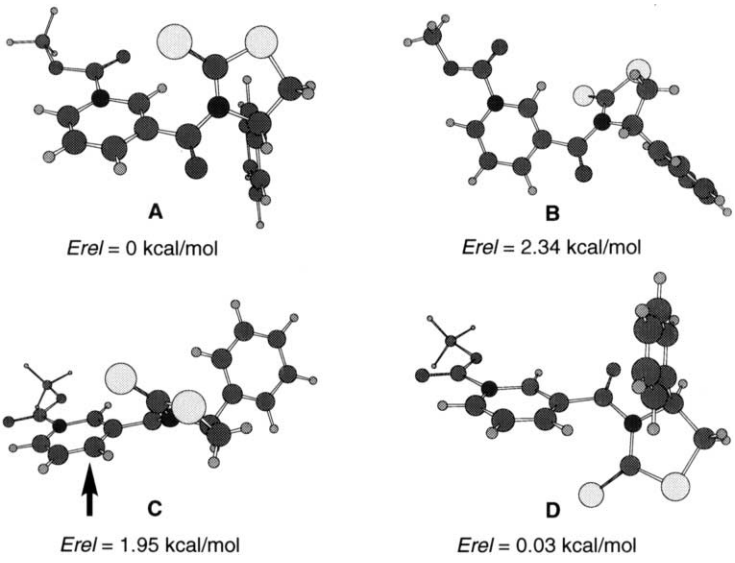


Figure 3. RHF/3-21G* optimized geometries for the pyridinium salt generated from **2b** with methyl chloroformate.

was carried out using a Merck Silica gel 60. TLC was carried out on a Merck Silica gel 60 PF_{254}. IR spectra were obtained as KBr pellets. ^1H NMR spectra were recorded at 270 or 400 MHz as dilute solutions in $CDCl_3$, CD_3CN or DMSO-d_6 and the chemical shifts were reported relative to internal TMS. ^{13}C NMR spectra were recorded at 67.8 or 100.4 MHz as dilute solutions in $CDCl_3$ and the chemical shifts were reported relative to internal TMS. High and low-resolution mass spectra were recorded at an ionizing voltage of 70 eV by electron impact. CD spectra were recorded as dilute solution in EtOH.

4.1.1. Preparation of (*S*)-4-phenyl-1,3-thiazolidine-2-thione. Concentrated sulfuric acid (3.0 ml, 54 mmol) was added dropwise to a round bottom flask containing (*S*)-2-phenylglicinol (2.1 g, 15.3 mmol) at 0°C, and the mixture was vigorously stirred for 2 h. After potassium *O*-ethyl dithiocarbonate (4.2 g, 26 mmol) was added, the solution was adjusted to pH 9 with 2N NaOH, and the solution was heated at 50°C for 3 h. Then, potassium *O*-ethyl dithiocarbonate (2.1 g, 13 mmol) was again added and the reaction mixture was stirred for further 6 h. After cooling to room temperature, the solution was acidified with 2N HCl and extracted with three 50 ml portions of $CHCl_3$. The combined extracts were washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude compound, which was subjected to column chromatography on silica gel to give two crystalline compounds. The less polar fraction was (*S*)-4-phenyl-1,3-thiazolidine-2-thione (1.27 g, 50%): $[\alpha]_D^{22}=+182°$ (*c* 1.0, $CHCl_3$); mp 194.5–195.0°C; IR (KBr) 3121, 1493, 1259, 1050 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.52 (dd, *J*=11.2, 8.3 Hz, 1H), 3.86 (dd, *J*=11.2, 8.1 Hz, 1H), 5.31 (dd, *J*=8.3, 8.1 Hz, 1H), 7.26–7.45 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 41.6, 67.4, 126.2, 129.1, 129.2, 137.9, 201.4; MS *m/z* 195 (M^+, 100%); HRMS calcd for $C_9H_9NS_2$ 195.0177, found 195.0182. The polar fraction was (*S*)-4-phenyl-1,3-oxazolidine-2-thione (0.4 g, 17%): ^1H NMR (270 MHz) δ 4.50 (dd, *J*=8.6, 6.3 Hz, 1H), 5.01 (dd, *J*=9.0, 8.6 Hz, 1H), 5.31 (dd, *J*=9.0, 6.3 Hz, 1H), 7.31–7.45 (m, 5H).

4.2. General procedure for the synthesis of nicotinic amides from 1,3-thiazolidine-2-thiones with nicotinoyl chloride

To a solution of nicotinoyl chloride hydrochloride (3 equiv.) in dry CH_2Cl_2 (4 ml for 1 mmol) was added Et_3N (9 equiv.) under nitrogen atmosphere. Then, 1,3-thiazolidine-2-thione (1 equiv.) in CH_2Cl_2 (4 ml for 1 mmol) was added dropwise at 0°C, and the reaction mixture was stirred for 4.5 h at room temperature. Usual work up gave a crude amide, which was chromatographed on silica gel (AcOEt/$CHCl_3$=1:1–2:1) to afford a pure nicotinic amide.

4.2.1. (2-Thioxo-1,3-thiazolidin-3-yl)-pyridin-3-yl-methanone (2a). 96% yield; mp 103.0–104.0°C; IR (KBr) 2362, 1677, 1588 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (dd, *J*=2.2, 0.8 Hz, 1H), 8.71 (ddd, *J*=5.8, 4.9, 1.6 Hz, 1H), 7.95 (ddd, *J*=8.0, 2.2, 1.6 Hz, 1H), 7.35 (ddd, *J*=8.0, 4.9, 0.8 Hz, 1H), 4.58 (t, *J*=7.3 Hz, 2H), 3.50 (t, *J*=7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 56.2, 130.0, 136.6, 149.9, 152.6, 169.4, 202.3; MS *m/z* 224 (M^+, 93), 106 (100), 78 (70); HRMS calcd for $C_9H_8ON_2S_2$ 224.0078, found 224.0084.

4.2.2. (4*S*)-(4-Phenyl-2-thioxo-1,3-thiazolidin-3-yl)-pyridin-3-yl-methanone (2b). 85% yield; mp 133.5–134.5°C; $[\alpha]_D^{22}=+206°$ (*c* 1.1, $CHCl_3$); IR (KBr) 3034, 1666, 1586, 1309 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.54 (1H, dd, *J*=11.4, 7.3 Hz), 3.89 (1H, dd, *J*=11.4, 7.6 Hz), 5.98 (1H, dd, *J*=7.6, 7.3 Hz), 7.32–7.48 (6H, m), 7.97 (1H, ddd, *J*=8.1, 2.2, 1.6 Hz), 8.71 (1H, dd, *J*=4.9, 1.6 Hz), 8.94 (1H, dd, *J*=2.2, 0.7 Hz); ^{13}C NMR (100 MHz) δ 38.2, 71.4, 123.4, 126.2, 129.1, 129.3, 130.2, 136.8, 137.8, 150.3, 152.9, 169.6, 202.5; MS *m/z* 300 (M^+, 66%), 106 (100), 78 (60); HRMS found 300.0409, calcd for $C_{15}H_{12}N_2OS_2$ 300.0391.

4.2.3. (4*S*)-(4-Benzyl-2-thioxo-1,3-thiazolidin-3-yl)-pyridin-3-yl-methanone (2c). 92% yield; mp 94.0–95.0°C; $[\alpha]_D^{22}=-155°$ (*c* 1.1, $CHCl_3$); IR (KBr) 3026, 1666, 1587, 1322 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.13–3.19 (2H, m), 3.53–3.60 (2H, m), 5.18–5.22 (1H, m), 7.28–7.41 (6H, m), 7.92 (1H, ddd, *J*=7.8, 2.2, 1.7 Hz), 8.72 (1H, dd, *J*=4.9, 1.7 Hz), 8.83 (1H, dd, *J*=2.2, 0.7 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 33.9, 36.9, 69.2, 123.0, 127.3, 129.0, 129.4, 130.2, 136.0, 136.3, 149.6, 152.3, 168.8, 201.4; MS *m/z* 314 (M^+, 74%), 106 (100), 78 (65); HRMS calcd for $C_{16}H_{14}N_2OS_2$ 314.0547, found 314.0527.

4.2.4. (4*S*)-(4-*tert*-Butyl-2-thioxo-1,3-thiazolidin-3-yl)-pyridin-3-yl-methanone (2d). 94% yield; mp 141.5–142.5°C; $[\alpha]_D^{22}=+497°$ (*c* 1.0, $CHCl_3$); IR (KBr) 2971, 1703, 1585 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.12 (9H, s), 3.31 (1H, dd, *J*=11.7, 2.1 Hz), 3.77 (1H, dd, *J*=11.7, 9.3 Hz), 5.26 (1H, dd, *J*=9.3, 2.1 Hz), 7.36 (1H, dd, *J*=7.9, 4.9 Hz), 7.98 (1H, dd, *J*=7.9, 2.2, 1.6 Hz), 8.71 (1H, dd, *J*=4.9, 1.6 Hz), 8.93 (1H, dd, *J*=2.2, 0.7 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 26.9, 31.4, 38.2, 74.2, 122.9, 130.2, 136.8, 150.3, 152.4, 169.4, 203.4; MS *m/z* 280 (M^+, 66%), 106 (100), 78 (71); HRMS calcd for $C_{13}H_{16}N_2OS_2$ 280.0704, found 280.0703.

4.3. General procedure for the synthesis of nicotinic amides from 1,3-oxazolidine-2-ones with nicotinic acid

To a solution of nicotinic acid (1.0 g, 8.1 mmol) in dry THF (20 ml) and triethylamine (1.7 ml) added pivaloyl chloride (1.0 ml, 8.1 mmol) at 0°C. After the suspension was stirred for 1 h, a mixture of 1,3-oxazolidine-2-one (1.2 mmol), and DMAP (0.5 mmol) in dry THF (12 ml) was added to the suspension. Then, the mixture was stirred for 21 h. Successive operations of evaporation of the solvent, neutralization with NH_4Cl, and extraction with $CHCl_3$ gave a crude product, which was purified by column chromatography to give a pure amide.

4.3.1. 3-(Pyridine-3-carbonyl)-1,3-oxazolidin-2-one (3a). 45% yield; mp 122.5–123.2°C; IR (KBr) 1772, 1682, 1586, 1483, 1380, 1333, 1213 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.75 (dd, *J*=5.0, 1.5 Hz, 1H), 7.95 (dt, *J*=7.9, 1.8 Hz, 1H), 7.38 (ddd, *J*=7.9, 5.0, 0.8 Hz, 1H), 4.52 (t, *J*=7.9 Hz, 2H), 4.21 (t, *J*=7.6 Hz, 2H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 167.70, 153.15, 152.68, 149.75, 136.51, 128.82, 122.67, 62.43, 43.44; MS *m/z* 192 (M^+, 12), 148 (100), 78 (89); HRMS calcd for $C_9H_8O_3N_2$ 192.0535, found 192.0539.

4.3.2. (4*S*)-4-Phenyl-3-(pyridine-3-carbonyl)-1,3-oxazolidin-2-one (3b). 79% yield; $[\alpha]_D^{22}=+130°$ (*c* 0.35, $CHCl_3$); mp 184.0–184.5°C; IR (KBr) 2970, 1799, 1685 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.37 (dd, *J*=9.0, 6.8 Hz, 1H), 4.81 (dd, *J*=9.0, 8.8 Hz, 1H), 5.64 (dd, *J*=8.8, 6.8 Hz, 1H), 7.34–7.44 (m, 6H), 7.96 (ddd, *J*=7.8, 1.8, 1.7 Hz, 1H), 8.74 (dd, *J*=4.9, 1.7 Hz, 1H), 8.89 (d, *J*=1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.6, 70.1, 122.8, 126.4, 128.9, 129.2, 129.4, 136.7, 137.5, 150.0, 153.0, 153.5, 167.3; MS *m/z* 268 (M^+, 6%), 106 (100), 78 (94); HRMS calcd for $C_{15}H_{12}N_2O_3$ 268.0848, found 268.0842.

4.3.3. (4*S*)-4-Benzyl-3-(pyridine-3-carbonyl)-1,3-oxazolidin-2-one (3c). 64% yield; mp 122.0–122.5°C; $[\alpha]_D^{28}=+144°$ (*c* 0.49, $CHCl_3$); IR (KBr) 2914, 1781, 1684 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.99 (dd, *J*=13.5, 9.0 Hz, 1H), 3.44 (dd, *J*=13.5, 3.4 Hz, 1H), 4.28 (dd, *J*=9.0, 5.3 Hz, 1H), 4.38(1H, dd, *J*=9.0, 8.3 Hz, 1H), 4.88–4.93(m, 1H), 7.23–7.41 (m, 6H), 7.92 (ddd, *J*=8.1, 1.8, 1.7 Hz, 1H), 8.76 (dd, *J*=4.9, 1.7 Hz, 1H), 8.85 (d, *J*=1.8 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 37.6, 55.7, 66.6, 122.6, 127.5, 129.0, 129.4, 134.6, 136.4, 149.6, 152.6, 153.0, 167.7; MS *m/z* 282 (M^+, 99), 106 (100), 78 (97); HRMS calcd for $C_{16}H_{14}N_2O_3$ 282.1005, found 282.1025.

4.4. General procedure for the synthesis of pyridinium salts with benzyl bromide

To a solution of a nicotinic amide (2.77 mmol) in dry CH_2Cl_2 (10 ml) was added BnBr (430 ml, 3.62 mmol), and the solution was stirred for 16 h at 50°C. Concentration of the solution resulted in the precipitation of the benzyl salt, which was filtered to give a colorless solid (2.36 mmol).

4.4.1. 1-Benzyl-3-(2-thioxo-1,3-thiazolidine-3-carbonyl)-pyridinium bromide (1a). 85% yield; mp 197.3–198.2 °C; IR (KBr) 3374, 3031, 1681, 1364, 1329, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 50°C) δ 3.89 (t, *J*=7.3 Hz, 2H), 4.71 (t, *J*=7.3 Hz, 2H), 6.12 (s, 2H), 7.59 (m, 3H), 7.64 (m, 2H), 7.91 (dd, *J*=7.6, 5.9 Hz, 1H), 8.51 (d, *J*=7.6 Hz, 1H), 8.93 (d, *J*=5.9 Hz, 1H), 10.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2, 56.9, 64.5, 127.7, 129.7, 129.8, 130.4, 132.1, 134.9, 143.9, 144.2, 147.4, 164.3, 204.9; MS *m/z* 224 ([M−Br–Bn]$^+$, 48), 213 (15), 123 (28), 106 (92), 91 (100), 78 (51); HRMS calcd for $C_9H_8N_2OS_2$ ([M−Br–Bn]$^+$) 224.0078, found 224.0084.

4.4.2. 1-Benzyl-3-(2-oxo-1,3-oxazolidine-3-carbonyl)pyridinium bromide (1b). 82% yield; mp 108.9–109.2°C; IR (KBr) 1783, 1684, 1633, 1363, 1201 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 9.33 (d, *J*=6.3 Hz, 1H), 8.63 (d, *J*=7.9, 1H), 8.01 (t, *J*=6.6 Hz, 1H), 7.66 (m, 2H), 7.38 (m, 3H), 6.15 (s, 2H), 4.69 (t, *J*=7.7 Hz, 2H), 4.24 (t, *J*=7.7 Hz, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 153.2, 152.7, 149.8, 136.5, 128.8, 122.7, 62.4, 43.4; MS *m/z* 192 ([M−Br–Bn]$^+$, 3), 148 (18), 106 (44), 91 (100), 78 (24); HRMS calcd for $C_9H_8O_3N_2$ ([M−Br–Bn]$^+$) 192.0534, found 192.0539.

4.4.3. 1-Benzyl-3-dimethylcarbamoylpyridinium bromide (1c). 92% yield; mp 158.0–159.0°C; IR (KBr) 2911, 1645, 1495, 1455, 1401 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.03 (s, 3H), 3.09 (s, 3H), 6.42 (s, 2H), 7.38–7.26 (m, 3H), 7.79 (d, *J*=4.9 Hz, 2H), 8.19 (dd, *J*=7.9, 6.1 Hz, 1H), 8.57 (d, *J*=7.9 Hz, 1H), 9.75 (d, *J*=6.1 Hz, 1H), 9.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.8, 40.1, 63.9, 128.7, 129.5 129.7, 129.9, 133.0, 136.4, 143.2, 144.1, 145.7, 163.8; MS *m/z* 150 ([M−Br–Bn]$^+$, 15), 106 (29), 91 (100), 78 (18); HRMS calcd for $C_8H_{10}N_2O$ ([M−Br–Bn]$^+$) 150.0793, found 150.0754.

4.5. General procedure for the addition of ketene silyl acetals to the pyridinium salts

To a solution of the pyridinium salt **1** (1 equiv.) and Et_3N (2 equiv.) in the appropriate solvent was added 1-methoxy-2-methyl-1-[(trimethylsilyl)oxy]-1-propene (2 equiv.). After being stirred for 3 h, the reaction mixture was concentrated to afford an oil, which was purified by silica gel column chromatography.

4.5.1. 2-[1-Benzyl-3-(2-thioxo-1,3-thiazolidine-3-carbonyl)-1,4-dihydropyridin-4-yl]-2-methyl-propionic acid methyl ester (5a). Addition of **4a** to **1a** gave **5a** as a major product: An oil; IR (Neat) 2947, 1722, 1660, 1569, 1423, 1395, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.36–7.30 (m, 5H), 6.02 (d, *J*=7.6 Hz, 1H), 4.89 (dd, *J*=7.6, 5.6 Hz, 1H), 4.54–4.43 (m, 3H), 4.25–4.17 (m, 1H), 4.07 (d, J=5.6 Hz, 1H), 3.65 (s, 3H), 3.48–3.26 (m, 2H), 0.89 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.2, 170.1, 148.4, 135.2, 128.8, 128.7, 128.2, 127.5, 107.4, 100.5, 58.6, 57.1, 51.8, 49.7, 39.1, 29.7, 22.3, 19.2; MS *m/z* 416 (M^+, 0.04), 315 (70), 106 (46), 91 (100), 78 (15); HRMS calcd for $C_{16}H_{15}ON_2S_2$ (M^+−101), 315.0670, found 315.0675.

4.5.2. 2-[1-Benzyl-3-(2-oxo-1,3-oxazolidine-3-carbonyl)-1,4-dihydropyridin-4-yl]-2-methyl-propionic acid methyl ester (5b). Addition of **4a** to **1b** gave **5b** as a major product: An oil; IR (Neat) 2980, 2948, 1772, 1723, 1669, 1652, 1587, 1385, 1328, 1282, 1257, 1214, 1182, 1133, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.22 (m, 5H), 7.12 (s,1H), 6.02 (dd, *J*=1.3, 7.8 Hz, 1H), 4.77 (dd, *J*=7.9, 5.6 Hz, 1H), 4.46–4.07 (m, 5H), 4.10 (d, *J*=5.6 Hz, 1H), 3.77 (m, 1H), 3.61 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.2, 169.8, 153.9, 144.1, 136.2, 129.3, 128.7, 127.8, 127.1, 104.5, 99.8, 62.0, 60.3, 58.0, 51.6, 49.3, 43.8, 40.1, 21.5, 19.3; MS *m/z* 384 (M^+, 1%), 283 (100), 228 (20), 106 (4), 91 (79); HRMS calcd for $C_{21}H_{24}O_5N_2$ 384.1685, found 384.1694.

4.5.3. 2-(1-Benzyl-3-dimethylcarbamoyl-1,4-dihydropyridin-4-yl)-2-methyl-propionic acid methyl ester (5c). Addition of **4a** to **1c** gave a 35:56:9 mixture of **5c**, **6c** and **7c**, which were separated by preparative TLC. **5c**: An oil; IR (Neat) 2931, 1725, 1671, 1602, 1385, 1260, 1160, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.17 (m, 6H), 6.04 (d, *J*=7.6 Hz, 1H), 4.58 (q, 1H), 4.31 (s, 2H), 3.97 (d, *J*=5.2 Hz, 1H), 3.58 (s, 3H), 3.00 (s, 6H), 1.10 (s, 3H),

1.06 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.3, 172.9, 137.3, 135.7, 128.6, 127.5, 127.0, 103.6, 100.1, 57.3, 51.6, 49.1, 42.3, 37.4, 20.9, 20.6; MS *m/z* 342 (M^+, 7.2%), 241 (92), 146 (35), 91 (100), 72 (26); HRMS calcd for $C_{20}H_{26}O_3N_2$ 342.1943, found 342.1914. **6c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.17 (m, 6H), 6.45 (d, *J*=10 Hz, 1H), 4.86 (m, 1H), 4.50 (d, *J*=4.6 Hz, 1H), 4.39 (d, *J*=16 Hz, 1H), 4.24 (d, *J*=16 Hz, 1H), 3.71 (s, 3H), 2.98 (s, 6H), 1.30 (s, 3H), 1.15 (s, 3H). **7c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.18 (m, 5H), 6.36 (d, *J*=6.1 Hz, 1H), 6.24 (d, *J*=6.7 Hz, 1H), 5.18 (s, 1H), 4.91 (m, 1H), 4.45 (d, *J*=16 Hz, 1H), 4.33 (d, *J*=16 Hz, 1H), 3.60 (s, 3H), 3.05 (s, 6H), 1.20 (s, 3H) 1.13 (s, 3H).

4.5.4. (4*S*,4′*S*)-4-(1-Methoxycarbonyl-1-methylethyl)-3-(4′-phenyl-2′-thioxo-1′,3′-thiazolidine-3′-carbonyl)-4*H*-pyridine-1-carboxylic acid methyl ester (8a). Addition of **4a** to **2b** in the presence of methyl chloroformate gave **8a** as a major product: An oil; ^{1}H NMR (400 MHz, $CDCl_3$, 50°C) δ 0.87 (3H, s), 0.95 (3H, s), 3.32 (1H, dd, *J*=11.0 Hz, 4.9 Hz), 3.61 (3H, s), 3.82–3.87 (1H, m), 3.87 (3H, s), 3.94 (1H, dd, *J*=11.0, 7.0 Hz), 5.04 (1H, dd, *J*=7.9, 5.5 Hz), 5.75 (1H, dd, *J*=7.0, 4.9 Hz), 6.91 (1H, d, *J*=7.9 Hz), 7.27–7.40 (5H, m), 7.78 (1H, s); MS *m/z* 460(M^+, 2%), 359 (100), 106 (81); HRMS calcd for $C_{22}H_{24}N_2O_5S_2$ 460.1127, found 460.1110.

4.5.5. (4*S*,4′*S*)-3-(4′-Benzyl-2′-thioxo-1′,3′-thiazolidine-3′-carbonyl)-4-(1-methoxycarbonyl-1-methylethyl)-4*H*-pyridine-1-carboxylic acid methyl ester (8b). Addition of **4a** to **2c** in the presence of methyl chloroformate gave a 78:22 mixture of **8b** and **9b**, which was purified by preparative TLC to give pure **8b**: an oil; $[\alpha]_D^{25}=-392°$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 2959, 1736, 1682, 1606, 1276 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 50°C) δ 1.13 (3H, s), 1.14 (3H, s), 2.99 (1H, dd, *J*=11.1, 1.5 Hz), 3.11 (1H, dd, *J*=13.3, 11.1 Hz), 3.49–3.54 (2H, m), 3.65 (3H, s), 3.88 (3H, s), 3.94 (1H, d, *J*=5.8 Hz), 4.84–4.89 (1H, m), 5.02 (1H, dd, *J*=7.8, 5.8 Hz), 6.94 (1H, d, *J*=7.8 Hz), 7.20–7.35 (5H, m), 7.67 (1H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$, 50°C) δ 21.4, 21.6, 33.4, 37.2, 41.8, 48.9, 51.9, 54.2, 70.5, 108.5, 113.7, 123.9, 127.1, 128.9, 129.4, 135.0, 136.8, 151.4, 170.6, 177.0, 200.2; MS *m/z* 474 (M^+, 3%), 373(100), 106(89); HRMS calcd for $C_{23}H_{26}N_2O_5S_2$ 474.1283, found 474.1284.

4.5.6. (4*S*,4′*S*)-4-(1-Methoxycarbonyl-1-methylethyl)-3-(4′-*tert*-butyl-2′-thioxo-1′,3′-thiazolidine-3′-carbonyl)-4*H*-pyridine-1-carboxylic acid methyl ester (8c). Addition of **4a** to **2d** in the presence of methyl chloroformate gave **8c** as a major product: ^{1}H NMR (400 MHz, $CDCl_3$, 50°C) δ 1.10 (9H, s), 1.12 (3H, s), 1.18 (3H, s), 3.22 (1H, dd, *J*=11.4, 2.1 Hz), 3.65 (3H, s), 3.77 (1H, dd, *J*=11.4, 8.5 Hz), 3.79 (1H, d, *J*=5.8 Hz), 3.87 (3H, s), 4.75 (1H, dd, *J*=8.5, 2.1 Hz), 5.02 (1H, dd, *J*=7.9, 5.8 Hz), 6.94 (1H, d, *J*=7.9 Hz), 7.58 (1H, s); MS *m/z* 440 (M^+, 1%), 339 (100), 106(72); HRMS calcd for $C_{20}H_{28}N_2O_5S_2$ 440.1440, found 440.1435.

4.5.7. (4*S*,4′*S*)-2-[1-Methoxycarbonyl-3-(4′-phenyl-2′-thioxo-1′,3′-thiazolidine-3′-carbonyl)-1,4-dihydropyridin-4-yl]-malonic acid diethyl ester (8d). Addition of **4b** to **2c** in the presence of methyl chloroformate gave a 47:53 mixture of **8d** and **9d**: ^{1}H NMR (270 MHz, $CDCl_3$) for **8d** δ 7.92 (s, 1H), 7.31–7.26 (m, 5H), 6.89 (d, *J*=8.2 Hz, 1H), 5.81–5.71 (m, 1H), 5.30 (dd, *J*=8.2, 4.9 Hz, 1H), 4.20 (q, *J*=7.3 Hz, 4H), 3.75 (s, 3H), 3.52–3.36 (m, 3H), 3.17–2.97 (m, 3H), 1.28 (m, 6H); ^{1}H NMR (270 MHz, $CDCl_3$) for **9d** δ 7.80 (s, 1H), 6.31 (d, *J*=9.6 Hz, 1H), 5.53 (m, 1H), 4.95 (m, 1H), 4.20 (q, *J*=7.3 Hz, 4H), 3.75 (s, 3H), 3.52–3.36 (m, 3H), 3.17–2.97 (m, 3H), 1.28 (t, *J*=7.3 Hz, 6H); MS *m/z* 532 (M^+, 5%), 373 (70), 314 (26), 295 (17), 231 (27), 106 (100), 91 (5); HRMS calcd for $C_{25}H_{28}O_7N_2S_2$ 532.1338, found 532.1294.

4.5.8. (4*S*,4′*S*)-4-(1-Methoxycarbonyl-1-phenylmethyl)-3-(4′-phenyl-2′-thioxo-1′,3′-thiazolidine-3′-carbonyl)-4*H*-pyridine-1-carboxylic acid methyl ester (8e). Addition of **4c** to **2c** in the presence of methyl chloroformate gave **8e** as a major product (67%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.41–7.23 (m, 10H), 6.64 (d, *J*=7.6 Hz, 1H), 5.24 (m, 1H), 5.00 (m, 1H), 4.30 (t, *J*=5.3 Hz, 1H), 4.16–4.08 (m, 2H), 3.79 (s, 3H), 3.68 (s, 3H), 3.45–3.32 (m, 2H), 3.23–3.16 (m, 1H), 2.99–2.91 (m, 1H); MS *m/z* 522 (M^+, 0.65%), 373 (100), 285 (17), 196 (25), 182 (21), 106 (93), 91 (22), 59 (15); HRMS calcd for $C_{27}H_{26}O_5N_2S_2$ 522.1284, found 522.1306.

4.5.9. (4*S*,4′*S*)-4-(1-Methoxycarbonyl-1-methylethyl)-3-(2′-oxo-4′-phenyl-1′,3′-oxazolidine-3′-carbonyl)-4*H*-pyridine-1-carboxylic acid methyl ester (10a). Addition of **4a** to **3d** in the presence of methyl chloroformate gave **10a** as a major product: ^{1}H NMR (400 MHz, $CDCl_3$, 50°C) δ 1.04 (3H, s), 1.12 (3H, s), 3.61 (3H, s), 3.89 (3H, s), 3.95 (1H, d, *J*=5.3 Hz), 4.27 (1H, dd, *J*=9.2, 8.6 Hz), 4.71 (1H, dd, *J*=9.2, 8.9 Hz), 4.99 (1H, dd, *J*=7.9, 5.3 Hz), 5.58 (1H, dd, *J*=8.9, 8.6 Hz), 6.89 (1H, d, *J*=7.9 Hz), 7.29–7.37 (5H, m), 7.71 (1H, s); MS *m/z* 327 (M^+-101, 100%), 106 (91); HRMS calcd for $C_{17}H_{15}N_2O_5$ ($M^+-C_5H_9O_2$) 327.0981, found 327.0972.

4.5.10. (4*S*,4′*S*)-3-(4′-Benzyl-2′-oxo-1′,3′-oxazolidine-3′-carbonyl)-4-(1-methoxycarbonyl-1-methylethyl)-4*H*-pyridine-1-carboxylic acid methyl ester (10b). Addition of **4a** to **3c** in the presence of methyl chloroformate gave **10b** as a major product, which was purified by preparative TLC to give pure **10b**: $[\alpha]_D^{24}=+171°$ (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 2955, 1782, 1735, 1685, 1618 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$, 50°C) δ 1.11 (3H, s), 1.16 (3H, s), 2.76 (1H, dd, *J*=13.2, 9.2 Hz), 3.31 (1H, dd, *J*=13.2, 3.5 Hz), 3.65 (3H, s), 3.87 (3H, s), 4.07 (1H, d, *J*=5.3 Hz), 4.11–4.30 (2H, m), 4.81–4.92 (1H, m), 5.06 (1H, dd, *J*=8.2, 5.3 Hz), 6.95(1H, d, *J*=8.2 Hz), 7.17–7.33 (5H, m), 7.58 (1H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$, 50°C) δ 20.2, 22.3, 38.2, 40.9, 48.6, 51.9, 54.2, 55.1, 66.6, 108.4, 111.5, 123.9, 127.3, 128.9, 129.3, 134.2, 135.2, 151.5, 153.3, 169.7, 176.9; MS *m/z* 341 (M^+-101, 100%), 106 (96); HRMS calcd for $C_{18}H_{17}N_2O_5$ ($M^+-C_5H_9O_2$) 341.1137, found 341.1115.

4.6. General procedure for the addition of organocopper reagents to the pyridinium salts

To a solution of a nicotinic amide (130 mg) in dry THF (1.0 ml) was added acid chloride (1.1 equiv.) at 0°C, and the solution was stirred for 1 h. After the solution was cooled to −70°C, an organocopper reagent (1.2 equiv.) in THF prepared from RLi (1 equiv.) with $CuBr{\cdot}SMe_2$

(2 equiv.) was added to the solution. The solution was stirred for 2 h and then allowed to warm to room temperature. Hydrolysis of the reaction mixture was done with saturated ammonium chloride solution by stirring for 1 h. The solution was extracted with ether to give a crude product, which was subjected to column chromatography on silica gel to give a pure 1,4-dihydropyridine.

4.6.1. (4*S*,4′*S*)-4-Methyl-3-(4′-phenyl-2′-thioxo-1′,3′-thiazolidine-3′-carbonyl)-4*H*-pyridine-1-carboxylic acid methyl ester (12a). Addition of MeCu to the nicotinium salt of **2a** formed by treatment with methyl chloroformate afforded **12a** as a major product: ^{1}H NMR (270 MHz, $CDCl_3$, 50°C) δ 0.84 (3H, d, J=6.8 Hz), 3.27–3.31 (1H, m), 3.55 (1H, dd, J=11.2, 8.8 Hz), 3.72 (1H, dd, J=11.2, 7.3 Hz), 3.91 (3H, s), 5.07 (1H, dd, J=8.2, 4.7 Hz), 5.70 (1H, dd, J=8.8, 7.3 Hz), 6.67 (1H, d, J=8.2 Hz), 7.30–7.42 (5H, m), 7.78 (1H, s); MS *m*/*z* 374 (M^+, 29%), 359 (28), 180 (89), 151 (100), 106 (41); HRMS calcd for $C_{18}H_{18}N_2O_3S_2$ 374.0759, found 374.0801.

4.6.2. (4*S*,4′*S*)-4-Phenyl-3-(4′-phenyl-2′-thioxo-1′,3′-thiazolidine-3′-carbonyl)-4*H*-pyridine-1-carboxylic acid methyl ester (12b). Addition of PhCu to the nicotinium salt of **2a** formed by treatment with methyl chloroformate afforded **12b** as a major product: ^{1}H NMR (270 MHz, $CDCl_3$, 50°C) δ 3.17 (1H, dd, J=11.0, 5.4 Hz), 3.33 (1H, dd, J=11.0, 7.3 Hz), 3.92 (3H, s), 4.77 (1H, d, J=3.2 Hz), 5.10–5.16 (2H, m), 6.78 (1H, d, J=8.1 Hz), 7.02–7.40 (10H, m), 8.00 (1H, s); MS *m*/*z* 436 (M^+, 11%), 242 (97), 213 (100), 182 (51); HRMS calcd for $C_{23}H_{20}N_2O_3S_2$ 436.0915, found 436.0891.

4.6.3. (4*S*,4′*S*)-(1-Benzoyl-4-phenyl-1,4-dihydropyridin-3-yl)-(4′-phenyl-2′-thioxo-1′,3′-thiazolidin-3′-yl)methanone (12c). Addition of PhCu to the nicotinium salt of **2a** formed by treatment with benzoyl chloride afforded **12c**: ^{1}H NMR (270 MHz, $CDCl_3$, 50°C) δ 3.06 (1H, dd, J=11.0, 5.4 Hz), 3.29 (1H, dd, J=11.0, 7.6 Hz), 4.82 (1H, dd, J=4.2, 1.5 Hz), 5.10 (1H, dd, J=7.6, 5.4 Hz), 5.23 (1H, dd, J=8.3, 4.2 Hz), 6.95–7.64 (16H, m), 7.89 (1H, d, J=1.2 Hz); MS *m*/*z* 482 (M^+, 8%), 259 (93), 182 (51), 111 (100); HRMS calcd for $C_{28}H_{22}N_2O_2S_2$ 482.1122, found 482.1141.

4.6.4. (4*S*,4′*S*)-(1-Benzoyl-4-phenyl-1,4-dihydropyridin-3-yl)-(4-benzyl-2′-thioxo-1′,3′-thiazolidin-3′-yl) methanone (12d). Addition of PhCu to the nicotinium salt of **2b** formed by treatment with benzoyl chloride afforded **12d**: ^{1}H NMR (400 MHz, $CDCl_3$, 50°C) δ 2.63 (1H, dd, J=11.3, 6.6 Hz), 2.70 (1H, dd, J=11.3, 1.8 Hz), 2.93 (1H, dd, J=13.4, 11.0 Hz), 3.32 (1H, dd, J=13.4, 3.4 Hz), 4.08–4.14 (1H, m), 5.00 (1H, br s), 5.20 (1H, dd, J=8.2, 3.7 Hz), 7.03–7.64 (16H, m), 7.86 (1H, s); MS *m*/*z* 496(M^+, 6%), 259 (91), 183 (49), 182 (46), 111 (100); HRMS calcd for $C_{29}H_{24}N_2O_2S_2$ 496.1279, found 496.1302.

4.6.5. (4*S*,4′*S*)-(1-Benzoyl-4-phenyl-1,4-dihydro-pyridin-3-yl)-(4′-methyl-2′-thioxo-1′,3′-thiazolidin-3′-yl)methanone (12e). Addition of PhCu to the nicotinium salt of **2c** formed by treatment with benzoyl chloride afforded **12e**: ^{1}H NMR (270 MHz, $CDCl_3$, 50°C) δ 0.73 (9H, s), 3.06 (1H, dd, J=11.5, 5.0 Hz), 3.23 (1H, dd, J=11.5, 9.0 Hz), 4.47 (1H, dd, J=9.0, 5.0 Hz), 4.60 (1H, dd, J=4.6, 1.0 Hz), 5.37 (1H, dd, J=8.2, 4.6 Hz), 7.12–7.62 (11H, m), 7.90 (1H, d, J=1.5 Hz); MS *m*/*z* 462 (M^+, 4%), 259 (91), 182 (33), 111 (100); HRMS calcd for $C_{26}H_{26}N_2O_2S_2$ 462.1436, found 462.1466.

4.6.6. (4*S*,4′*S*)-3-(2′-Oxo-4′-phenyl-1′,3′-oxazolidine-3′-carbonyl)-4-phenyl-4*H*-pyridine-1-carboxylic acid methyl ester (14a). Addition of PhCu to the nicotinium salt of **3a** formed by treatment with benzoyl chloride afforded **14a** as a major product: ^{1}H NMR (270 MHz, $CDCl_3$, 50°C) δ 3.88 (3H, s), 3.95 (1H, d, J=5.1 Hz), 4.66–4.73 (2H, m), 4.99 (1H, dd, J=5.1, 7.9 Hz), 5.58 (1H, J=7.6, 7.9 Hz), 6.87(1H, d, J=7.9 Hz), 7.28–7.38 (10H, m), 7.69 (1H, s); MS *m*/*z* 404 (M^+, 25%), 327 (54), 213 (100), 182 (39); HRMS calcd for $C_{23}H_{20}N_2O_5$ 404.1372, found 404.1347.

4.7. General procedure for the addition of trimethylbenzyltin to the pyridinium salts

A solution of the amide (1 equiv.) in dry CH_2Cl_2 was cooled to 0°C under nitrogen atmosphere. An acylating agent (1.5 equiv.) was added dropwise to the solution, and the solution was stirred for 1 h at 0°C. After addition of benzyltrimrthyltin (2 equiv.), the solution was stirred for 23 h at room temperature. KF (20 mg) and H_2O (10 drops) were added to the solution, and the solution was stirred for 15 h. The reaction mixture was filtered, and the filtrate was dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude 1,4-adduct as an oil, which was purified by silica gel column chromatography to give a dihydropyridine (hexane/AcOEt/CH_2Cl_2=10:2:5).

4.7.1. (4*S*,4′*S*)-4-Benzyl-3-(4′-phenyl-2′-thioxo-1′,3′-thiazolidine-3′-carbonyl)-4*H*-pyridine-1-carboxylic acid methyl ester (12f). 134 mg (72%); An oil; ^{1}H NMR (270 MHz, $CDCl_3$, 50°C) δ 2.41 (1H, dd, J=13.2, 7.6 Hz), 2.62 (1H, dd, J=13.2, 4.9 Hz), 3.44 (1H, dd, J=10.2, 8.3 Hz), 3.52–3.65 (2H, m), 3.84 (3H, s), 4.99 (1H, dd, J=8.2, 5.1 Hz), 5.55 (1H, dd, J=8.3, 7.6 Hz), 6.66 (1H, d, J=8.2 Hz), 6.86–6.90 (2H, m), 7.10–7.44 (8H, m), 7.74 (1H, s); MS *m*/*z* 450 (M^+, 2%), 359 (87), 256 (89), 106 (100); HRMS calcd for $C_{24}H_{22}N_2O_3S_2$ 450.1072, found 450.1046.

4.7.2. (4*S*,4′*S*)-4-Benzyl-3-(2′-oxo-4′-phenyl-1′,3′-oxazolidine-3′-carbonyl)-4*H*-pyridine-1-carboxylic acid methyl ester (14b). 145 mg (85%); an oil; ^{1}H NMR (270 MHz, $CDCl_3$, 50°C) δ 2.71–2.74 (2H, m), 3.59 (1H, dd, J=11.7, 5.5 Hz), 3.82 (3H, s), 4.17 (1H, dd, J=8.5, 6.7 Hz), 4.55 (1H, dd, J=8.5, 7.8 Hz), 5.06 (1H, dd, J=8.3, 5.5 Hz), 5.27 (1H, dd, J=7.8, 6.7 Hz), 6.73 (1H, d, J=8.3 Hz), 6.94–6.97 (2H, m), 7.15 (2H, dd, J=5.1, 2.0 Hz), 7.27–7.44 (6H, m), 7.61 (1H, s); MS *m*/*z* 327(M^+−91%), 106 (56), 105 (100); HRMS calcd for $C_{17}H_{15}N_2O_5$ (M^+-C_7H_7) 327.0981, found 327.0973.

4.7.3. Synthesis of (*S*)-4-phenyl-1,4-dihydropyridine-3-carboxylic acid methyl ester (16). To a solution of dihydropyridine **12c** (0.95 g, 2.0 mmol) in dry THF (40 ml) was added 0.50 $moll^{-1}$ sodium methoxide solution in methanol (8.8 ml, 4.4 mmol) was added, and the solution was then stirred at rt for 7.5 h. Saturated ammonium

chloride solution was added to the reaction mixture at 0°C, and the pH adjusted to 8–9 and extracted three times with CH_2Cl_2. The combined extracts were concentrated to give a crude product which was subjected to column chromatography using CH_2Cl_2 as an eluent solvent, affording **16** (269 mg, 66%): decomposition point 83.0°C; IR ($CHCl_3$) 3474, 2953, 1696 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.58 (3H, s), 4.51 (1H, d, J=4.9 Hz), 4.87 (1H, ddd, J=7.6, 4.9, 1.6 Hz), 5,71 (1H, br s), 6.03 (1H, dd, J=7.6, 4.4 Hz), 7.14–7.37 (6H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 38.6, 51.0, 102.5, 107.6, 122.4, 126.2, 127.6, 128.2, 136.3, 148.1, 168.3; MS m/z 215 (M^+, 28%), 214 (90), 213 (79), 182 (100); HRMS calcd for $C_{13}H_{13}NO_2$ 215.0946, found 215.0930.

4.7.4. Synthesis of (*S*)-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylic acid methyl ester (17). Dihydropyridine **16** (286 mg, 1.33 mmol) was dissolved in ethanol (10 ml) and PtO_2 (49 mg) was added to the solution. The solution was stirred for 43 h under 1 atm of hydrogen atmosphere. This was subjected to column chromatography using a 4:2:1 mixture of hexane, ethyl acetate and dichloromethane as an eluent solvent to yield pure **17** (220 mg, 76%). Recrystallization of **17** from diethyl ether gave an analytical specimen: mp 135.0–136.0°C; IR ($CHCl_3$) 3469, 2952, 1675, 1627 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.81–1.86 (1H, m), 1.98 (1H, tt, J=12.7, 4.9 Hz), 2.96 (1H, dt, J=12.5, 3.7 Hz), 3.09–3.15 (1H, m), 3.58 (3H, s), 4.03 (1H, d, J=5.1 Hz), 4.59 (1H, br s), 7.14–7.31 (5H, m), 7.75 (1H, d, J=6.3 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) d 29.1, 36.4, 36.5, 50.7, 96.9, 125.8, 127.7, 128.0, 143.4, 146.4, 168.6; MS m/z 217 (M^+, 82%), 213 (74), 182 (100), 158 (95); HRMS calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1100.

4.7.5. Synthesis of (3*R*,4*R*)-4-phenylpiperidine-3-carboxylic acid methyl ester (18). Tetrahydropiperidine **17** (220 mg, 1.01 mmol) was dissolved in ethanol (5 ml) and acetic acid (5 ml), and PtO_2 (43 mg) was added to the solution. The solution was stirred under 1 atm of hydrogen atmosphere for 67 h. After filtration, saturated $NaHCO_3$ was added and extracted with dichloromethane for three times. The combined extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to give a crude *cis* and *trans* mixture of **18**, which was used in the next reaction without further purification: ^1H NMR (270 MHz, $CDCl_3$); δ 1.57–3.40 (m, 9H), 3.43 and 3.68 (each s, 2.6H and 0.4H, respectively), 7.19–7.35 (m, 5H).

4.7.6. Synthesis of (3*R*,4*R*,1′*S*,2′*R*,5′*S*)-3-methoxylcarbonyl-4-phenylpiperidine-1-carboxylic acid menthyl ester (19). To a solution of a crude **18** and triethylamine (1.2 ml, 8.6 mmol) in dry dichloromethane (5.0 ml) (+)-menthyl chloroformate (0.85 ml, 4.0 ml) was added dropwise at rt. After the solution was stirred for 19 h, the reaction mixture was extracted with dichloromethane. This was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude oily product, which was purified by silica gel column chromatography using a 10:1:5 mixture of hexane, ethyl acetate and dichloromethane as a eluent solvent to give pure **19** (281 mg, 69% from **17**). This was recrystallized from hexane to yield analytical specimen: $[\alpha]_D^{23}$=+101° (c 0.52, $CHCl_3$); mp 96.0–97.0°C; IR (KBr) 2917, 1725, 1690 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 50°C) δ 0.80 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=5.6 Hz), 0.91 (3H, d, J=5.4 Hz), 0.94–2.13 (10H, m), 2.55–2.70 (1H, m), 2.87–3.02 (3H, m), 3.22 (1H, dd, J=13.8, 4.0 Hz), 3.44 (3H, s), 4.29–4.33 (2H, m), 4.58 (1H, dt, J=10.7, 4.4 Hz), 7.19–7.29 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$, 50°C) δ 16.7, 21.0, 22.2, 23.9, 26.1, 26.4, 31.6, 34.7, 41.7, 43.4, 44.1, 45.6, 46.2, 47.7, 51.2, 75.4, 126.7, 127.4, 128.3, 142.4, 155.1, 171.9; MS m/z 401 (M^+, 2%), 264 (87), 262 (35), 218 (100), 214 (92); HRMS calcd for $C_{24}H_{35}NO_4$ 401.2566, found 401.2563.

4.8. General procedure for the synthesis of 3-dimethylcarbamoyl-1,4-dihydropyridines

To a solution of a 1,4-dihydropyridine in ether (2 ml) dimethylamine (40 wt% solution in water, 100–250 μl) was added, and the solution was stirred for 2 h at rt. After dried over anhydrous $MgSO_4$, the solution was concentrated and the residue was separated by preparative TLC using a 1:1 mixture of hexane and ethyl acetate or a 4:1 mixture of CH_2Cl_2 and ethyl acetate as an eluent solvent to afford an oily pure 3-dimethylcarbamoyl-1,4-dihydropyridine.

4.8.1. (*R*)-2-(3-Dimethylcarbamoyl-1,4-dihydropyridine-4-yl)-2-methylpropionic acid methyl ester (20a). Aminolysis of **8b** (7.1 mg) with dimethylamine (131 μl) gave **20a** (2.7 mg) in 58% yield: IR (Neat) 2933, 1711, 1627, 1604 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 50°C): δ 7.12 (br s, 1H), 6.88 (br d, J=8.10 Hz, 1H), 5.00 (dd, J=5.4, 8.1 Hz, 1H), 3.89 (d, J=5.4 Hz, 1H), 3.84 (s, 3H), 3.60 (s, 3H), 3.07 (s, 6H); CD (EtOH) 245 nm ($\Delta\varepsilon$=11.8); MS m/z (rerative intensity) 295 (M^+−Me, 1), 209 (M^+−101, 100), 165 (41), 106 (9); HRMS calcd for $C_{10}H_{13}N_2O_3$ (M^+−101) 209.0926, found 209.0877.

4.8.2. (*S*)-4-Phenyl-1,4-dihydropyridine-3-carboxylic acid dimethylamide (20b). Aminolysis of **12c** (18 mg) with dimethylamine (200 μl) gave **20b** (9.4 mg) in 78% yield: IR (Neat) 2960, 2934, 1727, 1625 cm^{-1}; ^{11}H NMR (270 MHz, $CDCl_3$, 50°C) δ 7.57–7.19 (m, 10H), 7.08 (m, 2H), 5.18 (dd, J=3.8, 8.2 Hz, 1H), 4.71 (d, J=3.8 Hz, 1H), 2.74 (s, 6H); CD (EtOH) 242 nm ($\Delta\varepsilon$=4.6); MS m/z (rerative intensity) 256 (5), 226 (M^+−106, 22), 182 (100), 105 (47); HRMS calcd for $C_{14}H_{14}N_2O$ (M^+106) 226.1106, found 226.1155.

4.8.3. (*R*)-4-Benzyl-1,4-dihydropyridine-3-carboxylic acid dimethylamide (20c). Aminolysis of **12f** (29.7 mg) with dimethylamine (250 μl) gave **20c** (15.7 mg) in 80% yield: IR (Neat) 2959, 2920, 1723, 1683, 1610 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 50°C): δ 7.27 (m,1H), 7.23 (d, J=4.6 Hz, 2H), 7.17 (t, J=4.6, 6.6 Hz, 2H), 6.96 (br s, 1H), 6.74 (br d, J=5.4 Hz, 1H), 4.92 (dd, J=4.0, 5.4 Hz, 1H), 3.81 (s, 3H), 3.76 (ddd, J=4.0, 5.1, 8.9 Hz, 1H), 2.97 (s, 6H), 2.84 (dd, J=5.1, 13.2 Hz, 1H), 2.66 (dd, J=8.9, 13.2, 1H); CD (EtOH) 244 nm ($\Delta\varepsilon$=1.3); MS m/z (rerative intensity) 240 (M^+−60, 61), 195 (100), 167 (26), 106 (20); HRMS calcd for $C_{15}H_{16}N_2O$ (M^+−60) 240.1263, found 240.1298.

4.9. Methods of calculation

All calculations on geometries and energies were performed with the program package PC SPARTAN Pro. Geometry optimizations were carried out by semiempirical AM1 methods for each structure obtained from MMFF calculations in conjunction with Monte Carlo searching. The four typical conformers obtained were selected, and their geometries and energies were optimized by ab initio calculations at RHF/3-21G* level.

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