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Stereoselective synthesis of 3,4-diaryl β-lactams

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ABSTRACT

Novel 3,4-diaryl β-lactams were prepared with high stereoselectivity in an efficient manner by a palladium-catalyzed [2+2] carbonylative cycloaddition of benzyl halides with heteroarylidene amines. The type of alkyl group linked to the nitrogen atom influences the reaction's stereoselectivity. Moreover, using chiral imines, separable diastereomeric mixtures of chiral 3,4-diaryl-β-lactams were isolated with good yields and high *trans* diastereoselections.

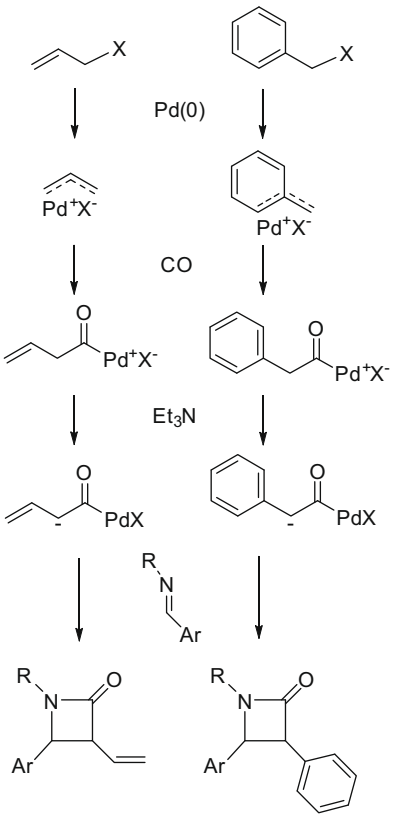
1. Introduction

The structure of 2-azetidinone is found in many compounds with pharmacological application such as antibacterial,[1,2] hypocholesterolemic,[3–5] antitumour,[6–9] enzyme inhibitor[10,11] and antiviral[12] agents. In numerous articles reported in the literature it has often been shown that the nature of the groups linked to the N, C-3 and C-4 of the β-lactam influences strictly biological activity and efficacy. These latter properties, together with possible toxicity, may increase or decrease also with small variations of substituents. Moreover, the ever increasing resistance of β-lactamases to the inhibitors causes a decrease in the β-lactam activity, keeping still live the interest of researchers towards new synthetic strategies for β-lactams having substituents of different structure.

Staudinger's strategy,[13] consisting of a [2+2] cycloaddition of ketene to imine, is still widely used; the *trans*/*cis* ratio of β-lactam changes depending on the substituents present in the reagents and on the reaction conditions.[14] The imines also generate 2-azetidinones by [2+2] cycloaddition reactions with acids,[15] α,β-unsaturated acids chlorides[9,16,17] and enolates of esters.[18,19] Other methods are sometimes reported for preparing the β-lactam nucleus, including the isocyanate–ketone cycloaddition,[20] the chromium carbene–imine reaction,[21] the hydroxamate cyclization[22] and the radical photocyclizations.[23,24]

Alper et al. reported the stereoselective synthesis of β-lactams by the rhodium- or cobalt-catalyzed expansion of the aziridinic ring.[25–29]

The palladium-catalyzed cyclocarbonylation of allyl phosphates in the presence of imines under strong CO pressure leads to the stereoselective synthesis of β-lactams.[30–32] We have simplified this reaction and made it more accessible in conditions and reactants. For instance, it has been possible to react also simple allyl halides to give 2-azetidinones in good yields and in stereoselective manner.[33] According to the mechanism proposed,[31,33] (Scheme 1) the reaction starts with the complexation of the allyl halide by Pd(0) and the insertion of CO with formation of an acyl-palladium-halide.



Scheme 1.

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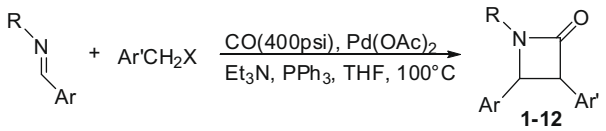
Subsequent action by base affords a carbanion α to the carbonyl that causes the [2+2] cycloaddition with the imine (Scheme 1).

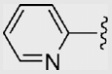
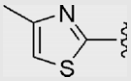
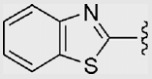
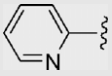
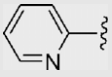
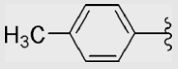
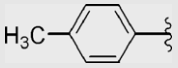
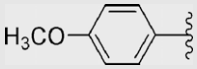
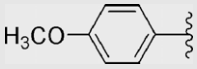
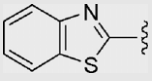
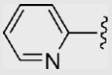
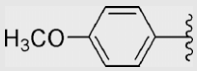
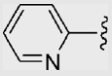
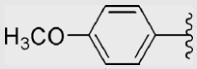
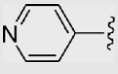
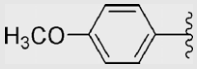
As an allyl halide is electronically very similar to a benzyl halide, we have considered the possibility that under the same reaction conditions a benzyl halide might also afford the benzyl-palladium-halide and, under basic conditions, could react with imines to afford 3-aryl-substituted β-lactams (Scheme 1). The results of this investigation are reported herein.

2. Results and discussion

The imine (1.0 mmol), benzyl halide (1.5 mmol), (Table 1) $Pd(OAc)_2$ (0.02 mmol), Ph_3P (0.08 mmol) and Et_3N (2.0 mmol) were dissolved in THF (20 ml) and the mixture was placed in an autoclave with a small magnet and subsequently filled with CO (400 psi). Heating to 100 °C under magnetic stirring was applied for 60–90 h.

Table 1

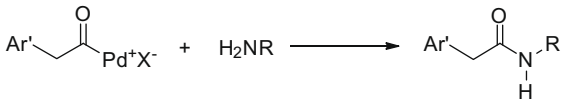


Entry	Imine		Halide		Time *t* (min)	Total yield[a] (%)	β-Lactam **1**–**12**	Product distribution[b] (%)	
	R	Ar	Ar′	X				*cis*	*trans*
1	Ph	Ph	Ph	Br	70	82	**1**	4	96
2	Ph	Ph	Ph	Cl	90	84	**1**	8	92
3	Ph		Ph	Br	60	58	**2**	12	88
4	*n*Bu	Ph	Ph	Br	90	85	**3**	—	100
5	*n*Bu		Ph	Br	90	78	**4**	5	95
6	*n*Bu		Ph	Br	90	97	**5**	13	87
7	*n*Bu		Ph	Br	70	70	**6**	Traces	99
8	*n*Bu		Ph	Cl	70	71	**6**	Traces	99
9	*t*Bu	Ph	Ph	Br	70	93	**7**	53	47
10	*t*Bu	Ph	Ph	Cl	70	91	**7**	52	48
11	*t*Bu	Ph		Br	70	88	**8**	84	16
12	*t*Bu	Ph		Cl	70	85	**8**	85	15
13	*t*Bu	Ph		Cl	70	88	**9**	99	Traces
14	*t*Bu	Ph		Br	60	95	**9**	99	Traces
15	*t*Bu		Ph	Br	60	97	**10**	91	9
16	*t*Bu			Br	60	70	**11**	100	—
17	*t*Bu			Cl	60	60	**11**	100	—
18	*t*Bu			Br	60	58	**12**	87	13

[a] Isolated yields.
[b] Diastereomeric ratios measured by GC and ^1H NMR spectroscopy.

Even with longer reaction times than the allyl halides, the benzyl halides afforded the 2-azetidinones **1**–**12**; their yields and isomeric distribution are reported in Table 1. The longer reaction times may be explained by the greater difficulty in the formation of the π-benzyl-Pd-halide complex as it needs partial interruption of the aromatic system. The yields and the diastereoselectivities are almost always fair or good. In particular, analysis of the results shows that a phenyl or a linear alkyl group (such as *n*butyl group) on the iminic nitrogen addresses the cyclization towards the formation of the *trans* isomer, (Table 1, entries 1–8).

The benzyl halide type (chloride or bromide) seems not to have any influence on yield or on diastereoselectivity (Table 1, entries 1, 2 and 7, 8). Conversely, a bulky group (such as *tert*-butyl group) on the iminic nitrogen addresses the cyclization towards the formation of the *cis* isomer, (Table 1, entries 11–18). An equimolar mixture of *cis*/*trans* structures has only been isolated once (Table 1, entries 9 and 10). When there was the *tert*-butyl group on the iminic nitrogen, the type of halogen and the Ar group do not significantly influence the yields or the products distribution (Table 1, entries 9, 10; 11, 12; 13, 14; 16, 17). The *trans*- and *cis*-structures were assigned on the basis of the value of coupling constants *J* in the ^{1}H NMR spectra between the protons at the C-3 and C-4, as often reported in the literature: a small *J* value (1.8–2.5 Hz) for a *trans* structure, a greater *J* value (5.8–6.5 Hz) for a *cis*-structure. In the reactions with more modest yields (Table 1, entries 3, 17 and 18), the amides have been isolated: compound **13**[34] in the entry 3 and compound **14**[35] in the entries 17, 18, respectively. A partial hydrolysis of the imine would afford an amine that, reacting with the acyl-palladium-halide, would lead to the amide formation (Scheme 2).



13: R, Ar' = C_6H_5
14: R = *t*-Bu, Ar' = *p*-$OCH_3C_6H_4$

13,14

Scheme 2.

For instance, when the *tert*-butylamine, instead of the imine, was reacted with the *p*-methoxy-benzylchloride under the same reaction conditions, amide **14** was produced in good yields. This may be a good and new methodology to synthesize a peptidic bond.

Considering the good stereoselectivity of the reaction, we decided to realize a new version of it with the aim of obtaining β-lactams in enantiomerically pure form. To this purpose, the (*R*)-benzylidene-*N*-phenylethylamine was reacted with the benzylbromide for a time of 60 h and under the same previously described conditions. From the reaction mixture, it was possible to isolate and characterize the two *trans*-diastereomers (3*R*,4*S*,1′*R*) and (3*S*,4*R*,1′*R*) in enantiomerically pure form and in a ratio of 5:3, (Table 2, entry 1).

The presence of the *cis*-isomers could only be seen by GC–MS and ^{1}H NMR of the crude reaction mixture. The low amount observed in each reaction (1–3%) did not allow their complete characterization. Analogously to previous reactions, a variable quantity of the amide **22**[36] was isolated; its possible formation has been described above. The reactions performed with other (*R*)-arylidene-*N*-phenylethylamines have given almost equal results (Table 2, entries 2–8). Furthermore, when the (*S*)-benzylidene-*N*-phenylethylamine was reacted with the benzylbromide under the same reaction conditions, the diastereomers (3*R*,4*S*,1′*S*)-**15** and (3*S*,4*R*,1′*S*)-**15** were isolated in an inverted ratio of 3:5. The ^{1}H and ^{13}C NMR spectra were similar to those of the two previous compounds **15**, while the specific rotation values were of opposite sign. The absolute configuration has been assigned by comparison with analogous compounds of which X-ray measurements were performed.[37]

3. Conclusion

The Torii's methodology,[31] consisting of a [2+2] cycloaddition of imines to allyl phosphates, that we have previously modified and used with allyl halides, has successfully been used with benzyl halides in this work. Moreover, the high stereoselectivity found has allowed the synthesis of β-lactams in enantiomerically pure form.

4. Experimental

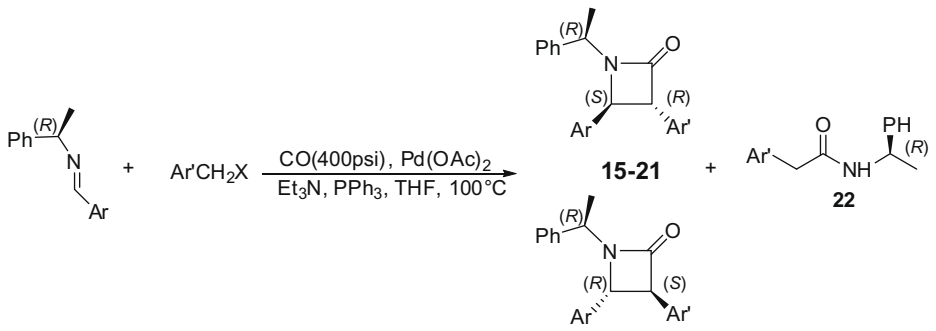
4.1. General

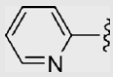
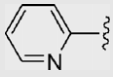
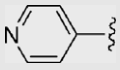
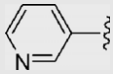
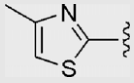
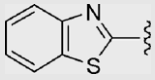
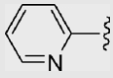
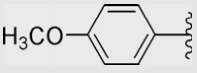
n-Butyllithium (*n*-BuLi) was a commercial solution in hexanes (Aldrich) and was titrated with *N*-pivaloyl-*o*-toluidine prior to use.[38] THF, triethylamine, 4-formylmorpholine, 2-pyridinecarboxaldehyde, 3-pyridinecarboxaldehyde, 4-pyridinecarboxaldehyde, 4-methylthiazole, 2-aminothiophenol, glycolic acid, *n*- and *t*-butylamine, palladium(II) acetate, triphenylphosphine, 4-methoxybenzyl chloride and bromide, 4-metylbenzylchloride, (*R*)-(+)-1-phenylethylamine were of commercial grade (Aldrich) and used without further purification. Benzaldehyde, aniline, benzyl chloride and bromide, of commercial grade (Aldrich) were purified by distillation prior to use. Petroleum ether refers to the 40–60 °C boiling fraction. The ^{1}H and the ^{13}C NMR spectra were recorded on a Bruker Avance 400 apparatus (400.13 and 100.62 MHz, for ^{1}H and ^{13}C, respectively) with $CDCl_3$ as solvent and TMS as internal standard (δ = 7.26 for ^{1}H spectra; δ = 77.0 for ^{13}C spectra). The IR spectra were recorded with an FT-IR spectrophotometer Digilab Scimitar Series FTS 2000. GC–MS analyses were performed with an Agilent Technologies 6850 series II gas chromatograph (5% phenyl-polymethylsiloxane capillary column, 30 m, 0.25 mm i.d.) equipped with a 5973 Network mass-selective detector operating at 70 eV. The electrospray ionization (HR-ESI-MS) experiments were carried out in a hybrid QqTOF mass spectrometer (PE SCIEX-QSTAR) equipped with an ion spray ionization source. MS (+) spectra were acquired by direct infusion (5 μL/min) of a solution containing the appropriate sample (10 pmol/μL) dissolved in a solution, 0.1% acetic acid, methanol/water 50:50 at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi (pounds per square inch) and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50 and 25 V relative to ground, respectively. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Polarimetric measurements were performed by a Jasco P-1020 polarimeter. Column chromatographies were performed on silica gel (63–200 mm) using petroleum ether/diethyl ether (Et_2O) mixtures as eluents. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe/septum cap techniques.

4.2. General procedure for the preparation of the compounds 1–12, 15–21

A mixture of 1.0 mmol of imine, 1.5 mmol of benzyl halide, 0.08 mmol of PPh_3, 0.02 mmol of $Pd(AcO)_2$ and 2.0 mmol of Et_3N was dissolved in 10 mL of solvent (THF) and placed in a 45 mL autoclave. The autoclave was purged, pressurized (400 psi CO) and then heated to 100 °C for 60–90 h. The crude mixture was chromatographed (silica gel, petroleum ether/Et_2O 1:1 for compounds **4**–**6**, **10** and **18**, petroleum ether/Et_2O 2:8 for **9**, **11** and **12** petroleum ether/Et_2O 4:6 for **16**, **17** and **21**, petroleum

Table 2



Entry	Imine	Halide		Total yield[a] (%)	β-Lactam **15–21**	Product distribution[b] (%)		
	Ar	Ar′	X			(3*R*,4*S*,1′*R*)	(3*S*,4*R*,1′*R*)	Amide **22**
1	Ph	Ph	Br	56	**15**	50	30	20
2		Ph	Br	90	**16**	56	37	7
3		Ph	Cl	81	**16**	51	34	15
4		Ph	Br	61	**17**	35	25	40
5		Ph	Br	78	**18**	54	34	12
6		Ph	Br	67	**19**	56	39	5
7		Ph	Br	52	**20**	50	44	4
8			Br	89	**21**	65	35	–

[a] Isolated yields.
[b] Diastereomeric ratios measured by GC and ^{1}H NMR spectroscopy.

ether/Et_2O 8:2 for **8**, **19** and **20**) to afford the already known pure β-lactams **1**,[39] **2**,[40] **3**,[41] **7**,[29] **15**[42] and the unknown β-lactams **4**–**6**, **8**–**12** and **16**–**21**, yields: 50–97%.

4.2.1. 1-Butyl-4-(4-methylthiazol-2-yl)-3-phenylazetidin-2-one 4

Total yield 78%. *cis*-**4**: Yield 11.7 mg, 3.9%, yellow oil; FT-IR ($CHCl_3$) 3065, 3030, 3008, 2964, 2933, 2875, 1749, 1629, 1454, 1401, 1315 cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3H), 1.38 (sextet, J = 7.3 Hz, 2H), 1.59 (quintet, J = 7.3 Hz, 2H), 2.31 (s, 3H), 3.08–3.15 (m, 1H), 3.58–3.66 (m, 1H), 4.93 (d, J = 5.6 Hz, 1H), 5.37 (d, J = 5.6 Hz, 1H), 6.65 (s, 3H), 7.11 7.31 (m, 5H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 13.6, 16.8, 20.2, 29.6, 41.1, 58.3, 60.8, 114.4, 126.6, 127.4, 128.7, 132.0, 152.7, 165.9, 168.0; GC–MS (70 eV) *m/z* 300 [M$^+$] (23), 201 (43), 200 (100), 183 (51), 139 (11), 118 (60), 90 (21), 71 (12); HRMS-ESI calcd for $C_{17}H_{20}N_2OS$ 300.13763; found 300.13769. *trans*-**4**: Yield 222 mg, 74%, yellow solid; mp = 42–44 °C, *n*-hexane; FT-IR ($CHCl_3$) 3066, 3030, 3011, 2962, 2931, 2874, 1748, 1401 cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 1.35 (sextet, J = 7.2 Hz, 2H), 1.56 (quintet, J = 7.2 Hz, 2H), 2.47 (s, 3H), 3.01–3.08 (m, 1H), 3.57–3.64 (m, 1H), 4.41 (d, J = 2.0 Hz, 1H), 4.88 (d, J = 2.0 Hz, 1H), 6.95 (s, 1H), 7,27–7.38 (m, 5H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 13.5, 17.0, 20.1, 29.7, 40.8, 60.5, 64.3, 114.3, 127.4, 127.8, 128.9, 134.2, 153.7, 167.3, 167.7; GC–MS (70 eV) *m/z* 300 [M$^+$] (3), 201 (95), 200 (100), 183 (5), 139 (3), 118 (11), 90 (9), 71(14); HRMS-ESI calcd for $C_{17}H_{20}N_2OS$ 300.13763; found 300.13771.

4.2.2. 4-Benzothiazol-2-yl-1-butyl-3-phenylazetidin-2-one 5

Total yield: 97%. *cis*-**5**: Yield 42 mg, 12.6%, yellow oil; FT-IR ($CHCl_3$) 3066, 3032, 3011, 2962, 2932, 2875, 1754, 1456, 1398, 1315 cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3H), 1.38 (sextet, J = 7.3 Hz, 2H), 1.62 (quintet, J = 7.3 Hz, 2H), 3.18 (dt, J = 7.3, 14.8 Hz, 1H), 3.70 (dt, J = 7.3, 14.8 Hz, 1H), 5.03 (d, J = 5.7 Hz, 1H), 5.47 (d, J = 5.7 Hz, 1H), 7.02–7.11 (m, 3H), 7.20 (d, J = 7.4 Hz, 2H), 7.30 (t, J = 7.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 13.6, 20.3, 29.6, 41.4, 58.8, 60.9, 121.6, 123.0, 125.2, 126.0, 127.6, 128.3, 128.6, 131.6, 135.0, 152.8, 167.5, 168.1; GC–MS (70 eV) *m/z* 336 [M$^+$] (22), 237 (33), 236 (100), 219 (20), 204 (3), 118 (38), 90 (11); HRMS-ESI calcd for

$C_{20}H_{20}N_2OS$ 336.13763; found 336.13768. *trans*-**5**: Yield 282 mg, 84%, yellow oil; FT-IR (film) 3062, 3030, 2958, 2931, 2871, 1762, 1436, 1394, 1313 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3, 3H), 1.38 (sextet, J = 7.3 Hz, 2H), 1.61 (quintet, J = 7.3 Hz, 2H), 3.12 (dt, J = 7.7, 14.8 Hz, 1H), 3.68 (dt, J = 7.7, 14.8 Hz, 1H), 4.51 (d, J = 2.1 Hz, 1H), 5.01 (d, J = 2.1 Hz, 1H), 7.29–7.40 (m, 5H), 7.44 (t, J = 8.2 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 13.5, 20.1, 29.7, 41.1, 61.0, 64.3, 121.9, 123.4, 125.7, 126.5, 127.3, 127.9, 128.9, 133.9, 134.8, 153.2, 167.4, 169.0; GC–MS (70 eV) *m/z* 336 [M^+] (2), 237 (48), 236 (100), 219 (1), 204 (3), 118 (7), 90 (3); HRMS-ESI calcd for $C_{20}H_{20}N_2OS$ 336.13763; found 336.13770.

4.2.3. 1-Butyl-3-phenyl-4-pyridin-2-ylazetidin-2-one 6

(From reaction with benzylbromide): total yield 70%. *cis*-**6**: Traces; GC–MS (70 eV) *m/z* 280 [M^+] (15), 180 (100), 152 (3), 90 (8), 77 (3). *trans*-**6**: Yield 194 mg, 69.3%, yellow oil; FT-IR (film) 3061, 3029, 2956, 2930, 2872, 1752, 1590, 1439, 1402 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.34 (sextet, J = 7.3 Hz, 2H), 1.50 (quintet, J = 7.3 Hz, 2H), 2.90–2.97 (m, 1H), 3.62 (dt, J = 7.3, 14.4 Hz, 1H), 4.34 (d, J = 2.0 Hz, 1H), 4.67 (d, J = 2.0 Hz, 1H), 7.25–7.37 (m, 7H), 7.75 (dd, J = 1.7, 7.6 Hz, 1H), 8.65 (d, J = 4.5 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 13.5, 20.1, 29.7, 40.6, 63.1, 64.1, 121.1, 123.2, 127.3, 128.7, 129.3, 135.0, 136.9, 150.0, 157.3, 168.1; GC–MS (70 eV) *m/z* 280 [M^+] (6), 180 (100), 152 (4), 90 (3), 77 (1); HRMS-ESI calcd for $C_{18}H_{20}N_2O$ 280.16553; found 280.16559. (From reaction with benzylchloride): total yield 71%. *cis*-**6**: traces. *trans*-**6**: Yield 197 mg, 70.3%.

4.2.4. 1-*tert*-Butyl-4-phenyl-3-*p*-tolylazetidin-2-one 8

(From reaction with 4-metylbenzylbromide): total yield 88%. *cis*-**8**: Yield 217 mg, 74%, yellow solid; mp = 102–103 °C, *n*-hexane; FT-IR ($CHCl_3$) 3030, 3010, 2976, 2926, 1732, 1517, 1456, 1368, 1349 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.16 (s, 3H), 4.66 (d, J = 5.8 Hz, 1H), 5.00 (d, J = 5.8 Hz, 1H), 6.84–6.89 (m, 4H), 7.06–7.12 (m, 5H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 20.9, 28.1, 54.4, 58.5, 59.4, 127.5, 127.7, 128.5, 130.0, 136.0, 137.5, 168.4; GC–MS (70 eV) *m/z* 293 [M^+] (<1), 194 (100), 179 (36), 165 (3), 132 (26), 104 (10), 77 (4); HRMS-ESI calcd for $C_{20}H_{23}NO$ 293.18592; found 293.18599. *trans*-**8**: Yield 41 mg, 14%, yellow oil; FT-IR ($CHCl_3$) 3030, 3011, 2976, 2927, 2873, 1736, 1515, 1456, 1367, 1347 cm^{-1}; .^1H NMR (400.13 MHz, $CDCl_3$) δ 1.32 (s, 9H), 2.33 (s, 3H), 3.93 (d, J = 1.9 Hz, 1H), 4.43 (d, J = 1.9 Hz, 1H), 7.11–7.16 (m, 4H), 7.33–7.42 (m, 5H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.1, 28.3, 54.7, 63.4, 63.5, 126.4, 127.2, 128.3, 128.9, 129.5, 132.6, 137.2, 140.5, 168.7; GC–MS (70 eV) *m/z* 293 [M^+] (<1), 194(100), 179 (34), 165 (3), 132 (4), 104 (4), 77 (3); HRMS-ESI calcd for $C_{20}H_{23}NO$ 293.18592; found 293.18602. (From reaction with 4-metylbenzylchloride): total yield 85%. *cis*-**8**: Yield 211 mg, 72%. *trans*-**8**: Yield 37 mg, 12.7%.

4.2.5. 1-*tert*-Butyl-3-(4-methoxyphenyl)-4-phenylazetidin-2-one 9

(From reaction with 4-methoxybenzylchloride): total yield 88%. *cis*-**9**: Yield 269 mg, 87%, yellow oil; FT-IR ($CHCl_3$) 3030, 3010, 2975, 2926, 1731, 1517, 1456, 1210 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.33 (s, 9H), 3.79 (s, 3H), 4.63 (d, J = 5.7 Hz, 1H), 4.99 (d, J = 5.7 Hz, 1H), 6.58 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H) 7.05–7.11 (m, 5H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 28.2, 54.5, 55.2, 58.2, 59.6, 113.9, 125.3, 127.5,127.8, 128.5, 137.5, 158.2, 159.1, 168.6; GC–MS (70 eV) *m/z* 309 [M^+] (4), 210 (100), 195 (10), 165 (12), 148 (93), 120 (16), 91 (10), 77 (7); HRMS-ESI calcd for $C_{20}H_{23}NO_2$ 309.18082; found 309.18090. *trans*-**9**: Traces; GC–MS (70 eV) *m/z* 309 [M^+] (<1), 210 (100), 195 (8), 165 (8), 148 (4), 120 (2), 91 (3), 77 (2). (From reaction with 4-methoxybenzylbromide): total yield 95%. *cis*-**9**: Yield 290 mg, 94%. *trans*-**9**: traces.

4.2.6. 4-Benzothiazol-2-yl-1-*tert*-butyl-3-phenylazetidin-2-one 10

Total yield 97%. *cis*-**10**: Yield 296 mg, 88%, yellow solid; mp = 200–202 °C, *n*-hexane; FT-IR ($CHCl_3$) 3066, 2978, 2930, 1748, 1370, 1350, 1229 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.42 (s, 9H), 4.90 (d, J = 6.0 Hz, 1H), 5.53 (d, J = 6.0 Hz, 1H), 7.02–7.09 (m, 3H), 7.20 (d, J = 7.4 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.91(d, J = 8.1 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 28.0, 55.2, 57.6, 59.0, 121.5, 122.9, 125.1, 125.9, 127.4, 128.2, 128.5, 132.0, 135.0, 152.4, 167.5, 170.7; GC–MS (70 eV) *m/z* 336 [M^+] (6), 280 (5), 236 (100), 219 (7), 163 (7), 135 (5), 118 (28), 90 (10), 57 (8); HRMS-ESI calcd for $C_{20}H_{20}N_2OS$ 336.13763; found 336.13772. *trans*-**10**: Yield 29 mg, 8.7%, yellow solid; mp 97–99 °C; FT-IR ($CHCl_3$) 3068, 2978, 2932, 1749, 1370, 1354, 1229 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.43 (s, 9H), 4.30 (d, J = 2.2 Hz, 1H), 5.04 (d, J = 2.2 Hz, 1H), 7.27–7.40 (m, 5H), 7.44 (t, J = 8.1 Hz, 1H), 7.51 (t, J = 8.1 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 28.1, 55.4, 60.4, 63.3, 122.0, 123.4, 125.7, 126.4, 127.4, 127.9, 129.0, 134.2, 134.8, 152.9, 167.8, 172.1; GC–MS (70 eV) *m/z* 336 [M^+] (1), 280 (1), 236 (100), 118 (5), 90 (3), 57 (4); HRMS-ESI calcd for $C_{20}H_{20}N_2OS$ 336.13763; found 336.13775.

4.2.7. *cis*-1-*tert*-Butyl-3-(4-methoxyphenyl)-4-pyridin-2-ylazetidin-2-one 11

(From reaction with 4-methoxybenzylbromide): total yield 70%. *cis*-**11**: Yield 217 mg, 70%, yellow solid; mp = 81–84 °C, *n*-hexane; FT-IR ($CHCl_3$) 3024, 2976, 2938, 1735, 1602, 1514, 1367, 1250 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.35 (s, 9H), 3.65 (s, 3H), 4.74 (d, J = 5.9 Hz, 1H), 5.17 (d, J = 5.9 Hz, 1H), 6.58 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 6.98 (dd, J = 7.6, 5.0 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 8.38 (d, J = 5.0 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 28.0, 54.5, 54.9, 57.9, 60.5, 113.3, 122.0, 122.3, 124.9, 129.6, 135.5, 148.7, 157.8, 158.2, 168.5; GC–MS (70 eV) *m/z* 310 [M^+] (6), 210 (100), 196 (4), 167 (13), 148 (19), 120 (7), 91 (4), 77 (3); HRMS-ESI calcd for $C_{19}H_{22}N_2O_2$ 310.17609; found 310.17615. (From reaction with 4-methoxybenzylchloride): total yield 60%. *cis*-**11**: Yield 186 mg, 60%.

4.2.8. 1-*tert*-Butyl-3-(4-methoxyphenyl)-4-pyridin-4-ylazetidin-2-one 12

Total yield 58%. *cis*-**12**: Yield 155 mg, 50%, solid; mp = 102–104 °C, *n*-hexane; FT-IR ($CHCl_3$) 3028, 2973, 2930, 1738, 1604, 1514, 1369, 1251 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.35 (s, 9H), 3.67 (s, 3H), 4.71 (d, J = 5.9 Hz, 1H), 4.96 (d, J = 5.9 Hz, 1H), 6.60 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 6.0 Hz, 2H), 8.36 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100.62 MHz) δ 28.2, 54.9, 55.1, 58.4, 58.5, 113.7, 122.5, 124.1, 129.7, 147.6, 149.1, 150.0, 158.7, 168.1; GC–MS (70 eV) *m/z* 310 [M^+] (2), 211 (100), 167 (15), 148 (55); HRMS-ESI calcd for $C_{19}H_{22}N_2O_2$ 310.17609; found 310.17617. *trans*-**12**: The *trans* isomer was isolated as unseparable mixture of *trans*- and *cis*-diastereomers; yield 23 mg, 7.5%; ^1H NMR (400.13 MHz) δ 1.33 (s, 9H), 3.79 (s, 3H), 3.87 (d, J = 1.8 Hz, 1H), 4.40 (d, J = 1.8 Hz, 1H), 6.88 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 5.2 Hz, 2H), 8.63 (d, J = 5.2 Hz, 2H); GC–MS (70 eV) *m/z* 310 [M^+] (<1), 211 (100), 167 (12), 148 (48); IR and ^{13}C NMR data were measured on the mixture; FT-IR ($CHCl_3$) 3028, 2975, 2935, 1739, 1603, 1515, 1369, 1252 cm^{-1}; ^{13}C NMR (100.62 MHz) δ 28.1, 28.2, 54.7, 54.9, 55.1, 55.2, 58.4, 58.5, 62.1, 63.1, 113.7, 114.4, 121.0, 122.5, 124.1, 126.7, 128.3, 129.7, 147.6,

149.1, 149.8, 150.0, 158.7, 159.2, 168.1, 168.4; HRMS-ESI calcd for $C_{19}H_{22}N_2O_2$ 310.17609; found 310.17613.

4.2.9. 3-Phenyl-1-(1-phenylethyl)-4-pyridin-2-ylazetidin-2-one 16

(From reaction with benzylbromide): total yield 90%. (−)-(3*R*,4*S*,1′*R*)-**16**: Yield 164 mg, 50%, yellow oil; $[\alpha]_D^{30.6} = -99.25$ (*c* 0.008, $CHCl_3$); FT-IR ($CHCl_3$) 3033, 3005, 2957, 2928, 2855, 1748 cm^{-1}; ^1H NMR (400.13 MHz, CDCl3) δ 1.83 (d, *J* = 7.1 Hz, 3H), 4.34 (d, *J* = 2.2 Hz, 1H), 4.50 (d, *J* = 2.2 Hz, 1H), 4.58 (q, *J* = 7.1 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 7.15–7.34 (m, 12 H), 7.53 (t, *J* = 7.6 Hz, 1H), 8.57 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 19.7, 54.3, 62.3, 63.2, 121.6, 122.9, 125.8, 126.9, 127.4, 128.4, 128.7, 129.0, 135.0, 136.5, 140.7, 149.8, 157.1, 168.1; GC–MS (70 eV) *m/z* 328 [M^+] (3), 180 (100), 167 (2), 152 (4), 105 (7), 77 (4); HRMS-ESI calcd for $C_{22}H_{20}N_2O$ 328.16553; found 328.16561. (+)-(3*S*,4*R*,1′*R*)-**16**: Yield 108 mg, 33%, yellow solid; mp = 114–117 °C, *n*-hexane; $[\alpha]_D^{31.4} = +113.9$ (*c* 0.015, $CHCl_3$); FT-IR ($CHCl_3$) 3032, 3006, 2960, 2928, 2856, 1749 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.34 (d, *J* = 7.1 Hz, 3H), 4.40 (d, *J* = 2.3 Hz, 1H), 4.43 (d, *J* = 2.3 Hz, 1H), 5.13 (q, *J* = 7.1 Hz, 1H), 7.14–7.34 (m, 12H) 7.64 (dd, *J* = 1.5, 7.6 Hz, 1H), 8.63 (dd, *J* = 1.5, 4.6 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 18.5, 52.4, 62.4, 63.4, 121.9, 123.3, 127.2, 127.5, 127.8, 128.0, 128.6, 128.8, 135.0, 136.7, 140.1, 149.9, 158.2, 168.4; GC–MS (70 eV) *m/z* 328 [M^+] (3), 180 (100), 167 (2), 152 (4), 105 (7), 77 (4); HRMS-ESI calcd for $C_{22}H_{20}N_2O$ 328.16553; found 328.16564. *2-Phenyl-N-[(1R)-phenylethyl]acetamide* **22**:[36] Yield 15 mg, 6.3%. (From reaction with benzylchloride): total yield 81%. (−)-(3*R*,4*S*,1′*R*)-**16**: Yield 134 mg, 41%. (+)-(3*S*,4*R*,1′*R*)-**16**: Yield 90 mg, 27.5%. *2-Phenyl-N-[(1R)-phenylethyl]acetamide* **22**:[36] Yield 28.6 mg, 12%.

4.2.10. 3-Phenyl-1-(1-phenylethyl)-4-pyridin-4-ylazetidin-2-one 17

Total yield 61%. (−)-(3*R*,4*S*,1′*R*)-**17**: Yield 69 mg, 21%, yellow oil; $[\alpha]_D^{28.2} = -93.3$ (*c* 0.01, $CHCl_3$); FT-IR ($CHCl_3$) 3032, 3005, 2959, 2928, 2854, 1748, 1601, 1454 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.87 (d, *J* = 7.2 Hz, 3H), 4.07 (d, *J* = 2.1 Hz, 1H), 4.27 (d, *J* = 2.1 Hz, 1H), 4.50 (q, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 5.7 Hz, 2H), 7.20–7.37 (m, 10H), 8.53 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 19.7, 54.7, 61.7, 64.2, 121.3, 126.9, 127.3, 127.9, 128.3, 128.5, 128.7, 129.1, 134.4, 147.0, 150.3, 167.7; GC–MS (70 eV) *m/z* 328 [M^+] (<1), 181 (100), 180 (71), 152 (9), 105 (15); HRMS-ESI calcd for $C_{22}H_{20}N_2O$ 328.16553; found 328.16562. (+)-(3*S*,4*R*,1′*R*)-**17**: Yield 49 mg, 15%, yellow oil; $[\alpha]_D^{29.4} = +103.3$ (*c* 0.012, $CHCl_3$); FT-IR ($CHCl_3$) 3032, 3006, 2960, 2928, 2855, 1748, 1602, 1454 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.45 (d, *J* = 7.2 Hz, 3H), 4.08 (d, *J* = 2.4 Hz, 1H), 4.17 (d, *J* = 2.4 Hz, 1H), 5.14 (q, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 5.9 Hz, 2H), 7.19–7.35 (m, 10H), 8.60 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 18.8, 53.0, 62.1, 64.3, 121.5, 127.0, 127.3, 127.9, 128.1, 128.8, 129.0, 134.3, 140.5, 148.4, 150.3, 167.5; GC–MS (70 eV) *m/z* 328 [M^+] (<1), 181 (100), 180 (68), 152 (12), 105 (14); HRMS-ESI calcd for $C_{22}H_{20}N_2O$ 328.16553; found 328.16559. *2-Phenyl-N-[(1R)-phenylethyl]acetamide* **22**:[36] Yield 58 mg, 24.4%.

4.2.11. 3-Phenyl-1-(1-phenylethyl)-4-pyridin-3-ylazetidin-2-one 18

Total yield 78%. (−)-(3*R*,4*S*,1′*R*)-**18**: Yield 138 mg, 42%, yellow oil; $[\alpha]_D^{27.2} = -79.9$ (*c* 0.012, $CHCl_3$). FT-IR ($CHCl_3$) 3033, 3009, 2928, 2855, 1745, 1379 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.85 (d, *J* = 7.1 Hz, 3H), 4.13 (d, *J* = 2.3 Hz, 1H), 4.33 (d, *J* = 2.3 Hz, 1H), 4.51 (q, *J* = 7.1 Hz, 1H), 7.20–7.36 (m, 11H), 7.49 (dd, *J* = 7.9, 1.8 Hz, 1H), 8.41 (d, *J* = 1.8 Hz, 1H), 8.53 (dd, *J* = 1.5, 4.8 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 19.6, 54.3, 60.5, 64.2, 123.7, 126.9, 127.3, 127.8, 128.4, 128.7, 129.0, 133.4, 133.8, 134.5, 140.4, 148.5, 149.8, 167.8; GC–MS (70 eV) *m/z* 328 [M^+] (<1), 181 (84), 180 (100), 152 (7), 105 (14), 77 (7); HRMS-ESI calcd for $C_{22}H_{20}N_2O$ 328.16553; found 328.16562. (+)-(3*S*,4*R*,1′*R*)-**18**: Yield 85 mg, 26%, yellow oil; $[\alpha]_D^{28.2} = +51.5$ (*c* 0.010, $CHCl_3$); FT-IR ($CHCl_3$) 3032, 3008, 2928, 2855, 1745, 1378 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.42 (d, *J* = 7.2 Hz, 3H), 4.14 (d, *J* = 2.3 Hz, 1H), 4.22 (d, *J* = 2.3 Hz, 1H), 5.15 (q, *J* = 7.2 Hz, 1H), 7.07–7.09 (m, 2H), 7.18–7.36 (m, 9H), 7.67 (dd, *J* = 7.9, 1.8 Hz, 1H), 8.48 (d, *J* = 1.8 Hz, 1H), 8.60 (dd, *J* = 1.3, 4.7 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 18.8, 52.7, 60.8, 64.3, 123.8, 127.3, 127.8, 128.1, 128.4, 128.8, 128.9, 134.0, 134.7, 139.5, 148.7, 149.4, 150.1, 168.3; GC–MS (70 eV) *m/z* 328 [M^+] (2), 181 (84), 180 (100), 152 (8), 105 (13), 77 (7); HRMS-ESI calcd for $C_{22}H_{20}N_2O$ 328.16553; found 328.16560. *2-Phenyl-N-[(1R)-phenylethyl]acetamide* **22**:[36] Yield 22 mg, 9.4%.

4.2.12. 4-(4-Methylthiazol-2-yl)-3-phenyl-1-(1-phenylethyl)-azetidin-2-one 19

Total yield 67%. (−)-(3*R*,4*S*,1′*R*)-**19**: Yield 130 mg, 37,5%, yellow oil; $[\alpha]_D^{23.0} = -88.1$ (*c* 0.010, $CHCl_3$); FT-IR ($CHCl_3$) 3033, 3009, 2928, 2855, 1745, 1379 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.86 (d, *J* = 7.1 Hz, 3H), 2.40 (s, 3H), 4.40 (d, *J* = 2.2 Hz, 1H), 4.59 (q, *J* = 7.1 Hz, 1H), 4.72 (d, *J* = 2.2 Hz, 1H), 6.83 (s, 1H), 7.21–7.33 (m, 10H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 16.9, 19.8, 54.8, 59.3, 63.5, 114.3, 126.8, 127.3, 127.6, 127.7, 128.5, 128.8, 134.2, 140.7, 153.3, 167.2, 167.7; GC–MS (70 eV) *m/z* 348 [M^+] (<1), 201 (71), 200 (100), 168 (4), 105 (15), 77 (7); HRMS-ESI calcd for $C_{21}H_{20}N_2OS$ 348.13763; found 348.13770. (+)-(3*S*,4*R*,1′*R*)-**19**: Yield 90 mg, 26%, yellow solid; mp = 83–86 °C, *n*-hexane; $[\alpha]_D^{23.0} = +100.6$ (*c* 0.012, $CHCl_3$); FT-IR ($CHCl_3$) 3034, 3008, 2928, 2854, 1745, 1380 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.49 (d, *J* = 7.2 Hz, 3H), 2.44 (s, 3H), 4.42 (d, *J* = 2.3 Hz, 1H), 4.69 (d, *J* = 7.2 Hz, 1H), 5.10 (q, *J* = 7.2 Hz, 1H), 6.89 (s, 1H), 7.11–7.13 (m, 2H), 7.23–7.34 (m, 8H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 16.9, 18.6, 53.0, 59.5, 63.7, 114.4, 127.2, 127.3, 127.7, 127.9, 128.7, 128.8, 134.1, 139.8, 153.3, 168.0, 168.1; GC–MS (70 eV) *m/z* 348 [M^+] (<1), 201 (69), 200 (100), 168 (4), 105 (16), 77 (6); HRMS-ESI calcd for $C_{21}H_{20}N_2OS$ 348.13763; found 348.13771. *2-Phenyl-N-[(1R)-phenylethyl]acetamide* **22**:[36] Yield 8 mg, 3.3%.

4.2.13. 4-Benzothiazol-2-yl-3-phenyl-1-(1-phenylethyl)-azetidin-2-one 20

Total yield 52%. (−)-(3*R*,4*S*,1′*R*)-**20**: Yield 100 mg, 26%, yellow solid; mp = 126–129 °C, *n*-hexane; $[\alpha]_D^{28.0} = -72.5$ (*c* 0.015, $CHCl_3$); FT-IR ($CHCl_3$) 3066, 3009, 2927, 2855, 1757, 1456, 1304 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.93 (d, *J* = 7.2 Hz, 3H), 4.47 (d, *J* = 2.2 Hz, 1H), 4.63 (q, *J* = 7.2 Hz, 1H), 4.83 (d, *J* = 2.2 Hz, 1H), 7.20–7.36 (m, 10H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 20.1, 55.7, 60.1, 63.6, 121.8, 123.4, 125.6, 126.4, 126.9, 127.3, 127.4, 127.9, 128.1, 128.7, 129.0, 134.0, 135.0, 140.7, 167.6, 169.3; GC–MS (70 eV) *m/z* 384 [M^+] (<1), 236 (100), 237 (49), 204 (4), 105 (10); HRMS-ESI calcd for $C_{24}H_{20}N_2OS$ 384.13763; found 384.13769. (+)-(3*S*,4*R*,1′*R*)-**20**: Yield 87,5 mg, 22,8%, yellow solid; mp = 97-100 °C, *n*-hexane; $[\alpha]_D^{31.0} = +86.1$ (*c* 0.013, $CHCl_3$); FT-IR ($CHCl_3$) 3066, 3012, 2927, 2855, 1753, 1455, 1304 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.53 (d, *J* = 7.2 Hz, 3H), 4.49 (d, *J* = 2.4 Hz, 1H), 4.81 (d, *J* = 2.4 Hz, 1H), 5.20 (q, *J* = 7.2 Hz, 1H), 7.10–7.12 (m, 2H), 7.22–7.36 (m, 8H), 7.43 (t, *J* = 8.1 Hz, 1H), 7.52 (t, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 18.6, 53.1, 60.2, 63.9, 121.9, 123.4, 125.8, 126.5, 127.3, 127.4, 127.9, 128.1, 128.8, 128.9, 133.9, 135.0, 139.6, 153.0, 168.0, 170.2; GC–MS (70 eV) *m/z* 384 [M^+] (2), 237(52), 236 (100), 204 (5), 105 (12); HRMS-ESI calcd for $C_{24}H_{20}N_2OS$ 384.13763; found 384.13768. 2-Phenyl-*N*-[(1R)-phenylethyl]acetamide **22**:[36] Yield 7 mg, 3%.

4.2.14. 3-(4-Methoxyphenyl)-1-(1-phenylethyl)-4-pyridin-2-yl-azetidin-2-one 21

Total yield 89%. (−)-(3*R*,4*S*,1′*R*)-**21**: Yield 207 mg, 58%, yellow solid; mp = 59–62 °C, *n*-hexane; $[\alpha]_D^{24.9} = -205.0$ (*c* 0.012, $CHCl_3$); FT-IR ($CHCl_3$) 3065, 3010, 2953, 2936, 1743, 1514, 1249, 1179, 1036 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 1.83 (d, *J* = 7.1 Hz, 3H), 3.78 (s, 3H), 4.27 (d, *J* = 2.0 Hz, 1H), 4.45 (d, *J* = 2.0 Hz, 1H), 4.57 (q, *J* = 7.1 Hz, 1H), 6.85–6.87 (m, 2H), 7.00 (d, *J* = 7.8 Hz, 1H), 7.15–7.20 (m, 8H), 7.54 (t, *J* = 7.8 Hz, 1H), 8.56 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100.62 MHz) δ 19.8, 54.4, 55.2, 61.9, 63.6, 114.2, 121.6, 121.9, 127.0, 127.2, 127.5, 128.5, 128.6, 136.5, 140.9, 149.8, 157.4, 159.0, 168.6; GC–MS (70 eV) *m/z* 358 [M^+] (2), 211 (40), 210 (100), 195 (5), 167 (10); HRMS-ESI calcd for $C_{23}H_{22}N_2O_2$ 358.17609; found 358.17617. (+)-(3*S*,4*R*,1′*R*)-**21**: Yield 111 mg, 31%, yellow oil; $[\alpha]_D^{25.7} = +110.0$ (*c* 0.012, $CHCl_3$); FT-IR (film) 3063, 3031, 2976, 2933, 1747, 1514, 1250, 1179, 1033 cm^{-1}; ^1H NMR (400.13 MHz) δ 1.35 (d, *J* = 7.1 Hz, 3H), 3.75 (s, 3H), 4.33 (d, *J* = 2.0 Hz, 1H), 4.38 (d, *J* = 2.0 Hz, 1H), 5.14 (q, *J* = 7.1 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.23–7.34 (m, 6H), 7.64 (t, *J* = 7.6 Hz, 1H), 8.62 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (100.62 MHz) δ 18.5, 52.3, 55.2, 61.8, 63.9, 114.2, 121.8, 123.2, 127.2, 127.6, 127.7, 128.5, 128.6, 136.7, 140.1, 149.9, 158.3, 159.0, 168.9; GC–MS (70 eV) *m/z* 358 [M^+] (2), 211 (35), 210 (100), 195 (5), 167 (12); HRMS-ESI calcd for $C_{23}H_{22}N_2O_2$ 358.17609; found 358.17619.

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