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Pd-Catalyzed Chemoselective Cross-Coupling Reaction of Triaryl- or Triheteroarylbismuth Compounds with 3,6-Dihalopyridazines

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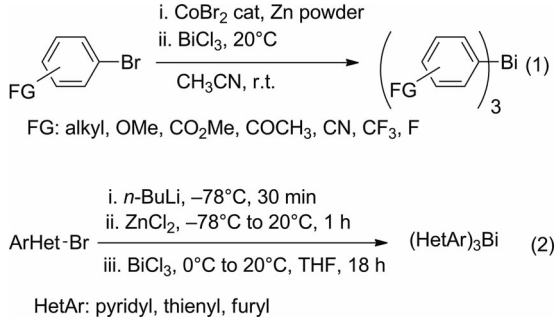
The cross-coupling reactions of 3,6-dihalopyridazines with triaryl- or triheteroarylbismuth compounds were performed under palladium catalysis. The reaction was highly chemoselective, affording functionalized aryl- or heteroarylpyridazinyl chlorides in moderate to good yields.

Introduction

Pyridazine derivatives are of considerable importance as building blocks for various applications in supramolecular chemistry[1] and as intermediates to afford pyrrole moieties by ring contraction.[2] Furthermore, compounds containing a 3,6-disubstituted pyridazinyl ring exhibit extensive biological activities.[3] In this context, relevant methods are of considerable importance to facilitate the preparation of new reactive pyridazine intermediates, which allow access to challenging dissymmetrical 3,6-disubstituted derivatives with high biological potentials.[4] Palladium-catalyzed cross-coupling reactions with pyridazinyl moieties have been previously explored[5] to produce 6-aryl-substituted 3-chloropyridazines, which are regarded as suitable intermediates for elaboration to 3,6-diarylpyridazines. A straightforward method consists of the cross-coupling reaction of 3,6-dichloropyridazine under Negishi[6] or Suzuki[7] conditions. However, when using these procedures, mixtures of mono- and diarylated products are formed in variable ratios.[6–8] The desymmetrization of 3,6-dichloropyridazine into 3-chloro-6-iodopyridazine affords better results,[9] but this procedure has not been extended so far. Until now, the most efficient way to prepare 6-aryl-substituted 3-chloropyridazines remains a multistep process involving a Pd-catalyzed cross-coupling reaction, starting from 3-chloro-6-methoxypyridazine and arylboronic acids, followed by cleavage of the methoxy group with hydroiodic acid and chlorination of the resulting pyridazinone intermediate with phosphorus oxychloride.[10] Léonel et al.[11] describe a convenient electrochemical reaction to give arylpyridazine derivatives in one step. This straightforward method allows the coupling of methoxy- or methylpyridazinyl chlorides with substituted aryl halides under nickel catalysis ($NiBr_2$bpy) in conjunction with the sacrificial anode process.[12] Unfortunately, the reaction conditions could not be applied to 3,6-dichloropyridazine, as the dihalopyridazinyl rings either act as coligands or compete with the 2,2′-bipyridine (bpy) and poison the nickel catalyst.[13]

Simultaneously, we recently developed a convenient and versatile method[14] to prepare triarylbismuth compounds bearing either electron-donating or electron-withdrawing groups. The process involves $BiCl_3$ and arylzinc reagents, prepared by a cobalt-catalyzed reaction (see Scheme 1, Equation 1), and advantageously can be extended to access heteroarylbismuth compounds {see Scheme 1, Equation 2).



Scheme 1. Advanced preparation of functionalized triaryl- and triheteroaryl-bismuth compounds.

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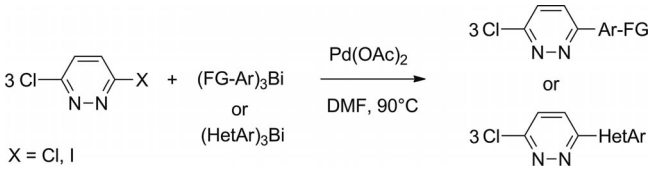
Because triarylbismuths are of growing interest as atom-efficient organometallic reagents in the formation of C–C bonds[15] and are considered as low or nontoxic,[16] we have explored their behavior in Pd-catalyzed cross-coupling reactions, starting from 3,6-dihalopyridazines.

Rao et al.[17] recently reported the preparation of unsymmetrical biphenyls through Pd-catalyzed cross-coupling reactions of aryl halides or aryl triflates with triarylbismuths, bearing mainly electron-donating groups. However, to the best of our knowledge, the scope of the reaction was limited to 2-iodopyridine and pyridin-2-yl trifluoromethanesulfonate,[16] and very recently to 2-bromo-thiophene and -benzofurans,[18] as the heteroaryl halide partners. The aim of this work is to design a general method targeting 3-halo-6-aryl- and 3-halo-6-heteroarylpyridazines, which are regarded as suitable precursors to original dissymmetrical pyridazines by a chemoselective monosubstitution of one halogen atom (see Scheme 2).



Scheme 2. Cross-coupling reaction of 3,6-dihalopyridazines and triaryl- or triheteroarylbismuth compounds.

Results and Discussion

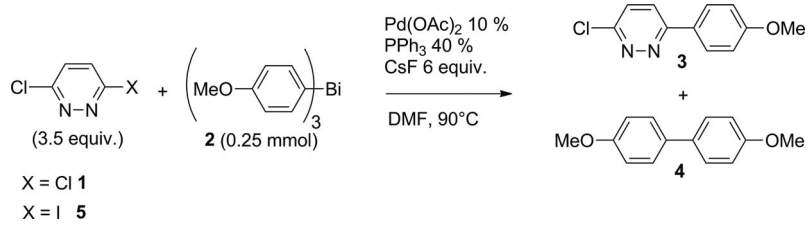
To reach our goal, we first studied the cross-coupling reaction of commercially available 3,6-dichloropyridazine (**1**) with tri-*p*-anisylbismuth (**2**), according to the standard reaction conditions described by Rao et al.[16,17] (see Scheme 3). As previously noted, the three aryl groups on the bismuth are transferable during the cross-coupling reaction with the aryl halide.[17] Thus, a slight excess amount of **1** (3.5 equiv.) versus **2** was used, and the reaction was carried out under argon in DMF (dimethylformamide) at 90 °C, in the presence of 10 mol-% $Pd(OAc)_2$ as the catalyst precursor, PPh_3 (40 mol-%) as the ligand, and an excess amount of CsF (6 equiv.).

Under these conditions, the reaction of **1** with **2** afforded the targeted monoarylated compound **3** in only a moderate isolated yield (43%) along with 4,4′-dimethoxy-1,1′-biphenyl (**4**, 17% by GC). Side product **4** was formed by the conversion, mediated by Pd catalysis, of tri-*p*-anisylbismuth (**2**) into the corresponding dimeric aryl product.[19,20] The reaction could be considered as chemoselective, as the formation of 3,6-bis(4-methoxyphenyl)pyridazine, the disubstituted product, was not observed. Moreover, when the reaction was conducted with an excess amount of **2** (4 equiv.) versus **1**, the formation of 3,6-bis(4-methoxyphenyl)pyridazine was never detected, even by GC analyses. No improvement in the yield was observed by the addition of NaI (1 equiv.).

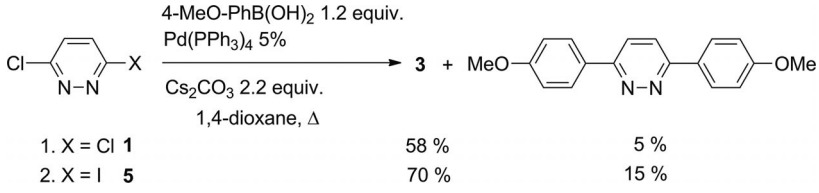
Finally, the replacement of **1** by 3-chloro-6-iodopyridazine (**5**) allowed the formation of the desired compound **3** in 81% isolated yield, and only trace amounts of **4** were detected. Cross-coupling reactions of *p*-anisylboronic acid with **1** and with **5** mediated by palladium catalysis were also performed to compare the reactivity of each of these organometallic reagents and the chemoselectivity (see Scheme 4).

Again, a better result was obtained, when the halide X was I rather than Cl. In the two runs, under Suzuki reaction conditions, a mixture of **3** and diarylated compound 3,6-bis(4-methoxyphenyl)pyridazine was observed (see Scheme 4, Run 2, 15% yield). However, under different reaction conditions, Lin and co-workers[7a] reported that a Suzuki cross-coupling reaction assisted by microwaves gave monoarylated product **3** in 73% isolated yield, starting from *p*-anisylboronic acid and **1**. In some cases, the diarylated compound was also observed.

Then, we examined the change of some parameters, such as the amounts of Pd catalyst, CsF, and PPh_3, in the model reaction involving compounds **5** and **2** (see Scheme 3, X = I; Table 1). Although it was predictable that the reaction



Scheme 3. Preliminary study of the cross-coupling reaction.



Scheme 4. Reaction of 3,6-dihalopyridazine with *p*-anisylboronic acid.

did not occur in the absence of the Pd catalyst (see Table 1, Entry 2), the quantity of the catalyst could be significantly reduced to 3 mol-% (see Table 1, Entry 3), without altering either the reaction time (2 h) or the yield (81%).

Table 1. Optimization of the cross-coupling reaction.

Entry[a]	$Pd(OAc)_2$ [mol-%]	PPh_3 [mol-%]	CsF [equiv.]	Reaction time [h]	Isolated yield [%]
1	10	40	6	2	81
2	0	0	6	24	0
3	3	12	6	2	81
4	3	12	0	3.5	82
5	1	4	0	24	72
6	3	0	6	3	50
7	3	0	0	24	55

[a] Reagents and conditions: Ar_3Bi (0.25 mmol) and 3-chloro-6-iodopyridazine (0.87 mmol) at 90 °C in DMF (3 mL).

Various activators such as K_3PO_4, Cs_2CO_3, or CsF[15] are usually required as a base to promote reactions involving triarylbismuths. Surprisingly, in the absence of CsF, the reaction proceeded slower, but still efficiently. The reaction was completed after only 3.5 h, upon using 3 mol-% $Pd(OAc)_2$ (see Table 1, Entry 4), and the time increased to 24 h when using a lower 1 mol-% $Pd(OAc)_2$ (see Table 1, Entry 5). Intriguingly, we also observed that the reaction could be carried out free of PPh_3 (see Table 1, Entry 6), despite a decreasing yield, and also free of both PPh_3 and CsF (see Table 1, Entry 7, reaction time 24 h). In the last two experiments, product **3** was obtained in 50–55% isolated yields, along with an increasing formation of **4**. On the basis of the above results, the mechanism, depicted in Scheme 5, is designed to account for Pd catalysis, even in the absence of PPh_3. The catalytic reaction is likely initiated by a transmetallation reaction (see Scheme 5, Step 1) between $Pd(OAc)_2$ and triarylbismuth, yielding a ArPdAr species as evidenced by Pd^{II} complexes.[21]

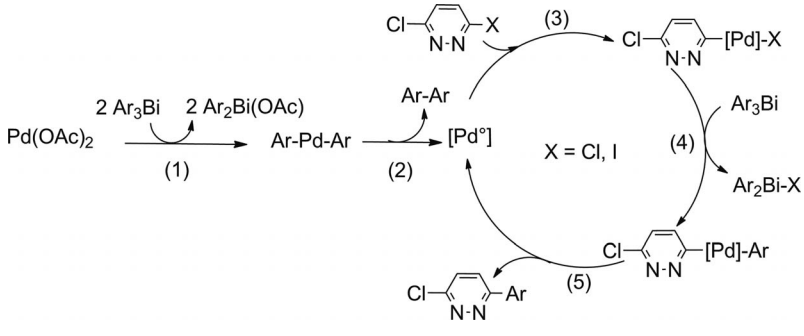
This intermediate undergoes a reductive elimination (see Scheme 5, Step 2), leading to biaryl formation and Pd^0 that is likely coordinated to the pyridazinyl moieties. After an oxidative addition of 3,6-dihalopyridazine (see Scheme 5, Step 3), a subsequent transmetallation with triarylbismuth takes place (see Scheme 5, Step 4), followed by a reductive elimination of Pd^0 (see Scheme 5, Step 5), as previously reported in the literature.[21,22] It is obvious that the presence of a base, such as CsF, in the process accelerates the rate of the cross-coupling reaction, probably by acting on the aryl group transfer from the bismuth to Pd^{II} or by promoting the reductive elimination step, as it has been established in palladium-catalyzed Suzuki–Miyaura reaction.[23]

We further investigated the cross-coupling reaction of 3-chloro-6-iodopyridazine (**5**) with several triarylbismuths, prepared by our optimized procedure,[14] to examine the scope and limits of the process. All of the reactions were first conducted at 90 °C in DMF with 3 mol-% $Pd(OAc)_2$ and 12 mol-% PPh_3, but without CsF.

The results are reported in Table 2. As expected, the cross-coupling reaction occurred efficiently with almost all of the triarylbismuth compounds, as moderate to high yields of the corresponding monoarylated compounds were obtained.

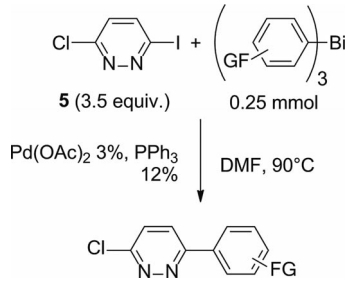
The nature and position of the functional groups seem to have a strong influence on the course of the reaction. In most cases, better yields were obtained with triphenylbismuth and the triarylbismuths bearing electron-donating groups in the *meta* or *para* position of the aromatic moiety (see Table 2, Entries 3, 4, 7, and 8) in comparison to those bearing electron-withdrawing groups. In addition, the yield for the cross-coupling reaction was lower when the electron-donating groups were in the *ortho* position compared to the *para* position of the triarylbismuth reagent, in accordance with steric hindrance effects (see Table 2, Entries 2–8). However, surprisingly, no reaction occurred when an *ortho*-methyl or -ethyl group was positioned on the aryl moiety, even in the presence of CsF (6 equiv.; see Table 2, Entries 5 and 6). The bismuth reagent and **5** were recovered, along with some trace amounts of 6,6′-dichloro-3,3′-bipyridazine, detected by GC analyses.

In the presence of electron-withdrawing groups, such as CO_2CH_3, CN, $COCH_3$, or CF_3, the chemoselective C–C couplings performed in only moderate yields that did not exceed 47% (see Table 2, Entries 9–16). However, for an unknown reason, the cross-coupling reaction efficiently occurred with F as a substituent (see Table 2, Entry 17). Amazingly, the formation of the biaryl homocoupling side product, from the bismuth reagent, was only observed when the aryl group was substituted in the *ortho* position by a $COCH_3$ group (see Table 2, Entry 12), and the cross-cou-



Scheme 5. Proposed mechanism for the cross-coupling reaction without PPh_3.

Table 2. Synthesis of 6-aryl-substituted 3-chloropyridazines.



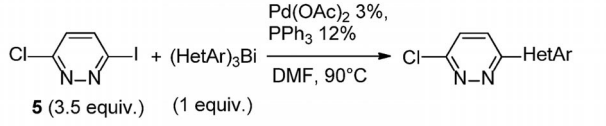
Entry[a]	FG	Product	Isolated yield [%]
1	–	**6**	90
2	2-OMe	**7**	43
3	3-OMe	**8**	67
4	4-OMe	**3**	82
5	2-Et	**9**	0 (0)[b]
6	2-Me	**10**	0 (0)[b]
7	3-Me	**11**	79
8	4-Me	**12**	86
9	2-CO_2Me	**13**	47
10	3-CO_2Me	**14**	39 (59)[b]
11	4-CO_2Me	**15**	30 (58)[b]
12	2-$COCH_3$	**16**	0 (0)[b]
13	3-$COCH_3$	**17**	32 (53)[b]
14	4-$COCH_3$	**18**	34 (55)[b]
15	4-CN	**19**	25 (37)[b]
16	4-CF_3	**20**	45 (54)[b] (50)[c] (53)[d]
17	4-F	**21**	80

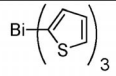
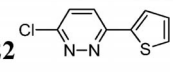
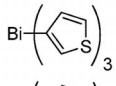
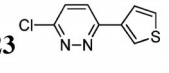
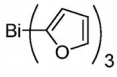
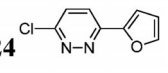
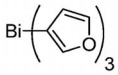
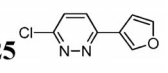
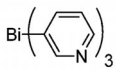
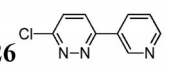
[a] Reagents and conditions. $(FGAr)_3Bi$ (0.25 mmol, FG = functional group), **5** (3.5 equiv.), solvent is DMF (3 mL), temperature = 90 °C, $Pd(OAc)_2$ (3%), PPh_3 (12%), no base added. [b] Reaction performed with CsF (6 equiv.). [c] Reaction performed with Cs_2CO_3 (6 equiv.). [d] Reaction performed with K_2CO_3 (6 equiv.).

pling reaction proceeded conveniently with CO_2CH_3 functional group (see Table 1, Entry 9). The transmetallation step (see Scheme 5, Step 4) may be sensitive to the presence of an electron-withdrawing group located on the aryl moiety, as observed in most of the tested reagents (see Table 2, Entries 10–11 and 13–16). The addition of CsF (6 equiv.) substantially enhanced the yields of the reactions and could be replaced by Cs_2CO_3 or K_2CO_3, without a significant effect on the course of the cross-coupling process, as illustrated in the reaction involving tris[4-(trifluoromethyl)-phenyl]bismuth (see Table 2, Entry 16).

Until now, only tris(2-thienyl)bismuth[17b,24] has been involved in a cross-coupling reaction with organic halides. Given the success of this simple method, we then extended the scope of the cross-coupling reaction to triheteroarylbismuth compounds, prepared by following our procedure,[14] and 3-chloro-6-iodopyridazine (**5**, see Table 3). The C–C coupling reactions were carried out under the same reaction conditions as previously used in Table 2. The yields in the monosubstituted pyridazine formation were approximately from 25 to 64%. In all of the tested reactions involving triheteroarylbismuth compounds, a striking and beneficial effect from the addition of CsF was observed (see Table 3, Entries 1–5), which led to a significant increase in the yields of the cross-coupling process (yields 60 to 99%). The yields seem to strongly depend on the position of the bismuth atom with respect to the five-membered heteroaromatic groups (see Table 3, Entries 1–4). Better results were obtained with 3-heteroarylbismuth compounds in comparison to the 2-substituted reagents (see Table 3, Entries 1–4). Likewise, the coupling of tris(3-pyridyl)bismuth was efficient, and the corresponding pyridazine **26** was formed in 48% yield (see Table 3, Entry 5).

Table 3. Synthesis of 6-heteroaryl-substituted 3-chloropyridazines.



Entry[a]	$Bi(HetAr)_3$	Product	Isolated yield (%)
1		**22** 	25 (99)[b]
2		**23** 	64 (90)[b]
3		**24** 	38 (74)[b]
4		**25** 	40 (96)[b]
5		**26** 	48 (60)[b]

[a] Reagents and conditions: $(HetAr)_3Bi$ (0.25 mmol), **5** (3.5 equiv.), solvent is DMF (3 mL), T = 90 °C; $Pd(OAc)_2$ (3%), PPh_3 (12%), no base added. [b] Reaction performed with CsF (6 equiv.).

Conclusions

We have disclosed an efficient, practical, and chemoselective method to prepare aryl- and heteroarylpyridazinyl chlorides that are versatile synthetic intermediates for the production of a number of dissymmetrical derivatives. This method relies on the peculiar reactivity of the dihalopyridazines versus triarylbismuths under Pd catalysis, allowing a delicate chemoselective cross-coupling reaction. The best results were obtained starting from the 3-chloro-6-iodopyridazine (**5**). As predicted,[15] the three aryl groups of the organobismuth reagents were transferable. The addition of a base, such as CsF, K_2CO_3, or Cs_2CO_3 was beneficial in the cross-coupling of aryl halides and triarylbismuth compounds,[15] but was less important in the reaction involving pyridazinyl halides. However, their influence was mainly evidenced in the reactions involving triarylbismuth reagents bearing electron-withdrawing group on the transferable aryl moiety, less studied until today, and heteroarylbismuth compounds.

Experimental Section

General Methods: All of the reactions were carried out under argon. All reagents and solvents were purchased from commercial suppliers and used without further purification. Column chromatography was performed with 35–70 mesh silica gel. Melting points were determined with a Büchi B545 capillary melting point apparatus. The ^{1}H, ^{13}C, and ^{19}F NMR spectroscopic data were recorded with a Bruker Avance II 400 NMR spectrometer, using irradiation frequencies of 400, 100, and 376 MHz, respectively. The chemical shifts for the ^{1}H, ^{13}C, and ^{19}F NMR spectra (δ) are given in part per million (ppm) and referenced internally according to the residual solvent resonances. Coupling constants were given in Hertz (Hz), and the abbreviations used are s (singlet), d (doublet), t (triplet), m (multiplet), dd (double doublet), and dt (double triplet). Infrared spectra were recorded with a FTIR Bruker Tensor 27 in ATR (attenuated total reflectance) mode between 5000 and 400 cm^{-1} with a diamond window. Mass spectra were measured with a GC–MS apparatus in EI mode [Chromatograph Trace Series 200, equipped with a capillary column CPSIL 5 CB/MS (l = 25 m, I.D. = 0.25 mm, 0.12 μm)], coupled with a GCQ ThermoFisher Scientific mass spectrometer. High resolution mass spectrometry (HRMS in ESI mode) was performed using the mass spectrometry service of the ICSN (Institut de Chimie et des Substances Naturelles), Gif sur Yvette, France. Compounds that have been previously described in the literature are linked to their corresponding bibliographic references, whereas compounds labeled by an asterisk (*) are, to the best of our knowledge, new compounds.

General Procedure for the Cross-Coupling Reaction between Triaryl- or Triheteroarylbismuth and 3-Chloro-6-iodopyridazine: A Schlenk tube containing anhydrous DMF (3 mL) was degassed with argon for 15 min, and then 3-chloro-6-iodopyridazine **5** (0.87 mmol, 3.5 equiv.), triaryl- or triheteroarylbismuth (0.25 mmol, 1.0 equiv.), palladium(II) acetate (7.5 μmol, 0.03 equiv.), and triphenylphosphane (0.03 mmol, 0.12 equiv.) were sequentially added. The mixture was stirred at 90 °C, until there was total consumption of the corresponding triaryl- or triheteroarylbismuth compound. After cooling to room temperature, the mixture was diluted with EtOAc (5 mL), and the resulting solution was washed with a saturated solution of NaCl (10 mL) and filtered through a pad of Celite, which was then rinsed with EtOAc (10 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), dried with Na_2SO_4, and filtered, and then the solvents were evaporated under vacuum. The crude product was purified by flash chromatography on silica gel, eluting with the appropriate solvents.

3-Chloro-6-phenylpyridazine[9] **(6):** After flash chromatography on silica gel (pentane/EtOAc, 90:10), compound **6** (129 mg, 90% yield) was obtained as a colorless solid, m.p. 145 °C; ref.[9] m.p. 160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.04 (m, 2 H), 7.84 (d, J = 9.0 Hz, 1 H), 7.57 (d, J = 9.0 Hz, 1 H), 7.55–7.50 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 155.8, 135.3, 130.7, 129.4, 128.7, 127.3, 126.4 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3047, 1989, 1600, 1570, 1532, 1495, 1447, 1394, 1309, 1259, 1188, 1163, 1143, 1088, 1031, 1007, 919, 854, 777, 740, 688, 564 cm^{-1}. MS (EI): m/z (%) = 192 (31), 191 (12), 190 (90), 164 (13), 163 (5), 162 (37), 103 (10), 102 (100), 126 (7), 127 (19), 76 (13), 75 (6), 74 (8), 51 (7).

3-Chloro-6-(2-methoxyphenyl)pyridazine[7a] **(7):** After flash chromatography on silica gel (pentane/EtOAc, 90:10), compound **7** (70 mg, 43% yield) was obtained as a colorless solid; m.p. 122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 9.0 Hz, 1 H), 7.94 (dd, J = 1.5 and 7.6 Hz, 1 H), 7.49–7.44 (m, 2 H), 7.12 (t, J = 7.6 Hz, 1 H), 7.02 (d, J = 9.0 Hz, 1 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 157.3, 155.1, 131.8, 131.3, 130.9, 127.3, 124.7, 121.5, 111.5, 55.8 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3079, 2919, 1597, 1567, 1531, 1491, 1460, 1437, 1403, 1298, 1263, 1245, 1181, 1151, 1124, 1089, 1050, 1026, 1000, 874, 855, 836, 784, 751, 692, 572 cm^{-1}. MS (EI): m/z (%) = 221 (5), 219 (16), 202 (6), 191 (5), 186 (13), 185 (100), 184 (6), 168 (5), 167 (16), 157 (21), 140 (5), 131 (14), 127 (5), 130 (9), 115 (8), 107 (5), 103 (7), 102 (17), 63 (9).

3-Chloro-6-(3-methoxyphenyl)pyridazine[25] **(8):** After flash chromatography on silica gel (pentane/EtOAc, 90:10), compound **8** (111 mg, 67% yield) was obtained as a colorless solid; m.p. 95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 9.0 Hz, 1 H), 7.68 (t, J = 2.0 Hz, 1 H), 7.57–7.52 (m, 2 H), 7.42 (t, J = 7.9 Hz, 1 H), 7.06 (dd, J = 7.9 and 2.0 Hz, 1 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 158.6, 155.9, 136.6, 130.3, 128.7, 126.5, 119.5, 116.9, 112.3, 55.7 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 2916, 2836, 1607, 1584, 1566, 1537, 1490, 1450, 1434, 1398, 1322, 1268, 1208, 1178, 1151, 1090, 1044, 1015, 900, 885, 836, 785, 761, 689, 666, 565 cm^{-1}. MS (EI): m/z (%) = 222 (19), 221 (39), 220 (58), 219 (100), 207 (9), 192 (7), 191 (17), 190 (20), 132 (8), 103 (6), 102 (21), 63 (9).

3-Chloro-6-(4-methoxyphenyl)pyridazine[7a] **(3):** After flash chromatography on silica gel (pentane/EtOAc, 90:10), compound **3** (135 mg, 82% yield) was obtained as a colorless solid, m.p. 160 °C; ref.[7a] m.p. 161–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 6.9 Hz, 2 H), 7.77 (d, J = 9.0 Hz, 1 H), 7.50 (d, J = 9.0 Hz, 1 H), 7.02 (d, J = 6.9 Hz, 2 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 158.3, 155.0, 128.7, 128.6, 127.6, 125.7, 114.7, 55.6 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3050, 3015, 2962, 2837, 1606, 1581, 1535, 1509, 1454, 1398, 1298, 1256, 1181, 1165, 1150, 1109, 1089, 1026, 1014, 1000, 858, 839, 820, 761, 635, 612, 565 cm^{-1}. MS (EI): m/z (%) = 222 (31), 221 (13), 220 (91), 194 (24), 193 (9), 192 (70), 149 (12), 133 (10), 132 (100), 117 (9), 89 (10), 63 (8).

3-Chloro-6-(3-methylphenyl)pyridazine[26] **(11):** After flash chromatography on silica gel (pentane/EtOAc, 90:10), compound **11** (120 mg, 79% yield) was obtained as a colorless solid; m.p. 87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1 H), 7.82 (d, J = 9.0 Hz, 1 H), 7.80 (d, J = 7.7 Hz, 1 H), 7.55 (d, J = 9.0 Hz, 1 H), 7.41 (t, J = 7.7 Hz, 1 H), 7.33 (d, J = 7.7 Hz, 1 H), 2.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 155.7, 139.2, 135.2, 131.5, 129.3, 128.7, 128.0, 126.5, 124.4, 21.7 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3084, 3039, 2918, 1950, 1607, 1592, 1567, 1535, 1492, 1402, 1376, 1317, 1262, 1192, 1144, 1094, 1038, 917, 887, 858, 835, 784, 761, 692, 671, 620 cm^{-1}. MS (EI): m/z (%) = 206 (31), 205 (12), 204 (100), 178 (12), 176 (36), 141 (25), 116 (69), 115 (91).

3-Chloro-6-(4-methylphenyl)pyridazine[27] **(12):** After flash chromatography on silica gel (pentane/EtOAc, 90:10), compound **12** (132 mg, 86% yield) was obtained as a colorless solid, m.p. 144 °C; ref.[27] m.p. 151–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.2 Hz, 2 H), 7.80 (d, J = 9.0 Hz, 1 H), 7.53 (d, J = 9.0 Hz, 1 H), 7.33 (d, J = 8.2 Hz, 2 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 155.5, 141.0, 132.5, 130.1, 128.6, 127.2, 126.1, 21.6 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 2917, 1610, 1571, 1508, 1429, 1396, 1311, 1260, 1192, 1159, 1148, 1087, 1022, 1005, 856, 813, 757, 709, 632, 611, 560 cm^{-1}. MS (EI): m/z (%) = 206 (31), 205 (13), 204 (95), 178 (13), 177 (5), 176 (38), 141 (16), 139 (6), 117 (8), 116 (82), 115 (100), 89 (13), 63 (5).

3-Chloro-6-[2-(methoxycarbonyl)phenyl]pyridazine* (13): After flash chromatography on silica gel (pentane/EtOAc, 70:30), compound **13** (88 mg, 47% yield) was obtained as a colorless solid; m.p. 178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, J = 7.8 and

1.0 Hz, 1 H), 7.62 (dt, *J* = 7.8 and 1.0 Hz, 1 H), 7.58–7.53 (m, 4 H), 3.74 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 161.0, 155.9, 137.7, 132.3, 130.8, 130.7, 130.5, 129.8, 129.6, 127.6, 52.5 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3036, 2961, 1722, 1605, 1565, 1533, 1433, 1407, 1328, 1305, 1284, 1239, 1177, 1149, 1111, 1090, 1034, 1026, 1000, 961, 925, 851, 816, 786, 770, 738, 712, 683, 660, 572, 559 cm^{-1}. MS (EI): *m*/*z* (%) = 248 (17), 235 (15), 233 (45), 219 (36), 218 (20), 217 (100), 192 (15), 190 (43), 189 (12), 186 (23), 185 (99), 183 (26), 170 (18), 162 (12), 153 (18), 128 (13), 127 (13), 126 (22), 102 (15). HRMS (ESI): calcd. for $C_{12}H_{10}ClN_2O_2$ $[M + H]^+$ 249.0431; found 249.0440.

3-Chloro-6-[3-(methoxycarbonyl)phenyl]pyridazine* (14): After flash chromatography on silica gel (pentane/EtOAc, 70:30), compound **14** (109 mg, 59% yield) was obtained as a colorless solid; m.p. 140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (s, 1 H), 8.34 (dd, *J* = 7.8 and 1.0 Hz, 1 H), 8.17 (d, *J* = 7.8 Hz, 1 H), 7.91 (d, *J* = 8.9 Hz, 1 H), 7.63 (t, *J* = 7.8 Hz, 1 H), 7.61 (d, *J* = 8.9 Hz, 1 H), 3.96 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 157.9, 156.2, 135.6, 131.7, 131.6, 131.3, 129.6, 128.9, 128.2, 126.4, 52.6 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3036, 2961, 1722, 1605, 1565, 1533, 1433, 1407, 1328, 1305, 1284, 1239, 1177, 1149, 1111, 1090, 1034, 1026, 1000, 961, 925, 851, 816, 786, 770, 738, 712, 683, 660, 572 cm^{-1}. MS (EI): *m*/*z* (%) = 250 (10), 248 (39), 217 (21), 192 (36), 191 (18), 190 (100), 189 (20), 129 (30), 101 (13), 75 (12). HRMS (ESI): calcd. for $C_{12}H_{10}ClN_2O_2$ $[M + H]^+$ 249.0431; found 249.0432.

3-Chloro-6-[4-(methoxycarbonyl)phenyl]pyridazine* (15): After flash chromatography on silica gel (pentane/EtOAc, 70:30), compound **15** (108 mg, 58% yield) was obtained as a colorless solid; m.p. 206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.5 Hz, 2 H), 8.12 (d, *J* = 8.5 Hz, 2 H), 7.88 (d, *J* = 9.0 Hz, 1 H), 7.61 (d, *J* = 9.0 Hz, 1 H), 3.96 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 157.8, 156.4, 139.3, 132.0, 130.5, 128.8, 127.3, 126.6, 52.6 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 2962, 1725, 1610, 1577, 1530, 1430, 1414, 1397, 1296, 1278, 1195, 1152, 1113, 1021, 1006, 957, 877, 837, 776, 748, 731, 694, 611, 559 cm^{-1}. MS (EI): *m*/*z* (%) = 250 (31), 249 (13), 248 (93), 220 (17), 217 (100), 189 (21), 160 (13), 129 (28), 126 (11), 75 (11). HRMS (ESI): calcd. for $C_{12}H_{10}ClN_2O_2$ $[M + H]^+$ 249.0431; found 249.0429.

6-(3-Acetylphenyl)-3-chloropyridazine* (17): After flash chromatography on silica gel (pentane/EtOAc, 50:50), compound **17** (93 mg, 53% yield) was obtained as a colorless solid; m.p. 133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (s, 1 H), 8.32 (d, *J* = 7.7 Hz, 1 H), 8.11 (d, *J* = 7.7 Hz, 1 H), 7.92 (d, *J* = 9.0 Hz, 1 H), 7.66 (t, *J* = 7.7 Hz, 1 H), 7.62 (d, *J* = 9.0 Hz, 1 H), 2.69 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7, 157.9, 156.3, 138.1, 135.9, 131.7, 130.4, 129.8, 128.9, 127.0, 126.4, 27.0 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3056, 2925, 1680, 1601, 1568, 1535, 1436, 1403, 1356, 1300, 1272, 1225, 1193, 1172, 1153, 1098, 1038, 1021, 963, 927, 904, 852, 839, 815, 793, 747, 678, 666, 630, 589 cm^{-1}. MS (EI): *m*/*z* (%) = 234 (25), 233 (9), 232 (74), 219 (33), 218 (15), 217 (100), 204 (17), 191 (17), 190 (11), 189 (50), 129 (8), 127 (8), 126 (6), 101 (7), 75 (7). HRMS (ESI): calcd. for $C_{12}H_{10}ClN_2O$ $[M + H]^+$ 233.0482; found 233.0477.

6-(4-Acetylphenyl)-3-chloropyridazine (18):* After flash chromatography on silica gel (pentane/EtOAc, 70:30), compound **18** (96 mg, 55% yield) was obtained as a colorless solid; m.p. 205 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.7 Hz, 2 H), 8.11 (d, *J* = 8.7 Hz, 2 H), 7.89 (d, *J* = 8.9 Hz, 1 H), 7.63 (d, *J* = 8.9 Hz, 1 H), 2.67 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7, 157.8, 156.4, 139.4, 138.5, 129.3, 128.9, 127.5, 126.6, 27.0 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3060, 1672, 1606, 1572, 1531, 1413, 1394, 1358, 1312, 1274, 1261, 1164, 1118, 1093, 1017, 1004, 962, 862, 831, 798, 763, 739, 644, 630, 613, 598 cm^{-1}. MS (EI): *m*/*z* (%) = 234 (11), 232 (27), 219 (34), 218 (12), 217 (100), 191 (10), 189 (28), 129 (5), 127 (6), 126 (6), 75 (7). HRMS (ESI): calcd. for $C_{12}H_{10}ClN_2O$ $[M + H]^+$ 233.0482; found 233.0493.

3-Chloro-6-(4-cyanophenyl)pyridazine[28] (19): After flash chromatography on silica gel (pentane/EtOAc, 70:30), compound **19** (60 mg, 37% yield) was obtained as a colorless solid; m.p. 240 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.3 Hz, 2 H), 7.88 (d, *J* = 9.0 Hz, 1 H), 7.84 (d, *J* = 8.3 Hz, 2 H), 7.65 (d, *J* = 9.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 156.8, 139.5, 133.1, 129.0, 127.9, 126.4, 118.4, 114.5 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3746, 3040, 2921, 2852, 2224, 1730, 1566, 1531, 1460, 1404, 1365, 1261, 1193, 1151, 1091, 1018, 856, 828, 796, 785, 763, 749, 691, 653, 564 cm^{-1}. MS (EI): *m*/*z* (%) = 217 (28), 216 (13), 215 (89), 189 (13), 188 (6), 187 (45), 152 (13), 128 (10), 127 (100), 125 (5), 100 (9), 75 (9), 74 (15).

3-Chloro-6-[4-(trifluoromethyl)phenyl]pyridazine[29] (20): After flash chromatography on silica gel (pentane/EtOAc, 70:30), compound **20** (105 mg, 54% yield) was obtained as a colorless solid; m.p. 181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.2 Hz, 1 H), 7.88 (d, *J* = 9.0 Hz, 2 H), 7.80 (d, *J* = 8.2 Hz, 2 H), 7.63 (d, *J* = 9.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 156.6, 138.6, 137.9, 132.7, 128.9, 127.7 (q, *J* = 32 Hz), 126.5 (q, *J* = 272 Hz), 126.3 (q, *J* = 4 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.7 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3037, 1615, 1536, 1417, 1402, 1323, 1260, 1161, 1108, 1067, 1016, 1005, 835, 798, 763, 739, 687, 600 cm^{-1}. MS (EI): *m*/*z* (%) = 261 (5), 260 (34), 259 (13), 258 (100), 239 (7), 232 (19), 231 (6), 230 (52), 195 (11), 180 (5), 175 (6), 171 (9), 170 (92), 169 (19), 151 (12), 120 (14), 75 (6).

3-Chloro-6-(4-fluorophenyl)pyridazine[25] (21): After flash chromatography on silica gel (pentane/EtOAc, 80:20), compound **21** (125 mg, 80% yield) was obtained as a colorless solid; m.p. 157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.02 (m, 2 H), 7.80 (d, *J* = 9.0 Hz, 1 H), 7.57 (d, *J* = 9.0 Hz, 1 H), 7.24–7.18 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5 (d, *J* = 251 Hz), 157.8, 155.8, 131.4 (q, *J* = 3 Hz), 129.3, 128.8, 126.1, 116.5 (d, *J* = 22 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –110.1 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3054, 1600, 1568, 1504, 1417, 1395, 1302, 1287, 1239, 1164, 1150, 1090, 1015, 863, 832, 764, 613, 560 cm^{-1}. MS (EI): *m*/*z* (%) = 210 (30), 209 (12), 208 (95), 182 (22), 181 (7), 180 (63), 145 (11), 121 (9), 120 (100), 100 (6), 75 (10), 74 (14).

3-Chloro-6-(2-thienyl)pyridazine[9] (22): After flash chromatography on silica gel (pentane/EtOAc, 70:30), compound **22** (146 mg, 99% yield) was obtained as a colorless solid, m.p. 151 °C; ref.[9] m.p. 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 9.0 Hz, 1 H), 7.66 (dd, *J* = 3.7 and 1.1 Hz, 1 H), 7.52 (dd, *J* = 5.0 and 1.1 Hz, 1 H), 7.49 (d, *J* = 9.0 Hz, 1 H), 7.17 (dd, *J* = 5.0 and 3.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 154.5, 139.5, 130.2, 128.6, 128.5, 127.2, 124.7 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3059, 1568, 1535, 1433, 1399, 1356, 1327, 1267, 1156, 1074, 1057, 963, 853, 835, 763, 710, 586 cm^{-1}. MS (EI): *m*/*z* (%) = 198 (35), 197 (11), 196 (100), 170 (11), 168 (33), 133 (22), 109 (8), 108 (86), 89 (8), 82 (11), 74 (7), 69 (10), 63 (8), 58 (8).

3-Chloro-6-(3-thienyl)pyridazine[26] (23): After flash chromatography on silica gel (pentane/EtOAc, 70:30), compound **23** (133 mg, 90% yield) was obtained as a colorless solid; m.p. 159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (dd, *J* = 3.0 and 1.3 Hz, 1 H), 7.75 (dd, *J* = 5.1 and 1.3 Hz, 1 H), 7.72 (d, *J* = 8.9 Hz, 1 H), 7.51 (d, *J* = 8.9 Hz, 1 H), 7.46 (dd, *J* = 5.1 and 3.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 154.9, 137.6, 128.7, 127.5, 126.2, 126.1, 125.8 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3077, 3041, 1572,

1532, 1430, 1388, 1299, 1255, 1215, 1153, 1097, 1026, 894, 860, 849, 806, 783, 747, 703, 633 cm^{-1}. MS (EI): *m*/*z* (%) = 199 (35), 198 (11), 197 (100), 171 (11), 169 (29), 133 (16), 108 (60).

3-Chloro-6-(2-furyl)pyridazine* (24): After flash chromatography on silica gel (pentane/EtOAc, 70:30), compound **24** (100 mg, 74% yield) was obtained as a colorless solid; m.p. 102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 9.0 Hz, 1 H), 7.62 (d, J = 1.8 Hz, 1 H), 7.51 (d, J = 9.0 Hz, 1 H), 7.36 (d, J = 3.4 Hz, 1 H), 6.60 (dd, J = 3.4 and 1.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 151.6, 150.0, 145.1, 128.5, 124.2, 113.0, 111.4 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3114, 3076, 2923, 2853, 2360, 1600, 1565, 1525, 1479, 1412, 1376, 1286, 1218, 1162, 1142, 1106, 1068, 1036, 1001, 904, 883, 835, 762, 661, 596 cm^{-1}. MS (EI): *m*/*z* (%) = 182 (32), 181 (10), 180 (100), 154 (11), 152 (36), 93 (5), 92 (61), 89 (13), 64 (17), 63 (32), 62 (8). HRMS (ESI): calcd. for $C_8H_6N_2OCl$ $[M + H]^+$ 181.0169; found 181.0172.

3-Chloro-6-(3-furyl)pyridazine* (25): After flash chromatography on silica gel (pentane/EtOAc, 70:30), compound **25** (130 mg, 96% yield) was obtained as a colorless solid; m.p. 169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 7.57 (m, 2 H), 7.49 (d, J = 9.0 Hz, 1 H), 7.01 (d, J = 1.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 153.7, 144.8, 142.5, 128.5, 125.8, 123.4, 108.6 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3132, 3094, 3040, 2922, 1985, 1703, 1616, 1592, 1567, 1535, 1509, 1413, 1392, 1326, 1261, 1154, 1114, 1070, 1045, 1010, 923, 875, 847, 819, 762, 735, 641, 590 cm^{-1}. MS (EI): *m*/*z* (%) = 182 (31), 181 (10), 180 (100), 154 (8), 152 (24), 92 (52), 89 (23), 64 (11), 63 (29), 62 (9). HRMS (ESI): calcd. for $C_8H_6N_2OCl$ $[M + H]^+$ 181.0169; found 181.0175.

3-Chloro-6-(3-pyridyl)pyridazine[7a] **(26):** After flash chromatography on silica gel (pentane/EtOAc, 50:50), compound **26** (86 mg, 60% yield) was obtained as a colorless solid; m.p. 155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20 (s, 1 H), 8.76 (dd, J = 7.7 and 1.7 Hz, 1 H), 8.45 (t, J = 7.7 Hz, 1 H), 7.89 (d, J = 9.0 Hz, 1 H), 7.64 (d, J = 9.0 Hz, 1 H), 7.49 (dd, J = 7.7 and 1.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 156.5, 151.7, 148.3, 134.8, 131.2, 129.0, 126.2, 124.2 ppm. ATR FTIR (neat): $\tilde{\nu}_{max}$ = 3044, 1590, 1566, 1534, 1481, 1431, 1394, 1359, 1320, 1265, 1193, 1173, 1152, 1121, 1101, 1048, 1023, 1001, 864, 808, 794, 757, 700, 638, 620, 572 cm^{-1}. MS (EI): *m*/*z* (%) = 192 (34), 191 (13), 190 (100), 164 (11), 163 (33), 128 (18), 104 (6), 103 (53), 101 (6), 76 (31), 75 (12), 74 (13), 51 (6), 50 (6).

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for all compounds are detailed.

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