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Selective Pd(II)-catalyzed Acylation of Pyrrole with Aldehydes. Application to the Synthesis of Celastramycin analogues and Tolmetin

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Abstract: The Pd(II)-catalyzed C-2 acylation of pyrrole with aldehydes in the presence of TBHP as oxidant has been studied for the synthesis of di(hetero)aryl ketones. The use of 2-pyrimidine as directing group leads to 2-acylpyrroles in moderate to good yields, although 2,5-diacylpyrroles are obtained as by products. This side-reaction could be avoided using 3-methy-2-pyridine as directing group, obtaining selectively 2-acylpyrroles. The reaction has been extended to a series of aromatic and heteroaromatic aldehydes, obtaining the best results with electron rich aromatic aldehydes. The methodology has been applied in the synthesis of pyrrolomycin alkaloid Celastramycin analogues and for an improved synthesis of Tolmetin, a nonsteroidal anti-inflammatory drug.

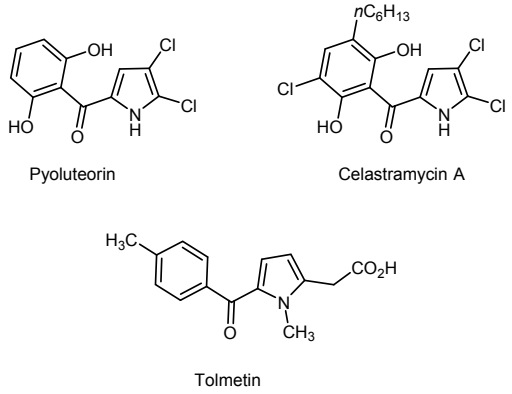
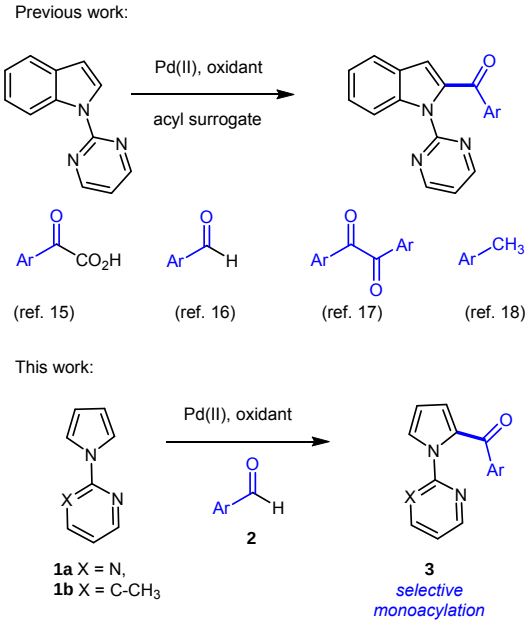


Figure 1. Selected alkaloids and pharmaceuticals with 2-aroylpyrrole framework.

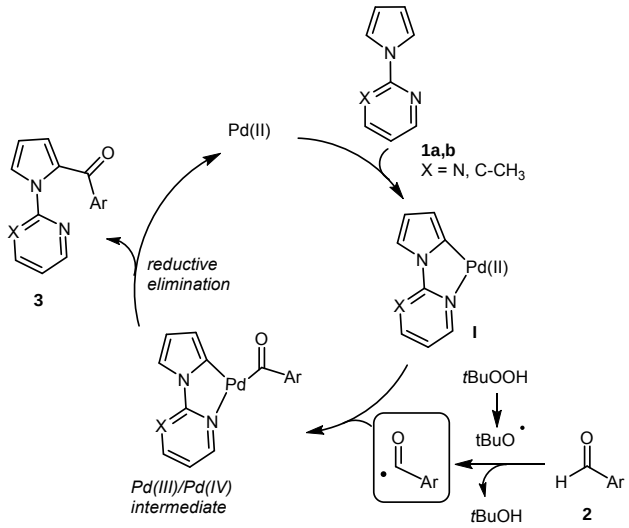
Introduction

Di(hetero)aryl ketones are important motifs present in natural products, pharmaceuticals or agrochemicals. In particular, various natural and synthetic molecules containing 2-aroylpyrrole cores have been extensively studied in the development of antibacterial, anti-fungal, and anticancer agents.[1] Pyrrolomycins[2] are a family of potent natural product antibiotics with nanomolar activity against Gram-positive and Gram-negative bacteria with the ability to target biofilms, which confers them a great potential for the development of new antimicrobial agents to face the antibiotic resistance problem.[3] For example, Pyoluteorin (Figure 1), a pyrrolomycin alkaloid isolated from several species of *Pseudomonas*, shows a broad bioprofile, demonstrating antibiotic, antifungal and herbicidal activity.[4] The alkaloid Celastramycin A (Figure 1) exhibits high activity against a series of multiresistant bacteria and mycobacteria and has also been identified as a potent innate immune suppressor.[5] Tolmetin (Figure 1) is a nonsteroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis, osteoarthrosis, pain, and ankylosing spondylitis.[6].
Therefore, the construction of 2-aroyl pyrroles has received considerable attention.[7] However, classical methodologies through Friedel-Crafts, Vilsmeier- Haack and Houben-Hoesch type acylations are frequently not regioselective, and require the use of stoichiometric quantities of Lewis or protic acids.[8] However, more environmentally friendly Friedel-Crafts acylation methods based on the use of solid catalysts have been applied only to acetylation of pyrrole.[9]

The development of efficient and catalytic methods to acylate pyrroles at C-2 is of significant value. For example, catalytic Friedel–Crafts acylation of heteroaromatics has been achieved using metal triflates as catalysts, though the procedure has been mainly applied to the synthesis of alkanoyl pyrroles.[10] More recently, an organocatalytic Friedel-Crafts acylation of pyrroles and indoles with acyl chlorides using 1,5-diazabicyclo[4.3.0]nonane (DBN) as a nucleophilic catalyst has been developed.[11] Transition-metal catalyzed acylation of (hetero)arenes via C-H bond activation is a good alternative to access di(hetero)aryl ketones,[12] but the method has been scarcely applied to pyrroles. A notable example is the palladium-catalyzed regioselective acylation of pyrroles with arylnitriles, which have proven successful even with N-H free pyrrole.[13]
In this context, the Pd(II)-catalyzed acylation of (hetero)arenes in the presence of an oxidant has recently emerged as catalytic alternative to classical acylation methods, reducing the production of toxic metal waste. Different directing groups and acyl sources are being studied for this purpose,[14] although further development is required to face mainly selectivity problems in order to be applied in the synthesis of more complex molecules. Examples reported in the literature involve Pd(II)-catalyzed acylation reactions of indole derivatives, where no selectivity problems arise. Thus, C-2 selective acylation of indoles has been described using 2–pyrimidine as a directing group on nitrogen and α-oxocarboxylic acids,[15] aldehydes,[16] α-diketones[17] and even toluene derivatives[18] as the acyl surrogates (Scheme 1).



Scheme 1.



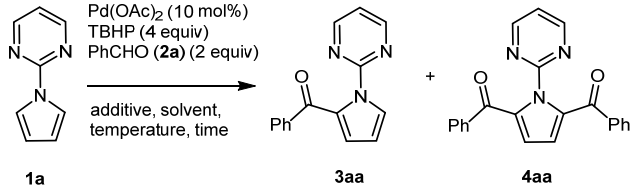
Scheme 2. Schematic mechanistic proposal

This acylation reaction has been only scarcely applied to pyrrole, and in this case the C2-acylated compound was obtained with a modest yield (41%), together with the corresponding 2,5-diacylated product in a significant amount (18%).[17] Diacylated products have also been obtained using 2-pyridine as directing group on pyrrole.[16a]The formation of diacylated products has been observed as a side reaction also in related systems, such as carbazoles.[19] Related protocols, as the ruthenium catalyzed carbonylative direct arylation of pyrroles using the 2-pyrimidine directing group have also been developed with high selectivity, although yields obtained with pyrrole were moderate to good, and generally lower than those obtained with indoles.[20] In this context, in connection with our previous work on Pd(II)-catalyzed C-H functionalization reactions,[21] we decided to study the palladium catalyzed acylation of pyrroles **1** for the regioselective formation of C-2 monoacylated pyrroles **3**. For this purpose, we selected first the 2-pyrimidine (**1a**, X = N) as directing group, which has been successfully used in these reactions with indole, but only one example has been reported with pyrrole.[17] Besides, we decided to study the 3-methyl-2-pyridine as directing group (**1b**, X = C-CH_3). We reasoned that, once the monoacylated compound **3b** is formed, the presence of the C-3 substituent on the directing group could result in a steric interaction with the acyl group in C-2 that may prevent the adoption of the required conformation to assist the second palladation, hampering the formation of diacylated products. Although the nature of all the intermediate species is not still clear, the generally accepted mechanism for this type of reactions involves the chelation assisted C-H activation to form a palladacycle **I**, that reacts with an acyl radical generated in the presence of an oxidant form the corresponding precursor (an aldehyde **2** in Scheme 2) to form an intermediate Pd(III) or Pd(IV) intermediate. Reductive elimination would give the acylated compound **3**, regenerating the active Pd(II) catalyst (Scheme 2). For this study, we decided to use aldehydes **2** as the acyl radical source, due to their wide availability and ease of generation in the presence of TBHP as oxidant.[14

Results and Discussion

We started testing reaction conditions related to those reported for the acylation of indoles with aldehydes,[16] using 2-pyrimidine as directing group[22] (**1a**), $Pd(OAc)_2$ as pre-catalyst in the presence of TBHP as oxidant. Using toluene as solvent at 90 ºC, the reaction took place obtaining ketone **3aa**, though in a moderate yield (53%), together with the diacylated product **4aa** (2%) (Table 1, entry 1). In the presence of acetic acid as additive, a similar yield was obtained (Table 1, entry 2), while the reactivity is almost completely lost when $Pd(CH_3CN)_2Cl_2$ was used a pre-catalysts (Table 1, entry 3). Lower conversions and isolated yields of **3aa** and were obtained when the solvent was changed to dioxane, THF or DCE (Table 1, entries 4-6), always isolating diketone **4aa** as the minor product, and recovering unreacted **1aa**. We next studied the effect of the acid additive, and we observed that the reactivity is almost completely shut down when stronger acids, such as *p*TsOH or TFA were used, recovering unreacted **1aa** (Table 1, entries 7-8). The effect of the acid additive has been shown to increase the reactivity by generating more electrophilic palladium species and, consequently, facilitating the C-H activation event. However, the acid may also have a detrimental effect by protonation of the substrate,[23] in accordance with the results obtained in the presence of strong acids. Thus, a significant increase of the reactivity was observed when less strongly acidic pivalic acid was used as an additive (Table 1, entries 9-14). The reaction was complete in only 3 hours at 90 ºC in the presence of 1 equiv. of pivalic acid, although it also led to a significant increase in the ratio of the formation of the diketone **4aa** (Table 1, entry 9). It was also necessary to use an excess of oxidant, as the use of less TBHP led to a loss of reactivity, with a low conversion after 24 h (Table 1, entry 10). Finally, the effect of amount of acid additive (0.5 or 0.75 equiv.) and the temperature (90 or 60 ºC) were studied (Table 1, entries 11-14), obtaining full conversion and a 71% isolated yield of **3aa** (Table 1, entry 13), although minor formation of **4aa** could not be avoided reducing the amount of benzaldehyde (**2a**) used (Table 1, entry 14).

Table 1. Acylation of **1a**. Optimization of reaction conditions

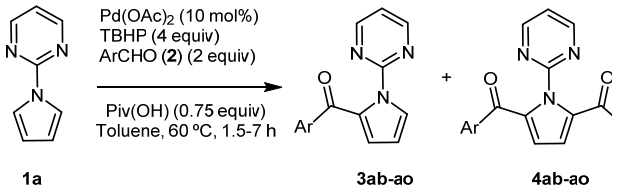


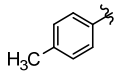
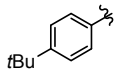
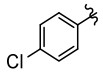
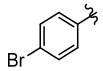
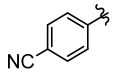
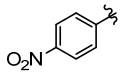
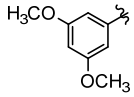
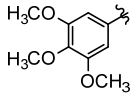
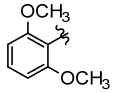
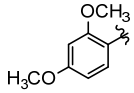
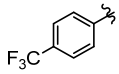
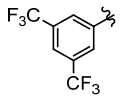
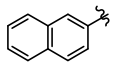
entry	Additive.	solvent	T [ºC]	t [h]	**3aa** [%][a]	**4aa** [%][a]
1	-	toluene	90	17	53[c]	2
2	AcOH[b]	toluene	90	24	51[c]	9
3[d]	AcOH[b]	toluene	90	24	9[c]	2
4	AcOH[b]	dioxane	90	17	41[c]	6
5	AcOH[b]	THF	60	24	34[c]	3
6	AcOHb)	DCE	60	24	48[c]	10
7	TsOH[b]	toluene	90	24	3[c]	-
8	TFA[b]	toluene	90	24	7[c]	-
9	PivOH[b]	toluene	90	3	46	23
10[e]	PivOH[b]	toluene	90	24	31[c]	9
11	PivOH[f]	toluene	90	1.5	66	17
12	PivOH[f]	toluene	60	1.5	69	10
13	PivOH[g]	toluene	60	2	71	16
14[h]	PivOH[g]	toluene	60	2.5	61	8

[a]Yield (%) of isolated pure compound. [b]1 equiv. [c]Unreacted **1a** was recovered. [d]$Pd(CH_3CN)_2Cl_2$ (10 mol%) was used. [e]3 equiv. of TBHP were used. [f]0.5 equiv. [g]0.75 equiv. [h]1.5 equiv. of PhCHO.

Once the reaction conditions were selected, we studied the application of this procedure to a series of aldehydes **2b-2o** with different substitution patterns on the aromatic ring. As depicted in Table 2, aromatic aldehydes bearing both electron withdrawing and electron donating groups can be used for the reaction. The use of *p*-alkyl substituted aldehydes **2b** and **2c** gave the highest ratio of the corresponding diketones **4ab** and **4ac** (Table 2, entries 1 and 2). On the other hand, the presence of halogens on the *para* position is well tolerated, giving moderate to good yields on the corresponding ketones **3ad-af** (Table 2, entries 3-5) in shorter reaction times, and with minor formation of the diketones **4**. The best results were obtained when electron donating groups are introduced in the aromatic ring (Table 2, entries 8-9), although when an *ortho*-substituent was present, the reaction was slower giving a lower yield of **3ak** and **3al**, possibly due to a steric effect (Table 2, entries 10-11). 2-Naphthaldehyde **2o** could also be used to obtain **3ao**, although together with a significant amount of the diketone **4ao** (Table 2, entry 14).

Table 2. Acylation of **1a** with aromatic aldehydes **2b-o**



entry	**2**	Ar	t [h)]	**3** [%][a]	**4** [%][a]
1	**2b**		1.5	61	24
2	**2c**		7	47	41
3	**2d**		3	66	8
4	**2e**		3	58	<5[b]
5	**2f**		1.5	64	5
6	**2g**		5	35[d]	-
7	**2h**		7	22[d]	-
8	**2i**		2.5	72	8
9	**2j**		2.5	70	8
10	**2k**		6	47[d]	10
11	**2l**		7	40[d]	8
12	**2m**[c]		7	33[d]	-
13	**2n**[c]		7	14[d]	-
14	**2o**		1.5	51[d]	19

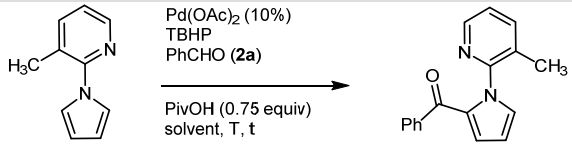
[a]Yield (%) of isolated pure compound. [b]Detected by ^1H NMR but not isolated. [c]Reaction temperature: 40 ºC. [d]Unreacted **1a** was recovered.

On the other hand, the aldehydes bearing electron-withdrawing groups gave sluggish reactions that required longer reaction times and gave only low yields of the corresponding ketones **3** (Table 2, entries 6-7, 12-13). In these cases, the corresponding diketones **4** were not detected. This reactivity pattern has also been described in related palladium catalyzed radical acylation reactions using aldehydes,[24] but it is opposite to the reactivity observed when α-diketones were used as acyl radical precursors.[17] Although the change of the structure of the aroyl

radical has a small effect on its polar character,[25] the observed trend could be correlated to the nucleophilicity of the resulting acyl radical. Thus the introduction of donating groups, mainly in the *p*-position, would increase the nucleophilicity of the acyl radical,[26] favoring the reaction with the electrophilic palladium atom in intermediate **I** (Scheme 2). Besides, the electron donating effect of the aroyl group could also stabilize the resulting palladium intermediate.[24b]

As has been shown, ketones **3** have been obtained as the major compounds with moderate to good yields but, in most cases, together with minor amounts of the corresponding diketones **4**. Although both products could be separated by chromatography, we decided to explore the use of 3-methyl-2-pyridine as directing group in order to avoid the formation of the diketones **4.** Thus, **1b** was reacted with benzaldehyde (**2a**), obtaining a moderate yield of ketone **3ba**, no detecting the formation of the corresponding diketone (Table 3, entry 1). Therefore, the reaction conditions were further optimized to improve the yield of **3ba** (Table 3). An increase in the reaction temperature (Table 3, entries 2-3) led to a significant increase of the yield of **3ba**, which was isolated in a 74%. The use of MW irradiation was also explored (Table 3, entries 4-6) but although the reactions were much faster, and full consumption of the staring material was observed in 10-20 minutes, the isolated yields of **3ba** were lower. The use of less aldehyde (1 equiv) and oxidant (2 equiv) gave lower yields. However, the reaction could be carried out with similar efficiency using 1.5 equiv of benzaldehyde at 120 ºC in toluene (Table 3, entry 7), although unreacted **1b** was recovered in this case. The change of the solvent did not improve the isolated yields of **3ba** (Table 3, entries 8-10).

Table 3. Acylation of **1b**. Optimization of reaction conditions

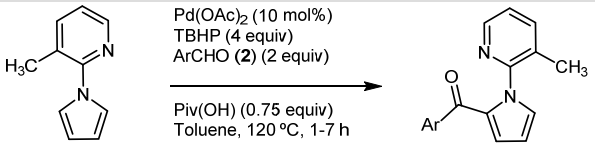


1b **3ba**

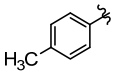
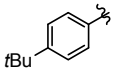
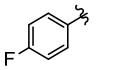
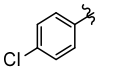
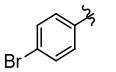
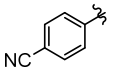
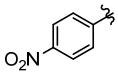
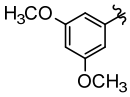
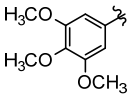
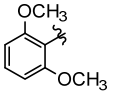
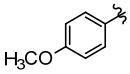
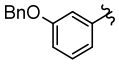
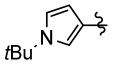
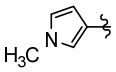
entry	**2a** [eq.]	TBHP [eq.]	solvent	T [ºC]	t [h]	**3ba** [%][a]
1	2	4	toluene	60	2	47
2	2	4	toluene	90	2	67
3	2	4	toluene	120	1.5	74
4	2	4	toluene	90[b]	0.16	56
5	1	2	toluene	90[b]	0.3	35
6	1	2	toluene	110[b]	0.3	50
7	1.5	3	toluene	120	1	74[c]
8	1.5	3	C_6H_5Cl	120	1	66
9	1.5	3	DCE	90	2.5	69
10	1.5	3	CH_3CN	90	8	30[c]

[a]Yield (%) of isolated pure compound. [b]Microwave irradiation (250 W). [c]Unreacted **1b** was recovered (20-30%)

Table 4. Acylation of **1b** with aromatic aldehydes **2b-t**



1b **3bb-bt**

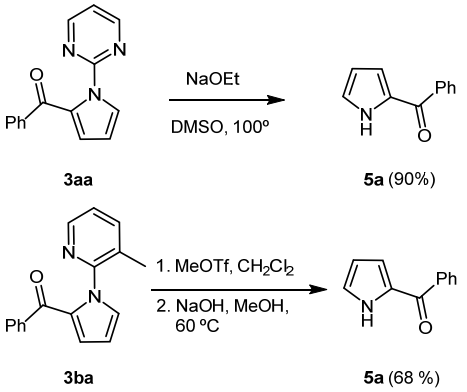
entry	**2**	Ar	t [h]	**3**	Yield [%][a]
1	**2b**		3.5	**3bb**	48[b]
2	**2c**		3.5	**3bc**	31[b]
3	**2d**		3	**3bd**	53[b]
4	**2e**		3	**3be**	43[b]
5	**2f**		3.5	**3bf**	44[b]
6	**2g**		3.5	**3bg**	43[b]
7	**2h**		7	**3bh**	11[b]
8	**2i**		1.5	**3bi**	65
9	**2j**		3.5	**3bj**	62
10	**2k**		7	**3bk**	39[b]
11	**2p**		1.5	**3bp**	60[b]
12	**2q**		2	**3bq**	61
13	**2r**		1.5	**3br**	71
14	**2s**		4.5	**3bs**	54[b]
15	**2t**		1.5	**3bt**	78

[a]Yield (%) of isolated pure compound. [b]Unreacted **1b** was recovered

We then extended the procedure to a series of aldehydes **2b-t** (Table 4). As expected, all reactions afforded selectively the corresponding ketones **3bb-bt** not detecting in any case the formation of the diacylated compounds. The same trend of reactivity for the aldehydes was observed, obtaining the best results with electron rich aromatic rings (Table 4, entries 8-9, 11-12). However, with the exception of **3bg** (Table 4, entry 6), the isolated yields of the ketones **3b** were in the same range or below the yields obtained for ketones **3a**. In this case, the procedure could be extended to the use of electron rich

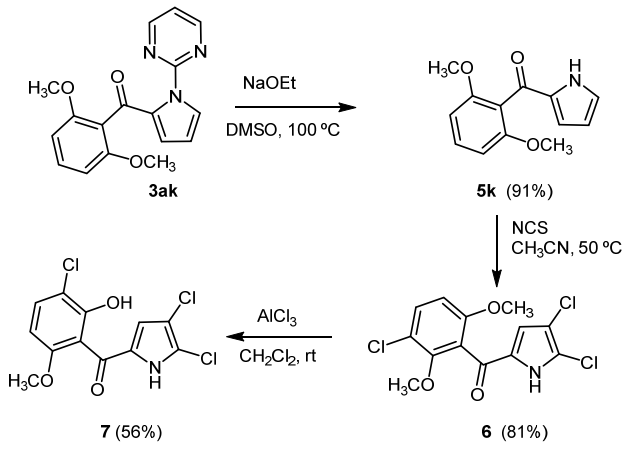
heteroaromatic aldehydes **2r-2t**, obtaining diheteroayl ketones **3br-bt** with good yields (Table 4, entries 13-15).

To test the applicability of these acylation reactions, it was first necessary to remove both directing groups in an efficient manner. Thus, the 2-pyrimidine directing group on **3aa** could be removed under previously described conditions[17] (Scheme 3), obtaining **5a** in excellent yield (90%). On the other hand, the 3-methyl-2-pyridine group could also be removed in good yield using the procedure described for removal of 2-pyridine group.[16a]



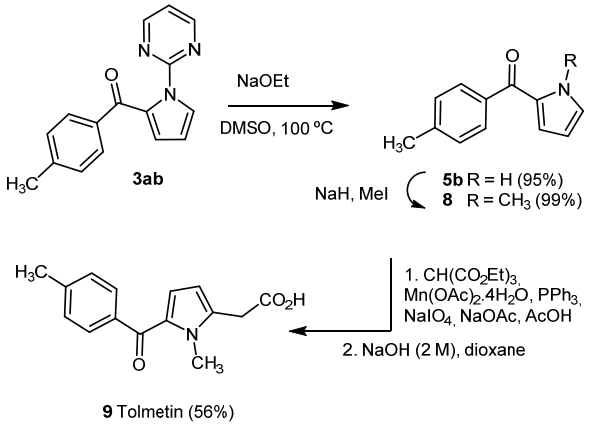
Scheme 3. Removal of the directing group

The prepared 2-acyl pyrroles **3** are advanced intermediates for the synthesis of more elaborated compounds. Thus, the compounds obtained could be derivatized to other potentially interesting structures. As shown on Scheme 4, the directing group could also be efficiently removed from **3ak** to yield **5k** in high isolated yield. This pyrrole **5k** has already been described as an intermediate in the synthesis of Pyoluteorin (Figure 1).[4a] Alternatively, the trichlorinated derivative **6** could be selectively obtained in high yield (81 %) using NCS.[27] This compound has been described to have activity as pesticide[28] and as glutamate release inhibitor.[29] Besides, selective demethylation using $AlCl_3$ afforded **7** in moderate yield. Both **6** and **7** could be considered as Celastramycin analogues (Figure 1), structures that have been recently identified to have interesting activity against pulmonary arterial hypertension.[30]



Scheme 4. Derivatization of **3ak**

Finally, the potential application of this acylation protocol in medicinal chemistry and natural products synthesis has also been demonstrated with the synthesis of Tolmetin, a non-steroidal anti-inflammatory drug. As shown on Scheme 5 Tolmetin could be easily obtained from C-2 *p*-toluoylpyrrole **3ab** in three steps. Deprotection and methylation of pyrrole was accomplished in nearly quantitative yield. to obtain **8**. The carboxylic acid side chain was introduced as the final step of the synthesis using the manganese-catalyzed intermolecular C-H coupling protocol described by Yamaguchi.[31] Thus, coupling of pyrrole **8** with triethyl methanetricarboxylate in the presence of $Mn(OAc)_2$, followed by hydrolysis and decarboxylation gave Tolmetin (**9**) in a good overall yield starting from pyrrole. This strategy effectively competes with or overcomes other reported procedures for the synthesis of this drug. It is a catalytic approach with atom-economy, which gives comparable or better overall yields. In fact, various described routes involve as key step a classical Friedel-Crafts aroylation of *N*-methylpyrrole acetate, prepared in three steps by traditional methods,[32] or *N*-methylpyrrole acetonitrile.[33] In the last case, it is noteworthy the synthesis of the pyrrole acetonitrile intermediate by photochemical generation of radicals. There is also one example using an organocatalytic Friedel-Crafts reaction using *p*-methyltoluoyl chloride and DBN as catalyst[11] but the overall yield is lower (19.3% vs 28.6%). Alternatively, the methylcarboxyl group has been introduced in the last step by a radical process, after the Friedel-Crafts acylation.[34]



Scheme 5. Synthesis of Tolmetin

Conclusion

In conclusion, the use of 2-pyrimidine as directing group allowed the C-2 metalation of pyrrole with $Pd(OAc)_2$ in toluene, which could be acylated with aldehydes in the presence of TBHP as oxidant. The presence of a moderately acidic additive, such as pivalic acid increases the reactivity. The reaction has been extended to a variety of aromatic aldehydes, bearing electron rich and electron deficient aromatic rings. However, in most of the cases, a minor amount of the corresponding diacylated product was obtained. This side reaction could be avoided using the 3-methyl-2-pyridinyl group as directing group, obtaining selectively monoacylated pyrroles in moderate to good yields. The so obtained acylated pyrroles have been used as

intermediates in the synthesis of celastramycin analogues and in an improved synthesis of Tolmetin.

Experimental Section

Acylation reactions of 1a with aldehydes. General procedure. Under argon atmosphere, a sealable reaction tube equipped with a stirring bar was charged with **1a** (1 mmol), $Pd(OAc)_2$ (0.1 mmol), PivOH (0.75 mmol) and corresponding aldehyde **2a-o** (2 mmol). Toluene was added (2 mL), and the mixture was stirred for 2 min until solids were dissolved. Then, TBHP (5.5 M in decane, 4 mmol) was added, the reaction tube was sealed and the reaction mixture was stirred at 60 °C for 1.5-7 h. After cooling to room temperature, the reaction mixture was filtered through silica gel and the filtrate was concentrated under vacuum. The residue was purified by column chromatography affording **3aa-ao** and **4aa-ao.** (See SI for characterization of diacylated compounds **4**).

Phenyl[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3aa)** (Table 1, entry 13). Following the general procedure, **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1mmol), PivOH (76.6 mg, 0.75 mmol), benzaldehyde **2a** (0.20 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 2 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/EtO_2 4/6) afforded **3aa** as a white solid whose data are coincidental to those reported[17] (179.7 mg, 71%): mp (CH_2Cl_2): 115-117°C (Lit. [17] 105-107 ºC); IR (ATR): 1740, 1641, 1566 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 6.35 (t, *J* = 3.2 Hz, 1H), 6.80 (dd, *J* = 3.2 , 1.5 Hz, 1H), 7.07 (t, *J* = 4.9 Hz, 1H,), 7.41 (t, *J* = 7.3 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.71 (t, *J* = 1.5 Hz, 1H), 7.93 (d, *J* = 7.3 Hz, 2H), 8.57 (d, *J* = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 185.9, 158.2, 156.8, 138.3, 132.4, 132.2, 129.6, 128.2, 127.9, 122.5, 118.5, 110.4 ppm; MS (ESI^+): *m/z* (rel intensity): 250 (MH^+, 100), 105 (1). HRMS (ESI^+): calcd. for $C_{15}H_{12}N_3O$ [MH^+]: 250.0980; found: 250.0986.

[1-(Pyrimidin-2-yl)-1*H*-pyrrol-2-yl](*p*-tolyl)methanone (3ab). Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-methylbenzaldehyde **2b** (0.22 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1,5 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 6/4) afforded **3ab** as white solid (160.7 mg, 61%): mp (CH_2Cl_2): 159-161 °C ; IR (ATR): 1641, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H), 6.35 (m, 1H), 6.79 (dd, *J* = 3.6, 1.6 Hz, 1H), 7.08 (t, *J* = 4.8 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.70 (dd, *J* = 2.9, 1.6 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 8.58 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 186.7, 158.2, 156.9, 143.3, 135.6, 132.4, 129.8, 128.9, 127.6, 122.2, 118.4, 110.3, 21.7 ppm; MS (ESI^+) *m/z* (rel intensity): 264 (MH^+, 100), 172(1), 119 (8). HRMS (ESI^+): calcd. for $C_{16}H_{14}N_3O$ [MH^+] 264.1137; found, 264.1143.

[4-(*tert*-Butyl)phenyl][1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (3ac). Following the general procedure, **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-(*tert*-butyl)benzaldehyde **2c** (0.33 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 9/1) afforded **3ac** as white solid (144.8 mg, 47%). mp (CH_2Cl_2): 121-123 °C; IR (ATR): 1735, 1641, 1573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H), 6.35 (m, 1H), 6.82 (dd, *J* = 3.6, 1.6 Hz, 1H), 7.10 (t, *J* = 4.8 Hz, 1H), 7.45-7.48 (m, 2H), 7.70 (dd, *J* = 2.9, 1.6 Hz, 1H), 7.90-7.93 (m, 2H), 8.60 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 186.5, 158.2, 156.9, 156.2, 135.6, 132.4, 129.7, 127.8, 125.2, 122.4, 118.4, 110.3, 35.1, 31.2 ppm; MS (ESI^+): *m/z* (rel intensity): 306 (MH^+, 100), 161 (1). HRMS (ESI^+): calcd. for $C_{19}H_{20}N_3O$ [MH^+] 306.1606; found, 306.1614.

(4-Fluorophenyl)[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3ad)**. Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-fluorobenzaldehyde **2d** (0.21 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3 h at 70 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 3/7) afforded **3ad** as white solid, whose data are coincidental to those reported[20] (177.0 mg, 66%). mp (CH_2Cl_2): 153-155 °C; IR (ATR):, 1645, 1602, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.35 (dd, *J* = 3.5, 3.0 Hz, 1H), 6.79 (dd, *J* = 3.6, 1.6 Hz, 1H), 7.06-7.12 (m, 3H), 7.71 (dd, *J* = 2.9, 1.6 Hz, 1H), 7.92-7.97 (m, 2H), 8.59 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 184.5, 165.4 (d, J = 25 3.5 Hz), 158.3, 156.7, 134.6, 132.1 (d, *J* = 9.1 Hz), 131.9, 128.0, 122.5, 118.5, 115.4 (d, *J* = 21.9 Hz), 110.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -106.41 ppm; MS (ESI^+): *m/z* (rel intensity): 268 (MH^+, 100), 123 (11). HRMS (ESI^+): calcd. for $C_{15}H_{11}FN_3O$ [MH^+] 268.0886; found, 268.0896.

(4-Chlorophenyl)[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3ae).** Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-chlorobenzaldehyde **2e** (281.1 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded none **3ae** as white solid (164.4 mg, 58%): mp (CH_2Cl_2): 134-136 °C; IR (ATR): 1645, 1573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.35 (t, *J* = 3.5 Hz, 1H), 6.79 (dd, *J* = 3.5, 1.5 Hz, 1H), 7.10 (d, *J* = 4.8 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.72 (dd, *J* = 3.5, 1.5 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 8.57 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 184.6, 158.2, 156.7, 138.7, 136.7, 131.8, 130.9, 128.5, 128.0, 122.5, 118.9, 110.6 ppm; MS (ESI^+): *m/z* (rel intensity): 286 (MH^++2, 26), 284 (MH^+, 100), 140 (2) 138 (6). HRMS (ESI^+): calcd. for $C_{15}H_{11}ClN_3O$ [MH^+] 284.0591; found, 284.0591.

(4-Bromophenyl)[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (3af). Following the general procedure **1a** (145.2 mg, 1mmol), $Pd(OAc)_2$ was treated with (22.5 mg, 0.1mmol), PivOH (76.6 mg, 0.75 mmol), 4-bromobenzaldehyde **2f** (281.1 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1.5 h at 70 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 6/4) afforded **3af** as white solid (211.0 mg, 64%): mp (CH_2Cl_2): 139-140 °C; IR (ATR): 1741, 1645, 1573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.34-6-36 (m, 1H), 6.79 (dd, *J* = 3.6 Hz, 1.6 Hz, 1H), 7.10 (t, *J* = 4.8 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.72 (dd, *J* = 2.9, 1.6 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 8.57 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 184.8, 158.2, 156.6, 137.1, 131.8, 131.5, 131.1, 128.0, 127.3, 122.5, 118.5, 110.6 ppm; MS (ESI^+): *m/z* (rel intensity): 330 (MH^++2,99), 328 (MH^+, 100), 184 (4), 182 (4). HRMS (ESI^+): calcd. for $C_{15}H_{11}BrN_3O$ [MH^+] 328.0085; found, 328.0094.

4-[1-(Pyrimidin-2-yl)-1*H*-pyrrole-2-carbonyl]benzonitrile (**3ag**). Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-formylbenzonitrile **2g** (262.3 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 5 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 3/7) afforded **3ag** as light brown solid (95.4 mg, 35%): mp (CH_2Cl_2): 176-178 °C; IR (ATR): 2230, 1645, 1570, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.38-6.40 (m, 1H), 6.83 (dd, *J* = 3.7, 1.6 Hz, 1H), 7.13 (t, *J* = 4.8 Hz, 1H), 7.70-7.72 (m, 2H), 7.76 (dd, *J* = 2.9, 1.6 Hz, 1H), 7.96-7.98 (m, 2H), 8.58 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 184.1, 158.6, 156.5, 141.9, 132.1, 131.4, 129.7, 129.0, 123.1, 118.7, 118.2, 115.5, 110.9 ppm; MS (ESI^+): *m/z* (rel intensity): 275 (MH^+, 100), 130 (12). HRMS (ESI^+): calcd. for $C_{16}H_{11}N_4O$ [MH^+] 275.0933; found, 275.0935.

(4-Nitrophenyl)[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3ah):** Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-nitrobenzaldehyde **2h** (302.2 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3ah** as yellow solid (58.8 mg, 22%). mp (CH_2Cl_2): 173-174 °C; IR (ATR): 1649,

1570, cm^{-1}; ^1H NMR (300 MHz, DMSO-*d*^{6}): δ 6.48-6.50 (m, 1H), 6.95 (dd, *J* = 3.7, 1.6 Hz, 1H), 7.42 (t, *J* = 4.9 Hz, 1H), 7.85 (dd, *J* = 2.8, 1.6 Hz, 1H), 7.99-8.02 (m, 2H), 8.31-8.34 (m, 2H), 8.75 (d, *J* = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 183.8, 158.3, 156.5, 149.8, 143.6, 131.4, 130.2, 128.7, 123.4, 123.3, 118.7, 111.0 ppm; MS (ESI^+): *m/z* (rel intensity): 295 (MH^+, 100), 150 (7). HRMS (ESI^+): calcd. for $C_{15}H_{11}N_4O_3$ [MH^+] 295.0831; found, 295.0835.

(3,5-Dimethoxyphenyl)[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3ai).** Following the general procedure **1a** (145.2 mg, 1 mmol), was treated with $Pd(OAc)_2$ (22.5 mg, 0.1mmol), PivOH (76.6 mg, 0.75 mmol), 3,5-dimetoxibenzaldehyde **2i** (332.3 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 2.5 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3ai** as white solid (222.8 mg, 72%): mp (CH_2Cl_2): 107-109 °C ; IR (ATR): 1737, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 3.77 (s, 6H), 6.34 (t, *J* = 3.2 Hz, 1H), 6.58 (t, *J* = 2.3 Hz, 1H), 6.81 (dd, *J* = 3.5, 1.5 Hz, 1H), 7.04-7.07 (m, 3H), 7.69 (dd, *J* = 3.1 Hz, 1.5 Hz, 1H), 8.58 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 185.3, 160.5, 158.3, 156.8, 140.1, 132.0, 128.0, 122.7, 118.5, 110.4, 107.4, 106.2, 55.6 ppm; MS (ESI^+): *m/z* (rel intensity): 310 (MH^+, 100), 165 (1). HRMS (ESI^+): Calcd. for $C_{17}H_{16}N_3O_3$ [MH^+] 310.1192; found. 310.1201.

[1-(Pyrimidin-2-yl)-1*H*-pyrrol-2-yl](3,4,5-trimethoxyphenyl)methanone (**3aj).** Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 3,4,5-trimethoxybenzaldehyde **3j** (392.4 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 2,5 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 6/4) afforded **3aj** as yellow solid (237.9 mg, 70%): mp (CH_2Cl_2): 124-126 °C ; IR (ATR): 1741, 1577 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 6H), 3.87 (s, 3H), 6.32 (dd, *J* = 3.5, 2.9 Hz, 1H), 6.81 (dd, *J* = 3.5, 1.6 Hz, 1H), 7.08 (t, *J* = 4.8 Hz, 1H), 7.20 (s, 2H), 7.68 (dd, *J* = 2.9, 1.6 Hz, 1H), 8.57 (d, *J* = 4.8 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 184.7, 158.2, 156.8, 152.8, 141.9, 133.2, 131.9, 127.9, 122.2, 118.2, 110.4, 107.1, 60.9, 56.2 ppm; MS (ESI^+): *m/z* (rel intensity): 340 (MH^+, 100), 172 (1). HRMS (ESI^+): calcd. for $C_{18}H_{18}N_3O_4$ [MH^+] 340.1297; found, 340.1310.

(2,6-Dimethoxyphenyl)[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (3ak). Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 2,6-dimetoxibenzaldehyde **2k** (332.3 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 6 h at 90 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 3/7) afforded **3ak** as yellow solid (143.9 mg, 47%): mp (CH_2Cl_2): 156-158 °C; IR (ATR): 1649, 1591cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 6H), 6.27 (dd, *J* = 3.8, 2.9 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 6.76 (dd, *J* = 3.8, 1.7 Hz, 1H), 7.20 (t, *J* = 4.8 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 2.9, 1.7 Hz, 1H), 8.71 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 182.5, 158.2, 158.1, 157.8, 134.1, 130.7, 129.9, 123.9, 119.1, 119.0, 110.3, 104.1, 56.1 ppm; MS (ESI^+): *m/z* (rel intensity): 310 (MH^+, 20), 172 (100), 158 (20), 98 (50). HRMS (ESI^+): calcd. for $C_{17}H_{16}N_3O_3$ [MH^+] 310.1192; found, 310.1185.

(2,4-Dimethoxyphenyl)[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3al).** Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 2,4-dimetoxibenzaldehyde **2l** (332.3 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 6/4) afforded **3al** as yellow solid (124.1 mg, 40%): mp (CH_2Cl_2): 137-138 °C; IR (ATR): 1602, 1570, 1441 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 3.69 (s, 3H), 3.79 (s, 3H), 6.27 (dd, *J* = 3.5, 3.1 Hz, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.43 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.70 (dd, *J* = 3.6, 1.7 Hz, 1H), 7.05 (t, *J* = 4.8 Hz, 1H), 7.58 (dd, *J* = 3.1, 1.7 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 8.54 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 181.9, 161.6, 160, 158.0, 157.0, 134.3, 133.4, 127.1, 121.8, 121.5, 118.4, 110.1, 102.0, 98.7, 55.8, 55.5 ppm; MS (ESI^+): *m/z* (rel intensity): 310 (MH^+, 100), 172 (31). HRMS (ESI^+): Calcd. for $C_{17}H_{16}N_3O_3$ [MH^+] 310.1192; found, 310.1196.

[1-(Pyrimidin-2-yl)-1*H*-pyrrol-2-yl[[4-(trifluoromethyl)phenyl]methanone (**3am).** Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-(trifluoromethyl)benzaldehyde **2m** (0.27 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 40 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 3/7) afforded **3am** as white solid (105.8 mg, 33%): mp (CH_2Cl_2): 103-104 °C; IR (ATR): 1649, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.38 (s, 1H), 6.83 (d, *J* = 1.7 Hz, 1H), 7.13 (t, *J* = 4.8 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.74-7.76 (m, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 8.60 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 184.6, 158.3, 156.6, 141.3, 133.6 (q, *J* = 32.5 Hz), 131.7, 130.3, 129.8, 128.5, 125.2 (q, *J* = 3.8 Hz), 123.7 (q, *J* = 271.1 Hz), 118.7, 110.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.9 ppm; MS (ESI^+): *m/z* (rel intensity): 318 (MH^+, 100), 173 (4). HRMS (ESI^+): Calcd. for $C_{16}H_{11}F_3N_3O$ [MH^+] 318.0854; found, 318.0861.

[3,5-bis(Trifluoromethyl)phenyl][1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3an).** Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 3,5-bis(trifluoromethyl)benzaldehyde **3n** (0.33 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 40 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 3/7) afforded **3an** as light-brown solid (52.9 mg, 14%): mp (CH_2Cl_2): 96-98 °C; IR (ATR): 1656, 1573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.43 (s, 1H), 6.87 (s, 1H), 7.18 (t, *J* = 4.3 Hz, 1H), 7.82 (s, 1H), 8.04 (s, 1H), 8.38 (s, 2H), 8.62 (d, *J* = 4.6 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 182.3, 158.3, 156.5, 140.1, 131.9 (q, *J* = 33.9 Hz), 130.8, 129.4 (q, *J* = 3.2 Hz), 129.4, 125.5 (q, *J* = 3.65 Hz), 123.6, 122.9 (q, *J* = 271.6 Hz), 118.8, 111.0 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.9 ppm; MS (ESI^+): *m/z* (rel intensity): 386 (MH^+, 100), 241 (1). HRMS (ESI^+): calcd. for $C_{17}H_{10}F_6N_3O$ [MH^+] 386.0728; found, 386.0728.

Naphthalen-2-yl[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (3ao). Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 2-naphthaldehyde **2o** (312.4 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1,5 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 1/1) afforded **3ao** as white solid (152.2 mg, 51%): mp (CH_2Cl_2): 110-112 °C; IR (ATR): 3052, 2999, 1739, 1641, 1573, 1530, 1444 cm^{1-}; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.39-6.41 (m, 1H), 6.88-6.89 (m, 1H), 7.02 (t, *J* = 4.7 Hz, 1H), 7.51-755 (m, 2H), 7.78 (d, *J* = 1.1 Hz, 1H), 7.85-7.91 (m, 3H), 8.04 (d, *J* = 8.4 Hz, 1H), 8.47 (s, 1H), 8.55 (d, *J* = 4.7 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.0, 158.2, 156.8, 135.7, 135.35, 132.4, 131.3, 129.5, 128.2, 128.2, 127.8, 126.4, 125.4, 122.5, 118.4, 110.5 ppm; MS (ESI^+): *m/z* (rel intensity): 300 (MH^+, 100), 155 (3). HRMS (ESI^+): calcd. for $C_{19}H_{14}N_3O$ [MH^+] 300.1137; found, 300.1141.

Acylation reactions of 1b with aldehydes. General procedure. Under argon atmosphere, a sealable reaction tube equipped with a stirring bar was charged with **1b** (1 mmol), $Pd(OAc)_2$ (0.1 mmol), PivOH (0.75 mmol) and corresponding benzaldehyde **2a-t** (2 mmol). Toluene was added (2 mL), mixture was stirred for 2 min until solids were dissolved. Then, TBHP (5.5 M in decane, 4 mmol) was added, reaction tube was sealed and the reaction mixture was stirred at 120 °C for 1.5-7 h. After cooling to room temperature, AcOEt (15mL) was added to reaction mixture and organic phase was washed with an aqueous solution of NaOH 2M (3 × 20 mL) the combined aqueous phase was extracted with AcOEt (2 × 15 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography affording **3ba-3bt**.

[1-(3-Methylpyridin-2-yl)-1*H*-pyrrol-2-yl](phenyl)methanone (3ba). (Table 3, entry 3) Following the general procedure **1b** (158.2 mg, 1

mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), benzaldehyde **2a** (0.20 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1.5 h at 120 ºC, purification by column chromatography (silica gel, petroleum ether/ AcOEt 7/3) afforded **3ba** as a yellow oil (202.5 mg, 74%): IR (ATR): 1739, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 3H), 6.37 (dd, *J* = 3.9, 2.6 Hz, 1H), 6.90 (dd, *J* = 3.9, 1.6 Hz, 1H), 7.10 (dd, *J* = 2.6, 1.6, 1H), 7.20-7.25 (m, 1H), 7.40 (dd, *J* = 8.2, 6.6 Hz, 2H), 7.43-7.54 (m, 1H), 7.56-7.64 (m, 1H), 7.79-7.91 (m, 2H), 8.33-8.38 (m, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 184.6, 152.4, 146.4, 139.4, 138.7, 131.9, 131.7, 130.0, 129.6, 129.4, 128.2, 123.7, 122.2, 109.8, 17.3 ppm; MS (ESI^+): *m/z* (rel intensity): 263 (MH^+, 100), 106 (2), 105 (33). HRMS (ESI^+): calcd. for $C_{17}H_{15}N_2O$ [MH^+] 263.1184; found, 263.1198.

1-(3-Methylpyridin-2-yl)-1*H*-pyrrol-2-yl][(*p*-tolyl)methanone (**3bb).** Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-methylbenzaldehyde **2b** (0,24 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether /AcOEt 7/3) afforded **3bb** as yellow oil (132.6 mg, 48 %): IR (ATR): 1739, 1458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 2.14 (s, 3H), 2.44 (s, 3H), 6.41 (dd, *J* = 3.9, 2.7 Hz, 1H), 6.94 (dd, *J* = 3.9, 1.6 Hz, 1H), 7.13 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.27 (d, *J* =8.1 Hz, 2H), 7.30-7.34 (m, 1H), 7.67 (dd, *J* = 7.5,1.2 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 8.41 (dd, *J* = 4.7, 1.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 184.5, 152.4, 146.4, 142.5, 139.4, 136.0, 131.8, 130.1, 129.6, 129.3, 128.8, 123.6, 121.8, 109.8, 21.6, 17.3 ppm; MS (ESI^+): *m/z* (rel intensity): 277 (MH^+, 100), 119 (37). HRMS (ESI^+): calcd. for $C_{18}H_{17}N_2O$ [MH^+] 277.1341; found, 277.1350.

[4-(*tert*-Butyl)phenyl][1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3bc).** Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-(*tert*-butyl)benzaldehyde **2c** (0.33 mL; 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3,5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bc** as brown solid (100 mg, 31%): IR (ATR) = 1741, 1454 cm^{-1}; mp (CH_2Cl_2): 75-79 °C; ^1H NMR (500 MHz, $CDCl_3$): *δ* 1.35 (s, 9H), 2.12 (s, 3H), 6.39 (dd, *J* = 3.9, 2.7 Hz, 1H), 6.95 (dd, *J* = 3.9, 1.6 Hz, 1H), 7.12 (dd, J = 2.7, 1.6Hz, 1H), 7.24-7.32 (m, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.64 (dd, *J* = 7.5, 1.2Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 8.38 (dd, *J* = 4.8, 1.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 184.4, 155.4, 152.4, 146.3, 139.4, 135.9, 131.8, 130.0, 129.4, 129.2, 125.1, 123.6, 121.8, 109.8, 35.0, 31.2, 17.2 ppm; MS (ESI^+): *m/z* (rel intensity): 319 (MH^+, 100), 162 (1), 161 (7). HRMS (ESI^+): calcd. for $C_{21}H_{23}N_2O$ [MH^+] 319.1810; found, 319.1819.

(4-Fluorophenyl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3bd):** Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-fluorobenzaldehyde **2d** (0.21 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bd** as white solid (148.7 mg, 53%): mp (CH_2Cl_2): 76-78 °C; IR (ATR): 1634, 1595, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 2.12 (s, 3H), 6.39 (d, *J* = 2.9 Hz, 1H), 6.89 (d, *J* = 3.8 Hz, 1H), 7.09-7.12 (m, 3H), 7.26-7.29 (m, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.96-7.82 (m, 2H), 8.37 (d, *J* = 4.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 183.2, 165.1 (d, *J* = 253.2 Hz), 152.2, 146.4, 139.5, 134.9 (d, *J* = 3.4 Hz) , 131.8 (d, *J* = 9.0 Hz), 131.4, 130.0, 129.7, 123.8, 122.0, 115.2 (d, *J* = 21.7 Hz), 110.0, 17.2 ppm; MS (ESI^+): *m/z* (rel intensity): 281 (MH^+, 100), 265 (<1), 243 (1), 123 (21). HRMS (ESI^+): calcd. for $C_{17}H_{14}FN_2O$ [MH^+] 281.1090; found, 281.1092.

(4-Chlorophenyl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (3be). Following the general procedure 3 **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-chlorobenzaldehyde **2e** (281.2 mg; 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3be** as white solid (128.6 mg, 43%): mp (CH_2Cl_2): 99-102 °C; IR (ATR): 1739, 1631, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 2.12 (s, 3H), 6.40 (dd, *J* = 3.9, 2.7 Hz, 1H), 6.89 (dd, *J* = 3.9, 1.6 Hz, 1H), 7.13 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.29 (dd, *J* = 7.6, 4.8Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.65 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 8.37 (dd, *J* = 4.8, 1.2 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 183.3, 152.2, 146.4, 139.5, 138.1, 137.0, 131.3, 130.8, 130.0, 129.9, 128.5, 123.8, 122.1, 110.1, 17.2 ppm; MS (ESI^+): *m/z* (rel intensity): 299 (MH^++2, 29), 297 (MH^+, 100), 271 (1), 141 (5), 139 (17). HRMS (ESI^+): calcd. for $C_{17}H_{14}ClN_2O$ [MH^+] 297.0795; found, 297.0802.

(4-Bromophenyl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (3bf). Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-bromobenzaldehyde **2f** (370.0 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bf** as white solid (149.2mg, 44 %): mp (CH_2Cl_2): 109-111 °C; IR (ATR): 1739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 2.11 (s, 3H), 6.40 (dd, *J* = 3.8, 2.7 Hz, 1H), 6.89 (dd, *J* = 3.8, 1.5 Hz, 1H), 7.10–7.16 (m, 1H), 7.29 (dd, *J* = 7.6, 4.8 Hz, 1H),7.57 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 8.37 (d, *J* = 3.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 183.4, 152.2, 146.4, 139.5, 137.5, 131.4, 131.3, 130.9, 130.1, 129.9, 126.7, 123.8, 122.2, 110.1, 17.4 ppm; MS (ESI^+): *m/z* (rel intensity): 343(MH^+ +2, 99), 341 (MH^+, 100), 185 (9), 183 (10). HRMS (ESI^+): calcd. for $C_{17}H_{14}BrN_2O$ [MH^+] 341.0290; found, 341.0293.

4-[1-(3-Methylpyridin-2-yl)-1*H*-pyrrole-2-carbonyl]benzonitrile (**3bg).** Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-formylbenzonitrile **2g** (262.2 mg; 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bg** as yellow solid (124.4 mg, 43%): mp (CH_2Cl_2): 112-115 °C; IR (ATR): 2230, 1739, 1634 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 2.11 (s, 3H), 6.41 (dd, *J* = 4.0, 2.7 Hz, 1H), 6.87 (dd, *J* = 4.0, 1.5 Hz, 1H), 7.16 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.30 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.67 (dd, *J* = 7.5,1.0 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.4 Hz, 2H), 8.36 (dd, *J* = 4.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 182.6, 151.9, 146.5, 142.4, 139.6, 132.1, 131.0, 130.7, 130.1, 129.7, 124.0, 122.9, 118.2, 115.1, 110.4, 17.2, ppm; MS (ESI^+): *m/z* (rel intensity): 288 (MH^+, 100), 130 (6). HRMS (ESI^+): calcd. for $C_{18}H_{14}N_3O$ [MH^+] 288.1137; found, 288.1141.

[1-(3-Methylpyridin-2-yl)-1*H*-pyrrol-2-yl](4-nitrophenyl)methanone (**3bh).** Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-nitrobenzaldehyde **2h** (302.2 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded as yellow oil **3bh** (32.4 mg, 11%): IR (ATR): 1745, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 2.16 (s, 3H), 6.46 (dd, *J* = 4.0, 2.6 Hz, 1H), 6.92 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.20 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.35 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.71 (ddd, *J* = 7.6, 1.8, 0.8 Hz, 1H), 7.94-8.08 (m, 2H), 8.20-8.35 (m, 2H), 8.41 (ddd, *J* = 4.8, 1.8, 0.7 Hz, 1H), ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 182.4, 151.9, 149.6, 146.50, 144.0, 139.6, 130.9, 130.9, 130.2, 130.1, 124.1, 123.4, 123.1, 110.5, 17.18 ppm; MS (ESI^+): *m/z* (rel intensity): 308 (MH^+, 100), 274 (1), 150 (3). HRMS (ESI^+): calcd. for $C_{17}H_{14}N_3O_3$ [MH^+] 308.1035; found, 308.1033.

(3,5-Dimethoxyphenyl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3bi).** Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 3,5-dimethoxybenzaldehyde **2i** (332.2, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bi** as yellow oil (209.2 mg, 65%): IR (ATR): 1727, 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 2.11 (s, 3H), 3.78 (s, 6H), 6.38 (dd, *J* = 3.9, 2.6 Hz,

1H), 6.61 (t, *J* = 2.3 Hz, 1H), 6.98 (dd, *J* = 3.9, 1.6 Hz, 1H), 7.00 (d, *J* = 2.3 Hz, 2H), 7.11 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.27 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.63 (ddd, *J* = 7.5, 1.8, 0.8 Hz, 1H), 8.36 (ddd, *J* = 4.8, 1.8, 0.7 Hz, 1H) ppm;^{13}C NMR (75 MHz, $CDCl_3$): *δ* 184.1, 160.5, 152.3, 146.3, 140.4, 139.4, 131.5, 130.1, 129.7, 123.7, 122.2, 110.0, 107.2, 104.5, 55.5, 17.2 ppm; MS (ESI^+): *m/z* (rel intensity): 323 (MH^+, 100), 165 (18). HRMS (ESI^+): calcd. for $C_{19}H_{19}N_2O_3$ [MH^+] 323.1396; found, 323.1406.

[1-(3-Methylpyridin-2-yl)-1*H*-pyrrol-2-yl](3,4,5-trimethoxyphenyl)methanone (3bj). Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 3,4,5-trimethoxybenzaldehyde **3j** (392.4 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bj** as yellow oil (217.9 mg, 62%): IR (ATR): 1726, 1630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 2.07 (s, 3H), 3.80 (s, 6H), 3.84 (s, 3H), 6.32 (dd, *J* = 3.9, 2.8 Hz, 1H), 6.91 (dd, *J* =3.9, 1.4 Hz, 1H), 7.03-7.08 (m, 1H), 7.10 (s, 2H), 7.20 (dd, *J* = 7.0, 3.5 Hz, 1H), 7.57 (d, *J* = 7.0Hz, 1H), 8.28 (d, *J* = 3.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 183.5, 152.7, 152.2, 146.2, 141.5, 139.4, 133.6, 131.4, 130.0, 129.4, 123.7, 121.5, 109.7, 107.0, 60.8, 56.2, 17.3 ppm; MS (ESI^+): *m/z* (rel intensity): 353 (MH^+, 100), 195 (10). HRMS (ESI^+): calcd. for $C_{20}H_{21}N_2O_4$ [MH^+] 353.1501; found, 353.1508.

(2,6-Dimethoxyphenyl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3bk).** Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 2,6-dimethoxybenzaldehyde **2k** (332.2, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bk** as yellow oil (126.0 mg, 39%). IR (ATR): 1641 1595 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 2.15 (s, 3H); 3.71 (s, 6H), 6.31 (dd, *J* = 3.9, 2.6 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 2H), 6.65 (dd, *J* = 3.9, 1.7 Hz, 1H), 7.05 (dd, *J* = 2.6, 1.7 Hz, 1H), 7.33-7.22 (m, 2H), 7.66-7.61 (m, 1H), 8.41 (ddd, *J* = 4.8, 1.8, 0.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 182.9, 157.7, 152.5, 146.1, 139.1, 133.5, 131.1, 130.3, 129.3, 123.7, 121.8, 118.9, 109.9, 103.9, 55.8, 16.7 ppm; MS (ESI^+): *m/z* (rel intensity): 323 (MH^+, 100), 185 (50), 165 (24). HRMS (ESI^+): calcd. for $C_{19}H_{19}N_2O_3$ [MH^+]: 323.1396; found, 323.1398.

(4-Methoxyphenyl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3bp).** Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-methoxybenzaldehyde **2p** (0.24 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1,5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bp** as yellow solid (174.9 mg, 60%): mp (CH_2Cl_2): 109-111 °C; IR (ATR): 3009., 2991, 1735, 1627, 1595, 1451, 1408 cm^{1-}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.09 (s, 3H), 3.80 (s, 3H), 6.36 (dd, J = 3.9, 2.7 Hz, 1H), 6.86-6.94 (m, 3H), 7.08 (dd, J = 2.7, 1.6 Hz, 1H), 7.23 (dd, *J* = 7.6, 4.6 Hz, 1H), 7.55-7.64 (m, 1H), 7.80-7.92 (m, 2H), 8.34 (dd, *J* = 4.6, 1.4 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 183.6, 162.8, 152.4, 146.3, 139.4, 131.8, 131.6, 131.2, 130.0, 129.0, 123.6, 121.4, 113.5, 109.7, 55.5, 17.3 ppm; MS (ESI^+): *m/z* (rel intensity): 293 (MH^+, 100), 185 (2), 136 (2), 135 (29). HRMS (ESI^+): calcd. for $C_{18}H_{17}N_2O_2$ [MH^+] 293.1290; found, 293.1293.

[3-(Benzyloxy)phenyl][1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3bq).** Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 3-(benzyloxy)benzaldehyde **3q** (424.5 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 2 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded as yellow oil **3bq** (224.2 mg, 61%): IR (ATR): 1645, 1595 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 2.13 (s, 3H), 5.11 (s, 2H), 6.40 (dd, *J* = 4.0, 2.6 Hz, 1H), 6.91 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.14 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.18 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 7.28 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.41-7.31 (m, 4H), 7.46-7.42 (m, 2H), 7.51-7.53 (m, 2H), 7.64 (ddd, *J* = 7.6, 1.8, 1.0 Hz, 1H), 8.40 (dd, *J* = 4.8, 1.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 184.3, 158.6, 152.4, 146.4, 140.0, 139.4, 136.7, 131.6, 130.1, 129.6, 129.3, 128.7, 128.1, 127.5, 123.7, 122.4, 122.3, 119.3, 114.9, 110.0, 70.1, 17.3 ppm; MS (ESI^+): *m/z* (rel intensity): 369 (MH^+, 100), 211 (6). HRMS (ESI^+): calcd. for $C_{24}H_{21}N_2O_2$ [MH^+] 369.1603; found, 369.1602.

[1-(*tert*-Butyl)-1*H*-pyrrol-3-yl][1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (3br). Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 1-(*tert*-butyl)-1*H*-pyrrole-3-carbaldehyde **3r** (226.8 mg, 1.5 mmol) and TBHP (5.5 M in decane, 0.54 mL, 3 mmol). After 1.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **3br** as white solid (216.7 mg, 71 %): mp (CH_2Cl_2): 133-134 °C; IR (ATR): 1612, 1526, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 1.51 (s, 9H), 2.10 (s, 3H), 6.34 (dd, *J* = 3.8, 2.7 Hz, 1H), 6.66 (dd, *J* = 2.9, 1.8 Hz, 1H), 6.79 (t, *J* = 2.9 Hz, 1H), 7.00 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.04 (dd, *J* = 3.8, 1.5 Hz, 1H), 7.21 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.49 (t, *J* = 1.8 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 8.38-8.26 (m, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 179.1, 152.8, 146.1, 139.2, 133.0, 130.2, 127.7, 124.0, 123.8, 123.4, 118.9, 118.5, 110.0, 109.4, 55.7, 30.6, 17.4 ppm; MS (ESI^+): *m/z* (rel intensity): 308 (MH^+, 100), 185 (33), 150 (5). HRMS (ESI^+): calcd. for $C_{19}H_{22}N_3O$ [MH^+] 308.1763; found, 308.1764.

(1-Methyl-1*H*-pyrrol-2-yl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3bs).** Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 1-methyl-1*H*-pyrrole-2-carbaldehyde **2s** (0.20 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 4.5 h at 85 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bs** as a brown solid (142.0 mg, 54 %): mp (CH_2Cl_2): 108-111°C; IR (ATR): 1739, 1609 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.12 (s, 3H), 3.81 (s, 3H), 6.14 (dd, *J* = 4.0, 2.4 Hz, 1H), 6.36 (dd, *J* = 3.8, 2.7 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 6.97-7.01 (m, 2H), 7.05 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.25 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 8.38 (dd, *J* = 4.9, 1.8 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 175.1, 152.4, 146.4, 139.5, 133.0, 130.8, 130.4, 129.7, 128.3, 123.5, 120.5, 120.0, 109.4, 107.8, 36.7, 17.3 ppm; MS (ESI^+): *m/z* (rel intensity): 266 (MH^+, 14), 185 (100), 108 (1). HRMS (ESI^+): calcd. for $C_{16}H_{16}N_3O$ [MH^+]: 266.1293; found, 266.1297.

Furan-3-yl[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (**3bt).** Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), furan-3-carbaldehyde **2t** (0.17 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether : AcOEt 7:3) afforded **3bt** as a brown-red oil (196.7 mg, 78 %): IR (ATR): 1627, 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.07 (s, 3H), 6.36 (dd, *J* = 3.7, 2.8 Hz, 1H), 6.76 (m, 1H), 7.08 – 7.04 (m, 2H), 7.24 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.40 (t, *J* = 1.7 Hz, 1H), 7.61 (dd, *J* = 7.6, 1.0 Hz, 1H), 8.01 (t, *J* = 1.1 Hz, 1H), 8.33 (dd, *J* = 4.9, 1.8 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 177.22, 152.2, 146.7, 146.3, 143.6, 139.4, 132.2, 130.2, 129.3, 126.8, 123.8, 119.7, 110.1, 110.0, 17.2 ppm; MS (ESI^+): *m/z* (rel intensity): 253 (MH^+, 100), 95 (16). HRMS (ESI^+): calcd. for $C_{15}H_{13}N_2O_2$ [MH^+] 253.0977; found, 253.0982.

Removal of the 2-Pyrimidyl Directing Group. General procedure. Under argon atmosphere, a solution of **3aa, 3ab** or **3ak** (1 mmol) and NaOEt (3 mmol) in DMSO (5 mL) was stirred at 100 °C for 2.5-3.5 h. The reaction was allowed to cool down, and EtOAc (10 mL) and H_2O (15 mL) were added. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layer were washed with H_2O (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography affording **5a,b,k**.

Phenyl(1*H*-pyrrol-2-yl)methanone (5a). Following the general procedure **3aa** (249.6 mg, 1 mmol) was treated with NaOEt (204.3 mg, 3

mmol) in DMSO (5 mL). After 2,5 h at 100 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **5a** as a white solid, whose data are coincidental to those reported[13] (153.6 mg, 90%): mp (CH_2Cl_2): 76-78 °C (Lit.[13] 77-78 ºC); IR (ATR): 3282, 1609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 6.35-6.38 (m, 1H), 6.92 (ddd, *J* = 3.8, 2.4, 1.3 Hz, 1H), 7.19 (td, *J* = 2.4, 1.3 Hz, 1H), 7.43-7.52 (m, 2H), 7.56-7.61 (m, 1H), 7.92-7.96 (m, 2H), 10.53 (br s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 186.1, 138.5, 131.8, 131.2, 129.0, 128.3, 125.8, 119.9, 111.0 ppm; MS (ESI^+): *m/z* (rel intensity): 172 (MH^+, 100), 105 (45). HRMS (ESI^+): Calcd. for $C_{11}H_{10}NO$ [MH^+] 172.0762; found, 172.0767.

(1*H*-Pyrrol-2-yl)(*p*-tolyl)methanone (**5b).** Following the general procedure **3ab** (287.0 mg, 1.09 mmol) was treated with NaOEt (222.1 mg, 3.27 mmol) in DMSO (10 mL). After 3 h at 100 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **5b** as white solid whose data are coincidental to those reported[13] (191.3 mg, 95%): mp (CH_2Cl_2): 120-122°C (Lit.[13] 118-119 ºC); IR (ATR) 3429, 1733, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 2.47 (s, 3H), 6.36 (dt, *J* = 3.8, 2.5 Hz, 1H), 6.94 (ddd, *J* = 3.8, 2.5, 1.4 Hz, 1H), 7.19 (td, *J* = 2.7, 1.4 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 2H), 10.54 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 184.8, 142.5, 135.8, 131.3, 129.2, 129.0, 125.5, 119.5, 110.9, 21.6 ppm; MS (ESI^+): *m/z* (rel intensity): 186 (MH^+, 89), 119 (29), 94 (8). HRMS (ESI^+): calcd. for $C_{12}H_{12}NO$ [MH^+] 186.0919; found, 186.0914.

(2,6-Dimethoxyphenyl)(1*H*-pyrrol-2-yl)methanone (**5k).** Following the general procedure **3ak** (347.1 mg, 1.12 mmol) was treated with NaOEt (229.1 mg, 3.37 mmol) in DMSO (10 mL). After 3.5 h at 100 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **7k** as orange solid, whose data are coincidental to those reported[4a] (234.6 mg, 91%): mp (CH_2Cl_2):192-194 °C; IR (ATR): 3278, 1623, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 3.75 (s, 6H), 6.24 (dt, *J* = 3.8, 2.4 Hz, 1H), 6.57 (ddd, *J* = 3.8, 2.4, 1.4 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 2H), 7.10 (td, *J* = 2.7, 1.4 Hz, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 10.00 (br s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 183.9, 157.8, 133.4, 130.7, 125.4, 119.2, 118.0, 110.7, 104.1, 56.0 ppm; MS (ESI^+): *m/z* (rel intensity): 254 (MNa^+, 100), 232 (MH^+, 2), 165 (7). HRMS (ESI^+): calcd. for $C_{13}H_{13}NNaO_3$ [MNa^+] 254.0793; found, 254.0785.

Deprotection of 3ba. Methyl trifluoromethanesulfonate (0.07 mL, 0.62 mmol) was added dropwise to a solution of **3ba** (131.9 mg, 0.50 mmol) in dry CH_2Cl_2 (7 mL) at 0 °C, and the resulting solution was stirred for 24 h at room temperature. Then, the solvent was removed under vacuum, and the residue was dissolved in MeOH (10 mL). A 2 M aq. NaOH solution (6 mL) was added. The resulting solution was stirred at 60 °C for 24 h. The solvents were removed, and the resulting residue was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with H_2O (2 × 15mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography afforded **5a** as a white solid (58.0 mg, 68 %).

(3-Chloro-2,6-dimethoxyphenyl)(4,5-dichloro-1*H*-pyrrol-2-yl)methanone (6). To a stirred solution of **5k** (113.5 mg, 0.49 mmol) in acetonitrile (6 mL), NCS (164.2 mg, 1.23 mmol) was added and the resulting solution was stirred 24 h at 50 °C. Then, the solvent was evaporated, and the residue was partitioned between water (100 mL) and diethyl ether (100 mL). The aqueous layer was separated and extracted with diethyl ether (2 × 50 ml). The combined extracts were washed with water (20 mL), dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (silica gel, petroleum ether/AcOEt 9/1) affording **6** as light brown solid (132.6 mg, 81%): mp (CH_2Cl_2): 171-173 ºC; IR (ATR,): 3219, 1729, 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 3.77 (s, 3H), 3.85 (s, 3H), 6.50 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 8.9 Hz, 1H), 7.42 (d, *J* = 8.9 Hz, 1H), 10.60 (br s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 181.1, 156.4, 153.9, 131.7, 129.8, 123.3, 122.3, 119.7, 119.0, 112.3, 107.9, 62.6, 56.2 ppm; MS (ESI^+): *m/z* (rel intensity): 340 (MH^++ 6, 1), 338 (MH^++ 4, 13), 336 (MH^++ 2, 52), 334 (MH^+, 53), 201 (24), 199 (110); HRMS (ESI^+): calcd. for $C_{13}H_{11}Cl_3NO_3$ [MH^+] 333.9805; found: 333.9803.

(3-Chloro-2-hydroxy-6-methoxyphenyl)(4,5-dichloro-1*H*-pyrrol-2-yl)methanone (7). A solution of **6** (121.0 mg, 0.36 mmol) in dry dichloromethane (4 mL) was added dropwise *via* syringe to a stirred suspension of $AlCl_3$ (964.4 mg, 7.23 mmol) in dichloromethane (4 mL) in ice bath. The reaction mixture was stirred for 24 hours at room temperature. Aqueous 5% sulfuric acid on ice was added to quench the reaction mixture, the organic phase was collected and the aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined extracts were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (silica gel, petroleum ether/AcOEt 8/2) affording **7** as white solid (64.5 mg, 56%): mp (CH_2Cl_2): 180-182 ºC; IR (ATR,): 3518, 3246, 1587 cm^{-1}; ^1H NMR (300 MHz, Acetone-d_6): 3.77 (s, 3H), 6.65 (s, 1H), 6.70 (d, *J* = 8.9 Hz, 1H), 7.42 (d, *J* = 8.9 Hz, 1H), 8.71 (br s, 1H), 12.00 (br s, 1H) ppm; ^{13}C NMR (75.5 MHz, Acetone-d_6): *δ* 180.7, 157.0, 151.2, 131.0, 130.8, 120.1, 117.0, 116.7, 113.2, 110.8, 104.2, 55.5 ppm; MS (ESI^+): *m/z* (rel intensity): 326 (MH^++ 6, 2), 324 (MH^++ 4, 23), 322 (MH^++ 2, 99), 320 (MH^+, 100), 187 (18), 185 (77); HRMS (ESI^+): calcd. for $C_{12}H_9Cl_3NO_3$ [MH^+] 319.9651; found: 319.9648.

(1-Methyl-1*H*-pyrrol-2-yl)(*p*-tolyl)methanone (8) A solution of **5b** (166.5 mg, 0.9 mmol) in dry dimethylformamide (3 mL) was added dropwise to a stirred suspension of NaH (60% in mineral oil, 39.6 mg, 0.99 mmol) in anhydrous DMF (3 mL). Then, CH_3I (0.07 mL, 1.8 mmol) was added and after 3.5 h at room temperature the reaction was quenched with water (20 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic phase was washed with water (2 × 15 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/AcOEt 9/1) affording **6** as colorless oil, whose data are coincidental to those reported[13] (177 mg, 99%): IR (ATR,): 1736, 1623 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 2.43 (s, 3H), 4.03 (s, 3H), 6.16 (dd, *J* = 4.1, 2.5 Hz, 1H), 6.76 (dd, *J* = 4.1, 1.7 Hz, 1H), 6.90 (t, *J* = 2.1 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* 186.0, 141.9, 137.2, 131.2, 130.6, 129.4, 128.8, 122.4, 108.0, 37.3, 21.5 ppm; MS (ESI^+): *m/z* (rel intensity): 200 (MH^+, 100), 119 (77). HRMS (ESI^+): calcd. for $C_{13}H_{14}NO$ [MH^+] 200.1075; found: 200.1066.

Synthesis of 2-[1-methyl-5-(4-methylbenzoyl)-1*H*-pyrrol-2-yl]acetic acid (**Tolmetin**, **9).** Under argon atmosphere, a solution of **6** (154.4 mg, 0.80 mmol), $Mn(OAc)_2{\cdot}4H_2O$ (4.9 mg, 0.02 mmol), triphenylphosphine (10.5 mg, 0.05 mmol), $NaIO_4$ (102.3 mg, 0.48 mmol), NaOAc (65.6 g, 0.80 mmol) and tri(ethoxycarbonyl)methane (0.08 mL, 0.4 mmol) in dry acetic acid (1 mL) was stirred at 70 °C for 24 h. After cooling the reaction mixture to room temperature, the mixture was added Me_2S (1 mL) and passed through a short pad of Celite (EtOAc) and the filtrate was evaporated under reduced pressure. KOH (2.5 M in water, 10 mL) and 1,4-dioxane (2 mL) were added and the reaction mixture was stirred at 110 °C for 24 h. After cooling the reaction mixture to room temperature, the mixture was evaporated under reduced pressure. The residue was extracted with EtOAc (2 × 15 mL). The water layer was poured into HCl (1.0 M, 20 mL) and extracted with EtOAc (2 × 15 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, petroleum ether/AcOEt 6/4) affording **7** as a white solid, whose data are coincidental to those reported[30a] (57.4 mg, 56%): mp (CH_2Cl_2) = 154-155 °C (Lit.[30a] 160-161 ºC); IR (ATR) 3225, 1739, 1619 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): *δ* 2.42 (s, 3H), 3.84 (s, 2H), 3.95 (s, 3H), 6.15 (d, *J* = 4.0 Hz, 1H), 6.63 (d, *J* = 4.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, acetone-d_6): *δ* 184.9, 170.2, 141.6, 137.7, 135.9, 131.0, 129.2, 128.6, 121.5, 109.2, 32.5, 31.9, 20.6 ppm; MS (ESI^+): *m/z* (rel intensity): 258 (MH^+, 100), 236 (54), 119 (54). HRMS (ESI^+): calcd. for $C_{15}H_{16}NO_3$ [MH^+] 258.1130; found: 258.1120

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[1] a) S. Cascioferro, M. V. Raimondi, M. G. Cusimano, D. Raffa, B. Maggio, G. Daidone, D. Schillaci, *Molecules* **2015**, *20*, 21658-21671; b) Y.-X. Liu, P.-X. Zhang, Y.-Q. Li, H.-B. Song, Q.-M. Wang, *Mol. Divers.* **2014**, *18*, 593-598.

[2] a) P. W. Le Quesne, Y. Dong, T. A. Blythe in *Alkaloids: Chemical and Biological Perspectives*, *Vol. 13*, (Ed. S. W. Pelletier), Pergamon, Amsterdam, **1999**, pp. 237-287; b) G. W. Gribble in *The Alkaloids*, *Vol. 71* (Ed. H.-J. Knolker), Academic Press, San Diego, **2012**, pp. 1-165.

[3] K. Valderrama, E. Pradel, A. M. Firsov, H. Drobecq, H. Bauderlique-le Roy, B. Villemagne, Y. N. Antonenko, R. C. *Antimicrob. Agents Chemother*. **2019**, *63*, e01450-19.

[4] a) K. V. Rao, G. C. Reddy, ***J. Agric. Food Chem.*** **1990**, ***38,*** 1260-1263; b) H. Gross, J. E. Loper, ***Nat. Prod. Rep.*** **2009**, ***26,*** 1408-1446.

[5] a) C. Pullen, P. Schmitz, K. Meurer, D. D. von Bamberg, S. Lohmann, S. De Castro Franca, I. Groth, B. Schlegel, U. Möllmann, F. Gollmick, U. Gräfe, E. Leistner, *Planta* **2002**, *216*, 162–167; b) H. Kikuchi, M. Sekiya, Y. Katou, K. Ueda, T. Kabeya, S. Kurata, Y. Oshima, *Org Lett.* **2009**, *11*, 1693-1695.

[6} For selected reviews, see: a) P. Hollingworth, *Br. J. Clin. Pharmacol.* **1983**, *32*, 73-77; b) A. Calin, *Br. J. Reumatol.* **1993**, *23*, 301-308; c) A. A. Ramadan, A. M. Elbakry, A. H. Esmaeil, S. A. Khaleel, *J. Pharm. Investig.* **2018**, *48*, 673-683; d) M. A. Akl, H. R. Ismael, F. I. A. Allah, A. A. Kassem, A. M. Samy, *Drug Dev. Ind. Pharma.* **2019**, *45*, 252-264.

[7] J. Bergman, T. Janosik in *Modern Heterocyclic Chemistry, Vol. 1* (Eds. J. Álvarez-Builla, J. J. Vaquero, J. Barluenga), Wiley-VCH Verlag & Co. KGaA, Weinheim, **2011**, pp. 269-375.

[8] a) A. R. Katritzky, K. Suzuki, S. K. Singh, H.-Y. He, *J. Org. Chem.* **2003**, *68*, 5720-5723, and references therein; b) R. J. Mullins, K. E. Schwieter in *Name Reactions in Heterocyclic Chemistry II* (Ed. J. J. Li), John Wiley & Sons, Inc., Hoboken, New Jersey, **2011**, pp. 53-59.

[9] G. Sartori, R. Maggi, *Chem. Rev*. **2006,** *106*, 1077-1104; b) G. Sartori, R. Maggi, *Chem. Rev*. **2011,** *111*, PR181-PR214.

[10] I. Komoto, J. Matsuo, S. Kobayashi, *Top. Catal.* **2002**, *19*, 43-47.

[11] J. E. Taylor, M. D. Jones, J. M. Williams, S. D. Bull, *Org Lett.* **2010**, *12*, 5740-5743.

(12) C. Pan, X. Jia, J. Cheng, *Synthesis* **2012**, *44*, 677-685.

[13] F. Jafarpour, H. Hazrati, M. Darvishmolla, *Adv. Synth. Catal.* **2014,** *356*, 3784-3788.

[14] For a review, see: a) S.-F. Wu, *Chem. Eur. J.* **2015**, *21*, 12252-12265. For relevant recent examples: b) K. Jing, J.-P. Yao, Z.-Y. Li, Q.-L. Li, H.-S. Lin, G.-W. Wang, *J. Org. Chem*. **2017**, *82,* 12715-12725; c) K. K. Jing, X.-N. Wang, G.-W. Wang, *J. Org. Chem*. **2019**, *84*, 161-172; c) G. Jiang, S. Wang, J. Zhang, J. Yu, Z. Zhang, F. Ji, *Adv. Synth. Catal.* **2019**, *361*, 1798-1802; d) M. San Segundo, A. Correa, *Chem. Sci.* **2019**, *10*, 8872-8879.

[15] C. Pan, H. Jin, X. Liu, Y. Cheng, C. Zhu, *Chem. Commun*. **2013**, *49*, 2933-2935.

[16] a) X.-B. Yan, Y.-W. Shen, D.-Q. Chen, P. Gao, Y.-X. Li, X.-R. Song, X.-Y. Liu, Y.-M. Liang, *Tetrahedron*, **2014**, *70*, 7490-7495; b) W. Wang, J. Liu, Q. Gui, Tan, *Synlett* **2015**, *26*, 771-778.

[17] C. Li, W. Zhu, S. Shu, X. Wu, H. Liu, *Eur. J. Org. Chem*. **2015**, 3743-3750.

[18] Y. Zhao, U. K. Sharma, F. Schröder, N. Sharma, G. Song, E. V. Van der Eyken, *RSC Advances*, **2017**, *7*, 32559-32563.

[19] S. Maiti, L. Burgula, G. Chakraborti, J. Dash, *Eur. J. Org. Chem*. **2017**, 332-340.

[20] J. Pospech, A. Tlili, A. Spannenberg, H. Neumann, M. Beller, *Chem. Eur. J.* **2014**, *20*, 3135-3141.

[21] a) V. Ortiz-de-Elguea, N. Sotomayor, E. Lete, E. *Adv. Synth. Catal.* **2015**, *357*, 463-473; b) A. Carral-Menoyo, V. Ortiz-de Elguea, M. Martínez-Nunes, N. Sotomayor, E. Lete, *Mar. Drugs* **2017**, *15*, 276; c) A. Carral-Menoyo, A. Misol, M. Gómez-Redondo, N. Sotomayor, E. Lete, *J. Org. Chem.* **2019**, *84*, 2048-2060; d) A. Carral-Menoyo, L. Sotorrios, V. Ortiz-de-Elguea, A. Díaz-Andrés, N. Sotomayor, E. Gómez-Bengoa, E. Lete, *J. Org. Chem.* **2020**, *85*, 2486-2503.

[22] See for example: a) S. Bag S, R. Jayarajan, U. Dutta, R. Chowdhury, R. Mondal, D. Maiti, *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 12538-12542; *Angew. Chem.* **2017**, *129*, 12712-12716 b) M. Brochetta, T. Borsari, S. Bag, S. Jana, S. Maiti, A. Porta , D. B. Werz, G. Zanoni, D. Maiti, *Chem. Eur. J.* **2019**, *25*, 10323-10327; c) S. Porey, X. Zhang, S. Bhowmick, V. K. Singh, S. Guin, R. S. Paton, D. Maiti, *J. Am. Chem. Soc.* **2020**, *142*, 3762-3774.

[23] J. Vana, J. Bartacek, J. Janusek, J. Roithova, M. Sedlak, *J. Org. Chem.* **2019**, *84*, 12746-12754.

[24] (a) J.-H. Chu, S.-T. Chen, M.-F. Chiang, M.-J. Wu, *Organometallics* **2015**, *34*, 953-966; b) J.-H. Chu, M.-F. Chiang, C.-W. Li, Z.-H. Su, S.-C. Lo, M.-J. Wu, *Organometallics* **2019**, *38*, 2105-2119.

[25] T. Caronna, G. Fronza, F. Minisci, O. Porta, *J. Chem. Soc. Perkin. Trans. 2* **1972**, 1477-1481.

[26] F. De Vleeschouwer, V. Van Speybroeck, M. Waroquier, P. Geerlings, F. De Proft, *Org. Lett*. **2007**, *9*, 2721-2724.

[27] M. V. Raimondi, D. Schillaci, S. Petruso, *J. Heterocycl. Chem.* **2007**, *44*, 1407-1411.

[28] Y. Hayse, N. Miki, K. Ohba, PCT Int. Appl., WO 9953758 A1 19991028, October 28, 1999; *Chem Abstr*. **1999**, *131*, 296499.

[29] T. Oshima, T. Kamigauchi, Y. Fukui, PCT Int. Appl., WO 9818760 A1 19980507, May 07, 1998. *Chem Abstr*. **1998**, *128*, 308396.

[30] R. Kurosawa, K. Satoh, N. Kikuchi, H. Kikuchi, D. Saigusa, M. Al-Mamun, M. A. H. Siddique, J. Omura, T. Satoh, S. Sunamura, M. Nogi, K. Numano, S. Miyata, A. Uruno, K. Kano, Y. Matsumoto, T. Doi, J. Aoki, Y. Oshima, M. Yamamoto, H. Shimokawa, *Circ. Res*. **2019**, 125, 309-327.

[31] K. Hattori, A. Ziadi, K. Itami, J. Yamaguchi, *Chem. Commun*. **2014**, *50*, 4105-4107.

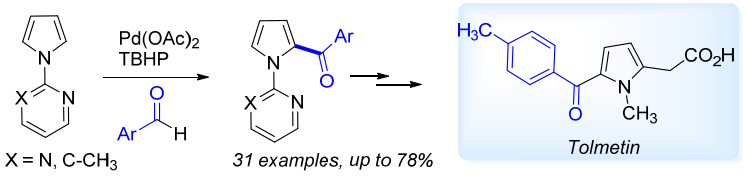
[32] L. A. Reddy, S. Chakraborty, R. Swapna, D. Bhalerao, G. C. Malakondaiah, M. Ravikumar, A. Kumar, G. S. Reddy, J. Naram, N. Dwivedi, A. Roy, V. Himabindu, B. Babu, A. Bhattacharya, R. Bandichhor, *Org. Proc. Res. Develop.* **2010,** *14,* 362–368, and references therein.

[33] B. Schweitzer-Chaput, M. A. Horwitz, E. de Pedro Beato, P. Melchiorre, *Nature Chem*. **2019**, *11*, 129-135.

[34] a) Z.-Q. Liu, Z. Li, *Chem. Commun*. **2016**, *52*, 14278-14281; b) E. Flórez-López, L. B. Gómez-Pérez, L. D. Miranda, *Tetrahedron Lett.* **2010**, *51*, 6000-6002. In a previous work of the synthesis of Tolmetin ethyl ester, see: c) E. Baciocchi, E. Muraglia, G. Sleiter, *J. Org. Chem.* **1992,** *57,* 6817-6820.

Entry for the Table of Contents

Key Topic: C-H Acylation



The oxidative C-H acylation of pyrrole with aldehydes has been carried out avoiding the formation of diacylated compounds. This acylation protocol has been applied as the key step for improved syntheses of Celastramycin analogues and non-steroidal anti-inflammatory drug Tolemtin,