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Iodine(III)-mediated aromatic amidation vs olefin amidohydroxylation. The amide *N*-substituent makes the difference☆

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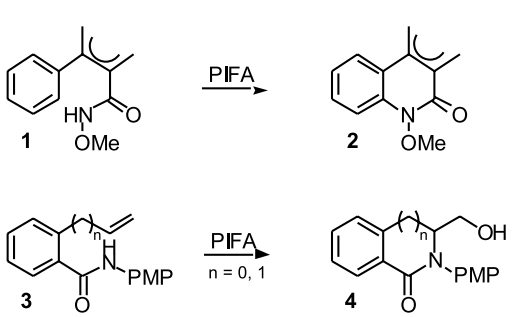
Abstract—A series of *N*-methoxy- and *N-para*-methoxyphenylacetamides simultaneously substituted at the α position by a benzyl and an allyl group have been treated with phenyliodine(III)bis(trifluoroacetate) to generate stabilized *N*-acylnitrenium intermediates. It has been observed that, when starting from *N*-methoxy substituted amides, such intermediates are intramolecularly trapped by nucleophilic arene rings to render the quinolinone skeleton. Alternatively, under the same reaction conditions, *N-para*-methoxyphenylamides afford pyrrolidinone derivatives through an olefin amidohydroxylation process.

1. Introduction

With the aim of developing the enormous potentiality that some hypervalent iodine reagents can provide in organic synthesis,[1] our group started a program directed to expand the applicability of phenyliodine(III)bis(trifluoroacetate) (PIFA) in heterocyclic chemistry.[2] Attracted by the clean transformations usually achieved, the mild conditions employed, and the low toxicity associated to it, we decided to expand the use of this iodine(III) reagent in new synthetic challenges. Thus, we have recently reported the synthesis of different heterocycle-fused quinolinones[3] of type **2** and 1,4-diazepin-2-ones[4] by an electrophilic aromatic amidation process, and the synthesis of the isoquinolinone and isoindolinone skeletons[5] of type **4** by a novel olefin amidohydroxylation reaction promoted by PIFA (see Scheme 1).[6] To explain the observed behavior, it is accepted[7] that when the mildly oxidant I(III) reagent reacts with properly substituted amides *N*-acylnitrenium intermediates are generated. Finally, in the presence of nucleophilic species, the so-obtained electrophilic intermediates are trapped intramolecularly to form new C–N linkages.

During the optimization of both protocols it was found that substitution on the amidic nitrogen played a determinant role in the success of the experiment. Thus, while the aromatic amidation protocol was best carried out on *N*-methoxy substituted amides, as **1** (see Scheme 1), the *N-para*-methoxyphenyl (PMP) substituted amides of type **3** were selected as the derivatives of choice to perform the amidohydroxylation process. Alerted by this intriguing observation, we were aware that a remarkable effect on the chemoselective outcome of the reaction would arise if the nitrenium intermediate were generated on a doubly-benzyl and allyl-substituted *N*-methoxy (or *N-para*-methoxyphenyl) acetamides of type **7** and **8**. According to our expectations, this intermediate would be eventually trapped univocally with only one of the internal nucleophiles. The results presented here will confirm this hypothesis.



Scheme 1. PIFA-mediated aromatic amidation and olefin amidohydroxylation reactions.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.06.007

Keywords: Hypervalent iodine; Quinolinones; Pyrrolidinones; *N*-acylnitrenium; PIFA.

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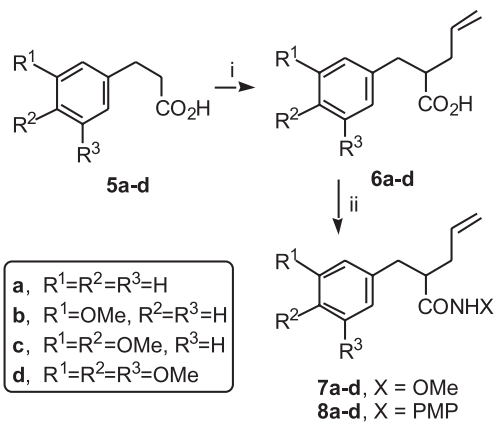
2. Results and discussion

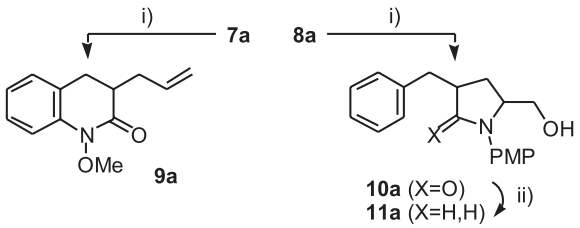
Amide precursors **7** and **8** were prepared (see Scheme 2) in a two-step sequence starting from commercially available hydrocinnamic acids **5a-d**, which were alkylated with allyl bromide under basic (LDA) conditions in good (69–98%) yields. With these substrates in hand, two series of amides were synthesized. Thus, by treatment of carboxylic acids **6a-d** with methoxylamine hydrochloride, amides **7a-d** were easily obtained when the reaction was assisted by the uronium-coupling reagent TBTU.[8] Alternatively, a combination of carbodiimide EDC and hydroxybenzotriazole HOBt was required to optimize the reaction of acids **6a-d** with *para*-anisidine to render amides **8a-d**.[9]



Scheme 2. Reagents and conditions: (i) LDA, AllylBr, THF, 0 °C to rt; (ii) for **7** series: $NH_2OMe{\cdot}HCl$, Et_3N, TBTU, MeCN; (ii) for **8** series: *p*-anisidine, EDC·HCl, Et_3N, HOBt, CH_2Cl_2, rt. Overall yields: 59% for **7a**, 70% for **7b**, 54% for **7c**, 63% for **7d**, 63% for **8a**, 78% for **8b**, 60% for **8c**, 54% for **8d**.

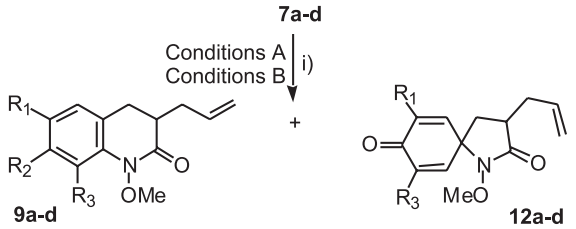
We first examined the behavior of amides **7a** and **8a** under the action of the I(III) reagent. Typically, a solution of 1.5 equiv. of PIFA in CF_3CH_2OH is added to a cold (−20 °C) solution of the amide in the same solvent (~5 mg/mL). When the starting material is consumed (~1 h), the reaction mixture is washed with Na_2CO_3 (10% aq.) and extracted with CH_2Cl_2. Finally, the residue is column chromatographed to afford the final products.

As originally planned, the optimized conditions employed for this transformation led to the construction of the quinolinone skeleton **9a** starting from amide **7a** (see Scheme 3). By altering the temperature and the solvent of the reaction (CH_2Cl_2), lowered yields were obtained but, in all cases, the allylic residue remained intact. Alternatively, amide **8a** was treated with PIFA under the same reaction conditions described above. In this case, the *N*-acyl-nitrenium ion generated was trapped by the olefin fragment with total chemoselectivity to afford pyrrolidinone **10a** in good yield without affecting the integrity of the benzyl group. Due to the instability of this pyrrolidinone compound, a full characterization was carried out on the corresponding reduced derivative **11a**, which was obtained by treatment of the crude **10a** with $BH_3{\cdot}SMe_2$.



Scheme 3. Reagents and conditions: (i) PIFA, CF_3CH_2OH, −20 °C (75% for **9a**); (ii) $BH_3{\cdot}SMe_2$, THF, 0 °C to rt (72% for **11a** two steps).

A number of 3-allyl-quinolin-2-ones of type **9** can be found in Nature.[10] For that reason, and in order to test the potential effect that substitution can exert on the chemoselectivity of the process, we decided to prepare a series of methoxy-substituted quinolinones **9a-d** from **7a-d**. In addition, and trying to get more information about the behavior of these amide precursors under the action of the oxidative I(III) reagent, a further reaction condition was tested on methoxyamides **7a-d**. It has been previously shown that TFA, employed as an additive in CH_2Cl_2 as solvent, can activate the cyclization of such kind of substrates.[7c] In Scheme 4 a comparison of both methods is presented.

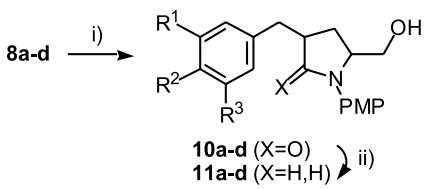


				Condt. A		Condt. B	
7	R^1	R^2	R^3	**9** (%)	**12** (%)	**9** (%)	**12** (%)
a	H	H	H	75	0	71	0
b	OMe	H	H	65	0	44	0
c	OMe	OMe	H	66	27*	28	43*
d	OMe	OMe	OMe	41	11	4	93

* Detected by GC-MS

Scheme 4. Reagents and conditions: (i) PIFA, CF_3CH_2OH, −20 °C (Condt. A); (i) PIFA, TFA, CH_2Cl_2, 0 °C (Condt. B).

Analogously, we next tried to expand the ability of PIFA to generate a series of pyrrolidinones **10** from the corresponding *N-para*-methoxyphenyl substituted amides **8** under the usual conditions depicted above (Scheme 5).



Scheme 5. Reagents and conditions: (i) PIFA, CF_3CH_2OH, 0 °C to rt; (ii) $BH_3{\cdot}SMe_2$, THF, rt. Overall yields: 72% for **11a**, 68% for **11b**, 67% for **11c**, 59% for **11d**.

As expected, in all cases under study, the action of PIFA on amides **8a-d** rendered chemoselectively pyrrolidinones **10a–d** as a series of unstable derivatives that were immediately reduced to the corresponding pyrrolidines **11a-d** in good overall yields.

The main observation that can be concluded from our experiments is that the cyclization process can take two

different pathways depending on the nature of the amide *N*-substituent to afford either quinoline or pyrrolidine skeletons. To sum up, when starting from *N*-methoxyamides **7a-d** quinolinones **9a-d** are obtained in all cases in moderate to good yields, along with the corresponding aza-spiro derivatives **12c** and **12d**, via intermedium **B**, when starting from **7c** and **7d**, respectively. In the latter cases, a methoxy group located in *para* position to the alkyl chain is responsible for the corresponding *ipso* attack of the internal electrophile.[11] When applying TFA as an activating agent, such process becomes dominant. Alternatively, intermedium **A** can be also trapped by the olefin fragment, when starting from amides **8a-d**, to form the heterocyclic core **C** stabilized as an aziridinium ion by the donating properties of the *para*-methoxyphenyl (PMP) group. This new intermediate is opened by a free trifluoroacetate group (delivered from PIFA), and the resulting non-isolated trifluoroacetylester is hydrolyzed during the work up (Na_2CO_3, H_2O) to render derivatives **10a-d**. A plausible mechanism for these transformations is shown in Figure 1.

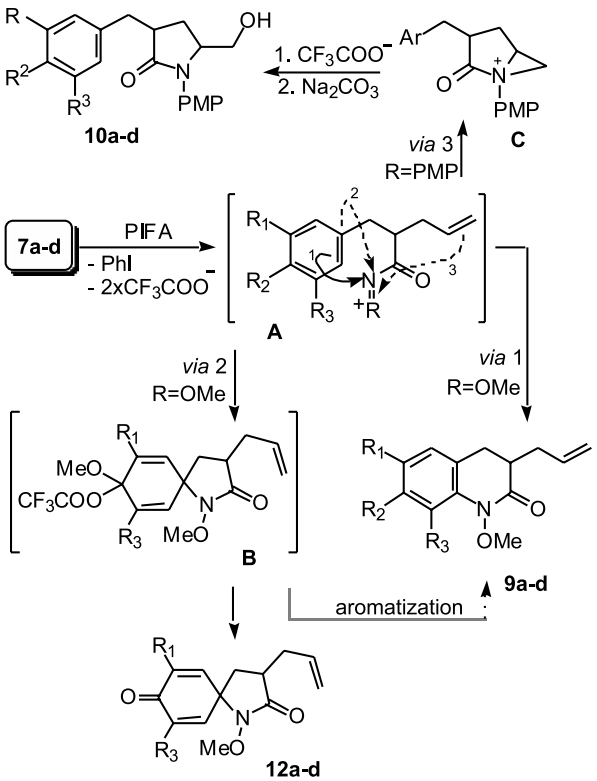


Figure 1. Proposed mechanisms for the transformation of amides **7** into quinolinones **9**, aza-spiro derivatives **12**, and pyrrolidines **10a-d**.

No simple explanation can be argued to justify these results. If we consider an electronic control in the reaction, no substantial differences can be estimated between the methoxy and the *para*-mehoxyphenyl groups. For that reason, we propose that steric effects may govern the course of the reaction since both groups have a significant difference in size volume. In fact, the notorious decrease in the yield for the transformation of amide **7d** into the 1,6,7,8-tetramethoxy substituted quinolinone **9d** as a result of a steric hindrance between methoxy groups in 1 and 8 positions, supports this suggestion.

3. Conclusions

In summary, the present work shows that the substituent required to stabilize the *N*-acylnitrenium intermediates generated by the action of PIFA on properly substituted amides can exert a selective control in the course of the cyclization reaction of 2-allyl-2-benzylacetamides to afford either 3-allyl-quinolin-2-ones or 3-benzyl-pyrrolidin-2-ones in good yields and complete selectivity.

4. Experimental

Melting points were measured in a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer R-1420 infrared spectrophotometer as KBr plates or as neat liquids and peaks are reported in cm^{-1}. NMR spectra were recorded on a Bruker ACE-250 instrument (250 MHz for ^1H and 62.83 MHz for ^{13}C) at 20 °C. Chemical shifts (δ) were measured in ppm relative to chloroform (δ=7.26 for ^1H or 77.00 for ^{13}C) as internal standard. Coupling constants, *J*, are reported in hertz. DEPT experiments were used to assist with the assignation of the signals. HRMS spectra were recorded at the University of Vigo on a VG Autospec M instrument.

4.1. General procedure for the α-alkylation of hydrocinnamic acids 5a-d

4.1.1. Synthesis of 2-allyl-3-phenylpropionic acid (6a). *n*-BuLi (26.2 mL, 1.6 M in *n*-hexane, 42 mmol) was added onto a cold (0 °C) solution of $^iPr_2NH$ (5.9 mL, 42 mmol) in 30 mL of THF, and the mixture was stirred for 30 min. Then, a solution of hydrocinnamic acid **5a** (3.0 g, 19.9 mmol) in 20 mL of THF was added dropwise over 20 min and stirring was continued for 30 min at the same temperature. The addition of allyl bromide (1.8 mL, 20.9 mmol) was followed by stirring until total consumption of the starting material (tlc, hexanes/EtOAc, 7/3, 6 h). For the work up, pH was adjusted to 2 by addition of HCl (3 M) and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. Then, pH of the aqueous layer was adjusted to 2 and extracted with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered, and the solvent was evaporated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 75/25) to afford carboxylic acid **6a** as a colorless oil (69%).[12]

4.1.2. 2-Allyl-3-(3-methoxyphenyl)propionic acid (6b). According to the general procedure carboxylic acid **6b** was obtained as a colorless oil from **5b** in 98% yield after purification by column chromatography (hexanes/EtOAc, 70/30). ^1H NMR: δ 2.26–2.47 (m, 2H, C*H*$_2$–CH=CH$_2$), 2.74–2.85 (m, 2H, CHCO, C*H*aAr), 2.99 (dd, *J*=15.8, 9.9 Hz, 1H, C*H*bAr), 3.80 (s, 3H, OCH_3), 5.08–5.16 (m, 2H, CH=C*H*$_2$), 5.72–5.88 (m, 1H, C*H*=CH$_2$), 6.77–6.81 (m, 3H, H_{arom}), 7.22 (t, *J*=7.9 Hz, 1H, H_{arom}), 11.1 (sa, 1H, COOH). ^{13}C NMR: δ 35.5, 37.2 (CH_2), 46.9 (CH), 55.0 (OCH_3), 117.5 (CH=*C*H$_2$), 111.8, 114.6, 121.2, 129.4, 134.6 (t-C_{arom}, *C*H=CH$_2$), 140.3, 159.5 (q-C_{arom}), 181.3 (CO). IR (film): 2900–3200 (OH), 1707 (CO). MS (EI) *m/z* (%): 220 (M^+, 24), 122 (100), 121 (58). HRMS calculated for $C_{13}H_{16}O_3$ 220.1099, found 220.1085.

4.1.3. 2-Allyl-3-(3,4-dimethoxyphenyl)propionic acid (6c). According to the general procedure carboxylic acid **6c** was obtained as a white solid from **5c** in 74% yield after purification by column chromatography (hexanes/EtOAc, 55/45) followed by crystallization from *n*-pentane. Mp: 64–65 °C (*n*-pentane). Lit.[13] 65–67 °C (benzene–hexane).

4.1.4. 2-Allyl-3-(3,4,5-trimethoxyphenyl)propionic acid (6d). According to the general procedure carboxylic acid **6d** was obtained as a white solid from **5d** in 68% yield after purification by column chromatography (hexanes/EtOAc, 40/60) followed by crystallization from hexanes. Mp: 85–87 °C (hexanes). Lit.[14] 87–89 °C. ^{1}H NMR: δ 2.24–2.44 (m, 2H, CH_2–CH=CH_2), 2.66–2.81 (m, 2H, CHCO, C*H*aAr), 2.91 (dd, *J*=10.3, 5.6 Hz, 1H, C*H*bAr), 3.80 (s, 9H, 3×OCH_3), 5.06–5.13 (m, 2H, CH=CH_2), 5.69–5.86 (m, 1H, C*H*=CH_2), 6.39 (s, 2H, H_{arom}). ^{13}C NMR: δ 35.6, 37.6 (CH_2), 46.9 (CH), 55.9, 60.7 (OCH_3), 117.5 (CH=*C*H_2), 105.7, 134.6 (t-C_{arom}, *C*H=CH_2), 134.4, 136.4, 153.0 (q-C_{arom}), 180.8 (CO). IR (KBr): 3000–3300 (OH), 1707 (CO). MS (El) *m*/*z* (%): 280 (M^+, 30), 182 (71), 181 (100). HRMS calculated for $C_{15}H_{20}O_5$ 280.1311, found 280.1302.

4.2. General procedure for the synthesis of *N*-methoxyamides 7a-d

4.2.1. Synthesis of 2-allyl-*N*-methoxy-3-phenylpropionamide (7a). Et_3N (0.3 mL, 2.1 mmol) was added dropwise onto a solution of carboxylic acid **6a** (200 mg, 1.05 mmol) and NH_2OMe·HCl (91 mg, 1.1 mmol) in MeCN (14 mL) as solvent. After stirring the mixture at room temperature for 30 min, TBTU (351 mg, 1.1 mmol) was added and the stirring was continued during 60 min. For the work-up, a saturated solution of NaCl (10 mL) was added and the solution was extracted with EtOAc (3×15 mL). The combined organic extracts were washed with HC1 5% aq. (15 mL), water (15 mL), 5% aq. $NaHCO_3$ (15 mL) and water again (15 mL). The organic layer was dried with Na_2SO_4, filtered, and the solvent was evaporated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 45/55) to afford amide **7a** as a colorless oil (86%). ^{1}H NMR: δ 2.20–2.30 (m, 1H, C*H*a–CH=CH_2), 2.37–2.47 (m, 2H, C*H*b–CH=CH_2, CHCO), 2.75 (dd, *J*=13.5, 5.1 Hz, 1H, C*H*aPh), 2.92 (dd, *J*=13.5, 8.3 Hz, 1H, C*H*bPh), 3.48 (s, 3H, OCH_3), 5.00–5.12 (m, 2H, CH=CH_2), 5.68–5.84 (m, 1H, C*H*=CH_2), 7.15–7.27 (m, 5H, H_{arom}), 9.80 (s, 1H, NH). ^{13}C NMR: δ 36.2, 38.0 (CH_2), 45.1 (CH), 63.6 (OCH_3), 116.9 (CH=*C*H_2), 126.1, 128.1, 128.9, 135.0 (t-C_{arom}, *C*H=CH_2), 139.1 (q-C_{arom}), 171.7 (CO). IR (film): 3166 (NH), 1655 (CO). MS (El) *m*/*z* (%): 219 (M^+, 2), 178 (21), 91 (100). HRMS calculated for $C_{13}H_{17}NO_2$ 219.1259, found 219.1254.

4.2.2. 2-Allyl-*N*-methoxy-3-(3-methoxyphenyl)-propionamide (7b). According to the general procedure amide **7b** was obtained as a colorless oil from **6b** in 71% yield after purification by column chromatography (hexanes/EtOAc, 50/50). ^{1}H NMR: δ 2.21–2.30 (m, 2H, C*H*a–CH=CH_2, CHCO), 2.39–2.51 (m, 1H, C*H*b–CH=CH_2), 2.73 (dd, *J*=13.3, 4.9 Hz, 1H, C*H*aAr), 2.89 (dd, *J*=13.3, 9.1 Hz, 1H, C*H*bAr), 3.54 (s, 3H, NHOCH_3), 3.76 (s, 3H, OCH_3), 5.02–5.13 (m, 2H, CH=CH_2,), 5.66–5.83 (m, 1H, C*H*=CH_2), 6.71–6.77 (m, 3H, H_{arom}), 7.17 (t, *J*=7.9 Hz, 1H, H_{arom}), 8.29 (s, 1H, NH). ^{13}C NMR: δ 36.3, 38.3 (CH_2), 46.2 (CH), 55.1, 64.2 (OCH_3), 117.4 (*C*H_2=CH), 111.7, 114.6. 121.3, 129.4, 134.9 (t-C_{arom}, *C*H=CH_2), 140.7, 159.6 (q-C_{arom}), 171.9 (CO). IR (film): 3177 (NH), 1648 (CO). MS (El) *m*/*z* (%): 249 (M^+, 3), 203 (12), 121 (100). HRMS calculated for $C_{14}H_{19}NO_3$ 249.1365, found 249.1375.

4.2.3. 2-Allyl-3-(3,4-dimethoxyphenyl)-*N*-methoxy-propionamide (7c). According to the general procedure amide **7c** was obtained as a colorless oil from **6c** in 73% yield after purification by column chromatography (hexanes/EtOAc, 45/55) followed by crystallization from *n*-pentane. Mp: 60–62 °C (*n*-pentane). ^{1}H NMR: δ 2.14–2.31 (m, 2H, C*H*a–CH=CH_2, CHCO), 2.35–2.52 (m, 1H, C*H*b–CH=CH_2), 2.70 (dd, *J*=13.5, 5.1 Hz, 1H, C*H*aAr), 2.87 (dd, *J*=13.5, 9.9 Hz, 1H, C*H*bAr), 3.57 (s, 3H, NHOCH_3), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.04–5.14 (m, 2H, CH=CH_2,), 5.67–5.83 (m, 1H, C*H*=CH_2), 6.68–6.78 (m, 3H, H_{arom}), 7.92 (s, 1H, NH). ^{13}C NMR: δ 36.3, 37.8 (CH_2), 46.2 (CH), 55.7, 64.2 (OCH_3), 117.2 (*C*H_2=CH), 111.0, 112.1. 120.8, 134.9 (t-C_{arom}, *C*H=CH_2), 131.7, 147.4, 148.6 (q-C_{arom}), 172.0 (CO). IR (KBr): 3178 (NH), 1654 (CO). MS (El) *m*/*z* (%): 279 (M^+, 12), 151 (100). HRMS calculated for $C_{14}H_{19}NO_3$ 279.1471, found 279.1476.

4.2.4. 2-Allyl-*N*-methoxy-3-(3,4,5-trimethoxyphenyl)-propionamide (7d). According to the general procedure amide **7d** was obtained as a colorless oil from **6d** in 92% yield after purification by column chromatography (hexanes/EtOAc, 40/60). ^{1}H NMR: δ 2.16–2.26 (m, 2H, C*H*a–CH=CH_2, CHCO), 2.35–2.47 (m, 1H, C*H*b–CH=CH_2,), 2.64 (dd, *J*=13.6, 4.7 Hz, 1H, C*H*aAr), 2.84 (dd, *J*=13.6, 9.3 Hz, 1H, C*H*bAr), 3.53 (s, 3H, NHOCH_3), 3.74 (s, 3H, OCH_3), 3.76 (s, 6H, 2×OCH_3), 4.99–5.09 (m, 2H, CH=CH_2), 5.63–5.79 (m, 1H, C*H*=CH_2), 6.34 (s, 2H, H_{arom}), 8.77 (s, 1H, NH). ^{13}C NMR: δ 36.5, 38.5 (CH_2), 46.0 (CH), 55.9, 60.6, 64.0 (OCH_3), 117.3 (*C*H_2=CH), 105.7, 134.9 (t-C_{arom}, *C*H=CH_2), 135.0, 136.2, 152.9 (q-C_{arom}), 171.9 (CO). IR (film): 3176 (NH), 1654 (CO). MS (El) *m*/*z* (%): 309 (M^+, 15), 181 (100). HRMS calculated for $C_{16}H_{23}NO_5$ 309.1576, found 309.1575.

4.3. General procedure for the synthesis of *N*-*para*-methoxyphenylamides 8a-d

4.3.1. Synthesis of 2-allyl-*N*-(*para*-methoxyphenyl)-3-phenylpropionamide (8a). A solution of carboxylic acid **6a** (300 mg, 1.6 mmol) in CH_2Cl_2 (2 mL) and a solution of *p*-anisidine (291 mg, 2.4 mmol) in CH_2Cl_2 (2 mL) were added sequentially to a cold (0 °C) solution of EDC·HCl (454 mg, 2.4 mmol) and HOBt (299 mg, 2.2 mmol) in the same solvent (4 mL). Then, Et_3N, (0.3 mL, 2.4 mmol) was added dropwise and the mixture was stirred at the same temperature for 2 h and at rt until total consumption of the starting material (tlc, 14 h). For the work-up the mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with HC1 5% aq. (2×15 mL) and with a saturated solution of $NaHCO_3$ (2×15 mL), dried over Na_2S0_4, filtered, and the solvent was evaporated under vacuum. The residue was

purified by crystallization from Et_2O to afford amide **8a** as a white solid (92%). Mp: 109–110 °C (Et_2O). ^1H NMR: δ 2.24–2.34 (m, 1H, C*H*a–CH=CH_2), 2.46–2.66 (m, 2H, C*H*b–CH=CH_2, CHCO), 2.81 (dd, J=13.5, 5.1 Hz, 1H, C*H*aPh), 2.99 (dd, J=13.5, 8.7 Hz, 1H, C*H*bPh), 3.72 (s, 3H, OCH_3), 5.05–5.16 (m, 2H, CH=CH_2), 5.75–5.91 (m, 1H, C*H*=CH_2), 6.73 (d, J=8.7 Hz, 2H, H_{arom}), 7.17–7.28 (m, 7H, H_{arom}), 7.64 (s, 1H, NH). ^{13}C NMR: δ 36.6, 38.5 (CH_2), 49.8 (CH), 55.2 (OCH_3), 117.0 (*C*H_2=CH), 113.7, 122.3, 126.2, 128.3, 128.8, 135.3 (t-C_{arom}, *C*H=CH_2), 130.5, 139.4, 156.2, (q-C_{arom}), 172.7 (CO). IR (KBr): 3295 (NH), 1654 (CO). MS (El) m/z (%): 295 (M^+, 32), 254 (27), 123 (100), 108 (21). HRMS calculated for $C_{19}H_{21}NO_2$ 295.1572, found 295.1582.

4.3.2. 2-Allyl-3-(3-methoxyphenyl)-*N*-(*para*-methoxyphenyl)propionamide (8b). According to the general procedure amide **8b** was obtained as a white solid from **6b** in 80% yield after crystallization from Et_2O. Mp: 78–79 °C (Et_2O). ^1H NMR: δ 2.27–2.36 (m, 1H, C*H*a–CH=CH_2), 2.39–2.61 (m, 2H, C*H*b–CH=CH_2, CHCO), 2.81 (dd, J=13.5, 5.1 Hz, 1H, C*H*aAr), 2.97 (dd, J=13.5. 8.7 Hz, 1H, C*H*bAr), 3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 5.06–5.18 (m, 2H, CH=CH_2), 5.76–5.92 (m, 1H, C*H*=CH_2), 6.73–6.81 (m, 5H, H_{arom}), 7.15–7.22 (m, 4H, H_{arom}, NH). ^{13}C NMR: δ 36.7, 38.6 (CH_2), 50.2 (CH), 54.9, 55.3 (OCH_3), 117.2 (*C*H_2=CH), 111.8, 113.8. 114.3, 121.2, 122.1, 129.4, 135.4 (t-C_{arom}, *C*H=CH_2), 130.5, 141.1, 156.3, 159.6 (q-C_{arom}), 172.5 (CO). IR (KBr): 3283 (NH), 1649 (CO). MS (El) m/z. (%): 325 (M^+, 21), 284 (24), 123 (100), 121 (52), 108 (21). HRMS calculated for $C_{20}H_{23}NO_3$ 325.1678, found 325.1694.

4.3.3. 2-Allyl-3-(3,4-dimethoxyphenyl)-*N*-(*para*-methoxyphenyl)propionamide (8c). According to the general procedure amide **8c** was obtained as a white solid from **6c** in 81% yield after crystallization from Et_2O. Mp: 123–124 °C (Et_2O). ^1H NMR: δ 2.25–2.33 (m, 1H, C*H*a–CH=CH_2), 2.39–2.58 (m, 2H, C*H*b–CH=CH_2, CHCO), 2.74 (dd, J=13.5, 4.3 Hz, 1H, C*H*aAr), 2.93 (dd, J=13.5, 8.7 Hz, 1H, C*H*bAr), 3.71 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.03–5.15 (m, 2H, CH=CH_2), 5.73–5.89 (m, 1H, C*H*=CH_2), 6.68–6.77 (m, 5H, H_{arom}), 7.11 (sa, 1H, NH), 7.22 (d, J=8.7 Hz, 2H, H_{arom}). ^{13}C NMR: δ 36.7, 38.1 (CH_2), 50.2 (CH), 55.1, 55.4, 55.6 (OCH_3), 116.9 (*C*H_2=CH), 111.0, 112.0, 113.7, 120.7, 121.9, 135.4 (t-C_{arom}, CH_2=*C*H), 130.6, 132.0, 147.2, 148.1, 156.1 (q-C_{arom}), 172.7 (CO). IR (KBr): 3319 (NH), 1654 (CO). MS (El) m/z (%): 355 (M^+, 44), 314 (63) 191 (68), 151 (100), 123 (89), 108 (26). HRMS calculated for $C_{21}H_{25}NO_4$ 355.1784, found 355.1770.

4.3.4. 2-Allyl-*N*-(*para*-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)propionamide (8d). According to the general procedure amide **8d** was obtained as a white solid from **6d** in 80% yield after crystallization from Et_2O. Mp: 120–121 °C (Et_2O). ^1H NMR: δ 2.24–2.33 (m, 1H, C*H*a–CH=CH_2), 2.38–2.59 (m, 2H, C*H*b–CH=CH_2, CHCO), 2.72 (dd, J=13.3, 4.4 Hz, 1H, C*H*aAr), 2.92 (dd, J=13.3, 9.3 Hz, 1H, C*H*bAr), 3.69 (s, 6H, 2×OCH_3), 3.73 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.03–5.16 (m, 2H, CH=CH_2), 5.73–5.89 (m, 1H, C*H*=CH_2), 6.37 (s, 2H, H_{arom}), 6.76 (d, J=8.9 Hz, 2H, H_{arom}) 7.07 (sa, 1H, NH), 7.22 (d, J=8.9 Hz, 2H, H_{arom}). ^{13}C NMR: δ 36.8, 39.1 (CH_2), 50.6 (CH), 55.3, 55.8, 60.7 (OCH_3), 117.2 (CH=*C*H_2), 105.7, 113.8, 121.8, 135.4 (t-C_{arom}, *C*H=CH_2), 130.6, 136.2, 153.03, 156.3 (q-C_{arom}), 172.5 (CO). IR (KBr): 3307 (NH), 1660 (CO). MS (El) m/z (%): 385 (M^+ 33), 344 (12), 221 (76), 204 (47), 181 (99), 123 (100), 108 (19). HRMS calculated for $C_{22}H_{27}NO_5$ 385.1889, found 385.1893.

4.4. General procedure for the cyclization of amides 7a–d with PIFA

4.4.1. Synthesis of 3-allyl-1-methoxyquinolin-2-one (9a). A solution of PIFA (147 mg, 0.34 mmol) in CF_3CH_2OH (10 mL) was added onto a cold (−20 °C) solution of amide **7a** (50 mg, 0.23 mmol) in 10 mL of the same solvent. The mixture was stirred at the same temperature until total consumption of the starting material (tlc, 60 min). The reaction was quenched with 10 mL of Na_2CO_3 (aq. 10%) and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with a saturated solution of NaCl (15 mL), dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 75/25) to afford quinolinone **9a** as a colorless oil which was crystallized from *n*-pentane (75%). Mp: 63–65 °C (*n*-pentane). ^1H NMR: δ 2.15–2.27 (m, 1H, C*H*a–CH=CH_2), 2.62–2.77 (m, 3H, C*H*b–CH=CH_2, H-3, H-4a), 2.94 (dd, J=19.8, 9.91 Hz, 1H, H-4b), 3.9 (s, 3H, OCH_3), 5.04–5.12 (m, 2H, CH=CH_2), 5.72–5.88 (m, 1H, C*H*=CH_2), 7.03 (t, J=7.1 Hz, 1H, H_{arom}), 7.14–7.31 (m, 3H, H_{arom}). ^{13}C NMR: δ 29.4, 33.9 (CH_3), 40.3 (CH), 62.4 (OCH_3), 117.7 (CH=*C*H_2), 112.0, 123.5, 127.6, 128.0, 134.9 (t-C_{arom}, CH=CH_2), 123.3, 137.4 (q-C_{arom}), 167.3 (CO). IR (KBr): 1684 (CO). MS (El) m/z (%): 217 (M^+, 100), 186 (52), 146 (67), 117 (76). HRMS calculated for $C_{13}H_{15}NO_2$ 217.1103, found 217.1092.

4.4.2. 3-Allyl-l,6-dimethoxyquinolin-2-one (9b). According to the general procedure quinolinone **9b** was obtained as a colorless oil from **7b** in 65% yield after purification by column chromatography (hexanes/EtOAc, 80/20) which was triturated with *n*-pentane. Mp: 40–41 °C (*n*-pentane). ^1H NMR: δ 2.13–2.26 (m, 1H, C*H*a–CH=CH_2), 2.58–2.73 (m, 3H, C*H*b–CH=CH_2, H-3, H-4a), 2.91 (dd, J=19.8, 9.91 Hz, 1H, H-4b), 3.79 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.03–5.11 (m, 2H, CH=CH_2), 5.71–5.89 (m, 1H, C*H*=CH_2), 6.72 (d, J=2.8 Hz, 1H, H_{arom}), 6.80 (dd, J=8.9, 2.8 Hz, 1H, H_{arom}), 7.11 (d, J=8.9 Hz, 1H, H_{arom}). ^{13}C NMR: δ 29.7, 33.8 (CH_2), 40.3 (CH), 55.4, 62.3 (OCH_3), 117.7 (CH=*C*H_2), 112.1, 113.2, 114.2, 134.9 (t-C_{arom}, *C*H=CH_2), 124.8, 130.9, 155.9 (q-C_{arom}), 166.6 (CO). IR (KBr): 1678 (CO). MS (El) m/z (%): 247 (M^+, 96), 217 (55), 188 (25), 175 (88), 162 (100). HRMS calculated for $C_{14}H_{17}NO_3$ 247.1208, found 247.1204.

4.4.3. 3-Allyl-l,6,7-trimethoxyquinolin-2-one (9c). According to the general procedure quinolinone **9c** was obtained as a colorless oil from **7c** in 66% yield after purification by column chromatography (hexanes/EtOAc, 60/40). ^1H NMR: δ 2.11–2.24 (m, 1H, C*H*a–CH=CH_2), 2.56–2.67 (m, 3H, C*H*b–CH=CH_2, H-3, H-4a), 2.86 (dd, J=20.1, 10.3 Hz, 1H, H-4b), 3.84 (s, 3H, OCH_3), 3.89 (s, 6H, 2×OCH_3), 5.02–5.09 (m, 2H, CH=CH_2), 5.70–5.89

(m, 1H, C*H*=CH_2), 6.67 (s, 1H, H_{arom}), 6.78 (s, 1H, H_{arom}). ^{13}C NMR: δ 29.1, 33.8 (CH_2), 40.6 (CH), 56.2, 56.3, 62.4 (OCH_3), 117.6 (CH=*C*H_2), 97.6, 111.8, 135.0 (t-Carom, *C*H=CH_2), 114.6, 130.9, 145.0, 148.4 (q-C_{arom}), 166.8 (CO). IR (film): 1678 (CO). MS (El) *m*/*z* (%): 277 (M^+, 39), 247 (100), 232 (40), 205 (81), 192 (39), 162 (20). HRMS calculated for $C_{15}H_{19}NO_4$ 277.1314, found 277.1310.

4.4.4. 3-Allyl-l,6,7,8-tetramethoxyquinolin-2-one (9d). According to the general procedure quinolinone **9d** was obtained as a white solid from **7d** in 41% yield after purification by column chromatography (hexanes/EtOAc, 50/50) and then by crystallization from *n*-pentane. Mp: 59–61 °C (*n*-pentane). ^{1}H NMR: δ 2.11–2.23 (m, 1H, C*H*a–CH=CH_2), 2.59–2.72 (m, 3H, C*H*b–CH=CH_2, H-3, H-4a), 2.82 (dd, *J*=20.2, 10.5 Hz, 1H, H-4b), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 5.04–5.10 (m, 2H, CH=CH_2), 5.74–5.90 (m, 1H, C*H*=CH_2), 6.45 (s, 1H, H_{arom}). ^{13}C NMR: δ 31.3, 33.3 (CH_2), 41.6 (CH), 56.1, 60.9, 61.4, 62.9 (OCH_3), 117.4 (CH=*C*H_2), 106.6, 135.3 (t-C_{arom}, *C*H=CH_2), 122.9, 126.0, 142.6, 144.4 150.3 (q-C_{arom}), 168.7 (CO). **IR** (KBr): 1684 (CO). MS (El) *m*/*z* (%): 307 (M^+, 75), 276 (100), 222 (93), 206 (56). HRMS calculated for $C_{16}H_{21}NO_5$ 307.1420, found 307.1412.

4.5. General procedure for the amidohydroxylation of amides 7a-d with PIFA

4.5.1. Synthesis of 4-benzyl-2-hydroxymethyl-1-(*para*-methoxyphenyl)pyrrolidine (11a). A solution of PIFA (219 mg, 0.51 mmol) in 7 mL of CF_3CH_2OH was added onto a cold (−20 °C) solution of amide **8a** (100 mg, 0.34 mmol) in 7 mL of the same solvent, and the mixture was stirred until total consumption of the starting material (tlc, 80 min). Then, 10 mL of Na_2CO_3 (aq. 10%) were added and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with a saturated solution of NaCl (15 mL), dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. Without any further purification, the resulting residue was dissolved in THF (4 mL), cooled to a 0 °C, and $BH_3{\cdot}SMe_2$ (1.7 mL, 2 M in THF, 3.4 mmol) was added dropwise. The reaction mixture was stirred at room temperature until total consumption of the starting material (tlc, 10 h). Then, MeOH was added slowly and the stirring was continued for 15 min. The solvent was removed under vacuum, and treatment with MeOH was repeated twice more. The final residue was purified by column chromatography (hexanes/EtOAc, 30/70) to afford pyrrolidine **11a** as a colorless oil (72%). Mixture of diastereoisomers 1.8/1. ^{1}H NMR: δ 1.39–1.65 (m, 4H, 2×H-3a, 2×H-3b), 1.99–2.12 (m, 1H, H-4 min.), 2.17–2.27 (m, 1H, H-4 maj.), 2.58–2.76 (m, 4H, 2×CH_2Ph), 2.86 (sa, 2H, 2×OH, exchange with D_2O), 2.89–3.14 (m, 4H, 2×H-5a, 2×H-5b), 3.33–3.41 (m, 2H, 2×C*H*aOH), 3.50–3.57 (m, 2H, 2×C*H*bOH), 3.73 (s, 6H, 2×OCH_3), 3.82–3.91 (m, 2H, 2×H-2), 6.54 (d, *J*=9.1 Hz, 2H, H_{arom} maj.), 6.59 (d, *J*=9.1 Hz, 2H, H_{arom} min.), 6.73–6.76 (m, 4H, H_{arom}), 7.15–7.32 (m, 10H, H_{arom}). ^{13}C NMR: δ 36.0, 37.9 (CH_2), 36.5, 38.9 (C-4), 39.8, 40.6 (CH_2), 48.9, 50.6 (CH_2), 55.7 (OCH_3), 67.0, 67.2 (CH_2OH), 69.3, 70.9 (C-2), 114.7, 114.8 (t-C_{arom}), 115.1, 115.9 (t-C_{arom}), 126.21 (t-C_{arom}), 128.4, 129.1 (t-C_{arom}), 139.9, 140.0 (q-C_{arom}), 141.5, 142.0 (q-C_{arom}), 152.7–153.2 (q-C_{arom}). IR (film): 3000–3400 (OH), 1508 (C=C). MS (El) *m*/*z* (%): 315 (M^++18, 20), 136 (100). HRMS calculated for $C_{19}H_{23}NO_2$ 297.1729, found 297.1727.

4.5.2. 2-Hydroxymethyl-l-(*para*-methoxyphenyl)-4-(3-methoxyphenyl)pyrrolidine (11b). According to the general procedure pyrrolidine **11b** was obtained as a colorless oil from **8b** in 68% yield after purification by column chromatography (hexanes/EtOAc, 20/80). Mixture of diastereoisomers 1.8/1. ^{1}H NMR: δ 1.40–1.66 (m, 4H, 2×H-3a, 2×H-3b), 2.04–2.14 (m, 1H, H-4 min.), 2.16–2.29 (m, 1H, H-4 maj.), 2.55–2.74 (m, 4H, 2×CH_2Ph), 2.89–3.15 (m, 4H. 2×H-5a, 2×H-5b), 3.21 (sa, 2H, 2×OH, exchange with D_2O), 3.35–3.42 (m, 2H, 2×C*H*aOH), 3.52–3.58 (m, 2H, 2×C*H*bOH), 3.73 (s, 6H, 2×OCH_3), 3.76–3.92 (m, 8H, 2×H-2, 2×OCH_3), 6.56 (d, *J*=9.1 Hz, 2H, H_{arom} maj.), 6.61 (d, *J*=9.1 Hz, 2H, H_{arom} min.), 6.72–6.77 (m, 10H, H_{arom}), 7.20 (m, 2H, H_{arom}). ^{13}C NMR: δ 35.9, 37.8 (CH_2), 36.3, 38.6 (C-4), 39.8, 40.4 (CH_2), 48.8, 50.4 (CH_2), 55.1, 55.7 (OCH_3), 67.0, 67.1 (CH_2OH), 69.3, 70.9 (C-2), 111.3, 111.4 (t-C_{arom}), 114.8, 114.9 (t-C_{arom}), 115.0, 115.1 (t-C_{arom}), 115.8 (t-C_{arom}), 121.5 (t-C_{arom}), 129.4 (t-C_{arom}), 141.6, 142.0 (q-C_{arom}), 152.6 (q-C_{arom}), 159.6 (q-C_{arom}). IR (film): 2900–3450 (OH), 1508 (C=C). MS (El) *m*/*z* (%): 345 (M^++18, 21), 136 (100). HRMS calculated for $C_{20}H_{25}NO_3$ 327.1834, found 327.1837.

4.5.3. 4-(3,4-Dimethoxyphenyl)-2-hydroxymethyl-1-(*para*-methoxyphenyl)pyrrolidine (11c). According to the general procedure pyrrolidine **11c** was obtained as a colorless oil from **8c** in 67% yield after purification by column chromatography (EtOAc). Mixture of diastereoisomers 1.7/1. ^{1}H NMR: δ 1.36–1.61 (m, 4H, 2×H-3a, 2×H-3b), 2.00–2.09 (m, 1H, H-4 min.), 2.12–2.25 (m, 1H, H-4 maj.), 2.47–2.69 (m, 4H, 2×CH_2Ph), 2.84–3.09 (m, 4H, 2×H-5a, 2×H-5b), 3.14 (sa, 2H, 2×OH, exchange with D_2O), 3.32–3.39 (m, 2H, 2×C*H*aOH), 3.48–3.58 (m, 2H, 2×C*H*bOH), 3.65 (s, 6H, 2×OCH_3), 3.71–3.83 (m, 14H, 2×H-2. 4×OCH_3), 6.50–6.58 (m, 4H, H_{arom}), 6.66–6.78 (m, 10H, H_{arom}). ^{13}C NMR: δ 35.8, 37.5 (CH_2), 36.3, 38.3 (C-4), 39.3, 39.7 (CH_2), 48.5, 50.1 (CH_2), 55.6, 55.7, 55.8 (OCH_3), 67.0, 67.1 (CH_2OH), 69.4, 70.8 (C-2), 111.0, 112.3 (t-C_{arom}), 114.7, 114.9 (t-C_{arom}), 155.5, (t-C_{arom}), 120.9 (t-C_{arom}), 132.4, 132.5 (q-C_{arom}), 141.8, 142.1 (q-C_{arom}), 147.2 (q-C_{arom}), 148.7 (q-C_{arom}), 152.4, 152.8 (q-C_{arom}). IR (film): 3000–3400 (OH), 1508 (C=C). MS (El) *m*/*z* (%): 375 (M^++18, 16), 136 (100). HRMS calculated for $C_{21}H_{27}NO_4$ 357.1940, found 357.1939.

4.5.4. 2-Hydroxymethyl-1-(*para*-methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)pyrrolidine (11d). According to the general procedure pyrrolidine **11d** was obtained as a colorless oil from **8d** in 67% yield after purification by column chromatography (EtOAc). Mixture of diastereoisomers 1.7/1. ^{1}H NMR: δ 1.39–1.68 (m, 4H, 2×H-3a, 2×H-3b), 2.02–2.14 (m, 1H, H-4 min.), 2.17–2.33 (m, 1H, H-4 maj.), 2.49–2.71 (m, 4H, 2×CH_2Ph), 2.89–3.14 (m, 4H, 2×H-5a, 2×H-5b), 2.71 (sa, 2H, 2×OH, exchange with D_2O), 3.33–3.44 (m, 2H, 2×C*H*aOH), 3.54–3.60 (m, 2H, 2×C*H*bOH), 3.72–3.82 (m, 30H, 2×H-2, 4×OCH_3), 6.37 (s, 4H, H_{arom}), 6.54 (d, *J*=8.9 Hz, 2H, H_{arom} maj.), 6.59 (d,

J=8.9 Hz, 2H, H_{arom} min.), 6.72–6.76 (m, 4H, H_{arom}). ^{13}C NMR: δ 36.1, 37.9 (CH_2), 36.3, 38.6 (C-4), 40.3, 40.8 (CH_2), 48.9, 50.6 (CH_2), 55.7, 56.0, 60.8 (OCH_3), 67.2, 67.2 (CH_2OH), 69.3, 70.9 (C-2), 105.8, 105.9 (t-C_{arom}), 114.8, 115.3 (t-C_{arom}), 116.2, (t-C_{arom}), 135.6, 135.7 (q-C_{arom}), 141.1, 141.6 (q-C_{arom}), 152.8 (q-C_{arom}), 153.1 (q-C_{arom}), 153.4 (q-C_{arom}). IR (film): 3100–3400 (OH), 1508 (C=C). MS (El) *m/z* (%): 405 (M^++18, 17), 136 (100). HRMS calculated for $C_{22}H_{29}NO_5$, 387.2046 found 387.2043.

4.5.5. Synthesis of 3-allyl-1-aza-1,7,9-trimethoxy-spiro[4.5]deca-6,9-dien-2,8-dione (12d). Typical procedure. TFA (0.03 mL, 0.45 mmol) was added onto a cold (0 °C) solution of amide **7d** (70 mg, 0.23 mmol) in CH_2C1_2 (2 mL) and then a solution of PIFA (146 mg, 0.34 mmol) in 3 mL of the same solvent was added slowly. The reaction mixture was stirred at the same temperature until total consumption of the starting material (tlc, 90 min). The reaction was quenched with 10 mL of a 10% aqueous solution of Na_2CO_3, and the aqueous layer was extracted with CH_2C1_2 (3×15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography (CH_2C1_2/EtOAc, 20/80) to afford the spiro derivative **12d** as a yellowish oil which was crystallized from *n*-pentane (93%). Mp: 72–74 °C. ^1H NMR: δ 2.00 (dd, J=12.7, 9.5 Hz, 1H, H-4a), 2.21–2.38 (m, 2H, H-4b, C*H*aHbCH=CH_2), 2.65–2.77 (m, 2H, CHa*H*bCH=CH_2, H-3), 3.67 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.11–5.18 (m, 2H, CH=CH_2), 5.64 (s, 2H, H-6, H-10), 5.68–5.84 (m, 1H, C*H*=CH_2). ^{13}C NMR: δ 35.1, 35.8 (CH_2), 36.7 (CH), 55.4, 55.5, 65.4 (OCH_3), 118.1 (CH=*C*H_2), 113.6, 115.9, 133.8 (*C*H=C, *C*H=CH_2), 61.4, 151.3, 151.6 (q-C), 172.6, 175.8 (CO). IR (KBr): 1707 (CO), 1684 (CON), 1619 (C=C). MS (EI) *m/z* (%): 293 (M^+, 99), 262 (48), 252 (100), 192 (74). HRMS calculated for $C_{15}H_{19}NO_5$, 293.1263 found 293.1263.

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References and notes

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