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On the Phenyliodine(III)-Bis(trifluoroacetate)-Mediated Olefin Amidohydroxylation Reaction

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When appropriately substituted amides are treated with PIFA in a non-nucleophilic solvent like trifluoroethanol, a stable *N*-acylnitrenium ion is generated. If under such conditions a C=C double bond is present in the molecule, an intramolecular cyclization process takes place in an *exo* mode with additional generation of a hydroxy group at the terminal position of the original olefin moiety to render a series of pyrrolidine and piperidine derivatives. In this paper, proofs are offered to conclude that, according to our assumption, an ionic mechanism rather than a radical one must be considered. Additionally, a study of the scope of this cyclization protocol is conducted using substrates with different substituents either on the amidic nitrogen or all along the carbon chain.

Introduction

The formation of C–N bonds is one of the fundamental issues in organic synthesis. Displacements by nitrogen containing nucleophiles,[1] Curtius or Beckmann rearrangements of carbonyl compounds,[2] nucleophilic attack to unsaturated C–N bonds, and reductive amination of aldehydes and ketones compiles the majority of the most popular procedures developed to carry out this task. Nevertheless, the amination at non-oxygenated carbon positions without the formation of by-products is an unusual transformation.[3] In this context, amination of double C–C bonds encompasses an attractive approach with atom economy, although it requires activation of either the double bond or the nitrogen functionality as a result of electrostatic repulsion between both groups. Besides, the 2+2 addition of the amine and the olefin is considered to be a forbidden process due to the large energy difference between the π(C=C) and the σ(N–H) orbitals.[4]

The use of hypervalent iodine reagents has gained over the last years an increasing number of adepts among the organic synthetic chemists for several reasons.[5] Firstly, we can benefit from the clean transformations usually achieved, the mild conditions required, and the low toxicity associated to them. And, secondly, in spite of the growing amount of novel applications shown by the specialized literature, there is still much reactivity of the I^{III} or I^{V} reagents to be discovered.[6] In this context, our group started a research program directed to expand the applicability of phenyliodine(III) bis(trifluoroacetate) (PIFA), one of the most active members of this family of compounds, in heterocyclic chemistry. Originally, we drew our attention to the PIFA-promoted intramolecular aromatic amidation reaction (see Figure 1), which turned out to be an efficient and productive way to form series of quinoline and benzodiazepine derivatives of general type **3**.[7] From the mechanistic point of view, it is suggested that when the mildly oxidant I^{III} reagent reacts with *N*-methoxy-substituted amides of type **1**, *N*-acylnitrenium intermediates **2** are generated.[8] Finally, in the presence of nucleophilic species (i.e. arene or heteroaromatic rings), the so-obtained electrophilic intermediates are trapped intramolecularly to form new C–N linkages.[9]

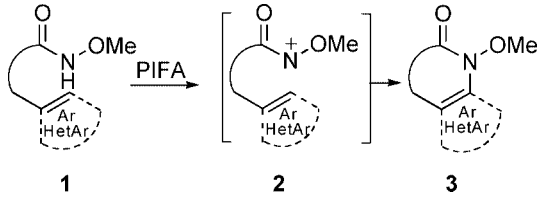

Figure 1. Intramolecular reaction of (hetero)aromatic rings with *N*-acylnitrenium ions generated by PIFA.

In order to enrich this strategy in the field of heterocyclic synthesis, we envisioned that olefin residues might play a similar role as the nucleophilic partner of the reaction. In fact, we have recently found that when *ortho*-substituted vi-

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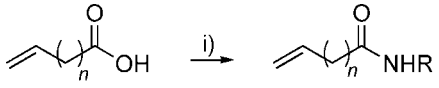
nyl or allyl benzamides are treated with PIFA, isoindolinones and isoquinolinones are obtained, respectively, proving the certainty of our assumption.[10] At the same time this research was being conducted, a beautiful contribution by the group of Nicolaou on the IBX [1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide] mediated olefin amidation to form δ-lactames, cyclic carbamates, 1,2-hydroxyamines, and amino sugars from the corresponding *N*-arylamides was published.[11] In that work, and contrarily to our own results, they also tested the action of PIFA on *N*-phenyl-4-pentenamide (**5b**, in this paper) with unproductive results. Alerted by this apparent contradiction with our initial promising results, we considered that a deeper study on the PIFA-mediated olefin amidohydroxylation reaction was required. In this paper we now explore the mechanistic insights, as well as the scope and applicability, of the presented reaction.

Results and Discussion

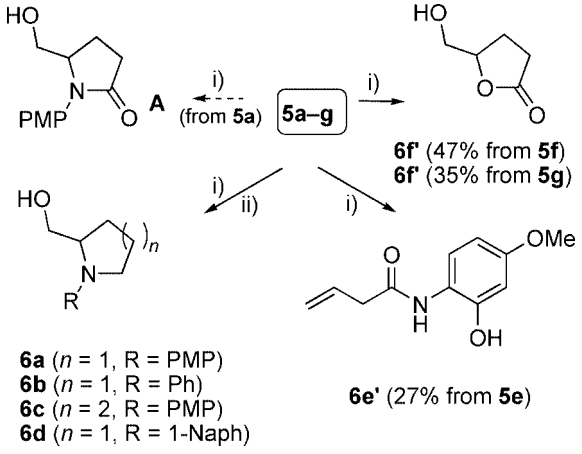
The first issues we had to address in our investigation were referred to the nature of the *N*-substituent and the tolerable length of the carbon chain in such a way that the preparation of β-lactam, pyrrolidine, and piperidine skeletons could be at hand assuming a selective *exo* cyclization mode for each case. Therefore, aromatic amides **5a**–**e** were prepared in satisfactory yields from unsaturated carboxylic acids **4a**–**c**, as shown in Scheme 1, by previous activation as acyl chlorides followed by treatment with the corresponding amines.[12] Additionally, aliphatic amides **5f**,**g** were also prepared for comparative studies.[13]



4a (*n* = 1) **5a** (*n* = 2, R = PMP) **5e** (*n* = 1, R = PMP)
4b (*n* = 2) **5b** (*n* = 2, R = Ph) **5f** (*n* = 2, R = cHex)
4c (*n* = 3) **5c** (*n* = 3, R = PMP) **5g** (*n* = 2, R = Me)
5d (*n* = 2, R = 1-Naph)

Scheme 1. Preparation of linear unsaturated amides **5a**–**g**. *Reagents and conditions:* i) (a) $(COCl)_2$, CH_2Cl_2, room temperature; (b) RNH_2, pyridine, CH_2Cl_2, room temperature (87% for **5a**; 82% for **5b**; 98% for **5c**; 80% for **5d**; 72% for **5e**; 78% for **5f**; 64% for **5g**).

The search for the optimal cyclization conditions was conducted using amide **5a** as a model compound by varying the solvent, temperature, and the presence of additives. Thus, complete recovery of the starting material was attained when amide **5a** was submitted to the action of PIFA in CH_2Cl_2 as solvent under different temperatures. This result did not change neither when $TiCl_4$ was used additionally nor when the reaction was run in the presence of $BF_3{\cdot}OEt_2$.[14] In the latter case, a complex mixture of polymeric nature was isolated. Fortunately, the selection of trifluoroethanol as the solvent, in the absence of additives, was crucial for a clean transformation of the starting material. However, the putative product **A** obtained (see Scheme 2) could not be purified and fully characterized due to its high instability.[15] Notwithstanding, it was found that application of the cyclization conditions followed by treatment with the complex $BH_3{\cdot}SMe_2$, as a convenient reducing agent, rendered nicely the 5-hydroxymethylpyrrolidine derivative **6a** as a pure and stable product. This selected protocol was then applied to the series of amides **5b**–**g**.

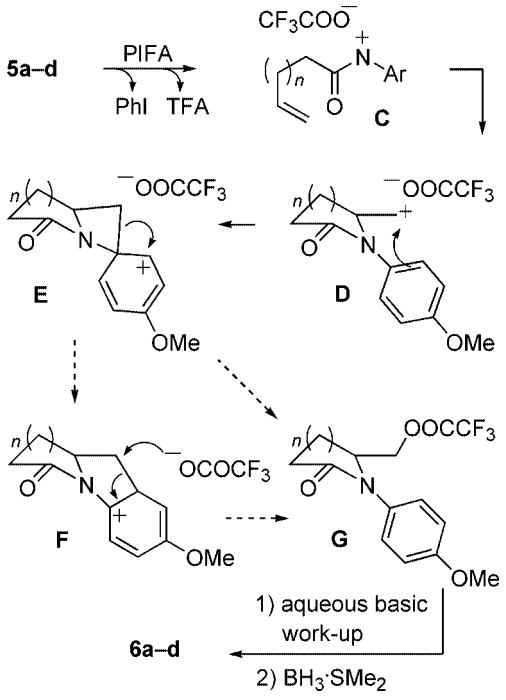


Scheme 2. PIFA-mediated cyclization of linear unsaturated amides **5a**–**f**. *Reagents and conditions:* i) PIFA, CF_3CH_2OH, –20 °C; ii) $BH_3{\cdot}SMe_2$, THF, 0 °C → room temperature (80% for **6a**; 82% for **6b**; 70% for **6c**; 83% for **6d**).

Thus, as shown in Scheme 2, it was found that pyrrolidine **6a** and piperidine **6c** were obtained in good overall yields through 5-*exo*-trig and 6-*exo*-trig cyclization modes, respectively.[16] Conversely, an analogous 4-*exo*-trig process was not favored and the formation of the desired β-lactam could not be detected. Instead, compound **6e′** was obtained, which can be considered as an evidence of the generation of an intermediate species (see intermediate **C** in Scheme 3) with a positive charge delocalized on the aromatic ring.[17] On the other hand, the need for an amide substituent of aromatic nature was corroborated by the formation of *N*-phenyl, *N*-*para*-methoxyphenyl, or *N*-naphthyl-substituted heterocycles **6a**–**d**, along with the formation of lactone **6f′** (instead of the expected pyrrolidine) when starting from the *N*-alkyl-substituted precursors **5f**,**g**.

An explanation for these divergent results could be proposed by inspection of the mechanistic insights of this I^{III}-mediated amidohydroxylation. As it has been mentioned above, although substrate **5a** resulted to be inert when dichloromethane was employed as solvent, the solution took a deep blue coloration that lasted for longer than 24 hours after addition of PIFA. Consequently, the generation of radical species was searched by EPR spectroscopy[18] and, as expected, a triplet with a_N value of 0.8 mT was observed, which is in good agreement with the presence of a nitrogen-centered radical of type **B** (Figure 2),[19] which results to be unproductive in this reaction.

Thus, in the absence of radical species when the reaction takes place in trifluoroethanol, and considering the key importance of the aryl group in the success of this reaction, we suggest that the mechanism for the intramolecular PIFA-mediated olefin amidohydroxylation can be described as follows (see Scheme 3).[20] Once the acyl-nitrenium ion **C**,



Scheme 3. Proposed mechanism for the intramolecular olefin amidohydroxylation.

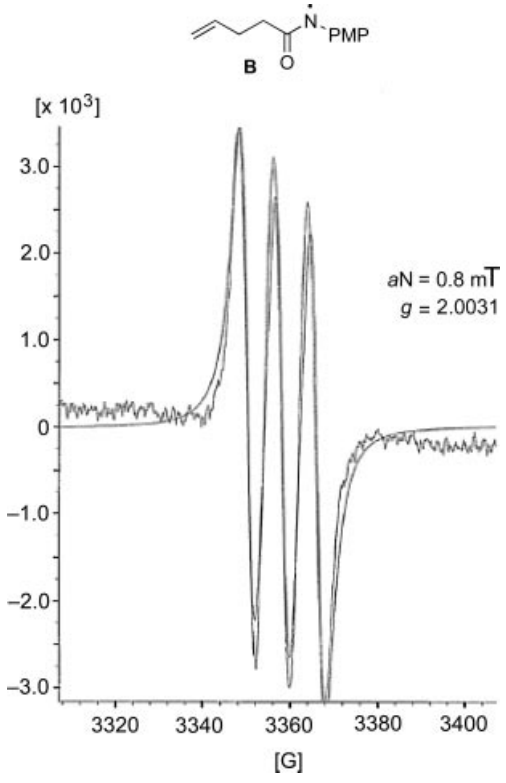
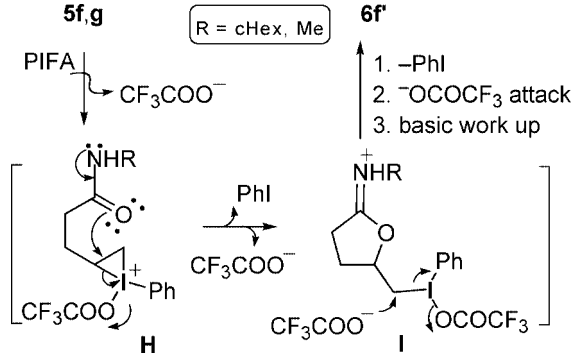


Figure 2. EPR spectrum of the amidyl radical **B**.

generated from **5a**–**d** by the action of PIFA, is formed and intramolecularly trapped by the olefin fragment in an *exo* mode, a primary carbocation **D** is formed and stabilized by the adjacent aryl group in a neighboring group participation. Now, it could be suggested that the resulting intermediate **E** either suffers migration to the more stable intermediate **F**, which is attacked by a trifluoroacetate group delivered by PIFA to form the heterocyclic core **G**, or it goes directly to **G**. This labile trifluoroester is hydrolyzed during the basic work up (Na_2CO_3, H_2O) to render, after borane reduction, the pyrrolidine or piperidine derivatives **6a**–**d**.

From the mechanistic proposal it also seems reasonable that a bicycle intermediate of type **E** derived from butenamide **5e** would be too strained to exist, which explains its apparent unfeasibility to render a cyclic derivative of β-lactamic nature under the explored conditions. On the other hand, the cyclohexyl or methyl groups in amides **5f**,**g**, respectively, do not allow an extended delocalization of the positive charge, which precludes the formation of the corresponding intermediate **C**. Consequently, instead of pyrrolidine formation, the reaction takes place through an alternative pathway, which includes olefin activation instead of nitrogen oxidation, leading to lactone **6f′**, as it is proposed in Scheme 4.[21]

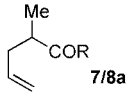
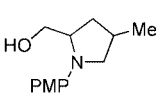
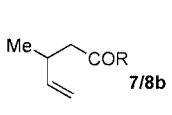
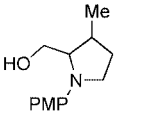
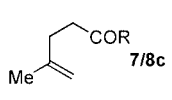
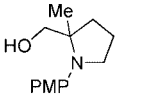
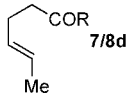
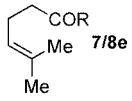
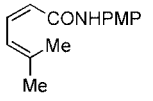
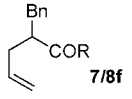
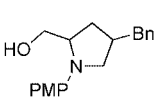
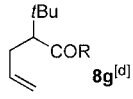
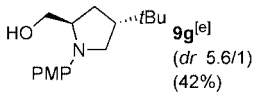
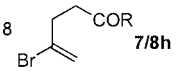
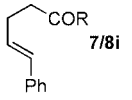
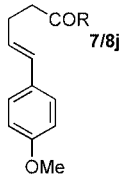
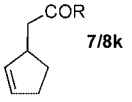
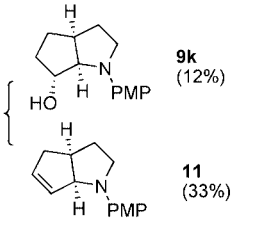


Scheme 4. Proposed mechanism for the transformation of amides **5f**,**g** into lactone **6f′**.

In order to explore the suitability of the presented cyclization for the access to a wide range of differently substituted pyrrolidine derivatives, a series of amides **8a**–**k** was prepared from the required precursors following different routes. Thus, while carboxylic acids **7a**,**b**,**d**,**k** could be purchased from different sources, carboxylic acids **7c**,**e**–**j** were prepared by known procedures including Claisen rearrangement of the corresponding allylic alcohols, allylic alkylation of the related acetic acids,[22] or alkylation of diethyl malonate with 2,3-dibromopropene followed by decarboxylation as for **8h**.[23] Finally, their transformation into amides **8a**–**k** was carried out by classical methods.[24]

Next, the cyclization protocol (one-pot treatment with PIFA followed by reduction with borane) was applied to the series of amides **8a**–**k** prepared (see Table 1). After careful optimization of the particular reaction conditions for each case, the formation of pyrrolidines **9a**–**c**,**f**,**g** was achieved in moderate to good yields. In particular, the generation of a quaternary carbon center (see **9c**) was not problematic. Conversely, we can suggest no reason for the fact that amides **8d**, and **8**,**i**,**j** suffered from complete degradation, without detection of heterocycle formation, considering

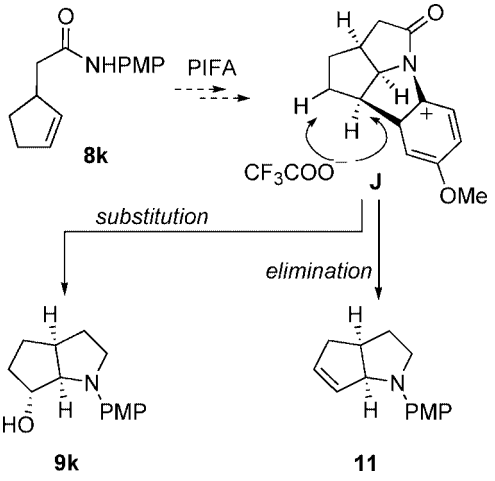
Table 1. PIFA-mediated cyclization of γ,δ-unsaturated amides **8a**–**k**.

Entry	Substrate[a]	Product	Yield (%)[b]
1	 **7/8a**		**9a** (*dr* 1.4/1) (54%)
2	 **7/8b**		**9b** (*dr* 2.3/1) (52%)
3	 **7/8c**		**9c** (74%)
4	 **7/8d**		---[c]
5	 **7/8e**		**10** (76%)
6	 **7/8f**		**9f** (*dr* 1.8/1) (72%)
7	 **8g**[d]		**9g**[e] (*dr* 5.6/1) (42%)
8	 **7/8h**		---[c]
9	 **7/8i**		---[c]
10	 **7/8j**		---[c]
11	 **7/8k**		**9k** (12%) **11** (33%)

[a] R = OH, carboxylic acids **7**; R = NHPMP, amides **8**. [b] Isolated yield after purification by flash chromatography. [c] A complex mixture of products was obtained. [d] Amide **8g** was directly prepared from the corresponding commercially available methyl ester (see supporting information). [e] Stereochemical elucidation has been possible only with **8g**. Major diastereoisomer is represented.

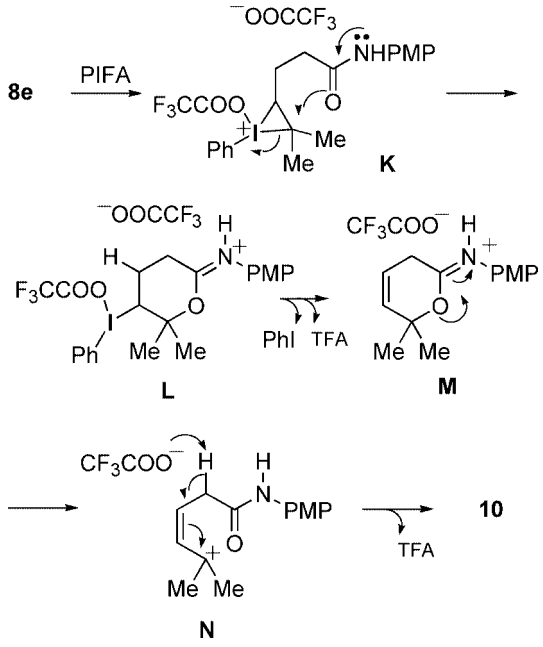
that they would go, respectively, through more favored secondary and benzylic carbocations of type **D**. In a similar way, the deactivation of the nucleophilic character of the olefin by the bromine atom in substrate **8h** can also explain that the expected pyrrolidine **9h** was not formed. It must be pointed out that, contrary to **9g** (*dr* = 5.6:1) and **9k** (*dr* = 100:0), pyrrolidines **9a**,**b**,**f** were obtained as inseparable mixture of diastereoisomers in variable proportions.[25] On the other hand, amide **8k** rendered the expected bicycle **9k**, along with its unsaturated derivative **11**, as a single diastereoisomer. This latter result, although synthetically useless, is quite coherent with our mechanistic proposal as expressed in Scheme 5. If we assumed the formation of the putative intermediate **J** (see **F** in Scheme 3), a nucleophilic attack, or deprotonation followed by elimination processes would render, respectively, cyclopenta[*b*]pyrroles **9k** and **11**.

In addition, the unique behavior of amide **8e** was evidenced by its transformation into the conjugated dienamide **10**.[26] In this particular case, we presume that, due to the electronically enriched olefin, activation of the double bond by the hypervalent iodine reagent, instead of nitrogen oxidation, is the favored process (see Scheme 6). An internal nucleophilic attack in iodonium salt **K**, followed by elimination of iodobenzene and a reopening process, leaves a tertiary allylic carbocation **N**, which suffers deprotonation to render the final compound.



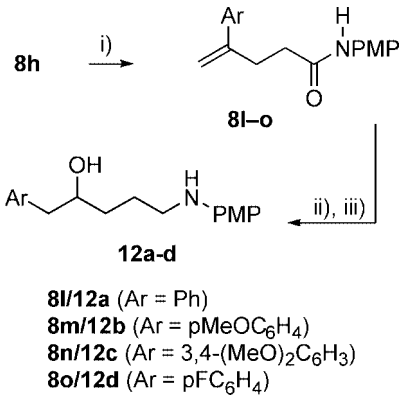
Scheme 5. Proposed mechanism for the formation of bicycles **9k** and **11**.

In an attempt to modify the electronic character around the double bond, we considered that application of the cyclization conditions on 4-aryl-substituted amides **8l**–**o** would



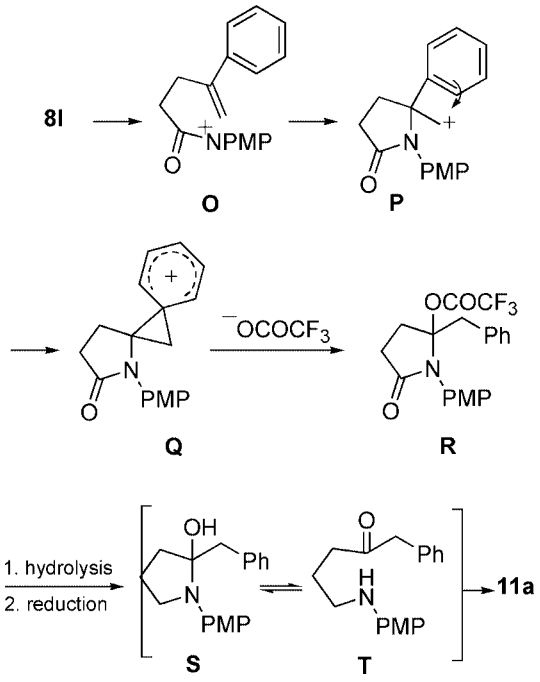
Scheme 6. Proposed mechanism for the formation of diene **10**.

be of interest. A Suzuki coupling process between amide **8h** and the corresponding boronic acids was the selected approach to prepare this series of amides, as it is expressed in Scheme 7. Contrary to our expectations, treatment of amides **8l**–**o** with PIFA in trifluoroethanol as solvent did not render the desired pyrrolidine derivatives of type **9**. Instead, linear amino alcohols **12a**–**d** were obtained in all cases, which were identified after extensive spectroscopic and mass spectrometric analyses. An explanation for this unusual result can be proposed as indicated in Scheme 8. We suggest that an aryl migration can take place from the initial cyclic intermediate **P** (see intermediate **D** in Scheme 3) through formation of a phenonium ion of type **Q**, which reacts with a trifluoroacetate group delivered by PIFA to render the trifluoroester **R**. Additional hydrolysis



Scheme 7. Synthesis and reactivity of 4-aryl-substituted γ,δ-unsaturated amides **8l**–**o**. Preparation of amino alcohols **12a**–**d**. *Reagents and conditions:* i) $ArB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, DMF/H_2O, 50 °C (63% for **8l**; 63% for **8m**; 52% for **8n**; 61% for **8o**); ii) PIFA, CF_3CH_2OH, 0 °C; (iii) $BH_3{\cdot}SMe_2$, THF, 0 °C → room temperature (37% for **8l**; 65% for **8m**; 83% for **8n**; 20% for **8o**).

and reduction steps leave an equilibrium mixture of the cyclic amino alcohol **S** and linear amino ketone **T** giving rise to the final amino alcohols **12a**–**d** due to the excess of the employed reducing agent.[27] Considering the ability of the aryl ring to stabilize the newly created positive charge and, hence, to migrate through the formation of phenonium ion **Q**, the whole process should be more favored with electron-enriched rings.[28] In fact, the so-obtained yields for each particular aryl ring can be used to support the mechanistic proposal.



Scheme 8. Proposed mechanism for the transformation of amides **8l**–**o** into amino alcohols **12a**–**d**.

In conclusion, the powerful potential of the hypervalent iodine reagent PIFA in organic synthesis, which includes its ability to generate *N*-acylnitrenium ions from adequately substituted amides, has been employed satisfactorily in the preparation of a series of pyrrolidine and piperidine derivatives from the corresponding γ,δ- and δ,ω-unsaturated amides. A mechanistic study of the PIFA mediated olefin amidohydroxylation reaction has been conducted to demonstrate that a radical pathway can be ruled out. The mild conditions that the cyclization reaction under study requires will probably find prompt applications in the synthesis of a number of nitrogen containing heterocycles of higher complexity. Finally, the treatment of 4-aryl-substituted amides under the described reaction conditions represents a new entry to the synthesis of linear and highly functionalized amino alcohols.

Experimental Section

Typical Procedure for the PIFA-Mediated Cyclization of Unsaturated Amides 5a–f and 8a–k. Synthesis of 2-(Hydroxymethyl)-*N*-(4-methoxyphenyl)pyrrolidine (6a): A solution of PIFA (438 mg, 1.02 mmol) in 10 mL of CF_3CH_2OH was added onto a cold

(–20 °C) solution of amide **5a** (139 mg, 0.68 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 with 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 0 °C, and $BH_3{\cdot}SMe_2$ (3.4 mL, 2 M in THF, 6.8 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 (EtOAc/MeOH, 96:4) to afford pyrrolidine **6a** as a pale brown oil (113 mg, 80%). ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.38–1.54 (m, 2 H), 1.56–1.75 (m, 2 H), 2.93–3.08 (m, 2 H), 3.40 (dd, J = 11.1, 7.5, Hz 1 H), 3.52 (br. s, 1 H), 3.59 (dd, J = 11.1, 2.8 Hz, 1 H), 3.63–3.73 (m, 4 H), 6.60 (d, J = 9.1 Hz, 2 H), 6.77 (d, J = 9.1 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 25.8, 30.8, 45.3, 55.7, 66.7, 71.9, 114.8, 142.2, 152.4 ppm. IR (film): $\tilde{\nu}$ = 3500–3000, 1508 cm^{-1}. MS (EI): m/z (%) = 225 (21) [M$^+$ + 18], 207 (1) [M$^+$], 136 (100). HRMS calcd. for $C_{12}H_{17}NO_2$ 207.1259, found 207.1269.

2-(Hydroxymethyl)-*N*-phenylpyrrolidine (6b): According to the typical procedure, pyrrolidine **6b** (145 mg) was obtained from amide **5b** (175 mg, 1 mmol) in 82% yield as a brown oil after purification by column chromatography (CH_2Cl_2/EtOAc, 3:7). ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.42–1.76 (m, 4 H), 3.02–3.08 (m, 2 H), 3.38 (dd, J = 11.5, 7.5 Hz, 1 H), 3.42 (br. s, 1 H), 3.53–3.71 (m, 2 H), 6.60 (d, J = 7.5 Hz, 2 H), 6.71 (t, J = 7.5 Hz, 1 H), 7.16 (t, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 25.6, 30.6, 43.9, 66.6, 71.9, 113.0, 117.5, 129.2, 148.2 ppm. IR (film): $\tilde{\nu}$ = 3550–3100, 1506 cm^{-1}. MS (EI): m/z (%) = 195 (15) [M$^+$ + 18], 177 (1) [M$^+$], 106 (100). HRMS calcd. for $C_{11}H_{15}NO$ 177.1154, found 177.1153.

2-(Hydroxymethyl)-*N*-(4-methoxyphenyl)piperidine (6c): According to the typical procedure, piperidine **6c** (155 mg) was obtained from amide **5c** (219 mg, 1 mmol) in 70% yield as a brown solid after purification by column chromatography (EtOAc) followed by crystallization from pentane. M.p. 42–44 °C (*n*-pentane). ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.45–1.62 (m, 6 H), 2.86 (br. s, 1 H), 3.04–3.09 (m, 2 H), 3.41 (dd, J = 10.7, 7.3 Hz, 1 H), 3.59–3.74 (m, 5 H), 6.58 (d, J = 9.1 Hz, 2 H), 6.77 (d, J = 9.1 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 23.0, 29.3, 32.6, 44.8, 55.7, 66.6, 76.5, 114.2, 114.8, 142.5, 152.0 ppm. IR (KBr): $\tilde{\nu}$ = 3500–3150, 1513 cm^{-1}. MS (EI): m/z (%) = 239 (10) [M$^+$ + 18], 201 (28), 199 (82), 136 (100), 108 (27). HRMS calcd. for $C_{13}H_{19}NO_2{\cdot}H_2O$ (M$^+$ + H_2O) 239.1521, found 239.1537.

2-(Hydroxymethyl)-*N*-(1′-naphthyl)pyrrolidine (6d): According to the typical procedure, pyrrolidine **6d** (188 mg) was obtained from amide **5d** (225 mg, 1 mmol) in 83% yield as brownish oil after purification by column chromatography (EtOAc). ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.56–1.61 (m, 2 H), 1.80–1.90 (m, 2 H), 3.25–3.29 (m, 2 H), 3.42–3.46 (m, 1 H), 3.61–3.65 (m, 1 H), 3.74–3.75 (m, 1 H), 6.60–6.61 (m, 1 H), 7.23–7.24 (m, 1 H), 7.32–7.36 (m, 1 H), 7.40–7.45 (m, 2 H), 7.77–7.81 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 25.3, 30.6, 44.0, 66.6, 71.9, 104.4, 117.3, 119.9, 123.4, 124.6, 125.7, 126.5, 128.6, 134.2, 143.4 ppm. IR (KBr): $\tilde{\nu}$ = 3500–3150 cm^{-1}. MS (EI): m/z (%) = 245 (73) [M$^+$ + 18], 157 (13), 156 (100), 129 (29), 115 (10). HRMS calcd. for $C_{15}H_{17}NO$ 227.1314, found 227.1310.

***N*-(2-Hydroxy-4-methoxyphenyl)-3-butenamide (6e′):** According to the typical procedure (in the absence of treatment with borane), amide **6e′** (56 mg) was obtained from amide **5e** (191 mg, 1 mmol) in 27% yield as a yellowish solid after purification by column chromatography (hexanes/EtOAc, 1:1). ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 3.18 (d, J = 7.1 Hz, 2 H), 3.71 (s, 3 H), 5.25–5.32 (m, 2 H), 5.88–6.05 (m, 1 H), 6.38 (dd, J = 8.7, 2.8 Hz, 1 H), 6.51 (d, J = 2.8 Hz, 1 H), 7.02 (d, J = 8.7 Hz, 1 H), 8.07 (br. s, 1 H), 9.09 (br. s, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 41.3, 55.3, 103.9, 106.3, 118.8, 120.8, 122.9, 130.3, 149.6, 158.6, 170.7 ppm. IR (KBr): $\tilde{\nu}$ = 3500–3150, 1651, 1607, 1530 cm^{-1}. MS (EI): m/z (%) = 207 (25) [M$^+$], 139 (100), 124 (59). HRMS calcd. for $C_{11}H_{12}NO_2$ (M$^+$ – OH) 190.0868, found 190.0858.

5-(Hydroxymethyl)-4,5-dihydrofuran-2-one (6f′): According to the typical procedure (in the absence of treatment with borane), furanone **6f′** (55 mg) was obtained from amide **5f** (181 mg, 1 mmol) in 47% yield (or from amide **5g** in 35% yield) as colorless oil after purification by column chromatography (EtOAc/MeOH, 95:5). All spectroscopic data was in agreement with the literature.[29]

2-(Hydroxymethyl)-*N*-(4-methoxyphenyl)-4-methylpyrrolidine (9a): According to the typical procedure, pyrrolidine **9a** was obtained from amide **8a** (219 mg, 1 mmol) carrying out the reaction at 0 °C. The final residue was purified by column chromatography (EtOAc) to afford pyrrolidine **9a** as a pale brown oil (119 mg, 54%). Mixture of diastereoisomers: 1.4:1. ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 0.97–1.00 (m, 2 × 3 H), 1.25–1.30 (m, 2 × 1 H), 1.42–1.47 (m, 2 × 1 H), 1.90–1.95 (m, 2 × 1 H), 2.84–3.01 (m, 2 × 2 H), 3.35–3.43 (m, 2 × 3 H), 3.73–3.90 (m, 2 × 4 H), 6.61–6.64 (m, 2 × 2 H), 6.67 (d, J = 8.7 Hz, 2 × 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 18.7, 18.9, 29.5, 30.6, 38.1, 38.9, 51.2, 52.5, 55.6, 66.7, 67.2, 69.7, 70.3, 114.6, 114.7, 115.0, 142.1, 142.3, 152.2, 152.4 ppm. IR: $\tilde{\nu}$ = 500–3150, 1512 cm^{-1}. MS (EI): m/z (%) = 239 (12) [M$^+$ + 18], 221 (1) [M$^+$], 136 (100), 108 (10). HRMS calcd. for $C_{13}H_{19}NO_2{\cdot}H_2O$ (M$^+$ + H_2O) 239.1521, found 239.1518.

2-(Hydroxymethyl)-*N*-(4-methoxyphenyl)-3-methylpyrrolidine (9b): According to the typical procedure, pyrrolidine **9b** was obtained from amide **8b** (219 mg, 1 mmol), carrying out the reaction at 0 °C. The final residue was purified by column chromatography (EtOAc) to afford pyrrolidine **9a** as a pale brown oil (115 mg, 52%). Mixture of diastereoisomers: 2.3:1. ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 0.90–0.94 (m, 2 × 3 H), 1.63–1.82 (m, 2 × 3 H), 2.98–3.16 (m, 2 × 2 H), 3.49–3.73 (m, 2 × 7 H), 6.59–6.62 (m, 2 × 2 H), 6.76–6.79 (m, 2 × 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 14.5, 16.0, 29.7, 33.0, 33.8, 34.5, 43.1, 43.3, 55.7, 62.5, 64.7, 75.2, 76.0, 114.8, 115.0, 142.2, 152.4, 152.5 ppm. IR: $\tilde{\nu}$ = 500–3150, 1514 cm^{-1}. MS (EI): m/z (%) = 239 (8) [M$^+$ + 18], 221 (2) [M$^+$], 136 (100), 108 (15). HRMS calcd. for $C_{13}H_{19}NO_2{\cdot}H_2O$ (M$^+$ + H_2O) 239.1521, found 239.1522.

2-(Hydroxymethyl)-*N*-(4-methoxyphenyl)-2-methylpyrrolidine (9c): According to the typical procedure, pyrrolidine **9c** was obtained from amide **8c** (219 mg, 1 mmol) carrying out the reaction at room temperature. The final residue was purified by column chromatography (hexanes/EtOAc, 6:4) to afford pyrrolidine **9c** as a pale brown oil (162 mg, 74%). ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.16 (s, 3 H), 1.55–1.73 (m, 4 H), 2.65 (br. s, 1 H), 3.09–3.12 (m, 2 H), 3.43 (t, J = 10.7 Hz, 2 H), 3.74 (s, 3 H), 6.60 (d, J = 8.9 Hz, 2 H), 6.78 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 23.2, 23.8, 36.1, 45.7, 55.7, 69.8, 72.5, 114.6, 114.8, 142.3, 152.3 ppm. IR: $\tilde{\nu}$ = 400–3100, 1513 cm^{-1}. MS (EI): m/z (%) = 239 (66) [M$^+$ + 18], 136 (100). HRMS calcd. for $C_{13}H_{19}NO_2{\cdot}H_2O$ (M$^+$ + H_2O) 239.1521, found 239.1520.

***N*-(4-Methoxyphenyl)-5-methylhexa-2,4-dienamide (10):** According to the typical procedure, amide **10** was obtained from amide **8e** (233 mg, 1 mmol) carrying out the reaction at 0 °C without further reduction. The final residue was purified by column chromatography (EtOAc) to afford amide **10** as a brownish liquid (176 mg, 76%). ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.84 (s, 3 H), 1.89 (s, 3 H), 3.78 (s, 3 H), 5.58 (d, J = 11.4 Hz, 1 H), 6.76 (d, J = 11.4 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 2 H), 7.29 (s, NH), 7.34 (d, J = 11.4 Hz, 1 H), 7.47 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 18.1, 26.7, 55.4, 114.6, 117.7, 121.6, 121.8, 131.2, 138.0, 145.4, 156.2, 164.9 ppm. IR: $\tilde{\nu}$ = 514 cm^{-1}. MS (EI): *m*/*z* (%) = 231 (25) [M$^+$], 123 (100), 108 (36). HRMS calcd. for $C_{14}H_{17}NO_2$ 231.1259, found 231.1262.

4-*tert*-Butyl-2-(hydroxymethyl)-*N*-(4-methoxyphenyl)pyrrolidine (9g): According to the typical procedure, pyrrolidine **9g** (110 mg) was obtained from amide **8g** (261 mg, 1 mmol) in 42% yield as a brown oil after purification by column chromatography (hexanes/EtOAc, 4:6). Mixture of diastereoisomers: 5.6:1. ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 0.93 (s, 9 H), 1.22–1.31 (m, 1 H), 1.47–1.52 (m, 1 H), 1.62–1.70 (m, 1 H), 2.70–2.76 (m, 1 H), 3.18–3.22 (m, 1 H), 3.38–3.44 (m, 1 H), 3.50–3.55 (m, 1 H), 3.70–3.80 (m, 4 H), 3.92 (br. s, 1 H), 6.63 (d, J = 8.8 Hz, 1 H), 6.77 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 27.6, 33.0, 33.2, 44.2, 47.6, 55.6, 66.6, 70.3, 114.7, 115.3, 142.3, 152.6 ppm. IR (film): $\tilde{\nu}$ = 3500–3150, 1513 cm^{-1}. MS (EI): *m*/*z* (%) = 263 (6) [M$^+$], 232 (46), 136 (100), 108 (31), 57 (47). HRMS calcd. for $C_{16}H_{25}NO_2$ 263.1883, found 263.1885.

When the reaction was carried out on amide **8k** (231 mg, 1 mmol) according to the typical procedure at –20 °C, compounds **11** (71 mg, 33% yield) and **9k** (28 mg, 12% yield) were obtained and purified by column chromatography (EtOAc).

(3a*R*,6a*R*)-*N*-(4-Methoxyphenyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[*b*]pyrrole (11): M.p. 90–92 °C (hexanes). ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.72–1.79 (m, 1 H), 1.90–1.97 (m, 1 H), 2.10–2.22 (m, 3 H), 2.40–2.45 (m, 1 H), 3.10–3.20 (m, 2 H), 3.74 (s, 3 H), 4.62–4.64 (m, 1 H), 5.91–5.93 (m, 1 H), 6.02–6.04 (m, 1 H), 6.62 (d, J = 8.7 Hz, 2 H), 6.78 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 29.1, 37.0, 41.2, 44.7, 55.7, 76.3, 114.4, 114.8, 133.1, 135.5, 142.5, 152.1 ppm. IR: $\tilde{\nu}$ = 367, 1507 cm^{-1}. MS (EI): *m*/*z* (%) = 233 (100) [M$^+$ + 18], 215 (59) [M$^+$], 200 (59), 136 (65), 77 (60). HRMS calcd. for $C_{14}H_{17}NO$ 215.1310, found 215.1313.

(3a*R*,6*R*,6a*R*)-*N*-(4-Methoxyphenyl)-octahydrocyclopenta[*b*]pyrrol-6-ol (9k): ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.42–1.53 (m, 2 H), 1.80–1.86 (m, 1 H), 1.87–1.95 (m, 1 H), 2.11–2.25 (m, 2 H), 2.43 (br. s, OH), 3.08–3.13 (m, 1 H), 3.14–3.21 (m, 1 H), 3.75 (s, 3 H), 3.94–3.95 (m, 1 H), 4.10–4.12 (m, 1 H), 6.64 (d, J = 9.0 Hz, 2 H), 6.79 (d, J = 9.0 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 27.6, 29.2, 31.6, 40.4, 44.6, 55.8, 79.0, 79.6, 114.9, 114.9, 142.1, 152.6 ppm. IR: $\tilde{\nu}$ = 450–3100, 2931, 1507 cm^{-1}. MS (EI): *m*/*z* (%) = 251 (62) [M$^+$ + 18], 233 (39) [M$^+$], 136 (100), 108 (49). HRMS calcd. for $C_{14}H_{19}NO_2$ 233.1416, found 233.1414.

5-(*p*-Methoxyphenylamino)-1-phenyl-2-pentanol (12a): According to the typical procedure, alcohol **12a** was obtained from amide **8l** (281 mg, 1 mmol) carrying out the reaction at 0 °C. The final residue was purified by column chromatography (EtOAc) to afford alcohol **12a** as a pale brown solid (105 mg, 37%). M.p. 57–59 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.55–1.83 (m, 4 H), 2.67–2.71 (m, 1 H), 2.81–2.85 (m, 1 H), 3.09–3.13 (m, 2 H), 3.75 (s, 3 H), 6.60 (d, J = 8.9 Hz, 2 H), 6.78 (d, J = 8.9 Hz, 2 H), 7.25–7.29 (m, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 26.1, 34.4, 44.2, 55.8, 72.4, 114.5, 114.9, 126.5, 128.6, 129.4, 138.4, 142.4, 152.2 ppm. IR: $\tilde{\nu}$ = 450–3100, 1508 cm^{-1}. MS (EI): *m*/*z* (%) = 285 (7) [M$^+$], 176 (99), 136 (100), 91 (84). HRMS calcd. for $C_{18}H_{23}NO_2$ 285.1729, found 285.1724.

1-(*p*-Methoxyphenyl)-5-(*p*-methoxyphenylamino)-2-pentanol (12b): According to the typical procedure, alcohol **12b** was obtained from amide **8m** (311 mg, 1 mmol) carrying out the reaction at 0 °C. The final residue was purified by column chromatography (EtOAc) to afford alcohol **12b** as a pale brown solid (205 mg, 65%). M.p. 88–90 °C (hexanes). ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.53–1.82 (m, 4 H), 2.60–264 (m, 1 H), 2.75–2.79 (m, 1 H), 3.09–3.12 (m, 2 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 6.59 (d, J = 7.8 Hz, 2 H), 6.78 (d, J = 7.8 Hz, 2 H), 6.86 (d, J = 7.4 Hz, 2 H), 7.13 (d, J = 7.4 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 26.1, 34.3, 43.2, 55.2, 55.8, 72.5, 114.0, 114.4, 114.9, 130.3, 130.3, 142.4, 152.2, 158.3 ppm. IR: $\tilde{\nu}$ = 450–3100, 1514 cm^{-1}. MS (EI): *m*/*z* (%) = 315 (3) [M$^+$], 176 (100), 136 (48), 121 (88). HRMS calcd. for $C_{19}H_{25}NO_3$ 315.1834, found 315.1815.

1-(3,4-Dimethoxyphenyl)-5-(*p*-methoxyphenylamino)-2-pentanol (12c): According to the typical procedure, alcohol **12c** was obtained from amide **8n** (341 mg, 1 mmol) carrying out the reaction at 0 °C. The final residue was purified by column chromatography (EtOAc) to afford alcohol **12c** as a pale brown solid (286 mg, 83%). M.p. 65–68 °C (hexanes). ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.54–1.83 (m, 4 H), 2.59–2.63 (m, 1 H), 2.76–2.80 (m, 1 H), 3.11–3.15 (m, 2 H), 3.74 (s, 3 H), 3.80–3.87 (m, 1 H), 3.87 (s, 6 H), 6.60 (d, J = 8.7 Hz, 2 H), 6.74–6.83 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 26.2, 34.6, 44.0, 45.7, 56.0, 56.1, 56.2, 72.7, 111.5, 112.7, 115.0, 115.1, 121.5, 131.0, 142.2, 147.9, 149.2, 152.7 ppm. IR: $\tilde{\nu}$ = 450–3100, 1514 cm^{-1}. MS (EI): *m*/*z* (%) = 186 (9), 176 (100), 151 (15), 136 (15). HRMS calcd. for $C_{20}H_{27}NO_4$ 345.1940, found 345.1935.

1-(*p*-Fluorophenyl)-5-(4-methoxyphenylamino)-2-pentanol (12d): According to the typical procedure, alcohol **12d** was obtained from amide **8o** (299 mg, 1 mmol) carrying out the reaction at 0 °C. The final residue was purified by column chromatography (EtOAc) to afford alcohol **12d** as a pale brown solid (61 mg, 20%). M.p. 73–76 °C (hexanes). ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.52–1.82 (m, 4 H), 2.64–2.69 (m, 1 H), 2.77–2.81 (m, 1 H), 3.09–3.12 (m, 2 H), 3.75 (s, 3 H), 3.80–3.84 (m, 1 H), 6.60 (d, J = 8.8 Hz, 2 H), 6.78 (d, J = 8.8 Hz, 2 H), 7.00 (d, J = 8.5 Hz, 2 H), 7.17 (dd, J = 8.5, 5.5 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 20 °C): δ = 26.1, 34.5, 43.3, 45.2, 55.8, 72.4, 114.6, 114.9, 115.2 (d, J = 21.1 Hz), 115.4 (d, J = 21.1 Hz), 130.7 (d, J = 7.3 Hz), 130.8 (d, J = 7.3 Hz), 134.1 (d, J = 2.7 Hz), 134.1 (d, J = 2.7 Hz), 142.3, 152.4, 160.7 (d, J = 252.7 Hz), 162.6 (d, J = 252.7 Hz) ppm. IR: $\tilde{\nu}$ = 450–3100, 1514 cm^{-1}. MS (EI): *m*/*z* (%) = 303 (4) [M$^+$], 176 (100), 136 (26), 109 (21). HRMS calcd. for $C_{18}H_{22}NO_2F$ 303.1635, found 303.1644.

Supporting Information (see also the footnote on the first page of this article): Experimental details for amides **5a**–**g** and **8a**–**o**, and ^{1}H NMR and ^{13}C NMR spectra of all new compounds.

Acknowledgments

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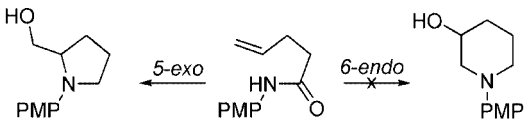
[16]



6a **5a** **6a′**

Due to the similar theoretical chemical shifts and multiplicities that both **6a** and its putative isomer **6a′** would afford in ^1H and ^{13}C NMR, an additional HMBC experiment was carried out to confirm the identity of pyrrolidine **6a** and, hence, to exclude the formation of **6a′**.
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