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Review

Recent applications of the PIFA-assisted intramolecular olefin amidation reaction: An advantageous approach to the synthesis of nitrogen-containing heterocycles

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ABSTRACT

This review focuses on the progress of the use of the hypervalent iodine reagent PIFA in the intramolecular olefin amidation reaction as an environmentally benign alternative over other related metal-assisted processes. The key step of this route embraces the oxidation of the nitrogen atom by the I(III) reagent to form an electronically deficient intermediate, and its succeeding trapping by the olefin fragment. A common behavior for a number of tailored designed substrates under such conditions is observed leading to the formation of a broad array of functionalized nitrogen-containing heterocycles.

KEYWORDS: hypervalent iodine, PIFA, heterocycles, olefin amidation, acylnitrenium

1. INTRODUCTION

The development of new synthetic procedures that embrace the concepts of sustainability and green chemistry should be a mandatory impulse for all organic chemists [1]. In particular, the search for substitutes of metals, especially when they have to be employed in stoichiometric quantities, meets today a growing number of adepts. As an increasingly attractive alternative, the selection of hypervalent iodine compounds has been the subject of intensive research over the last years as judged by the number of contributions to specialized publications that can be found [2]. The low toxicity, readily availability, easy handling, and the environmentally friendly nature of this kind of reagents have allowed its application to a wide range of useful organic transformations. Indeed, hypervalent iodine reagents are now extensively used in organic synthesis as a mild, safe, and economical alternative to heavy metal reagents such as lead (IV), thallium (III) and mercury (II) [3].

In particular, we became interested in developing a new, metal-free protocol for the olefin amidation reaction as a safer and less toxic entrance to the synthesis of nitrogen containing heterocycles with complete atom economy. Figure 1 compiles a wide spectrum of different existing approaches for that task. Although favourable from a thermodynamic point of view, all these approaches have been designed to overcome the high activation energy that is developed (electrostatic repulsion) when the nitrogen and the olefin fragment get closer to each other (the free energy value for the addition of NH_3 to ethylene has been estimated to be -15 kJ/mol) [4]. Besides, the great energy gap between the π (C=C) and the σ (N–H) orbitals makes the [2+2] addition of the N–H bond over the olefin fragment troublesome and, hence, it requires either olefin or nitrogen activation. Thus, from the less attractive protocols that require the use of stoichiometric quantities of metals [5], a number of powerful oxidative

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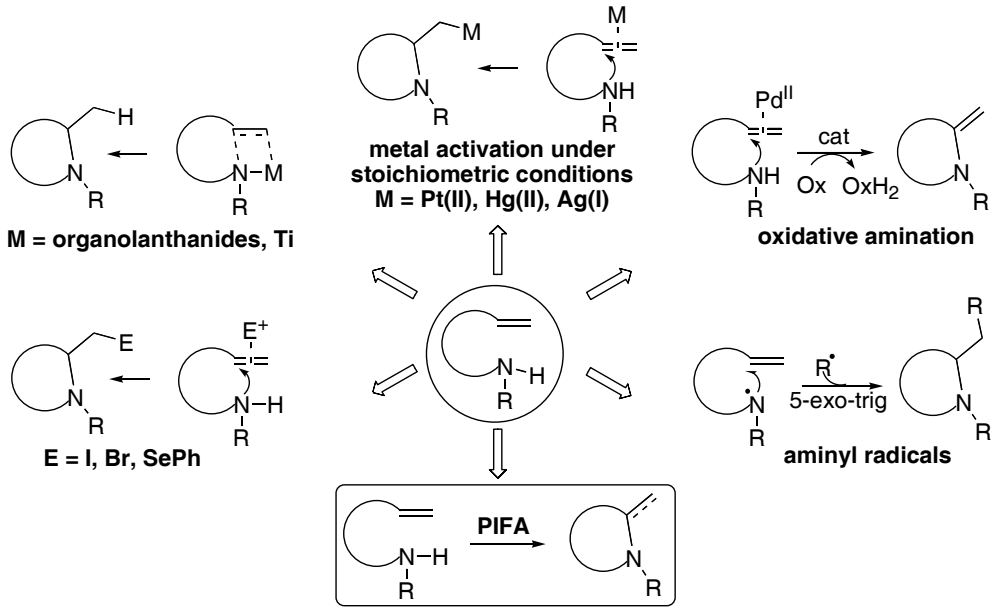


Figure 1. Different approaches for the intramolecular olefin amination reaction.

amination processes have emerged under catalytic conditions, most frequently using palladium and organolanthanide reagents [6]. The olefin amination process can be also facilitated if the double bond is previously activated by the use of electrophilic reagents [7], or by generation of a nitrogen-centered radical, a powerful approach to has found wide application in the synthesis of many different natural products [8].

In this context, and in addition to the above mentioned protocols, part of our recent research has focused on the ability of the iodine (III) reagent PIFA [*bis*(trifluoroacetoxy)iodobenzene] to construct hydroxymethyl substituted 5- and 6-membered N-heterocycles (pyrrolidines, piperidines, isoquinolines, indolines, and isoindolines) from properly substituted unsaturated amides, a long-lasting project that will be disclosed in the following sections. A second piece of information required to give an overall picture of this transformation comes from the use of the pentavalent iodine reagent IBX [o-iodoxybenzoic acid]. When applied to the same kind of substrates, IBX results to be an excellent alternative to accomplish the synthesis of differently substituted lactams. As shown in Figure 2, substrates of general structure **I** behave

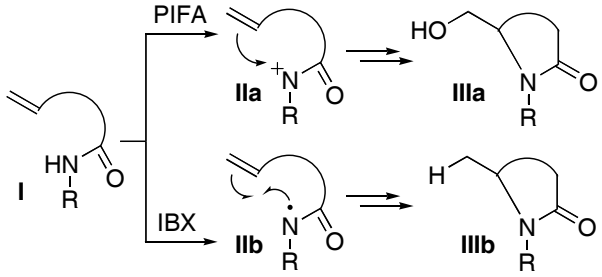


Figure 2. General description of the PIFA- and IBX-mediated olefin amidation reaction.

in a different way as a result of the type of intermediate **II** that each of these reagents generates, and taking, therefore, a distinctive detour giving rise to heterocycles of type **IIIIa** and **IIIb**, respectively. In addition, literature also shows related metal-free oxidative cyclization of ureas onto unactivated alkenes using iodosyl-benzene (PhIO) and an acid promoter [9].

Since the chemistry of the I(V) reagents (i.e. IBX) has been recently reviewed [10], including its application to the synthesis of nitrogen-containing heterocycles [11], the aim of this review will focus exclusively on the synthetic uses and mechanistic aspects of the I(III) reagent.

2. DEVELOPMENT OF THE REACTION AND MECHANISTIC PROPOSALS

Inspired in our own precedents related to the electrophilic aromatic amidation reaction promoted by PIFA on properly activated substrates of type **IV** (see Figure 3) [12], we tried to extend the same strategy to olefins in the assumption that the N-acylnitrenium intermediate that is generated from **IV** (and stabilized by the action of the electron-donating methoxy group) to form quinolinones of type **IIIc**, would not only be formed also from **V**, but it would behave as well in a similar manner to yield an heterocyclic system when trapped intramolecularly with the olefin fragment.

To carry out this study [13] we first prepared a series of linear amides **1a-g** with a terminal double bond, and substituted at the nitrogen atom by different aryl and alkyl groups (see Scheme 1). We found that the reaction with PIFA in trifluoroethanol (TFEA) as solvent only takes place with aryl-substituted amides to give, after basic work up, the pyrrolidine **2a,b,e** and the piperidine **2d**, but not the β-lactam **2c**, skeletons, with generation of a hydroxy group at the terminal position of the original double bond. On the contrary, alkyl-substituted amides **1f,g** were transformed under the same reaction conditions to the hydroxymethyl-lactone **4a**. As a consequence of their low stability, heterocycles **2a,b,d,e** were reduced with borane to produce the corresponding derivatives **3** in 70-89% yield over three steps (cyclization, hydrolysis, and reduction). Formally, the overall transformation can be considered a racemic metal-free alternative to the Sharpless osmium catalyzed aminohydroxylation [14].

Considering the key importance of the N-substituent in the success of this reaction, we suggest the following mechanism to explain these results (see Schemes 2 and 3). Once the nitrenium ion **VI** is formed and trapped by the olefin in an *exo* mode, a primary carbocation **VII** is formed and stabilized by the aryl group in a neighboring group participation (**VIII-IX**). Then, the trifluoro-acetate group delivered by PIFA opens these intermediates to yield a labile trifluoroester **X** that is hydrolyzed during the basic work up.

As mentioned before, the olefin amidohydro-xylation reaction didn't take place with the

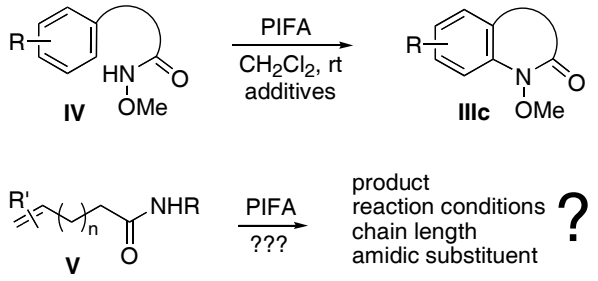
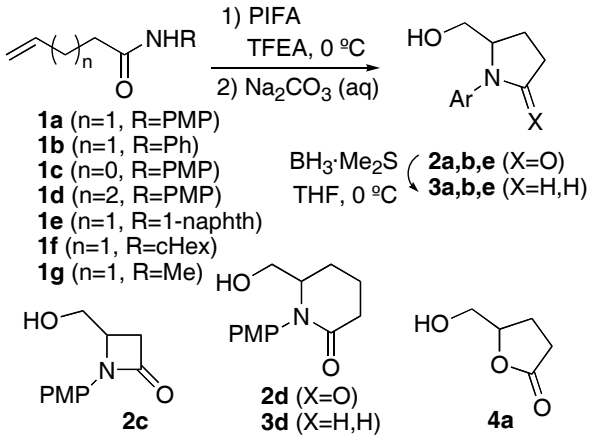


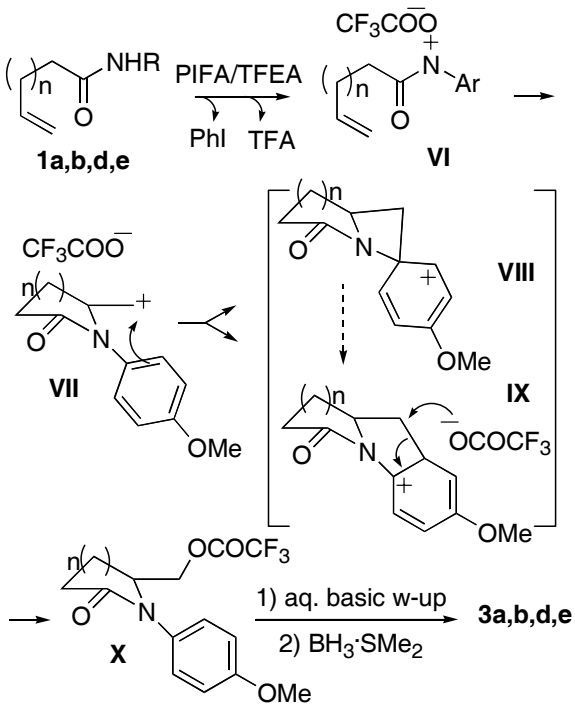
Figure 3. Previously reported approach for the PIFA-mediated aromatic amidation reaction and general proposal for the olefin amidation.



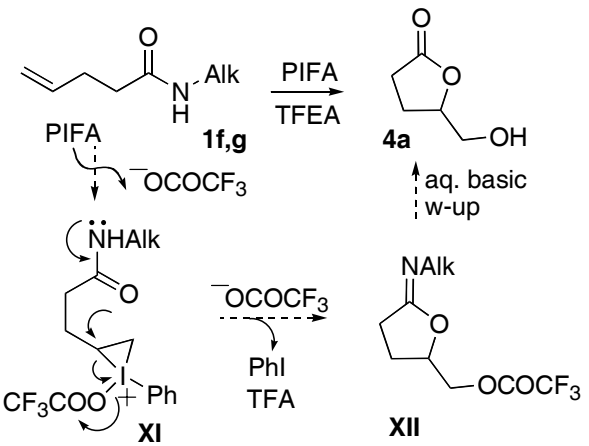
Scheme 1. Development of the PIFA - assisted olefin amidohydroxylation reaction.

alkyl substituted amides **1f,g**. It can be suggested (see Scheme 3) that since the alkyl group can not stabilize a nitrenium ion of type **VI**, an activation process of the double bond takes place (**XI**), instead of nitrogen oxidation, to promote a nucleophilic internal attack yielding the final lactone **4a** after basic hydrolysis of intermediate **XII.** This preferential formation of lactones over lactams is not unusual [15].

An additional piece of information (see Figure 4) that supports a ionic-rather than a radical–mechanism for this reaction comes from the fact that substrate **1a** resulted to be inert when CH_2Cl_2 was employed as solvent, instead of trifluoroethanol (TFEA). In fact, under those conditions, the solution took a deep blue coloration that lasted for longer than 24 hours after addition of PIFA. Consequently, the



Scheme 2. Proposed mechanism for the olefin amido-hydroxylation reaction.



Scheme 3. Proposed mechanism for the lactonization reaction.

generation of radical species was searched by EPR spectroscopy [16] 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 **XIII** [17] which results to be unproductive.

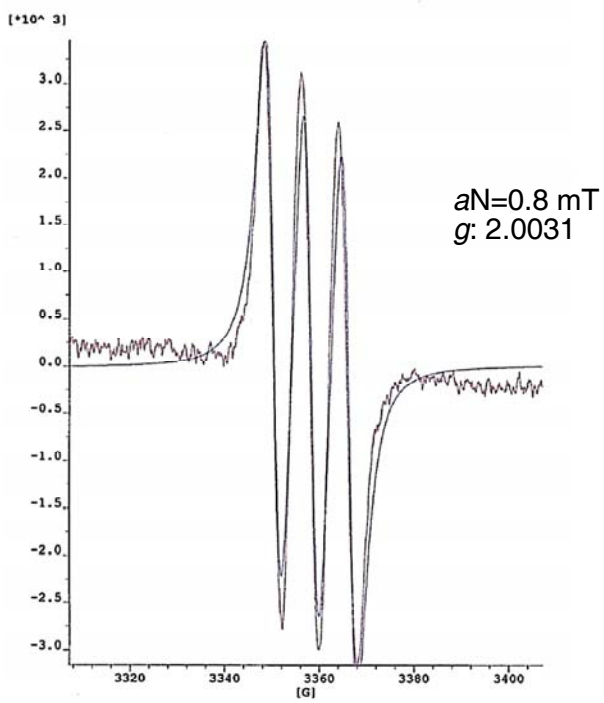
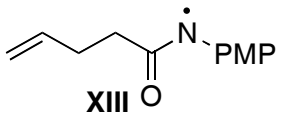


Figure 4. EPR spectrum of amidyl radical **XIII**.



With all this information in hand, the series of differently substituted pyrrolidines of type **3** was extended (see Chart 1). With the only exception of **3l,m**, inseparable mixture of the two possible diastereoisomers were formed. For those particular cases, the stereochemistry of the major isomer was fully established.

3. EXTENSION TO N-METHOXY- AND N-PHTHALIMIDO-AMIDES

As mentioned before, the failure of the N-alkyl substituted amides **1f,g** to perform the expected olefin amidation can be attributed to the low stabilization that nitrenium intermediates achieve under such structural conditions. Contrarily, and in addition to N-aryl substituents as in **1a,b,d,e**, some others groups have been also used (see Figure 5) to attain the required stabilization of these deficient intermediates. In fact, N-phthalimidoamides **7** and N-methoxyamides **8**

have been employed as starting materials for that purpose, which on treatment with PIFA are oxidized to species **VIa-c**, respectively.

Some years ago [18], Kikugawa´s group reported that *N*-phthalimido-*N*-acylnitrenium ions could be generated from *N*-acylaminophthalimides by treatment with trivalent iodine compounds (PIFA and HTIB). Under such conditions, the nitrenium ions underwent intramolecular electrophilic substitution reactions to afford *N*-aminonitrogen heterocycles in high yields. More recently [19], this approach has been also extended to the use of such type of substrates in an olefin amido-hydroxylation reaction. The reaction takes place (see Scheme 4) from unsaturated amides of type **5** in refluxing chloroform with a slight excess of PIFA. Contrarily to the above-referred results from amides of type **1**, in which an *exo* attack is exclusively observed, substrates **5a-f** are usually transformed into the corresponding heterocycles **6a-f** as a mixture of two regioisomers (**6** and **6'**). These results are compatible with the generation of an aziridinium intermediate that is opened by a trifluoroacetate anion in a 5-*exo* or 6-*endo* cyclization modes, respectively.

More recently [20], Wardrop and his group have extended this synthetic study to unsaturated N-metoxyamides of type **7** as a highly versatile method for the preparation of five- to eight-membered hydroxylactams **9**. In this particular case (see Scheme 5), the use of 1.0 eq. of TFA is required, in combination with 1.2 eq. of PIFA, to get high yields in the cyclization reaction. The regiochemical (**8** vs **8'**) and stereochemical results are explained on the basis of the controlled ring opening of the ionic intermediate **XIV** by the trifluoroacetate anion. In other words, this attack takes place predominantly at the less encumbered position, and the E/Z disposition of the substituents around the olefin fragment is reflected in the diastereoselectivity of the cyclic compounds. Finally, due to the lability of esters **8**/**8'**, a methanol/ammonia quench was employed to remove the trifluoroacetate group, providing the final heterocycles **9**/**9'**.

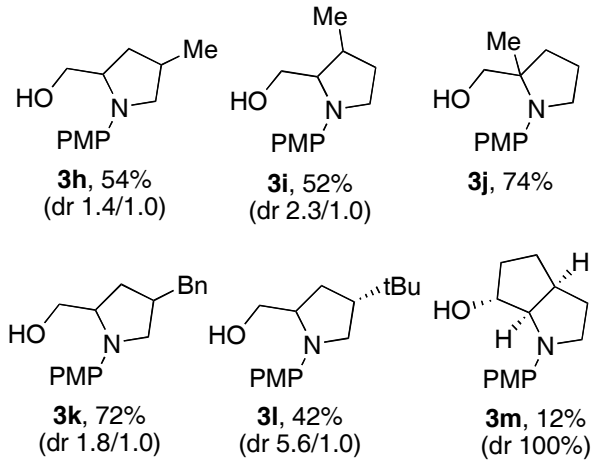


Chart 1. Preparation of pyrrolidines **3h-m**. Yields are referred to the mixture of diastereoisomers.

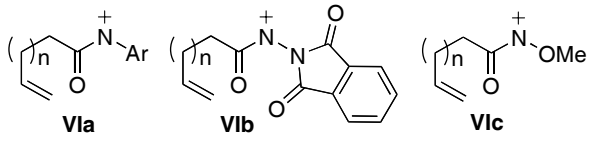
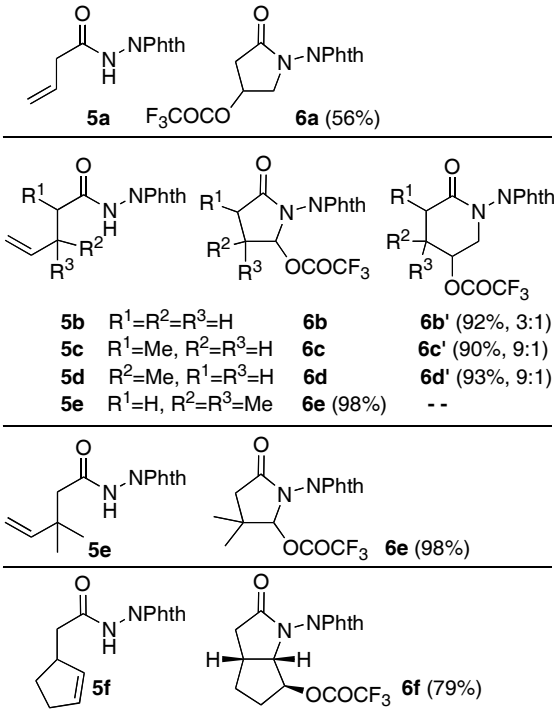
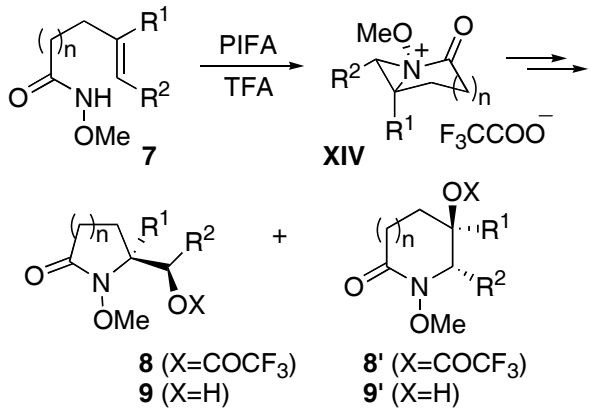


Figure 5. Stabilized acylnitrenium ions.

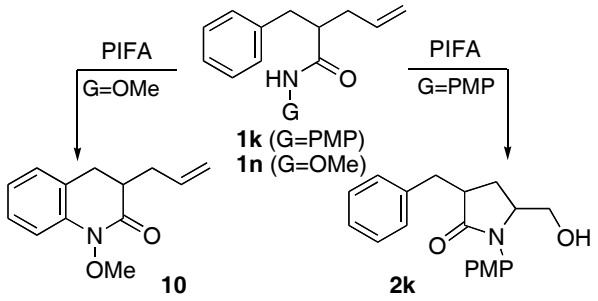


Scheme 4. Intramolecular cyclization of alkenyl N-acylaminophthalimides **5a-f** with PIFA to afford derivatives **6a-f**.

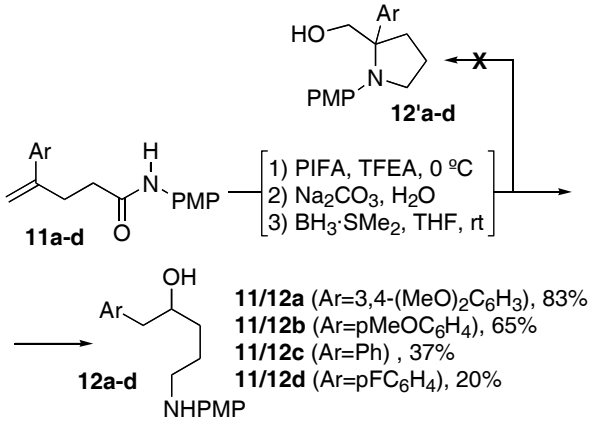


Scheme 5. Intramolecular cyclization of unsaturated N-methoxyamides **7** with PIFA to afford derivatives **9**.

An additional experiment that shows the relevancy of the amidic substituent in the outcome of the reaction is shown in Scheme 6 [21]. We found that the appropriate selection of the group attached to the nitrogen atom of the starting material can exert a complete chemoselective control during the evolution of the so-formed nitrenium intermediate when substituted by either an aryl group (to perform an aromatic amidation reaction) or by a methoxy group (to assist an olefin amido-hydroxylation reaction). Scheme 6 clearly shows this divergent behavior when starting from an adequately α,α-disubstituted amide. It was found that starting from N-methoxyamide **1n**, a 3-allylquinoline **10** is obtained and, contrarily, when starting from N-arylamide **1k**, a 3-benzylpyrrolidine **2k** is obtained, and in both cases with complete chemoselectivity.



Scheme 6. Chemoselective reactions in amides **1k,n**.

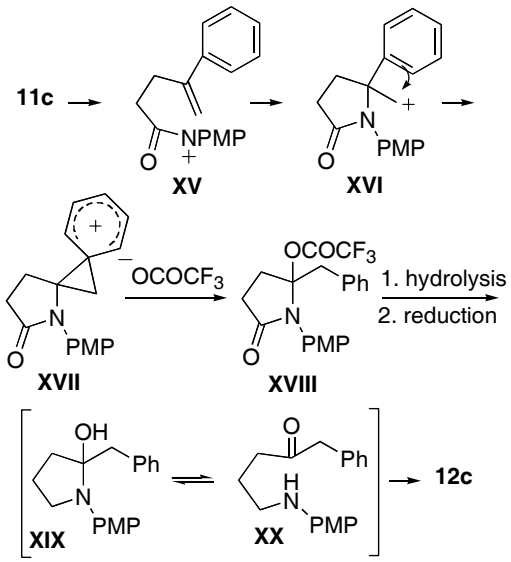


Scheme 7. Preparation of δ-aminoalcohols **12a-d**.

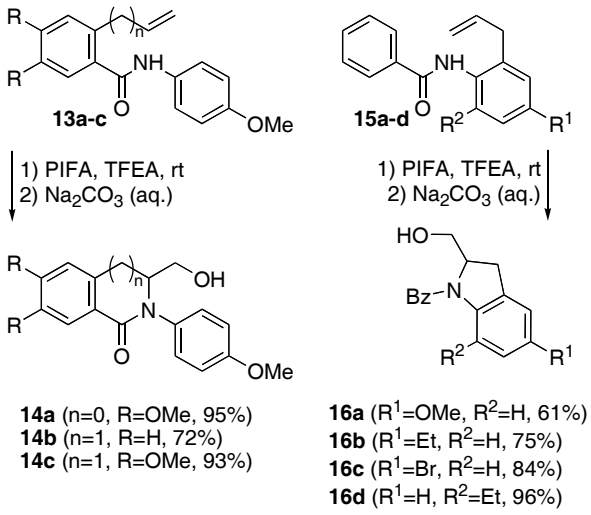
4. PREPARATION OF δ-AMINO- ALCOHOLS

In order to get more information about the insights of the PIFA-mediated olefin amidation reaction, we considered that application of the cyclization conditions to electronically differentiated 4-aryl substituted amides **11a-d** would be of interest [13]. A Suzuki coupling process was selected to insert the corresponding aryl groups onto the preformed unsaturated 4-bromoamide. Contrary to our previous routine, treatment of amides **11** with PIFA in trifluoroethanol as solvent, followed by a reductive step, did not render the expected pyrrolidine derivatives of type **3 (~12'a-d)**. Instead (see Scheme 7), linear δ-aminoalcohols **12a-d** were obtained in all cases.

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 cyclic intermediate **XVI** (~intermediate **VII** in Scheme 2) through formation of a phenonium ion of type **XVII**, which reacts with a trifluoroacetate group delivered by PIFA to render the trifluoroester **XVIII**. Subsequent hydrolysis and reduction steps leave an equilibrium mixture of the cyclic aminoalcohol **XIX** and linear aminoketone **XX** that gives rise to the final aminoalcohols **12a-d** due to the excess of the employed reducing agent. This explanation is coherent with previously reported lactonization processes with phenonium ion participation [22]. Considering the ability of the aryl ring to stabilize the newly created positive charge and, hence, to migrate through the formation of phenonium ion **XVII**, the whole process should be more favored



Scheme 8. Proposed mechanistic explanation for the transformation of amides **11** into δ-aminoalcohols **12**.



Scheme 9. Preparation of isoindolinone, isoquinolinone, and indoline skeletons through an olefin amidation process.

with electron-enriched rings [23]. In fact, the so-obtained yields for each particular aryl ring can be used to support the mechanistic proposal.

5. PREPARATION OF ISOINDOLINONES, ISOQUINOLINONES AND INDOLINES

Following the general proposal described in Section 2, we have also explored the feasibility of this approach in the synthesis of isoindolinone, isoquinolinone, and indoline skeletons through a PIFA-promoted olefin amidation process. This process could be eventually employed in the construction of a number of related natural and synthetic products of interest by the direct formation of C-N bonds.

The preparation of required precursors **13a-c** (see Scheme 9) was accomplished by the amidation of the corresponding 2-iodobenzoic acid with para-anisidine, followed by Stille coupling reactions, employing either tributylvinyltin or allyltributyltin and $Pd(PPh3)_2Cl_2$ as catalyst, to render the desired vinyl or allyl substituted benzamides **13a-c** in highly satisfactory overall yields.

In order to ensure positive results, we envisaged that an increased nucleophilicity of the styrene fragment (R=OMe) would facilitate the cyclization onto the electronically deficient nitrogen atom generated, a consideration that is not required for the non-conjugated allyl substituted substrates (R=H, OMe). For that purpose, amide **13a** reacted with PIFA in trifluoroethanol as solvent at room temperature in the absence of any activating agent. As anticipated, the 5-*exo*-trig cyclization took place smoothly to afford isoindolinone **14a** in 95% yield. Analogously, the behavior of amides **13b,c** was also studied. When both amides were treated with PIFA under the same conditions, a 6-*exo*-trig cyclization took place to afford isoquinolinones **14b,c** in 72% and 93% yield, respectively.

Analogously, N-benzoyl-2-allylanilines **15a-d** have been also selected as substrates of interest to perform the PIFA-mediated olefin protocol as a new entrance to the synthesis of the indoline skeleton (see Scheme 9). The preparation of these precursors was accomplished in a two-step sequence starting from the corresponding *N*-allylaniline by an aza-Claisen rearrangement [24] followed by a subsequent *N*-protection process of the so-obtained 2-allylaniline with benzoyl chloride. When substrates **15a-d** were submitted to the action of the hypervalent iodine reagent PIFA, the proposed amidohydroxylation reaction proved to be suitable for the projected transformation and, hence, they rendered successfully the

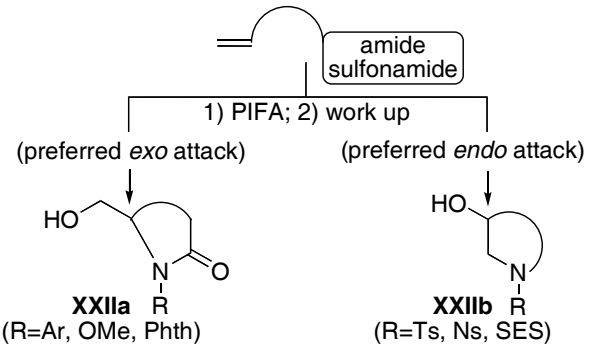


Figure 6. Comparison between the PIFA-mediated olefin amidation and olefin sulfonamidation reactions.

corresponding 2-hydroxymethylindoline derivatives **16a-d** [25].

6. SULFONAMIDES

To further demonstrate the potential of the presented methodology and its extension to the synthesis of related heterocycles, it is shown in Figure 6 recent achievements communicated by Michael´s group [26]. They have discovered that treatment of sulfonamidoalkenes with $PhI(OAc)_2$ and TFA in the absence of any metal catalyst, and also employing PIFA in CH_2Cl_2 as solvent at room temperature, results in a clean conversion into the *endo* aminohydroxylation product of type **XXIIb**. This preferential formation of, in example, piperidines over pyrrolidines starkly contrasts with the preferred *exo* cyclization mode shown in the previous sections of this review to afford heterocycles of general structure **XXIIa**. Several sulfonamide protecting groups such as para-toluensulfonyl (Ts), 2- and 4-nitrobenzene-sulfonyl (Ns), and trimethylsilylethanesulfonyl (SES) afforded the 6-*endo* aminotrifluoro-acetoxylation products in excellent yields, which under saponification conditions yielded the final heterocycles.

CONCLUSIONS

In conclusion, the powerful potential of the inexpensive and readily available hypervalent iodine reagent PIFA in organic synthesis has been exemplified in the preparation of a series of hydroxymethyl-substituted nitrogen-containing heterocycles. All of them (pyrrolidines, piperidines, γ-aminoalcohols, isoquinolines, isoindolines, and indolines) have been prepared thanks to the ability of the hypervalent iodine reagent to generate *N*-acylnitrenium ions from adequately substituted amides. Subsequent steps results, in the overall, in an efficient strategy to include a 1,2-aminoalcohol fragment in the skeleton of such heterocycles.

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