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# Metal-free catalytic vicinal diamination of alkenes*

Kilian Muñiz

*Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, E-43007 Tarragona, Spain and Catalan Institution for Research and Advanced Studies (ICREA), Pg. Lluís Companys 23, E-08010 Barcelona, Spain*

*Abstract*: The development of an intramolecular vicinal diamination protocol using metal-free conditions is discussed. The reaction uses a bromide source to generate a Br(I) catalyst in situ from a benign terminal oxidant such as sodium chlorite. The reaction is of great scope and surpasses the transition-metal catalyses developed so far for these types of reactions.

*Keywords*: alkenes; bromine; catalysis; diamination; oxidation.

## INTRODUCTION

Vicinal diamines represent an important functional group within organic molecules. This class of compounds is present in molecules of biological and pharmaceutical importance, serves as ligands for transition metals, and may be used as monomer in the construction of advanced materials. The synthesis of 1,2-diamines usually requires a combination of synthetic manipulation of suitable precursors [1]. A useful alternative consists in the direct oxidative intramolecular 1,2-diamination of alkenes, a reaction that has received some attention over recent years [2]. In particular, transition-metal catalysis has enabled the realization of several vicinal diamination reactions [3–7]. We here summarize recent work on an alternative approach to replace transition-metal catalysis by suitable reaction conditions using halides as catalyst precursors.

## HALOGEN-MEDIATED REACTIONS

Over the course of the development of the intramolecular diamination of alkenes, we had initiated the use of a halonium promoter already at an early stage. In collaboration with Barluenga and González, it was found that the cationic iodonium reagent $IPy_2BF_4$ (Py = pyridine) is capable of promoting the transfer of two nitrogen atoms from a urea group to a terminal alkene (Scheme 1) [3d]. Despite the demonstrated scope of the reaction, the formation of minor amounts of aminooxygenation products [8] in some cases and the rather harsh reaction conditions rendered this protocol less appealing.

The mechanism of this transformation was proposed to consist of an iodonium formation upon interaction between the I(I) species and the alkene, followed by two nucleophilic substitution processes to form the two individual C–N bonds. This proposal was corroborated by selective deuterium labeling experiments on alkene **1**. The corresponding cyclic urea products were obtained as single diastereoisomers (Scheme 2).

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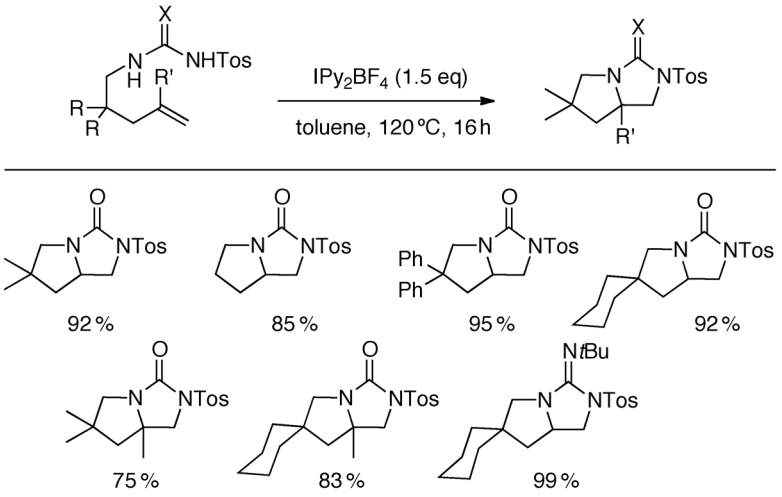
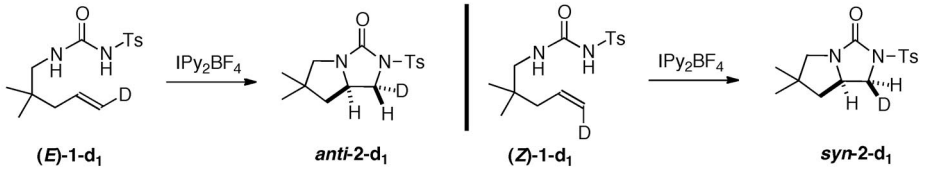



**Scheme 1** $IPy_2BF_4$-mediated intramolecular diamination of ω-alkenyl ureas.

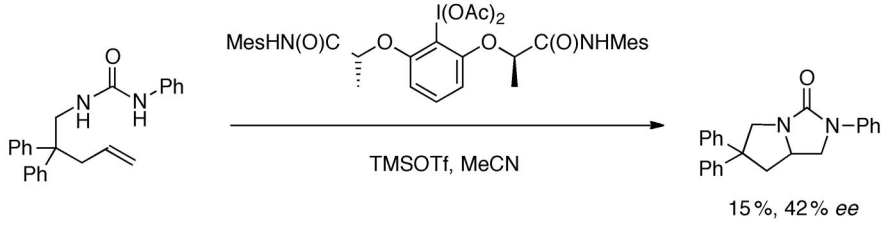



**Scheme 2** Mechanistic investigation on $IPy_2BF_4$-mediated intramolecular diamination.

Widenhoefer could significantly improve on this protocol by replacing $IPy_2BF_4$ with *N*-iodosuccinimide [9]. Although two equivalents of the reagent were required, the reaction could be conducted at room temperature and could be extended to diastereoselective reactions as well. The mechanism was proposed to follow the same pathways of the reaction with $IPy_2BF_4$. Importantly, however, for the present examples aminooxygenation did not compete with the desired diamination.

Finally, Wirth developed an elegant approach toward an enantioselective intramolecular difunctionalization of alkenes using a reagent combination of a chiral hypervalent iodine reagent and trimethylsilyl (TMS) triflate [10]. While aminooxygenation was accomplished for the usual *N*-tosylates ureas, an aniline derivative led to diamination with acceptable enantioselective induction (Scheme 3).

This approach is related to an intermolecular enantioselective diamination of styrenes published by our group, which uses a similar hypervalent iodine reagent derived from a lactic ester. It represents the first step toward the development of a general asymmetric diamination [11].




**Scheme 3** Enantioselective intramolecular diamination using a chiral iodine(III) reagent.

## HALOGEN-CATALYZED DIAMINATION REACTIONS

During the screening of some transition-metal halides as potential catalysts for the catalytic intramolecular diamination of alkenes, we found that metal bromides in the presence of iodosobenzene diacetate as oxidant gave rise to a particularly clean diamination reaction [12]. Control experiments revealed that these processes were not the result of metal catalysis, but rather originated from oxidation of the bromide with $PhI(OAc)_2$, presumably to acetyl hypobromite BrOAc as the catalytically active species. Upon optimization of the conditions, both ureas and sulfamides could be employed as nitrogen sources [13].

The use of ureas or sulfamides with the two nitrogen sources tethered within a single functional group is crucial for the success of the reaction. The proposed catalytic cycle is shown in Fig. 1 for sulfamides [13]. The reaction starts by oxidation of the bromide to a Br(I) species such as acetyl hypobromide. This species should then form an N–Br intermediate at the more acidic and more reactive nitrogen of the sulfamide and initiate an intramolecular oxidation of the alkene to form a bromonium intermediate. The alternative of a direct bromonium formation from BrOAc itself cannot be ruled out. Intramolecular opening of this intermediate gives an aminobrominated intermediate, which undergoes intramolecular nucleophilic substitution. This approach allows one to efficiently displace the bromine through a nitrogen group within the final C–N bond formation and thus releases the original catalyst precursor. Hence, the reaction is truly catalytic in bromine.

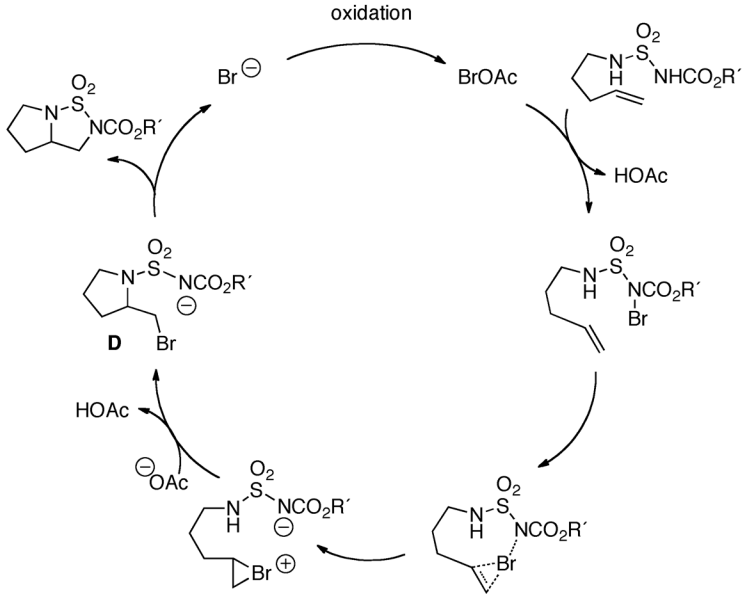
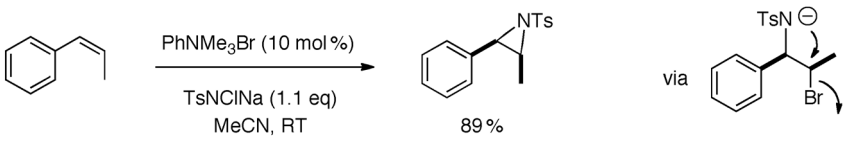



**Fig. 1** Catalytic cycle for the bromine-catalyzed intramolecular diamination of alkenes.

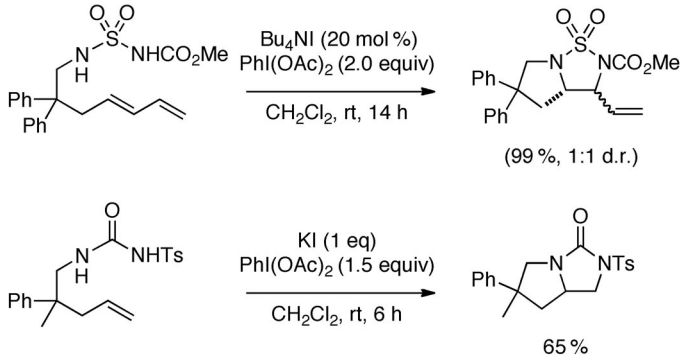
Reactions of this type are rare. The major problem in the development of halogen catalysis consists in the difficult regeneration of the original halide species and hence to avoid catalyst deactivation through formation of stable side-products, for example, in the form of alkyl halides. The concept to regenerate the halide throughout the catalytic cycles via a nucleophilic substitution with a suitable nitrogen source was introduced by Sharpless who reported an efficient bromine-catalyzed aziridination of alkenes using chloramine-T as nitrogen source and oxidant. After bromonium ion formation, opening with chloramine-T followed by bromine-assisted abstraction of the chlorine, an intermediate for immediate C–N bond formation arises that releases the bromide catalyst precursor (Scheme 4) [14,15].




**Scheme 4** Bromine-catalyzed aziridination of alkenes.

Apart from bromine, we discovered that iodine can play a related role in metal-free catalysis for intramolecular diamination as well. For example, a 1,3-butadiene can be quantitatively oxidized to the corresponding 1,2-diamine derivative, although without diastereoselectivity (Scheme 5). Parallel to our publication, Chang described the combination of stoichiometric amounts of potassium idodide and $PhI(OAc)_2$ for an intramolecular diamination of ureas [16]. The same group also reported on the use of a related chlorine-mediated diamination.




**Scheme 5** Intramolecular diamination reactions using an iodide/iodine(III) reagent combination.

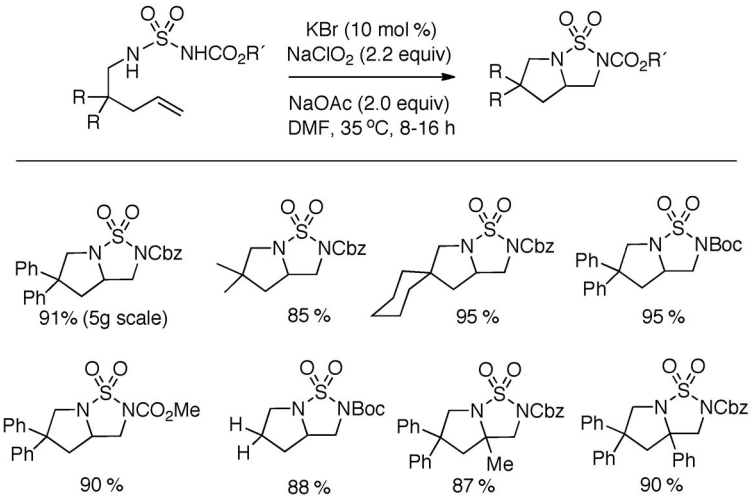
Since iodosobenzene diacetate generates iodobenzene as stoichiometric by-product, it can hardly be considered as an optimum oxidant. Subsequent screening revealed that the commercially attractive and environmentally more benign sodium chlorite could be employed as well. Under these conditions, a series of terminal alkenes could be employed in the intramolecular metal-free diamination with a substrate scope that could be conveniently raised to 5 g. In addition to achiral substrates, acceptable diastereomeric induction could be achieved for starting materials with a chiral backbone or an allylic ether substituent (Scheme 6).

A terminally mono-deuterated substrate revealed the same reaction outcome as in the case for the reaction mediated by $IPy_2BF_4$ (Scheme 2) and suggested an identical stereochemical pathway. This was further underlined by the entirely diastereoselective reaction course of internal alkenes (Scheme 7).

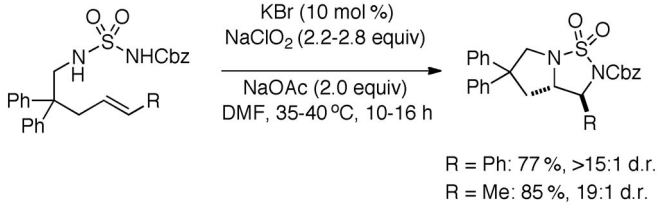
In addition to these examples, six-membered ring annelation reactions, which are usually kinetically disfavored, are compatible with the current metal-free methodology (Scheme 8).

Finally, the conditions can also be employed for a series of acrylate derivatives, which undergo clean cyclization to the corresponding 2,3-diamino acid derivatives (Scheme 9). The reaction proceeds in very good yields, although the diastereoselectivities are not optimum.

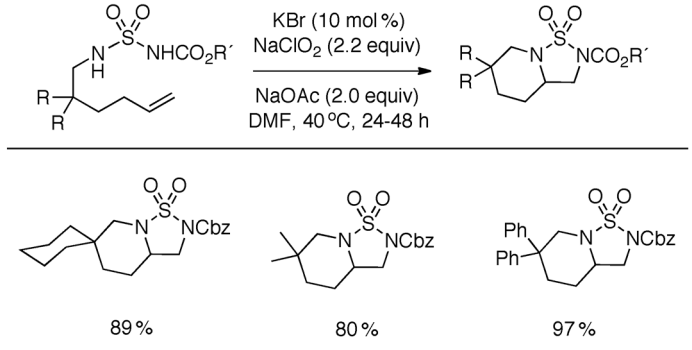
 



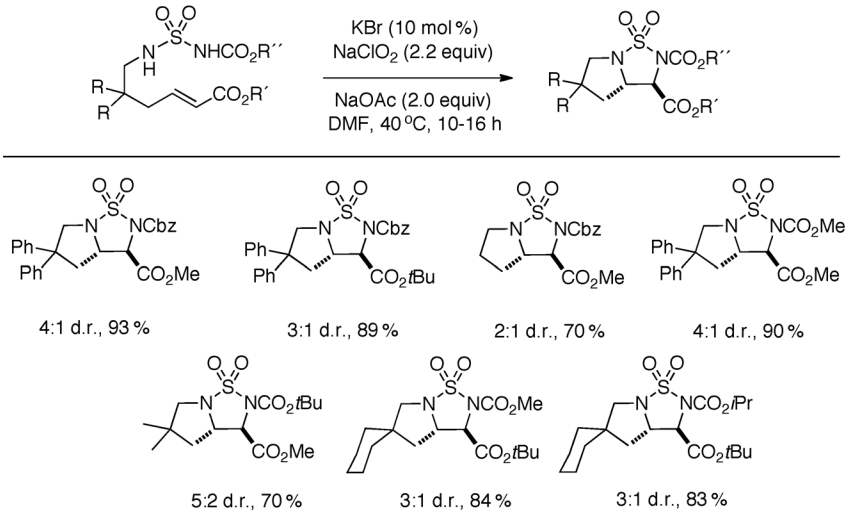

**Scheme 6** Bromine-catalyzed intramolecular diamination of ω-alkenyl sulfamides.




**Scheme 7** Diastereoselective bromine-catalyzed intramolecular diamination.




**Scheme 8** Diamination of terminal alkenes under piperidine formation.




**Scheme 9** Bromine-catalyzed intramolecular diamination of acrylates.

All these examples convincingly demonstrated that the usual transition-metal catalysis for the intramolecular diamination of alkenes could be replaced by simple halide catalysis. This reaction surpasses the individual scope of the respective transition-metal catalyses and provides general conditions for this type of transformation.

The use of sulfamides as nitrogen source also bears the inherent advantage of convenient deprotection protocols. This was demonstrated earlier for a stepwise or total removal of all nitrogen substituents to provide differently substituted aminomethylpyrrolidine cores. In addition, an application in the synthesis of peptidic derivatives was reported recently for the 2,3-diamino acid derivatives (Fig. 2) [3f].

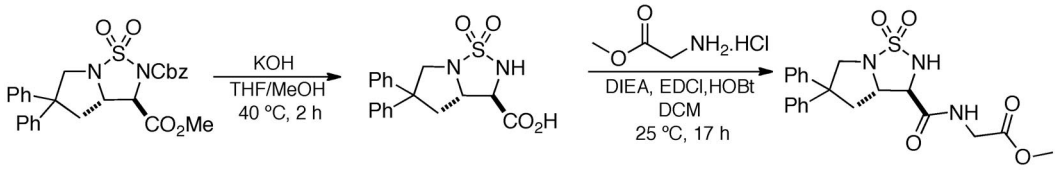



**Fig. 2**

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