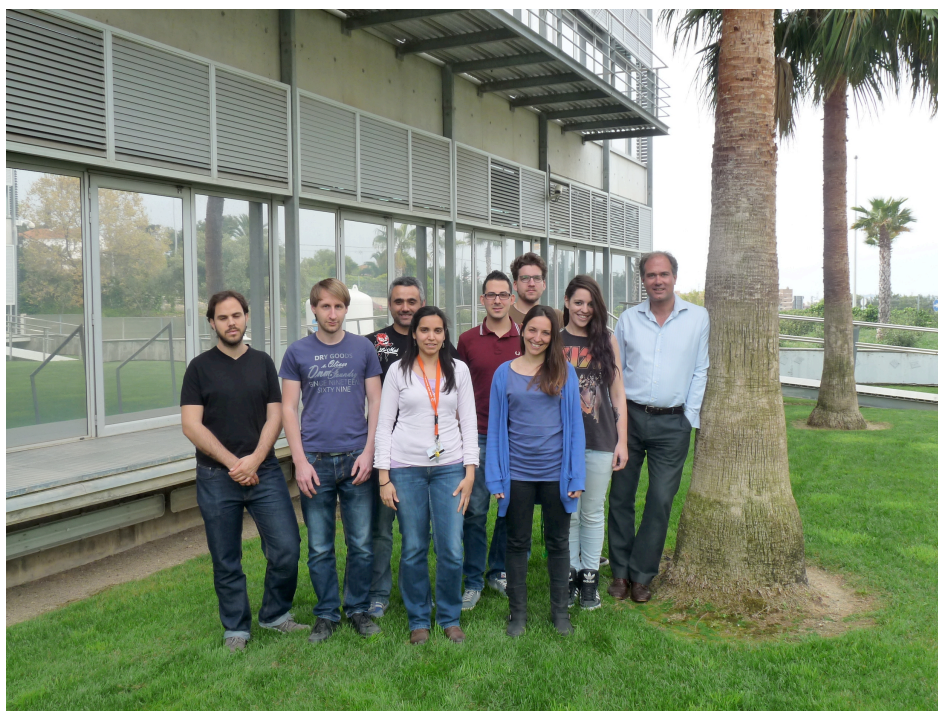


Muñiz Research Group



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Abstract

The Muñiz group has continued the development of new synthetic methodology for advanced oxidative amination of organic molecules. For 2014, work on this topic focussed

on the realisation of economic transformations under environmentally benign metal-free conditions.

Major advances were made in the area of hypervalent iodine(III) chemistry and halogenated amide reagents.

We have continued working on our most important recent research theme, which confers to the development of new homogeneous amination chemistry based on the methodology of high oxidation state reagents. To this end, we mainly focus on iodine(III) reagents with unprecedented iodine-nitrogen bonds. An addition to this theme has been the development of aminations using chlorinated amides. These projects have demonstrated to provide significant synthetic possibilities under unprecedented mild conditions.

Metal-free amination by hypervalent iodine chemistry

We had explored the chemistry of unique hypervalent iodine reagents of the general formula $\text{PhI}[\text{N}(\text{SO}_2\text{R})_2]_2$ over past years. While these reagents have shown a generally broad applicability in the amination of hydrocarbon molecules such as alkenes, 1,3-butadienes, acetylenes, allylic C-H groups and arenes, cumulated unsaturated systems such as allenes had escaped the corresponding amination. In general, these compounds represent difficult substrates for selective oxidation reactions. We therefore explored the reactivity of our isolated hypervalent iodine reagent **A** in the task of a selective amination of allenes (Figure 1).

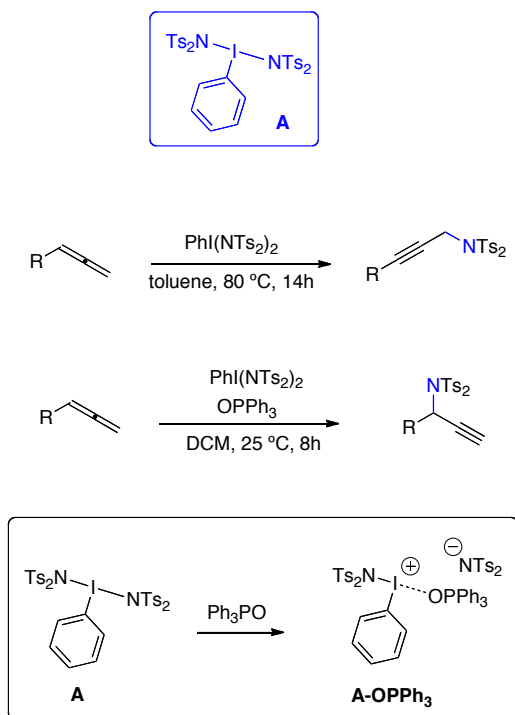


Fig. 1 – Selective amination of allenes.

This approach proved successful for a series of allenes. In general, interaction between reagent

A and a mono-substituted allene gave rise to the corresponding propargylamine. The reaction proceeds with excellent selectivity giving rise to the products with the newly formed C-N bond at the terminal position. In contrast, addition of triphenylphosphine oxide to compound **A** modifies the hypervalent iodine reagent, presumably to a species of the type **A-OPPh₃**. The latter inverts the regioselectivity of the amination reaction, so that propargyl amines with an internal C-N bond are now formed preferentially. The reaction can also be applied to higher-substituted allenes. This successful realisation of an unprecedented oxidative conversion of allenes demonstrates the power of metal-free amination.

In a second project, we have explored a new synthetic approach to indoles from simple 2-vinyl anilines. Such reactions have been investigated previously for transition-metal mediated processes. However, given the importance of indoles in important fields such as medicinal and pharmaceutical chemistry or biology, contamination by metal traces can constitute a significant problem. To overcome this challenge, we developed a new oxidative indole synthesis based on a single hypervalent iodine reagent (Figure 2).

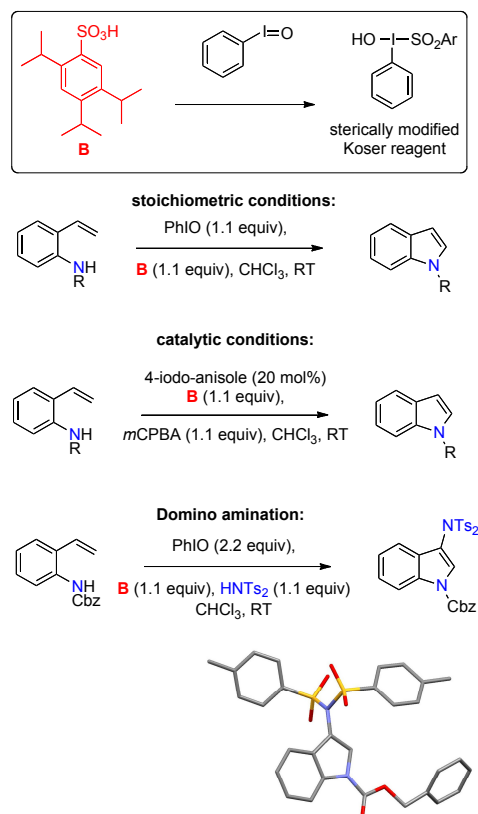


Fig. 2 – Development of iodine-mediated and catalysed indole syntheses.

The development of a suitably modified Koser reagent was the key to success in this project. To this end, we identified the sterically congested arylsulfonic acid **B** as the most successful sulfonic acid for an in situ formation of a suitably modified Koser reagent. This reagent then promotes the cyclisation of a given 2-vinyl aniline into the corresponding indole derivative. The reaction is of broad generality tolerating most functional groups. The reaction can also be conducted under catalytic conditions, when mCPBA is employed as terminal oxidant. 4-Iodo-anisole was identified as the optimum iodine reagent as Koser catalyst precursor. Unlike most other methodology in the area, it is particularly important that our approach leads to 2,3-unsubstituted indoles. Such an approach has also allowed us to investigate potential domino aminations. A demonstration of this type has resulted in the sequential amination of 2-vinyl tosylanilide followed by a second amination with an in situ generated hypervalent iodine reagent and bistosylimide. The latter reagent is reminiscent of a derivative of **A** and leads to selective 3-amination of the indole core.

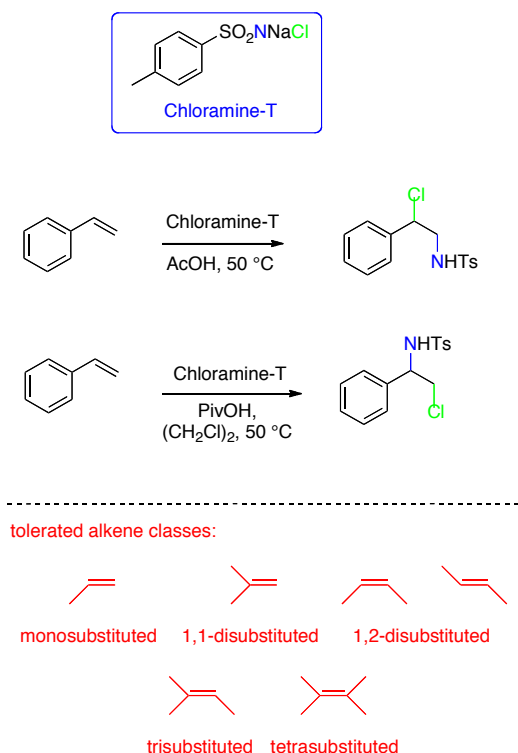


Fig. 3 – Acid activation of chloramine-T and aminochlorination of alkenes.

In another project, we have explored the synthetic potential of chloramine-T as an ubiquitous oxidant. This particular compound

has been used widely in combination with transition metals of all kinds. However, we have now made the unprecedented discovery that activation with simple Bronsted acid provides conditions, under which the protonated chloramine-T directly engages in a vicinal aminochlorination of alkenes. The reaction is of striking generality and tolerates all six different classes of alkenes alike, which is a very common observation in oxidation chemistry (Figure 3). More importantly, the regioselectivity of the aminochlorination can be predicted by the respective use of acid activator. While a reaction in acetic acid leads to an aminochlorination with the amine placed at the more accessible position of the former alkene, activation with pivalic acid in dichloroethane provides the alternative regioisomer.

Metal-mediated amination using copper reagents

Finally, our interest in metal-promoted diamination led us to explore the application of economic copper reagents in the selective diamination of 1,3-butadienes (Figure 4). This particular difunctionalisation had been underrepresented in comparison to related vicinal processes. We could now demonstrate that copper bromide in the presence of phosphate base promotes an entirely regioselective 1,4-diamination. Besides the occurrence of 1,4-diaminebut-2-enes in natural products, these compounds also serve as interesting building blocks for advanced organic synthesis. The present transformation adds just another protocols to our long-term work on the development of diamination reactions.

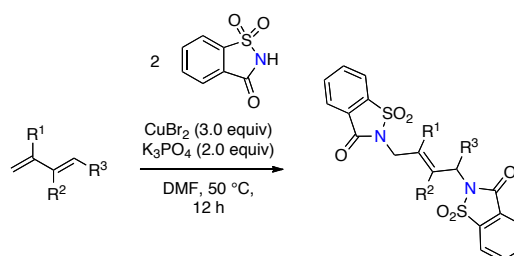


Fig. 4 – Copper-mediated 1,4-diamination of 1,3-butadienes.

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