

Muñiz Research Group



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Abstract

The Muñiz group has continued with its efforts to develop sustainable synthetic methodology for advanced oxidative transformation of organic molecules. For 2015, 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 molecular iodine catalysis.

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 iodine reagents. To this end, we mainly focus on defined iodine(III) reagents for unprecedented carbon-boron and carbon-nitrogen bond formation. These projects have demonstrated to provide significant synthetic possibilities under unprecedented mild conditions.

Metal-free borylation by hypervalent iodine chemistry

In order to expand our expertise on hypervalent iodine chemistry, we investigated the synthesis of arylboronic esters, which are key components for modern cross-coupling reactions. Their high versatility has made C-C coupling events based on them one of the most versatile themes in the field, which was recognized by a Nobel Prize in 2010. To contribute an alternative synthetic approach, the unprecedented direct formation of aryl boronic esters, in particular aryl pinacolboranes, through an effective coupling between diaryliodonium salts and bis(pinacolato)diboron pinB–Bpin under mild conditions and without any requirement for a metal promoter was developed.

arylation of boron groups: strategy

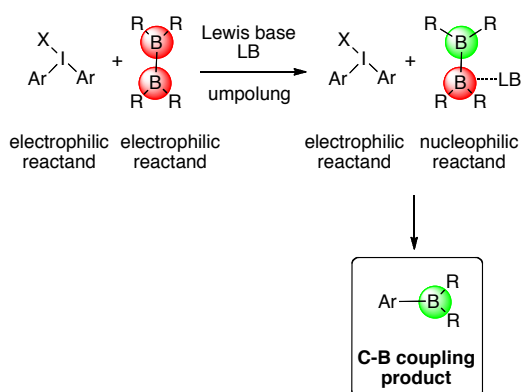


Fig. 1 – Selective amination of allenes.

A synthetic approach of such a type of direct C-B bond formation appears unconventional at first sight, as it involves the combination of two reactants that are of exceedingly electrophilic nature (Figure 2, below). To accomplish the targeted carbon-boron bond formation, we envisioned that presence of Lewis base could be employed for the activation of the diboron reactant. Such an interaction should be favorable as it would constitute an umpolung of

the native electrophilic boron atom resulting in a more nucleophilic character^[18] for effective C-B bond formation with the electrophilic iodine(III) reagent.

A subsequent screening between various diphenyliodonium salts and bis(pinacolato)diboron was undertaken and confirmed the correctness of the initial hypothesis for the acetate derivative (Figure 2). Methanol was identified as the best solvent, and the expected product was formed in high yield and isolated in 77%. This transformation leads to two important conclusions: First, methanol as solvent could play a crucial role in activating the diboron reagent through a state such as **A**. Secondly, the pronounced dependence of the reaction on the counterion of the diphenyliodonium reagent suggests participation of this anion as well. This may include a direct interaction between the solvated acetate with the diboron reagent (state **B**) or a participation of its negative charge throughout the hydrogen-bonding network of the protic solvent (state **C**). For the latter scenario, the activation is reminiscent to the more common activation with methoxide base.

Once the conceptual verification of the C-B bond formation had been accomplished, the reaction was further extended to various diboron compounds and diaryliodonium salts. By this it was possible to establish a general protocol for C-B coupling of this type.

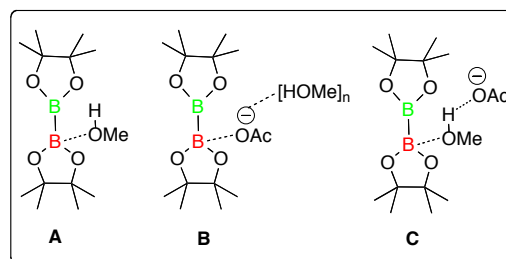
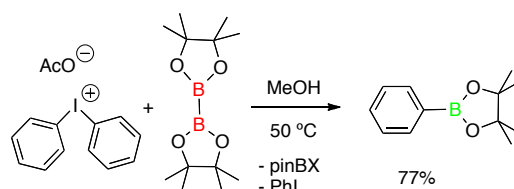


Fig. 2 – Development of iodine-mediated and catalysed indole syntheses.

Iodine-catalysed aliphatic C-H amination

The major focus was placed on the development of new homogeneous iodine catalysis. Within this context, the group was interested in the

development of a catalytic C-H amination reaction. For the intramolecular case, this reaction is known as the classic Hofmann-Löffler reaction.

Catalytic conditions could indeed be developed for this particular reaction. The final protocol uses 2.5 mol% of molecular iodine in combination with a defined hypervalent iodine reagent $\text{PhI}(\text{mCBA})_2$ [mCBA = 3-chlorobenzoate] (Figure 3). Visible light irradiation is usually sufficiently effective to promote the reaction. The optimum wavelength was determined to be at 400 nm, which allows violet LED to be used.

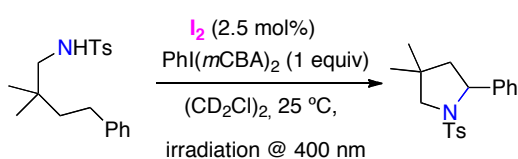


Fig. 3 – Selective amination of allenes.

The overall process is rather complex and consists of two intertwined catalytic cycles (Figure 4). In a set of control experiments, the mechanism of two intertwined catalytic cycles was confirmed. Intermediates and individual steps were clarified using physical-organic control experiments including kinetic isotope effects, Hammett correlation, stoichiometric reagent combination and quantum yield determination.

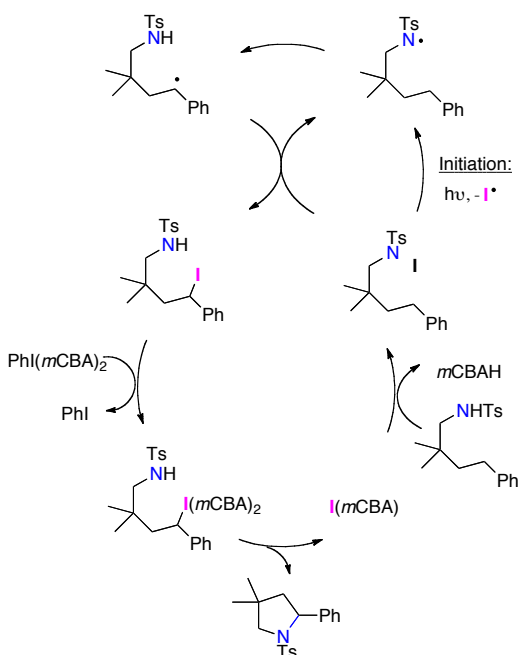


Fig. 4 – Catalytic cycles involved in the iodine catalyzed Hofmann-Löffler reaction.

One of the major accomplishments in this context was the isolation and structural characterization of the iodine catalyst as tetrabutylammonium its derivative (Figure 5). A control reaction for the standard substrate provided the expected product in 90% yield. This confirms that the actual reaction is based on a monomeric iodine(I) catalyst and overall proceeds within the iodine(I/III) manifold.

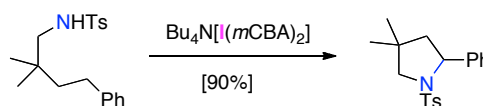
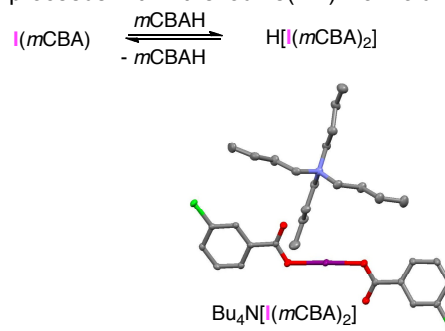
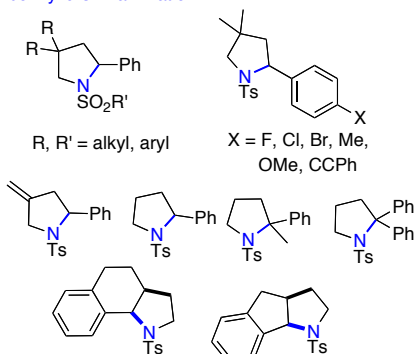


Fig. 5 – Catalyst, acid adduct and isolation of an ammonium derivative.

benzylic C-H amination



aliphatic C-H amination (1°, 2°, 3° C-H groups)

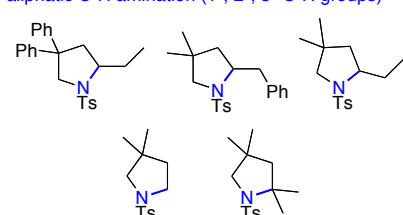
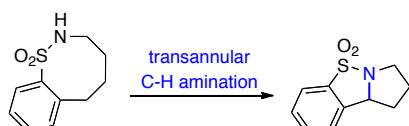
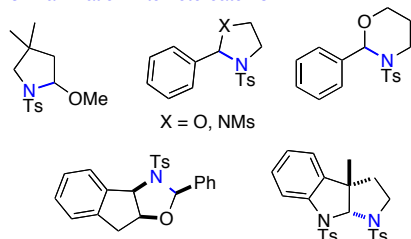
C-H amination α to heteroatoms

Fig. 6 – Substrate scope of the iodine catalyzed Hofmann-Löffler reaction.

The reaction is of unusually high substrate scope. Successful products include various pyrrolidines with and without backbone substitution and C-N bond forming events at benzylic positions including formation of quaternary centers (Figure 6). This scope is extended to the application of chiral substrates. While achiral stereocontrol is not successful due to the involvement of radical pathways, cyclic stereocontrol leads to single diastereoisomers as products. Finally, the reaction is not limited to benzylic positions, but also tolerates non-functionalized aliphatic C-H groups including primary, secondary and tertiary C-H bond alike. It works well for selective amination in α -position to heteroatoms including tryptamine derivatives. Finally, it could also be employed successfully within a transannular C-H amination reaction.

Articles

“A Mild Carbon-Boron Bond Formation from Diaryliodonium Salts”

Chem. Commun. (2015) 51, 14068

N. Miralles, R. M. Romero, E. Fernández, K. Muñiz

“An Iodine Catalyzed Hofmann-Löffler Reaction”

Angew. Chem. (2015) 127, 8405; *Angew. Chem. Int. Ed.* 2015, 54, 8287

C. Martínez, K. Muñiz

“Amidato complexes of ruthenium, rhodium and iridium from concise N-H bond activation: exploration in catalysis”

Tetrahedron (2015), 71, 4465

R. M. Romero, L. Fra, A. Lishchynskyi, C. Martínez, J. Streuff, K. Muñiz