Carbonylation

The development of efficient and environmentally benign methods for the synthesis of industrially relevant molecules is central to improving the green credentials of the pharmaceutical and fine chemicals industries. In this respect, catalysis is a key chemistry for achieving this. Of the broad arrays of catalytic reactions, the functionalisation of hydrocarbon feedstocks into more complex molecules using carbonylation is key area of research.

Carbonylation is formal addition of C=O unit into a molecule and the most atom efficient route to this is by using carbon monoxide (CO). Carbonylation is one of the core industrial technologies for the conversion of bulk materials into products of value for example, olefins can be converted by carbonylation to a variety of products such as alcohols, aldehydes and carboxylic acid derivatives. It has also been employed for the efficient synthesis of amides.

Despite its position as a core transformation industrially, carbonylations are rarely used in the synthesis of complex pharmaceutical molecules. Beller *et al*. have hypothesised that this may be due to a reluctance by the research communities to operate the high pressure equipment involved when running reaction involving gasses, though they note that a number of catalytic methods for carbonylations are carried out at ambient to low pressures. [1]

1. A. Brennführer, H. Neumann and M. Beller, Palladium-Catalyzed Carbonylation Reactions of Aryl Halides and Related Compounds, *Angew. Chem. Int. Ed.*, 2009,

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48, 4114-4133.

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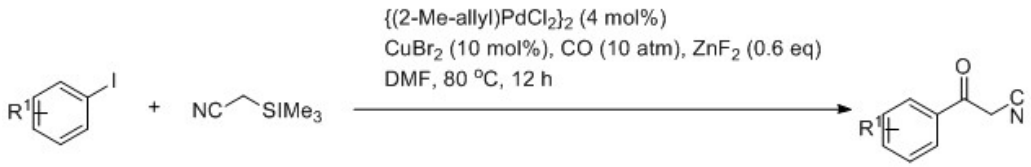
Case studies

Carbonylative α-arylations have seen a lot of interest over the years; however, initial methods were limited to the use of malonate derivatives as starting materials.[1][2][3] Catalytic systems for the intermolecular carbonylative α-arylation of ketones have been developed although these reactions were limited to the use of C-nucleophiles furnished with a carbonyl group.[4][5][6][7] Thus, extending carbonylative α-arylation towards nitriles as readily available coupling partners represents an attractive goal for further development. The resultant β-ketonitrile products from such methods are useful bifunctional intermediates for the synthesis of pharmaceutically relevant compounds.[8][9][10][11] As important optically active intermediates, the diversity of available β-ketonitriles has a significant impact on the range of structures that can be accessed.[12][13][14][15][16][17] As such, the conventional methods for the synthesis of β-ketonitriles through acylation of acetonitriles or carbonylative coupling of trimethylsilylacetonitrile (**Scheme 1**) are limited to the formation of β-ketones that are unsubstituted at the α-position.[18]



Scheme 1: ***β-ketonitrile formation from carbonylative coupling of trimethylsilylacetonitrile ([18])***

Although recent approaches have been reported that enable access to α-substituted β-ketonitriles, these protocols do not allow for the generation of a quaternary α-carbon centre.[19][20] As a result, the development of protocol that allows access to β-ketonitriles from aryl halides, carbon monoxide and uses nitriles as a simple abundant feedstock represents an advantageous achievement. CHEM21 researchers have developed the first example of such a transformation using a commercially available catalyst system that allows for the selective formation of α-disubstituted β-ketonitriles under low CO pressures with the use of unactivated nitriles (**Scheme 2**).[21]

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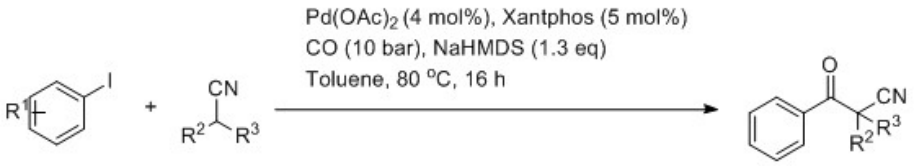

Scheme 2: ***CHEM21 Approach and first example of the synthesis of α-disubstituted β-ketonitriles from unactivated nitriles([21])***

The method is applicable to the synthesis of 24 α-disubstituted β-ketonitriles in good to excellent yields, which were achieved in a straightforward appraoch. The approach allows for the selective carbonylative α-arylation in an atom economical manner using CO gas.

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