WHITE PAPER

Five of the most useful transformations in modern organic synthesis: lessons from old and new reactions

Introduction

The monumental efforts put by the pharmaceutical industry since World War II into the pursuit of new biologically active molecules has undoubtedly been a major driver for the evolution of synthetic organic chemistry. Incredible creativity has gone into translating decades of chemical knowledge and new discoveries into a toolbox of efficient reactions, enabling the synthesis of very complex multi-functional molecules.

Over the past 25 years, several scientists have been recognized with the Nobel Prize for the invention of synthetic methodologies that have changed the way chemists approach molecular design. Pd-catalyzed cross-couplings, asymmetric hydrogenation, epoxidation and olefin metathesis have led to the development of completely new synthetic strategies and played a key role in the discovery and synthesis of new important drugs (e.g. L-Dopa,[1] Ledipasvir, Losartan,[2] Atorvastatin).

Despite the achievements, modern synthetic organic chemistry is often perceived as an established discipline with limited innovation. While its role remains unquestionably at the centre of new drug discovery/development, R&D efforts have progressively moved to other areas,[3,4,5] notoriously at the interface between biology and chemistry. From this perspective, it is interesting to look at how chemical strategies have evolved from the end of the 1900's to present days.

Brown and Boström[6] found that a limited number of reactions dominate the chemical landscape of modern medicinal chemistry, based on an analysis of the medicinal chemistry literature at two time points, 1984 and 2014. The most common reactions used in 1984 were still in use in 2014, with a few exceptions (increase of Suzuki–Miyaura chemistry over the years, increase in amide bond formations, and decrease in heterocyclic synthesis).

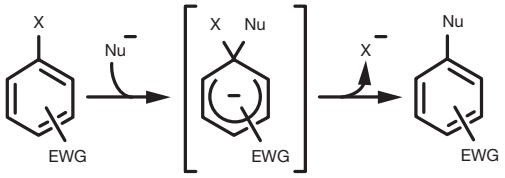
The five most widely used reaction in medicinal chemistry include a fascinating mix of "traditional" reactions encountered by chemistry students in their first years of study and sophisticated newer transformations: aromatic nucleophilic substitution (SNAr), amination/alkylation of amines, amine protection and deprotection, amide synthesis, and C-C cross-coupling.

Functionalisation of aryl compounds

The aromatic nucleophilic substitution is an extremely useful tool for the functionalisation of aryl compounds and it has been around since the early 50's. As all substitution reactions, a nucleophile, such as an amine or an alcohol, displaces a leaving group on the aromatic ring, which is usually a halide. It typically follows three main mechanisms:

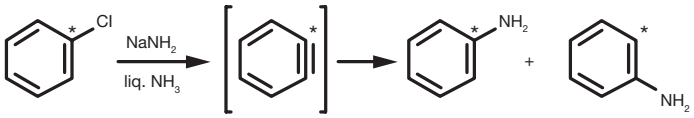
- Addition-elimination mechanism, the most common one for substituted aryl halides
- Benzyne mechanism, relevant to unsubstituted aryl halides
- Aromatic SN1 of diazonium salts, occurring in the case of aromatic diazonium salts

The aromatic nucleophilic substitution is the method of choice for aromatic alcohols and other nucleophilic functionalities. For the synthesis of amines however, it is being progressively abandoned in favour of milder, more robust and efficient catalytic method, the Pd-catalysed Buchwald-Hartwig C¬-N coupling.

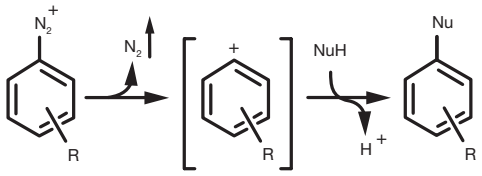


EWG = electron - withdrawing group

Addition-elimination mechanism



Benzyne mechanism



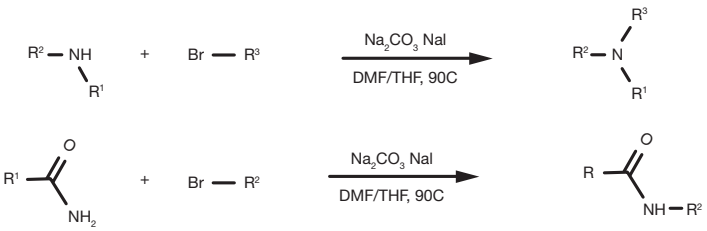
Aromatic SN1

Synthesis of amines

The Buchwald-Hartwig amination of aryl halides is the first of the two main routes to adding amine functionality to organic molecules, the second one is the nucleophilic substitution of alkyl halides. A third obvious synthetic approach is the reductive amination of carbonyls, which seems however much less frequently used.[6]

Often referred to as alkylation of amines, the nucleophilic substitution of alkyl halides with aliphatic or heteroaromatic amines is a "historical" organic reaction. It's simple, well established and still a primary method for the alkylation of amines with aliphatic compounds.

The reaction occurs at relatively high temperatures and often requires the use of a strong base, such as sodium bis(trimethylsilyl)amide and cryogenic conditions.

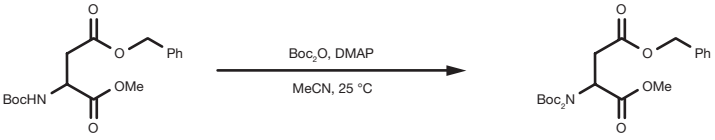


The rate of alkylation follows the order primary amine > secondary amine > tertiary amine and the reactivity of the halide derivative follows the electronegativity of the halide substituent. Bromide and iodides are the most practical building blocks, while chlorides remain common for their broad commercial availability. Sodium iodide is often used to generate *in-situ* a more reactive alkyl iodide when the starting material is a different halide.

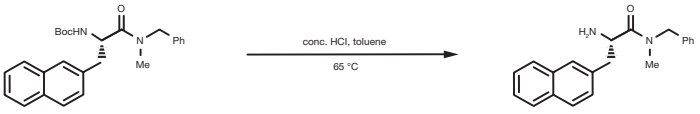
The nucleophilic substitution of alkyl halides is not considered a green reaction as it produces a halide ion side product and it can be demanding from the calorimetric viewpoint. Big scale industrial methods for the production of simple amines tend in fact to prefer the amination of alcohols as the side product is water. Despite that, it remains an indispensable tool in the synthetic organic chemist's toolbox.

Handling amines in multifunctional compounds

Given the frequency of the amine functionality in bioactive molecules, it is not surprising that amine protection and deprotection reactions are a common occurrence in synthetic chemistry. The BOC (tert-butyloxycarbonyl) protecting group, chemically a di-tert-butyl dicarbonate (Boc2O), is probably the most common amine protecting group in non-peptide chemistry. The process usually achieves high yields and fast conversions under flexible and relatively mild conditions.



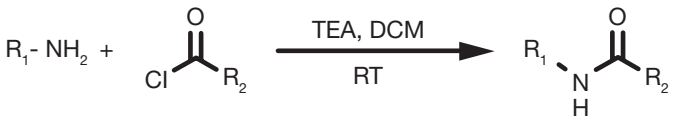
The deprotection of a BOC-protected amine is a simple carbamate hydrolysis in acidic conditions. The reaction is usually fast and happens at room temperature. Biphasic systems can be used, with the protected amine dissolved in the organic phase, mixed with the aqueous solution of the acid.



These reactions have remained unchanged over the years. Their simplicity, broad substrate scope and robustness make them extremely practical and enable flexibility in the synthesis of multi-functional compounds.

Synthesis of amides

The next class of common organic functionality, conceptually following amines, are amides. The Schotten-Baumann reaction, or the acylation of amine by acyl chloride, has been the standard for a long time. The reaction proceeds rapidly at room temperature in aprotic solvents in the presence of a base, but it suffers from the instability of the acyl chlorides and some hazards related to the release of hydrochloric acid as a by-product and often other chloro-derivatives from the decomposition of the starting materials.



The coupling between the amine and an anhydride is a safer, cleaner and mechanistically related alternative, the only significant difference being the acid by-product: hydrochloric acid in one case, a carboxylic acid in the other.

Significant progress in the synthesis of amides has been achieved in the last three decades by research in the field of peptide synthesis. These advances have *de facto* made the Schotten-Baumann reaction a thing of the past.

The big variety of peptide coupling reagents that are commercially available nowadays share a fundamental chemical principle: the synthesis of a highly activated ester. These activated esters can then be efficiently coupled to an amine using reaction conditions similar to the Schotten–Baumann reaction (base, aprotic solvent, RT) without its main drawbacks.

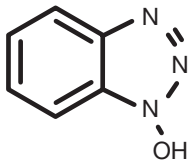
The most common reagents belong to two main groups:

- Carbodiimmides
- Hydroxybenzotriazole Aminium/Uronium or Phosphonium salts

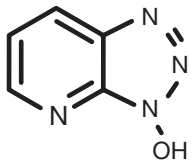
The two most common carbodiimmides are dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC) and 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC). They react with carboxylic acids to form a highly reactive O-acylisourea that can be converted to an amide by reacting with an amine, with high yields and short reaction times.

In case of chiral molecules, the reaction is often performed in the presence of a triazole to avoid spontaneous racemisation, a common occurrence with amidation of O-acylsourea. In this case the activation step should be better described as a two-step DCC/Hydroxybenzotriazole activation.

The most common triazoles are 1-hydroxy-benzotriazole (HOBt), and 1-hydroxy-7-aza-benzotriazole (HOAt).



HOBt



HOAt

A strategy to avoid the two-step acyl activation process in peptide chemistry is made possible by using ammonium/uronium or phosphonium salts of the hydroxytriazoles mentioned above. This way it is possible to avoid completely the use of DCC and the formation of the O-acylisourea intermediate.

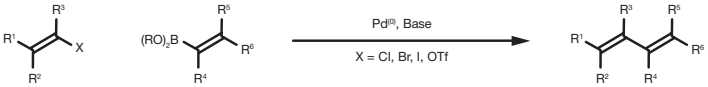
HOBt has a corresponding uronium salt called HBTU and its common phosphonium salts are called BOP and PyBOP. The corresponding uronium and phosphonium salts of HOAt are HATU and AOP/PyAOP respectively.

The history of amide chemistry over the arc of the last 25 years, inspired and driven by problems and solutions from a different field (aminoacid conjugation in peptide synthesis), is a great example of how organic synthesis can evolve over time, while maintaining its fundamental principles unchanged.

Formation of C-C bonds

The fifth and final reaction of this review addresses one of the biggest challenges in organic synthesis, the formation of C-C bonds. Carbon-Carbon cross-coupling reactions represent one of the biggest revolutions in organic chemistry and have rapidly become ubiquitary in the synthesis of fine chemicals. Their invention won Akira Suzuki, Ei-Ichi Neghishi and Richard Heck the Nobel Prize for Chemistry in 2010.

Among the various types of cross-coupling, the Suzuki-Miyaura – usually simply called “Suzuki coupling” - is arguably the one with the broadest utility and applicability. The Suzuki chemistry is based on the Pd(0) catalysed coupling of an aryl or vinyl halide with an aryl or vinyl boronic acid.



Its advantages over similar reactions reside in the mild conditions, common availability of the starting materials and their general low toxicity. Boronic acids are easily prepared, widely available on the market and reasonably cheap. As a matter of fact, they present lower environmental impact and safety hazards than organozinc or organostannane compounds, the substrates of choice for C-C bond formation until the 1990's.

Since its invention in 1979,[7] significant progresses have been made and the use of boronic acids, esters and trifluoroborates salts is now widely reported, while even alkyl boronic acids can be used as substrates (with the use of late generation catalysts).

The scope of the other coupling partner has also expanded over time to include pseudo-halides, such as triflates or aryl diazonium salts, and alkyl halides. The relative reactivity of the halide/pseudo-halide coupling partner can be summarised as follows:

R-I > R-Br > R-OTf >> R-Cl

Aryl > Vinyl >> Alkyl

Recent generation homogeneous Pd catalysts have reduced the catalyst loading by orders of magnitude, contributing to the economy of the reaction and enabling a growing number of commercial processes. It is possible – in fact beneficial – to screen many different catalysts, from relatively simple Pd(0) complexes, such as Pd acetate and Pd tetrakis, or various forms of Pd precatalysts + phosphine ligand to fully formed (pre)catalysts, often as air-stable complexes for an easier handling by the bench chemist.

Conclusions

These "top 5 reactions" tell us a fascinating story, made of tradition and a constant, sometimes subtle flow of innovation. While new inventions occasionally provide leaps forward that change profoundly the chemical landscape, innovation is driven by the sum of small steps in the applications and reaction conditions,[8] often inspired by research in adjacent fields.

For example, while SNAr and BOC protection/deprotection have remained substantially unchanged, amide synthesis has benefited from progress in the field of peptide chemistry and significant progress has been made in the field of amination of aromatic substrates.

A few common traits unify all these reactions: robustness, flexibility, broad substrate and reaction conditions scope.[9] The importance of other, more niche transformations cannot be understated, nonetheless. They represent some incredible chemical innovations and while not as widespread as the "top 5" discussed above, they play a key role in accessing chemical space that would be otherwise inaccessible.

The research in the field of synthetic organic chemistry is focused on overcoming the historical overreliance on just a few robust synthetic transformations. Its aim is to expand the sampling of the chemical space in modern organic synthesis,[10] while also trying to find new solutions for unaddressed chemical problems.[10]

The commercial availability of starting materials, building blocks and reagents has played and will continue to play a key role in supporting the development of the field. Thermo Fisher Scientific offers a comprehensive portfolio of fine chemicals, reagents and chemical essentials through the Acros Organics and Alfa Aesar brands. All products are available in research and bulk quantities and designed to support synthetic organic chemists at all stages of their work, from early stage R&D to advanced process chemistry and production.

Explore the organic chemistry resource center, featuring industry and research trends in organic synthesis.

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