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Recent Developments of Stetter Reaction: A Brief Review

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ABSTRACT

In this short review definition, mechanism, and recent developments of the Stetter reaction, in the period last ten years from 2011 to 2021 are presented. This reaction comprises N-heterocyclic carbene (NHC)-catalyzed umpolung of aldehydes followed by their capturing with activated carbon-carbon double bonds (Michael acceptors). This work includes also progresses in the inter-molecular and intra-molecular versions and enantioselective transformations. Underscoring the recent advances in the applications of Stetter reaction in the synthesis of various heterocyclic systems and total synthesis of natural products have been also introduced.

1. Introduction

The Stetter reaction is fundamental and plays an essential role in the total synthesis of natural products and biologically active compounds. 1,4-bifunctional compounds such as γ-ketonitriles, γ-ketoesters, and γ-diketones represent mainly the products of the Stetter reaction. It can be defined as the 1,4-conjugate addition of an aldehyde to an a,β-unsaturated compound, initially catalyzed generally by NHC-carbenes. This creates an unnatural functional group interval that cannot be created using conventional methods, but rather through a specific process called umpolung (polarity reversal) (Bugaut & Glorius, 2012; Enders & Balensiefer, 2004).

The strategy was first developed by Stetter and Schreckenberg in 1973 (Stetter & Schreckenberg, 1973). In 1976, Stetter developed the thiazolium-catalyzed highly selective conjugate addition method to connect a wide variety of aliphatic aldehydes and (hetero) aromatic with Michael acceptors (Dvorak & Rawal, 1998). This reaction carries on an intermolecular, as well as intramolecular style (Moore, et al., 2011; Um, et al., 2011; MináKim, et al., 2011). The catalysis take place by using a broad range of NHC-carbenes derived from thiazolium salts and triazolium salts that are generally applicable in enantioselective Stetter reactions (Kerr & Rovis, 2004; Enders, Han & Henseler, 2008; Enders & Kallfass, 2002; Murry, et al., 2001; Qi, et al., 2011). In this paper, we are going to introduce a brief review about the Stetter reaction due to the huge applications in different important fields. This include reaction mechanism, limitations of the reaction and recent developments in the last ten years. In each year from 2011 until now, one example has been introduced with citing related literature. It has been found that this reaction huge number of contributions has been reached in the recent time and much researchers are involved on the development this reaction in the abroad.

2. Reaction Mechanism

Breslow demonstrated the mechanism of the benzoin reaction catalyzed by a thiazolium salt or a cyanide anion, proceeding via the key enaminol intermediate (called the Breslow intermediate) (Moore, et al., 2011). The mechanism of the Stetter reaction is similar to that of the benzoin reaction, the difference being the irreversible nature in this case as well as the addition of the Breslow intermediate to Michael acceptors).

According to the proposed mechanism for the NHC-catalyzed Stetter reaction, the resulting free carbene I from

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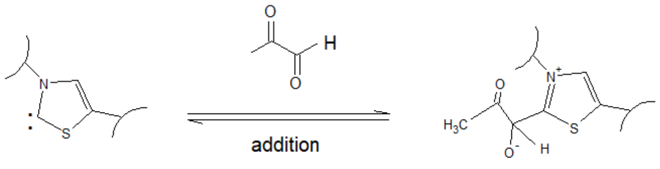
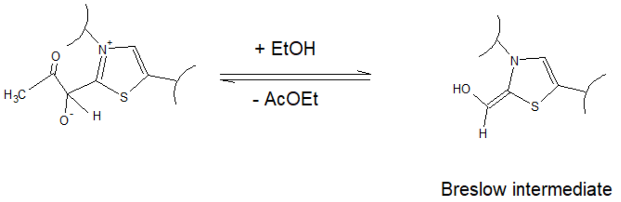
the azolium precursor upon formerly treatment with base, adds to the aldehyde (Equation. 1), generating nucleophilic Breslow intermediate III, via the tetrahedral intermediate II as displayed below (Equation 2) (Moore, et al., 2011).



I

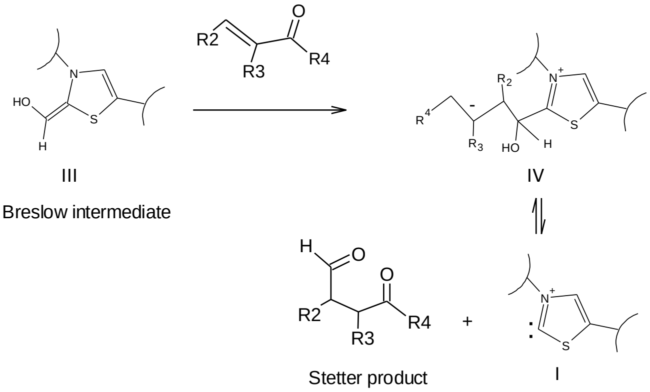
Equation. 1. Addition of thiazolium salt to the α-ketoaldehyde



II III

Equation. 2. Formation of Breslow intermediate

Then the Breslow intermediate III can lead to the intermediate IV by irreversible addition to the Michael acceptor. Proton transfer and subsequent release of free NHC-carbene gives the aimed Stetter product as follows (Scheme 1) (Breslow, 1958).



Scheme. 1. Reaction of Breslow intermediate with Michael acceptor resulting the Stetter product

Generally, Formation of enantioselective 1,4-bifunctional compounds can be realized by using chiral NHCs, which can lead to an asymmetric reaction.

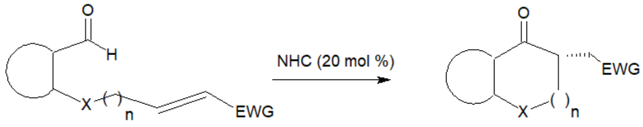
2.1. Limitations and Scope of the Reaction

Aryl aldehydes such as benzaldehyde or 2-heteroaromatic aldehyde together with γ-aryl substituted- β,γ-unsaturated- or β-alkyl β,γ-unsaturated-α-ketoester as α-ketoester acceptors are the Stetter reaction components. Aliphatic aldehydes have been also used in restricted manner instead of the aromatic aldehyde component because of the formation of both the Stetter and cross-benzoin products. In addition, a variety of NHC-precatalysts in order to enhance the chemo-, region-, and enantioselectivity of Stetter reaction.

It is obvious that the development scope in recent years of intramolecular Stetter reaction still thoroughly differ in comparison to intremolecular Stetter reaction. In contrast to intermolecular one, high yields and enantioselectivities with the intramolecular Stetter reaction were achieved by Ciganek, Enders, Rovis and many others. Meanwhile a major limitation to the intermolecular Stetter reaction is the restricted substrate scope. The lower enantioselectivity of the intermolecular reaction makes one of the reaction deficit and could possibly because of the easily racemization process of the 1,4-addition products during the reaction periods. The other reaction problem of the intermolecular Stetter reaction could be the formation of the contrary Crossbenzoin product on account of Stetter product as inseparable mixture (Enders, et al., 1996; Trost, Shuey, & DiNinno Jr, 1979; Fang, et al., 2011; Liu, et al., 2011; DiRocco, et al., 2012; Jousseaume, Wurz & Glorius, 2011).

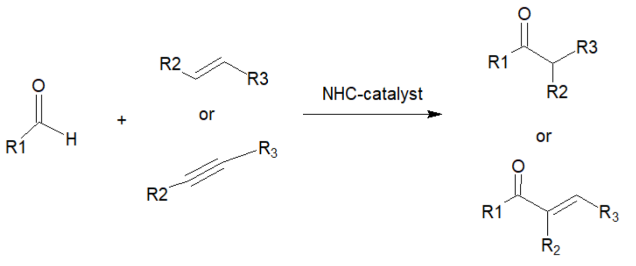
2.2. Chronological developments of Stetter reaction beginning from 2011 to 2021

Rong and co-workers synthesized in 2011 a chiral triazolium camphor NHC-catalyst that observed as highly effective for enantioselective intramolecular Stetter reaction (Equation 3) (Rong, et al., 2011).



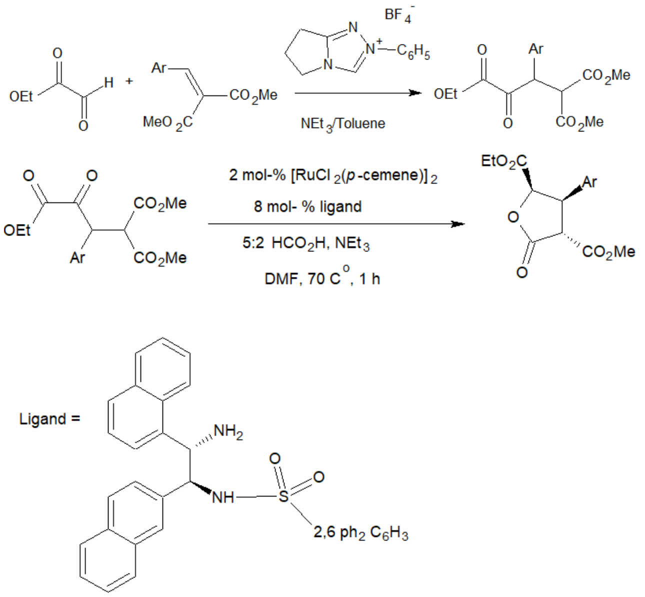
Equation. 3. Enantioselective intramolecular Stetter reaction via chiral camphor NHC-catalyst

In 2012 a recent class of transformations was accomplished by A. T. Biju and co-workers. Umpolung of aldehydes and subsequently addition of the acyl anion equivalent to inactivated carbon–carbon multiple bond leads to the hydroacylation reaction (Equation 4) (Biju, Kuhl & Glorius, 2011).



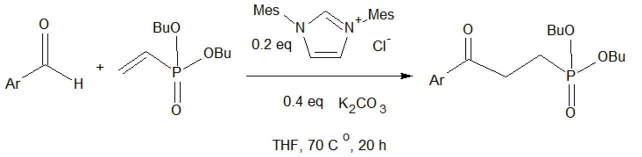
Equation. 4. NHC-catalyzed Hydroacylation reaction of aldehyde

In 2012 K. M. Steward, and co-workers have displayed a dynamic kinetic transformation method as an useful asymmetric synthesis to synthesize five-membered lactones from β-aryl α-keto esters via asymmetric transfer hydrogenation reaction. In the reaction racemic compounds can be converted into enantiomerically enriched products using a newly constituted (arene)$RuCl_2$(monosulfonamide) ligand (Scheme 2) (Steward, Gentry & Johnson, 2012).



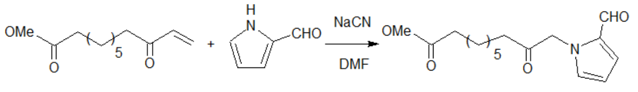
Scheme. 2. Asymmetric synthesis of five-membered lactones from β-aryl α-keto esters

In 2014 A. Patra, and co-workers presented a simple Synthesis of important class of molecules namely γ-Ketophosphonates using an intermolecular Stetter reaction beginning from vinylphosphonates. The used N-heterocyclic carbene catalysis are derived from N-mesitylimidazolium chloride (Equation 5) (Patra, Bhunia, & Biju, 2014; Zhang, et al., 2013; Ghosh, et al., 2018; Rezazadeh Khalkhali, Wilde, & Gravel, 2020).



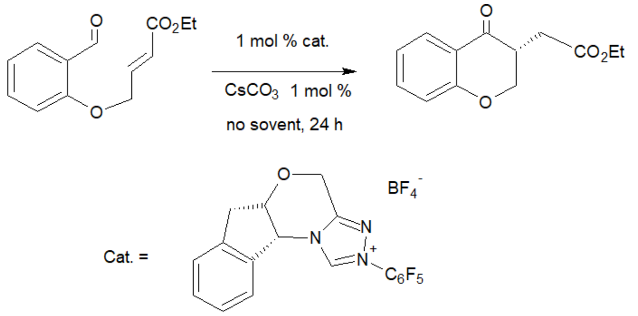
Equation. 5. Synthesis of γ-Ketophosphonates from vinylphosphonates as an intermolecular Stetter reaction.

In 2015, Schäfer research group used the cyanide ion to obtain a nucleophile from the electrophilic carbon atom in various aldehydes via Stetter reaction. Methyl 12-aryl- and methyl 12-heteroaryl -l9,12-dioxododecanoates represent the products of this reaction (Equation 6) (Hinkamp & Schäfer, 2015; Zobel & Schäfer, 2016; Büttner, Steinbauer & Werner, 2015).



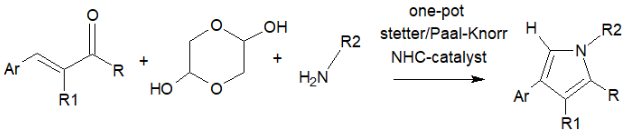
Equation. 6. Synthesis of Methyl 12-aryl- and methyl 12-heteroaryl -l9,12-dioxododecanoates via cyanide-catalayzed Stetter reaction

In 2016 Ema and co-workers have applied a solvent-free intramolecular asymmetric Stetter reaction using 0.2-1 mol % of 1,2,4-triazolium NHC-catalyst (Rovis catalyst). This reaction was performed using Rovis catalyst and cesium carbonate as base in a solvent-free under and argon atmosphere at 30 °C (Equation 7) (Ema, et al., 2016; Harnying, et al., 2021; Shen, et al., 2021; Ranjbari, Tavakol & Manoukian, 2021).



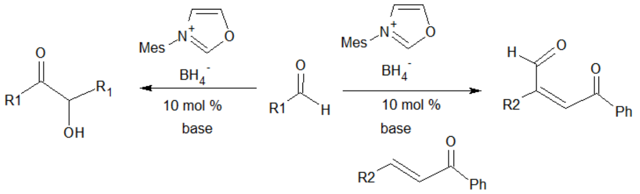
Equation. 7. A 1,2,4-triazolium NHC-catalyzed solvent-free intramolecular asymmetric Stetter reaction

In 2017 a number of 1,2,4-trifunctionalized pyrroles have been synthesized by Glorius and co-workers. Under using Glycolaldehyde dimer as a C1-buildingblock NHC-catalyzed hydroformylation occur, followed by a Paal-Knorr condensation using primary amines in a one-pot synthesis (Equation 8) (Fleige & Glorius, 2017; Zarganes-Tzitzikas, Neochoritis & Dömling, 2019).



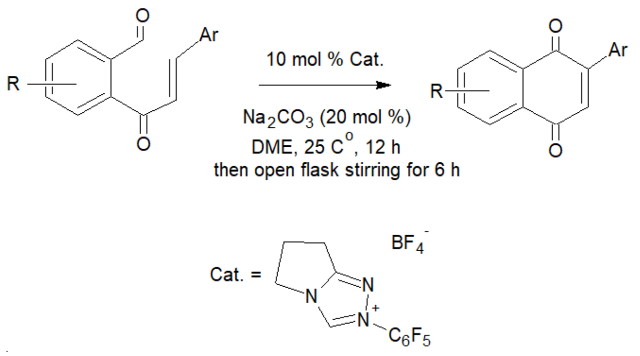
Equation. 8. A one-pot synthesis of 1,2,4-trifunctionalized pyrroles

Krishna and co-workers used oxazolium salts as catalysts for the umpolung of aldehydes to synthesize α-hydroxy ketones in high yields. In comparison to common thiazolium and triazolium salts, N-mesityl oxazolium salt catalyzed homobenzoin reaction of aromatic, heteroaromatic and aliphatic aldehydes was found to be an effective to apply on demanding substrates such as β-alkyl-α,β-unsaturated ketones and electron-rich aromatic aldehydes (Stetter reaction) (Equation 9) (Garapati & Gravel, 2018).



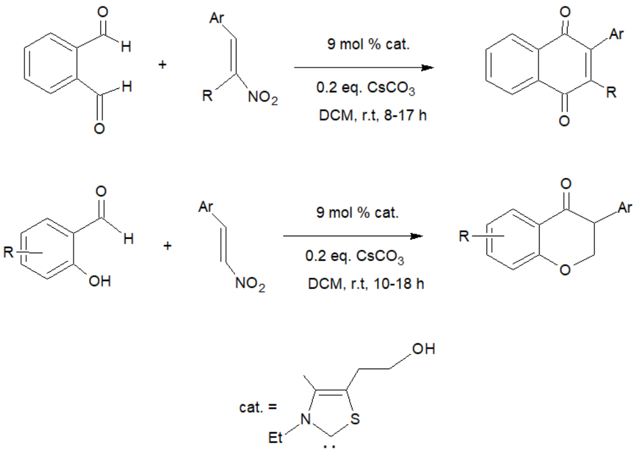
Equation. 9. Synthesis of α-hydroxy ketones and β-alkyl-α,β-unsaturated ketones via umpolung of aldehydes

In 2018 A. Ghosh, and co-workers synthesized 2018 the synthetically valuable 1,4-naphthoquinone derivatives using the NHC-catalyzed intramolecular Stetter reaction and subsequently air oxidation. This oxidation reaction is an application of the cross dehydrogenative coupling (CDC) firstly found by Chao-Jun Li at McGill University (Equation 10) (Ghosh, et al., 2018).



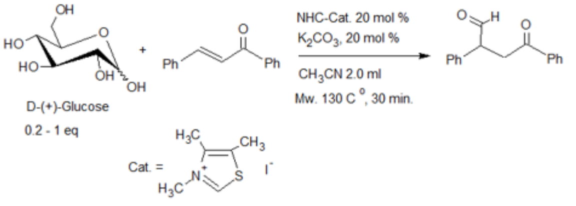
Equation. 10. NHC-catalyzed intramolecular Stetter reaction and subsequently air oxidation

In 2018 Building of optically pure sugar-based naphthoquinones and dihydroisoflavanones have been obtained by using NHC-Catalyzed dual Stetter reaction. R. N. Mitra, and co-workers used a mild and powerful NHC-organocatalysis to construct cascade cyclization, homoatomic C−C cross-coupling, and heteroatomic O−C bond formation, and utilizing nitro substituent as EWG under mild conditions (Scheme 3) (Mitra, et al., 2018; Barman, et al., 2021; Chen, Gao & Ye, 2020).



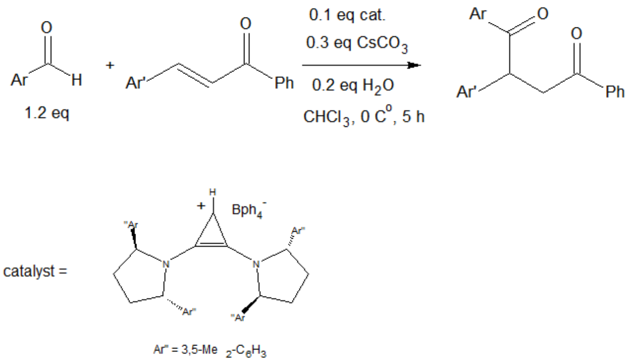
Scheme. 3. Synthesis of optically pure sugar-based naphthoquinones and dihydroisoflavanones.

In 2019 M. Draskovits, and co-workers utilized recently different sugars as a raw material and N-heterocyclic carbene catalysis to achieve formylation of α,β-unsaturated compounds in a connecting Stetter reaction. Herewith the selectivity of NHCs for aldehydes in the reducing sugars for either intercepted dehomologation or a following redoxlactonisation were thoroughly demonstrated (Equation 11) (Draskovits, et al., 2019; Zhu, et al., 2022; Draskovits, et al., 2018).



Equation. 11. Formylation of α,β-unsaturated compounds using sugars

In 2021 M. R. Khalkhali, and co-workers presented the role of Bis(amino)cyclopropenylidenes catalyst together with a substoichiometric amount of water as an additive on simple aldehydes and enones to reach a highly enantioselective intermolecular Stetter Reaction. Enantioselectively 1,6-conjugate addition reactions were also reached using Chiral BACs Bis(amino)cyclopropenylidenes catalyst on paraquinone methides (Equation 12) (Wang, et al., 2021; Zhou, Bao & Yan, 2022; Li, et al., 2022).



Equation. 12. Chiral BACs-catalyzed Enantioselectively 1,6-conjugate addition reaction

3. Conclusion

Since the Stetter reaction is actually a special C-C bond formation reaction by a 1,4-addition reaction in the presence of a nucleophilic catalyst, it is first catalyzed by cyanide and then catalyzed by a thiazolium salt or NHCs developed. It has shown, the Stetter reaction competes with the respective 1,2-addition, known as the benzoin condensation. Nonetheless, the benzoin-condensation is reversible, and since the Stetter reaction results in more stable molecules, the chief product is consequential of 1,4-addition. In this review, different kinds of Stetter inducing inter and intramolecular, dual Stetter reaction, Stetter cascade and radically Stetter reaction have been described. Moreover, the importance of the Stetter reaction in the total synthesis of natural products and biologically active compounds may be displayed. It has been also, shown that the Stetter reaction is one of the most significantly simple reactions playing vital role in the total synthesis of natural products.

Competing Interests

The authors have declared that no competing interests exist.

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