Contributions from the Stetter Reaction to the Organic Chemistry

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1. Introduction

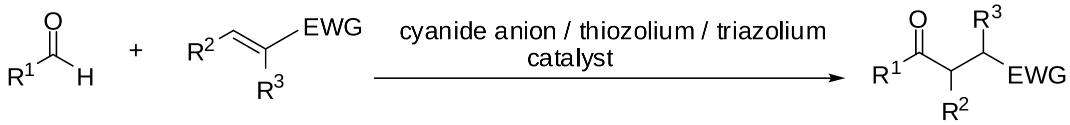
1.1 General

In the synthetic organic chemistry, construction of carbon-carbon bond is one of the most fundamental reactions. Therefore, new strategies for development of carbon-carbon bonds have been continuous to be the most challenging and attractive endeavour to synthetic organic chemists. Several C-C bond forming reactions such as Aldol reaction,[1] Suzuki coupling,[2] Grignard reaction,[3] Baylis-Hillman reaction,[4,5] Heck reaction,[6] Diels-alder reaction[7] and Wittig reaction[8] *etc*. have been well established. Applications of these reactions in the synthesis of various molecular frameworks including carbocycles, heterocycles, medicinally important compounds and natural products are efficiently performed. The Stetter reaction[9-21] is yet another important carbon-carbon bond forming reaction which is growing rapidly in recent years. Large number of articles published in literature is the clear indicator of the importance of this reaction. It possesses atom economy, stereo and regio-selectivity which are the most essential requirements for the development of an efficient synthetic reaction. It enables a new catalytic pathway for the synthesis of various 1, 4-bifunctional molecules such as diketones, ketoesters and ketonitriles *etc*. can be catalyzed by a broad range of thiazolium and triazolium salts which make this reaction more attractive in the synthetic organic chemistry. Even after the 35 years of its birth, there is no complete review on this reaction though a number of publications found in recent years. Therefore, We felt urgency of the review on the Stetter reaction covering the literature of about three decade will be useful for growth this reaction in organic chemistry. Hence, we have taken the opportunity of writing this review, which covering all the literature of last 35 years to recent ones and also describes the way how the reaction was grown with respect of asymmetric and intramolecular versions. Another important purpose of writing this review is to provide an exposer to the Stetter reaction which indeed may help for its development, and also this may motivate organic chemists to think of the new applications of the reaction. Pioneering work done by Ciganek, Enders, Glorius, Trost and Rovis are found to be very fruitful for the development of Stetter reaction.

1.2 The Stetter reaction-Origin

In 1973, Hermann Stetter[22-26] reported the conjugate addition of aldehydes to α, β-unsaturated compounds, which yield 1,4-dicarbonyl compounds in the presence of cyanide anion or thiazolium salt as a catalyst.

Since then 1,4 addition of aldehydes to Mic hael acceptors in the presence of cyanide anion or thiazolium or triazolium salt catalyst has been known as Stetter reaction (eq 1).



Eq. 1

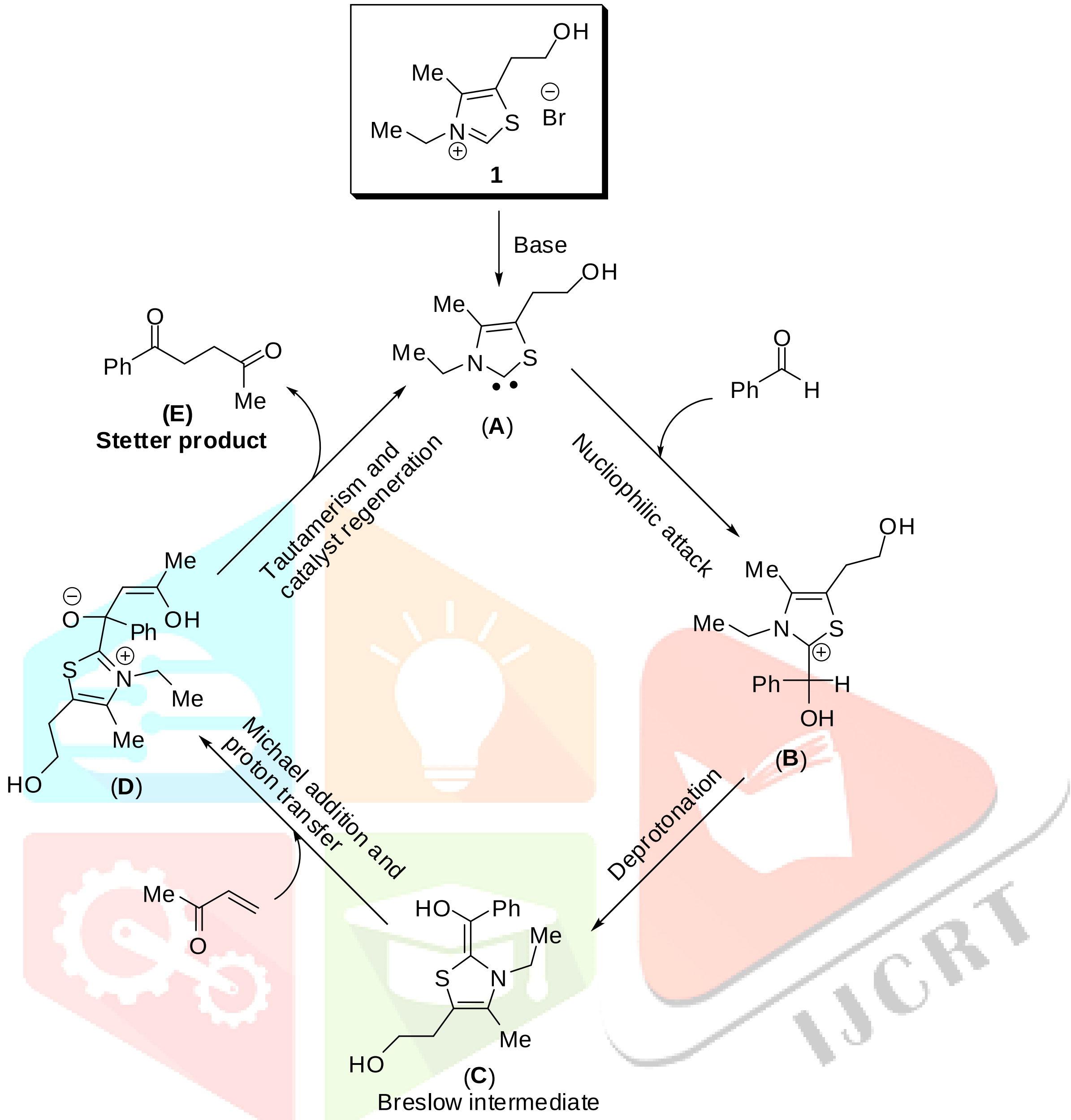
R^1= alkyl, aryl, heteroaryl
R^2= H, alkyl, aryl
R^3= H, EWG
EWG= electron withdrawing group:
CHO, COR, CO_2R, CN, $CONH_2$ (R= alkyl, aryl)

1.3

Mechanism

The key step in the reaction mechanism[27-29] is the conversion of the carbonyl group from an electrophile to a nucleophile in an umpolung process. The most accepted mechanism is described for the reaction between methyl vinyl ketone (MVK) and benzalaldehyde where 3,4-dimethyl-5-(2-hydroxyethy1)thiazolium bromide (**1**) used as a catalyst, which is illustrated in Scheme 1**.** It is assumed that during the process, thiazolium salt **1,** undergo deprotonation at its most acidic position to form thiazoline-2-ylidene **A**, which, then go through nucleophilic addition with benzaldehyde to generate thiazolium adduct **B**. The thiozolium adduct **B** upon deprotonation forms an enaminol-type intermediate **C** (Breslow intermediate) which acts as a nucleophilic acylation reagent (**C**) and reacts with MVK (Michael acceptor) to form zwitterionic enolate **D**. The tautomeric rearrangement of **D** generates the Stetter product **E** and regenerate the thiazoline-2-ylidene **A**.

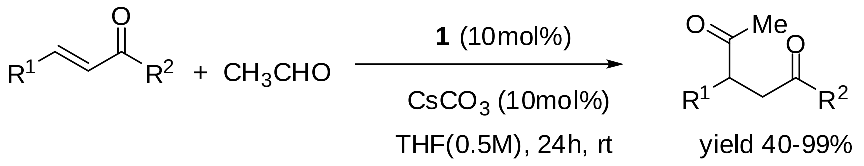
Scheme 1 Mechanism of Stetter reaction catalyzed by thiozolium catalyst



2. Intermolecular Stetter reaction

Stetter and co-workers[30- 37] transformed a variety of aliphatic and aromatic aldehydes into 1,4-dicarbonyl compounds with different Michael acceptors. Since then, this reaction came upon exponential growth in terms of flexibility in the three essential components *i.e.* electrophiles, Michael acceptors and catalysts. A verity of electrophiles, Michael acceptors and catalysts has been employed successfully. We would like to discuss all these aspects in this review comprehensively, the facets mentioned by Enders[10] are also covered in order to provide easy understanding and continuity in the text.

Very recent and interesting work on Stetter reaction is reported by Yang and co-workers.[38] In which a facile addition of Michael acceptors with acetaldehyde in the presence of thiazolium bromide catalyst (**1**) resulted into 1,4-dicarbonyl compounds with about 99 % yield (eq 2).

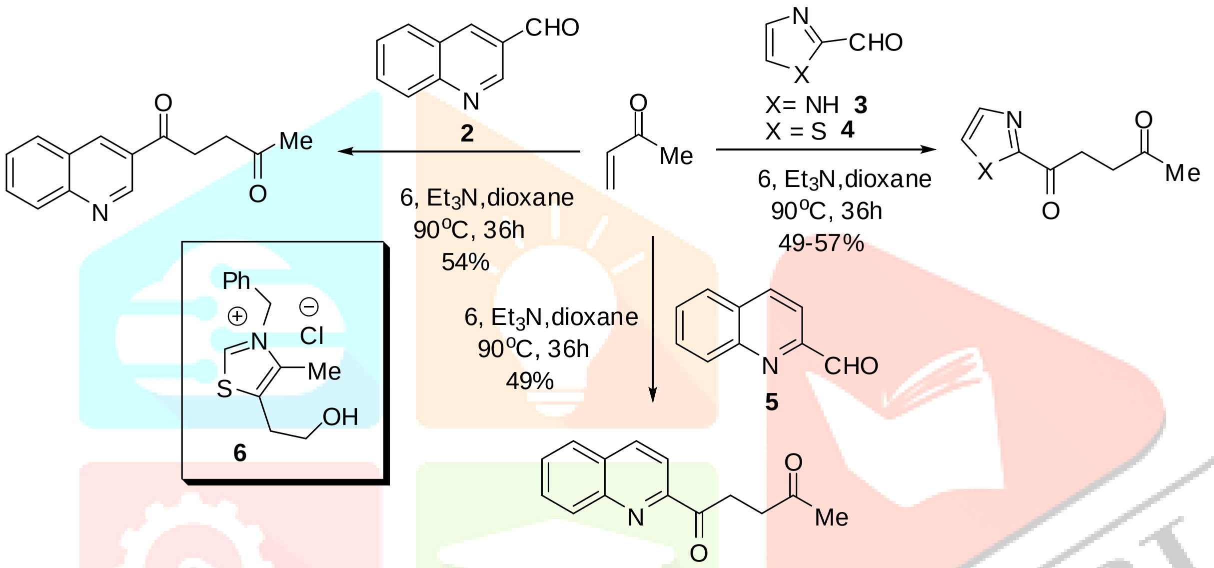


Eq 2

R^1= Ph, 4-BrPh, 4-MePh, 4-ClPh, 2-naphthyl
R^2= Me, Ph, 3-MeOPh, 4-CNPh

Civcir and co-workers[39] successfully employed variety of aldehydes with different heterocyclic core *viz* imadazole, thiozole and quinoline aldehydes (**2-5**) as electrophiles in the intermolecular Stetter reaction with MVK in the presence of thiozolium chloride catalyst (**6**) (Scheme 2).

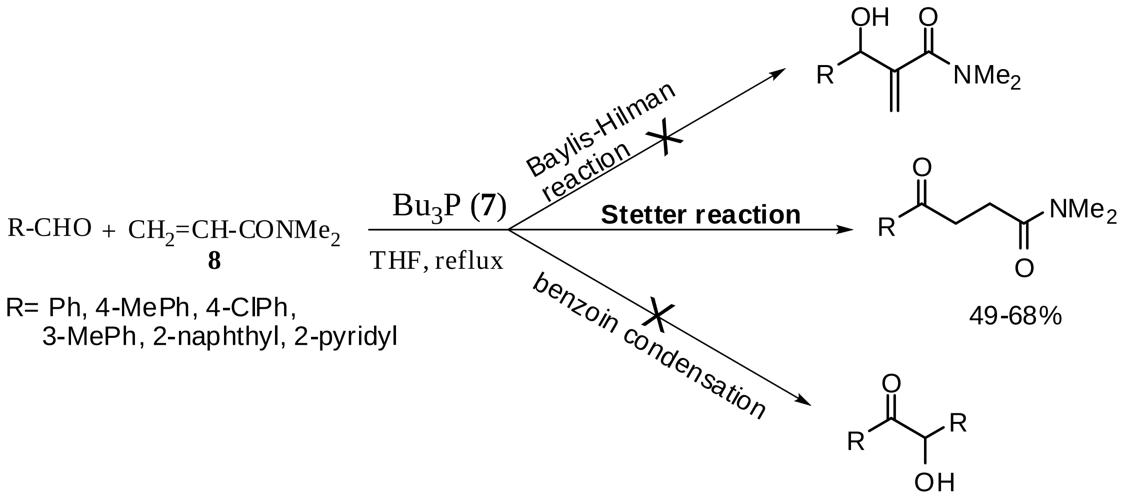
Scheme 2 Imadazole, thiophene and quinoline aldehydes as electrophiles in Stetter reaction.



2.1 Tributylphosphine catalyst

Kim and co-workers[40] for the first time reported tributylphosphine (Bu_3P) (**7**) catalyzed Stetter reaction for the facile synthesis of *N,N'*dimethyl-3-aroylpropionamides. Interesting point to be mentioned here is that, the prior intention of the authors was to get a Baylis-Hilman adduct of acrylamide, instead they got a Stetter product in reasonable yields. The Baylis-Hilman product and the another expected, benzoin condensation products were not observed in the present reaction due to the low electrophilicity of the β-position of *N,N*-dimethylacrylamide (**8**) (Scheme 3).

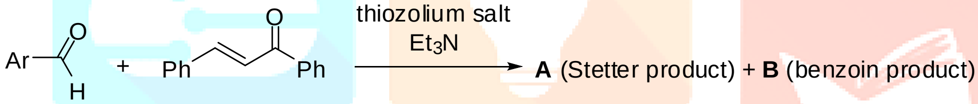
Scheme 3 Bu_3P catalyzed Stetter reaction by Kim and co-workers



2.2 Substitution effect

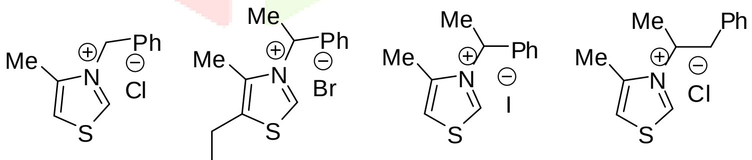
Castells and coworkers[41] employed different thiazolium salts (**6, 9-12)** to study the effect of substitution on the Stetter *vs* benzoin condensation reaction. The highest yield of Stetter product (84%) is obtained for furfural aldehyde with thiozonium chloride catalyst (**6**) (Table 1).

Table 1 Benzoin *vs* Stetter reaction by Castlles and co-workers



Thiazolium salt	Yield of (**A**)%	Yield of (**B**)%
6	84	-
9	56	3
10	26	10
11	-	20
12	-	15

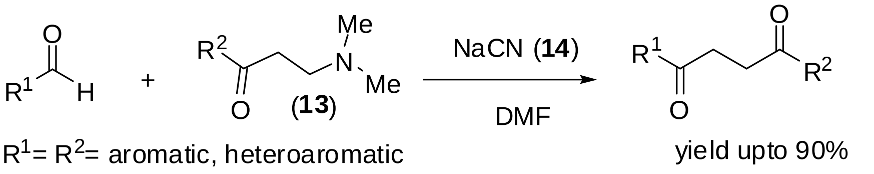
(**A**) Ar-CO-CH(Ph)-CH_2-CO-Ph
(**B**) Ar-CO-C(OH)(Ar)-CH(Ph)-CH_2-CO-Ph
Ar = Ph, furyl



(**9**) (**10**) (**11**) (**12**)

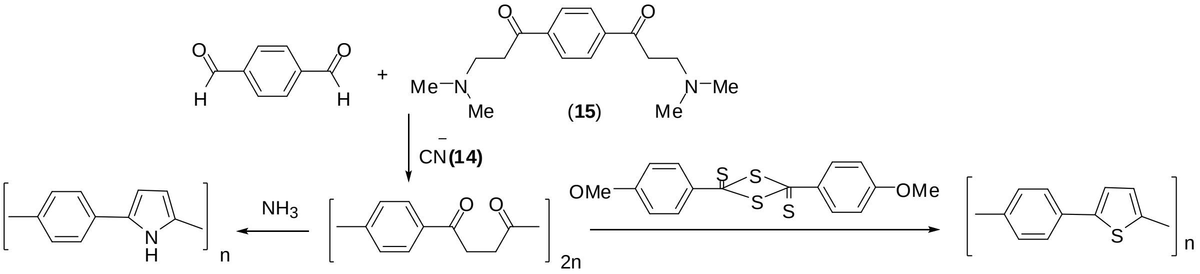
2.3 Mannich base precursors

Phillips and co-workers[42] reported Stetter reaction between aldehydes and Mannich base precursors (**13**) for the synthesis of 1,4-diketones with high yield by using NaCN as a catalyst (**14**) (eq 3). Mejjer and co-workers[43] further extended the same strategy to a variety of aromatic aldehydes and Mannich bases (**15**) and successfully obtained the Stetter products in good yields. Further they used the so obtained Stetter adducts for the preparation of heterocyclic polymers (Scheme 4).



Eq 3

Scheme 4 Stetter reaction by Mejjer and Co-workers

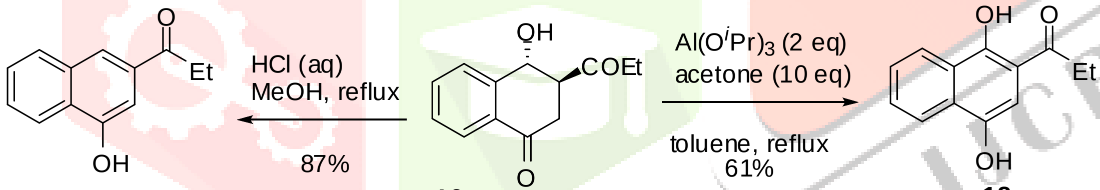


2.4 Cascade reactions

2.4.1 Stetter-aldol reactions

Ye and co-workers[44] reported an interesting cascade Stetter-aldol reaction for the synthesis of 3-substituted-4-hydroxytetralones (**16**) with *trans*-selectivity using phthalaldehyde and various Michael acceptors (Table 2). These 3-substituted-4-hydroxytetralones on oxidation followed by the dehydration gave the corresponding napthol (**17**) and napthalenediol (**18**) derivatives in good yield (Scheme 5). Interestingly the isolated Stetter product upon aldol reaction gave 3-substituted-4-hydroxytetralones with *cis*-selectivity which is contrary to the cascade procedure (Scheme 6).

Scheme 5 Dehydration and oxidation of 4-hydroxytetralone



Scheme 6 Synthesis of cis-4-hydroxytetralone by separated Stetter reaction followed by aldol reaction.

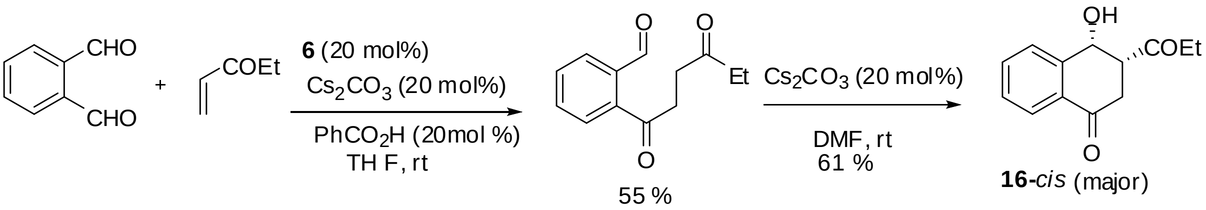
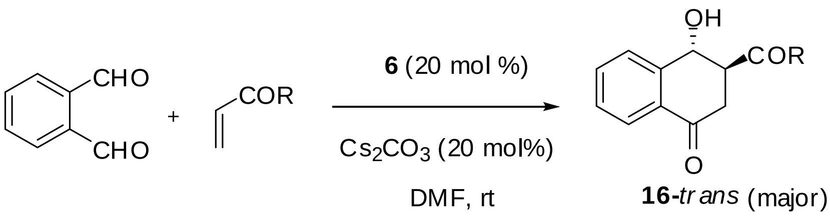
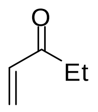
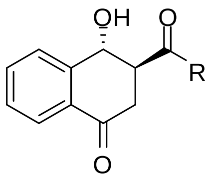
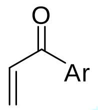
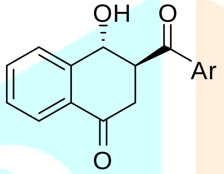
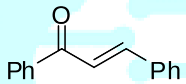
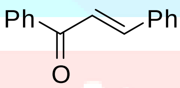
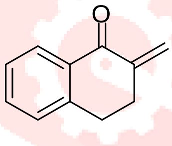
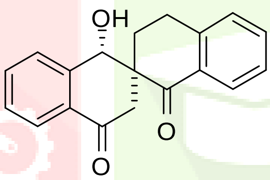
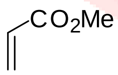
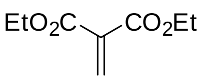
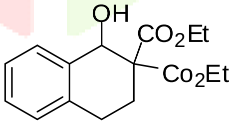


Table 2 Synthesis of *trans*-4-hydroxytetralones *via* cascade Stetter-aldol reaction

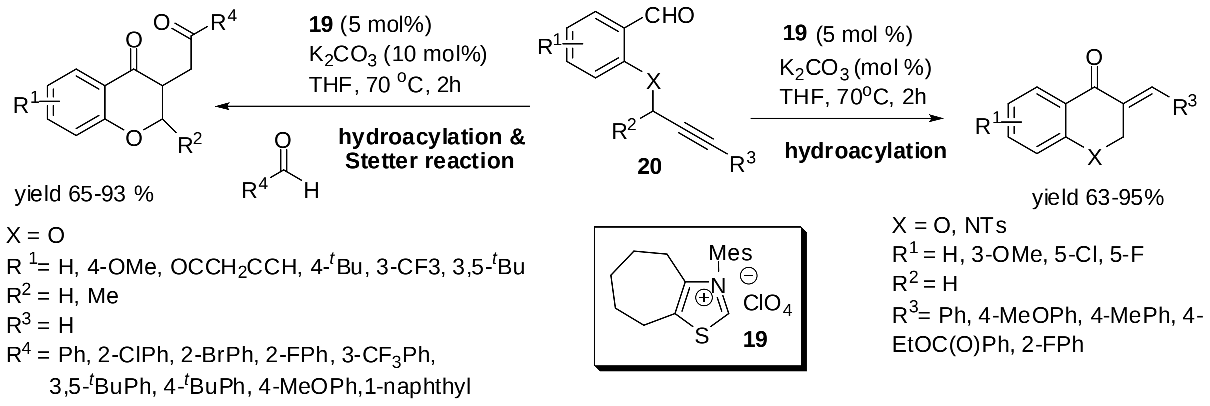


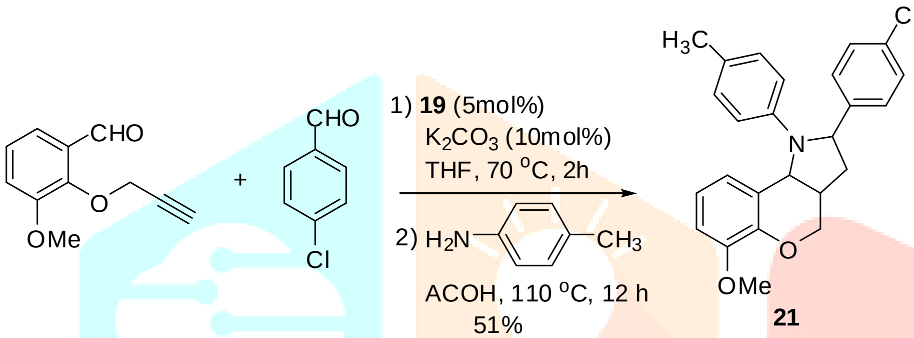
Micheal acceptor	16	yield (%)	trans:cis
		72	8:1
		Ar = Ph 53 Ar = 4-MeOPh 47 Ar = 4-ClPh 54 Ar = EtOPh 31 Ar = 2-naphthyl 52 Ar = 2-furyl 52	7:1 6:1 7:1 7:1 8:1 6:1
	/	trace	/
	/	trace	/
		70	9:1
	/	trace	/
		57	/

2.4.2 Hydroacylation-Stetter reactions

Glorius and co-workers[45] have reported for the first time an organocatalyzed hydroacylation of unactivated alkynes. The alkynes where involved in cascade process of hydroacylation of uncativated triple bond followed by intermolecular Stetter reaction with an aldehyde in presence of thiazolium catalyst (**19**) (5 mol%) and K_2CO_3 (10 mol%) leading to the formation of 1,4-diketones. On the other hand these unactivated alkynes (**20)** in the absence of aldehydes gave chromanones (Scheme 7). This methodology was further applied to the one-pot synthesis of benzopyranopyrrole derivatives (**21**) through hydroacylation-Stetter reaction followed by condensation with *p*-toluidine (eq 4).

Scheme 7 Organo catalyzed hydroacylation and Stetter reaction cascade by Glorius and co-workers.

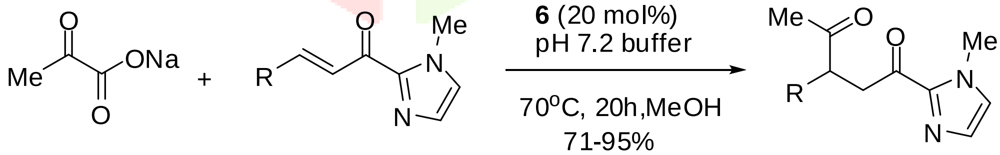




Eq 4

2.5 Stetter reaction under neutral aqueous condition

Scheidt and co-workers[45] carried out the Stetter reaction under neutral aqueous condition in a biomimetic fashion. Thiozolium catalyst (**6**) produces reactive carbonyl nucleophile with sodium pyruvate , that readily undergoes conjugate addition to β-substituted 2-acyl imidazoles which gave the Stetter product (eq 5).



Eq 5

R = Ph, 4-MePh, 4-MeOPh, 4-ClPh, 4-BrPh,2MeOPh, 2-ClPh, 2-BrPh, 2CF$_3$Ph, 2-furyl, 2-thiophene.

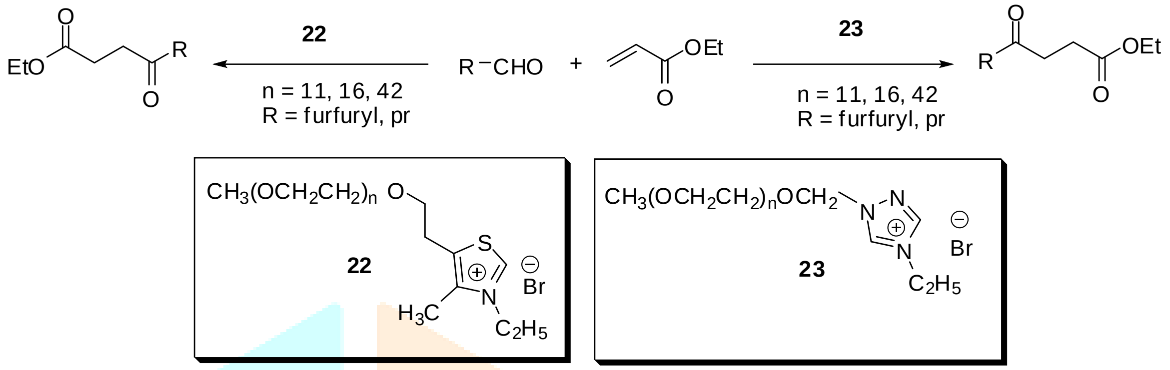
2.6 Polymer supported intermolecular Stetter reaction

In the recent years polymers are found to be playing important role in various chemical reactions as a support for reagents and catalysts. Generally polymer supports are recognized to probe up the reaction manipulation, product isolation and catalyst recycling. This strategy is successfully applied to the Stetter reaction by various research groups.

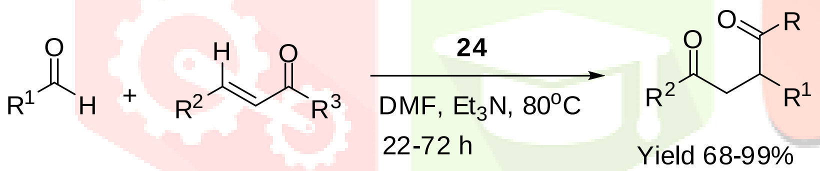
2.6.1 Polymer supported catalysts

For the first time Sell and co-workers[47] reported the polymer-supported thiaolium salt catalyzed Stetter reaction. Recently Xie and co-workers[48,49] synthesized the polyether substituted thiozolium and triazolium ionic liquids (**22**, **23**) and successfully employed them, as catalysts in the Stetter reaction. Representative examples are shown in Scheme 8.

Scheme 8 Polyether substituted thiozolium and triazolium salts catalyzed Stetter reaction by Xie and co-workers



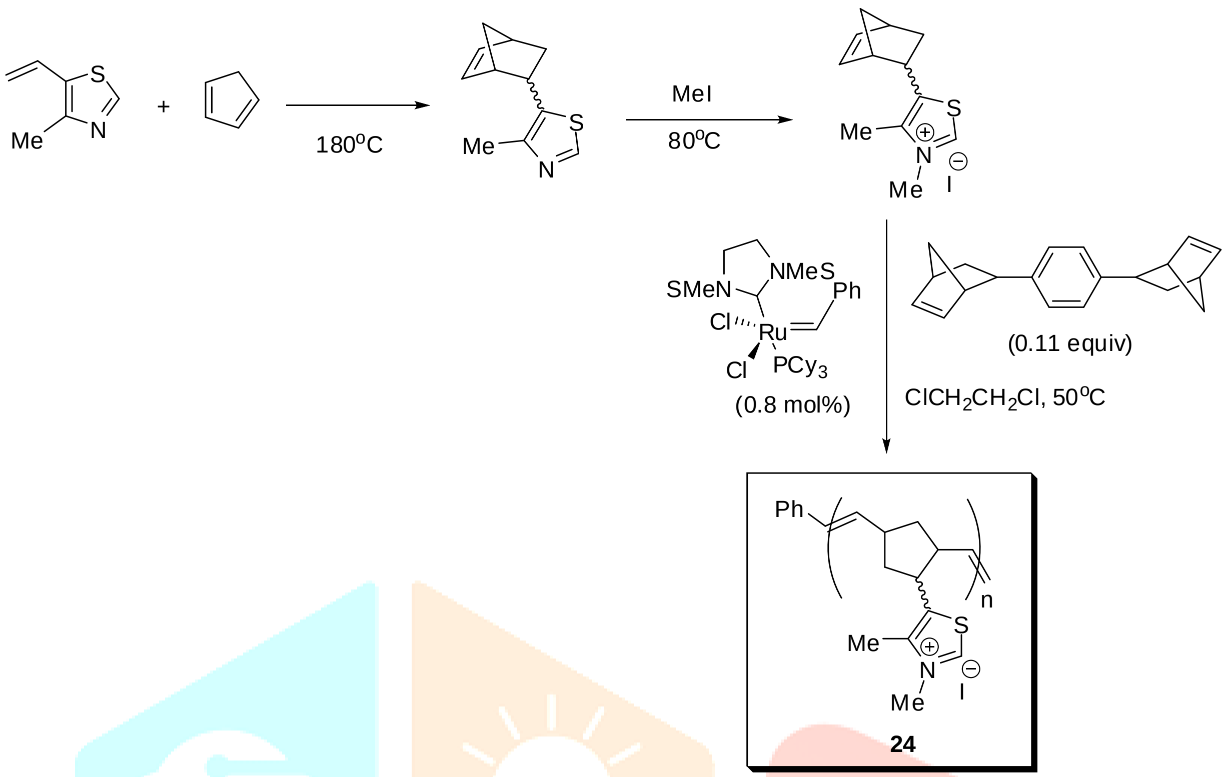
Barrett and co-workers[50] prepared high-loading ROMP (Ring Opening Metathesis Polymerisation) gel-supported thiazolium iodide (**24**), through ROM polymerization of the corresponding norbornene-derived monomer (Scheme 9). Thus obtained ionic ROMPgel was used successfully as an efficient catalyst for Stetter reaction to synthesize 1,4-dicarbonyl products in high yields (eq 6). Notably ROMPgel is reused in up to four consecutive reactions without significant loss of catalytic activity.



Eq 6

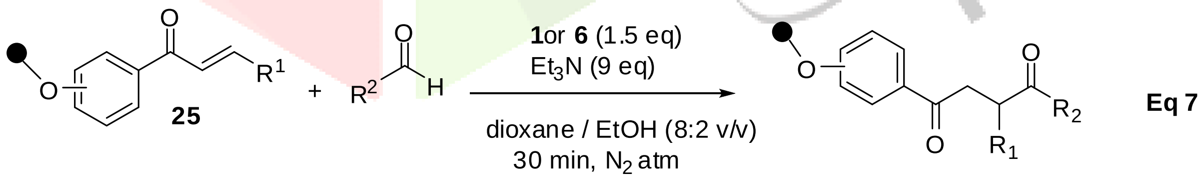
R^1= pent, nan, NMe-Indole, cyclohexane
R^2= H, Ph, 4-ClPh, 2-ClPh, 4-OMePh
R^3=Ph, 4-ClPh, 4-OMePh, napthelen, Me

Scheme 9 Preparation of ROMPgel -supported thiozolium iodide



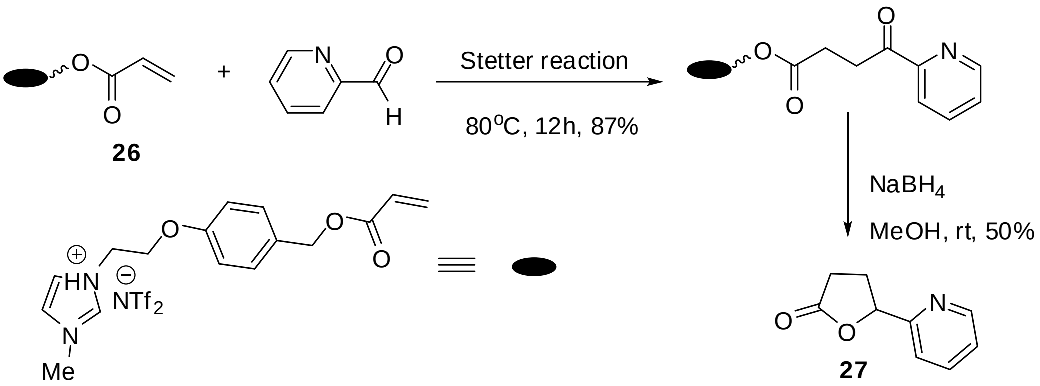
2.6.2 Polymer supported Micheal acceptors

Raghavan and Anuradha[51] reported Stetter reaction of aromatic, hetero aromatic and aliphatic aldehydes in solid-phase. Resin bound Micheal acceptor (**25**) on treatment with aldehydes in dioxane / EtOH provided Stetter products in 55-75% isolated yield after cleavage from solid-suport. The reactions of aromatic and heteroaromatic aldehydes are catalyzed by thiazolium bromide salt **(1)** whereas reactions of aliphatic aldehydes are promoted by thiazolium chloride salt **(6)** (eq 7). However cyanide anion catalysed Stetter reaction with aromatic aldehydes was failed to give 1,4-diketones.



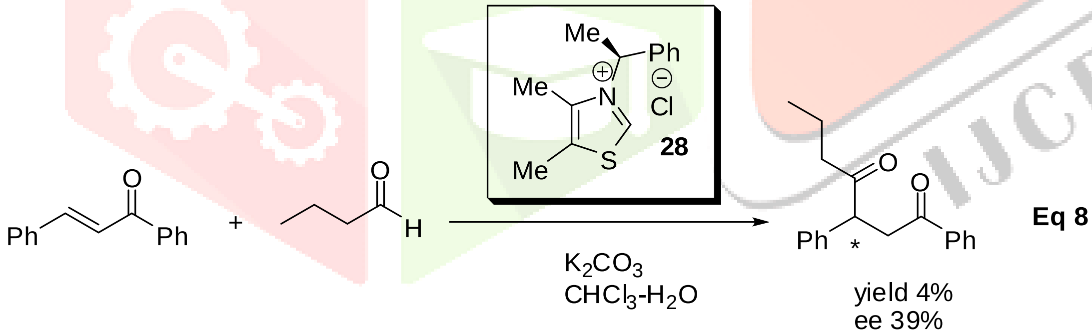
Gree and co-workers[52] synthesized novel acrylic ester-derived TSIL (**26**) (Task Specific Ionic Liquids). They were further succeeded to get 1,4-dicarbonyl compound by treating it with the pyridine-2-carboxaldehyde *via* Stetter reaction. Subsequent treatment with $NaBH_4$ afforded a lactone (**27**) (Scheme 10).

Scheme 10 Stetter reaction of acrylic ester-derived TSIL



2.7 Asymmetric intermolecular Stetter reaction

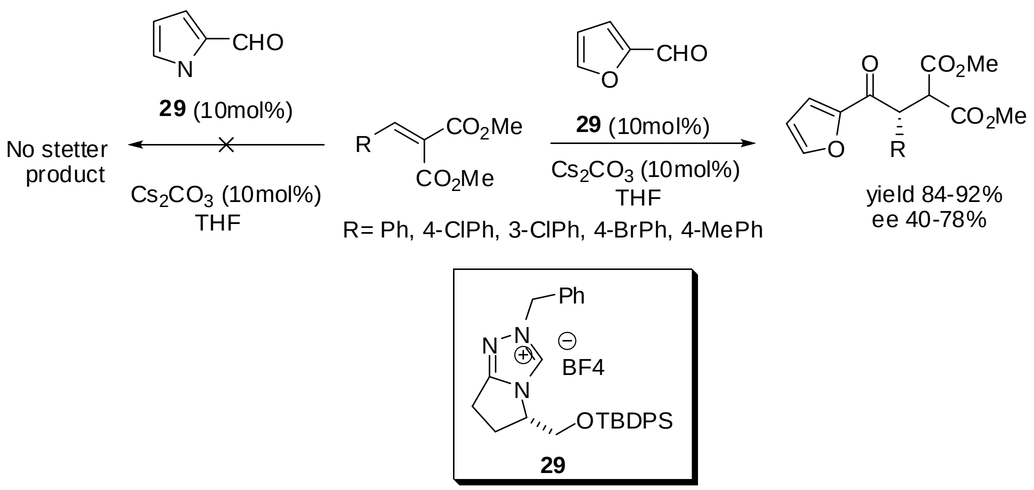
In the earlier days less attention has been paid to the intermolecular Stetter reaction and its asymmetric version because of the fact that the β-substituent of Michael acceptor often influence and decreases the reactivity. But after Enders and co-workers[53] 'first asymmetric intermolecular Stetter reaction' report, it has been developed significantly. Enders and co-workers employed chiral thiazolium catalyst (**28**) and obtained the desired Stetter adduct in 33% *ee* and 4% overall yield (eq 8) and hence opened the doors for others to work on these aspect. In the present review all the developments in asymmetric version of the reaction are discussed. The facets discussed by Diez[11] are also included in the present review in order to maintain continuity in the text.



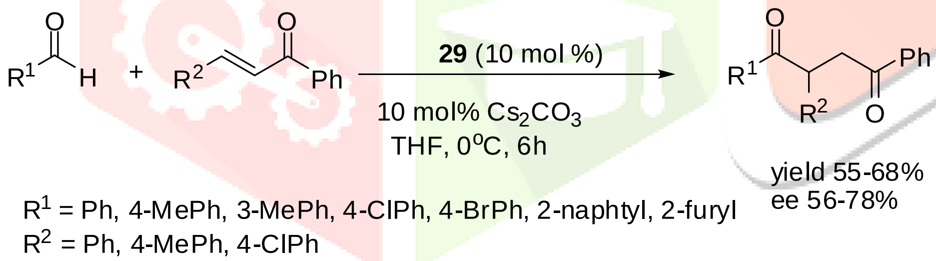
2.7.1 Chiral triazolium salt catalysts

Enders and group[54] succeeded to get the good yields and excellent *ee* in the reaction between 2-furancarbaldehyde and arylidenemalonates to afford ketomalonates by using triazolium catalyst (**29**) (10 mol%) and Cs_2CO_3 (10 mol%) base in THF solvent. In contrast, no Stetter product was obtained in the case of 2-pyrrolecarbaldehyde (Scheme 11).

Scheme 11 Intermolecular asymmetric Stetter reaction by Eders and Han.



The same research group extended triazolium salt (**29**) catalyzed asymmetric intermolecular Stetter reaction to several aromatic aldehydes and α,β-unsaturated ketones to get 1,4-diketones in 49-78% yields and 56-78% *ee* (eq 9). In these reactions the *ee* of Stetter products was further enhanced up to 99% by recrystallization[55] (the absolute configuration of 1,4-diketones was determined to be (*R*) by comparison of its optical rotation). This steriochemical outcome can be explained by the trasition state models (Fig. 1). Assuming that the silyl branch of the catalyst blocks the *Si*-face of the Breslow intermediate and the 1,4-addition would occur at its less hindered *Re*-face. The chalcone then reacts from its *Si*-face to give the (*R*) Stetter product.



Eq 9

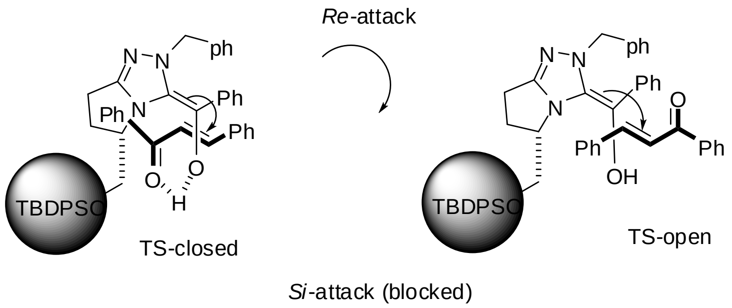


Fig 1. Proposed transition states

Rovis and co-workers[56] envisaged nitroalkenes as Michael accepters and successfully ran intermolecular asymmetric Stetter reaction with variety of heteroarylaldehydes. The bicyclic triazonium salts (**30-35**) (Chart 1) have found to be very good catalysts for these reactions giving excellent yields and enatiosectivity, in particular the fluorinated catalyst (**34**) has shown remarkable activity and enantioselectivity (Table 3).

Chart 1 Asymmetric intermolecular Stetter reaction in the presence of bicyclic triazolium catalysts by Rovis and co-workers.

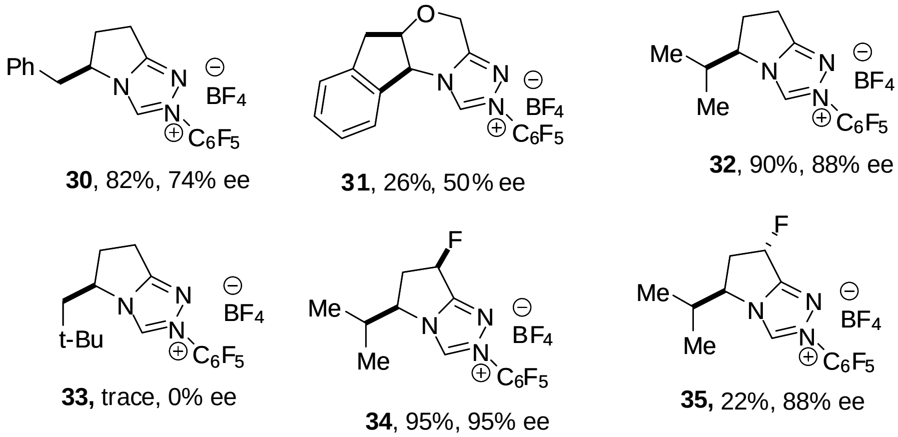
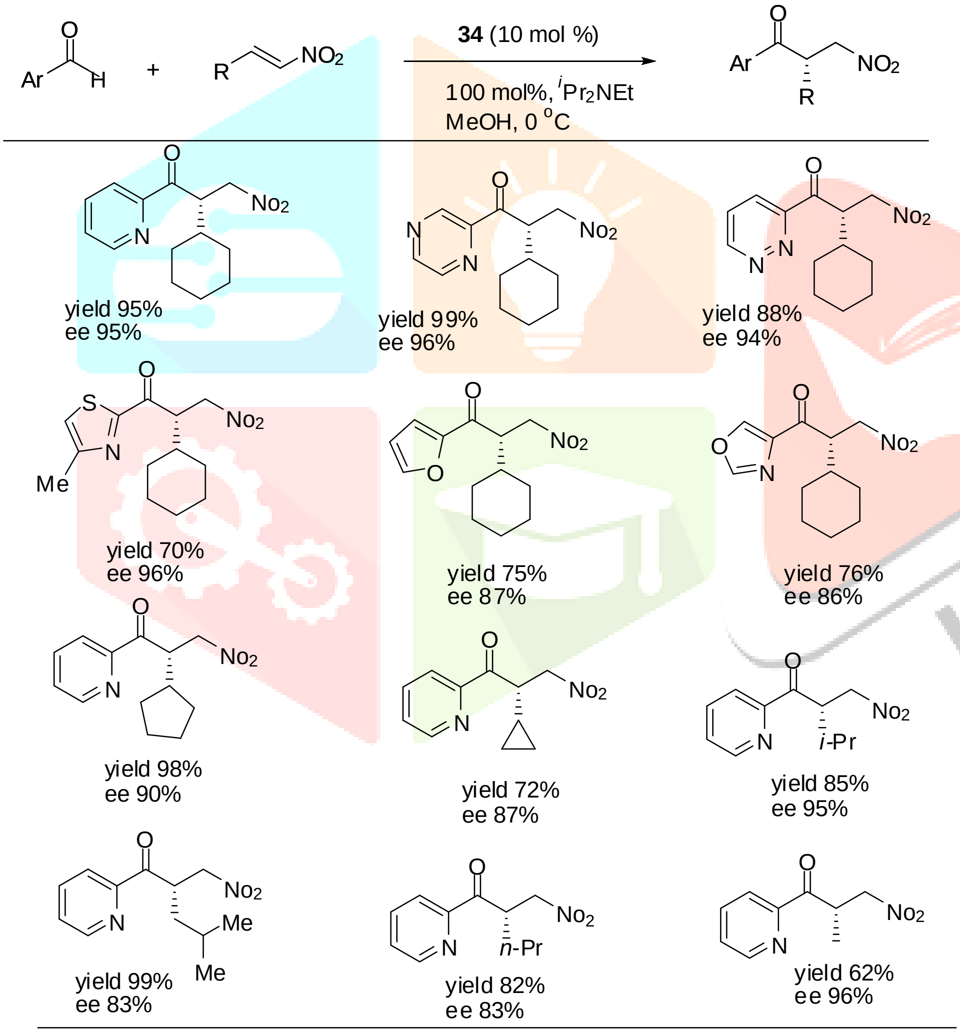
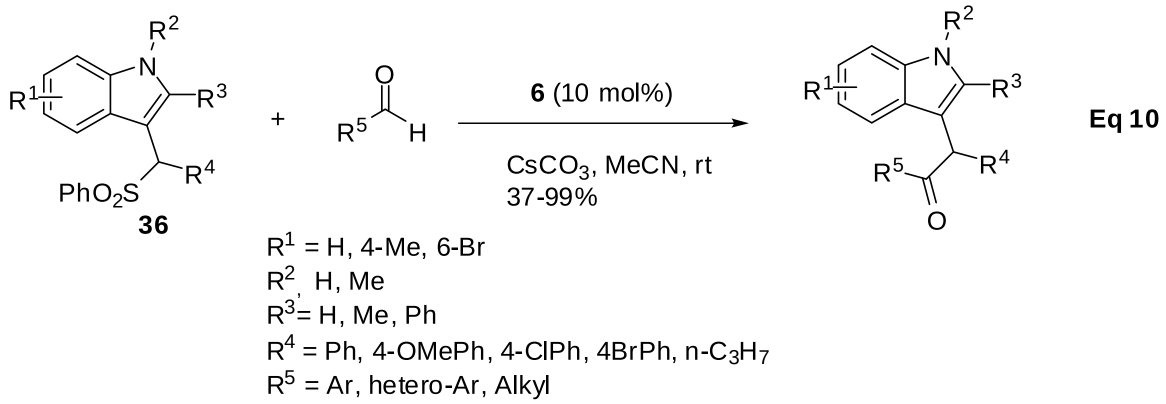
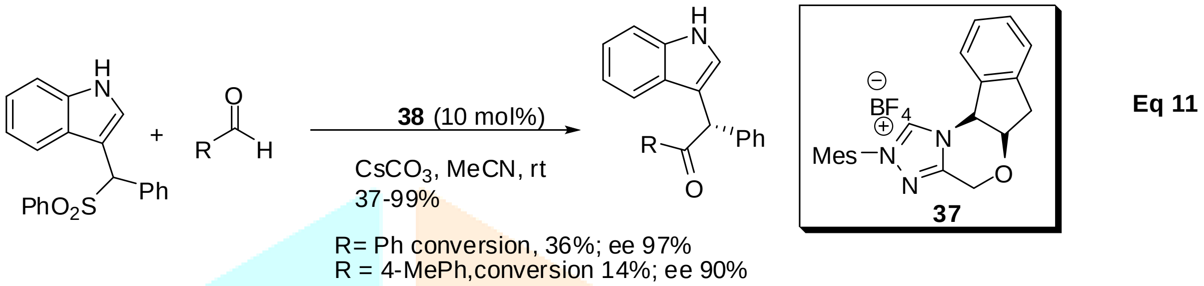


Table 3 Asymmetric intermolecular Stetter reaction in the presence of flurine-modified triazolium catalyst by Rovis and co-workers.

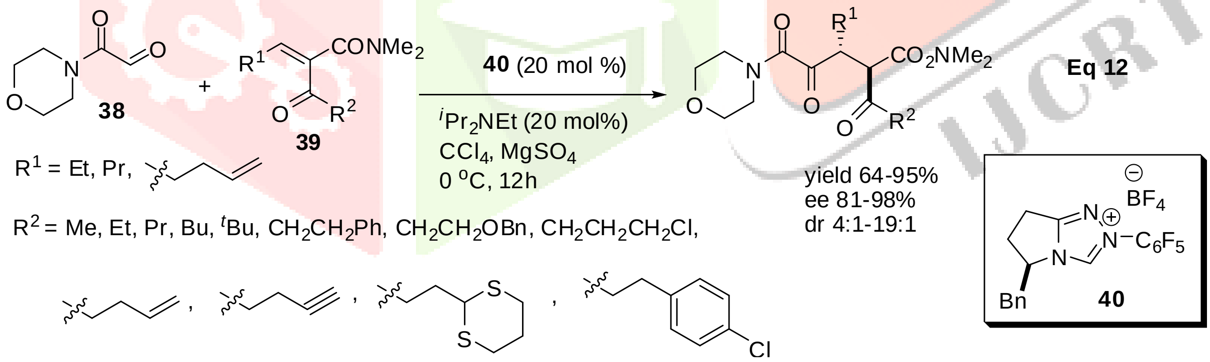


For the first time, You and co-workers[57] reported intermolecular Stetter type reaction of 3-(1-arylsulfonylalkyl)indoles (**36**) as electrophiles with alkyl, aryl and heteroaryl aldehydes to provide α-(3-indolyl)ketone derivatives in 37-99% yield (eq 10). Enantioselective version of this methodology was also successful in the presence of chiral triazolium salt (**37**) and afford upto 97% *ee* (eq 11).

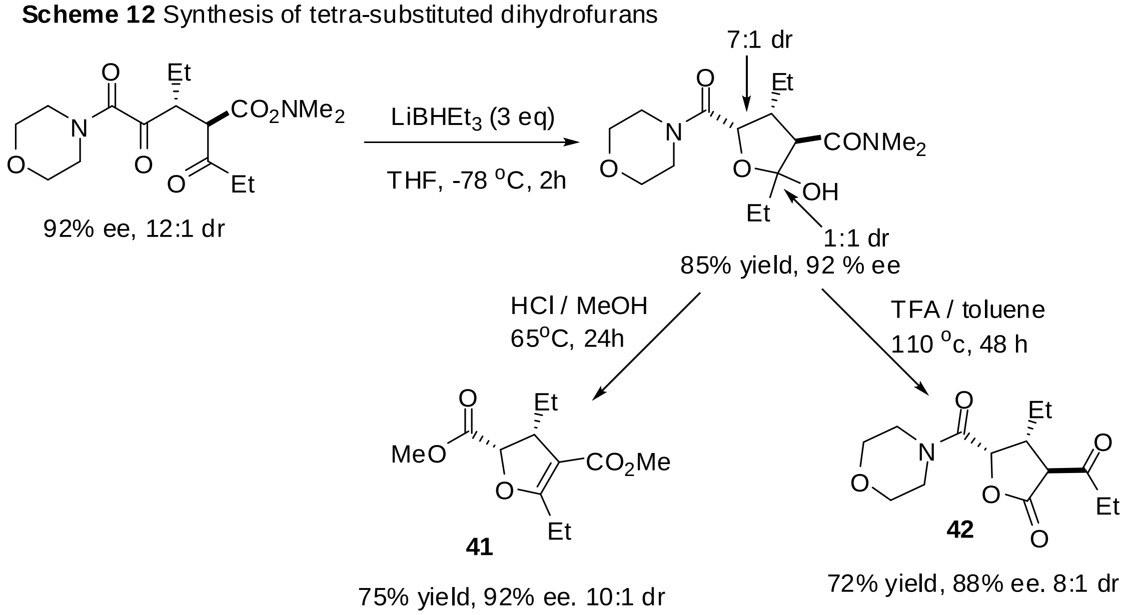


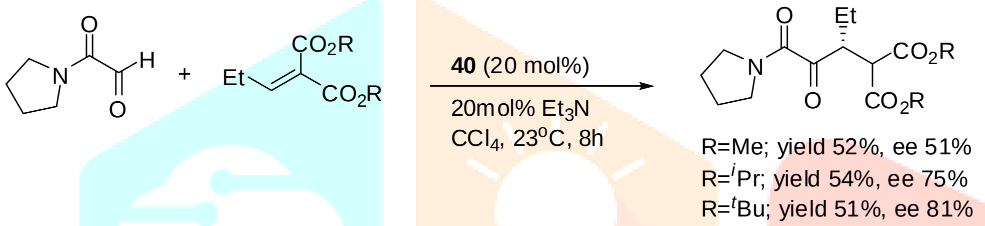


Rovis and Liu[58] reported highly enantio and diasterioselective intermolecular Stetter reaction of glyoxamide (**38**) and alkylidene ketamides (**39**) in presence of a chiral triazolinyl catalyst (**40**) in excellent yield (eq 12). Further 1,4-dicarbonyl compounds were used as synthons for the synthesis of tetra-substituted dihydrofurans, which are common substrate found in many natural products and lactones (**41**, **42**) (Scheme 12). The same research group extended the catalytic activity of this novel catalyst in case of alkylidenemalonates (**43**) and obtained excellent yield and selectivity[59] (eqs 13 and 14).

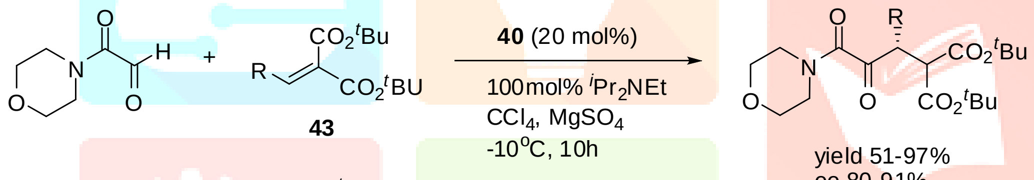


Scheme 12 Synthesis of tetra-substituted dihydrofurans



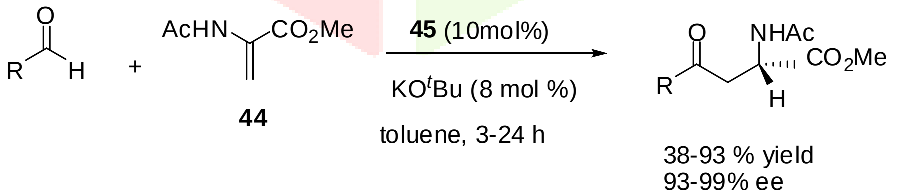


Eq 13



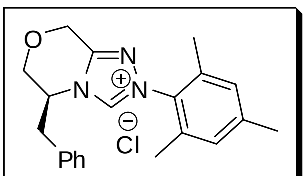
Eq 14

Very recently Glorius and co-workers[60] reported highly enantioselective intermolecular Stetter reaction between aldehydes and Michael acceptors (**44**). They used chiral triazolium catalyst (**45**) to synthesize aminoacid derivatives *via* stereoselective proton transfer as a key step (eq 15).



Eq 15

R = Ph, 2-FPh, 3-BrPh, 3,4-(Cl)$_2$Ph, 4-MePh, 4-ClPh, 4-CF$_3$Ph, 4-CNPh, 4-BrPh, 4-CO$_2$MePh, 1-napthyle, ferrocinyl, fur-2-yl, non

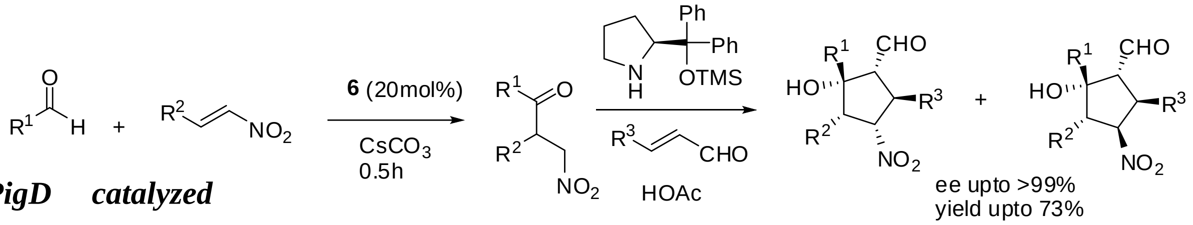


45

2.7.2 Tandem Stetter-Micheal-aldol reactions

Very recently Lee and co-workers[61] synthesized substituted cyclopentanes containing a quaternary carbon centers and five stereogenic centres. The sequential reactions *i.e* Stetter-Micheal-aldol, starting from heteroaromatic aldehydes, nitroalkanes and α,β-unsaturated aldehydes *via* [1+2+2] strategy provided cyclopentanes in excellent enatioselectivity (Scheme 13).

Scheme 13 Synthesis of substituted cyclopentanes *via* Stetter-Micheal-aldol reactions by Lee and co-workers.



R^1=pyrin-2-yl, furan-2-yl, R^2=n-C_6H_{13}, n-C_3H_{11}, n-Ph$(CH_2)_2$

2.7.3 PigD catalyzed reaction

For the first time Muller and co-worker[62] reported ThDP–dependent enzyme, PigD (**46**) catalyzed intermolecular asymmetric Stetter reaction very recently. Table 4 shows the percentage of conversion and Chart 2 shows the yields and enantio selectivity of the Stetter products.

Chart 2 Asymmetric intermolecular Stetter products by PigD catalyst.

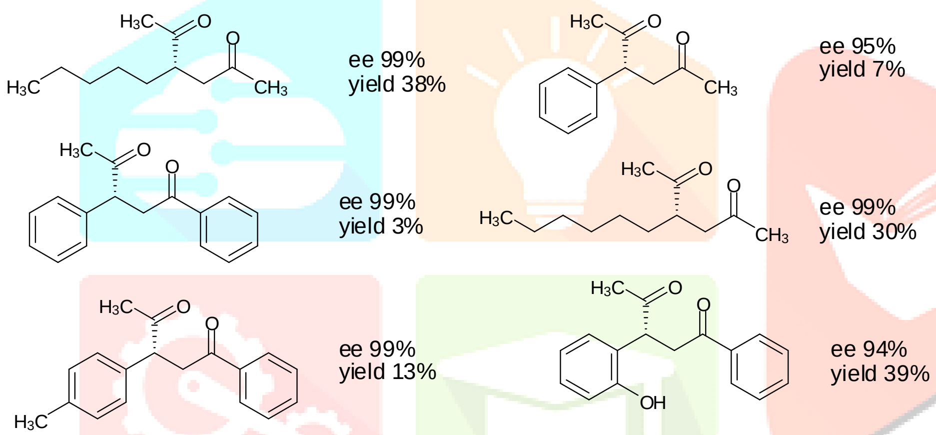
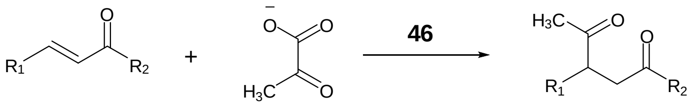
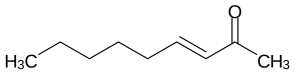
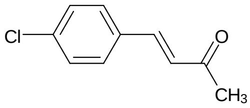
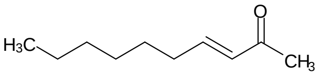
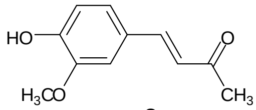
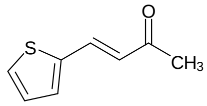
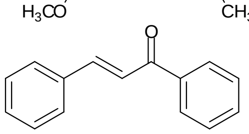
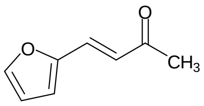
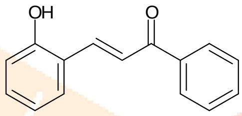
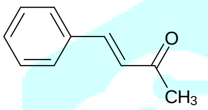
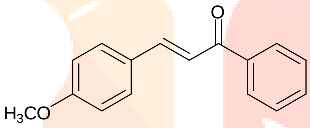
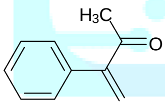
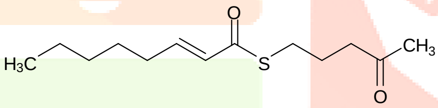


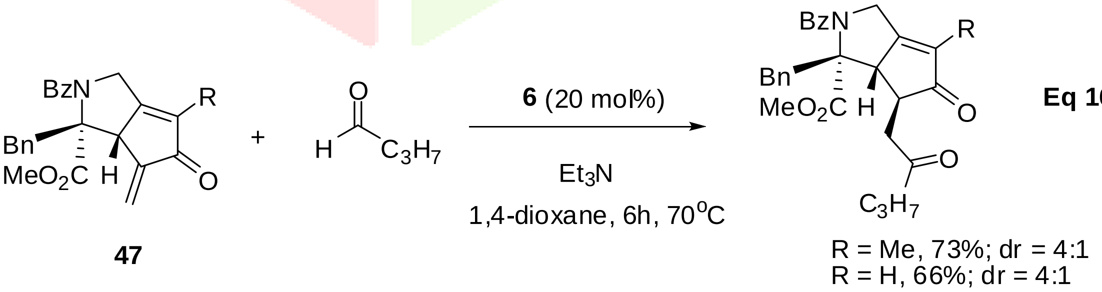
Table 4 Substrate conversions by PigD catalyzed asymmetric intermolecular Stetter reaction.



unsaturated ketone	conv. %	unsaturated ketone	conv. %
	27		33
	27		2
	15		14
	10		39
	12		5
	5		50

2.7.4 *Enantiopure Micheal acceptor*

Brummond and co-workers[63] reported asymmetric intermolecular Stetter reaction between ennatiopure α-methylene cyclopentenones (**47**) and aliphatic aldehydes in the presence of thiozolium catalyst (**6**) and Et_3N, the reaction pattern is shown in eq 16.

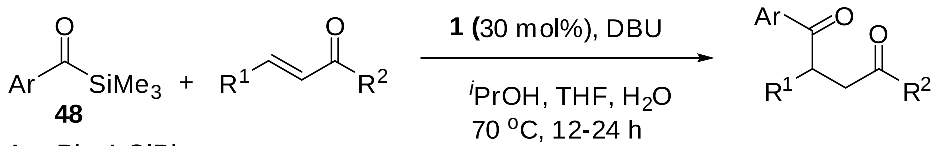


Eq 16

3. Sila-Stetter reaction

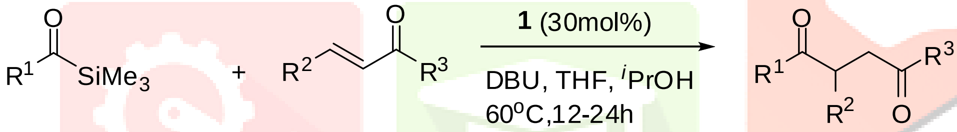
Scheidt and group[64,65] developed new Stetter reaction between acylsilanes (**48**) as acyl anion precursors and α,β-unsaturated systems which is known as sila-Stetter reaction. In this strategy the desired 1,4-dicarbonyl compounds were obtained in good yields (Table 5) by the use of thiozolium salt (**1**) as a catalyst. Interestingly electron withdrawing groups on either side of α,β-unsaturated system had no significant influence and acylsilane did not self condense under the given reaction conditions (eq 17). This process significantly increased the scope of the Stetter reaction by utilizing acylsilanes as tunable acyl anion progenitors. The same group reported a direct nucleophilic addition of carbonyl unit to nitroalkenes leading to the formation of β-nitroketones. The addition of base in the process leads to the decomposition of the nitroalkene. The acyl anion equivalent was generated *in situ* from the corresponding thiazolium carbinol (**49**) and the activation of the nitroalkene by the addition of thiourea (**50**) led to higher yields of the β-nitroketones[66] (eq 18).

Table 5 Sila-Stetter reaction by Scheidt and group



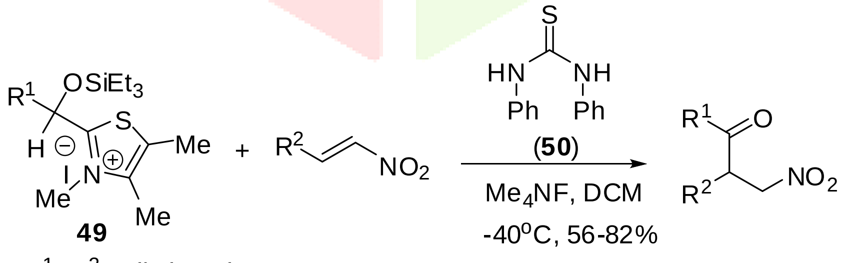
Ar= Ph, 4-ClPh

Entry	R^1	R^2	yield (%)
1	Ph	4-ClPh	82
2	Ph	4-OMePh	80
3	1-Napth	Ph	72
4	4-BrPh	Ph	66
5	4-ClPh	Ph	74
6	2-ClPh	Ph	68
7	4-MePh	Ph	84
8	3-OMePh	Ph	75
9	4-OMePh	Ph	77
10	4-HOPh	Ph	50



Eq 17

R^1=Ph, 4-ClPh, 4-MePh, Me, cy
R^2=H,Ph, 4-ClPh, 4-BrPh, 2-ClPh, 4-MePh, 4-OHPh, 4-OMePh, CO_2Et, 1-naphthyl
R^3=Ph, 4-ClPh, 4-MeOPh, OEt, OMe, Me, ^{t}Bu

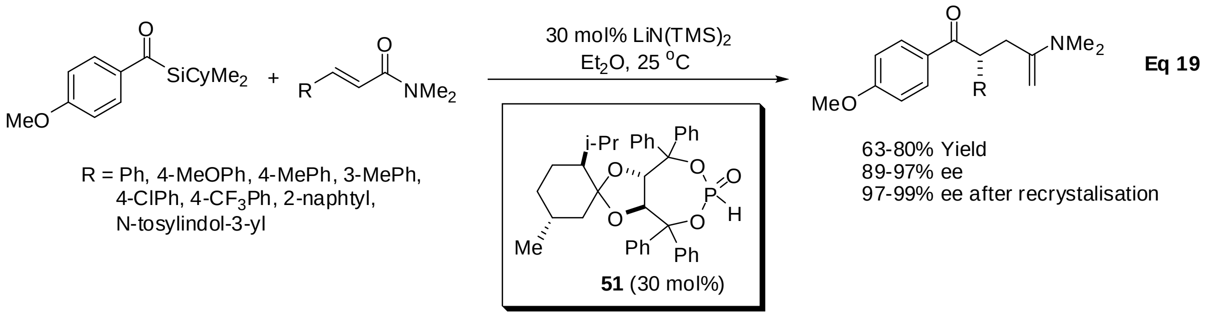


Eq 18

R^1=R^2= alkyl, aryl

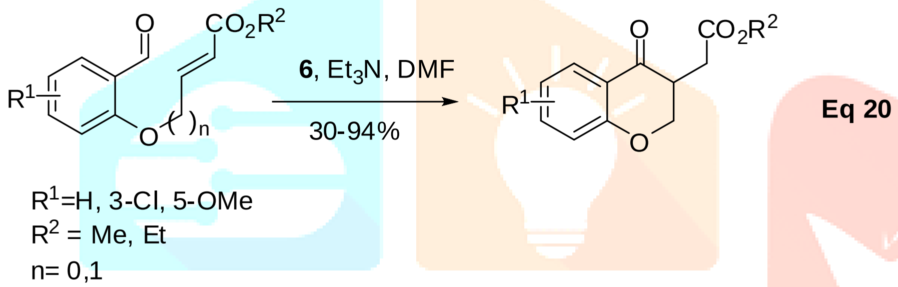
3.1 Asymmetric sila-Stetter reaction

Jhonson and coworkers[67] reported an enantioselective, intermolecular sila-Stetter reaction. They have used ADDOL phosphate (**51**) as a catalyst to get good yields . It is observed that the enantioselectivity of the Stetter product has been enhanced by the process of recrystalization. Representative examples are shown in eq 19.

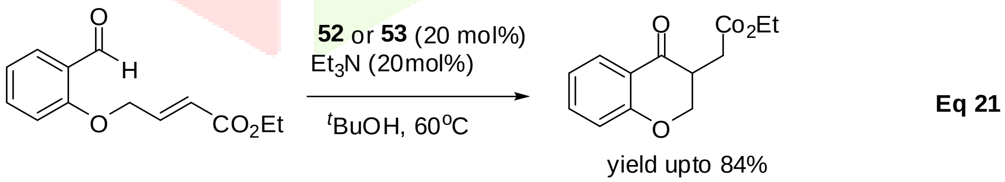


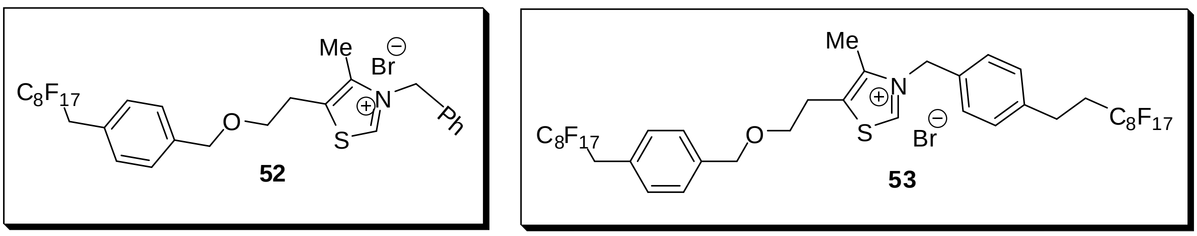
4. Intramolecular Stetter Reaction

The intramolecular Stetter reaction is expected for the systems containing both the nucleophile and Michael acceptor in the same molecule. Intramolecular version was studied by various research groups and significant progress has been made in recent years. First intramolecular reaction of the Stetter reaction was reported by Ciganek[68] in 1995 between 2-formylphenoxycrotonates and formylphenoxyacrylates. Best results are observed for the thiozolium salt catalyst (**6**) and the base, Et_3N (eq 20).

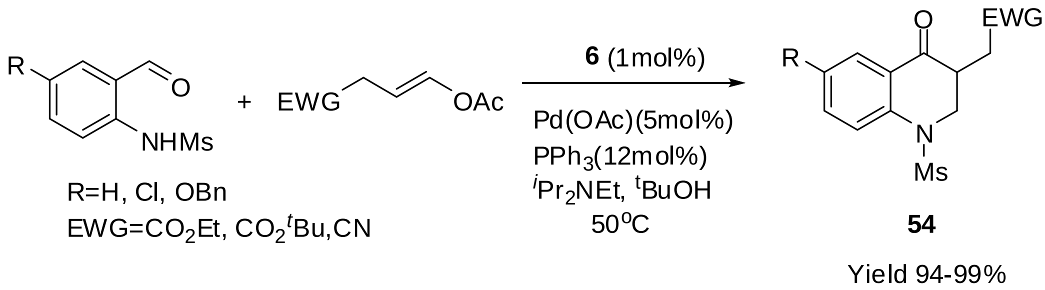


Hara and co-workers[69] prepared the fluorus thiozolium salts (**52**, **53**) and further they succeeded to employ theses as catalysts for the intramolecular Stetter reaction of the salicylaldehyde derivatives. The fluorus thiozolium salts have shown good catalytic activity and more importantly, their efficiency was found to be the same even after the recovery (eq 21).

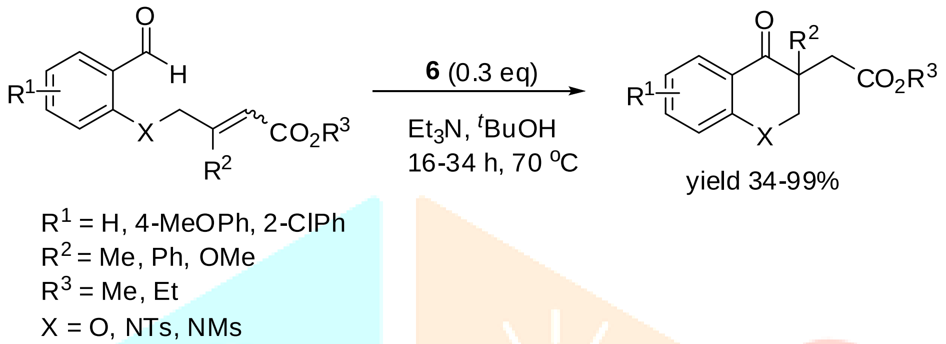




Hamada and co-workers[70] developed one-pot sequential multistep process for the synthesis of 3-substituted 2,3-dihydroquinoline-4-ones (**54**) through the cascade process, which involves a Pd-catalysed allylic amination and thiozolium salt (**6**) catalyzed intramolecular Stetter reaction (eq 22). The same research group synthesized the chroman-4-ones and 2,3-dihydroquinolin-4-ones using salicylaldehyde derivatives *via* intramolecular Stetter reaction[71] (eq 23).



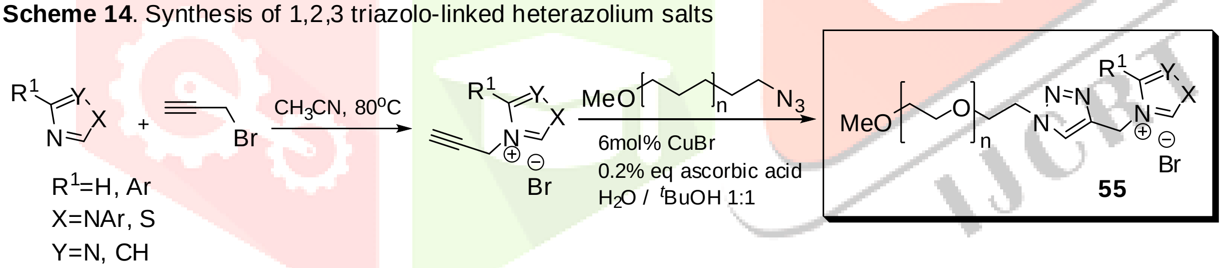
eq 22

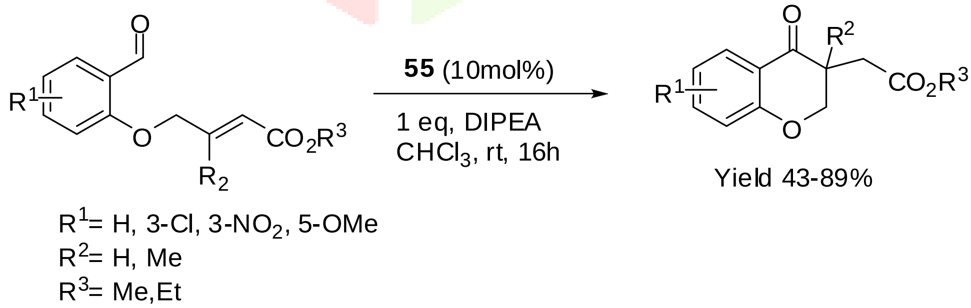


Eq 23

Zeitler and Marger[72] reported the synthesis of 1,2,3 triazolo-linked heterazolium salt (**55**) *via* Cu-catalysed [3+2]-cycloaddition (Scheme 14). The catalytic performance of this new catalyst was successfully examined in the intramolecular Stetter reactions (eq 24).

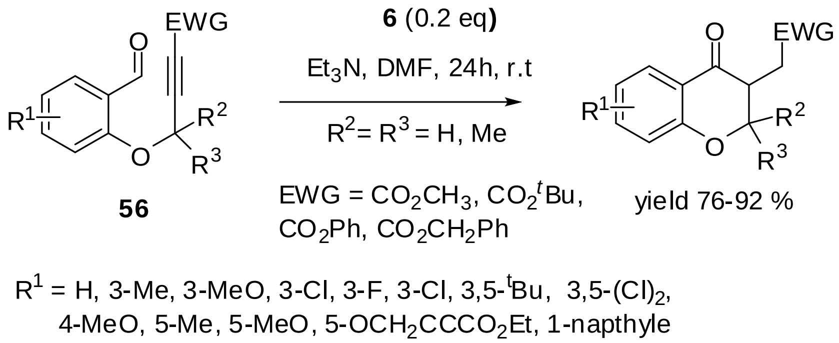
Scheme 14. Synthesis of 1,2,3 triazolo-linked heterazolium salts





Eq 24

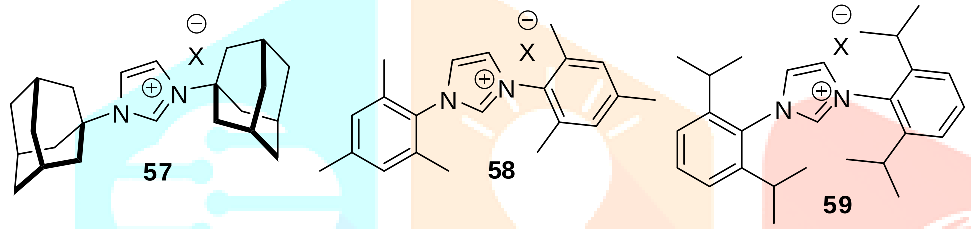
Recently Liu and co-workers[73] reported an interesting intramolecular Stetter reaction. In which, a series of chromone derivatives is obtained from the salicylaldehyde-derived alkynes (**56**) in 76-92 % yield (eq 25).



eq 25

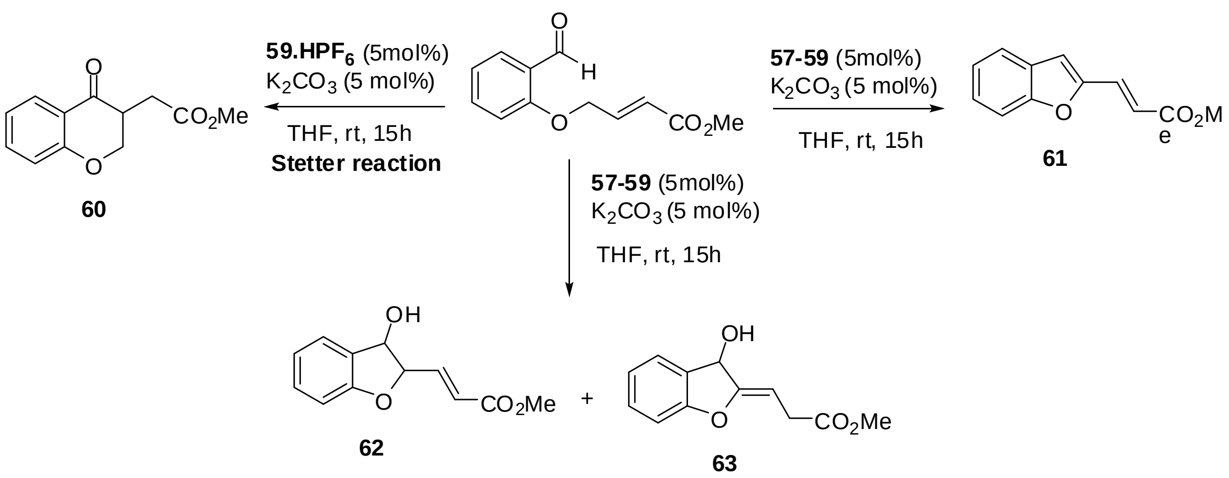
Very recently, for the first time Ren and co-workers[74] reported imidazolium salt catalyzed intramolecular Stetter reaction. In this reaction they found that counter ion of the salt significantly influences the efficiency of starting material conversion. Among the salts they examine, the imidazolium salt **59. HPF$_6$** afford the Stetter product (**60**) in 43% yield. They also found that all these catalysts give benzofurane derivatives (**61-63**) in excellent yield (Scheme 15, Table 6).

Table 6 Imidazolium salt catalyzed Stetter reaction and benzofurane derivatives



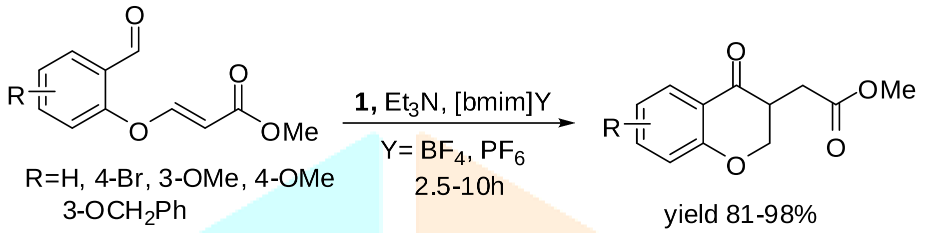
Entry	Catalyst	Yield(%) 60	61	62+63
1	**59.HPF$_6$**	43		
2	**59.HBF$_4$**			94
3	**59.HCl**		90	21
4	**58.HPF$_6$**			72
5	**58. BF$_4$**		12	88
6	**58.HCl**		81	17
7	**57.HPF$_6$**			66
8	**57.HBF4**		35	62
9	**57.HCl**		80	

Scheme 15 Imidazolium salt catalyzed Stetter reaction and benzofurane derivatives



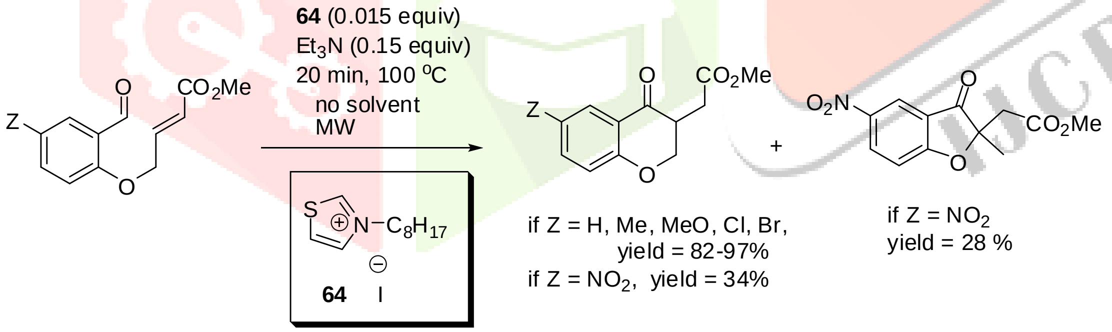
4.1 Microwave assisted intramolecular Stetter reaction

Microwave assisted reactions has been emerged as a convincing technique for promoting a diversity of reactions. The main advantage of performing reaction under microwave irradiation is rate-enhancement, superior yield and selectivity in solvent free condition. Stetter reaction also been performed under these conditions successfully by various research groups. For the first time Yadav and co-workers[75] adopted this technique to the intermolecular Stetter reaction in 2003. Later Yang and co-workers[76] conducted Stetter reaction in imidazolium-type room temperature ionic liquid (RTILs) solvents, in the presence of thiazolium salt (**1**) catalyst and Et_3N base. They were able to achieve the excellent yield in shorter reaction time (eq 26).



Eq 26

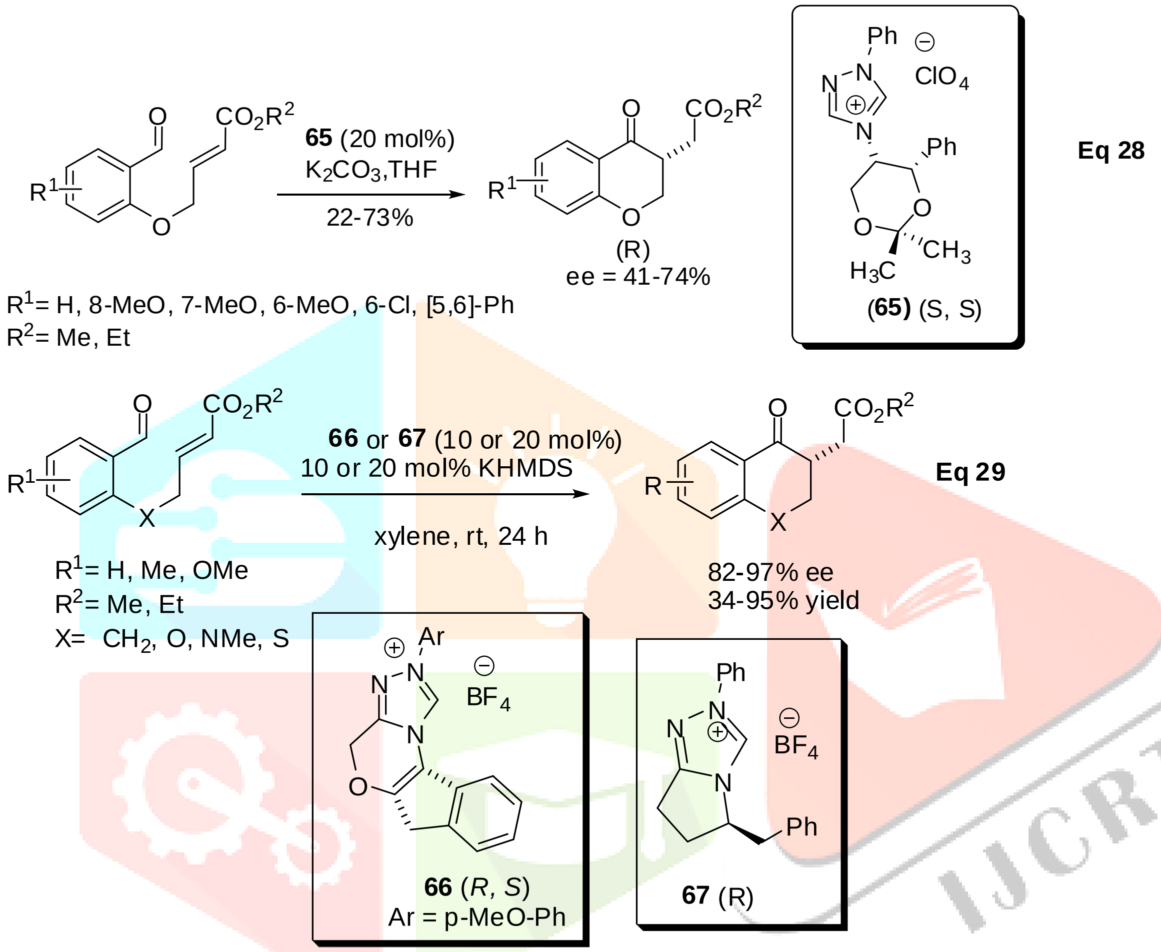
Vo-Thanh and Aupoix[77] demonstrated N-alkylation of thiazoles with n-alkyl bromides and iodides under solvent free microwave activation condition. Further alkylthiazolium salt **64** shows the best catalytic activity in intramolecular Stetter reaction under solvent free condition. In the case of 3-NO_2 salisaladehyde derivative, retro-Michel addition product obtained in 28% yield along with Stetter product (34 %) (eq 27).



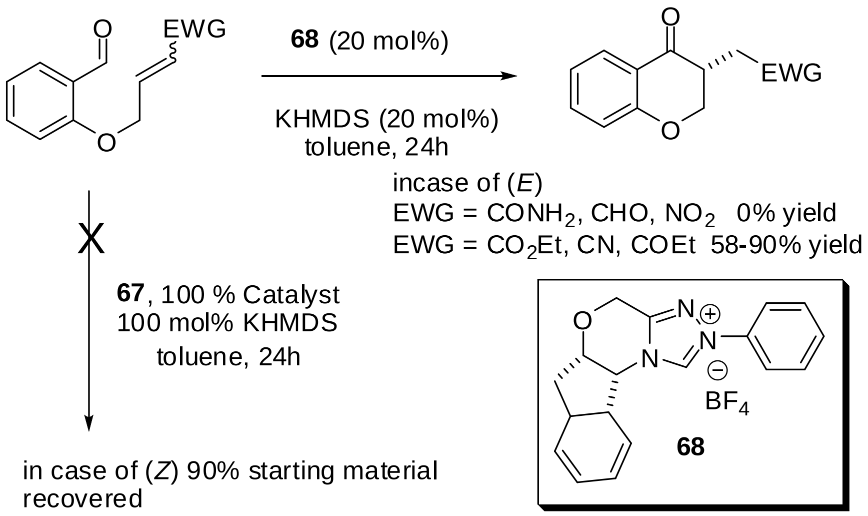
Eq 27

4.2 Asymmetric intramolecular Stetter reaction

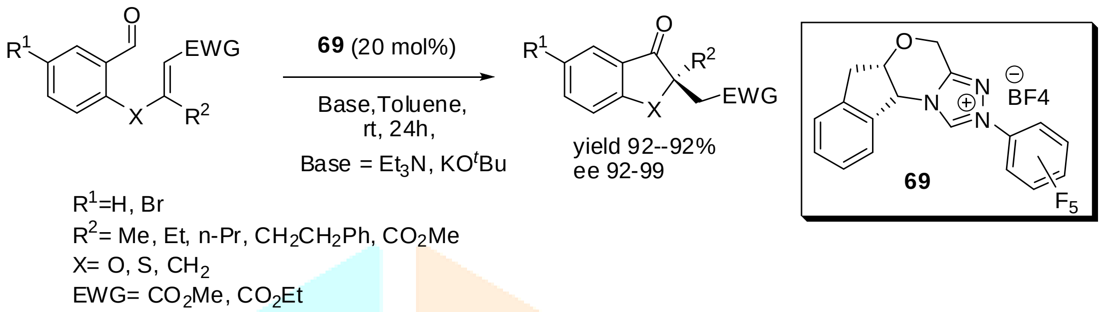
The first asysmmetric intramolecular Stetter reaction was reported in 1996 by Enders[78] *et al*. using the chiral triazolium catalyst (**65**). In this reaction enantioselective synthesis of various 4-chromanones was done with 41-74% enantiomeric excess and 22-73% yield (eq 28). Rovis and co-workers[79-88] achieved great progress in asymmetric intramolecular version. They have reported aminoindanol-derived triazolium catalyst (**66**) and the phenylalanine based catalyst (**67**) for asymmetric intramolecular Stetter reaction to get the chromanones *via* cyclization of the salicylaldehyde derivatives.[79] A broad range of different chromanones as well as their aza-, thia- and carbocyclic analogues were obtained in 34-95% isolated yield and 82-97% *ee* (eq 29). Here in this case the electronic nature of the triazole precatalyst is found to control the yield of reaction. Later the same group studied the effect of the Michael acceptors in the asymmetric intramolecular Stetter reaction.[80] It was established that, *E*-alkenes are cyclised in good enantioselectivity and moderate yield, whereas no reaction is observed in the case of *Z*-alkanes even under the stoichiometric reaction conditions with chiral triazonium salt (**68**) (Scheme 16). It was also demonstrated that the functional groups such as esters, ketones and nitriles are effective in activating the Michael acceptor while in case of α, β-unsaturated amides, aldehydes and nitro-alkenes no reaction was found.



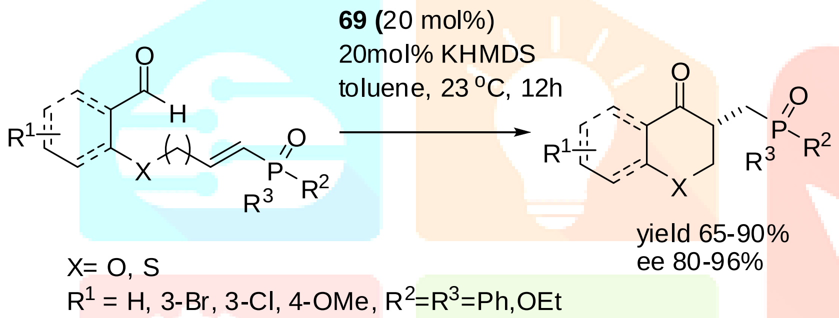
Scheme 16 Effect of Michael aceeptor in the asymmetric intramolecular Stetter reaction



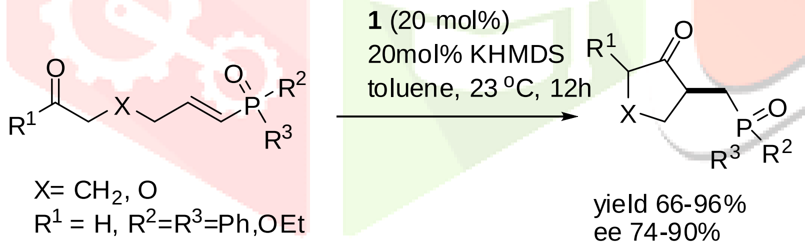
The same research group[81,82] further employed the chiral triazolium catalyst **(69)** to synthesize 1,4-dicarbonyl compounds *via* intramolecular asymmetric Stetter reaction with a quaternary stereocenter in high yield and selectivity under remarkable mild conditions (eq 30). Later they employed the same catalyst for the reaction of vinylphosphine oxides and vinylphoshonates as electrophic acceptor. In this strategy, both aromatic (eq 31) and aliphatic substrates (eq 32) provide a phosphorus-containing compound in excellent yield and enatioselectivity, which is difficult to prepare in other process.[83]



eq 30



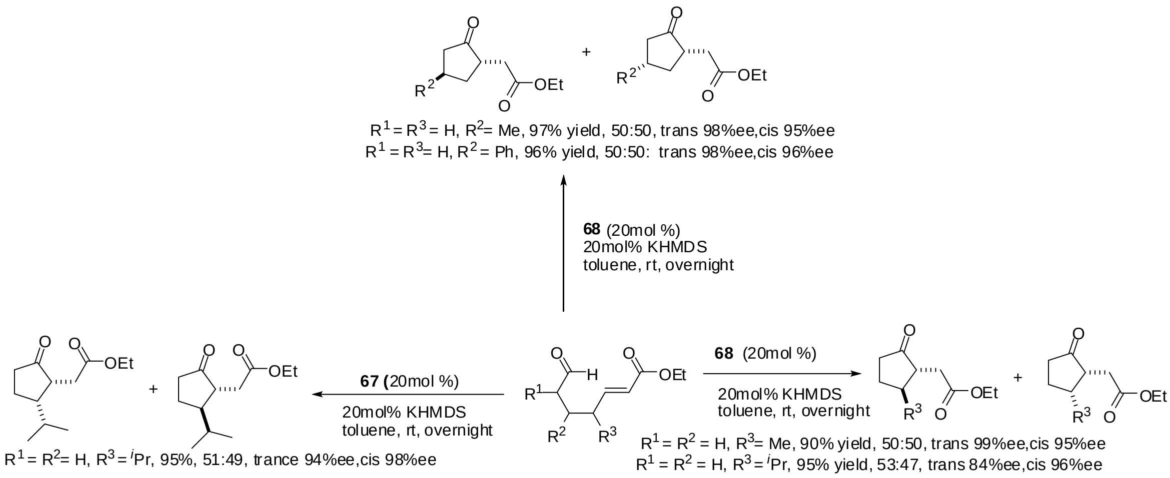
eq 31



eq 32

Rovis and Reynolds[84] synthesised 2,3-, 2,4- and 2,5-disubstituted cyclopentanones using the intramolecular Stetter reaction (Scheme 17). Further, they determined the kinetic and thermodynamic ratios for 2,3- and 2,4-disubstituted cyclopentanones. Kinetic ratios were determined by cyclization with 1 equivalent of achiral triazolium salt (**70**) and thermodynamic ratios were determined by heating the substrates in toluene in the presence of excess triethylamine (Scheme 18). Later the same research group have developed an intramolecular Stetter reaction, on a variety of trisubstituted Michael acceptors with a high enantio- and diastereoselectivity.[85] They manage to afford the desired products in good yield and control the high enantio and diastereo selectivity by tuning the olefin geometry of the Michael acceptor (Table 7).

Scheme 17 Synthesis of 2,3-; 2,4- and 2,5-disubstituted cyclopentanones *via* intramolecular Stetter reaction



Scheme 18 Kinetic and thermodynamic ratios of disubstituted cyclopentanones

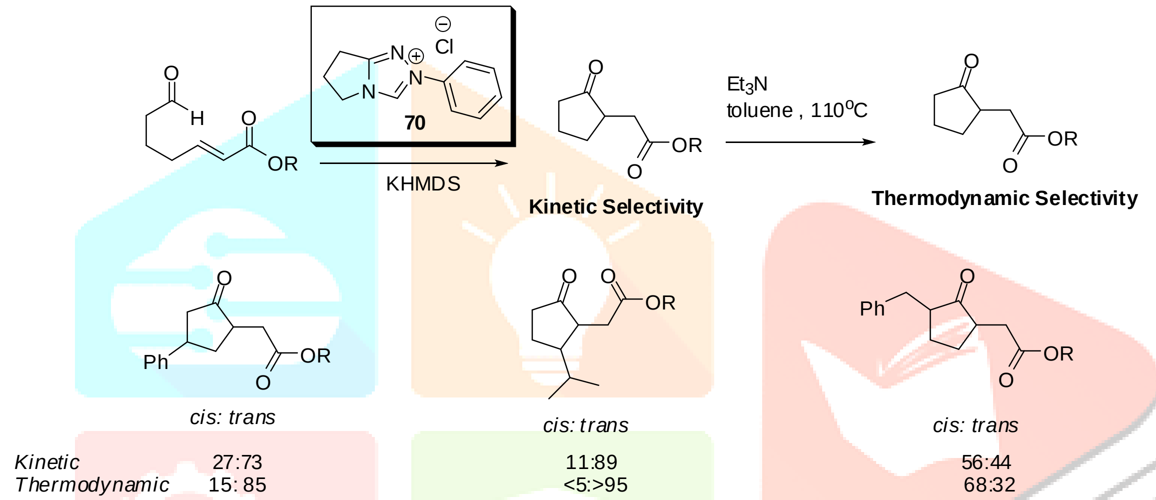
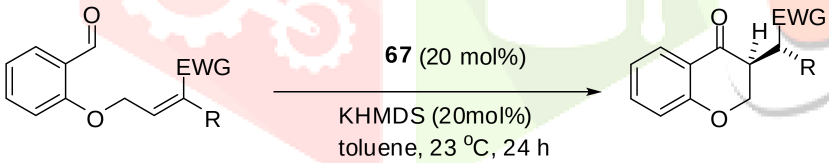
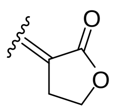
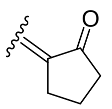


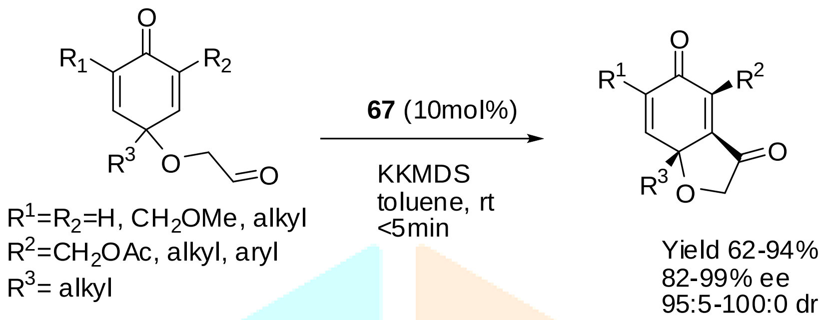
Table 7 Enatio and diasterio selective intermolecular Stetter reaction by Rovis and Alaniz



EWG	R	yield (%)	ee (%)	dr (%)
CO_2Me	Me	94	95	30:1
CO_2Et	Et	95	92	35:1
CO_2Et	n-Bu	53	94	12:1
CO_2Et	Bn	80	84	20:1
CO_2Me	allyl	95	83	13:1
CO_2Me	Me	85	55	10:1
		95	94	10:1
		80	95	18:1

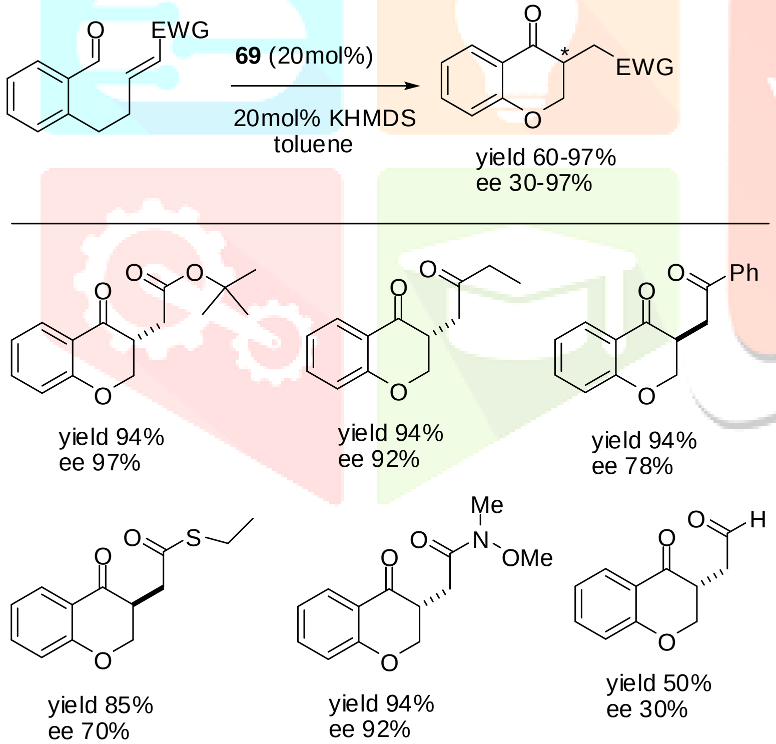
Rovis and Liu[86,87] further demonstrated the concept of disymmetrization for the enatio- and diasterioselective synthesis of hydrobenzofuranones in the intramolecular Stetter reaction.

Cyclohexadienones were used as substrates, providing these hydrobenzofuranones with three contiguous stereocenters. Moreover, the very short reaction time demonstrates the potential of this reaction (eq 33). The same research group[88] studied the comparison of the variety of triazolium salts on the selectivity and reactivity in the intramolecular Stetter reaction. In addition, variety of Michael acceptors such as α,β-unsaturated aldehydes, amides, nitriles, esters, thioesters and ketones employed successively. Importantly they identified triazolium pre-catalyst (**69**) bearing electron deficiently arylgroups that consistently provide better yield and selectivity for this reaction (Table 8).



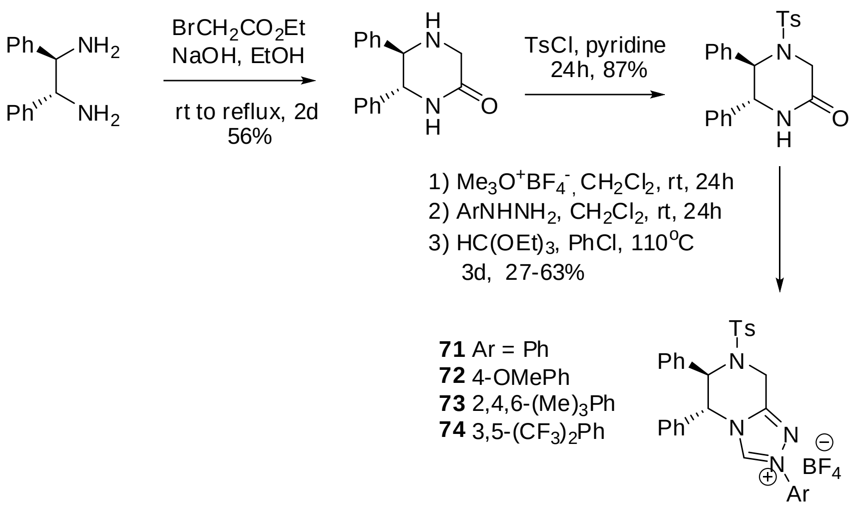
Eq 33

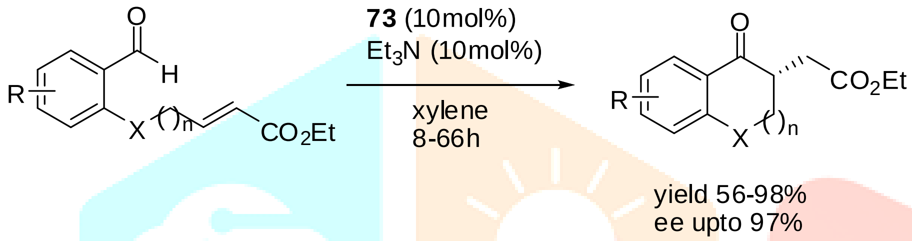
Table 8. Comparison of the triazolium salts on the selectivity and reactivity in the intramolecular Stetter reaction by Rovis and co-workers



Very recently You and co-workers[89] synthesized a series of chiral triazolium salts (**71-74**) from the commercially available (1R, 2R)-DPEN (Scheme 19). They further reported intramolecular Stetter reaction in excellent enatioselectivity (up to 97%) and yield (up to 98%) in the presence of triazolium salt (**73**) and Et_3N (eq 34).

Scheme 19 Synthesis of triazolium salts by You and co-workers



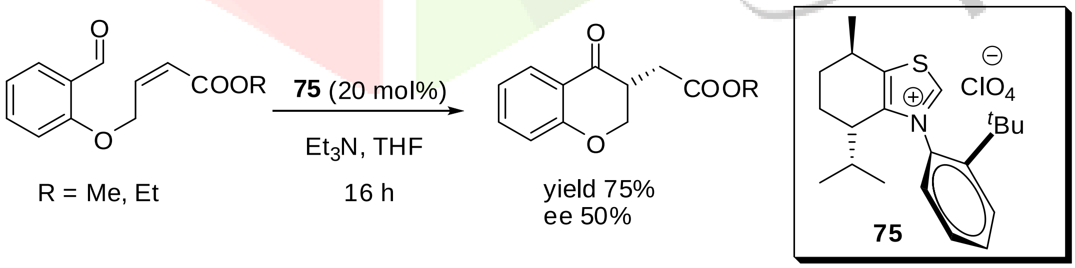


Eq 34

R = H, 4-OMe, 4-Me, 4-Cl, 4-Br, 4-NO_2, 3-OMe, 3-NEt_2, 2-Me, 3-OMe
X = O, S
n = 0,1

4.2.1 Chiral thiazolium salt catalysts

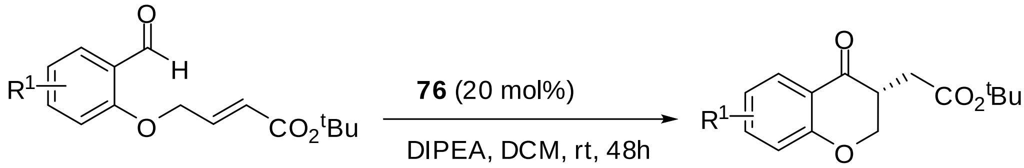
Bach and co-workers[90] successfully employed chiral thiazolium catalyst (**75**) to the intramolecular asymmetric Stetter reaction of salicylaldehyde derivatives and obtained the chroman derivatives upto 75% yield and 50% *ee* (eq 35).



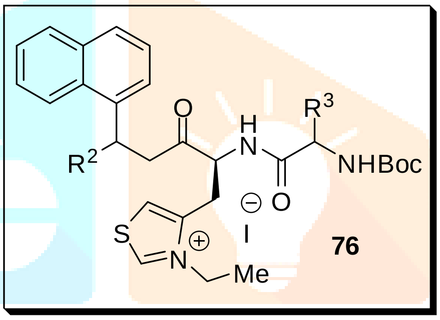
Eq 35

Miller and co-workers[91] reported the synthesis of chroman-4-ones *via* asymmetric intramolecular Stetter reaction with peptide precatalysts (**76**), which are incorporated with a thiazolylalanine moiety in their structure. Among the designed precatalysts, the catalyst family bearing the thiazolylalanine group in an internal position has shown better activity and moderate to good enantioselectivities (Table 9).

Table 9 Intramolecular asymmetric Stetter reaction using peptide based precatalyst by Miller and co-workers

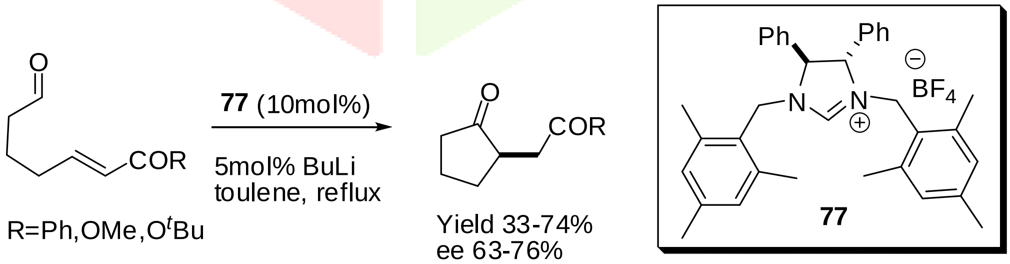


R^1	R^2	R^3	yield (%)	ee (%)
H	(R)-Me	L-Phe	20	55
H	(S)-Me	D-Phe	20	81
H	(S)-Me	L-Phe	28	80
H	(S)-Me	L-Val	22	65
H	(S)-Me	L-Thr(Bn)	67	73
3-Me	(S)-Me	L-Thr(Bn)	45	73
4-MeO	(S)-Me	L-Thr(Bn)	17	73
5-NO_2	(S)-Me	L-Thr(Bn)	78	0



4.2.2 Chiral imidazolium salt catalysts

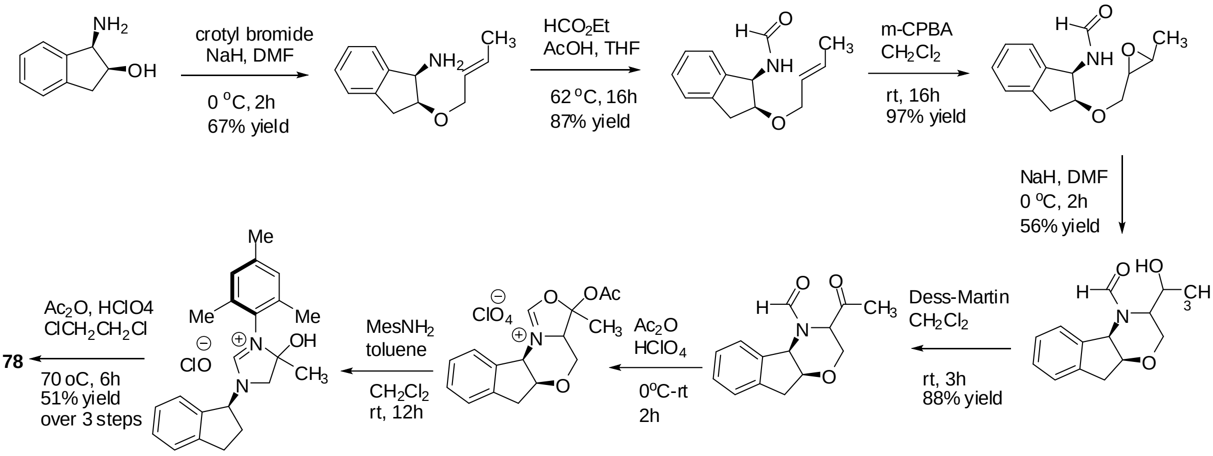
Matsumoto and Tomioka[92] have developed chiral C_2 symmetric imidazolidene catalyst (**77**) for intramolecular Stetter reaction of aliphatic aldehydes. Alterations in the steric and electronic nature of the Michael acceptor have been found to affect the efficiency of the reaction to a small extent (eq 36).



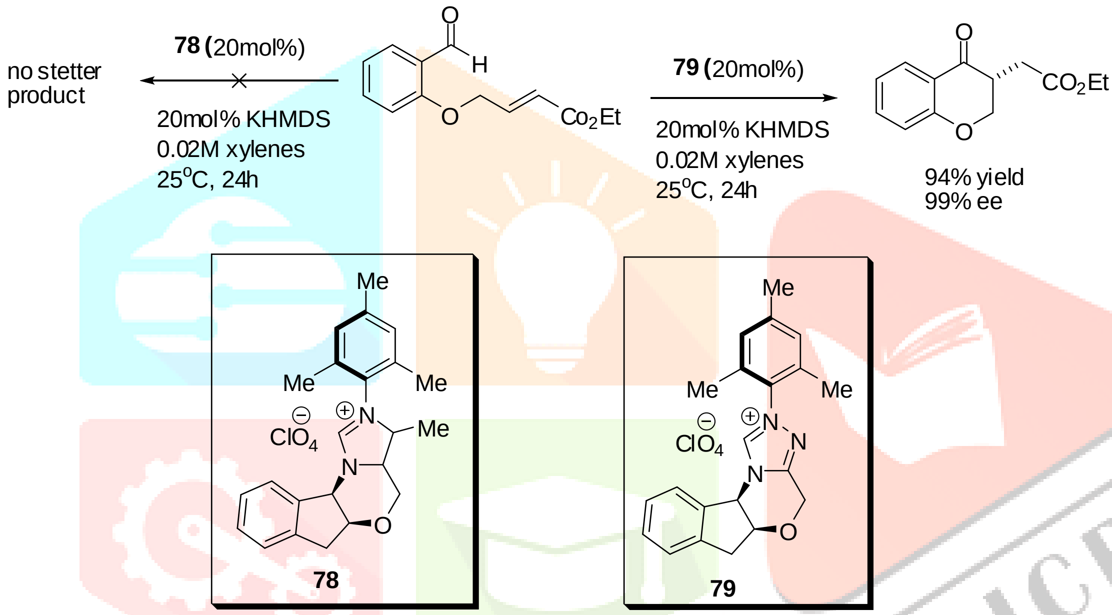
Eq 36

Bode and co-workers[93] reported the synthetic route for the new imidazolium salt **78** (Scheme 20). They investigated the catalytic activity of the same on Stetter reaction and some other reactions and also compared the results with triazolium salt catalyst **79**. In the presence of **79** the intramolecular Stetter product was found 94% yield and 98% ee, whereas in case of **78** no Stetter product was formed. This study confirms clear differences in reactivity and mechanism between these two classes of catalysts (Scheme 21).

Scheme 20 Synthesis of chiral imidazolium salt by Bode and co-workers



Scheme 21 Synthesis of chiral imidazolium salts catalyzed Stetter reaction by Bode and co-workers



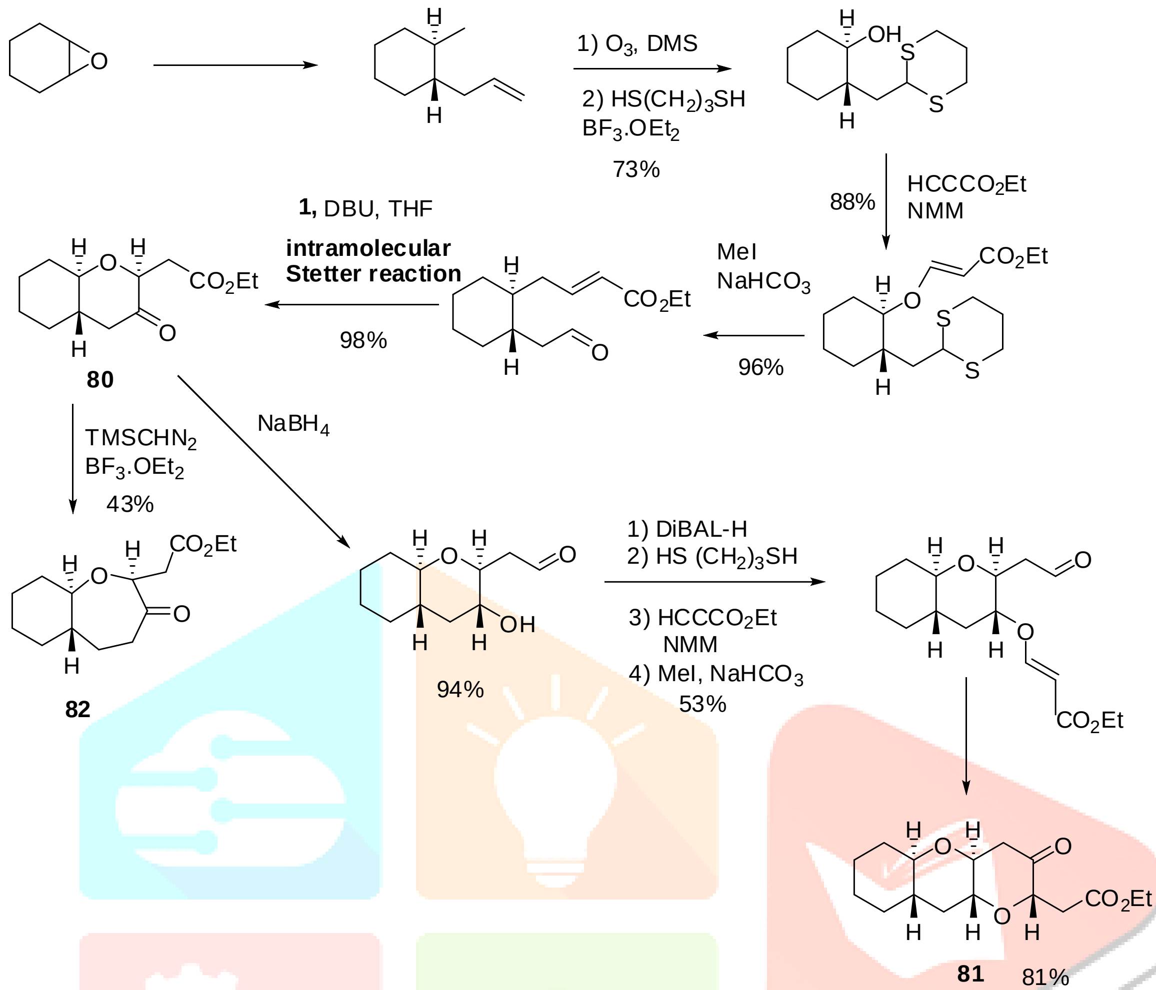
5. Applications

Due to the occurrence of various functional groups in the proximity of Stetter adducts, they have become significant substrates for synthesis of a number of heterocyclic molecules.[94,95] These adducts have also been elegantly employed as valuable synthons in the synthesis of important carbocycles, natural products and biologically active molecules. Their Synthetic applications have been broadly divided into two sections: i) Carbocyclic / heterocyclic molecules, ii) Natural products and biological active molecules.

5.1 Carbocyclic / heterocyclic molecules

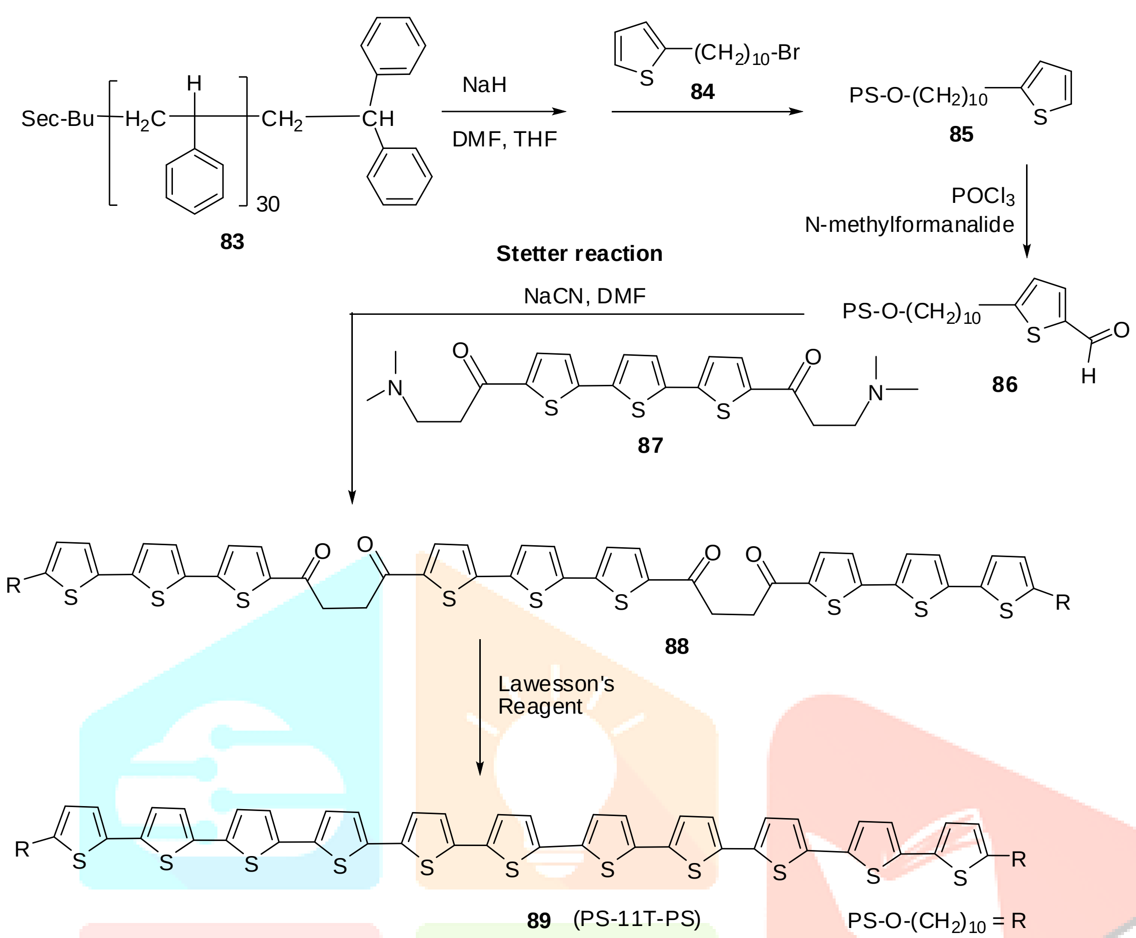
McErlean and co-workers[96] reported first example of intramolecular Stetter reaction between an aliphatic aldehyde and acrylate unit for the synthesis of trans, syn-fused pyranone (**80**) as a single diastereomer. This was further used to synthesize a trans, syn, trans-fused polycyclic ether array (**81**) and oxepanone (**82**) through ring expansion (Scheme 22).

Scheme 22 Synthesis of polycyclic ethers and oxepanone *via* intramolecular Stetter reaction

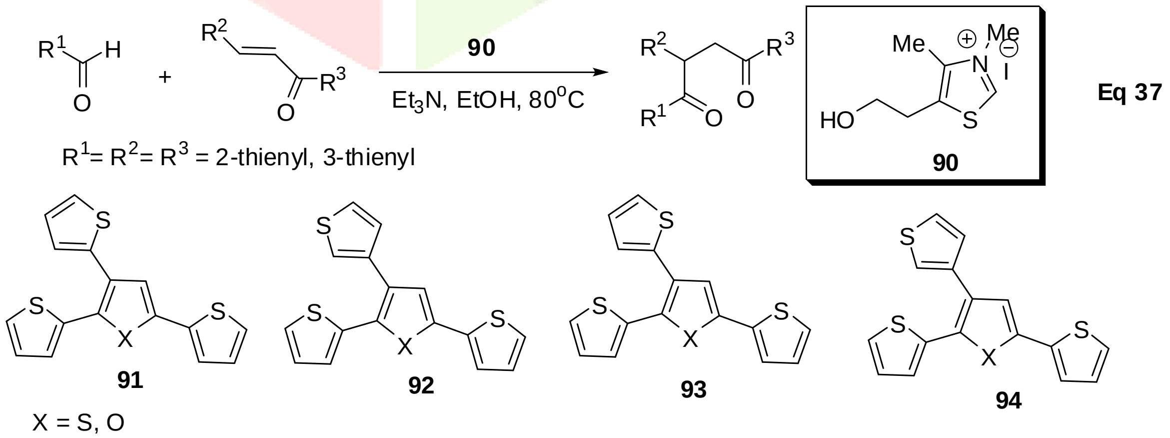


A triblock copolymer PS-11T-PS (**89**) was synthesized by Hempenius and co-workers[97] by R-coupling of thiophene rings **84** of the middle block and the monodispersity of the two polystyrene outer blocks. Monofunctional polystyrene **83** is first modified with an R-terthiophene unit **84** to form **85**, and two of these units are coupled in a double Stetter reaction of **86** with a difunctional R-terthiophene (**87)** to yield a tetraketone (**88**). From which the triblock copolymer (**89**) was formed by treating with excess Lawesson's reagent (Scheme 23).

Scheme 23 Synthesis copolymer PS-11T-PS by Hempenius and co-workers *via* Stetter reaction



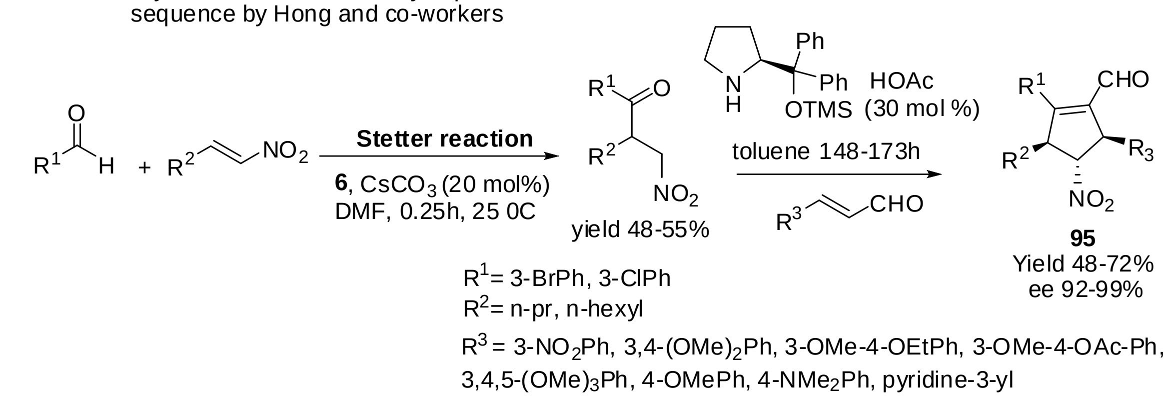
Perrine and group[98] reported isomeric branched quaterthienyls (thienylterthiophenes) (**91-94**) from the respective trithienyl 1,4-butanediones. Trithienyl 1,4-butanediones obtained in 86-87% yield with 20% molar quantity of 3,4-dimethyl-5-(2-hydroxyethy1)thiazolium iodide catalyst (**90**) and 60% molar quantity of Et_3N *via* the Stetter reaction (eq 37).

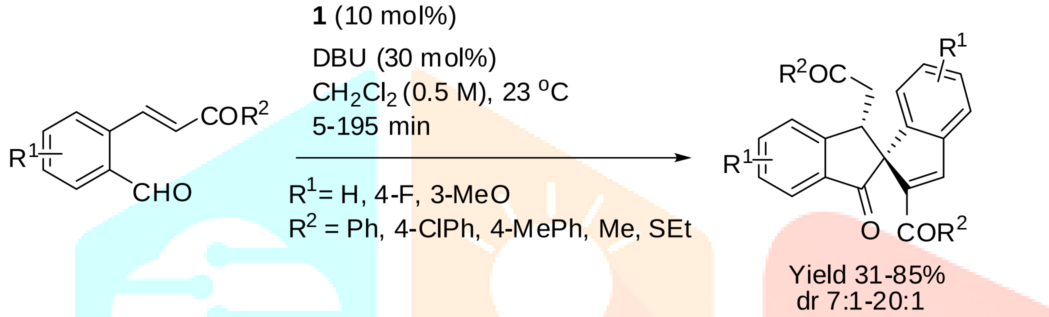


5.1.1 Michael-aldol reactions

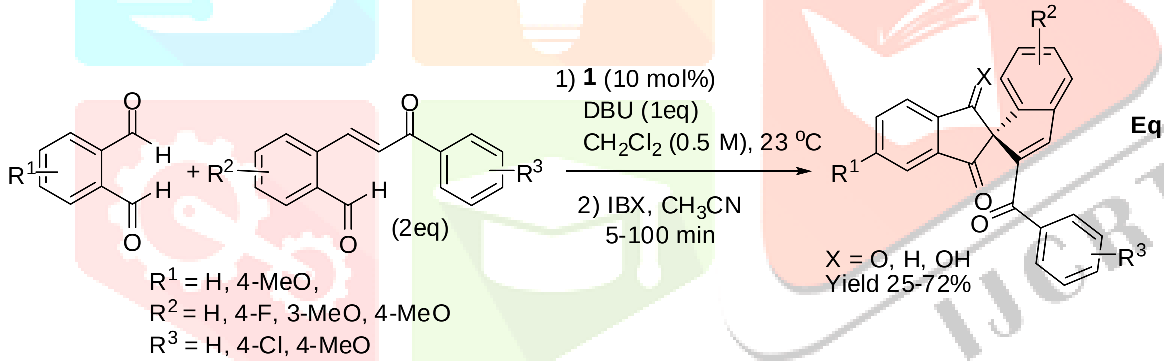
Hong and co-workers[99] recently reported substituted cyclopentenes (**95**) by the Stetter reaction and Michael-aldol condensation of aromatic aldehydes, nitroalkenes and α, β-unsaturated aldehydes *via* the [1+2+2] annulations strategy following the reaction sequence shown in Scheme 24. Later Gravel and co-workers[100] reported a simple synthesis of spiro bis-indanes through domino Stetter-aldol-Michel (eq 38) and Stetter-aldol-aldol reactions (eq 39).

Scheme 24 Synthesis of substituted cyclopentenes *via* Stetter-Michael-aldol condensation reaction sequence by Hong and co-workers





Eq 38

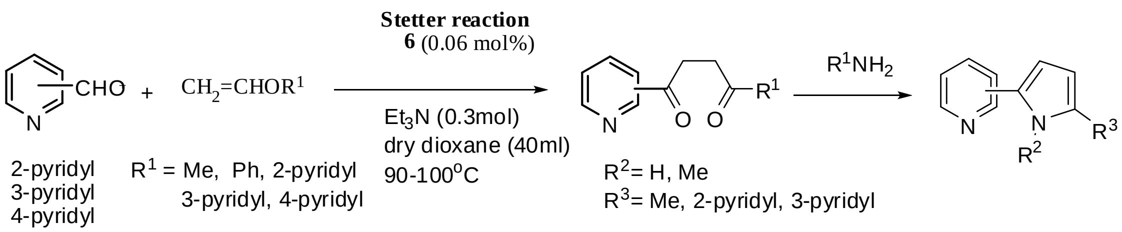


Eq 39

5.1.2 Paal-Knorr reaction

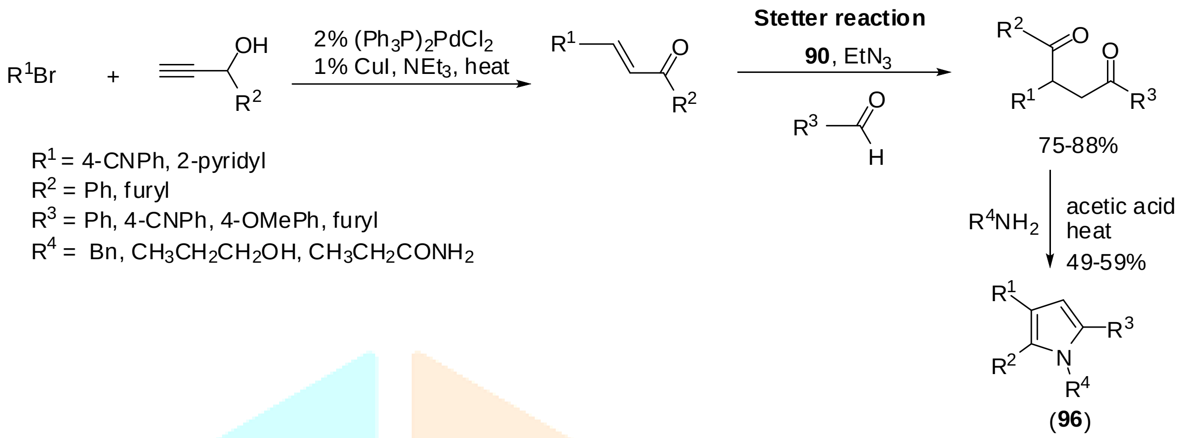
Jones and co-workers[101] synthesized pyrrolylpyridines *via* Paal-Knorr reaction. The pyridyl diketones which are the precursors for this reaction were obtained by the Stetter reaction of the appropriate pyridinecarboxaldehydes and vinylketone (Scheme 25).

Scheme 25 Synthesis of pyrrolylpyridines *via* Stetter and Paal-Knorr reaction by Jones and co-workers



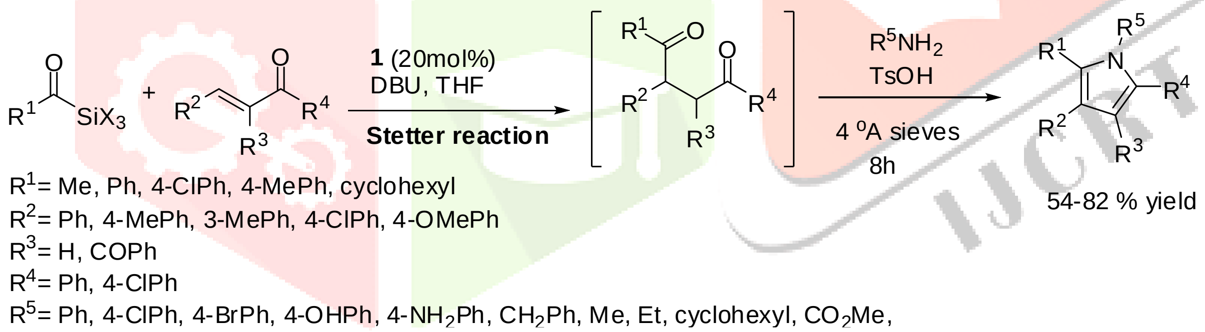
Muller and co-workers[102] synthesized 1,2,3,5-tetrasubstituted pyrroles (**96**) by a one-pot, three-step, four-component process in 49-59% isolated yields. The reaction follows a sequence of coupling-isomerisation-Stetter reaction-Paal-Knorr reaction as shown in Scheme 26.

Scheme 26 One-pot four component reaction for the synthesis of tetrasubstituted pyrroles *via* Coupling-Isomerization-Stetter-Paal-Knorr sequence



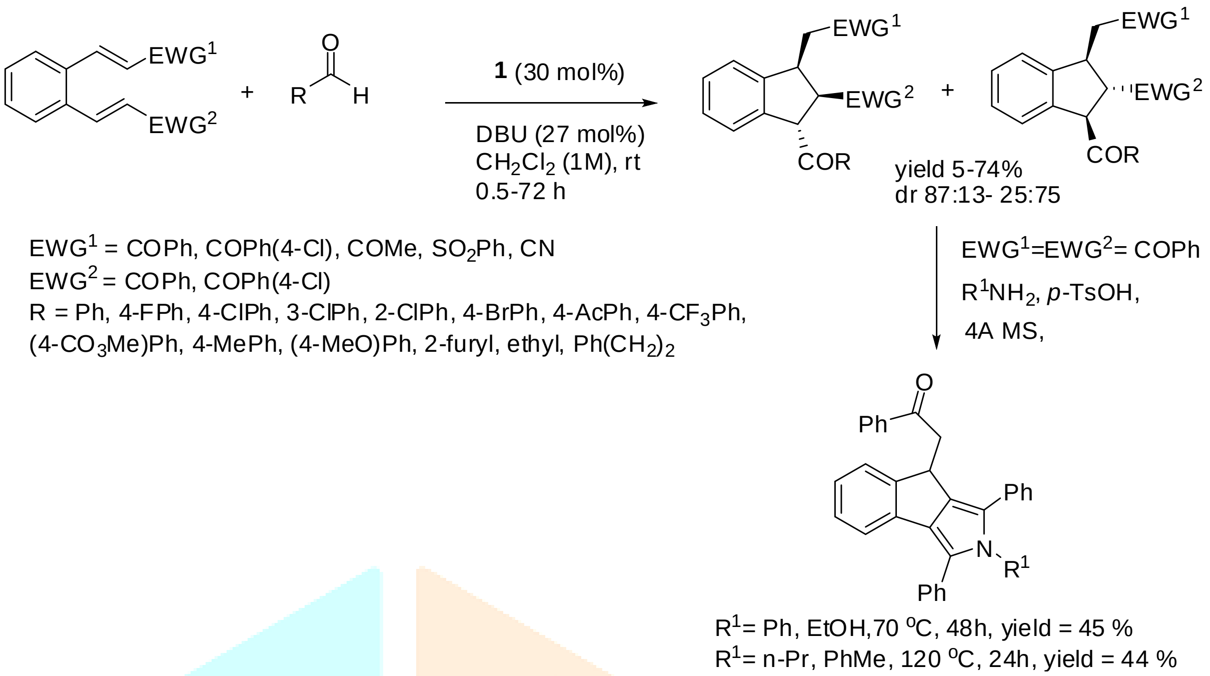
Scheidt and Bharadwaj[103] described an efficient one-pot multicomponent synthesis of highly substituted pyrroles *via* sila-Stetter reaction and Paal-Knorr reaction. Acyl silanes and unsaturated carbonyl compounds generates 1,4-corbonyl compounds *in situ* through sila-Stetter reaction and subsequent addition of various amines (Paal-Knorr reaction) affording pyrroles in one-pot operation (Scheme 27).

Scheme 27 Synthesis of highly substituted pyrroles *via* sila-Stetter reaction and Paal-Knorr reaction



Gravel and co-workers[104] synthesized highly substituted indanes through domino Stetter-Michael reaction in good diasterioselectivity. This process represents the first example of domino reaction involving the enolate intermediate generated from Stetter reaction. These indanes were further converted into fused pyrrole containing heterocycles *via* Paal-Knorr synthesis (Scheme 28).

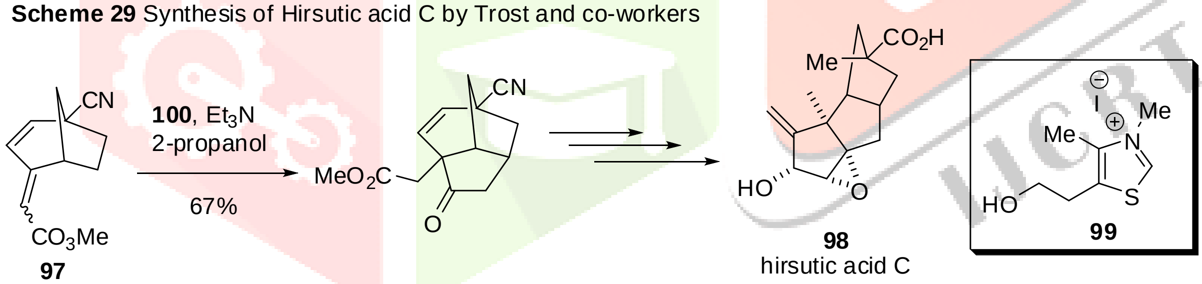
Scheme 28 Synthesis of fused pyrroles *via* Stetter-Micheal-Paal-Knorr reactions by Gravel and Larios



5.2 Natural products and biological active molecules

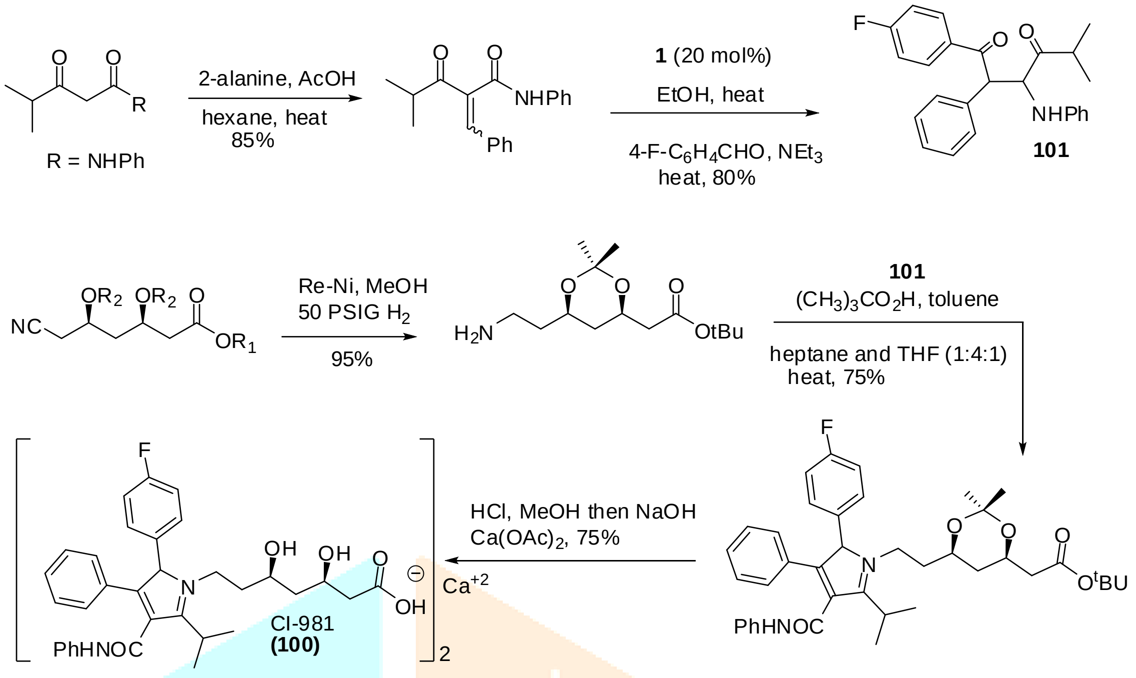
Trost and co-workers[105] reported hirsutic acid C (**98**) *via* intermolecular Stetter reaction of **97** in the presence thiozolium catalyst (**99**). Which is the representative of a novel tricyclic sesquiterpene class, whose members possess potential antibiotic and antitumor activity (Scheme 29).

Scheme 29 Synthesis of Hirsutic acid C by Trost and co-workers



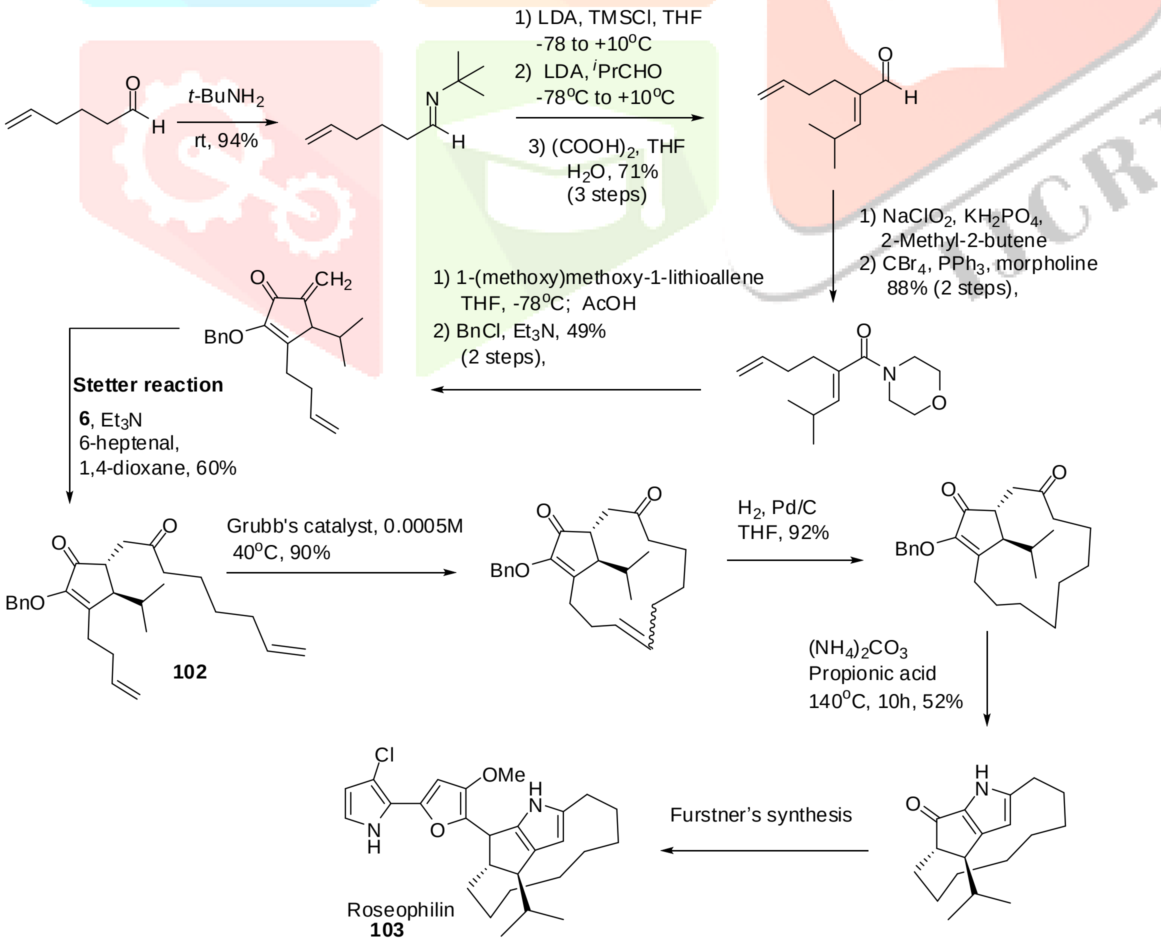
CI-981 (**100**), a potent and tissue selective inhibitor of HMG-CoA reductase was synthesized by Roth and co-workers.[106,107] The key step in the process was carried out using the Stetter reaction (Scheme 30).

Scheme 30 Synthesis of CI-982 *via* Stetter reaction by Roth and et al



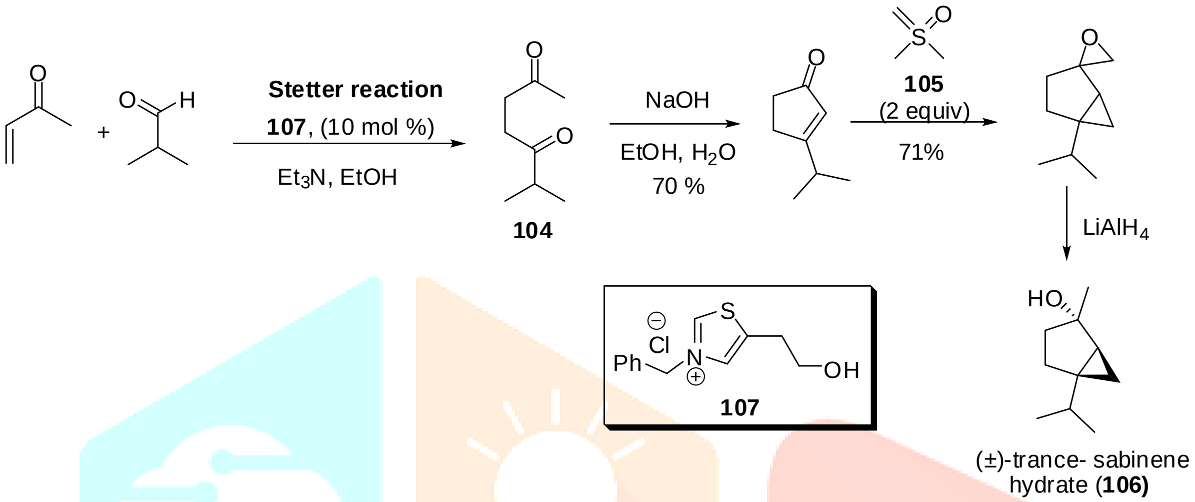
Tius and Harrington[108,109] reported the total synthesis of roseophilin (**103**) starting from 5-hexenal. The key intermediate diene (**102**) was constructed by the Stetter reaction as shown in Scheme 31.

Scheme 31 Total synthesis of roseophiline *via* Stetter reaction by Tius and Harrington



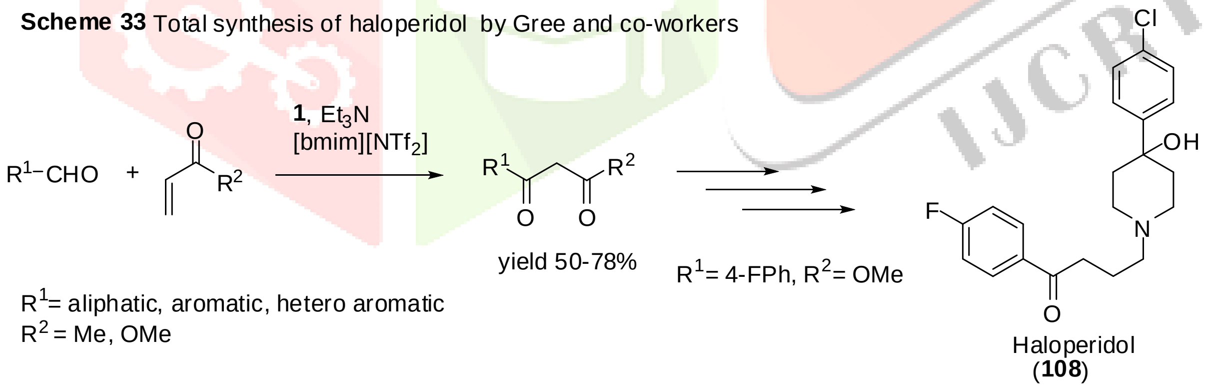
A simple procedure for the synthesis of sabinene hydrate [110] (**106**) was developed by Galopin in 28% overall yield. The initial stage of synthesis requires the Stetter reaction to prepare a dione (**104**). Which is further upon intramolecular aldol condensation gives cyclopentenone. The cyclopentenone is reacted with Corey-Chaykovysky (**105**) reagent which is upon reduction with $LiAlH_4$ gives a mixture of (±)-*trans*-sabinene hydrate (±) (Scheme 32).

Scheme 32 Total synthesis of (±)-trans- sabinene hydrate *via* intramolecular Stetter reaction



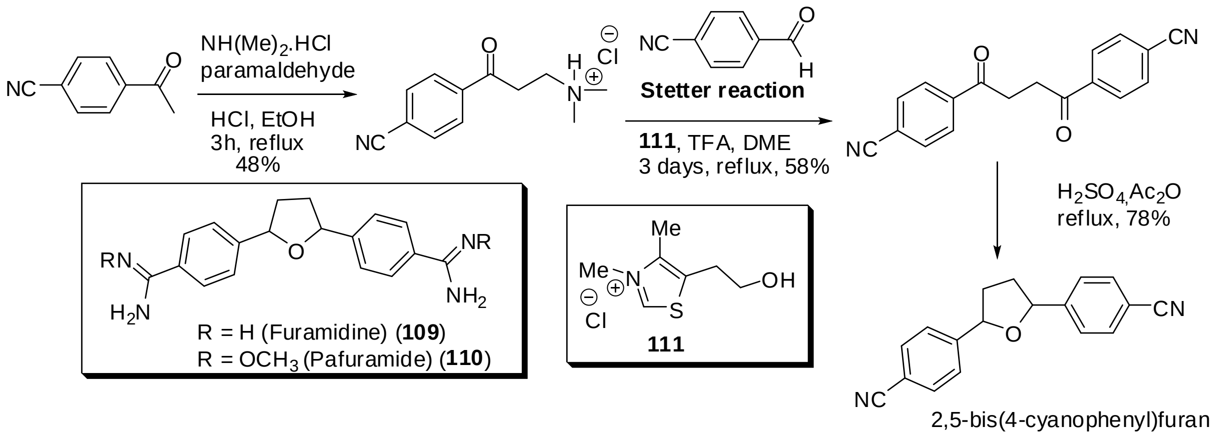
Gree and co-workers[111] reported the total synthesis of haloperidol (**108**), a typical antipsychotic agent, by using [bmim][NTf_2] ionic liquid as a solvent in the Stetter reaction (in the presence of thiazolium salts (**1**) as catalyst and Et_3N as a base). Furthermore, it is claimed that it is possible to recycle and reuse the ionic liquid (Scheme 33).

Scheme 33 Total synthesis of haloperidol by Gree and co-workers



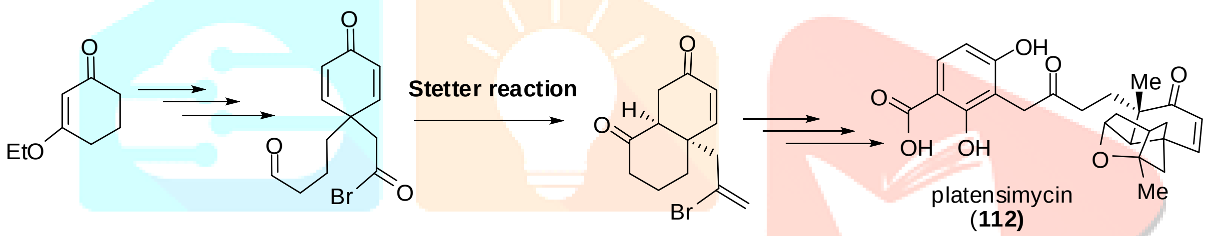
A new synthetic approach to 2,5-bis(4-cyanophenyl)furan, a key intermediate in the synthesis of Furamidine (**109**) and Pafuramide (**110**) has been described by Suthiwangcharoen and Stephens[112] *via* modified Stetter reaction as shown in Scheme 34.

Scheme 34 Synthesis of Furamidine and Pafuramide *via* modified Stetter reaction by Suthiwangcharoen and Stephens



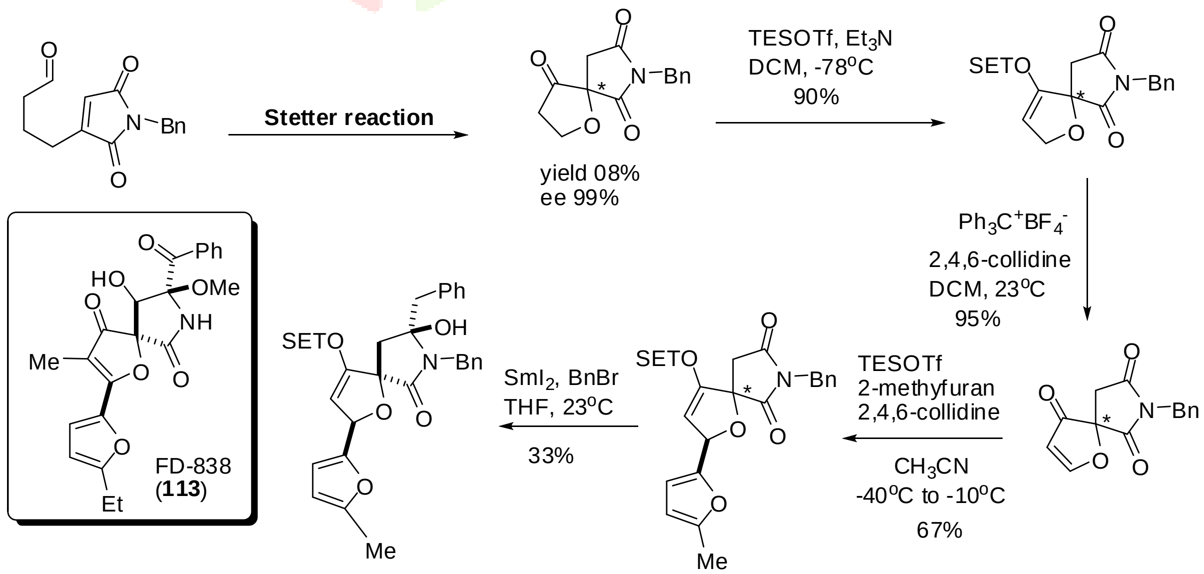
Nicolaou and co-workers[113] reported the total synthesis of (±)-platensimycin (**112**). The procedure involves an intramolecular Stetter reaction and radical cyclization to form the key C-C bonds *en route* to the cage-like structure of (±)-platensimycin (Scheme 35).

Scheme 35 Synthesis of platensimycin *via* Stetter reaction by Nicolaou and co-workers



Rovis and Orellana[114] synthesised spirofuranone-lactam core unit possessing a natural product FD-838 (**113**) with key catalytic intramolecular asymmetric Stetter reaction. The appropriate maleimide in the Stetter reaction provides the spirofuranone-succinimide as a single enatiomer in good yield. In addition to this they developed a simple protocol for the installation of the furan ring and alkylation of the succinimide ring (Scheme 36).

Scheme 36 Synthesis of FD-838 core *via* Stetter reaction by Rovis and Orellana



6. Conclusions and future of the reaction

This review demonstrates the both the reaction development and application point of view. The details in this review clearly indicate that the Stetter reaction has become one of the most useful carbon-carbon bond forming reaction. Although there is significant progress in designing and synthesizing various chiral catalysts, in the asymmetric Stetter reaction version it is still essential to discover more and more efficient chiral catalysts. Therefore, there are challenges in front of organic chemists to develop the Stetter reaction in all the essential components *i.e* electrophiles, Micheal acceptors and catalysts. This review will offer the opportunity and also challenge to organic chemists to discover novel methodologies to solve problems in synthesizing drugs and other important biological molecules by using the Stetter strategy in the years to come.

7. Abbreviations

Ac	acetyl
Ar	aryl
BF_3.OEt	boron trifluride etherate
Bn	benzyl
Bu	butyl
Cy	cyclohexyl
DBU	1, 8-diazabicyclo [5.4.0] undec-7-ene
DCM	dichloromethane
de	diastereomeric exess
DIPEA	N,N'-diisopropylethylamine
DiBAL-H	diisobutyl aluminium hydride
DME	1, 2-dimethoxyethane
DMF	dimethylformamide
DMS	dimethylsulfide
DPEN	diphenylethylenediamine
dr	diasteriomeric ratio
Et	ethyl
EWG	electron withdrawing group
ee	enatiomeric excess
IBX	iodoxybenzoic acid
KHMDS	potassium hexamethyl disilazide
LDA	lithium diisopropylamide
Me	methyl
Mes	mesityl

MS	molecular sieves
MVK	methyl vinyl ketone
MW	microwave
mCPBA	*meta*-chloroperoxybenzoic acid
NMM	N-methylmorpholine
Non	nonyl
Ph	phenyl
Pent	pentyl
Pr	propyl
ROMP	ring opening metathesis polimerization
rt	room temperature
TADDOL	*trans*-α,α'-(dimethyl-1,3-dioxolane-4,5-diyl)-bis(diphenylmethanol)
TBDPS	*tert*-butyldiisopropylsilyl
TESOTf	trimethylsilyl triflurometHane sulfonate
TFA	trifluroacetic acid
THF	tetrahydrofuran
ThDP	thiaminediphasphate
TMS	trimethylsilyl
TS	transition state
TSIL	task specific ionic liquid
Ts	tosyl
TsOH	*pera*-toluenesulfonic acid
^{t}Bu	*tert*-butyl

8. Acknowledgments

We express our gratitudes to our colleagues and friends for their suggestions and helpful discussions.

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