Journal of Scientific Research
Banaras Hindu University, Varanasi

Vol. 63, 2019 :155-167
ISSN : 0447-9483

DIPOLES AS REACTIVE INTERMEDIATES IN SYNTHESIS

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Abstract:

An overview of the novel transformations that were developed in the author's laboratory is presented. The involvement of transient dipolar species is the unifying factor of these reactions. Assembly of two electrophilic components, multicomponent reactions and intriguing skeletal rearrangement reactions have been developed via this approach.

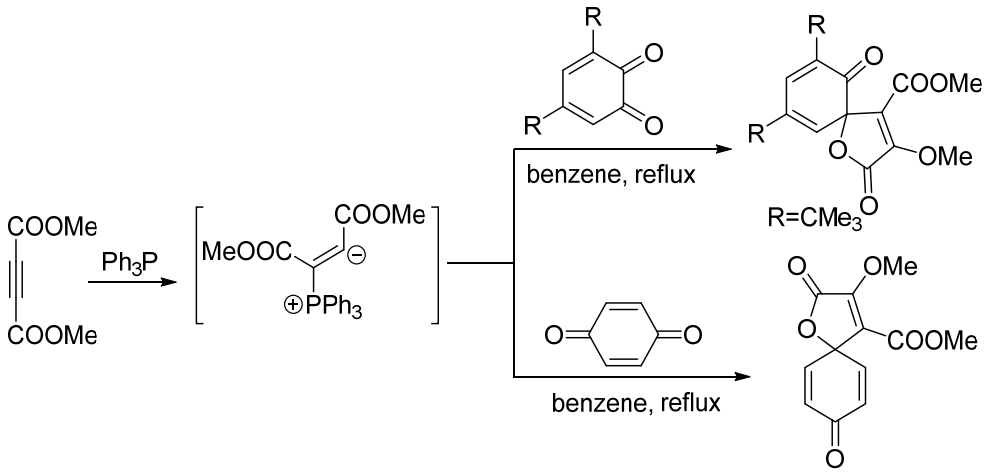
Introduction

Organic reactions are typically classified on the basis of *reactive intermediates* such as carbanions, carbocations, free radicals, carbenes, dipoles etc. Dipoles and zwitterions are formed in a number of reactions; however, they are seldom discussed under the broad ambit of *reactive intermediates*. This anomaly becomes more glaring when one considers the numerous versatile and well-studied transformations, such as the Mitsunobu[1] and Morita-Baylis-Hilmann[2] reactions that proceed via dipolar intermediates. A large share of our group's activities mainly revolved around *generation and interception of various dipoles* to carry out useful transformations that are difficult or even impossible to realize otherwise. A brief discussion of selected examples of our efforts spanning nearly three decades is presented below.

The codification and rationalization of the chemistry of dipoles was done by Huisgen in 1960s.[3] He also demonstrated the synthetic utility and versatility of this method. Important contributions by Acheson and Winterfeldt also enriched the area.[4] Despite the utility of various dipoles, there were few systematic investigations on their reactions. Much of the research in our group has addressed this glaring knowledge gap in synthesis. We have devised reactions wherein transient dipoles generated by the addition of nucleophiles to electron deficient unsaturated compounds are trapped by a suitable third component. Typical nucleophiles that are useful in this regard include triphenylphosphine, pyridine, quinoline, isoquinoline, dimethoxycarbene, isocyanides and N-heterocyclic carbenes (NHC). Such transformations developed in our laboratory may be classified into two broad categories; one the union of two electrophiles in presence of a nucleophilic catalyst and the other multicomponent reactions (MCR) wherein the nucleophile itself ends up as part of the final product.[5] The nature of the nucleophilic initiator is the major factor that determines the course of the reaction. Therefore, it is appropriate and convenient that these reactions are discussed based on the same classification.

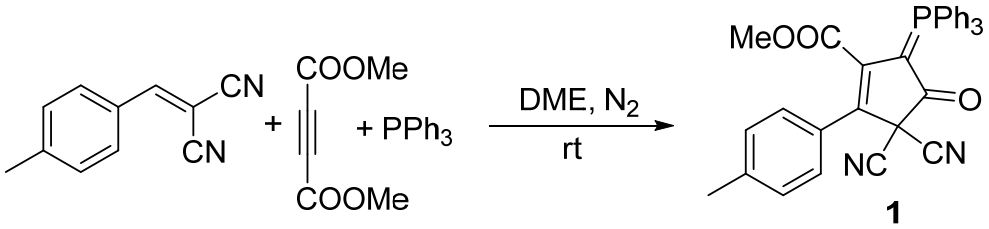
1. Reactions of triphenylphosphine–derived dipoles

Interception of 1, 3-dipolar intermediates generated via the addition of triphenylphosphine to dimethyl acetylenedicarboxylate (DMAD) by *ortho*- and *para*-quinones to afford spirocyclic lactones constitutes one of the earliest reports of dipolar cylisations from our group (Scheme 1).[6]



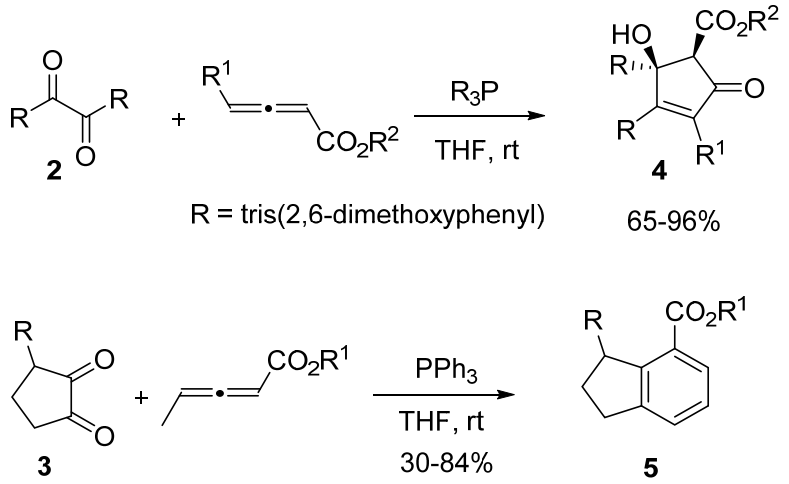
Scheme 1: Interception of phosphine-DMAD zwitterion with quinones

Phosphine-DMAD zwitterion may also be intercepted with electrophilic components such as dicyanostyrenes or β-nitrostyrenes to form cyclopentenylphosphorane derivatives **1**.[7] A representative example is provided in Scheme 2.



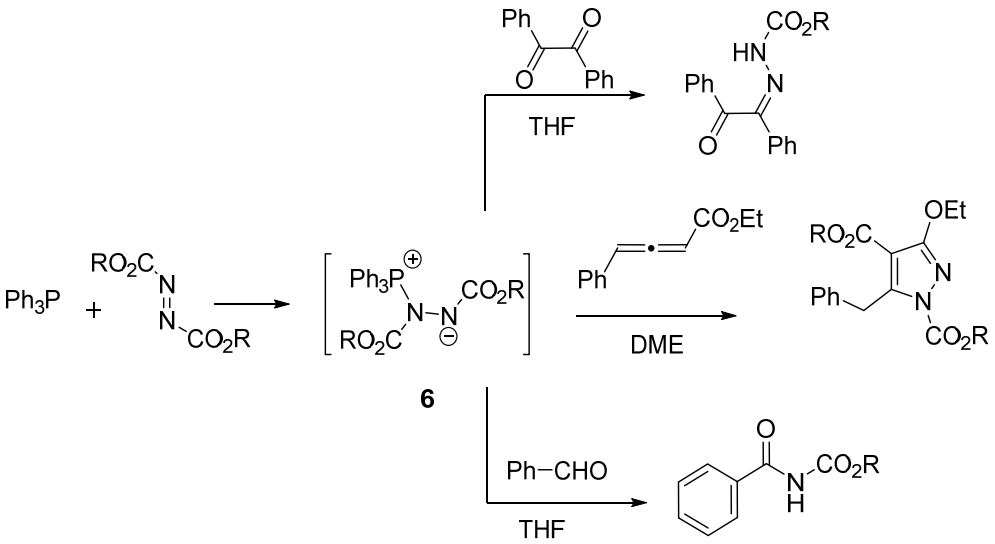
Scheme 2: Interception of phosphine-DMAD zwitterion by dicyanostyrene

Similar zwitterions may also be generated from the addition of phosphine to allenoates. They exhibit a more varied reactivity pattern that is controlled by the nature of substituents on the allenoate as well as the trapping agent. This point is illustrated by the cyclization reactions depicted in Scheme 3. Two different 1,2-diones **2** and **3** on reaction with phosphine-allenoate dipoles afforded cyclopentenone derivative **4** and the benzannulation product **5** respectively.[8]



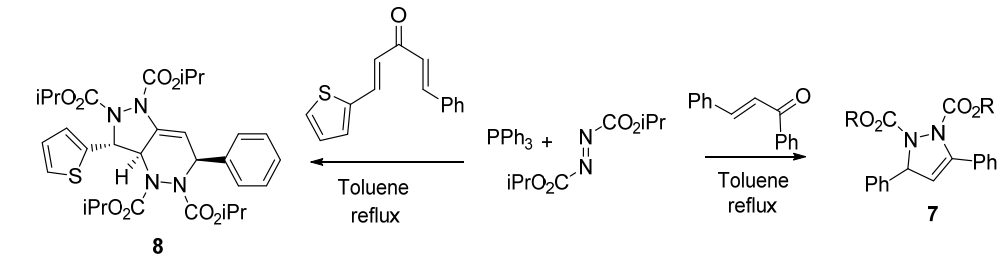
Scheme 3: Reactions of phosphine-allenoate dipole

The dipole **6** formed by the addition of phosphine to diazadicarboxylates is the well-known intermediate (known as Huisgen zwitterion) in Mitsunobu reaction. We have developed N-C bond forming reactions of Huisgen zwitterion by judicious choice of intercepting reactants. Selected examples of such cases where allenoates, 1, 2-diones and aldehydes were used as interceptors are presented in Scheme 4. It may be noted that most of these reactions involved unprecedented migrations of groups.[9]



Scheme 4: Trapping of Huisgen zwitterion with various electrophiles

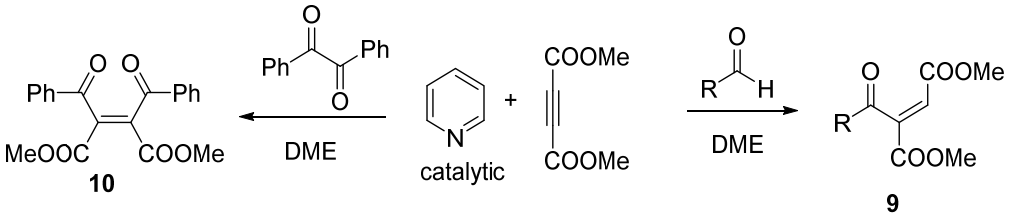
An important and mechanistically intriguing cyclization reaction of Huisgen zwitterion was discovered when it was reacted with chalcones and dienones (Scheme 5). Pyrazoline derivatives **7** and pyrazolopyridazine derivatives **8** were respectively obtained in high yields.[10]



Scheme 5: Pyrazoline formation from Huisgen zwitterion and chalcones

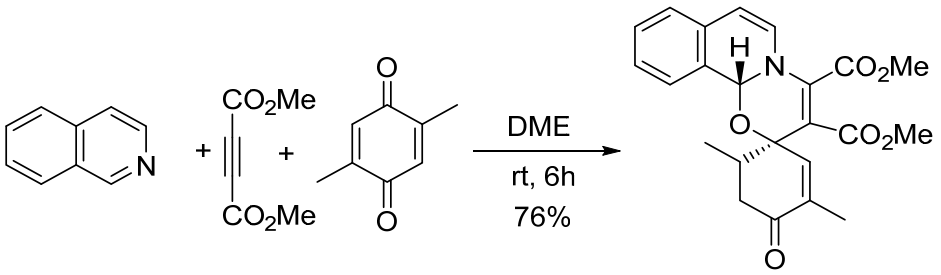
1. Reactions of nitrogen heterocycles–derived dipoles

A cyclization reaction between pyridine and DMAD, reported by Diels and Alder, constitutes the earliest example of pyridine-derived dipole formation and trapping.[11] Exposure of this dipole to aldehydes and dicarbonyl compounds result in interesting rearrangements that afford products such as **9** and **10** (Scheme 6).[12]



Scheme 6: Selected reactions of pyrdine-DMAD dipole

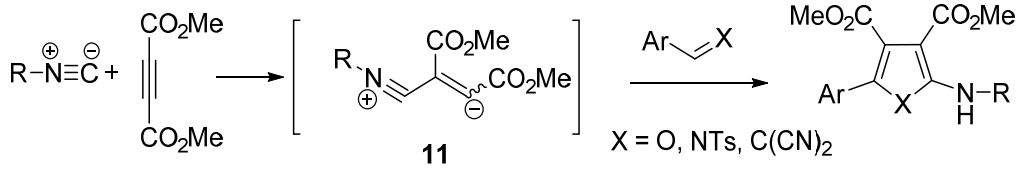
Dipoles may also be formed by the addition of quinoline and isoquinoline to DMAD. These dipoles tend to undergo diastereoselective MCRs when a suitable third component is introduced. A typical example is depicted in Scheme 7.[13]



Scheme 7: Three-component reaction of isoquinoline, DMAD and a *p*-quinone

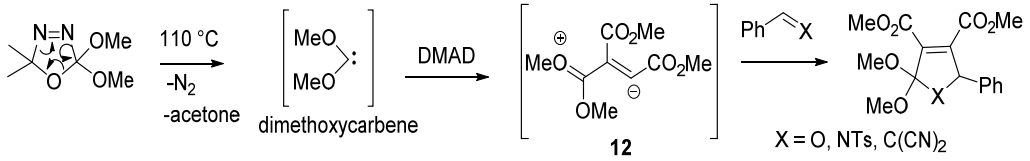
2. Multicomponent Reactions (MCRs)-dipoles derived from nucleophilic carbenes

Dipoles generated from nucleophilic carbenes such as isocyanides and dimethoxycarbene typically interact with third components in MCRs to afford a variety of products. The tendency of the divalent carbene carbon to attain tetravalency is the driving force behind these reactions. The interception of isocyanide-DMAD dipole **11** with aldehydes, N-tosylimines and electron deficient alkenes afforded 2-aminofurans, 2-aminopyrroles and aminocyclopentadienes respectively (Scheme 8).[14]



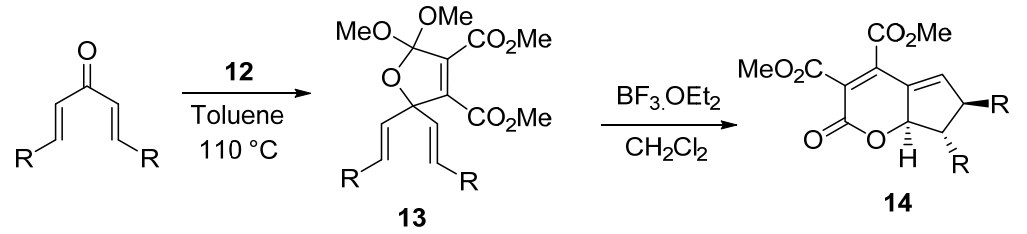
Scheme 8: MCRs of isocyanide-DMAD dipole

The isocyanide-DMAD dipole is very versatile and reacts efficiently with a number of other interceptors too. Similar reactivity is also exhibited by dimethoxycarbene-DMAD dipole **12** that is normally generated via the Warkentin protocol[15] as shown in Scheme 9.[16]



Scheme 9: Generation and reaction of dimethoxycarbene with DMAD

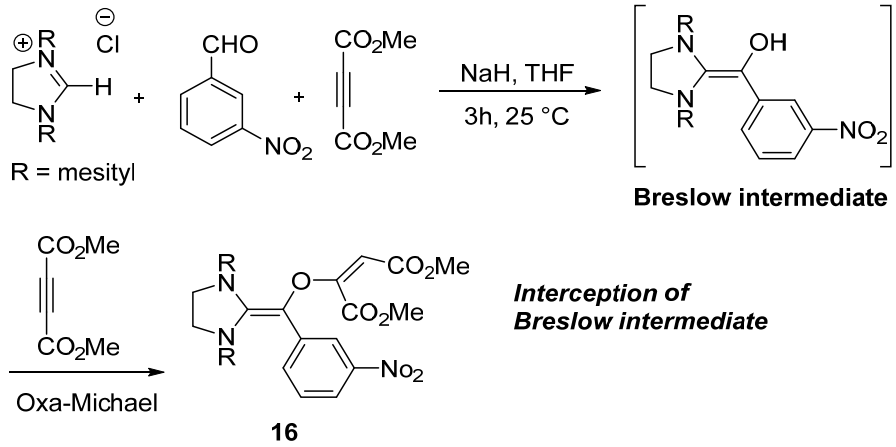
The products of such MCRs are rich in functionality and can undergo intriguing further transformations. For example, the adduct **13** formed from **12** and dienones underwent a completely stereoselective interrupted-Nazarov rearrangement to form bicyclic lactones **14** (Scheme 10).[17]



Scheme 10: Interception of dipole **13** with dienones and interrupted Nazarov rearrangement

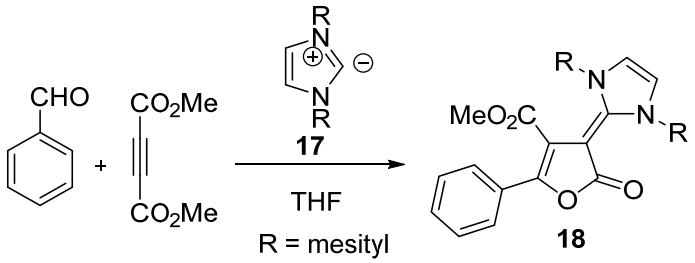
3. N-heterocyclic carbene (NHC) as initiator

The utility of NHCs as organocatalysts has been well-established.[18] In addition to this, NHCs may also take part in MCRs as nucleophilic carbenes analogous to isocyanides and dimethoxycarbene. This aspect of NHC chemistry was investigated by our group and it led to some interesting observations. For example, the reaction of 1,3-dimesityl imidazolin-2-ylidene **15,** DMAD and aromatic aldehydes furnished 2-oxy maleate derivative **16** as the only product (Scheme 11). This reaction is important for two reasons. It constitutes the first ever MCR of an NHC. More importantly, this constitutes the first indirect experimental proof for the formation of Breslow intermediates from NHC and aldehyde. The oxy-maleate **16** is formed via the hetero-Michael addition of enol oxygen of the Breslow intermediate to DMAD. It may be noted here that the structure of **16** was confirmed by single crystal X-ray analysis.[19]



Scheme 11: Interception of Breslow intermedite in a MCR

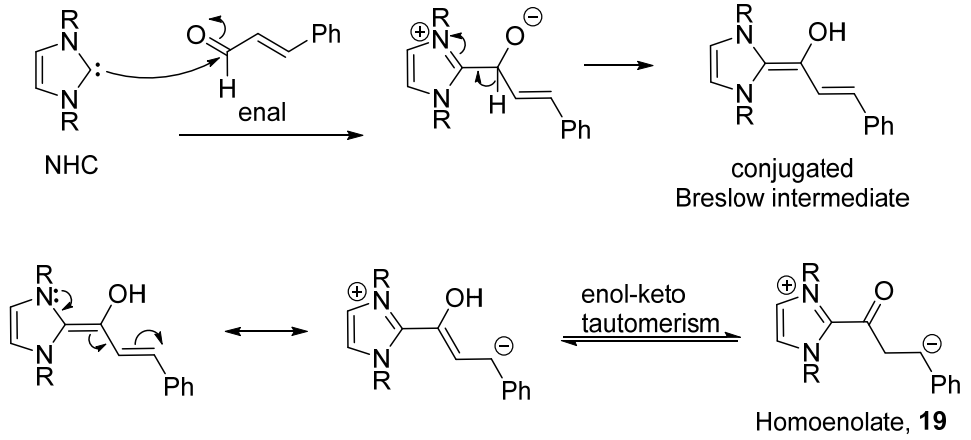
A less nucleophilic NHC, 1,3-dimesityl imidazol-2-ylidene **17**, however, reacted differently with aldehydes and DMAD to afford unsaturated iminolactones **18** as products (Scheme 12).[19]



Scheme 12: MCR of NHC **17**, DMAD and aldehydes

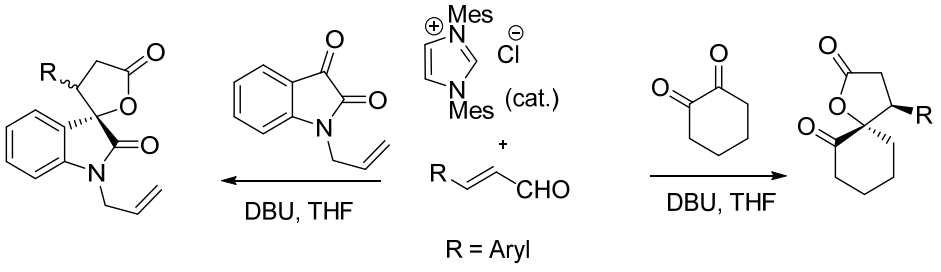
4. NHCs as catalysts

In addition to the utility of NHCs as one carbon synthons, we have also developed novel reactions that are promoted by NHCs.[20] The latter is perhaps the most widely used class of promoters in *modern organocatalysis*. It is important to recall that the remarkable progress in this area is made possible by the pioneering work of Breslow who provided the mechanistic rationalization of interaction of NHC with aldehydes.[21] The *Breslow intermediate* formed from aldehyde and NHC (see Scheme 11) functions as an acyl anion equivalent (e g. benzoin reaction). Analogous reactive intermediate generated via the action of NHC on α,β-unsaturated aldehyde behaves as a *homoenolate* **19** (Scheme 13). This type of reactivity was first demonstrated independently by Glorius and Bode in 2004 in their reports of γ-lactonisation of enals and aldehydes.[22]



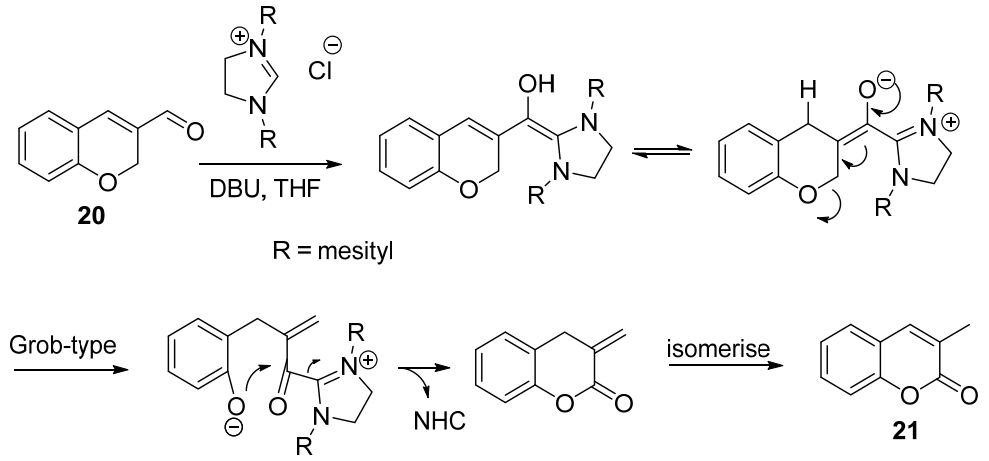
Scheme 13: Homoenolate formation from NHC and α,β-unsaturated aldehyde

We investigated the interactions of NHC-homoenolates with various 1,2-diones and a number of interesting and useful transformations were developed. A few selected examples are presented in Scheme 14.[23]



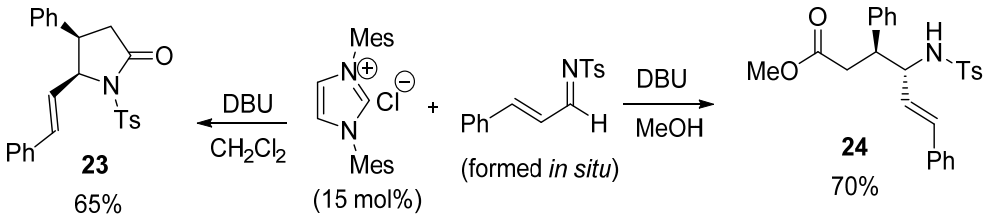
Scheme 14: Spiroannulations of NHC-homoenolates and cyclic 1,2-diones

Homoenolate derived from 2*H*-chromene-3-carboxaldehyde **20** underwent a rearrangement to furnish 3-methylcoumarin **21** (Scheme 15). The reaction proceeds via a sequential Grob-fragmentation and lactonisation as depicted in Scheme 15.[24]



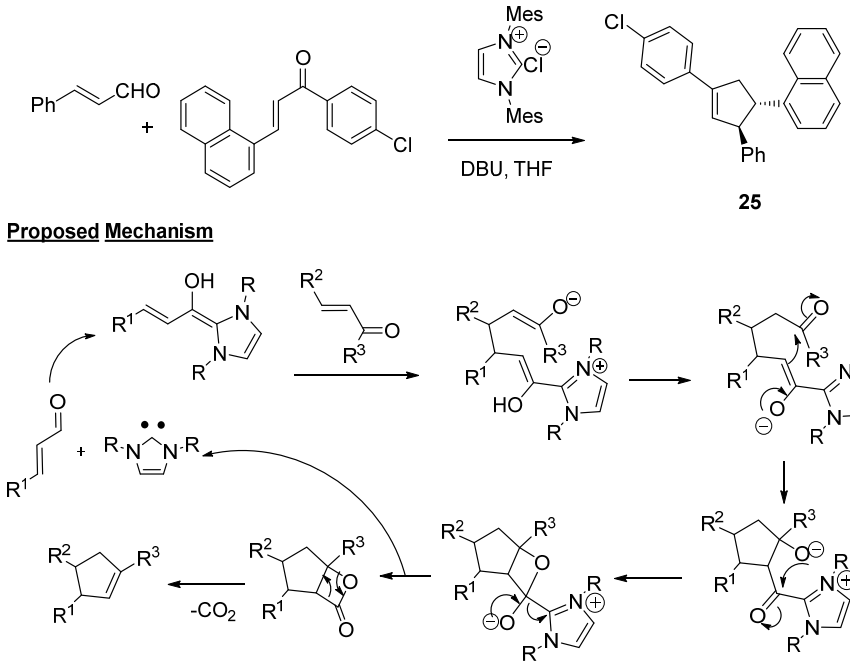
Scheme 15: NHC-promoted rearrangement of 2*H*-chromene-3-carboxaldehyde

NHC-homoenolates can react with activated imine electrophiles such as the sulfonylimine **22** to afford γ-aminobutyric acid (GABA) derivatives **23** or *cis*-γ-lactam derivative **24**. Either of the pathways of this divergent reaction may be selected by the choice of solvent alone. GABA derivative **23** is selectively formed in CH_2Cl_2 whereas reaction run in methanol affords the lactam **24** (Scheme 16).[25]



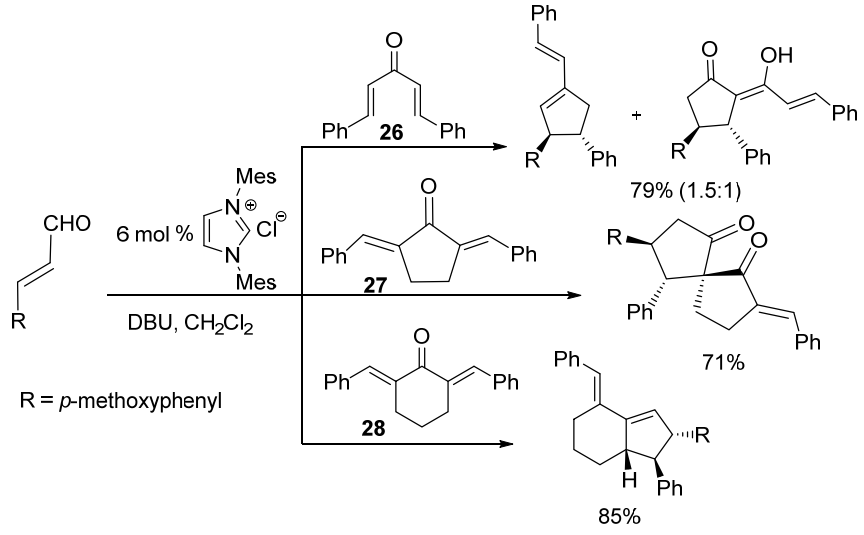
Scheme 16: Divergent pathways in homoenolate-sulfonylimine reaction

Our group reported in 2006 that the homoenolate species can interact with chalcones in a Michael-initiated cyclisation reaction to afford cyclopentene derivatives **25** in excellent distereoselectivity (Scheme 17). This was an important milestone in the development of NHC-homoenolate chemistry as the Michael type reactivity was demonstrated for the first time. The involvement of a β-lactone intermediate was unambiguously established by IR spectroscopic monitoring of the reaction.[26]



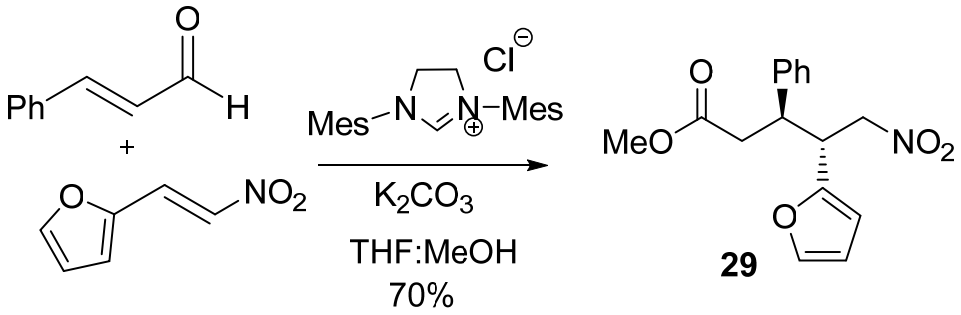
Scheme 17: NHC-homoenolates in cyclopentene synthesis

The above reaction is highly sensitive to the nature of enone. We found that dienones of three different structural types (**26-28**) afforded different products under identical reaction conditions (Scheme 18).[27]



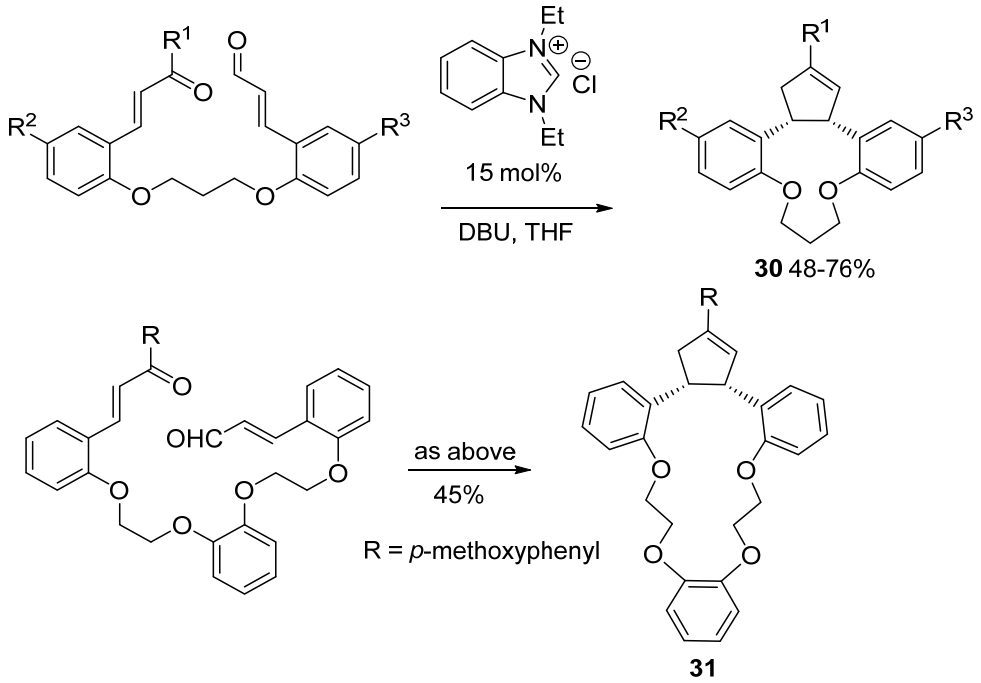
Scheme 18: Pathways of reactions of NHC-homoenolates with various dienones

Concise, diastereoselective assembly of multifunctional compounds such as **29** can be achieved via the Michael addition reaction of homoenolates and nitrostyrenes (Scheme 19).[28]



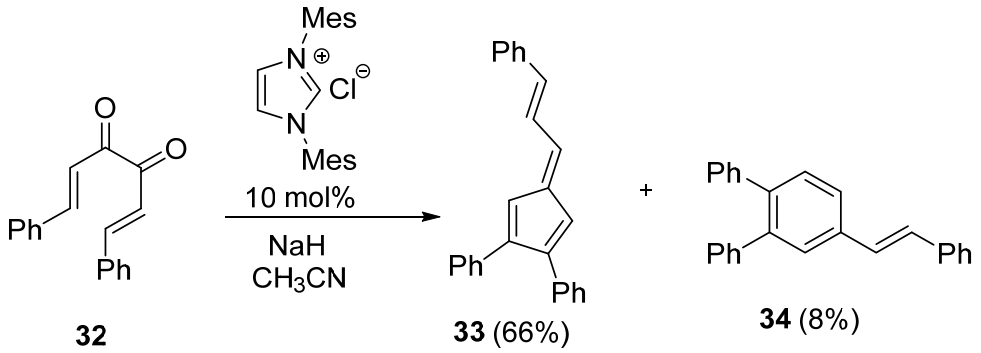
Scheme 19: Diastereoselective Michael addition reaction of homoenolates and nitrostyrenes

Homoenolate-chalcone cyclisation can be employed to construct macrocyclic derivatives as exemplified by formation of the cyclic ethers **30** and **31**. The latter resembles crown ethers and may be termed as a *semicrown* (Scheme 20).[29]



Scheme 20: Construction of macrocyclic ethers via homoenolates

Exposure to NHCs can trigger skeletal rearrangement reactions in multifunctional compounds such as cinnamil **32**. This rearrangement afforded a mixture of 2,3,7-triaryl vinylfulvenes **33** and minor amounts of *o*-terphenyl derivatives **34** (Scheme 21).[30]



Scheme 21: NHC-catalyzed rearrangement of cinnamil

In addition to the above selected examples, a number of other intriguing NHC-catalyzed transformations were also developed in our laboratory.[31]

2. Conclusion

In summary, a variety of non-trivial product classes can be accessed from simple starting materials by exploiting the unique reactivity of dipoar species. The intermediacy of dipoles allows the facile union of reaction partners that would be otherwise inert towards each other. These reactions, generally proceed under mild conditions, afford good to excellent yields of products and display good stereoselectivity levels. On a number of occassions, novel mechanistic pathways were observed which have opened up avenues for further investigations.

3. References

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