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Engaging Zwitterions in Carbon−Carbon and Carbon−Nitrogen Bond-Forming Reactions: A Promising Synthetic Strategy

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ABSTRACT

An Account of carbon−carbon and carbon−nitrogen bond-forming reactions mediated by zwitterions generated by the addition of organic nucleophiles to activated unsaturated systems highlighting their synthetic potential is presented.

Introduction

Carbon−carbon and carbon−heteroatom bond-forming reactions are central to organic synthesis. Despite the enormous progress made during the last few decades in the application of polar, pericyclic, and radical reactions in such bond construction, there is the perennial quest to discover newer and simpler reactions in this area. Polar reactions customarily utilize a variety of reactive intermediates in carbon−carbon and carbon−heteroatom bond-forming reactions. In this context, it was observed that a class of potentially useful dipolar species, viz., zwitterions resulting from the addition of nucleophiles to activated π systems, although known for a long time, have not been recognized adequately by researchers. The present Account is aimed at creating awareness among chemists in general and organic chemists in particular on the usefulness of zwitterions in synthesis. {The term "zwitterions" is used in this Account only to describe the transient intermediates formed from the addition of neutral nucleophiles (e.g., pyridine) to electrophilic receptors [e.g., dimethyl acetylenedicarboxylate (DMAD)]. By convention, such species are also denoted by common terms such as "dipoles" and "ylides". However, a more general "zwitterion" is preferred to distinguish them from classical 1,3-dipoles, such as nitrones, azides, etc., and do away with the structural limitations imposed by the definition of the term "ylide".} To a large extent, the Account will be focused on the novel zwitterion-mediated reactions uncovered in the author's laboratory recently. An adequate description of related work done by other investigators is also included for the sake of coherence and to place our work in proper perspective.

From a historical viewpoint, the report by Diels and Alder in 1932 that pyridine reacts with DMAD **2** to afford a 1:2 adduct constitutes an early instance of the involvement of zwitterions in organic synthesis.[1] The structure of this adduct was established as **5** by the detailed investigations of Acheson[2] almost 3 decades later. Shortly thereafter, consequent to his postulation of the concept of dipolar cycloadditions,[3] Huisgen recognized this reaction as the 1,4-dipolar variant of the classical Diels−Alder reaction involving the intermediate **3** (Scheme 1). More insight into the mechanistic underpinnings of 1,4-dipolar cycloaddition reactions was also provided by Huisgen.[4] Independent investigations by Acheson[5] and Winterfeldt[6] in closely related areas provided further examples of similar reactions. The synthetic potential of the methodology, however, remained untapped until recently.

The general strategy of generating zwitterionic species by the addition of aprotic organic bases to electrophilic π systems and employing them for further transformations has been exploited by chemists since then, often without deliberate design. A number of reactions, such as 1,4-dipolar cycloadditions, a few 1,3 variants, Morita−Baylis−Hillman (MBH) reaction,[7] transformations mediated by *N*-heterocyclic carbenes (NHCs)[8] and many other reactions,[9] employ this strategy as their working principle. Despite the apparent potential of the above-mentioned and related transformations, there has been no attempt to rationally categorize these reactions and explore new possibilities.

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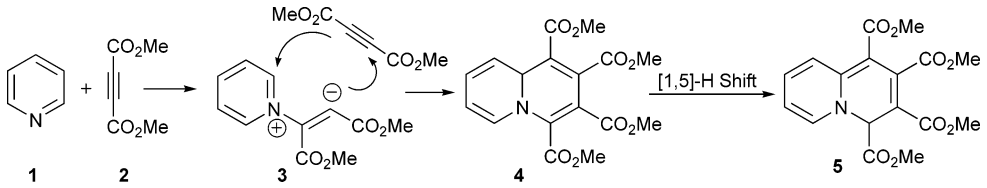
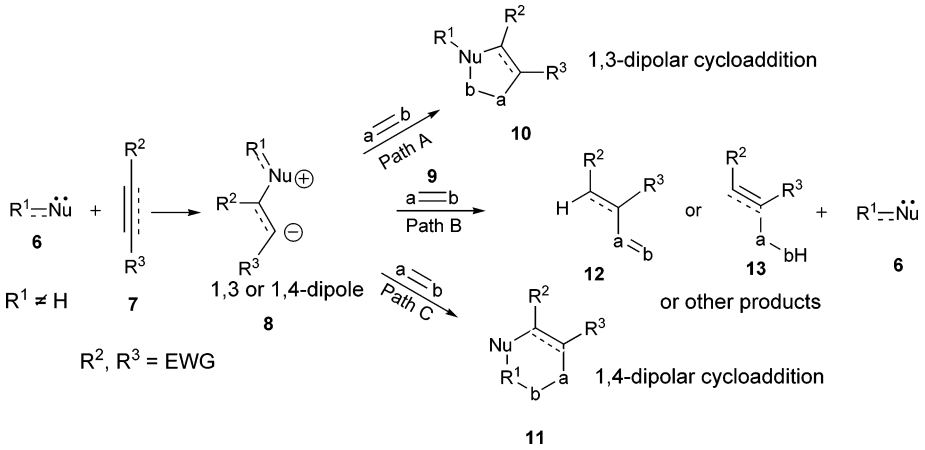
Scheme 1. Reaction of Pyridine and DMAD



Scheme 2. Schematic Representation of Zwitterion Chemistry



A generalized and thematic representation of the rationale of such reactions can be given as shown in Scheme 2.

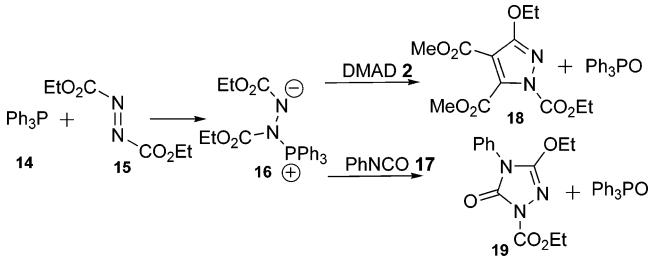
Pivotal to the events in this class of reactions is the generation of dipolar/zwitterionic intermediate **8** by the addition of aprotic nucleophiles **6** to activated π systems, such as alkenes, their diaza analogues, and alkynes, collectively represented as **7**. The zwitterion can have a 1,3 or 1,4 disposition depending upon the nature of the nucleophile. Subsequent interception of the zwitterion **8** with **9**, which stands for a large variety of compounds, can take different routes. Overall, three-component dipolar cycloadditions result when the nucleophile is retained in the product as in path A and C, whereas the nucleophile plays a catalytic role en route to **12**, **13**, or other products (path B). The nature of the product formed in path B, largely depends upon the nucleophile **6** and substituents R^2 and R^3 on the receptor **7**. Reactions that are governed by the events in path B, which lie scattered in the literature, form the subject matter of this Account. It is evident from the above scheme that path B surpasses both the other options possible for **8** in terms of variety and in principle falls under the realm of organocatalysis.

An important transformation that fits well into the category designated as path B is the MBH reaction (cf. Scheme 29). The MBH reaction and its variants have received a lot of attention recently, and a number of reviews have addressed various aspects of this reaction.[7e−g] In view of these reviews, a detailed discussion on the MBH reaction is not attempted in this Account.

Nucleophilic Catalysis

The following sections comprise similar reactions initiated by different nucleophiles viz., phosphines, pyridine, and tertiary amines. Other nucleophiles such as isocyanides and nucleophilic carbenes are excluded from this Account, because these generally lead to multicomponent reactions incorporating the nucleophile. Selected examples from the literature that have either significantly contributed to the present understanding of the mechanistic events or demonstrated the synthetic potential of the strategy are included.

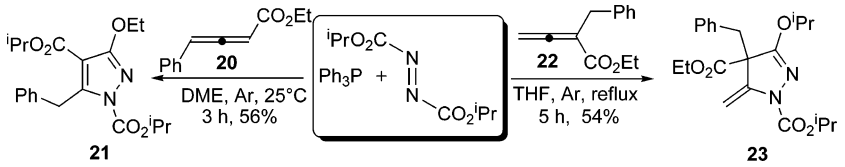
Scheme 3. Interception of Triphenylphosphine−DEAD Zwitterion



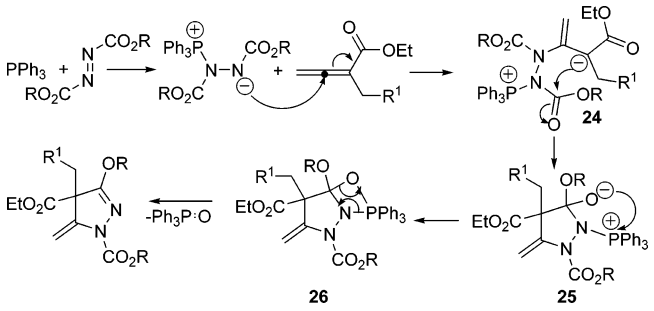
Phosphines. The phenomenal success of trialkyl/triaryl phosphines in organocatalysis[10] can be attributed primarily to their pronounced nucleophilicity and the exceptional stability that a phosphonium ion lends to a neighboring anionic center. Zwitterionic species and phosphonium ylides are thus common intermediates in reactions mediated by phosphines. Huisgen recognized the involvement of zwitterionic intermediate **16** in reactions of triphenylphosphine **14** and diethyl azodicarboxylate (DEAD) **15** and explained the formation of cycloaddition products, such as **18** and **19**, in its reaction with DMAD and phenyl isocyanate (Scheme 3).[11] Later, the zwitterion **16** was recognized as the key intermediate in the famous Mitsunobu reaction,[9a] which is the best known method for effecting a clean stereochemical inversion of chiral alcohols.

Recent work from our laboratory disclosed an interesting reactivity pattern exhibited by zwitterion **16** in its

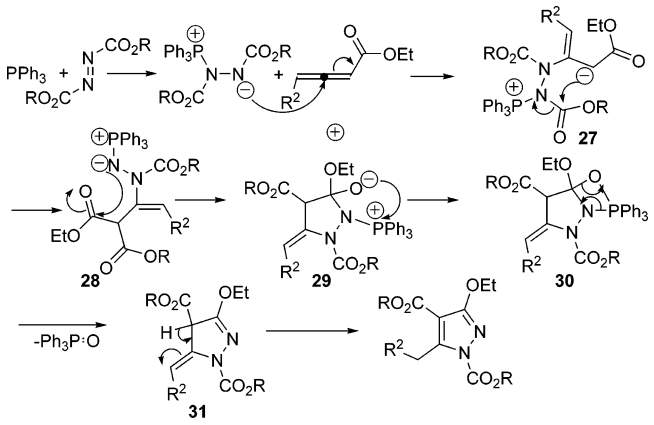
Scheme 4. Reaction of Phosphine−DIAD Zwitterion with Allene Esters



Scheme 5. Mechanism of the Formation of Functionalized Pyrazolines



Scheme 6. Mechanism of the Formation of Fully Substituted Pyrazoles



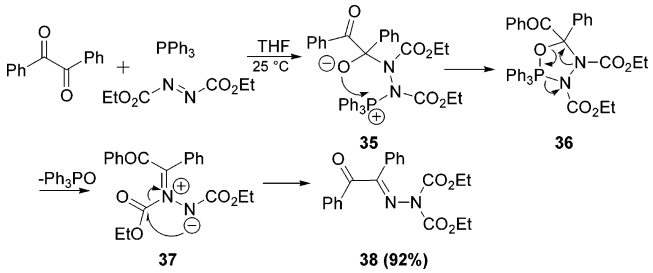
reactions with electron-deficient allenes.[12] The reactions culminated in a facile synthesis of highly functionalized pyrazolines and fully substituted pyrazole derivatives (Scheme 4).[13] It is noteworthy here that electrophilic allenes, such as **20**, are also known to generate zwitterions when exposed to phosphines (vide infra).[10a] These results, however, demonstrate the clear preference of triphenylphosphine for dialkyl azodicarboxylates over such allenes.

The following mechanistic postulate may be invoked to rationalize the formation of highly functionalized pyrazolines (Scheme 5).

Formation of fully substituted pyrazole took place via a novel rearrangement involving the nitrogen−carbon migration of the carboalkoxy group. The following rationalization may be advanced to explain the product formation (Scheme 6).

Recently, Lee reported the reactions of the zwitterion **16** with carbonyl compounds, such as aldehydes, ketones, and α-ketoesters, to afford various products (Scheme 7).[14a] Interestingly, independent investigations in our laboratory showed that the reaction of **16** with diaryl-1,2-diones proceeded with a rearrangement to afford dicarboethoxy monohydrazones of the respective diones (Scheme 8).[14b] This novel rearrangement involves a unique nitrogen−nitrogen migration of a carboethoxy group.

Scheme 8. Reaction of Phosphine and DEAD with Benzil: Our Results

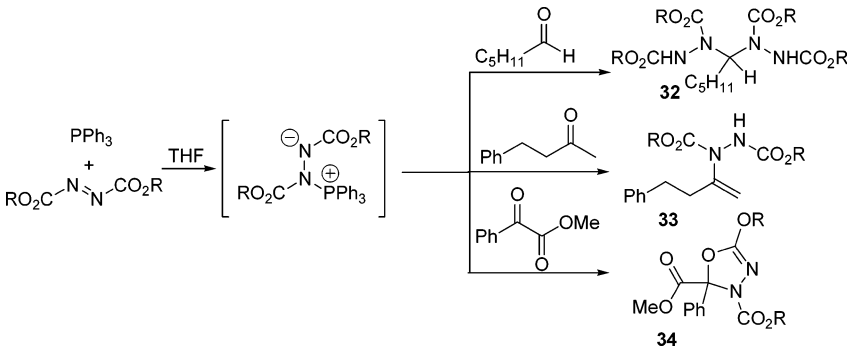


An in-depth study of the reactivity of the zwitterion **16** toward various dicarbonyl compounds revealed fascinating reactivity patterns. With *o*-benzoquinones, it afforded dihydro-1,2,3-benzoxadiazole derivatives, whereas isatins reacted with **16** to produce spirooxadiazoline derivatives (Scheme 9).[15]

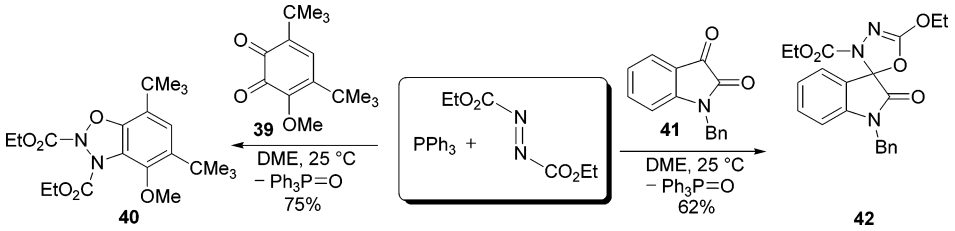
A mechanistic rationalization for the formation of dihydro-1,2,3-benzoxadiazoles from quinones is provided in Scheme 10.

Johnson and Tebby[16] established the intermediacy of a similar zwitterion **49** in the reaction of triphenylphosphine **14** with DMAD **2**, and this was to form the basis of a wide variety of transformations later. This zwitterionic

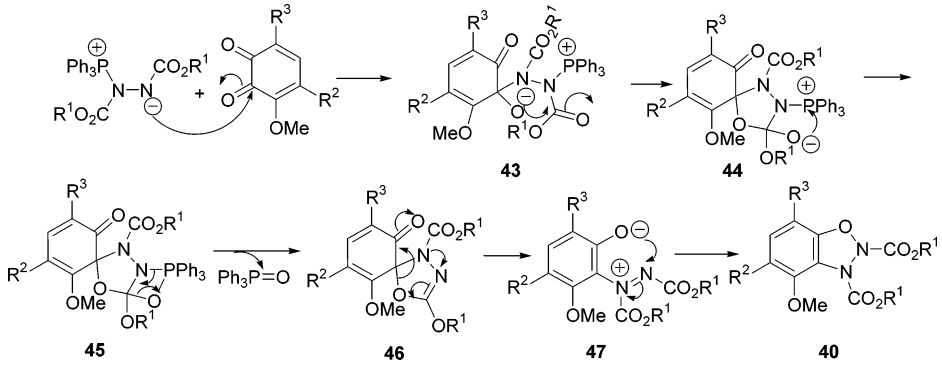
Scheme 7. Reaction of Phosphine and Azodicarboxylates with Carbonyl Compounds: Lee's Study



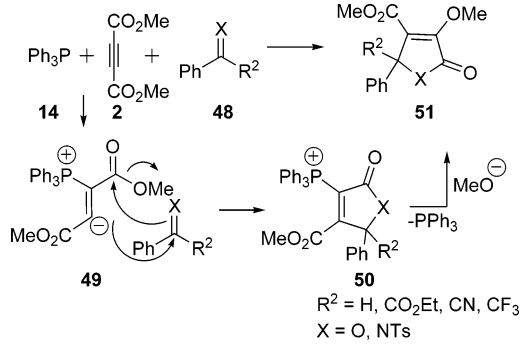
Scheme 9. Reaction of Phosphine−DEAD Zwitterion with Quinones and Isatins



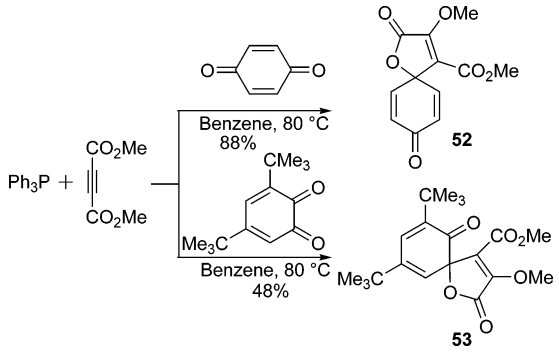
Scheme 10. Mechanism of the Formation of Dihydro-1,2,3-benzoxadiazole Derivatives from *o*-Quinones and DEAD under Phosphine Catalysis



Scheme 11. Reaction of Phosphine−DMAD Zwitterion with Carbonyl Compounds



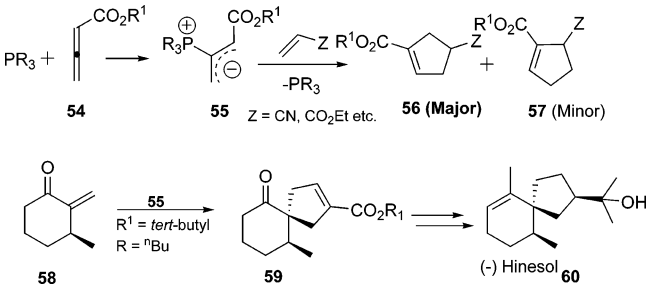
Scheme 12. Interception of Phosphine−DMAD Zwitterion with *o*- and *p*-Quinone



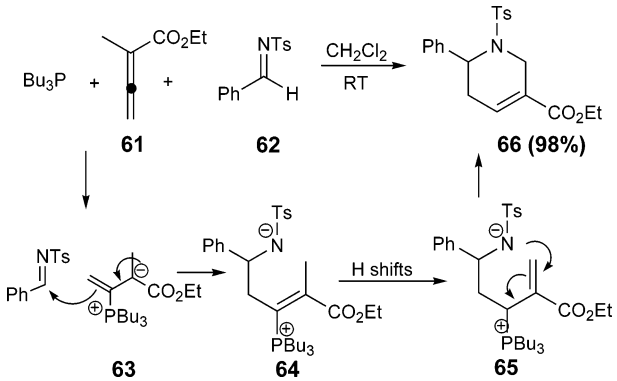
species was shown to undergo annulation reactions with electrophiles, such as aldehydes,[17a] α-ketonitriles,[17b] α-ketoesters,[17b] and *N*-tosylimines,[17c] to provide highly substituted unsaturated γ-lactones and lactams (Scheme 11). The annulation is reminiscent of the analogous reactions of the zwitterion **16** given in Scheme 3.

Novel spirocyclic lactones **52** and **53** were synthesized in our laboratory by the phosphine-mediated reaction of DMAD with *o*- and *p*-quinones (Scheme 12).[18] The zwitterion, not surprisingly, exhibits a complete preference for the quinone carbonyl group, leaving the enone double bonds intact.

Scheme 13. Reactions of Phosphine−Allenic Ester Zwitterion

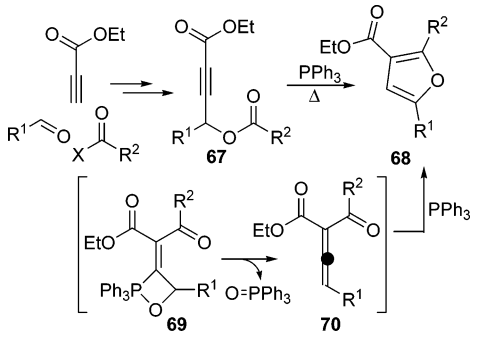


Scheme 14. Phosphine-Catalyzed Tetrahydropyridine Synthesis

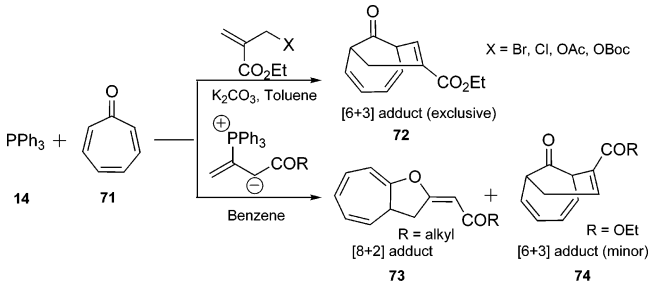


Electron-deficient allenic esters also show a proclivity to add phosphines, and the resulting species behaves like a "true 1,3-dipole" of structure **55**, thus constituting the overall umpolung addition of a variety of protic nucleophiles to such allenes and acetylenes under phosphine catalysis (Scheme 13).[19] Dipolarophiles, such as DMAD, fumarates, and *N*-tosylimines,[17c] underwent facile [2+3] cycloaddition reactions with this zwitterion.[20] The reac-

Scheme 15. Krische's Furan Synthesis



Scheme 16. Phosphine-Mediated Reaction of Tropone with Allylic Compounds or Allenes



tions exhibit high regioselectivity, especially in those cases where there are sterically demanding substituents on either of the reactants. Very high enantioselectivity was observed with chiral phosphines.[21] The strategy was successfully employed in the first synthesis of (−)-hinesol **60**, which is used for enhancing cerebral blood circulation and metabolism.[22]

Subtle structural changes in the receptor allenic ester can alter the reactivity completely. For example, in a recent synthesis of highly functionalized tetrahydropyridines by phosphine-mediated [4+2] annulation, which can be viewed as equivalent to a formal hetero Diels−Alder reaction, the initial intermediate **63** manifests 1,4-dipolar character (Scheme 14).[23] Substitution of the hydrogen at the 2 position of the allenic ester with an alkyl group effectively blocks the α attack, which is known to lead to the usual [3+2] cyclization. The phosphine-mediated [4+2] annulation has been employed in the racemic total synthesis of indole alkaloids, such as alstonerine and macroline.[24]

Krische reported yet another remarkable phosphine-mediated heterocyclic construction in the reductive condensation of γ-acyloxy butynoates to deliver substituted furans (Scheme 15).[25] Because the starting butynoates are easily obtained by the addition of ethyl propiolate to aldehydes followed by acylation, this method represents a powerful diversity-oriented protocol for the convergent synthesis of furans.

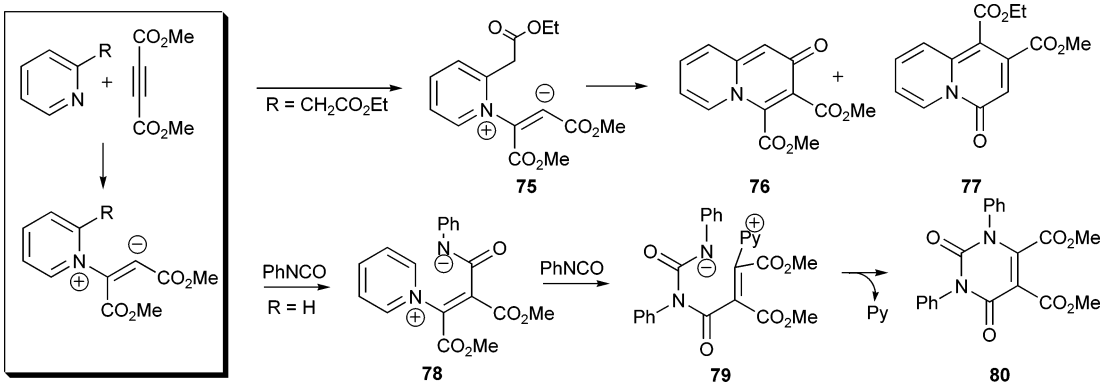
A phosphine-mediated [6+3] annulation reaction of modified allylic compounds, including derivatives of MBH adducts, with tropone was reported recently by Du et al.[26a] The exclusive formation of the [6+3] adduct and easy availability of the C-3 component make the process especially attractive. It is, however, noteworthy that an earlier report describes the phosphine-mediated reaction of tropone with allenic ester/ketones to afford [8+2] cycloadducts as the major products, whereas the corresponding [6+3] cycloadducts are formed in trace amounts only.[26b] Scheme 16 summarizes both of these transformations.

Pyridine. A large variety of nitrogen heterocycles are known to form zwitterionic species by the addition to activated olefins and acetylenes. Of these, pyridine deserves special attention owing to the variety of transformations that it mediates. Following Diels and Alder's observation[1,2] of the reaction of pyridine with DMAD (Scheme 1), Winterfeldt has shown that intramolecular cyclization of the initially formed 1,4-dipole to a carbonyl group can be achieved in the case of ethylpyridylacetate to give *2H*-quinolizone as the major product in polar solvents; the *4H*-quinolizone predominates in nonpolar solvents.[6] Later, Huisgen was successful in intercepting the 1,4-dipole **3** with phenyl isocyanate, leading to a pyrimidindione derivative, with eventual elimination of pyridine in the course of the reaction (Scheme 17).[4]

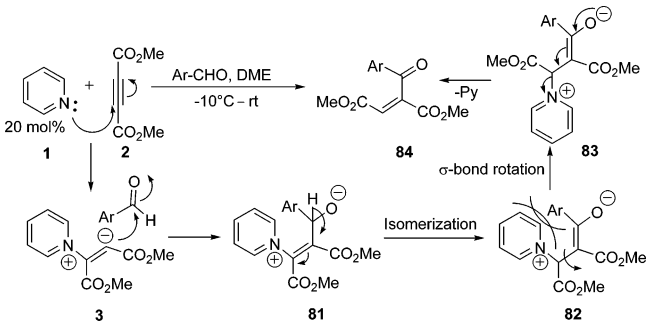
Apart from these early studies, no effort to harvest the synthetic potential of the zwitterionic intermediates was made until recent investigations in our laboratory revealed novel reactivity profiles of the zwitterions of the type **3**. The efficient interception of **3** by aldehydes resulted in the stereoselective formation of benzoyl fumarates (Scheme 18).[27a,b]

Interception of the zwitterion **3** with *N*-tosylimines and activated olefins provided easy access to 1-azadienes[27c]

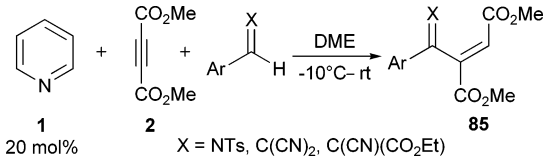
Scheme 17. Reactions of Pyridine−DMAD Zwitterion



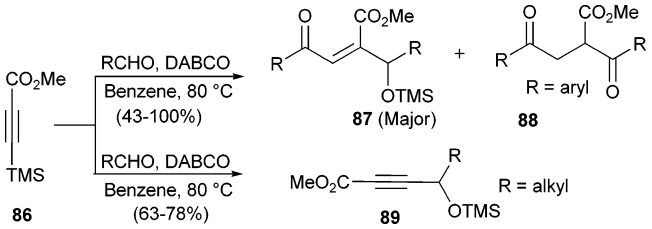
Scheme 18. Interception of Pyridine−DMAD Zwitterion with Aldehydes



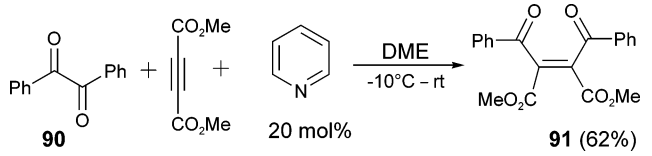
Scheme 19. Reactions of Pyridine−DMAD Zwitterion



Scheme 20. MBH-Type Reaction of Propiolates



Scheme 21. Pyridine-Catalyzed Stereoselective Synthesis of Dibenzoyl Maleates



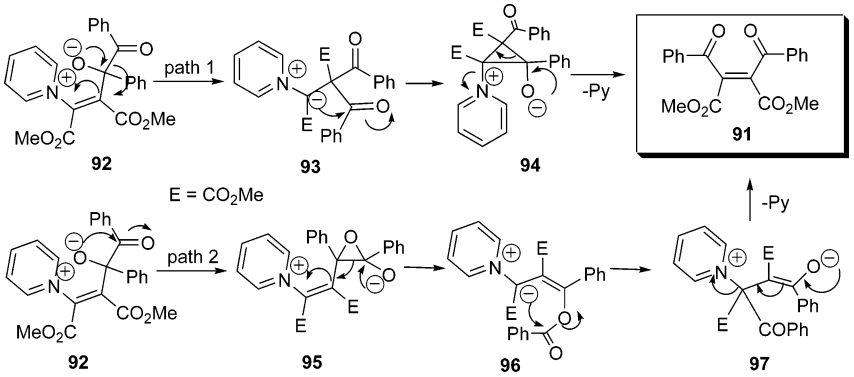
and highly substituted butadienes,[27d] respectively, under very mild conditions (Scheme 19). It is noteworthy that these reactions require only catalytic amounts of pyridine (20 mol %) and proceed with complete stereoselectivity, affording only the trans products.

A few interesting observations can be made by comparing the above-mentioned transformation with MBH reaction. Mechanistically, both reactions are initiated by the generation and subsequent addition of a zwitterionic species to the aldehyde. The tetrahedral intermediate undergoes protonation−elimination sequence in the MBH reaction, while in the present pyridine-mediated reaction, an isomerization resulting in a formal 1,3-H shift is operative. The nucleophilic catalyst is regenerated in both of the sequences. An additional feature of the present reaction is the completely stereoselective formation of the olefinic bond as a result of the steric demands inherent in the intermediate leading to the final product.[27c,d] It is noteworthy that a recent report on the mechanistic aspects of the MBH reaction suggests the involvement of a key intermediate incorporating two molecules of the aldehyde.[7d] In this context, an MBH-type reaction of alkynes reported by Matsuya et al. deserves special mention.[28] They observed that diazabicyclo[2.2.2]octane (DABCO) catalyzes the reaction of β-silylated propiolates and aromatic aldehydes, affording two products. Aliphatic aldehydes, however, afforded an alkyne product (Scheme 20).

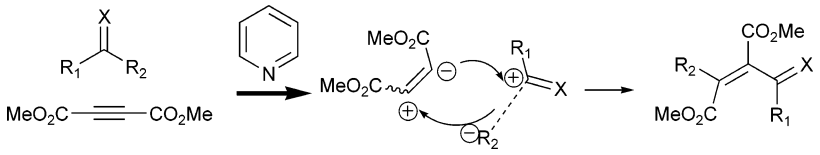
We speculated that the zwitterion **3** was likely to add to 1,2-dicarbonyl compounds, such as benzil, and that the tetrahedral intermediate stood a good chance of undergoing cleavage of the relatively weak 1,2 C−C bond (BE ≈ 70 kcal) and concomitant acyl migration to produce a new zwitterion, which would stabilize (neutralize) itself by the ejection of pyridine. While ordinary ketones were found to be inert toward the zwitterion **3**, 1,2-diones, such as benzil, underwent an unprecedented transformation (Scheme 21).[29] Probable mechanistic pathways for the formal insertion of DMAD to benzil are depicted in Scheme 22. The initially formed pyridine−DMAD zwitterion **3** adds to benzil furnishing the alkoxide intermediate **92**. In path 1, a 1,2 migration of the benzoyl group with its pair of electrons to afford the pyridinium ylide **93** and subsequent generation of a cyclopropane intermediate **94** is conceived. Elimination of pyridine from **94** furnishes the product. Alternatively, as shown in path 2, alkoxide **92** can transform to an epoxyderivative **95**, which then collapses to the pyridinium ylide **96**. An intramolecular benzoyl transfer followed by elimination of pyridine affords the final product **91** via **97**.[29]

Although superficially this reaction is reminiscent of the Liebig benzilic acid rearrangement,[30] it is important to recognize that mechanistically it is quite distinct from

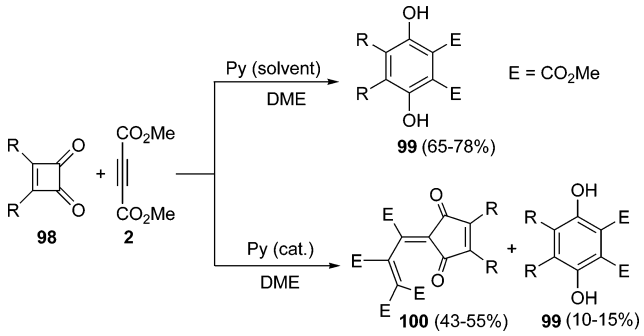
Scheme 22. Mechanistic Proposals for the Formation of 91



Scheme 23. Outline of Pyridine-Mediated Transformations



Scheme 24. Pyridine-Mediated Synthesis of Hexasubstituted Benzenes



the latter. In the transformation presented in Scheme 22, the system is predisposed against undergoing a benzilic acid rearrangement because that would produce an energetically untenable species, with the carbonyl group conjugated to a highly electrophilic pyridinium fumarate system. For the record, acyl transfer in benzilic acid rearrangement occurs *only* in reactions involving 1,2,3-tricarbonyl compounds that have no other options available.[31]

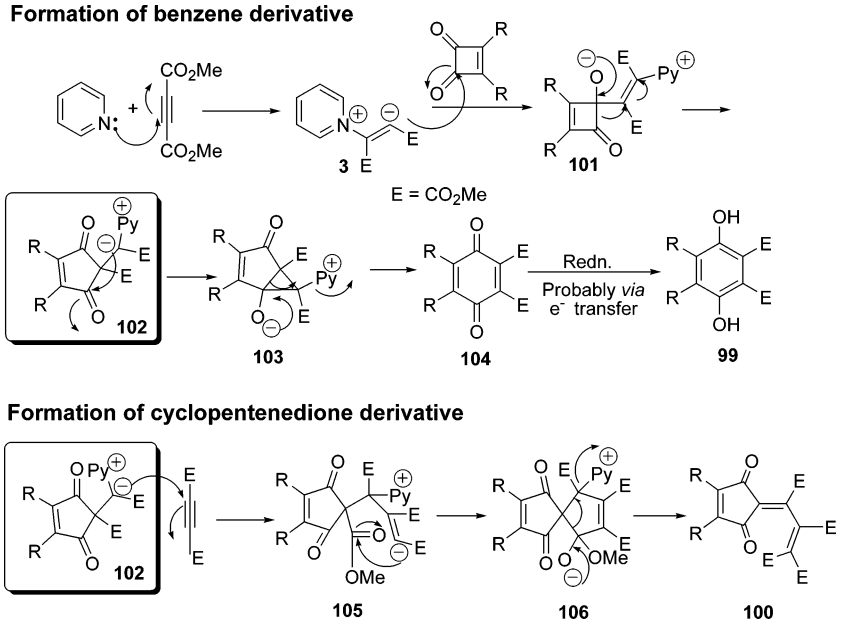
The above-described novel pyridine-mediated reactions discovered in our laboratory share some interesting common features. Two electrophiles that are otherwise inert tend to undergo a reactivity umpolung in the presence of a catalytic amount of pyridine as generalized in Scheme 23. The ease with which this surprising "summersault" of reactivity is achieved and the variations possible in the second electrophile, especially with regard to cyclic systems, should make this strategy very attractive from synthetic as well as mechanistic vantage points.

Subsequent investigations in our laboratory have revealed a very interesting reactivity of the pyridine−DMAD zwitterion toward cyclobutene-1,2-diones (Scheme 24). When diaryl cyclobutene-1,2-diones **98** were treated with DMAD in pyridine, hexasubstituted benzene derivatives **99** were obtained.[32] The reaction, however, took a different course when pyridine was employed in catalytic amounts. When the reaction was run in the presence of 20 mol % of pyridine, highly substituted cyclopentenedione derivatives **100** were formed as the major products, whereas the benzene derivatives were formed only in minor amounts.

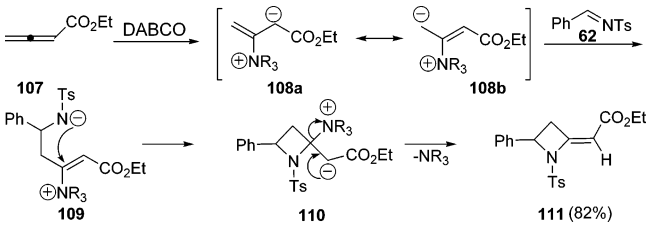
Mechanistic proposals outlining the formation of the two products are depicted in Scheme 25. Because the cyclopentenedione derivative incorporates an additional mole of DMAD, it is reasonable to assume that the availability of DMAD in the system may be the deciding factor for this reaction. When pyridine is used in large excess (as a solvent), the equilibrium for the formation of zwitterion **3** is shifted in favor of **3**, thereby reducing the concentration of "free" DMAD in the system. This eventually results in the ring enlargement to produce the benzene derivative. With only a catalytic amount of pyridine present, the concentration of the zwitterion **3** is minimal and free DMAD is available in the system to react with the intermediate **102**.[32]

Tertiary Amines. Although not quite as productive as phosphine catalysis, amines also initiate various transformations by generating zwitterionic intermediates from

Scheme 25. Mechanistic Proposals for the Pyridine-Mediated Reactions of DMAD with Cyclic Diones



Scheme 26. Interception of DABCO−Allene Ester Zwitterion with *N*-Tosylimine



activated olefins and acetylenes. From a historical perspective, one of the earliest examples pertinent to the present discussion involves the formation of a 1:1 adduct in the reaction of *N*,*N*-dimethylaniline and ethyl azodicarboxylate reported in 1922 by Diels.[33] Nitrogen heterocycles, such as DABCO, dimethyl aminopyridine (DMAP), diazabicyclo[5.4.0]undecane (DBU), etc., are known to form zwitterions with allene esters. Shi et al. reported that, when DABCO is used as the catalyst, *N*-tosylimines can undergo formal [2+2] cycloaddition with 2,3-butadienoates to afford azetidine derivatives (Scheme 26).[34a]

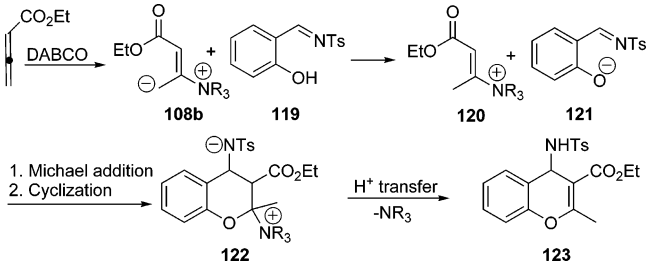
When DMAP is used as the catalyst, dihydropyridine derivative **118** is formed (Scheme 27). It is noteworthy that both the products **111** and **118** were obtained when the aza-Baylis−Hillman reaction was attempted on *N*-tosylimines.[34b]

Very recently, Shi et al. reported that the DABCO-catalyzed reaction of salicyl *N*-tosylimine **119** with ethyl-2,3-butadienoate at room temperature afforded the chromene derivative **123** in excellent yield.[35] The zwitterion **108b** deprotonates the imine **119** to afford **120** and **121**. Subsequent Michael addition and cyclization followed by proton transfer affords chromene **123** with the regeneration of the catalyst (Scheme 28).

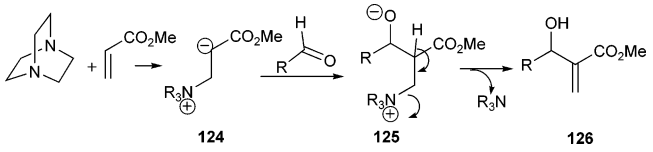
Subsequently, the same group has reported the DBU-catalyzed reaction of salicylaldehyde with 2,2-disubstituted allene esters to furnish the benzopyran derivatives.[36]

The most widely acclaimed of the amine-catalyzed reactions is undoubtedly the MBH reaction,[7] for which DABCO is the catalyst of choice. The reaction sequence involves the generation of a zwitterionic species from the amine and the activated olefin and subsequent addition of the enolate to a second electrophile, often an aldehyde.[7d] Elimination of the amine furnishes the allyl alcohol as the final product (Scheme 29). Despite its sluggish nature and structural limitations associated with the olefinic partner, the reaction enjoys immense popularity primarily because of the versatile nature of the products and the consequent scope for numerous further transformations that they can undergo.[7e−g] As stated earlier, a detailed discussion on the MBH reaction is not attempted here, because the purpose has been served adequately by a number of recent reviews on this topic.[7e−g]

Scheme 28. DABCO-Catalyzed Synthesis of Chromenes



Scheme 29. MBH Reaction

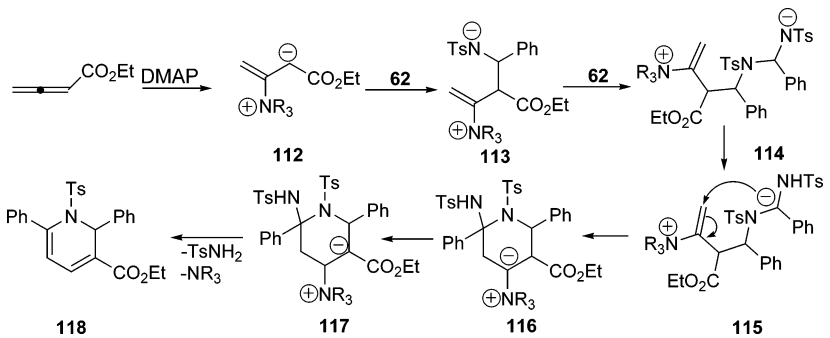


Other Nucleophiles

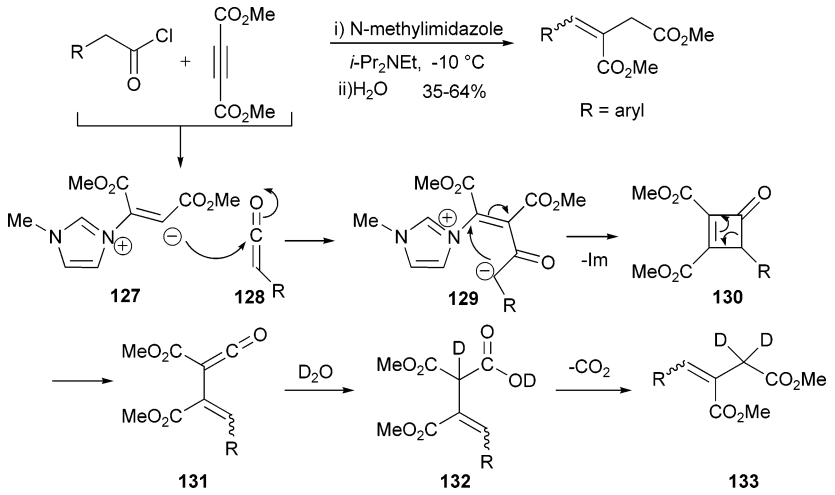
Carbon nucleophiles, such as enamines[37] (including heterocycles, such as pyrrole and indole),[38] isocyanides,[39] dialkoxycarbenes,[40] various ylides,[38] and *N*-heterocyclic carbenes (NHCs),[41] also afford dipolar intermediates upon the addition to activated unsaturated systems. Often, the zwitterions in this category tend to retain the nucleophile in further transformations, thus leading to multicomponent reactions (MCRs). A recent Account on MCRs initiated by dipolar intermediates covers the literature on this subject.[42] A few exceptions to this common reactivity as exhibited by the Breslow-type intermediates generated from NHCs and aldehydes are also known.[43] A number of recent reviews are available on the reactions catalyzed by NHCs.[8d,41b]

It should also be mentioned here that dipolar species are known to arise from the addition of a number of heteroatom nucleophiles, such as sulfides, sulfoxides, imines, nitriles, imidazoles, thiazoles, etc., to various electron-deficient π systems.[38] The chemistry of such systems, however, has received only scant attention. A

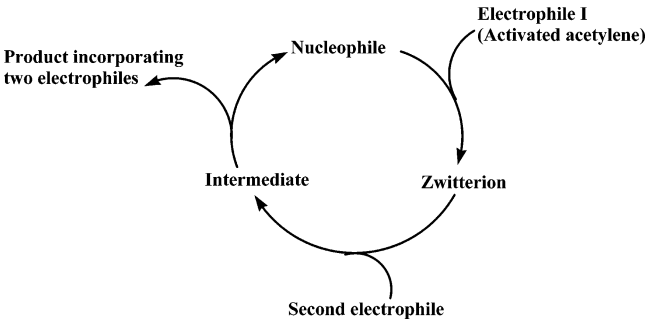
Scheme 27. Interception of DMAP−Allene Ester Zwitterion with *N*-Tosylimine



Scheme 30. Interception of an Imidazole−DMAD Zwitterion with Ketenes



Scheme 31. Schematic Representation of a Nucleophile-Triggered Combination of Two Electrophiles



recent report on the chemistry of a zwitterion generated by the addition of 1-methylimidazole to DMAD deserves special mention in this context. This zwitterion is intercepted by ketenes, which in turn are generated in situ by the action of Hunig's base on acyl halides, to afford dimethyl 2-(4-arylidene) succinates (Scheme 30).[44] The mechanism of the reaction is particularly interesting, and it is supported by the incorporation of deuterium only at the α carbon of the succinate derivatives.

It is evident from the foregoing discussion that a zwitterion, generated in situ upon the reaction with various electrophiles, results in different final products, with the nucleophile playing the crucial role of a catalyst. An oversimplified yet schematic version of the theme of this Account can be rendered as follows (Scheme 31).

Conclusion

The reactions described in this Account can be broadly classified under the category "*union of two electrophiles using a nucleophilic catalyst*". Discussion has been limited to organic nucleophiles, and in principle, this class of reactions falls under the broader realm of organocatalysis. In general, discussions on organocatalysis[45] have been focusing only on asymmetric catalysis, and much of the potentially useful "planar" chemistry in this area is still lying dormant. Also, despite the wide use of zwitterionic intermediates in many reactions, a classification based on the underlying principle of the process has eluded the literature of organic chemistry. It is expected that in coming years the huge potential hidden in the simple yet powerful methodology outlined here will attract the attention of a broad range of organic chemists.

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