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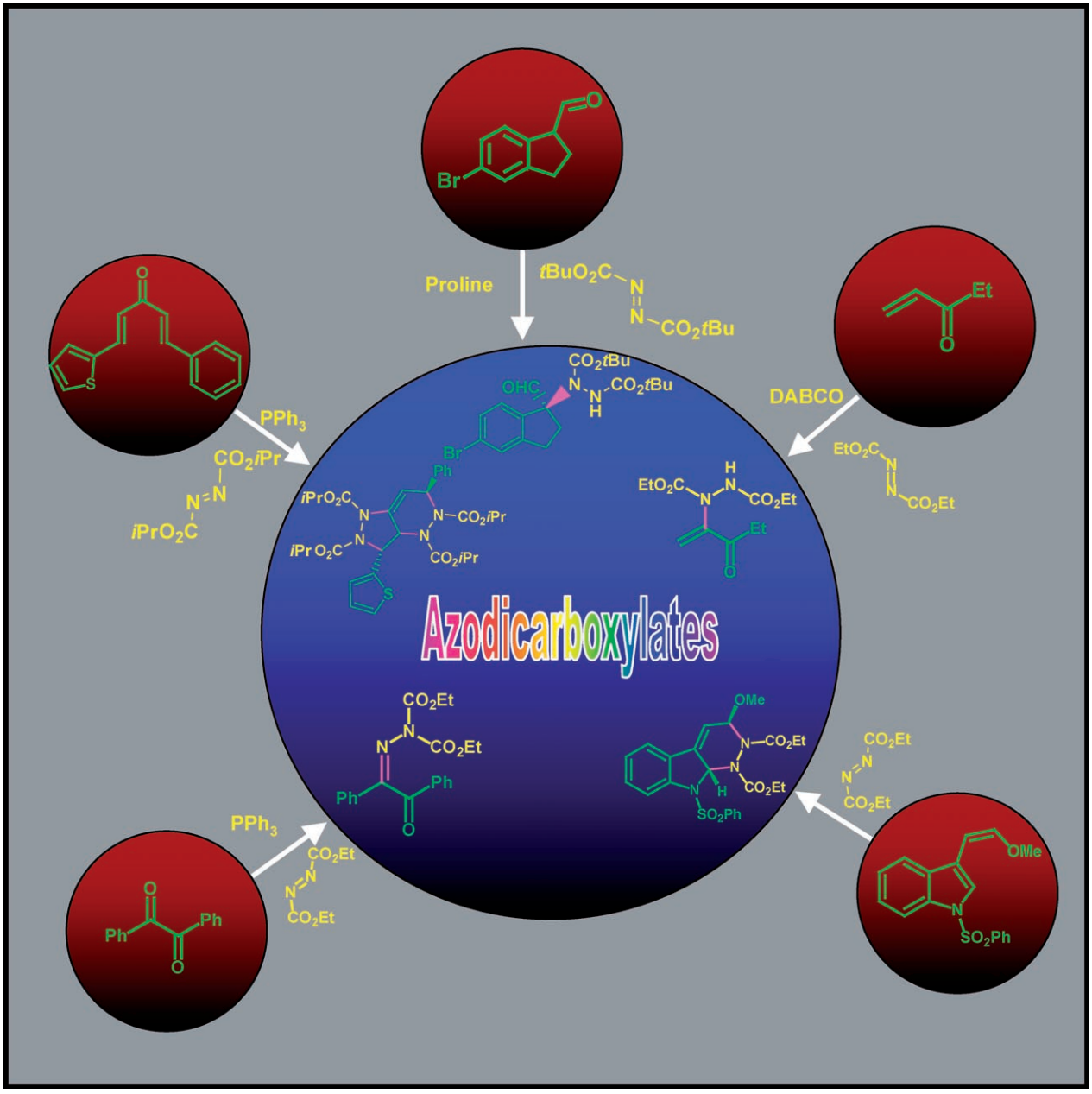
Carbon–Nitrogen Bond-Forming Reactions of Dialkyl Azodicarboxylate: A Promising Synthetic Strategy

Vijay Nair,* A. T. Biju, Smitha C. Mathew, and Beneesh Pattoorpadi Babu[a]

Dedicated to Professor Rolf Huisgen on the occasion of his 88th birthday



Abstract: Azodicarboxylates have found applications in electrophilic amination reactions and in pericyclic reactions. The nucleophilic trigger in Mitsunobu reactions, that is, the zwitterion formed from triphenylphosphine and dialkyl azodicarboxylate, has been utilized recently in various heterocyclic constructions. This Focus Review summarizes the potential utility of azodicarboxylates in various carbon–nitrogen bond-forming reactions.

Keywords: amination reactions · azodicarboxylates · C–N bond formation · heterocycles · Huisgen zwitterion

1. Introduction

Carbon–nitrogen bond-forming reactions assume great importance in organic chemistry, since an overwhelming number of biologically active compounds, natural as well as nonnatural, are amino compounds or derivatives thereof.[1] Although a plethora of methods are known to accomplish carbon–nitrogen bond construction,[2] there is the quest for newer and more efficient methods, both from the synthetic and mechanistic standpoints. In spite of the fact that azodicarboxylate has been known since the seminal work of Curtius in 1894,[3] its application to organic synthesis, barring its crucial role in the Mitsunobu inversion, has been limited until recently. This is surprising since the work of Diels,[4] Kharasch,[5] Huisgen,[6] and Alder[7] had clearly pointed to the usefulness of diethyl azodicarboxylate in carbon–nitrogen bond formation by radical, pericyclic, and electrophilic reactions. This review is aimed at shedding light on the synthetic potential of azodicarboxylates as reagents in organic synthesis, beyond their role in the Mitsunobu reaction. Special emphasis is given to the reactions of the Huisgen zwitterion,[6] which shows different modes of reactivity towards various electrophiles.

2. Dialkyl Azodicarboxylates

Dialkyl azodicarboxylates, with a central azo functionality flanked by two carboalkoxy groups, are excellent electrophiles and can readily participate in zwitterion formation. They are commercially available, and some of the common azodicarboxylates are listed in Figure 1.

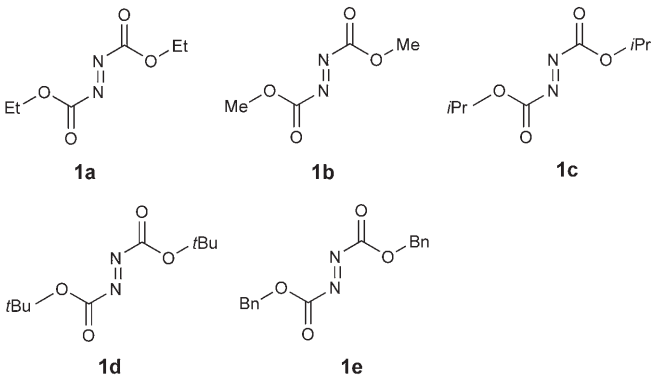
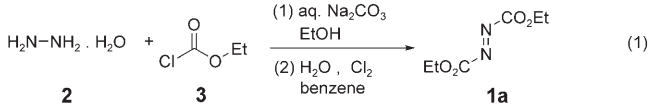


Figure 1. Common azodicarboxylates.

Diethyl azodicarboxylate (DEAD) is an orange liquid readily prepared from ethyl chloroformate and hydrazine followed by oxidation of the resulting diethyl hydrazine dicarboxylate with chlorine [Eq. (1)].[8] It is sensitive to heat and light and should be stored in a dark container under refrigerated conditions. Owing to the danger of explosion during purification and handling, usage of DEAD is rapidly declining and is being replaced by diisopropyl azodicarboxylate (DIAD).



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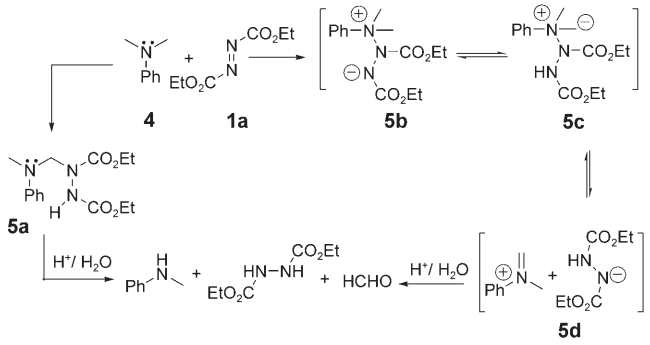
[a] Dr. V. Nair, A. T. Biju, S. C. Mathew, B. P. Babu
Organic Chemistry Section
National Institute for Interdisciplinary Science and Technology (CSIR)
Trivandrum 695019 (India)
Fax: (+91) 471-2491712
E-mail: vijaynair_2001@yahoo.com

3. Reactions of DEAD

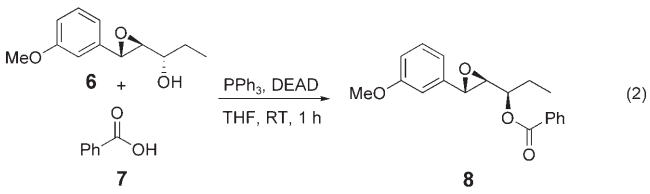
As early as 1922, Diels reported[4a] the reaction of DEAD with *N,N*-dimethyl aniline to afford a 1:1 adduct **5a**; the acid hydrolysis of the adduct afforded *N*-methyl aniline, formaldehyde, and hydrazine dicarboxylate. Thus, DEAD in principle acts as a demethylating agent. Huisgen proposed the existence of zwitterionic intermediates **5b** and **5c** almost three decades later (Scheme 1).[9] Interestingly, Huisgen subsequently favored its formulation as the ion pair **5d**.[6a]



Scheme 1. Demethylation using DEAD.

3.1. Mitsunobu Reaction

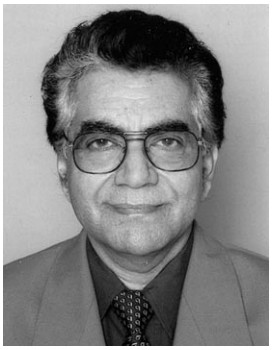
The Mitsunobu reaction,[10] discovered in 1971, involves the stereospecific reaction of an alcohol and a carboxylic acid in the presence of triphenylphosphine and DEAD to give the corresponding ester. The reaction of chiral secondary alcohol **6** gave the corresponding ester **8** with inverted configuration [Eq. (2)].[11]



The Mitsunobu protocol has been utilized in aminations, cyclodehydrations, deoxygenations, and dehydrative alkylations, thereby allowing the formation of different functional groups, and is an effective method for creating new carbon–carbon bonds. It has received a lot of attention recently, and a number of reviews have addressed various aspects of this

Abstract in Malayalam:

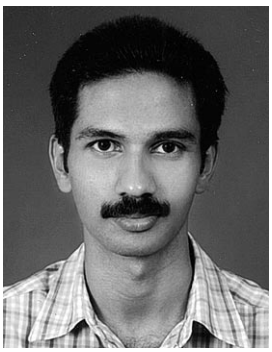
(സിന്തറ്റിക് ഓർഗാനിക് കെമിസ്ട്രിയിൽ സ്വിറ്റർഅയോണുകൾ സവിശേഷ ശ്രദ്ധ ആകർഷിക്കുന്ന മദ്ധ്യവർത്തികളാണ്. ട്രൈഫിനൈൽ ഫോസ്ഫീൻ-അസോഡൈകാർബോക്സിലേറ്റ് സ്വിറ്റർഅയോൺ (ഹൂയ്സ്ഗൻ സ്വിറ്റർഅയോൺ) അത്തരത്തിലുള്ള ഒന്നാണ്. 'മിറ്റ്സുനോബൂ' രാസപ്രവർത്തനത്തിൽ പ്രസ്തുത സ്വിറ്റർഅയോണിന്റെ പങ്ക് വിശദമായ അവലോകനങ്ങൾക്ക് ഇതിനകം തന്നെ വിധേയമായിട്ടുണ്ട്. കാർബൺ-നൈട്രജൻ രാസബന്ധനങ്ങൾ രൂപപ്പെടുത്താനും ഈ സ്വിറ്റർഅയോൺ ഫലപ്രദമായി വിനിയോഗിക്കാവുന്നതാണ്. ഈ അവലോകനത്തിൽ പ്രസ്തുത മേഖലയിലുള്ള കണ്ടെത്തലുകളെ വിശദമായി പ്രതിപാദിക്കുന്നു.).



Vijay Nair *has PhD degrees from the Banaras Hindu University (1967, with Professor R. H. Sahasrabudhey) and the University of British Columbia (1969, with Jim Kutney), and he was a postdoctoral fellow with Gilbert Stork at Columbia University. After 16 years with Lederle Laboratories (American Cyanamid Company) in Pearl River, NY, he returned to India and joined the Regional Research Laboratory (CSIR) in 1990 (recently renamed as National Institute for Interdisciplinary Science and Technology, NIIST) . From 1997 to 2001 he was the Director of the Institute and is presently Raja Ramanna Fellow there. Dr. Nair is a Fellow of the Indian Academy of Sciences and a Silver Medalist of the Chemical Research Society of India.*

A. T. Biju *obtained his M.Sc. (1st rank) in chemistry from Mahatma Gandhi University (2001). He has recently completed his PhD under the guidance of Dr. Vijay Nair at the NIIST (CSIR). Presently he is working as a postdoctoral fellow with Professor Tien-Yau Luh at the National Taiwan University.*

Smitha C. Mathew *obtained her M.Sc. in chemistry from Mahatma Gandhi University (2002). She has recently completed her Ph.D. under the guidance of Dr. Vijay Nair at the NIIST (CSIR). Currently, she is working as a postdoctoral fellow with Dr. Jean-Luc Parrain at Universite Paul Cezanne d'Aix-Marseille – CNRS.*

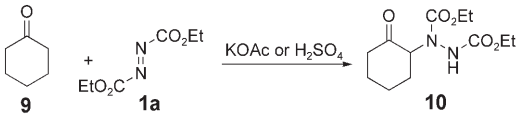


Beneesh P. B. *obtained his MSc degree in chemistry from the University of Calicut in 2003 with first rank. Currently he is a senior research fellow working towards his PhD in the group of Dr. Vijay Nair at the NIIST (CSIR).*

reaction.[12] In view of these reviews, especially a very recent one, a detailed discussion of the Mitsunobu reaction is not attempted here.

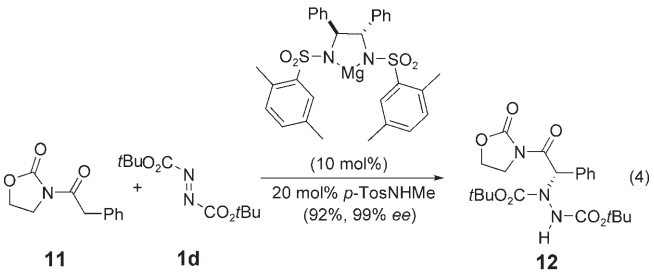
3.2. Amination Reactions

The history of electrophilic amination of carbonyl compounds using azodicarboxylates dates back to 1954 when Huisgen observed the α-aminated product upon treating cyclohexanone with DEAD.[9] The reaction involves the addition of the enolate anion or enol to the azoester, which is catalyzed by potassium acetate or sulfuric acid [Eq. (3)].



(3)

Subsequent work by a number of research groups has shown that dialkyl azodicarboxylates are excellent Michael acceptors having widespread applications in the electrophilic amination of carbonyl compounds.[13] Recently this strategy has been applied to enantioselective carbon–nitrogen bond-forming reactions using metal complexes and organocatalysts.[14] This methodology has emerged as a useful protocol for the synthesis of amino acids and their derivatives. Enantioselective amination of *N*-acyl oxazolidinone **11** with di-*tert*-butyl azodicarboxylate (DTAD) was reported by Evans and Nelson using the magnesium bis(sulfonamide) complex.[15] The reaction afforded the hydrazide **12** in 92% yield [Eq. (4)]. The same group also reported the catalytic enantioselective amination of enolsilanes **13** using a C_2-symmetric copper(II) complex as chiral Lewis acid [Eq. (5)].[16]



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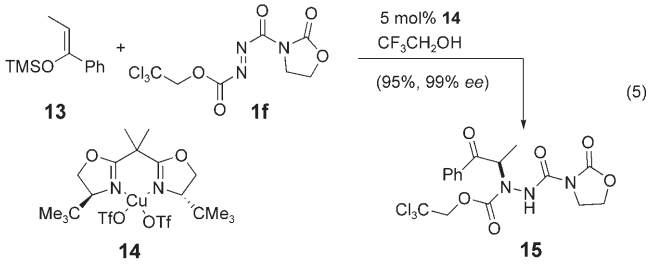

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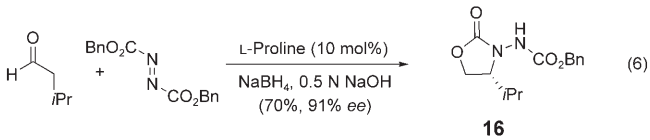
The direct organocatalytic α-amination of aldehydes with dialkyl azodicarboxylates was reported independently by Jørgensen [Eq. (6)] and List [Eq. (7)].[17] These reactions proceed with excellent enantioselectivity, leading to the formation of optically active α-amino aldehydes, α-amino alcohols, α-amino acids, and *N*-amino oxazolidinones. Proline-catalyzed asymmetric α-amination of ketone **18** with azodicarboxylate afforded α-hydrazino ketone **19**. which can be easily functionalized to α-aminated ketones and alcohols [Eq. (8)].[18] Very recently, enantioselective α-amination of aryl ketones with azodicarboxylates catalyzed by primary amines derived from cinchona alkaloids has been reported.[19] Enantioselective α-amination of functionalized indane carboxaldehydes **20** using (*R*)-proline afforded the chiral amino aldehyde **21** in excellent optical purity [Eq. (9)].[20]



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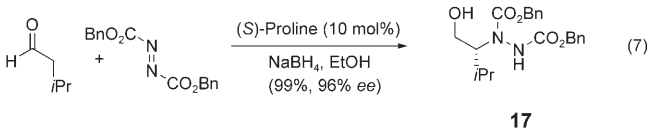

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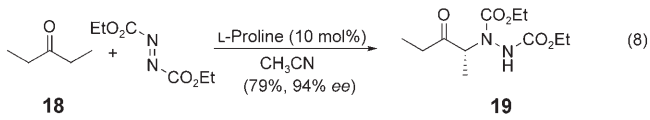

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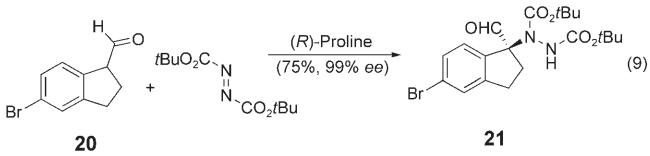
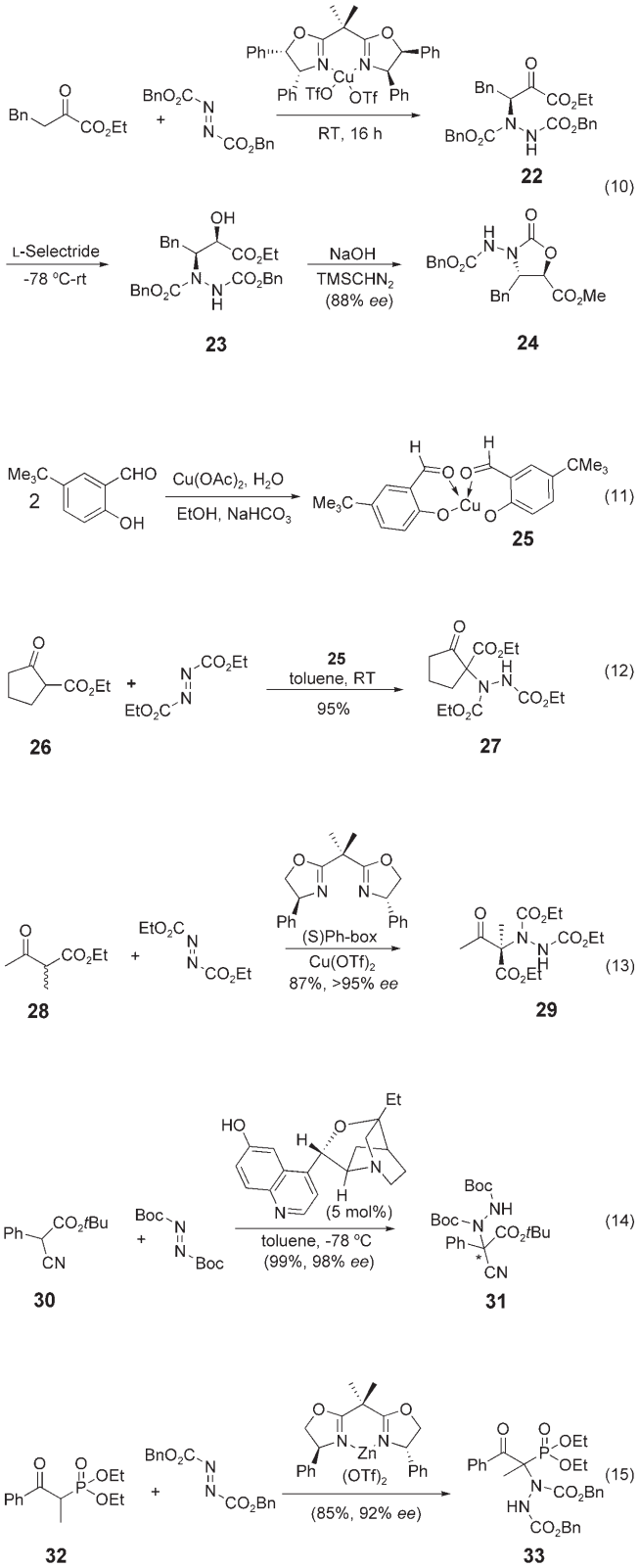


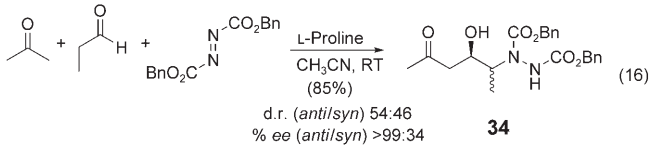
(9)

Enantioselective α-amination reaction of α-ketoesters with azodicarboxylates using a chiral bisoxazoline copper complex with subsequent reduction leading to the synthesis of *syn*-α-amino-β-hydroxy ester **23** was reported by Juhl and Jørgensen.[21] Compound **23**, upon hydrolysis followed by esterification, furnished *N*-amino oxazolidinone **24** in 56% yield after four steps [Eq. (10)]. DEAD serves as an excellent Michael acceptor in the reaction with active methylene compound **26** under catalysis by copper (II) bis-(5-*tert*-butylsalicylaldehyde) to afford **27** [Eqs. (11) and (12)].[22] Jørgensen et al. reported the α-amination of α-substituted-β-ketoester **28** catalyzed by a chiral copper(II) bisoxazoline (box) complex with DEAD [Eq. (13)].[23] Enantioselective organocatalytic amination of α-cyanoacetate **30** with dialkyl azodicarboxylate catalyzed by a cinchona base afforded **31**

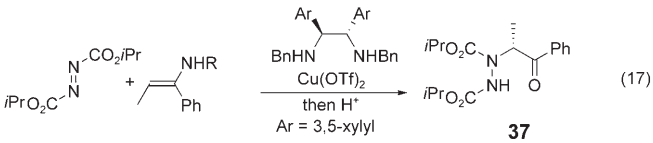
in excellent yield and optical purity [Eq. (14)].[24] Enantioselective amination of β-keto phosphonate **32** with azodicarboxylate catalyzed by zinc bisoxazoline complexes has been reported recently by Jørgensen et al. [Eq. (15)].[25]



The one-pot synthesis of β-amino alcohol **34** can be accomplished from aldehydes and ketones using DEAD and L-proline.[26] This is a typical organocatalytic asymmetric assembly reaction in which both aldehyde and ketone act as donors in one pot [Eq. (16)]

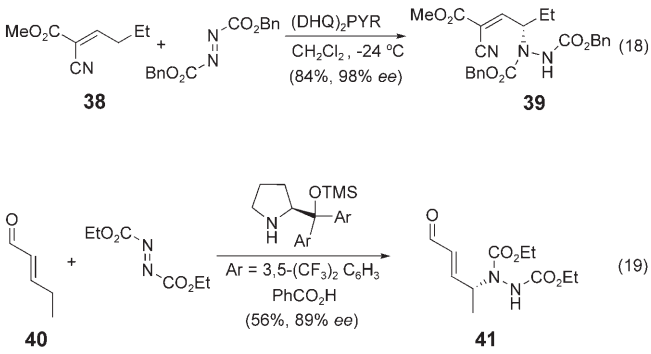


Kobayashi et al. reported the catalytic asymmetric amination of ene–carbamate **35** using azodicarboxylate catalyzed by a chiral diamine–Cu^{II} complex. The reaction resulted in the formation of optically active α-amino carbonyl compound **37**, which can be readily converted into 1,2-diamines in excellent yield.[27a] Very recently, the same group reported the electrophilic amination of enesulfonamide **36** under similar conditions [Eq. (17)].[27b]



35 R = CO_2Bn,94% yield, 95% *ee*
36 R = SO_2PMP 70% yield, 91% *ee*

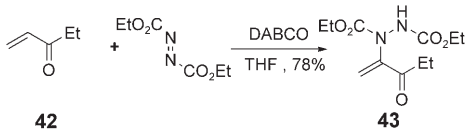
Enantioselective metal-free electrophilic γ-amination of alkylidene cyanoacetate **38** using azodicarboxylate in the presence of the commercially available cinchona alkaloid derivative $(DHQ)_2PYR$ has been reported by Jørgensen et al. [Eq. (18)].[28a] Subsequently, the same group reported the organocatalytic asymmetric γ-amination of α,β-unsaturated aldehydes and azodicarboxylates leading to the formation of **41** in good yield [Eq. (19)].[28b]



3.3. Aza-Baylis–Hillman Reaction

The Morita–Baylis–Hillman[29] reaction has been widely used as a method for carbon–carbon bond formation. In the

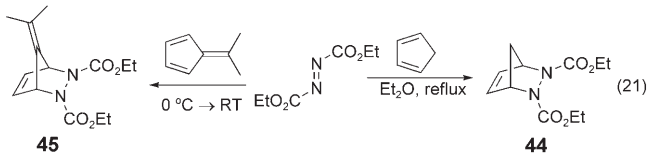
aza version of this reaction, the aldehyde component is replaced by nitrogen electrophiles like imines, azodicarboxylates, etc. Synthesis of α-(*N*,*N*′-dicarboethoxy)hydrazino-α,β-unsaturated ketone **43** can be achieved by treating DEAD with alkyl vinyl ketones under DABCO catalysis in a Baylis–Hillman reaction [Eq. (20)].[30]



42 **43** (20)

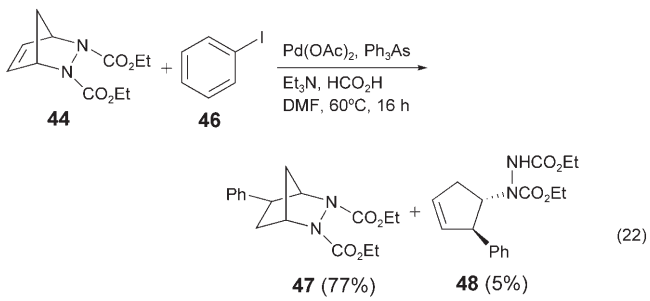
3.4. Pericyclic Reactions

As early as 1925 Diels had reported the [4+2] cycloaddition of cyclopentadiene and DEAD. Interestingly this constituted the first definitive example of the "Diels–Alder" reaction.[4b,31] Similarly, pentafulvenes undergo facile [4+2] cycloaddition with DEAD, leading to the formation of azabicyclic olefin **45** [Eq. (21)].[32]



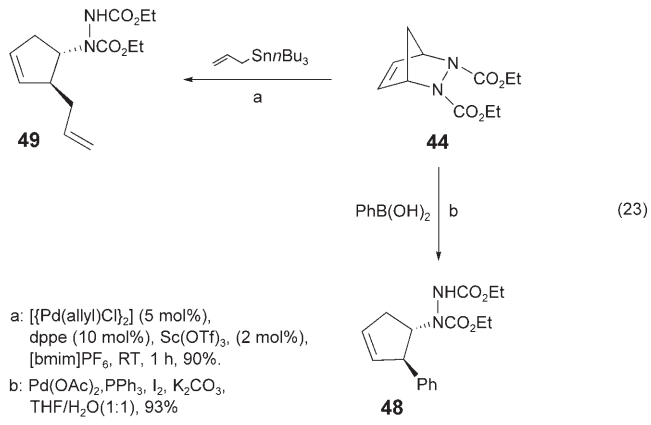
45 **44** (21)

Kaufmann and co-workers observed the formation of hydroarylated bicyclic hydrazine **47** during the palladium-catalyzed hydroarylation reaction of bicyclic hydrazine **44**. In this reaction, a small amount of 3,4-disubstituted cyclopentene derivative **48** was also isolated [Eq. (22)].[33] Radhakrishnan and co-workers reported the palladium(0)/Lewis acid mediated ring opening of azabicyclic olefin with organostannane, leading to the synthesis of 3,4-disubstituted hydrazinocyclopentene derivative **49** in excellent yield.[34] The reaction of phenyl boronic acid with bicyclic alkene in the presence of a $Pd(OAc)_2/PPh_3/I_2$ catalyst system afforded 3-phenyl-4-hydrazino cyclopentene **48** [Eq. (23)].[35]

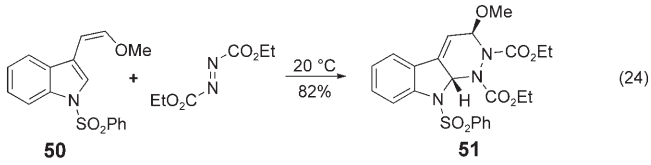


44 **46** **47** (77%) **48** (5%) (22)

DEAD reacts with a variety of conjugated dienes to yield [4+2] cycloadducts. When the diene moiety is a vinyl aromatic system, cycloaddition is a tool for the synthesis of annulated tetrahydropyridazine derivatives.[36] Thus, indole derivative **50** on treatment with DEAD at room temperature affords cycloadduct **51** in high yield [Eq. (24)].

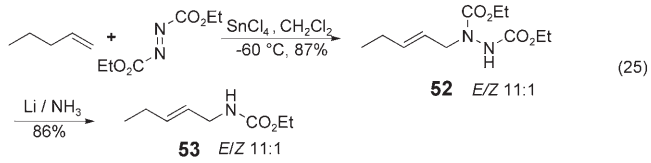


49 **44** (23) **48**



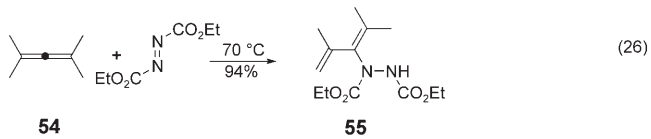
50 **51** (24)

The reaction of DEAD with alkenes possessing allyl hydrogen atoms to yield the allylic hydrazodicarboxylate has been known from the pioneering work of Alder.[7a,b] The reaction proceeds with selectivity for the *E* alkene. A useful application of the ene reaction with DEAD is in the synthesis of allyl amine **53**, which is readily available by reduction of the initial adduct **52** with Li/NH_3 [Eq. (25)].[37] Allenes with alkyl substituents react with DEAD to give ene product **55** in excellent yield [Eq. (26)].[38]



52 *E*/*Z* 11:1 (25)

53 *E*/*Z* 11:1

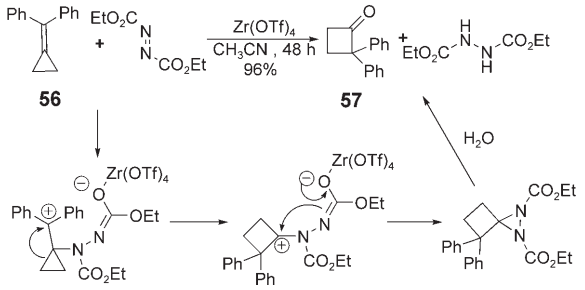


54 **55** (26)

3.5. Ring-Expansion Reactions

Methylene cyclopropane (MCP) in the presence of DEAD as reagent and zirconium triflate as catalyst in acetonitrile

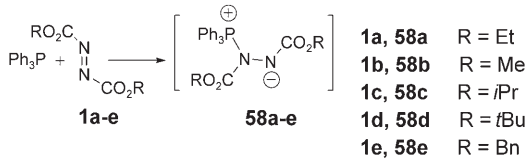
undergoes a ring-expansion reaction to give cyclobutanone derivative **57** in high yield.[39] This method provides a safe and convenient synthetic route for the synthesis of substituted cyclobutanones under mild conditions. A plausible mechanism for this ring-expansion reaction of MCPs promoted by DEAD and zirconium triflate is shown in Scheme 2.



Scheme 2. Mechanism for the ring expansion of MCPs.

3.6. Phosphine–Azoester Zwitterions

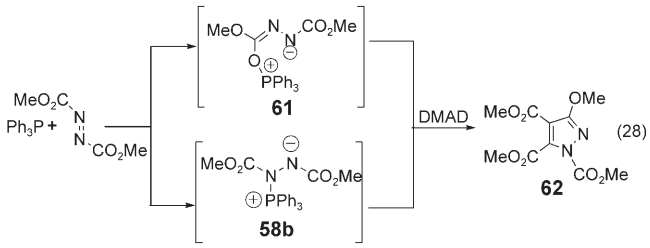
Dialkyl azodicarboxylates, on reaction with nucleophiles, have been known to readily participate in zwitterion formation. If the nucleophile is triphenylphosphine and the receptor is a dialkyl azodicarboxylate, the resultant zwitterionic intermediate is called the Huisgen zwitterion (**58**, Scheme 3).[6]



Scheme 3. Huisgen zwitterions.

Historically, the reaction of triethylphosphite with DEAD leading to the formation of **60**, an ethyl derivative of diethylphosphoric acid-1,2-dicarboethoxy hydrazide, presumably via the zwitterion **59**, was reported by Morrison [Eq. (27)].[40] He also mentioned the formation of triphenylphosphine oxide and diethyl hydrazodicarboxylate as the products in the reaction of triphenylphosphine with DEAD.

Cookson and Locke reported the reaction of triphenylphosphine and dimethyl azodicarboxylate with DMAD (dimethyl acetylenedicarboxylate), affording the pyrazole derivative **62**, and it was postulated to occur via the intermediate **61**.[41] However, the correct structure of the zwitterion was established as **58b** by Huisgen [Eq. (28)].[6b] He demonstrated the nucleophilicity of **58b** by its reaction with DMAD, leading to the formation of **62** in 71% yield. The zwitterion **58** is therefore called the Huisgen zwitterion. In view of the facts outlined above, it is most appropriate that the zwitterion be called the Huisgen zwitterion.



In general, the Huisgen zwitterion can be intercepted with eletrophiles, resulting in the formation of a tetrahedral intermediate. This intermediate undergoes a domino process to deliver the product with efficient carbon–nitrogen bond formation. In all the reactions of the Huisgen zwitterion with electrophiles, triphenylphosphine oxide is isolated as a by-product (Figure 2).

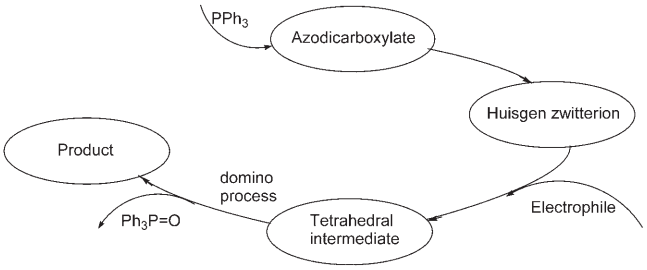
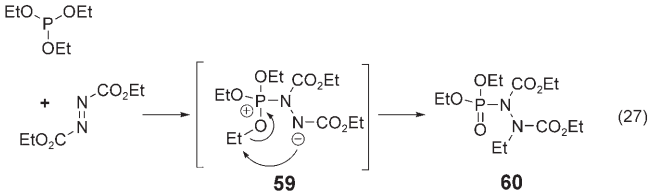
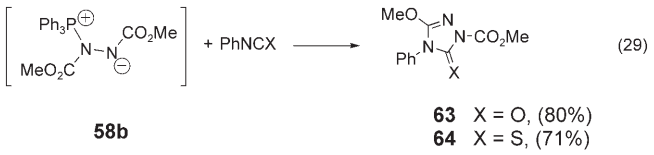


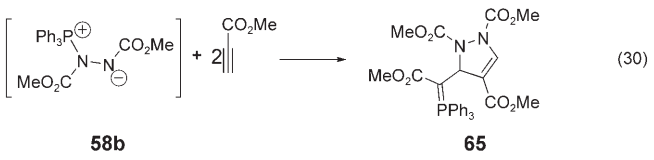
Figure 2. General reaction pattern of Huisgen zwitterions.

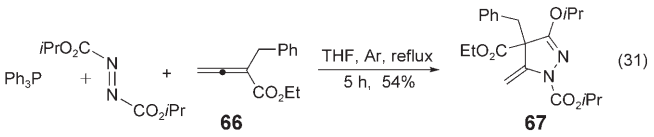
The reaction of isocyanates and isothiocyanates with the Huisgen zwitterion affords the triazole derivatives **63** and **64** [Eq. (29)].[6b] Interestingly, the reaction of the Huisgen zwitterion with two equivalents of methyl propiolate affords the heterocyclic methylene phosphorane **65** in 58% yield [Eq. (30)].[6b] Recent work in our laboratory has uncovered an interesting reactivity pattern of the zwitterion **58** in its reactions with electron-deficient allenes. The reactions led to a facile synthesis of highly functionalized pyrazolines and fully substituted pyrazole derivatives [Eqs. (31) and (32)].[42] It is interesting to note that electrophilic allenes like **68** are also known to generate zwitterions when exposed to phosphines.[43] Our results, however, demonstrate the clear preference of triphenylphosphine for dialkyl azodicarboxylates over such allenes.

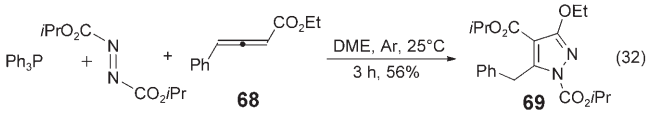
The following mechanistic postulate may be invoked to rationalize the formation of functionalized pyrazolines and



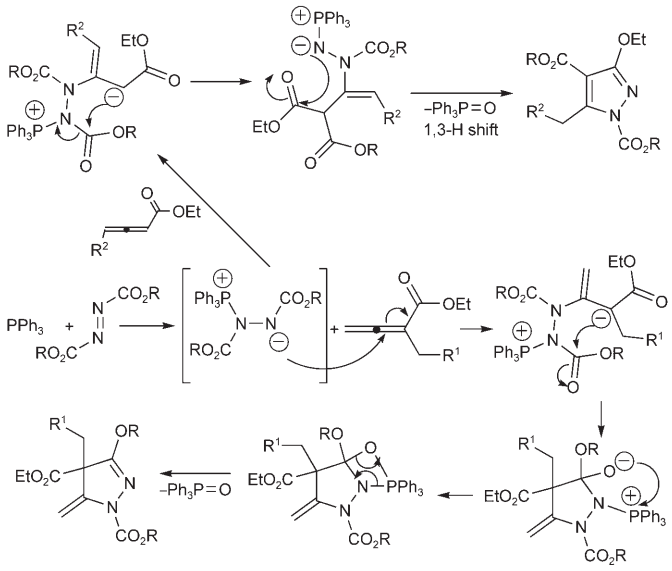






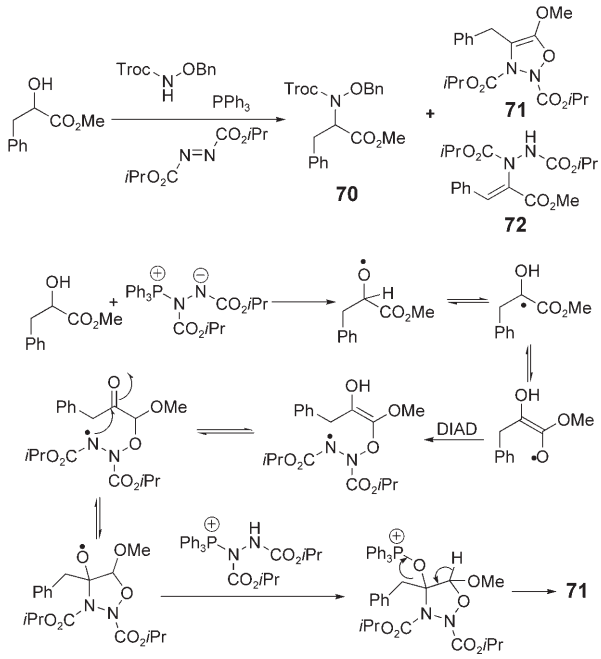


fully substituted pyrazoles. The fully substituted pyrazoles are formed by a unique nitrogen-to-carbon migration of the ester group (Scheme 4).



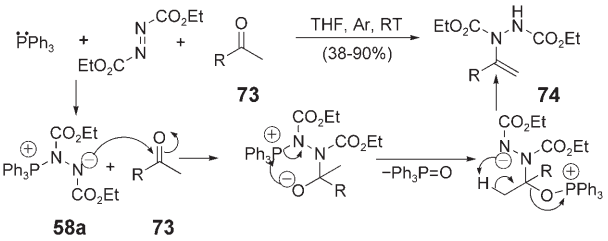
Scheme 4. Tentative mechanism of pyrazole formation.

Kolasa and Miller[44] reported the Mitsunobu reaction of α-hydroxy esters with *N*-[(trichloroethoxy)carbonyl]-*O*-benzyl hydroxylamine. In addition to the desired Mitsunobu product **70**, they isolated the enol adducts **71** and **72** as side products. Evidently, the side products were derived from the α-hydroxy esters and azodicarboxylate. A mechanistic postulate for the formation of the adduct **71** is outlined in Scheme 5.



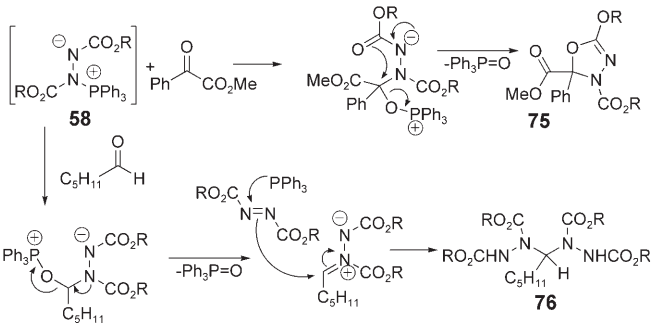
Scheme 5. Mitsunobu reaction of α-hydroxy esters. Troc = trichloroethoxy carbonyl.

A facile synthesis of vinyl hydrazine dicarboxylate from ketones possessing α-hydrogen atoms by reaction with the Huisgen zwitterion was reported by Liu[45] and Lee.[46] Independent investigation in our laboratory has uncovered the reaction of the Huisgen zwitterion with various cyclic and acyclic ketones possessing α-hydrogen atoms to afford vinyl hydrazine dicarboxylates (Scheme 6). It is interesting to note that this reaction with conjugated ketones possessing α-hydrogen atoms is an efficient method for the synthesis of 1,3-dienes containing nitrogen substituents.[47]



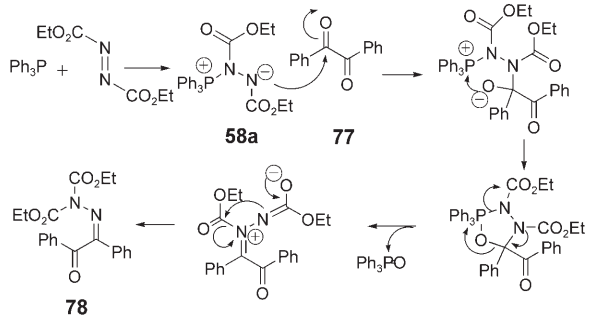
Scheme 6. Synthesis of vinyl hydrazine dicarboxylate.

Recently Lee et al. reported the reactions of the zwitterion **58** with carbonyl compounds like α-ketoesters, α-diketones, and aliphatic aldehydes to afford various products (Scheme 7).[46] Interestingly, independent investigations in

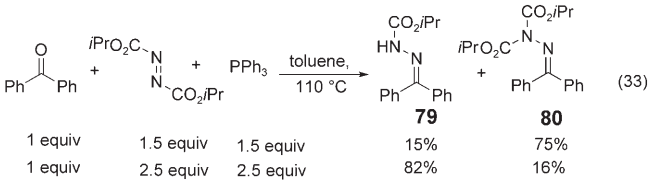


Scheme 7. Reaction of Huisgen zwitterion with α-ketoesters and aliphatic aldehydes.

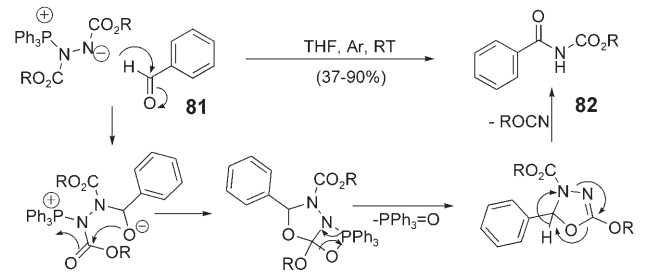
our laboratory showed that the reaction of **58** with diaryl-1,2-dione **77** proceeded with rearrangement to afford dicarboethoxy monohydrazones **78** of the respective diones.[48] This novel rearrangement involves a unique nitrogen-to-nitrogen migration of a carboethoxy group (Scheme 8). Subsequent work revealed that the zwitterion generated from triphenylphosphine and DIAD reacts with diaryl ketones to afford two products, the hydrazone derivatives **79** and **80**, whose ratio depends on the concentration of the zwitterion [Eq. (33)].[49]



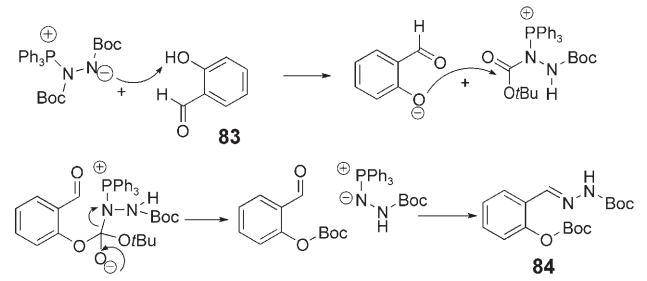
Scheme 8. Reaction of Huisgen zwitterion with diaryl-1,2-diones.



Very recent investigations in our laboratory showed that the reaction of the Huisgen zwitterion with an aromatic aldehyde leads to a facile synthesis of acyl carbamate **82** (Scheme 9).[50] Girard et al. reported the facile conversion of salicylaldehyde to protected hydrazone derivative **84** (in 84% yield) in the presence of triphenylphosphine and di-*tert*-butyl azodicarboxylate.[51] It is noteworthy that this is an exception to the normal Mitsunobu reaction. Usually, phenols afford the alkyl aryl ethers under Mitsunobu conditions whereas hydrazones are formed from salicylaldehyde (Scheme 10). It may be recalled that the reaction of DEAD with aldehydes was known to afford acyl hydrazine dicarboxylates, presumably by a radical mechanism.[7c]

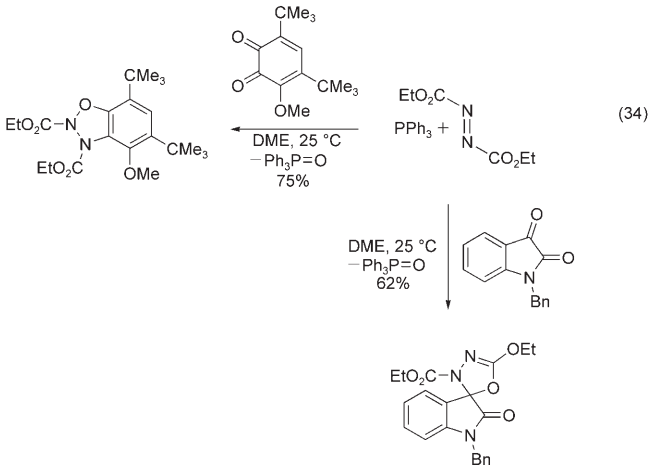


Scheme 9. Synthesis of acyl carbamate.



Scheme 10. Reaction of Huisgen zwitterion with salicylaldehyde.

In related work, we examined the reactivity of the Huisgen zwitterion with various cyclic 1,2-diones. The zwitterion on reaction with 3-methoxy-4, 6-di *tert*-butyl-1,2-benzoquinone afforded the dihydro-1,2,3- benzoxadiazole derivative. The reaction of the zwitterion with N-substituted isatins resulted in the formation of spirooxadiazolines in good yield [Eq. (34)].[52]



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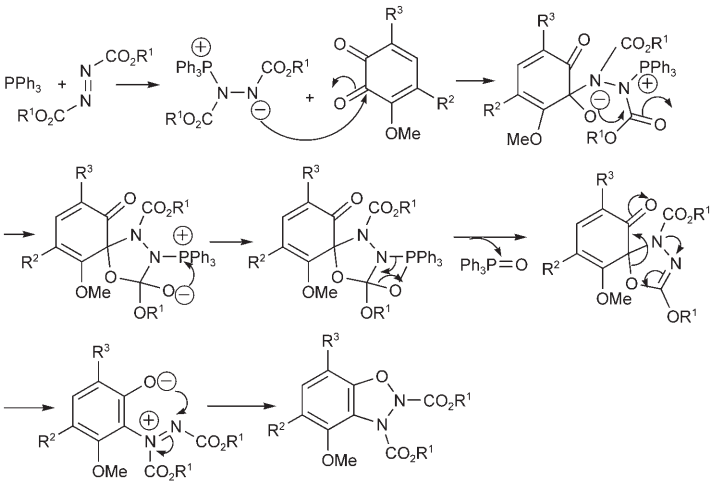
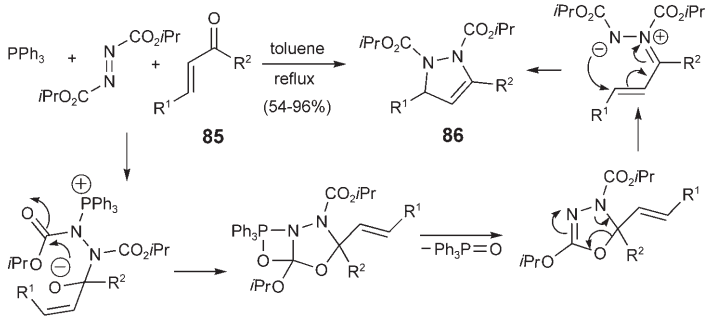
A mechanistic rationalization for the formation of dihydro-1,2,3-benzoxadiazoles from quinones is provided in Scheme 11. Another interesting reactivity pattern was exhibited by **58** in its reactions with chalcones and dienones. Reaction of **58** with chalcones, under toluene reflux, afforded pyrazoline derivatives **86** in good yields (Scheme 12).[53]

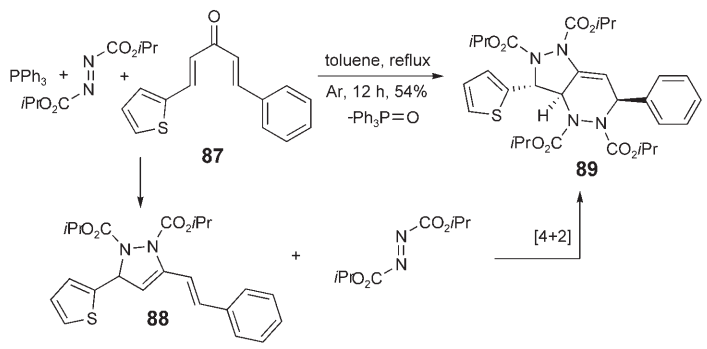


Scheme 11. Tentative mechanism of benzoxadiazole formation.



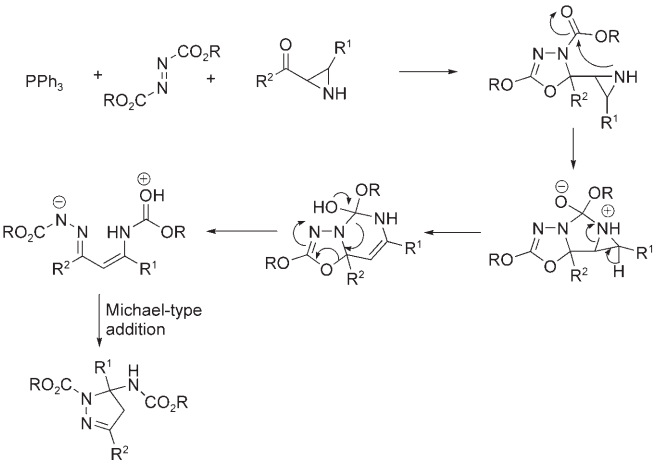
Scheme 12. Reaction of Huisgen zwitterion with chalcones.

Interception of **58** with dienones affords the highly functionalized pyrazolopyridazine derivatives **89** by a cycloaddition reaction of the initially formed vinyl pyrazoline derivative with the excess DIAD present in the reaction medium (Scheme 13). The intermediate vinyl pyrazoline derivative **88** was isolated along with a trace amount of the pyrazolopyridazine derivative by treating dienone **87** with 1.2 equivalents of DIAD and triphenylphosphine.



Scheme 13. Reaction of Huisgen zwitterion with dienones.

Very recently, the reaction of **58** with acyl aziridines leading to the formation of pyrazolines in excellent yield was reported by Wang and co-workers.[54] Mechanistically, the reaction proceeds with the formation of oxadiazoline by the interception of **58** with the keto group of the acyl aziridine followed by a domino sequence to furnish the pyrazoline (Scheme 14).



Scheme 14. Reaction of Huisgen zwitterion with acyl aziridines.

4. Conclusions

This Focus Review exposes the rich and fascinating chemistry of dialkyl azodicarboxylates, especially from the standpoint of efficient carbon–nitrogen bond-forming reactions. Some of these reactions result in the formation of nitrogen heterocycles with potentially interesting biological activity. Also azodicarboxylates have found use in amination reactions leading to the formation of optically pure α-amino acid derivatives. It is reasonable to assume that the great synthetic potential of azodicarboxylates will attract the attention of a broad range of organic chemists.

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