

# Recent development of reactions with $\alpha$ -diazocarbonyl compounds as nucleophiles

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The nucleophilic addition reaction of diazo-compound derived anions or enolates with electrophilic C=O and C=N bonds have been summarized. The subsequent reactions of the addition products demonstrate diverse reactivities of the diazocarbonyl compounds bearing other functional groups and their potential in organic synthesis. Asymmetric catalysis is also possible with diazocarbonyl compounds as nucleophiles.

## 1. Introduction

$\alpha$ -Diazocarbonyl compounds have been extensively studied over many years. One of the most important applications of  $\alpha$ -diazocarbonyl compounds is for the generation of metal carbene species. In the reaction of diazo compounds with transition metal catalysts the negatively polarized diazo carbon interacts with the empty orbital of the transition metal, followed by dinitrogen extrusion. The electrophilic metal carbene species thus generated have diverse reactivities, which can typically undergo cyclopropanations, X–H (X = C, O, S, N, etc.) bond insertions, 1,2-shift and ylide formations. Some of these reactions have been well established as standard synthetic methodologies.<sup>1</sup>

Diazo compounds are ambiphilic reagents. As shown in Scheme 1, from the resonance structure **B**, **C**, **D** of the diazo group it is obvious that the carbon, to which the diazo group is attached, has a partial negative charge and thus is nucleophilic.<sup>2</sup> Electrophiles usually attack at the carbon atom, while the terminal nitrogen of the diazo group is attacked by nucleophiles. Although in general diazo compounds decompose rapidly when treated with acids, they are relatively stable under basic conditions. Thus it is possible to generate the anion **E** which bears a diazo group through base-promoted deprotonation of acyl diazomethane. This type of anion is highly reactive and can add to C=O or C=N bond efficiently. In this nucleophilic addition, the diazo group remains unchanged, which allows further transformations.

Compared with acyl diazomethanes,  $\alpha$ -diazo  $\beta$ -ketoesters **F** are more stable. For these diazo compounds, transition metal catalysis usually requires high temperature and long reaction time. If  $\alpha$ -diazo  $\beta$ -ketoesters are treated with strong base, deacylation may occur from **G** to afford the anion of diazoacetate **H**. On the other hand, it is possible to generate Ti or Si enolates **I** from  $\alpha$ -diazo  $\beta$ -ketoesters. The enolates thus generated can undergo C=O, C=N additions, as well as

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focuses on the application of transition metal complexes of N-heterocyclic carbenes and synthesis of small biological compounds.

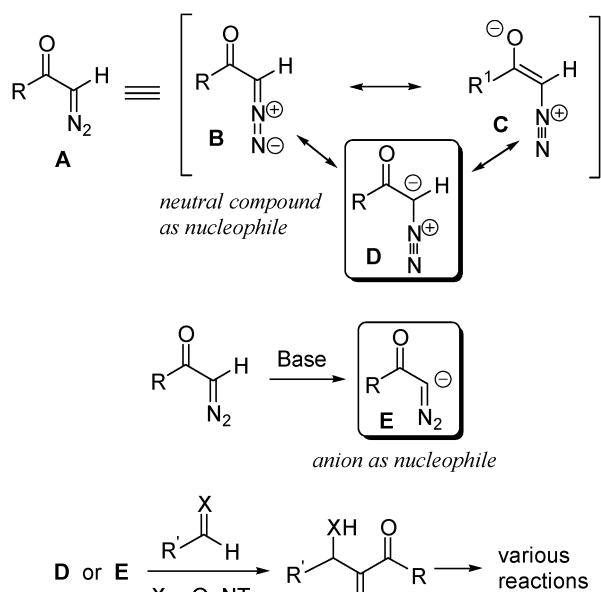
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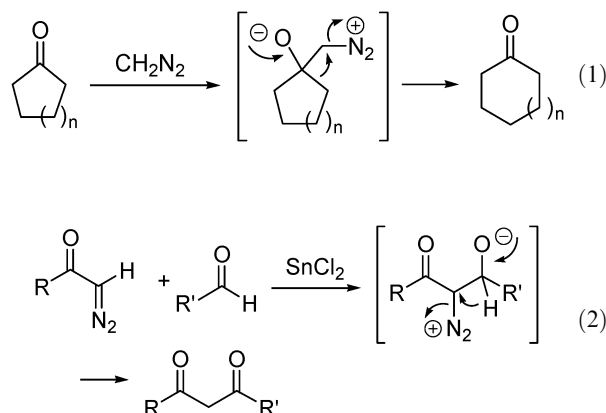


Scheme 1

Michael additions. Similarly, the addition product **J** retains the diazo functionality, which allows further transformations (Scheme 2).

The nucleophilic addition with diazo compounds as nucleophiles has been known for a long time. Some of these reactions have been developed into useful methods in organic synthesis. For example, the homologation of ketones with diazoalkanes is the nucleophilic addition of diazoalkenes to a carbonyl group followed by 1,2-alkyl migration (Buchner–Curtius–Schlotterbeck reaction).<sup>3</sup> This reaction is particularly useful in one-carbon ring expansion of cyclic ketones with diazoalkanes (eqn (1)). Another example is the Roskamp reaction in which the Lewis acid-catalyzed addition of  $\alpha$ -acyl diazomethane is

followed by a 1,2-H shift and extrusion of dinitrogen, affording  $\beta$ -keto carbonyl compounds (eqn (2)).<sup>4</sup>

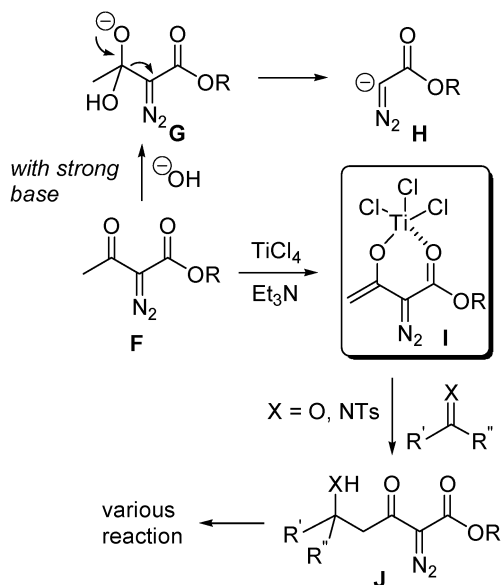


More recently, asymmetric catalysis with diazo compounds as nucleophiles has made some progress. Particularly, high enantioselectivities have been achieved in several catalytic systems of C=N addition with acyl diazomethanes. These new developments have aroused the interest in the chemistry of these “old” compounds. In this review, we will summarize the most recent developments in this area, which will include: (1) nucleophilic addition by acyl diazomethanes; (2) nucleophilic addition by  $\alpha$ -diazo  $\beta$ -ketoester derived enolates; (3) asymmetric nucleophilic addition with diazo compounds; (4)  $\alpha$ -diazo carbonyl compounds as nucleophiles in Pd-catalyzed reactions.

## 2. Nucleophilic addition by acyl diazomethanes

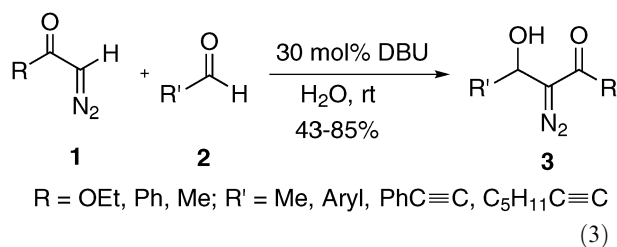
The traditional method of nucleophilic addition of an acyl diazomethane to an aldehyde or ketone requires deprotonation of the acyl diazomethane to generate highly reactive anion species. The deprotonation is usually achieved by the treatment of the acyl diazomethane at low temperature with strong base, such as butyllithium, lithium diisopropyl amide (LDA), sodium hydride, potassium hexamethyl disilyl amide (KHMDS), or NaOH. Although the anion species thus generated can efficiently add to ketones or aldehydes to afford  $\alpha$ -diazo- $\beta$ -hydroxy carbonyl compounds, the strong basic reaction conditions make these reactions less attractive for synthetic organic chemists. The use of organometallic derivatives of diazo carbonyl compounds enables the same transformation under milder conditions.<sup>5</sup> Moody and Morfitt report that ethyl diazoacetate (EDA) can be converted to zinc EDA derivatives, which subsequently react smoothly with aldehydes to afford  $\alpha$ -diazo- $\beta$ -hydroxy esters in reasonable yields that are comparable or better than those obtained from other methods.<sup>6</sup> Sarabia and López-Herrera later utilized this diethylzinc approach to the reaction of EDA with aldehyde sugars, leading to the improvement of yields with shorter reaction times.<sup>7</sup>

We have recently developed more straightforward reaction conditions for this nucleophilic addition. With a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the acyl diazomethanes can add to aldehydes at room temperature, giving the expected addition products **3** in moderate to good

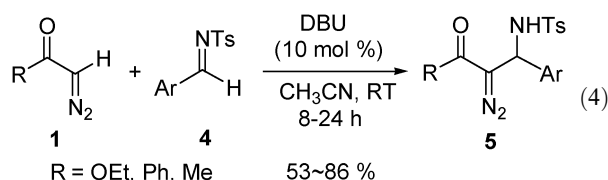


Scheme 2

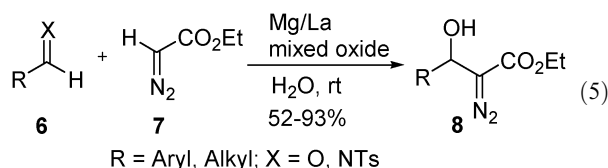
yields (eqn (3)).<sup>8</sup> Furthermore, it is found that this reaction can be carried out in H<sub>2</sub>O, affording the addition products in comparable yields.<sup>9</sup>



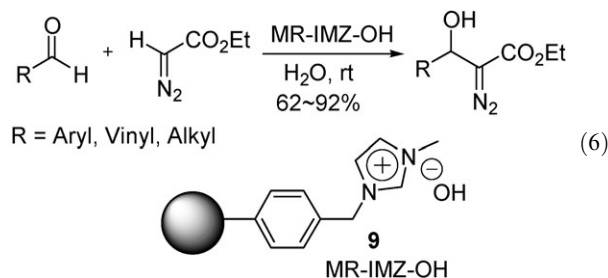
Under the same reaction with DBU catalysis, the addition of acyl diazomethanes to *N*-tosylimines **4** also works well to afford the corresponding β-tosylamino α-diazo carbonyl compounds **5** in good yields (eqn (4)).<sup>8,10</sup> Since the basicity of DBU is not enough to deprotonate the acyl diazomethane, the reaction must occur through direct nucleophilic addition of diazo compound to C=O or C=N bonds, followed by proton transfer.



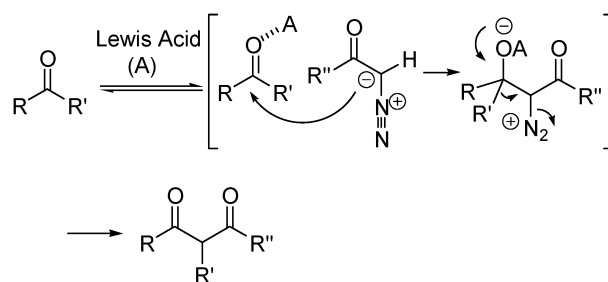
Kantam *et al.* have recently reported that Mg/La mixed oxide could promote the aldol-type reaction of EDA with aldehyde and *N*-tosylimine (eqn (5)). The reaction can be carried out in water. It was suggested that the EDA anion was formed through deprotonation by the mixed oxide.<sup>11</sup>



The same research group further developed polymer-supported imidazonium salt **9** as the catalyst in the nucleophilic addition of EDA to aldehydes (eqn (6)). The reaction could be carried out in water. The catalyst could be separated by simple filtration, recovered and reused several times without distinct loss of activity.<sup>12</sup>



Contrary to the direct addition under basic conditions, a different approach is to activate the ketone or aldehyde with Lewis acid, as shown in Scheme 3. Under such conditions, the dinitrogen extrusion usually occurs with the nucleophilic

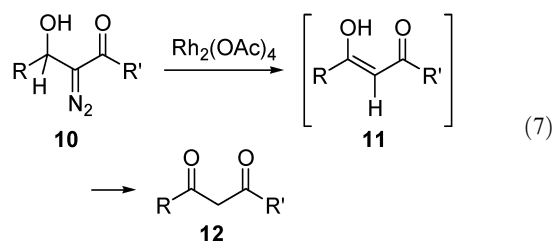


Scheme 3

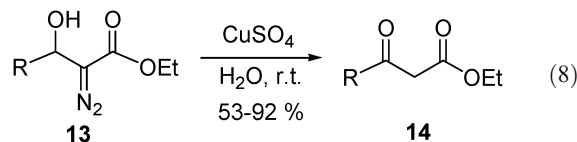
addition affording 1,3-dicarbonyl compounds as the products. This type of reactions has been an efficient method to prepare 1,3-dicarbonyl compounds, as has been represented by the Roskamp reaction.<sup>4</sup>

Under certain conditions, the Lewis acid or protic acid catalyzed addition of diazoester to C=O or C=N bonds may proceed with retention of the diazo functionality. This makes possible the asymmetric catalysis of C-C bond formation with chiral acids (*vide infra*).

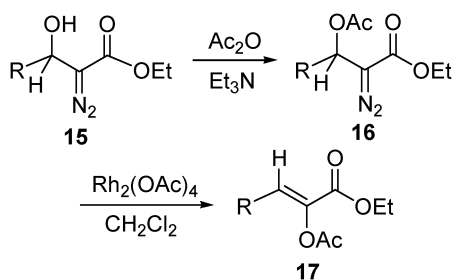
The β-hydroxyl α-diazo carbonyl compounds **10** obtained by the nucleophilic addition can further undergo a variety of transformations. For instance, catalysis with a transition metal complex such as Rh<sub>2</sub>(OAc)<sub>4</sub> gives 1,2-hydride shift products **11**, which rearrange to 1,3-dicarbonyl compounds **12** (eqn (7)). This is the same transformation as the Lewis acid-promoted reaction of diazo compound with aldehydes.



Recently, we have found that CuSO<sub>4</sub> can efficiently catalyze the reaction of β-hydroxy α-diazo carbonyl compounds **13** in water, giving the 1,3-dicarbonyl compounds **14** in high yields (eqn (8)). In combination of our DBU-catalyzed addition of acyl diazomethane to aldehydes, this two-step transformation from aldehyde and acyl diazomethane constitutes a 'green' and convenient preparative method for β-keto esters.<sup>13</sup>

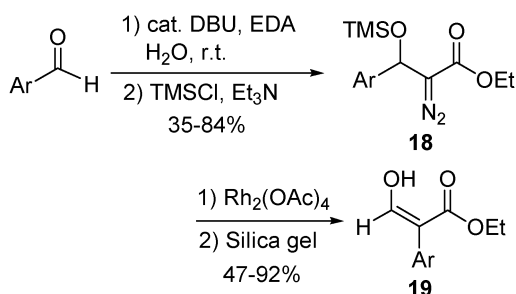


The β-hydroxyl group of the addition products can be further transformed into other groups with the diazo functionality kept intact. Subsequent transition metal catalyzed reaction may result in a different reaction pattern of the diazo compounds. For example, when the β-hydroxy is converted to β-acetoxy group, the Rh(II)-catalyzed reaction of the resultant β-acetoxy α-diazo carbonyl compounds **16** results in 1,2-acetoxy group migration, rather than 1,2-hydride migration (Scheme 4).<sup>14</sup>



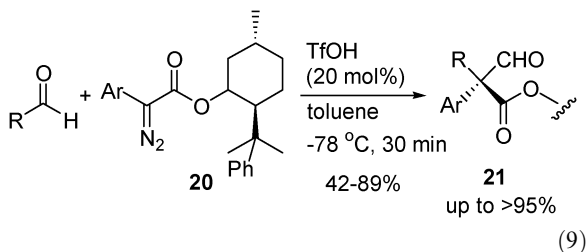
Scheme 4

We have systematically studied the effects of  $\beta$ -substituents on the 1,2-migratory aptitude of  $\text{Rh}(\text{II})$  carbenes. It is revealed that although 1,2-H migration is predominant in general, the  $\beta$ -substituent may override this migratory preference.<sup>10,15</sup> This property could be useful in organic synthesis, as demonstrated by the  $\text{Rh}(\text{II})$ -catalyzed reaction of  $\beta$ -trimethylsiloxy  $\alpha$ -diazo esters **18** (Scheme 5).<sup>9</sup> The predominant 1,2-aryl group migration provides a useful approach to prepare  $\beta$ -hydroxy  $\alpha$ -arylacrylates **19**. The preference for 1,2-aryl migration in these cases can be reasonably interpreted by steric effects. The bulky siloxy group promotes the large aryl group to migrate, instead of small hydrogen.

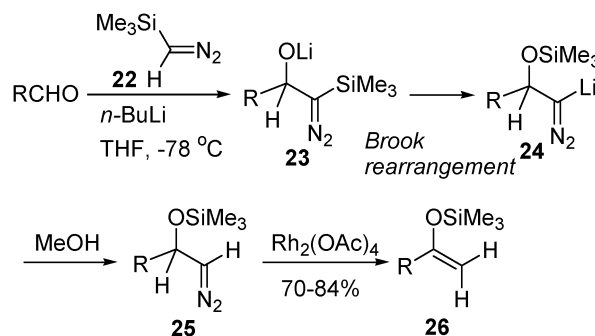


Scheme 5

$\text{TfOH}$ -catalyzed reaction of aryl diazoacetate with aldehydes has been studied by Maruoka and co-workers.<sup>16</sup> The reaction proceeds through nucleophilic addition of diazo carbon to aldehyde, followed by 1,2-aryl migration rather than 1,2-H migration. The reaction provides a new way to generate all-carbon quaternary centers. Moreover, with aryl diazoacetates bearing chiral auxiliary as substrate, the reaction gives products **21** with high diastereoselectivity (eqn (9)).



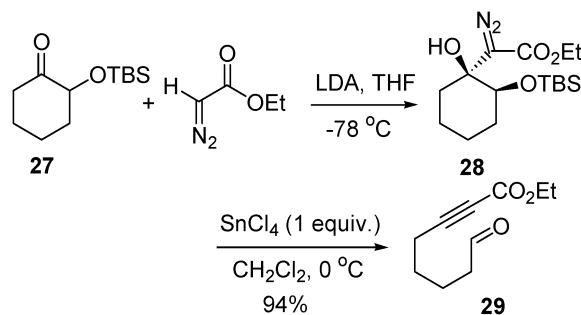
Aggarwal and co-workers studied the reaction of lithium (trimethylsilyl)diazomethane **22** with aldehydes (Scheme 6). Under ordinary conditions terminal alkynes are expected as the product. However, if the nucleophilic reaction at  $-78^\circ\text{C}$  was followed by addition of  $\text{MeOH}$  and catalytic  $\text{Rh}_2(\text{OAc})_4$  and then warmed to  $0^\circ\text{C}$ , terminal silyl enol ether **26** could be



Scheme 6

obtained in good yields. The reaction was suggested to involve Brook rearrangement of the addition intermediate **23** and  $\text{Rh}(\text{II})$  carbene 1,2-hydride migration.<sup>17</sup> In the following paper, a switch of 1,2 C–H migration to C–C migration was observed when  $\text{Rh}_2(\text{O}_2\text{CCF}_3)_4$ , rather than  $\text{Rh}_2(\text{OAc})_4$ , was added as catalyst in the same reaction system. Normally,  $\text{Rh}(\text{II})$  carbene 1,2 C–C migration is not competitive as compared with 1,2 C–H insertion. This study demonstrates remarkable effect of ligands in controlling the reaction pathway of the  $\text{Rh}(\text{II})$  carbene.<sup>18</sup>

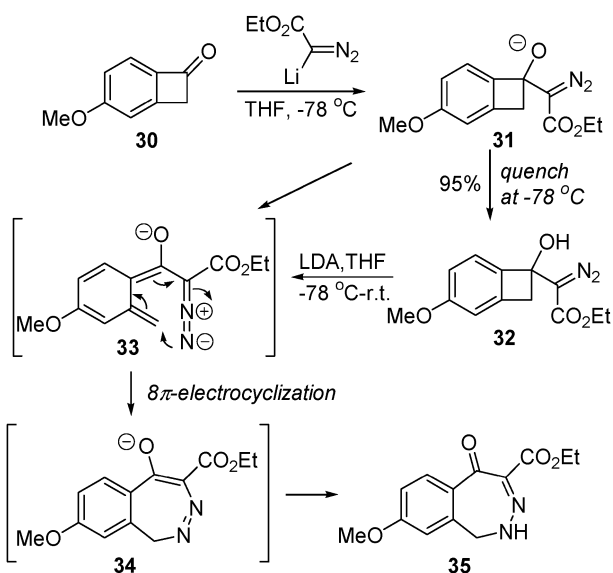
Recently, Draghici and Brewer have reported a  $\text{SnCl}_4$ -promoted ring fragmentation of  $\gamma$ -siloxy- $\beta$ -hydroxy- $\alpha$ -diazoesters **28**, which can be a useful method to prepare tethered aldehyde ynoates **29** (Scheme 7). The reaction is suggested to proceed through elimination of the Lewis acid-activated  $\beta$ -hydroxy group.<sup>19</sup>



Scheme 7

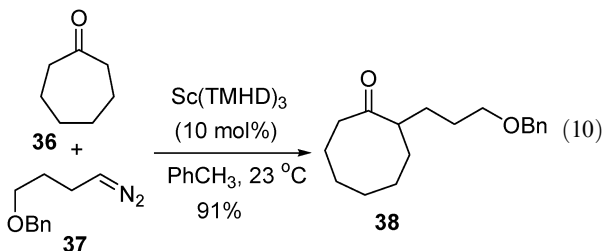
Nenoto investigated the nucleophilic addition of lithiated diazoacetate to benzocyclobutenone (Scheme 8). The initial addition product alkoxide **31** could be transformed into the corresponding alcohol **32**, which could be isolated in high yield when the reaction was quenched at  $-78^\circ\text{C}$ . When the alcohol **32** was further treated with  $\text{LDA}$  at  $-78^\circ\text{C}$  and then warmed to room temperature, diazepine product **35** was obtained in good yield. The formation of diazepine is attributed to oxy-anion accelerated electrocyclic ring-opening, which is followed by  $8\pi$  electrocyclization. Diazepine could be obtained directly in the reaction of lithiated diazoacetate to benzocyclobutenone by warming the reaction to room temperature upon the completion of nucleophilic addition. The overall transformation is a net insertion of diazomethane unit into cyclobutenone.<sup>20</sup>

The homologation of cyclic ketones with diazo alkanes is a widely utilized approach in organic synthesis. A recent development of this reaction is the realization of a  $\text{Sc}(\text{III})$ -catalyzed process with substituted diazomethanes. Unlike

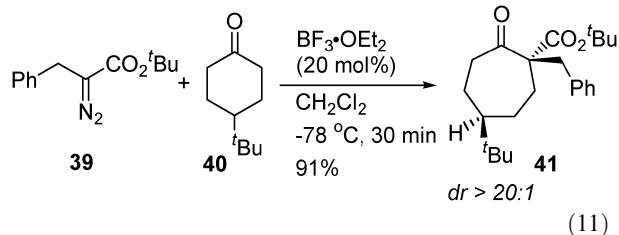


Scheme 8

the acyl-substituted diazomethanes, alkyl or aryl-substituted diazomethane derivatives are highly unstable. Consequently, their application in organic synthesis is rather limited as compared with their acyl substituted counterparts. With the recent development of several mild protocols to prepare non-stabilized diazoalkanes,<sup>21</sup> their reactions as diazo nucleophiles are revisited. Moebius and Kingsbury have reported that with Sc(III) catalysts, the ring expansion of cyclic ketones with a variety of alkyl- or aryl-substituted diazomethanes such as **37** proceed well at room temperature (eqn (10)).<sup>22</sup>

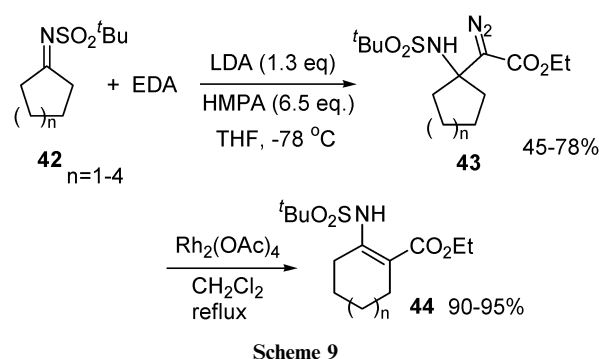


Very recently, Maruoka and co-workers reported a  $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed six-membered ring expansion with an  $\alpha$ -alkyl diazoacetate.<sup>23</sup> The reaction generates seven-membered rings having an all-carbon quaternary center in highly stereoselective manner, as demonstrated by the formation of **41** from **39** and **40** (eqn (11)).



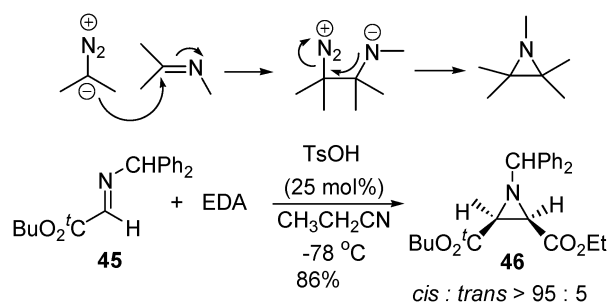
Nucleophilic addition of deprotonated EDA to *N*-tert-butylsulfonyl cycloketimines occurred to afford addition products, which can be converted into cyclic enamines via  $\text{Rh}_2(\text{OAc})_4$ -catalyzed ring expansion (Scheme 9).<sup>24</sup>

The acid-catalyzed reaction of acyl diazomethane with imines led to the formation of aziridine products (aza-Darzens



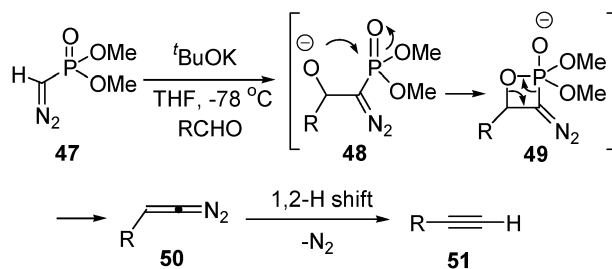
Scheme 9

reaction). This is an alternative method for nitrogen transfer to alkenes as compared to the common metal nitronoid process. Johnston and co-workers discovered that TsOH was a highly efficient Brønsted acid catalyst that catalyzed the direct aza-Darzens reaction, affording aziridines with high *cis* selectivity (Scheme 10).<sup>25</sup>



Scheme 10

The nucleophilic addition of diazo phosphonate **47** to aldehydes under basic conditions is a valuable way to synthesize terminal and internal alkynes (Seyforth–Gilbert reaction).<sup>26</sup> The reaction is driven by the interaction of the oxygen anion and the  $\text{P}=\text{O}$  double bond of the nucleophilic addition intermediate **48** (Scheme 11). This reaction has been widely used in organic synthesis. More recently, milder reaction conditions have been developed by using dimethyl-2-oxopylphosphonate, from which the diazophosphonate anion was generated by base-promoted deacetylation.<sup>27</sup>

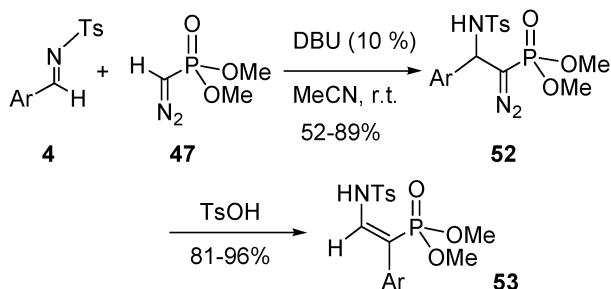


Scheme 11

The nucleophilic addition of  $\alpha$ -diazophosphonate **47** to aryl *N*-tosylimine **4** in the presence of catalytic DBU has been studied in our group (Scheme 12). The reaction afforded  $\alpha$ -aryl  $\beta$ -(*N*-tosyl)amino phosphonate derivatives **52** in good yields as stable products. These addition products were further



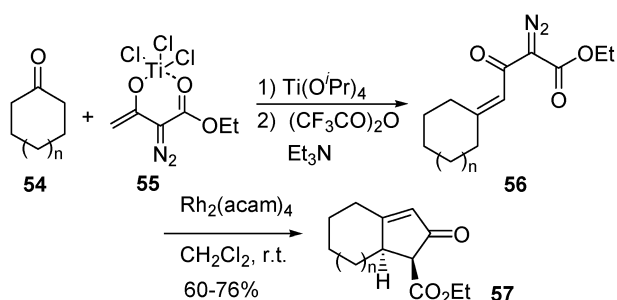
subjected to TsOH-catalyzed diazo decomposition to yield  $\alpha$ -aryl  $\beta$ -(*N*-tosyl)enamino phosphonates **53** through 1,2-aryl migration. The Rh(II)-catalyzed reaction of **52** afforded a mixture of 1,2-aryl and 1,2-H migration products.<sup>28</sup>



Scheme 12

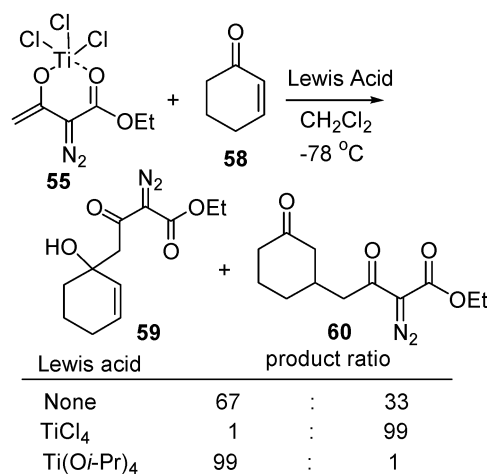
### 3. Nucleophilic addition by $\alpha$ -diazo $\beta$ -ketoester derived enolates

$\beta$ -Keto  $\alpha$ -diazocarbonyl compounds are more stable than acyl diazomethanes and enolates can be generated from them. Calter and co-workers reported the nucleophilic addition to aldehydes of Ti(IV) enolate **55** that was derived from  $\beta$ -keto  $\alpha$ -diazocarbonyl compounds.<sup>29</sup> However, the reaction of the same Ti(IV) enolate with less reactive ketones was found to be very sluggish. To enhance the reactivity of the carbonyl group, one equivalent of Ti(O<sup>*i*</sup>Pr)<sub>4</sub> was introduced to the reaction system, and under such conditions the nucleophilic addition occurred smoothly and afforded the expected alcohol in reasonable yields.<sup>30</sup> The addition product could be dehydrated with (CF<sub>3</sub>CO)<sub>2</sub>O–Et<sub>3</sub>N at room temperature, affording  $\alpha,\beta$ -unsaturated diazocarbonyl compounds **56**. Subsequent Rh<sub>2</sub>(acac)<sub>4</sub>-catalyzed intramolecular C–H insertion yielded bicyclic fused cyclopentenone derivatives **57** in moderate yields (Scheme 13). This three-step operation constitutes an efficient approach to bicyclic fused cyclopentenone derivatives, which are important structural units of many natural products.



Scheme 13

The nucleophilic addition of Ti(IV) enolates to  $\alpha,\beta$ -unsaturated carbonyl compounds such as **58** inevitably meets selectivity problems, namely 1,2- vs. 1,4-addition. An interesting Lewis-acid additive effect was observed in this type of nucleophilic addition. In the reaction of enone **58** with Ti(IV) enolate **55**, a mixture of 1,2- and 1,4- addition products **59** and **60** was obtained in a ratio of 67 : 33 when there was no additive added. Adding one equivalent of Ti(O<sup>*i*</sup>Pr)<sub>4</sub> increased the ratio to 99 : 1. Surprisingly, with TiCl<sub>4</sub> as additive under otherwise



Scheme 14

identical conditions the selectivity was completely reversed to 1 : 99 (Scheme 14). This remarkable Lewis acid-controlled switch of selectivity can be rationalized by a dimeric structure that involves bridging chlorine atoms (Fig. 1).<sup>31</sup>

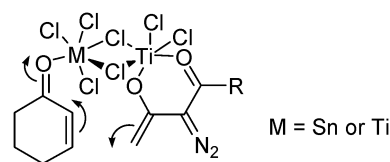
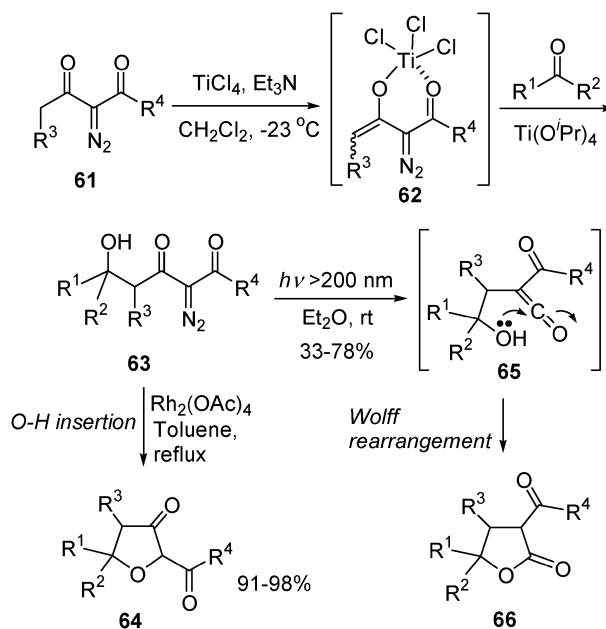


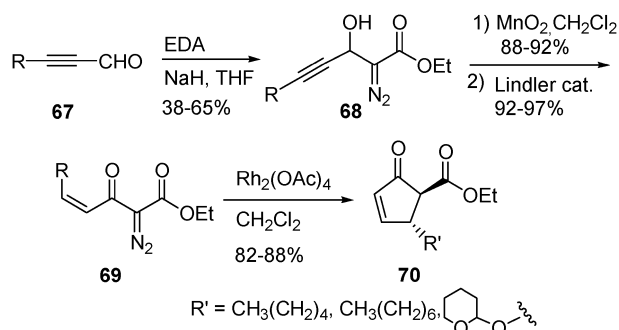
Fig. 1

The addition products **63** of Ti(IV)-enolate **62**, derived from  $\beta$ -keto  $\alpha$ -diazo carbonyl compounds, to ketones can be further converted into 3-keto tetrahydrofuran derivatives **64** by Rh<sub>2</sub>(OAc)<sub>4</sub>-catalyzed diazo decomposition. Alternatively, the same addition products undergo photo-induced Wolff rearrangement/intramolecular nucleophilic addition of ketene intermediate **65**, affording  $\gamma$ -butyrolactone derivatives **66** (Scheme 15).<sup>32</sup>



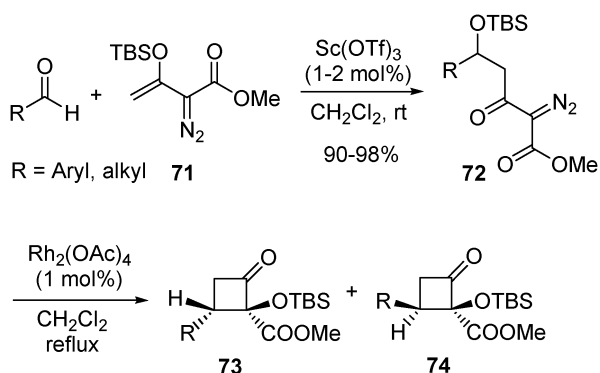
Scheme 15

Deng and co-workers reported the nucleophilic addition of EDA to alkynyl aldehydes (Scheme 16).<sup>33</sup> The hydroxyl group of the addition products **68** could be further converted to  $\beta$ -keto  $\alpha$ -diazo carbonyl compounds **69** through oxidation and hydrogenation, in which the triple bond was hydrogenated to a *cis* double bond. Finally,  $\text{Rh}_2(\text{OAc})_4$ -catalyzed intra-molecular C–H insertion gives cyclopentenone derivatives **70** in excellent yields.



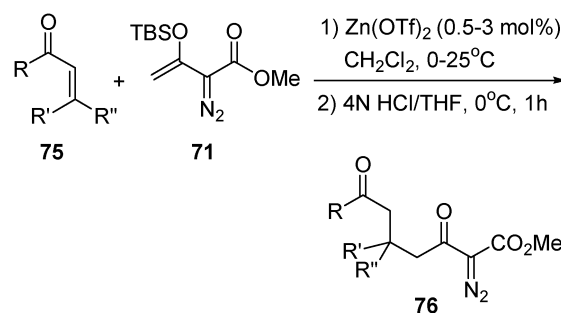
Scheme 16

Silicon enolates derived from  $\beta$ -keto  $\alpha$ -diazoesters such as **71** have been successfully used in Mukaiyama–aldol type reaction with aromatic and aliphatic aldehydes. Doyle and co-workers reported that scandium(III) triflate was an efficient catalyst in this reaction for the aldehydes with strong electron withdrawing groups.  $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction of the addition products **70** affords cyclobutanone derivatives **73** and **74** (Scheme 17). The predominant 1,4 C–H insertion is attributed to the activation effect of the OTBS group. Furthermore, with the strategy of using Lewis-acid activation as the case of addition to ketones, the nucleophilic addition of  $\beta$ -keto  $\alpha$ -diazoester-derived enolates can be extended to the reaction with imines.<sup>34</sup>



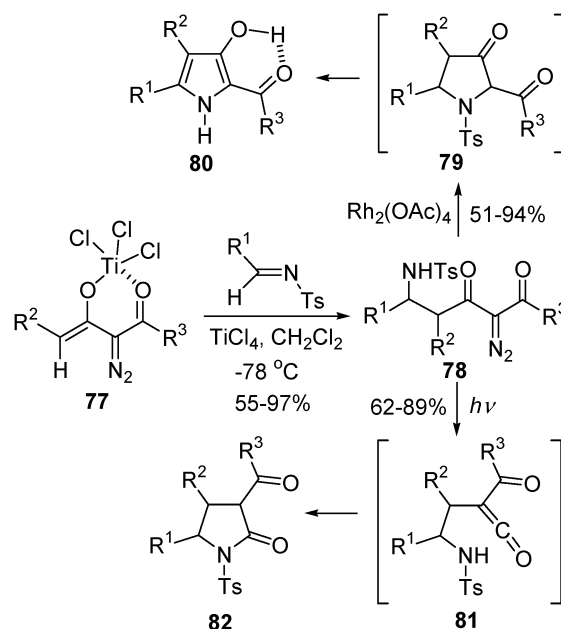
Scheme 17

Catalytic Mukaiyama–Michael type addition of methyl 3-(trialkylsilyloxy)-2-diazo-3-butenate **71** to  $\alpha,\beta$ -unsaturated enones **75** has been reported by Doyle and co-workers. In this reaction, zinc(II) triflate was found to be a suitable catalyst, and under the optimized reaction conditions the Mukaiyama–Michael addition products **76** were obtained in excellent yields for a wide range of enone substrates under the optimized reaction conditions (Scheme 18).<sup>35</sup>



Scheme 18

The reaction of Ti(IV)-enolates derived from  $\beta$ -keto  $\alpha$ -diazo carbonyl compounds with *N*-tosylimine was found very sluggish. Similar to the reaction of Ti(IV)-enolates with ketones, it was found that through activation of *N*-tosylimine with one equivalent of TiCl<sub>4</sub>, the reaction with Ti(IV)-enolates occurred smoothly, affording  $\delta$ -(*N*-tosyl)amino  $\alpha$ -diazocarbonyl compounds **78** in good yields (Scheme 19). Subsequent  $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction of the addition products led to the formation of pyrrole derivatives **80**, presumably through elimination of the initially formed intra-molecular N–H insertion products **79**. Similarly, irradiation of the addition products **78** with a high-pressure Hg lamp resulted in Wolff rearrangement, affording ketene intermediates **81**, which were trapped by an internal *N*-tosyl-protected amino group to finally give  $\gamma$ -lactam derivatives **82**.<sup>36</sup>



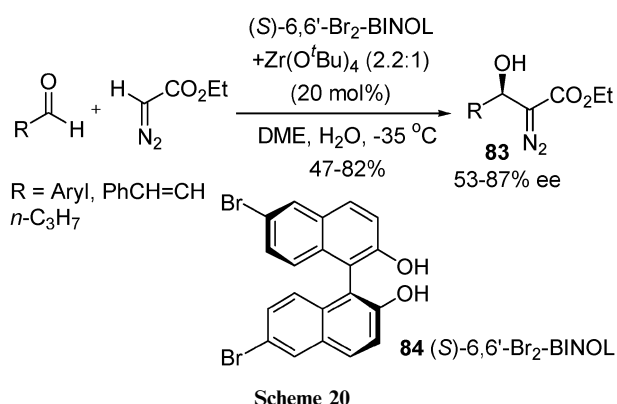
Scheme 19

#### 4. Asymmetric nucleophilic addition with diazo compounds

Asymmetric C–C bond formation has been one of the most important topics in organic synthesis over many years. Aldol reaction and Michael addition are the two powerful

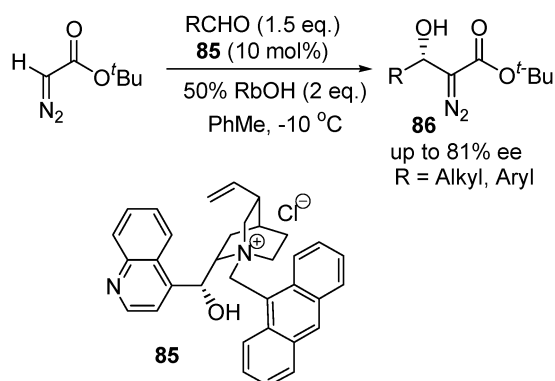
and efficient C–C bond-forming reactions and their asymmetric catalysis has attracted great attentions. Since the  $\alpha$ -diazocarbonyl compounds can serve as nucleophiles in aldol-type and Michael-type reactions, it would be a natural extension to further develop asymmetric reactions with these diazo group-containing nucleophiles.

Thus we proceeded to investigate the reaction of EDA with aldehydes under chiral Lewis acid catalysis. After screening a series of catalysts, including B(III), Ti(IV) and Al(III) complexes, and various BINOL derived chiral ligands, it was concluded that a Zr(IV) catalyst, prepared from Zr(O<sup>t</sup>Bu)<sub>4</sub> and 2.2 equivalents of (*S*)-6,6'-Br<sub>2</sub>-BINOL **84** was effective for the addition reaction, giving the products **83** with moderate to good enantioselectivity (Scheme 20). Double activation of the aldehyde substrate and the EDA by the chiral Zr(IV) complex has been proposed to account for the enantioselectivity.<sup>37</sup>



Scheme 20

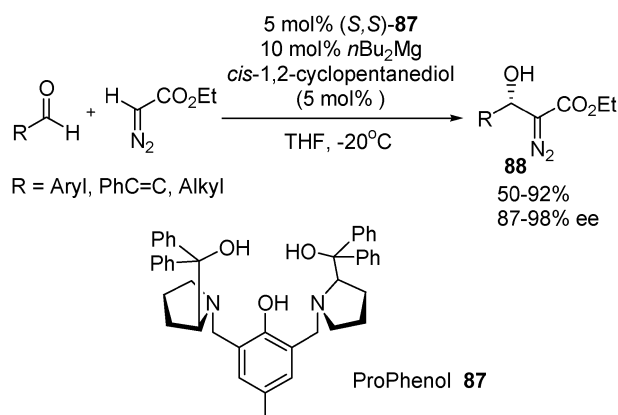
Nishida and co-workers then developed a reaction system with a chiral phase-transfer catalyst for the aldol-type reaction of aldehydes with *tert*-butyl diazoacetate. By using a cinchonidinium salt as a chiral catalyst, a similar level of enantioselectivity has been achieved (Schemes 21).<sup>38</sup>



Scheme 21

More recently, Trost and co-workers reported a Mg-catalyzed system for the direct aldol addition of EDA to aldehydes. With their chiral prophenol ligand **87** and a diol

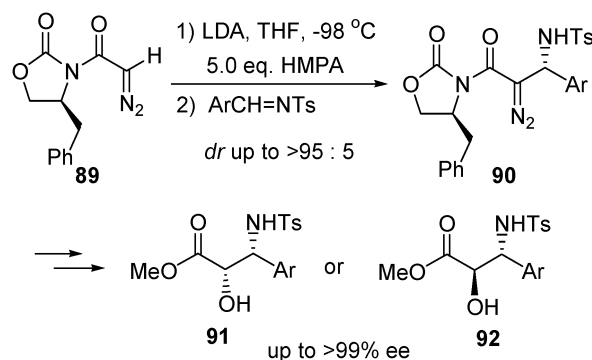
additive, the reaction affords the addition products with enantioselectivity up to 98% ee (Scheme 22).<sup>39</sup>



Scheme 22

The direct aldol addition product can be further converted into synthetically useful compounds. The diazo group can be oxidized with dimethyl dioxirane (DMD) to a keto group, which is subsequently reduced with NaBH<sub>4</sub> to a hydroxyl group with high *anti* selectivity.<sup>40</sup> Thus the overall transformation from EDA and aldehydes is a three-step synthesis of *anti*  $\alpha,\beta$ -dihydroxy esters.

The corresponding asymmetric addition of diazo group-containing nucleophiles to C=N bonds was initially attempted by the chiral auxiliary approach.  $\alpha$ -Diazocarbonyl compounds **89** tethered with chiral auxiliaries were synthesized and their reaction with *N*-tosylbenzaldimine was examined. Diazo amides tethered with Evans' chiral oxazolidinone auxiliary afforded addition products **90** with good diastereoselectivity (Scheme 23). The nucleophilic addition proceeded with high diastereoselectivity over a wide range of aromatic *N*-tosylimines. It was suggested that the rigidity of the amide bond in the deprotonated diazo amide was responsible for the observed high diastereoselectivities, as shown in Fig. 2. The diazo group of the addition products **90** were oxidized with dimethyldioxirane (DMD) after removal of the chiral auxiliary. Subsequent reduction of the oxo group with NaBH<sub>4</sub> produced *anti*- $\alpha$ -hydroxy- $\beta$ -amino esters **91** and **92** with high diastereoselectivities, while Pd/C-catalyzed hydrogenation afforded *syn*- $\alpha$ -hydroxy- $\beta$ -amino esters.<sup>41</sup>



Scheme 23



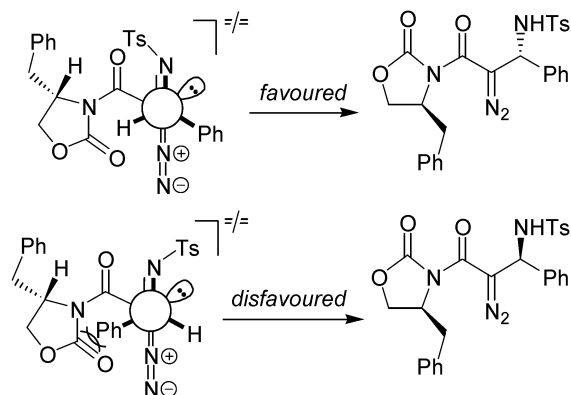
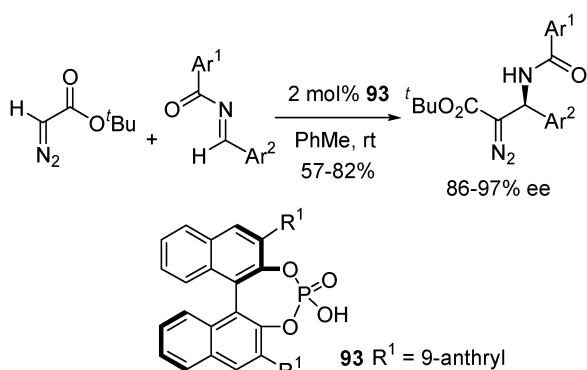
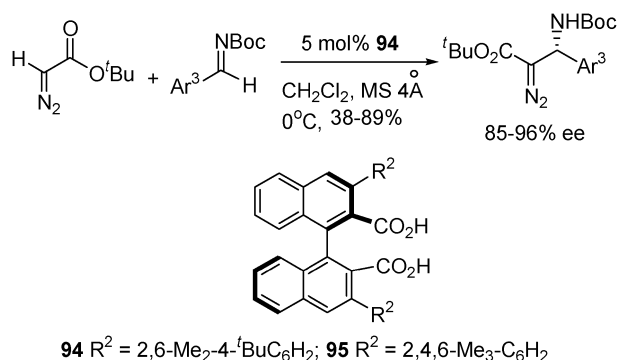


Fig. 2

The next challenge for this reaction would be asymmetric catalytic C=N bond addition. This has been recently reported by Terada *et al.* with chiral binaphthol monophosphoric acid **93** (Scheme 24),<sup>42</sup> and by Maruoka with chiral dicarboxylic acid **94** (Scheme 25). In both cases, high enantioselectivities have been achieved.<sup>43</sup>

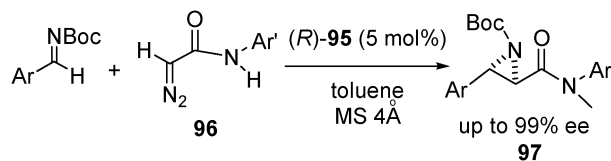


Scheme 24



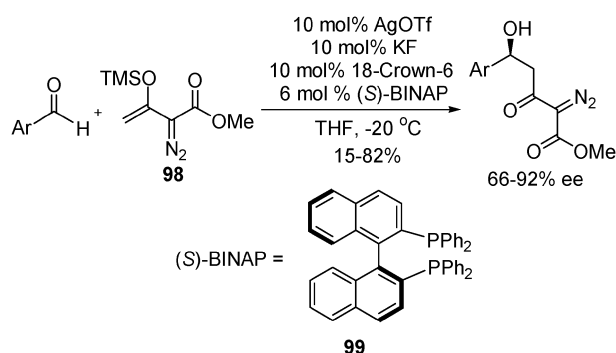
Scheme 25

Catalytic enantioselective aza-Darzens reactions have recently repeated by Maruoka<sup>44a</sup> and Akiyama.<sup>44b</sup> In Maruoka's report, an axially chiral dicarboxylic acid catalyst is found to be highly efficient in initiating the reaction of *N*-Boc imines with diazoacetamides **96**, affording aziridines with high enantioselectivities (Scheme 26).



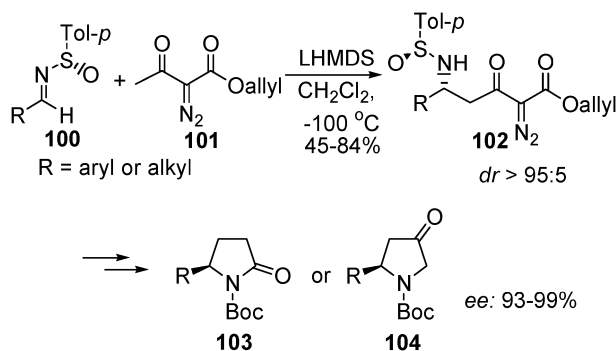
Scheme 26

Asymmetric catalysis in Mukaiyama aldol type reaction with  $\beta$ -keto  $\alpha$ -diazoester-derived silicon enolate **98** has been developed by Doyle and co-workers. With AgOTf and (*S*)-BINAP ligand **99**, high enantioselectivity has been achieved (up to 92% ee) (Scheme 27).<sup>45</sup>



Scheme 27

The corresponding asymmetric C=N bond addition was studied with the chiral auxiliary approach. Mukaiyama type addition with the silyl enol of  $\alpha$ -diazoacetate and chiral *N*-(benzylidene)-*p*-toluene **100** was first investigated under catalysis with Lewis acids, such as Et<sub>2</sub>O·BF<sub>3</sub>, TiCl<sub>4</sub>, Cu(OTf)<sub>2</sub>, La(OTf)<sub>3</sub> and TBSOTf. However, only TBSOTf showed reaction and provided a low yield of the expected addition product. It was then found that straightforward generation of the enolate with a strong base [lithium bis(trimethylsilyl)-amide] LHMSD gave the addition product in good yield with excellent diastereoselectivity. The addition products **102**, after converting the *N*-sulfinyl group to *N*-butyloxycarbonyl group, could be transferred to 2-oxopyrrolidines **103** and 3-oxopyrrolidines **104** with photo-induced Wolff rearrangement or Rh(II)-catalyzed intramolecular N-H insertion (Scheme 28). The overall transformation constitutes a new route to



Scheme 28

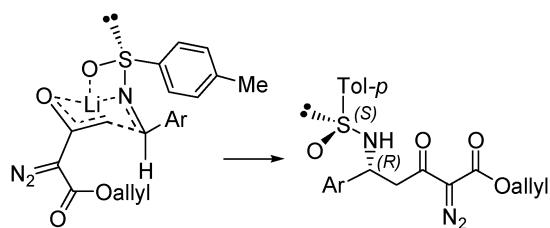


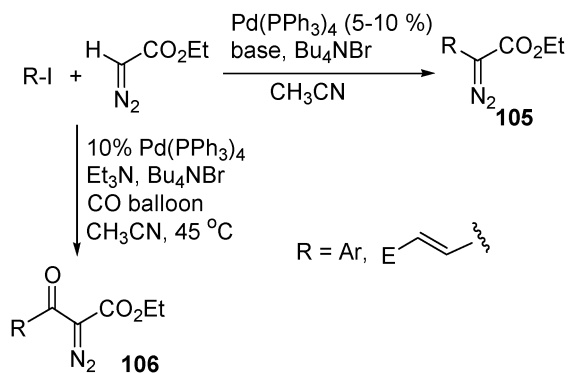
Fig. 3

5-substituted 2-oxo- and 3-oxopyrrolidines of high enantiomeric purity.<sup>46</sup>

The stereochemical outcome of the nucleophilic addition is consistent with the previous reports of the addition of enolates derived from esters or ketones to *N*-sulfinyl imines. We could thus conclude that the sense of induction can be similarly predicted by invoking a six-membered Zimmerman–Traxler-type transition state as previously suggested for the similar addition of acetate enolates to *N*-sulfinyl imines (Fig. 3), in which the chelation of  $\text{Li}^+$  with the sulfinyl oxygen plays a vital role in controlling the attack of the enolate to the *Re* face of the imine.

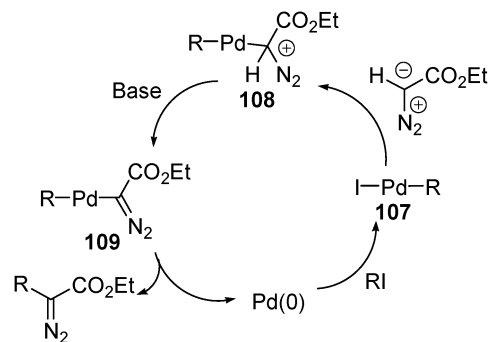
## 5. $\alpha$ -Diazocarbonyl compounds as nucleophiles in Pd-catalyzed reactions

Palladium-catalyzed cross-coupling reactions are among the most powerful methods for the formation of C–C bonds. In general, the Pd-catalyzed cross-coupling involves (1) oxidative addition; (2) transmetalation/nucleophilic substitution/ligand exchange; (3) reductive elimination. In the second step, various carbon nucleophiles derived from active methylene compounds, such as ketones, esters, amides and nitriles, have been applied. However, diazo compounds have not been used as cross-coupling partners in Pd-catalyzed reactions. A recent study from our group has indicated that EDA undergoes efficient Pd-catalyzed cross-coupling with aryl or vinyl iodides (Scheme 29). Remarkably, the diazo functionality remains unchanged in this reaction. Moreover, carbonylation occurs prior to the coupling when the reaction is carried out under an atmosphere of CO, affording  $\beta$ -keto  $\alpha$ -diazo carbonyl compounds **105** in moderate yields. This reaction represents a novel approach to introduce diazo functionality to organic compounds.<sup>47</sup>



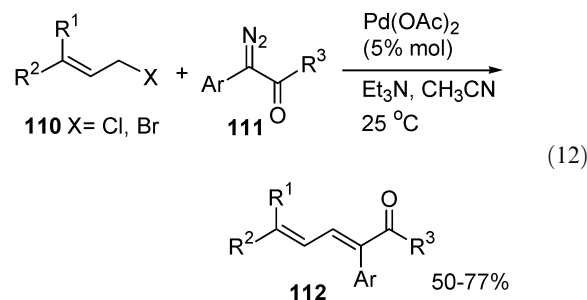
Scheme 29

The proposed mechanism for this reaction involves oxidative addition of  $\text{Pd}(0)\text{L}_n$  with aryl or vinyl iodide affording the  $\text{Pd}(\text{II})$  intermediate **107** followed by EDA coordination to  $\text{Pd}(\text{II})$  intermediate **108** (Scheme 30). Deprotonation followed by reductive elimination afforded the final coupling product. Remarkably, nitrogen extrusion, which is a very facile process for transition metal-complexed diazo compounds, does not occur in this process. This indicates the electron back donation from Pd in intermediate **108** is not as strong as from  $\text{Rh}(\text{II})$  or  $\text{Cu}(\text{I})$  in similar complexes, which are known to generate metal carbenes efficiently from diazo compounds.<sup>1</sup>

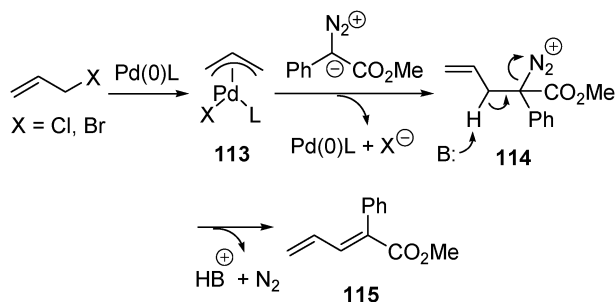


Scheme 30

$\pi$ -Allylic palladium complexes are important intermediates in palladium-catalyzed reactions. The  $\pi$ -allylic palladium complexes are electrophilic in character and react with various nucleophiles such as amines, alcohols and carbon nucleophiles. In particular, the reactions with carbon nucleophiles have been developed into a valuable method for the formation of C–C bonds. The common carbon nucleophiles used in Pd-catalyzed allylation include anions or enolates derived from carbonyl compounds such as ketones, esters and 1,3-dicarbonyl compounds. We have conceived that it may be possible to employ  $\alpha$ -diazocarbonyl compounds as nucleophiles in the reaction of  $\pi$ -allylic palladium complexes. The investigation based on this idea led to the development of a palladium-catalyzed reaction of allylic halides **110** with aryl diazoacetates **111**. The reaction resulted in dinitrogen extrusion and generation of carbon–carbon double bonds, affording 1,3-diene derivatives **112** as the products (eqn (12)). The reaction with aryl diazoacetates proceeds well for a variety of allylic bromides and chlorides and also with high stereoselectivity.<sup>48</sup>



A plausible reaction pathway to account for the formation of dienes is considered as shown in Scheme 29. The reaction is initiated by the reduction of  $\text{Pd}(\text{II})$  to  $\text{Pd}(0)$  by the diazo



Scheme 31

compound, followed by the formation of  $\pi$ -allylpalladium complex **115**. For the diazo substrate to interact with the  $\pi$ -allylpalladium complex, there are two possibilities. One is direct attack of the allyl ligand, and the other is the attack of palladium. In the chemistry of  $\pi$ -allylpalladium complexes, it has been suggested that “soft” carbon centered nucleophiles, defined as those derived from conjugate acids whose  $pK_a < 25$ , usually attack the allyl ligand. On the contrary, “hard” carbon-centered nucleophiles, defined as those derived from conjugate acids whose  $pK_a > 25$ , attack the metal center of the  $\pi$ -allyl palladium complex, and the substitution occurs through subsequent transmetalation and reductive elimination. The  $pK_a$  values of conjugate acids of diazoesters and diazoketones have been estimated to be between  $-5$  and  $-2$ , respectively.<sup>1a</sup> Therefore, the  $\alpha$ -diazocarbonyl compounds are categorized as “soft” nucleophiles, which attack the allyl ligand. Subsequent deprotonation and dinitrogen extrusion from intermediate **114** lead to the formation of 1,3-diene product **115** (Scheme 31). However, other pathways involving coordination of the diazo substrate to palladium, and formation of a Pd carbene can not be strictly ruled out.

## Conclusions

The transformations shown in this article demonstrates that  $\alpha$ -diazocarbonyl compounds can function as nucleophiles under various conditions without decomposition of diazo functionality. This makes possible a variety of transformations other than the traditional process that directly decomposes the diazo functionality with generation of the metal carbene intermediate. Although in general  $\alpha$ -diazo carbonyl compounds are prepared by diazo transfer reactions of the corresponding carbonyl compounds, the addition reactions of nucleophiles containing diazo groups provide alternative and complementary methods to prepare highly functionalized diazo compounds. Further transition metal catalyzed reactions of the addition products demonstrate novel reactivity of these functionalized diazo compounds. Some of these reactions may find synthetic utilities. In particular, the condensation of diazo compounds with  $C=O$  or  $C=N$  is very useful because it can introduce a diazo group as well as a hydroxyl or an amino group in a single reaction step. Although further efforts are needed to improve both reactivity and selectivity, the stereo-control that has been achieved in this type of nucleophilic addition demonstrates the potential of this novel approach to generate C–C bonds with chiral centers.

## Acknowledgements

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