Russian Chemical Reviews **84** (7) 737 – 757 (2015) © 2015 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RCR4522

Recent advances in the chemistry of Rh carbenoids: multicomponent reactions of diazocarbonyl compounds

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Multicomponent reactions of diazo compounds catalyzed by Rh^{II} complexes become a powerful tool for organic synthesis. They enable three- or four-step processes to be carried out as one-pot procedures (actually as one step) with high stereoselectivity to give complex organic molecules, including biologically active compounds. This review addresses recent results in the chemistry of Rh-catalyzed multicomponent reactions of diazocarbonyl compounds with the intermediate formation of N-, O- and C=O–ylides. The diastereo- and enantioselectivity of these reactions and the possibility of using various co-catalysts to increase the efficiency of the processes under consideration are discussed.
The bibliography includes 120 references.

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I. Introduction

Aliphatic diazo compounds (ADC) are of great importance in organic chemistry and primarily in organic synthesis. Actually, every class of organic compounds can be prepared using diazo compounds.[1–6] A great impetus to the development of the chemistry of ADC was given by the broad application of catalytic methods for the synthesis and the use of transition metal complexes for selective transformations of diazo compounds into various target molecules. Metallocarbenes (carbenoids) are key intermediates in these reactions. These compounds are of major significance in synthetic and theoretical organic chemistry. The advances in this area of chemistry have been covered in a number of previous reviews,[7–10] the comprehensive monograph [11] published in 1998, and several relatively recent reviews concerned with the detailed consideration of different aspects and achievements in this rapidly progressing area of chemistry of aliphatic diazo compounds.[12–22]

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Current research interests of the authors: organic chemistry, reactions of ammonium ylides, catalytic reactions of diazocarbonyl compounds.

Received 17 October 2014
Uspekhi Khimii **84** (7) 737 – 757 (2015); translated by T N Safonova

At the present time, the emphasis is given to the promising area of research in the chemistry of catalytic transformations of ADC dealing with multicomponent processes. These reactions of ADC are initiated by transition metal complexes in the presence of several reagents and enable a multistep process to be carried out actually as a one-pot procedure with high diastereo- and enantioselectivity.

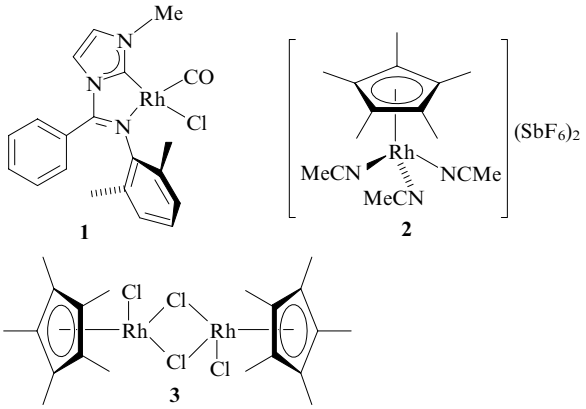
The present review considers main advances in the new stage of the development of chemistry of ADC related to Rh-catalyzed multicomponent reactions of diazocarbonyl compounds that proceed through the intermediate formation of ammonium, oxonium and carbonyl ylides. A small introductory section is devoted to main types of catalysts based on rhodium complexes that are used in these reactions. The review covers mainly studies published since 2000 up to the present, but in some cases earlier publications are included to complete the picture and for the systematic and logical presentation.

II. Main types of catalysts based on rhodium complexes

Numerous rhodium-based catalysts play a significant role in reactions of diazocarbonyl compounds, Rh^{II} complexes being most frequently used in these processes. Catalysts based on Rh^{I} are employed to a much lesser extent, although in recent years they found a niche in this area of research due to their unique catalytic activity in some chemical processes. Thus, Rh^{I} complexes **1** and related complexes with chelating N-heterocyclic iminocarbene

ligands proved to be much more efficient in the *cis*-stereoselective cyclopropanation[23–26] than Rh^{II} complexes.

Structures 1–3



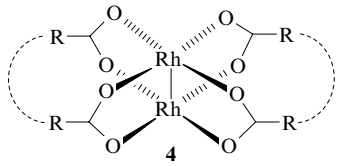
Complexes of Rh^{III}, for example tris(acetonitrile)(η^5-pentamethylcyclopentadienyl)rhodium(III) hexafluoroantimonate (**2**) and di-μ-chlorido-bis[chlorido(η^5-pentamethylcyclopentadienyl)rhodium(III)] (**3**), came into use in the chemistry of diazocarbonyl compounds only quite recently. However, despite the limited use, these complexes were shown to be very efficient and selective catalysts for reactions of diazo compounds with compounds containing $C(sp^2)-H$ bonds. In some cases, the use of these complexes made it possible to avoid undesirable side reactions, which usually occur in the presence of other rhodium catalysts.[27–31]

Divalent rhodium complexes Rh_2L_4 or Rh_2L_2 with bi- or tetradentate ligands L play an essential role in the chemistry of diazocarbonyl compounds. These complexes can catalyze a wide range of reactions, such as the insertion into C–H and X–H bonds (X = O, N, S, Si),[32–37] the cycloaddition,[14, 38, 39] the formation of ylides and so on.[11] The structure of the ligands L has a substantial effect on the pathway and selectivity of the catalytic reaction. Therefore, the structural features and efficiency of Rh^{II} complexes in different processes have received considerable attention in recent years.[16, 40]

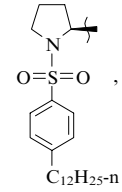
Dirhodium carboxylates **4**, which are derivatives of achiral or chiral mono- or dicarboxylic acids ($L = RCO_2^-$, $R^*CO_2^-$) containing various substituents (alkyl, aryl, perfluoroalkyl, *etc.*),[16, 40] belong to the most abundant class of rhodium catalysts.

The structure of chiral ligands is a key issue for the enantioselective reactions since the degree of enantioselectivity strongly depends on the nature of such ligands. The following compounds can serve as ligands in chiral rhodium catalysts: carboxylic acids based on pyrrolidine derivatives, for example, (2*S*)-*N*-(4-dodecylphenylsulfonyl)prolinate (*S*-DOSP), (2*S*)-*N*-(4-*tert*-butylphenylsulfonyl)prolinate, *etc.*; phthalimide derivatives, for example, *N*-phthaloyl-(*S*)-*tert*-leucinate (*S*-PTTL), *N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate (*S*-TCPTTL), (*S*)-(+)-(1-adamantyl)phthalimidoacetate, *etc.*; cyclopropane derivatives, for example, (*S*)-(+)-1-(4-bromophenyl)-2,2-diphenylcyclopropanecarboxylate (*S*-BTPCP); other cyclic and heterocyclic compounds.[16, 40]

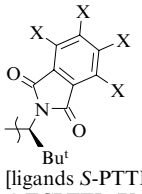
Structures 4



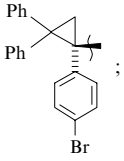
R = Me, n-C_7H_{15}, Bu^t, C_3F_7,



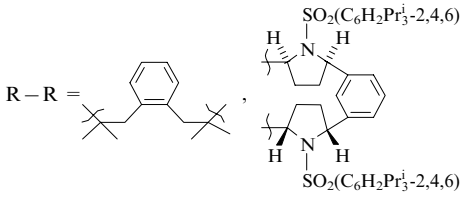
(ligand *S*-DOSP)



[ligands *S*-PTTL (X = H), *S*-TCPTTL (X = Cl)]

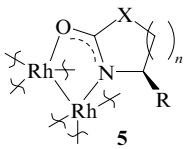


(ligand *S*-BTPCP)



Carboxamidates **5** belong to another widely used type of rhodium complexes (only one of the four ligands is shown for the simplicity).

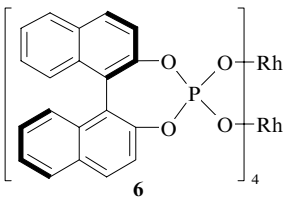
Structures 5

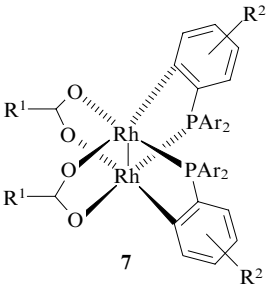


R = H, Alk, Ar, C(O)R′, CO_2R'; *n* = 0–2; X = CR′R″, O, NR′;
for example: *n* = 1, R = CO_2Me: X = CH_2, O, NAc;
n = 0, R = CO_2Bu^i, X = CH_2

The electrophilicity of the rhodium centre decreases in the series dirhodium perfluorocarboxylates > carboxylates > carboxamidates. This, as a rule, leads to higher selectivity of the reactions of diazocarbonyl compounds in the presence of Rh^{II} carboxamide complexes as the catalysts. The reactivity of carboxamide complexes can also be varied by changing the structure of the ligand, for instance,

Structures 6, 7





$R^1 = C_nF_{2n+1}$, Me;
R^2 = 4-Me, 4-CF_3, 4-C_3F_7;
Ar = Ph, 4-MeC_6H_4,
3-$Me_2C_6H_3$, *etc.*

by introducing the strained oxazetine ring, like in dirhodium tetrakis(isobutyl-2-oxazetidine-(4*S*)-carboxylate) (structure **5**: $n = 0$, R = CO_2Bu^i, X = CH_2).

Phosphorus-containing rhodium catalysts, primarily dirhodium(II) phosphates, for example, dirhodium tetrakis(1,1′-binaphthyl-2,2′-diylphosphate) (**6**), and complexes **7** with *ortho*-metallated phosphine ligands[16] are also of interest.

III. Generation and transformations of ammonium ylides

III.1. Intermolecular transformations of N-ylides in three-component reactions

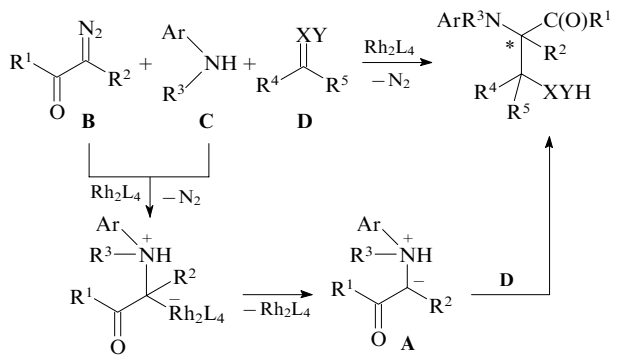
Ammonium ylides **A** generated from α-diazocarbonyl compounds **B** and nitrogen-containing compounds **C** are highly reactive intermediates, which readily react with various electrophilic reagents **D** (Scheme 1). Extensive studies of the scope of three-component reactions based on transformations of intermediate ammonium ylides **A** demonstrated that these reactions can easily be carried out with a large range of the following classes of substrates **B**–**D**:

— diazo compounds — diazoacetic acid esters,[41–43] α-substituted diazoacetates,[41–50] α-diazoketones[42,43,51] and diazophosphates;[48]

— nitrogen-containing compounds — primary and secondary aromatic amines,[41–45,47,49,50,52–54] amides[46,48] and phosphoramidates[48] (see †);

— electrophilic reagents — imines,[44,46,48,50] aldehydes,[41,49,52–54] diazenes,[42] as well as α,β-unsaturated carbonyl compounds.[43,45,47,51,56]

Scheme 1

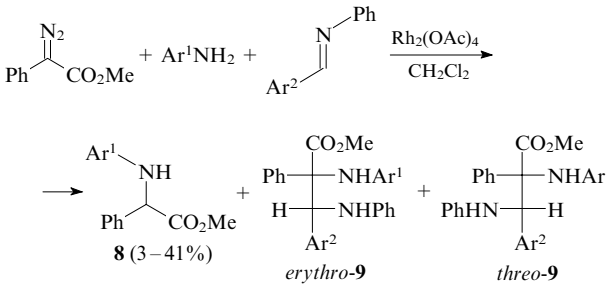


Section III deals with Rh^{II}-catalyzed three-component reactions (3MCR) of diazocarbonyl compounds with nitrogen-containing substrates in the presence of different types of electrophilic reagents. The diastereo- and enantioselectivity of these reactions and the use of co-catalysts in order to increase the selectivity of the processes under study are discussed.

III.2. Reactions with imines

The dirhodium tetraacetate-catalyzed decomposition of α-aryldiazoacetates in the presence of aromatic amines and imines was one of the first described three-component reactions of diazo compounds.[44] The reaction gave the following two major products: methyl 2-aryl-2-(arylamino)acetate **8** (generated through the insertion of intermediate carbenoid into the amine N–H bond) and the product of the three-component reaction — methyl 2,3-diaryl-2,3-di(arylamino)propanoate **9** (Scheme 2).

Scheme 2



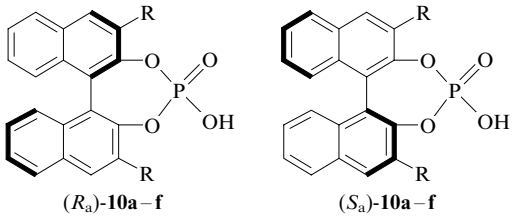
Ar^1 = 4-$O_2NC_6H_4$, 4-$F_3CC_6H_4$, 2,4-$(O_2N)_2C_6H_3$ (yield of **9** is 50%–78%, *dr* ⩽ 96 : 4); Ar^1 = Ph, 4-ClC_6H_4 (yield of **9** is 26%–66%, *dr* ⩽ 91 : 9); Ar^2 = 4-$O_2NC_6H_4$

It was shown[44] that in the presence of *N*-methylaniline, the reaction affords mainly N–H insertion products (yield 52%, ratio **8** : **9** = 87 : 13), whereas the reactions with primary aromatic amines give diamino esters **9** as the major products (26%–78%), while the N–H insertion proceeds to a lesser extent (3%–41%). The introduction of electron-withdrawing substituents into aromatic amines (Ar^1 = 4-XC_6H_4; X = CF_3, NO_2) facilitates the formation of substituted diamines **9** as the major products, the reaction being diastereoselective to give mainly *erythro* isomers (*erythro* : *threo* ⩽ 96 : 4; see Scheme 2).[44]

Since α,β-diamino esters are important components of various biologically active compounds,[57] attempts were made to perform the enantioselective reaction in the presence of co-catalysts. Chiral phosphoric acids[46,48,50] and squaramide derivatives[50] were tested as such co-catalysts.

The use of dirhodium tetraacetate with the addition of co-catalysts, such as 3,3′-substituted 1,1′-binaphthyl-2,2′-diylhydrophosphates **10a**,**b**, in the reactions of α-substituted diazoacetates with carbamates (precursors for ammonium ylides) and imides made it possible to prepare individual (2*R*,3*S*)- or (2*R*,3*R*)-α,β-diamino esters **11** (Scheme 3).[46]

Structures 10



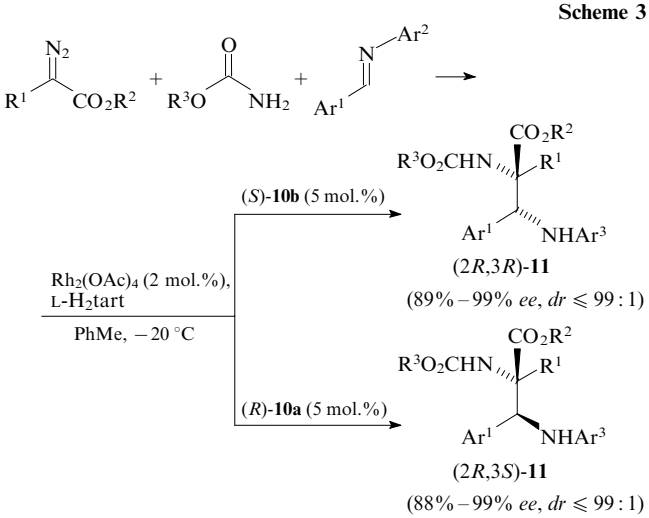
(R_a)-**10a**–**f** (S_a)-**10a**–**f**

R = 3,5-$(F_3C)_2C_6H_3$ (**a**), $SiPh_3$ (**b**), phenanthren-9-yl (**c**), 2,4,6-$Pr^i_3C_6H_2$ (**d**), 4-FC_6H_4 (**e**), 4-$F_3CC_6H_4$ (**f**)

For instance, it was found that the reactions performed in the presence of acids (R_a)-**10a** and (S_a)-**10b** as co-catalysts afford (2*R*,3*S*)-2-[(alkoxycarbonyl)amino]-3-(arylamino)-propanoates *syn*-**11** or (2*R*,3*R*)-isomers *anti*-**11**, respectively, in high yields with high diastereo- and

† Aliphatic amines, being strong nucleophiles, can poison or modify rhodium and other catalysts employed in these reactions (see Ref. 55 and references cited therein). Therefore, nitrogen-containing substrates bearing a less nucleophilic nitrogen atom are most commonly used in these processes as components of ammonium ylides.

Scheme 3



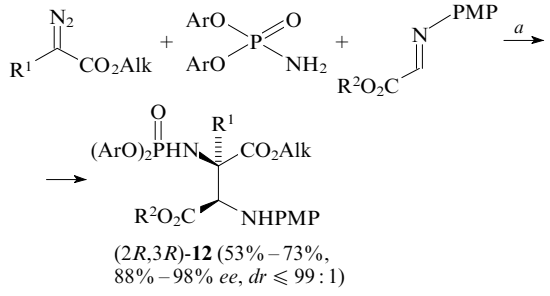
R^1 = Ph, XC_6H_4 (X = 4-Me, 4-F, 4-Br, *etc.*), Bn, Me;
R^2 = Me, Et; R^3 = Bn, Bu^t; Ar^1 = Ph, YC_6H_4 (Y = 2-Br, 3-Br, 4-Br, 4-O_2N, *etc.*); Ar^2 = Ph, PMP, *etc.*); PMP is *p*-methoxyphenyl; H_2tart is tartaric acid

enantioselectivity: the yield of (2*R*,3*S*)-**11** was up to 81% [ratio (2*R*,3*S*) : (2*R*,3*R*) = 9 : 1, 99% *ee*], the yield of (2*R*,3*R*)-**11** was up to 89% [ratio (2*R*,3*R*) : (2*R*,3*S*) = 99 : 1, 99% *ee*] (see Scheme 3)[46] (see ‡).

In the authors' opinion, the stereochemistry of the reaction products produced in these three-component processes is controlled by *R*- and *S*-co-catalysts **10a** and **10b** *via* hydrogen bonding with intermediate ammonium ylide and imine. Meanwhile, the role of dirhodium tetraacetate is apparently only to generate Rh carbenoid and intermediate ammonium ylide **A** (see Scheme 1).[46]

To extend the range of imines used in three-component processes, attempts were made to perform the reaction with (*E*)-2-[(4-methoxyphenyl)imino]acetates.[48] The use of carbamates as precursors for ammonium ylides in these reactions led to no effect. However, the employment of phosphoramidates for this purpose was quite successful. The reaction of diazoacetates in the presence of co-catalyst (S_a)-**10c** (R is phenathren-9-yl) gave (2*R*,3*R*)-2-[(diaryloxy)phosphorylamino]-3-(4-methoxyphenylamino)succinates **12** in good yields with high diastereo- and enantioselectivity [(2*R*,3*R*) : (2*R*,3*S*) ⩽ 99 : 1, 88%–98% *ee*] (Scheme 4)[48] (see §).

Scheme 4

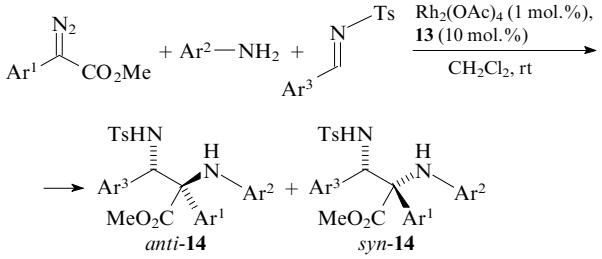


R^1 = Ph, PMP, XC_6H_4 (X = 4-Hal, 3-Cl), Bu^n, Bz;
R^2 = Me, Et, Pr^i, Bu^t; (*a*) $Rh_2(OAc)_4$ (2 mol.%), (*S*)-**10c** (2.5 mol.%), PhMe, rt; PMP is *p*-methoxyphenyl

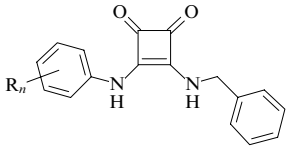
‡ Hereinafter, the values of the enantiomeric excess (*ee*) refer to the major stereoisomer.

The reactions with *N*-arylsulfonylimines exhibiting relatively low reactivity in the presence of phosphoric acid derivatives **10** or urea (thiourea) derivatives as co-catalysts do not produce α,β-diamines, but give almost exceptionally N–H insertion products.[50] By contrast, the application of 3-arylamino-4-(benzylamino)cyclobut-3-ene-1,2-diones **13** as co-catalysts for the decomposition of α-aryldiazoacetates by dirhodium tetraacetate in the presence of arylamines and *N*-tosylimines resulted in the preparation of the corresponding (2*R*,3*S*)-2-arylamino-3-(4-methylphenylsulfonamido)-propanoates **14** in 40%–70% yields with good diastereoselectivity (*anti* : *syn* ⩽ 85 : 15) (Scheme 5) (see ¶).[50]

Scheme 5



Ar^1 = Ph, XC_6H_4 (X = 4-Me, 4-MeO, 4-Br, *etc.*);
Ar^2 = Ph, YC_6H_4 (Y = 2-Cl, 2-I, 2-MeO, *etc.*);
Ar^3 = ZC_6H_4 (Z = 4-Br, 4-O_2N, 4-Me, *etc.*); Ts = 4-$MeC_6H_4SO_2$

13 =  (R_n = 4-CF_3, 3,5-$(CF_3)_2$)

III.3. Reactions with 1,2-disubstituted diazenes

Studies of three-component reactions involving ammonium ylides and (*E*)-diazene-1,2-dicarboxylates are of interest, because these reactions would be expected to form new C–N bonds. Actually, the reaction of N-ylides, which are generated from ethyl 2-diazoacetate or 2-diazo-1-phenylethanone and aromatic amines, with diethyl azodicarboxylate (DEAD) affords 1-(1-arylamino-2-ethoxy-2-oxoethyl)hydrazine-1,2-dicarboxylates **15** or 1-(1-arylamino-2-oxo-2-phenylethyl)hydrazine-1,2-dicarboxylates **16**, respectively, in good yields (Scheme 6).[42]

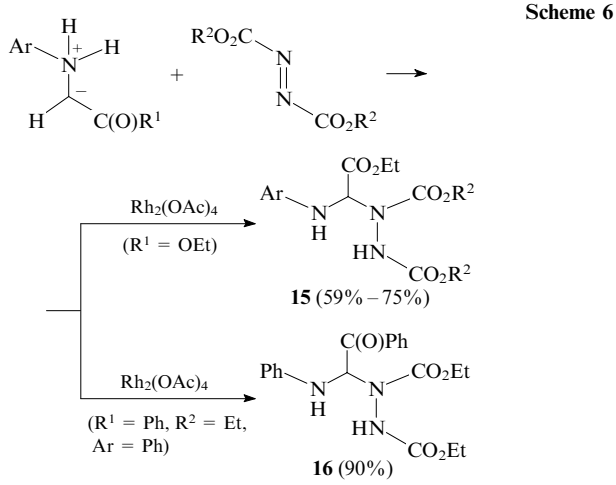
However, attempts to synthesize related aminals by the reactions of phenyl diazoacetate or diazomalonate with aniline and DEAD failed; instead, the reactions produced methyl 2-phenyl-2-(phenylimino)acetate (**17**) and dimethyl 2-(phenylimino)malonate (**18**), respectively, in good yields (Scheme 7).[42]

The similar reaction with diazomalonate and *p*-nitroaniline as precursors for intermediate ammonium ylide affords

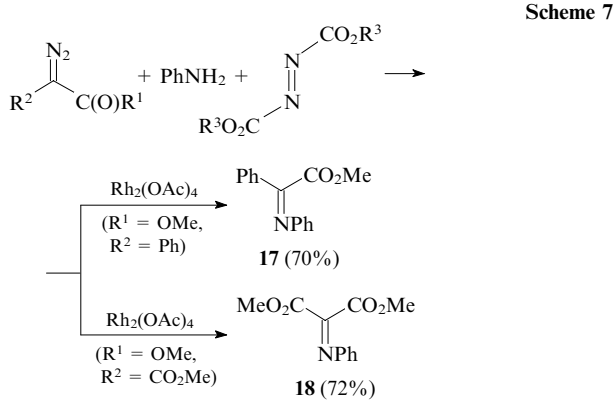
§ Hereinafter, unless otherwise specified, the total yield of two diastereomers is given.

¶ Hereinafter, as in most of original publications, the formation of products as a racemate is not mentioned for the simplicity.

Scheme 6

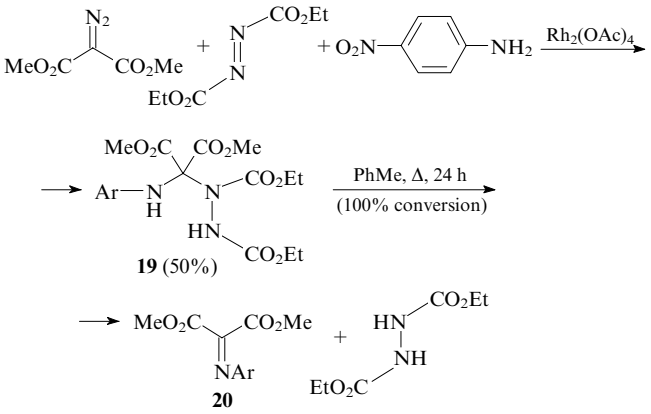


Scheme 7



diethyl 1-(2-arylamino-1,3-dimethoxy-1,3-dioxoprop-2-yl)hydrazine-1,2-dicarboxylate (**19**) in 50% yield.[42] The heating of the latter in toluene gives imine **20** and diethyl hydrazine-1,2-dicarboxylate (Scheme 8).[42]

Scheme 8



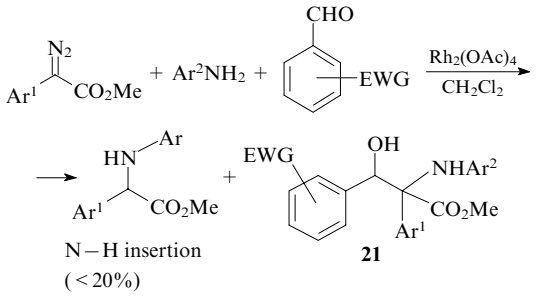
Ar = 4-$O_2NC_6H_4$

Apparently, imines **17** and **18** are generated in the reactions of phenyl diazoacetate and diazomalonate from unstable aminals **15** and **16**, which, under the reaction conditions, eliminate hydrazinedicarboxylate to give the corresponding imines.[42]

III.4. Reactions with aldehydes

The three-component reaction of α-aryldiazoacetates with aromatic amines and aldehydes produces a mixture of methyl 2-aryl-2-arylaminoacetates (N–H insertion products) and methyl 2,3-diaryl-2-arylamino-3-hydroxypropanoates **21**.[41,44] In these reactions, the yields of target aminohydroxy esters **21** are 40%–74% (the isomer ratio *erythro* : *threo* varies from 1 : 1 to 2 : 1), whereas the yields of N–H insertion by-products are not higher than 20% (Scheme 9).[41]

Scheme 9



Ar1 = Ph, PMP; EWG = 4-NO_2, 2-NO_2; Ar2 = 2-$MeOC_6H_4$, Ph (yield of **21** is 65%–74%), 4-XC_6H_4 (X = Cl, CF_3, NO_2, OMe; yield of **21** is 40%–58%)

The results of the reactions of the *in situ* generated ammonium ylides with aldehydes substantially depend on the nature of substituents in all components of 3MCR. Unlike the reactions with imines,[44] these processes are characterized by substantially lower diastereoselectivity.[41]

As mentioned above for the reactions of N-ylides with imines, the three-component reaction can usually be performed with high enantioselectivity using a mixture of an achiral Rh catalyst and chiral Brønsted acid.[46,48,50] In most cases, the application of only a chiral Rh catalyst in these reactions proved to be inefficient due, apparently to the fact that the reaction proceeds through 'free' ammonium ylide (which is not complexed with the chiral catalyst).[52]

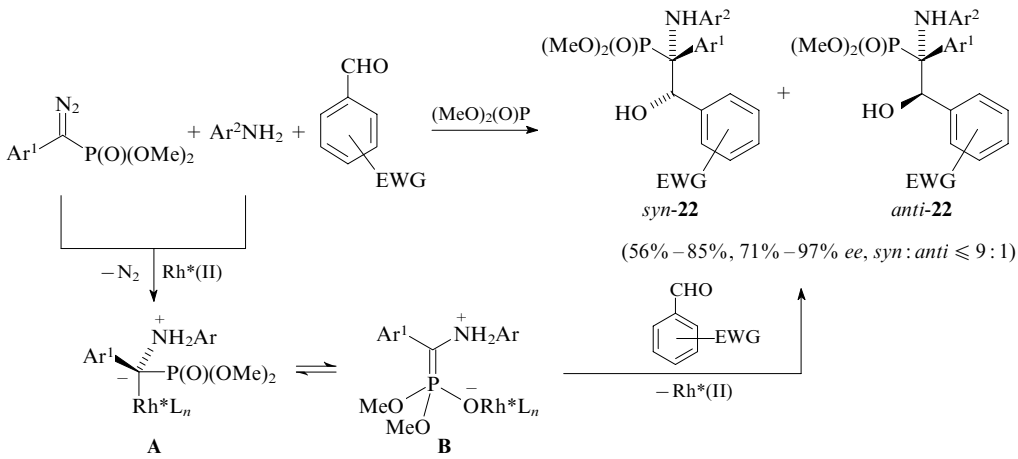
However, it was found that the reactions of dimethyl [diazo(aryl)methyl]phosphonates with aromatic amines and aldehydes in the presence of chiral rhodium catalysts afford target 3MCR products — dimethyl [(1*S*,2*S*)-1,2-diaryl-1-arylamino-2-hydroxyethyl]phosphonates **22** — with good enantioselectivity (Scheme 10).[52]

The complexes Rh_2(*S*-PTAD)$_4$ [*S*-PTAD is (*S*)-(+)-(1-adamantyl)phthalimidoacetate] and Rh_2(*S*-PTTL)$_4$ (see structures **4**) were found to be the most efficient catalysts for these reactions.[52] For example, the reactions in the presence of Rh_2(*S*-PTAD)$_4$ give α-amino-β-hydroxy esters in 56%–85% yields with good diastereo- and enantioselectivity (*syn* : *anti* ⩽ 9 : 1, 71%–97% *ee*). According to the results of calculations, high enantioselectivity of the addition of ylide to the C=O group of aldehyde in these reactions is provided by the coordination of the N-ylide intermediate to the chiral rhodium catalyst (structures **A** and **B** in Scheme 10).[52]

Analogous reactions in the presence of Rh_2(*S*-PTTL)$_4$ also gave target aminohydroxy esters **22** in high yields (65%–83%), but the enantioselectivity of the process was not higher than 86%.[52]

The employment of the achiral rhodium catalyst–chiral Brønsted acid pair proved to be a very efficient version of the enantioselective synthesis of α-amino-β-hydroxy

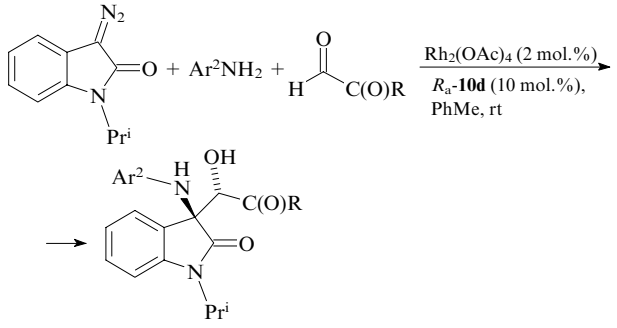
Scheme 10



Ar^1 = Ph, XC_6H_4 (X = 4-Cl, 4-Me, 4-MeO, *etc.*); Ar^2 = YC_6H_4 (Y = 2-Me, 2-F, 4-Cl, *etc.*); EWG = 4-NO_2, 4-CO_2Me, *etc.*; Rh*(II) = Rh_2(*S*-PTAD)$_4$

esters.[49, 53] Thus, the three-component reaction of 3-diazo-*N*-isopropylindolin-2-one with aromatic amines in the presence of ketals catalyzed by $Rh_2(OAc)_4$ and the co-catalyst (R_a)-**10d** (R = 2,4,6-$Pr^i_3C_6H_2$) affords substituted (3*S*)-3-arylamino-3-[(*S*)-1-hydroxy-2-oxoethyl]-1-isopropylindolin-2-ones **23** in high yields with high diastereo- and enantioselectivity (Scheme 11).[53]

Scheme 11

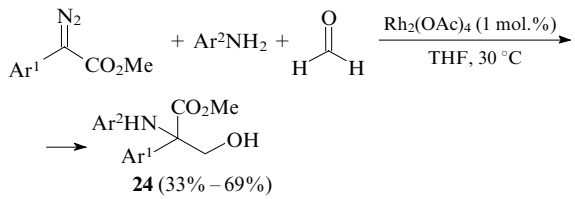


23 (⩽99%, 80%–99% *ee*, *dr* ⩽38 : 1)

R = OEt, Me, Ph; Ar^2 = XC_6H_4 (X = 2-Br, 2-CN, 2-C(O)Me, 4-NO_2, *etc.*)

The tree-component reaction of α-aryldiazoacetates with amines and aldehydes provides an efficient approach to α-aryl-substituted derivatives of serine **24** (Scheme 12).[49] For example, the dirhodium tetraacetate-catalyzed decomposition of α-aryldiazoacetates in the presence of aromatic amines and formaldehyde produces target methyl 2-aryl-2-arylamino-3-hydroxypropanoates **24** in yields of up to 69%.

Scheme 12

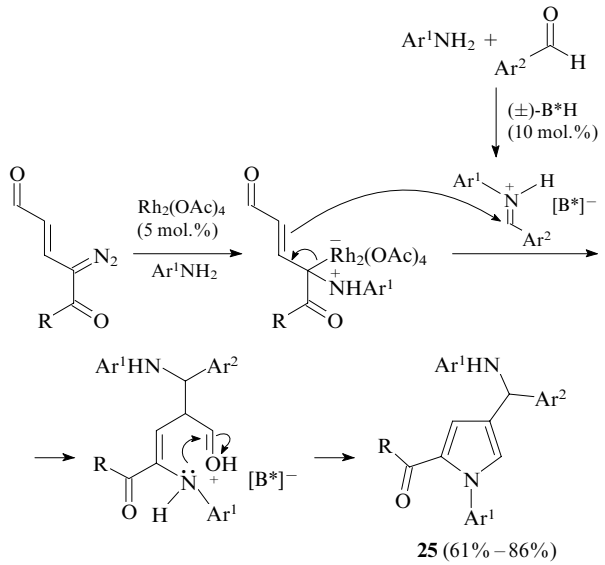


24 (33%–69%)

Ar^1 = Ph, XC_6H_4 (X = 4-Hal, 4-Me, *etc.*); Ar^2 = YC_6H_4 (Y = 2-Bu^t, 4-O_2N, *etc.*)

An interesting example of the three-component process involving ammonium ylides is the catalytic reaction of 5-substituted (*E*)-4-diazo-5-oxopent-2-enals with aromatic amines and aldehydes in the presence of racemic 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (±)-B*H as the co-catalyst, which produces 1-aryl-4-aryl(arylamino)-methyl-2-acyl-1*H*-pyrroles **25** (Scheme 13).[54]

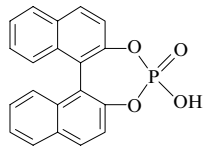
Scheme 13



25 (61%–86%)

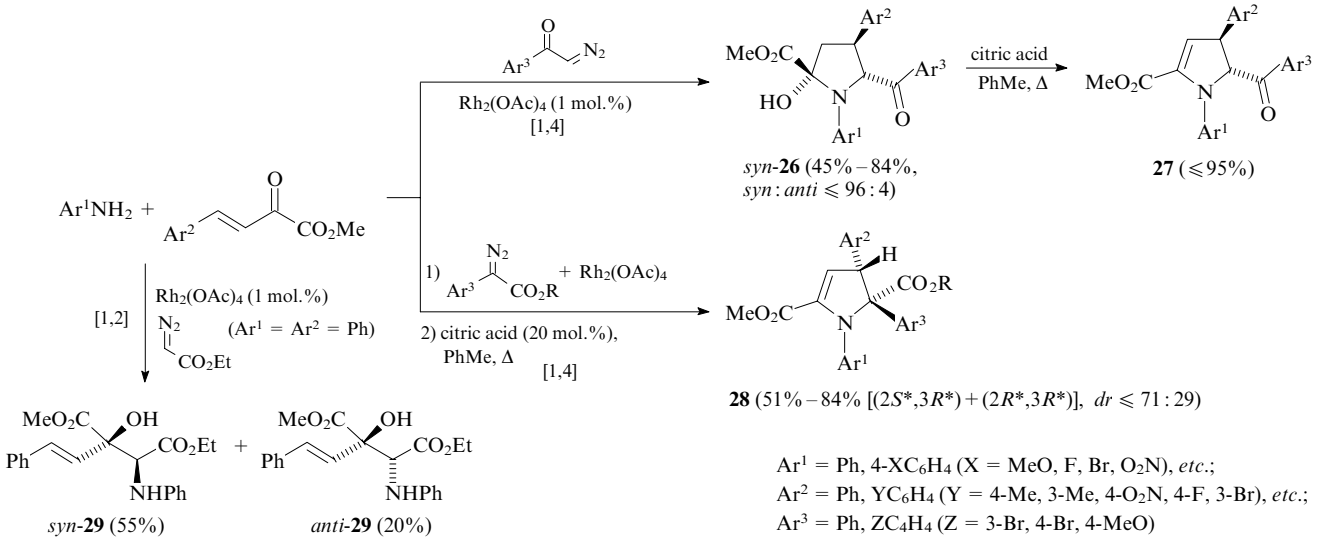
R = Ph, OBn, *etc.*; Ar^1 = Ph, XC_6H_4 (X = 2-F, 4-Br, 4-MeO, *etc.*); Ar^2 = Ph, YC_6H_4 (Y = 4-Cl, 4-MeO, 4-O_2N, *etc.*)

(±)-B*H =



Apparently, ammonium ylide coordinated to the Rh catalyst essentially activates the C=C bond of the ylide intermediate, which readily reacts with imine to give finally substituted pyrroles **25** in good yields.[54]

Scheme 14



III.5. Reactions with α,β-unsaturated carbonyl compounds

Three-component reactions involving α,β-unsaturated carbonyl compounds proceed as either the 1,2- or 1,4-addition depending on the reactant structure.[43, 45, 51] Besides, in the case of α,β-unsaturated ketones, the initial 1,4-addition products can be further transformed into various heterocyclic structures. The main synthetic applications of catalytic three-component reactions of diazo compounds involving (*E*)-methyl 4-aryl-2-oxobut-3-enoates are shown in Scheme 14.[43, 45, 51]

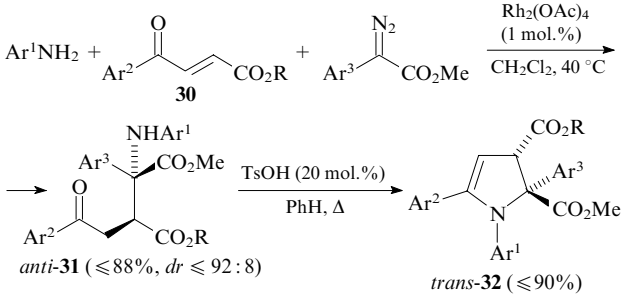
The three-component Rh^{II}-catalyzed reaction of 1-aryl-2-diazoethanones with aromatic amines and β,γ-unsaturated α-keto esters proceeding through a series of nucleophilic 1,4-additions of ammonium ylide to β,γ-unsaturated α-keto ester followed by the cyclization gives rise to (2*S*,4*S*,5*R*)-methyl 1,4-diaryl-5-acyl-2-hydroxypyrrolidine-2-carboxylates **26** in good yields with high diastereoselectivity (isomer ratio *syn* : *anti* ⩽ 96 : 4).[51] The treatment of 5-hydroxypyrrolidines **26** with citric acid leads to the dehydration of these compounds, thus providing an efficient route to (4*S*,5*R*)-methyl 1,4-diaryl-5-acyl-4,5-dihydro-1*H*-pyrrole-2-carboxylates **27** (see Scheme 14).[51]

α-Aryldiazoacetates exhibit similar reactivity. However, in these reactions pyrrolidines are generated *via* a two-step reaction as a complex mixture of four stereoisomers, which is of little practical significance for the synthesis.[43, 45] Therefore, the one-pot dehydration of these isomers with citric acid is considered as an approach of choice, which can be used to prepare (2*S*,3*R*)-1,2,3-triaryl-2,3-dihydro-1*H*-pyrrole-2,5-dicarboxylates **28** in good yields.[43, 45]

The generation of harder ammonium ylides from ethyl diazoacetate makes it possible to perform the reaction as the selective nucleophilic 1,2-addition of N-ylides to β,γ-unsaturated α-keto esters, resulting in the formation of a mixture of *syn* and *anti* isomers of 2-hydroxy-2-[(*E*)-styryl]-3-(phenylamino)succinate (**29**), with the *syn* isomer predominating (*syn* : *anti* = 73 : 27), in a total yield of 75% (see Scheme 14).[43]

(*E*)-Methyl 4-aryl-4-oxobut-2-enoates **30** display a somewhat different reactivity than the above-considered 2-oxo analogues. The three-component reaction of α-aryldiazoacetate with aromatic amines and 4-oxoenoates **30** affords nucleophilic 1,4-addition products — (2*R*,3*S*)-2-aryl-2-arylamino-3-aroylsuccinates **31** — in 53% – 88% yields (Scheme 15).[47]

Scheme 15



Upon heating in benzene in the presence of *p*-toluenesulfonic acid (TsOH; 20 mol.%), initial adducts **31** are transformed almost quantitatively into the corresponding (2*R*,3*S*)-1,2,5-triaryl-2,3-dihydro-1*H*-pyrrole-2,3-dicarboxylates **32** in yields of up to 90% (see Scheme 15).[47]

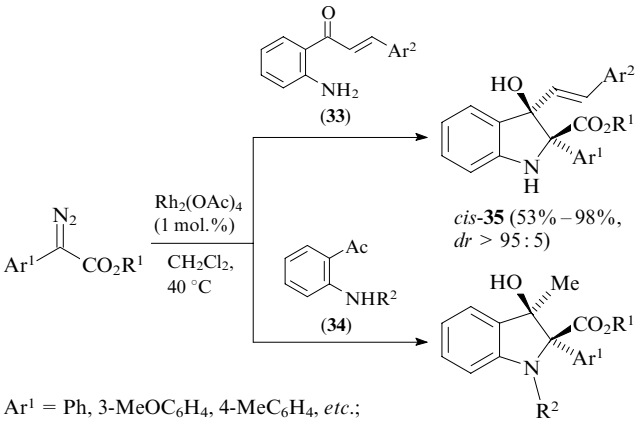
III.6. Intramolecular reactions of N-ylides

The reactions of ammonium ylides, which are generated through the catalytic decomposition of α-aryldiazoacetates in the presence of (*E*)-1-(2-aminophenyl)-3-arylprop-2-en-1-ones **33** and 1-(2-aminophenyl)ethanones **34**, are formally two-component processes. However, these reactions can be considered as an intramolecular version of three-component reactions, because they proceed with the participation of three functional groups (C=N_2, NH_2 and C=O).[56]

These reactions provide a convenient route to (2*S*,3*R*)-2-aryl-3-hydroxy-3-[(*E*)-styryl]indoline-2-carboxylates **35** and (2*S*,3*R*)-2-aryl-3-hydroxy-3-methylindoline-2-carboxylates **36**, because they proceed with high yields and diastereoselectivity (isomer ratio *cis* : *trans* > 95 : 5) (Scheme 16).[56] It is assumed that the reaction initially gives intermediate ammonium ylide, which enters into an intramolecular

reaction with the carbonyl group of the starting amino substrates **33** and **34** to form the corresponding indoles **35** and **36**.[56]

Scheme 16



Ar^1 = Ph, 3-$MeOC_6H_4$, 4-MeC_6H_4, *etc.*; R^1 = Me, Et; Ar^2 = Ph, XC_6H_4 (X = 4-F_3C, 4-MeO, 3-Cl, *etc.*); R^2 = Me, Bn, *etc.*

IV. Oxonium ylides

IV.1. Three-component reactions involving oxonium ylides

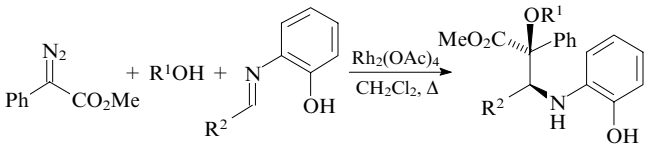
Like N-ylides, oxonium ylides generated through the catalytic decomposition of diazocarbonyl compounds in the presence of hydroxy-containing substrates proved to be very reactive intermediates in three-component reactions with various electrophilic reagents. These reactions can be performed with a broad range of hydroxy-containing compounds, including water,[58–62] aliphatic and aromatic alcohols.[60,63–75] Imines,[58,60,61,63,64,67,69] aldehydes,[63] diazenes,[63,66,72,76] cyclic ketones[65,68,73,77] and α,β-unsaturated carbonyl compounds[59,71,72,74,75] served as an electrophilic component in these processes. In addition to rhodium complexes, tetraisopropoxytitanium was employed to generate oxonium ylides in multicomponent reactions.[73,77]

IV.2. Reactions with imines

In one of the first studies[63] concerned with 3MCR of α-aryldiazoacetates, a series of Rh^{II}-based catalysts was tested and the nature of the ligand was found to have a substantial effect on the ratio of main reaction products. Thus, the reaction of α-aryldiazoacetates with alcohols and imines in the presence of dirhodium tetrakis(trifluoroacetate) with electron-withdrawing ligands affords β-amino esters **37** in 65%–81% yields with good diastereoselectivity (*erythro* : *threo* ⩽ 85 : 15) (Scheme 17). The main competing reaction (O—H insertion) occurs to a much lesser extent (< 20%) compared to the reactions in the presence of other Rh catalysts.[63] Meanwhile, the use of chiral catalysts, such as Rh_2(*S*-DOSP)$_4$ (see structures **4**) and dirhodium tetrakis[*N*-1,8-naphthoyl-(*S*)-*tert*-leucinate], results in the formation of a racemic mixture of amino esters **37**.[63]

The selectivity of such reactions can be increased with the use of imines based on 2-aminophenol possessing high electrophilicity of the C=N bond.[64] For example, the Rh^{II}-catalyzed reaction of methyl α-phenyldiazoacetate in the presence of alcohols and *N*-(hydroxyphenyl)imines affords 2,3-disubstituted (2*S*,3*S*)-methyl 2-alkoxy-3-(2-hydroxyphenylamino)propanoates **38** in good yields with high diastereoselectivity (*erythro* : *threo* > 98 : 2; the ratio of the reaction products 3MCR : OH insertion ⩽ 95 : 5) (Scheme 18).[64]

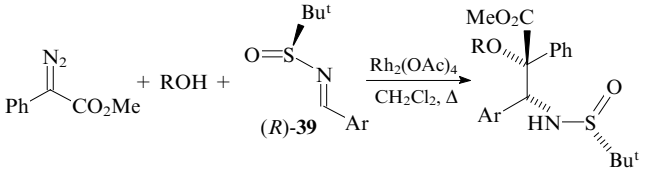
Scheme 18



R^1 = Me, Pr^i, Bn, *etc.*; R^2 = Ph, PMP, 4-$O_2NC_6H_4$, *etc.*

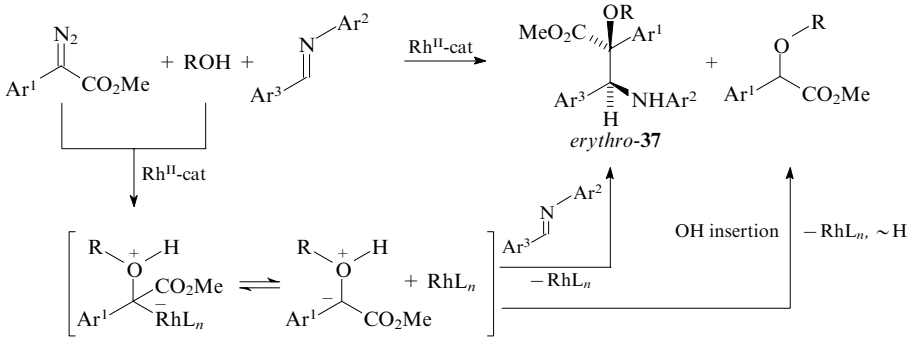
The unexpectedly high stereoselectivity was observed in the $Rh_2(OAc)_4$-catalyzed three-component reactions of α-phenyldiazoacetate with alcohols and (*R*)-*N*-(*tert*-butylsulfinyl)imines **39**. It was found that these reactions give (2*R*,3*R*)-methyl 3-[(*R*)-*tert*-butylsulfinylamido]-2-alkoxypropanoates **40** exceptionally as (*R*,*R*,*R*)-isomers (Scheme 19). The synthesis of these enantiomers is of importance for the preparation of optically active β-amino

Scheme 19



R = Bn, Et, Pr^i, *etc.*; Ar = 4-$O_2NC_6H_4$, 2,4-$(O_2N)_2C_6H_3$

Scheme 17

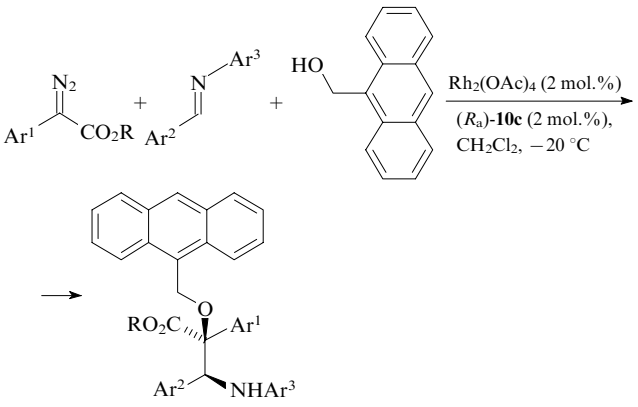


Ar^1, Ar^2 = Ph, PMP; Ar^3 = 4-$O_2NC_6H_4$; R = Bn, 4-$MeOC_6H_4CH_2$; Rh^{II} cat, see the text; **37**: yield ⩽ 81, *erythro* : *threo* ⩽ 85 : 15

alcohols and β-amino-α-hydroxyamino acid derivatives.[64] This reaction was accompanied by the formation of O–H insertion products as by-products.

One way to suppress the competitive O–H insertion reaction is to use an achiral Rh^{II} catalyst combined with chiral phosphate (R_a)-**10c**.[67] Under these conditions, the catalytic decomposition of α-aryldiazoacetates in the presence of imines and 9-hydroxymethylanthracene gives (2*S*,3*S*)-2-(anthracen-9-ylmethoxy)-2,3-diaryl-3-(arylamino)-propanoates *syn*-**41** in high yields with high diastereo- and enantioselectivity (*syn* : *anti* > 99 : 1) (Scheme 20).[67]

Scheme 20

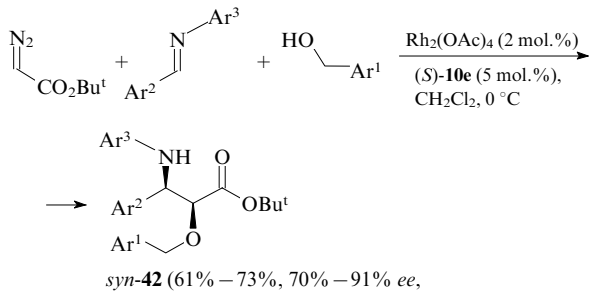


syn-**41** (84%–98%, 84%–99% *ee*, *dr* > 99 : 1)

Ar^1 = Ph, PMP, 2-BrC_6H_4, *etc.*; R = Me, Et; Ar^2 = Ph, XC_6H_4 (X = 2-Me, 2-Cl, 4-Br, *etc.*); Ar^3 = Ph, PMP

Unlike the reactions of α-aryldiazoacetates, similar reactions of unsubstituted diazoacetates that proceed through the intermediate formation of oxonium ylides are usually characterized by low diastereoselectivity (for example, *syn*-**42** : *anti*-**42** ⩽ 82 : 18).[60] Nevertheless, the decomposition of *tert*-butyl diazoacetate in the presence of substituted benzyl alcohols and arylimines catalyzed by $Rh_2(OAc)_4$ and ligand (S_a)-**10e** (R = 4-FC_6H_4) produces (2*S*,3*R*)-*tert*-butyl 3-aryl-3-arylamino-2-(arylmethoxy)propanoates **42** in good yields with good enantioselectivity as a results of the three-component reaction (Scheme 21).[60]

Scheme 21

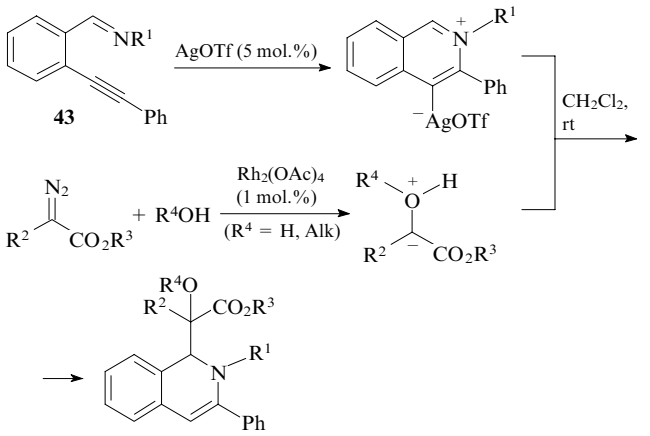


syn-**42** (61%–73%, 70%–91% *ee*, *dr* ⩽ 82 : 18)

Ar^1 = 2,6-$Cl_2C_6H_3$; Ar^2 = Ph, XC_6H_4 (X = 4-F_3C, 4-MeO, 4-Cl, *etc.*); Ar^3 = PMP

The new scope of three-component processes using co-catalysts in the chemistry of oxonium ylides has been recently demonstrated for the reactions of diazoacetates with N-substituted (phenylethynyl)benzylideneamines **43** in the presence of water or alcohols.[69] For instance, the $Rh_2(OAc)_4$-catalyzed decomposition of diazoacetates in the presence of AgOTf (Tf = CF_3SO_2) as the co-catalyst gives 2-R^2-substituted 2-alkoxy-2-(2,3-diaryl-1,2-dihydroisoquinolin-1-yl)acetates **44** in yields of up to 93% (Scheme 22).[69] The highest diastereoselectivity was observed in the reactions of diazoacetates and *N*-arylimines containing the phenyl moiety or electron-excessive substituents in the aryl ring (R^1 = Ph; R^2 = Ph, PMP, 4-MeC_6H_4).

Scheme 22

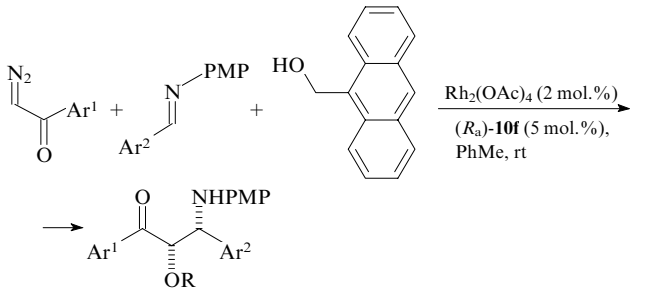


44 (43%–93%, *dr* ⩽ 76 : 24)

R^1 = Ph, XC_6H_4 (X = 3-Cl, 4-Br, *etc.*); R^2 = Ph, YC_6H_4 (Y = 4-Me, 4-MeO, 3-Br, *etc.*); R^3 = Me, Et; R^4 = H, Me, Pr^i, Bu^t, Bn

The dirhodium tetraacetate-catalyzed decomposition of diazoacetophenones in the presence of 9-hydroxymethylanthracene, imines and the co-catalyst (R_a)-**10f** (R = 4-$F_3CC_6H_4$) produces (2*S*,3*R*)-2-alkoxy-1,3-diaryl-3-(arylamino)propan-1-ones *syn*-**45** in good yields with excellent diastereo- and enantioselectivity (*syn* : *anti* > 97 : 3) (Scheme 23).[70]

Scheme 23



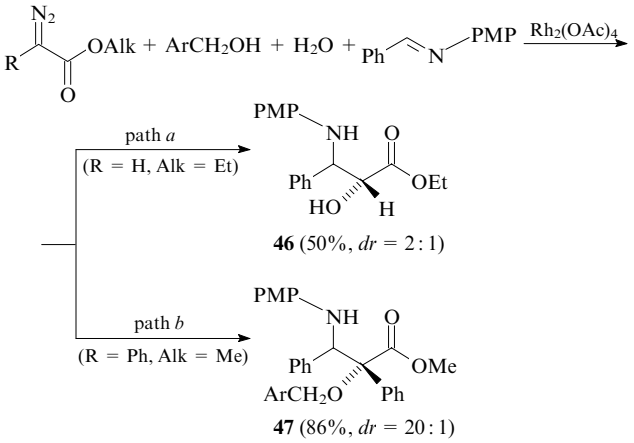
syn-**45** (70%–88%, 87%–98% *ee*, *dr* > 97 : 3)

Ar^1 = Ph, XC_6H_4 (X = 2-Br, 3-Br, 4-Cl);
Ar^2 = Ph, YC_6H_4 (Y = 2-F_3C, 4-F, 4-Me, *etc.*)

Oxonium ylides generated from ethyl diazoacetate and H_2O proved to be more reactive nucleophiles in reactions with imines than ylides produced from alcohol (ROH = $ArCH_2OH$), and their reactions afford compound **46** as the major product (Scheme 24, path *a*). Meanwhile, the opposite situation is observed for α-aryldiazoacetates,

and their reaction gives compound **47** as the major product (path *b*).[61]

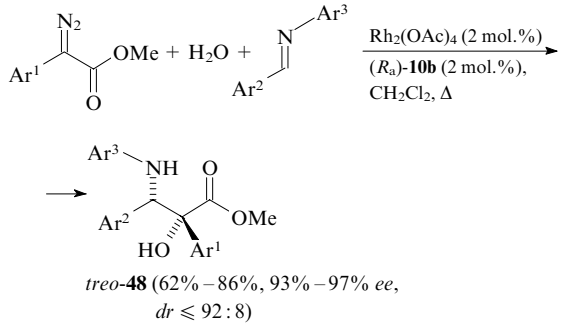
Scheme 24



Ar is anthracen-9-yl

A series of (2*R*,3*R*)-methyl 2,3-diaryl-3-arylamino-2-hydroxypropanoates **48** were obtained in good total yields with high diastereo- and enantioselectivity (*threo* : *erythro* ⩽ 92 : 8) by the three-component reaction of α-aryldiazoacetates with a large range of diarylimines and H_2O catalyzed by dirhodium tetraacetate and ligand (R_a)-**10b** (Scheme 25).[61]

Scheme 25



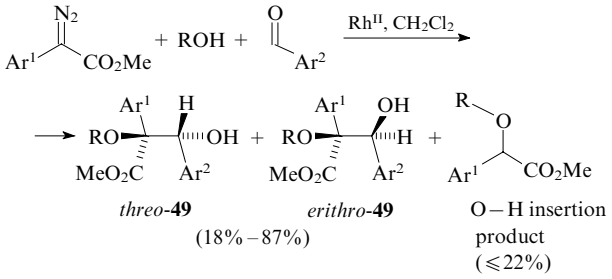
Ar^1 = Ph, PMP, 2-MeC_6H_4, *etc.*;
Ar^2 = Ph, XC_6H_4 (X = 4-F_3C, 2-Br, 4-Me, *etc.*); Ar^3 = PMP

In the authors' opinion, the high diastereoselectivity of the reactions under consideration is attributed to low reactivity of oxonium ylides generated from α-aryldiazoacetates and H_2O, and the use of chiral phosphate (R_a)-**10b** provided high enantiomeric purity of the resulting (arylamino)hydroxypropanoates **48**.[61]

IV.3. Reactions of oxonium ylides with aldehydes

The Rh^{II}-catalyzed three-component reactions with alcohols and aldehydes were studied using α-aryldiazoacetates as model diazo compounds.[63] It was found that the O–H insertion that occurs as the side reaction can be suppressed and methyl 2-alkoxy-2,3-diaryl-3-hydroxypropanoates **49** can be synthesized in good yields only with the use of arylaldehydes containing electron-withdrawing substituents (Scheme 26).[63] Thus, the best results in the reactions with benzyl (BnOH) and 4-methoxybenzyl (PMBOH) alcohols were obtained with the use of *p*-nitrobenzaldehyde: other things being equal, the isomer ratio *threo*-**49** : *erythro*-**49** was 97 : 3 (see Scheme 26).[63] The employment of the standard catalysts $Rh_2(OAc)_4$ and $Rh_2(tfa)_4$ (tfa is trifluoroacetate) gave comparable results, whereas the application of chiral Rh_2(*S*-DOSP)$_4$ (see structures **4**) led to a considerable decrease in the diastereoselectivity of the process.[63]

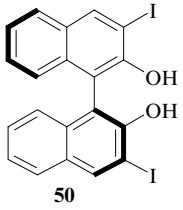
Scheme 26



Ar^1 = Ph, PMP, *trans*-styryl; Ar^2 = $X_nC_6H_5$ (X_n = 4-O_2N, 2-O_2N, 4-NC, 4-F_3C, 4-MeO, 2,4-$(O_2N)_2$); R = Bn, PMB, Me, Bu^t, *etc.*

The use of zirconium complexes with (*S*)-3,3′-diiodo-1,1′-binaphthyl-2,2′-diol (**50**) as co-catalysts results in a substantial increase in the efficiency of the reactions of α-aryldiazoacetates with alcohols and many aromatic aldehydes containing various substituents in the nucleus,[66] which makes it possible to prepare α-alkoxy-β-hydroxy esters **49** (Ar^1 = Ph, 4-BrC_6H_4, 3-MeC_6H_4; Ar^2 = Ph, PMP, 4-BrC_6H_4, *etc.*; R = Bn) in 60%–82% yields with high diastereo- and enantioselectivity (*erythro* : *threo* ⩽ 93 : 7, 89%–98% *ee*).[66]

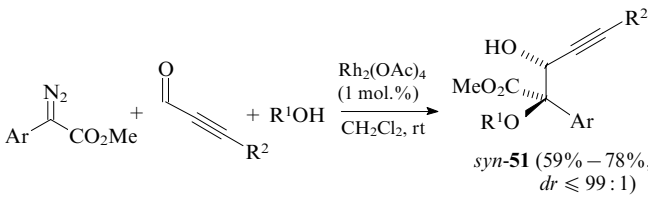
Structure 50



Meanwhile, the use of *p*-nitrobenzaldehyde in the analogous three-component reaction resulted in the formation of the target hydroxy ester **49** (Ar^1 = Ph, R = Bn) in a yield of only 43%, and the *erythro* : *threo* ratio decreased to 7 : 3 with 60% *ee*.[66]

In addition to aromatic aldehydes,[63, 66] alkyn-2-als were found to be good electrophiles in reactions with oxonium ylides.[72] For instance, the Rh^{II}-catalyzed reaction of α-aryldiazoacetates with alcohols and alkynals gives 2,5-disubstituted (2*R*,3*R*)-methyl 2-alkoxy-3-hydroxypent-4-ynoates *syn*-**51** in good yields with high diastereoselectivity (*syn* : *anti* ⩽ 99 : 1) (Scheme 27).[72] The use of water instead of alcohol for the generation of oxonium ylide leads to a

Scheme 27

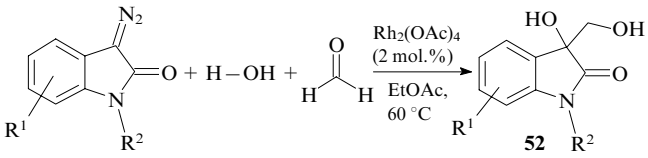


Ar = Ph, XC_6H_4 (X = 3-Cl, 4-F, 4-MeO, *etc.*);
R^1 = H, Bn, *etc.*; R^2 = H, $SiMe_3$, Ph, *etc.*

substantial decrease in the diastereoselectivity of the reaction (*syn* : *anti* ratio decreases to 73 : 27), but the corresponding dihydroxy esters are produced in quite good yields (56% – 75%).[72]

Another interesting example of the three-component reaction involving oxonium ylides is the Rh^{II}-catalyzed decomposition of N-substituted 3-diazoindolin-2-ones in an aqueous formaldehyde solution, in which water serves as a structural component of ylide (Scheme 28).[62] The reaction affords the corresponding N-substituted 3-hydroxy-3-(hydroxymethyl)indolin-2-ones **52**. The yield of the product substantially depends on the nature of aryl substituents in diazo compounds.

Scheme 28



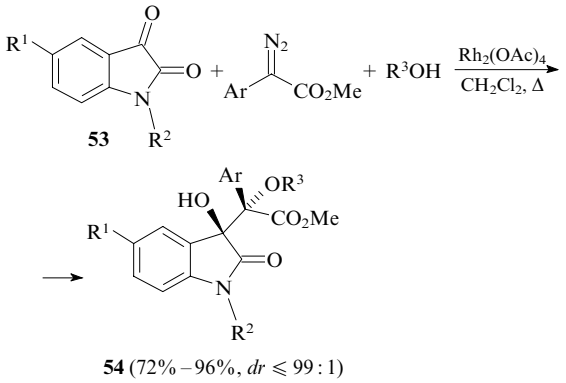
R^1 = 7-Cl, 5-Me, 4-Cl, H; R^2 = Bn, Me, CO_2Me (yield of **52** is 52% – 74%); R^1 = 6-Cl, 5-Cl, 5-F, 5-Br; R^2 = Bn, Me (yield of **52** is 26 – 55%)

IV.4. Reactions with cyclic ketones

The Rh^{II}-catalyzed three-component reaction of α-diazoacetates with 1,5-disubstituted 1*H*-indole-2,3-diones **53** and alcohols gives (*S**)-methyl 2-alkoxy-2-aryl-2-(*S**)-3-hydroxy-2-oxoindolin-3-ylacetates **54** in high yields with high diastereoselectivity (*erythro* : *threo* ⩽ 99 : 1) (Scheme 29).[65]

The titanium compound $Ti(OPr^i)_4$ proved to be an efficient co-catalyst in the Rh^{II}-catalyzed three-component reactions of diazo esters (R^1 = Me, Et, Bu^n, *etc.*) with cyclic ketones (Scheme 30).[77] It is hypothesized that in the reaction with unsubstituted *p*-benzoquinone, $Ti(OPr^i)_4$ interacts with intermediate Rh carbenoid to form ylide **A** through an O atom of one of its alkoxy groups, and this ylide enters into the 1,4-addition reaction with benzoquinone to form hydroquinones **55** (see Scheme 30). By contrast, the reaction of 2,5-disubstituted *p*-benzoquinones (R^3 = Me) occurs

Scheme 29



54 (72% – 96%, *dr* ⩽ 99 : 1)

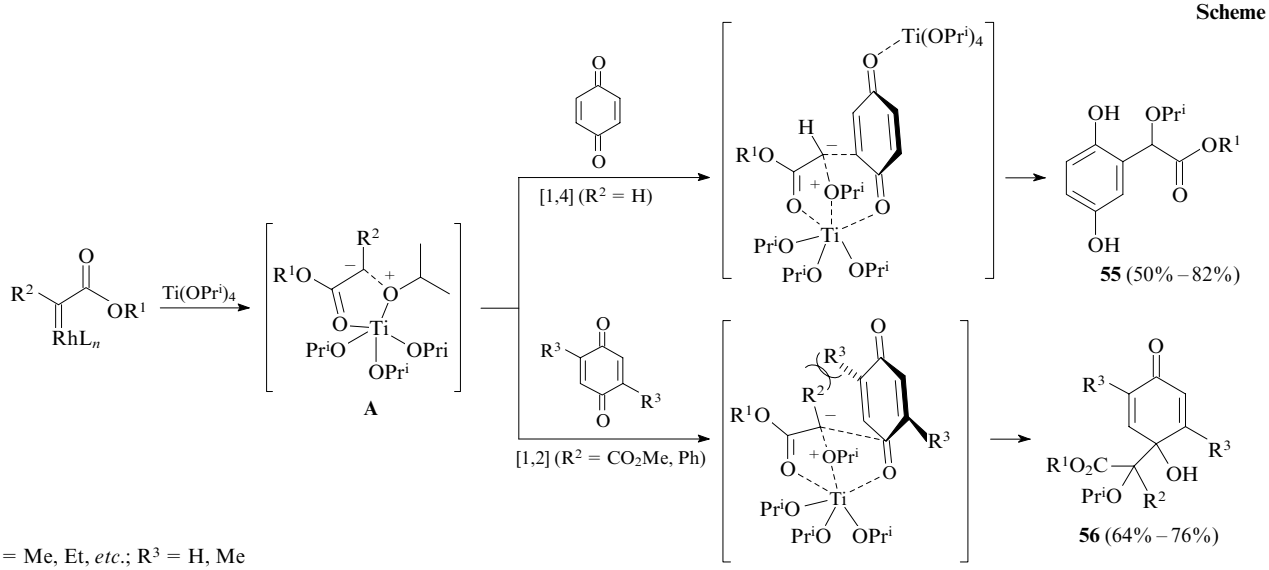
Ar = H, Ph, PMP, *etc.*; R^1 = H, NO_2, Cl, Br; R^2 = H, Me, Ph; R^3 = H, Me, Bn, *etc.*

as the 1,2-addition of O-ylide to the carbonyl group of quinone (due apparently to steric hindrance created by substituents at the double bond of quinone or the R^2 group of the diazo compound), resulting in the formation of adduct **56**.[77]

The application of $Ti(OPr^i)_4$ as a co-catalyst and a donor of the RO group in the three-component reaction of ethyl diazoacetate with 1,4-disubstituted azetidine-2,3-diones **57** also leads to the formation of target 3MCR products — ethyl 2-(3-hydroxy-4-oxoazetidin-3-yl)-2-isopropoxyacetates **58** — in good yields but with low diastereoselectivity (*anti* : *syn* ⩽63 : 37) (Scheme 31).[68] The use of MeOH in the standard modification of 3MCR (*i.e.*, in the absence of the co-catalyst) makes it possible to prepare hydroxy ester **58** in yields of up to 88%, with *syn*-**58** predominating (*syn* : *anti* ⩽9 : 1).[68]

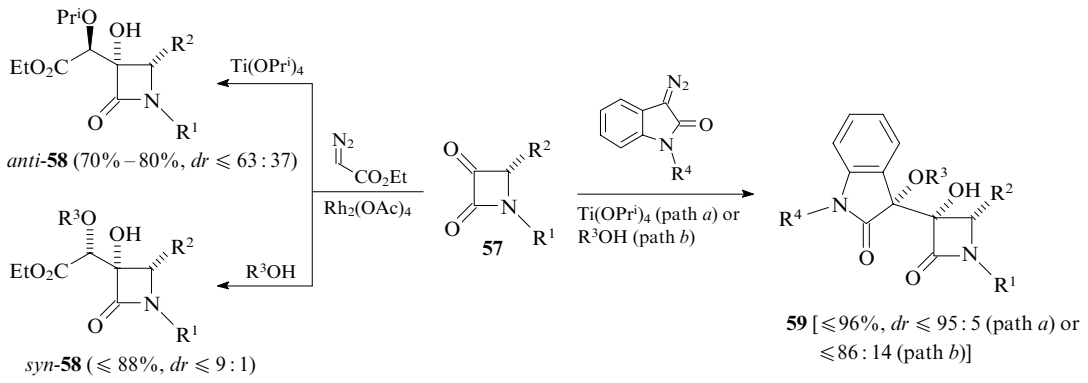
The corresponding three-component reactions of diazo-2-oxoindoles with azetidine-2,3-diones **57** [with $Ti(OPr^i)_4$ or alcohols] give substituted 3-alkoxy-3-(3-hydroxy-2-oxoazetidin-3-yl)indolin-2-one *syn*-**59** as the major products in good yields (57% – 96%) (see Scheme 31). However, the diastereoselectivity of the reaction in the presence of $Ti(OPr^i)_4$ is much higher than that with alcohols (*syn* : *anti* ⩽ 95 : 5).[73]

Scheme 30



R^1 = Me, Et, *etc.*; R^3 = H, Me

Scheme 31



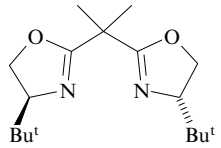
R^1 = PMP, Bn, *etc.*; R^2 = 4-MeC_6H_4, 2,2-dimethyl-1,3-dioxolan-4-yl; R^3 = Me, Pr^i, *etc.*; R^4 = H, Me, 4-$O_2NC_6H_4C(O)$

IV.5. Reactions with α,β-unsaturated carbonyl compounds

The application of co-catalysts was also found to be very efficient in the nucleophilic 1,4-addition reactions of oxonium ylides with α,β-unsaturated carbonyl compounds [59, 71, 74] and imines.[75]

Experiments with the Rh^{II}-catalyzed reaction of α-aryldiazoacetates with water and (*E*)-3-aryl-1-(1-methyl-1*H*-imidazol-2-yl)prop-2-enones demonstrated [59] that Lewis acids with appropriate ligands are required as the co-catalysts in order to achieve good results in 3MCR. The best results were obtained in the presence of the zinc triflate co-catalyst with (4*S*,4*S*′)-2,2′-(propane-2,2-diyl)bis[4-(*tert*-butyl)-4,5-dihydrooxazole] (**60**) as the ligand and with the addition of Brønsted acid (TsOH), which substantially increased the rate and selectivity of the reaction.[59]

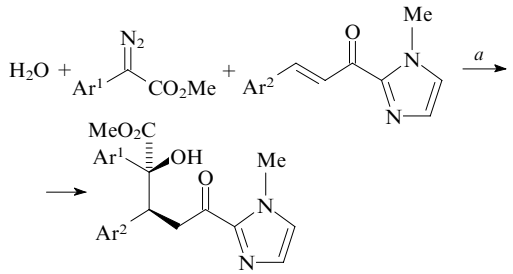
Structure (*S*)-60



(*S*)-**60**

In the case of α-aryldiazoacetates containing both electron-donating and -withdrawing substituents in the aryl nucleus, the products of the three-component reaction — (2*S*,3*S*)-methyl 2,3-diaryl-2-hydroxy-5-(1-methyl-1*H*-imidazol-2-yl)-5-oxopentanoates **61** — were synthesized in good yields with high diastereo- and enantioselectivity (*syn*:*anti* ⩽ 99:1) (Scheme 32).[59]

Scheme 32

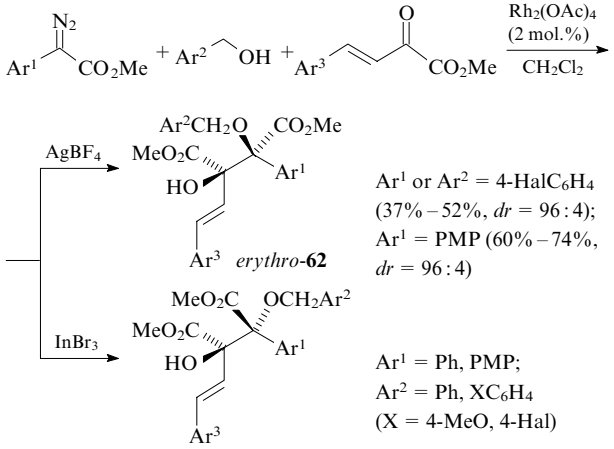


61 (61%–86%, 85%–99% *ee*, *dr* ⩽ 99:1)

Ar^1 = Ph, PMP, 3-ClC_6H_4; Ar^2 = Ph, XC_6H_4 (X = 4-Br, 4-O_2N, 4-MeO, *etc.*); (*a*) $Rh_2(OAc)_4$ (2 mol.%), (*S*)-**60**, $Zn(OTf)_2$ (30 mol.%), TsOH (40 mol.%), CH_2Cl_2, −8 °C

Unlike the enantioselective synthesis, in which the reaction product with the opposite configuration of the stereocentre can be obtained by replacing the chiral catalyst by its enantiomer,[71] the development of the strategy providing a high level of the control over the diastereoselectivity of the formation of new stereocentres is a more complex problem. Nevertheless, the study of the Rh^{II}-catalyzed three-component reaction of α-aryldiazoacetates, alcohols and β,γ-unsaturated α-keto esters showed that the diastereoselectivity of the reaction can, in principle, be changed by using $AgBF_4$ instead of $InBr_3$ as the co-catalyst (Scheme 33).[71] Thus, the nucleophilic 1,2-addition of oxonium ylide to β,γ-unsaturated α-keto ester in the presence of $AgBF_4$ as the co-catalyst affords (2*S**,3*R**)-dimethyl 2-aryl-2-aryloxy-3-hydroxy-3-[(*E*)-styryl]succinates *erythro*-**62** in 37%–74% yields with excellent diastereoselectivity (see Scheme 33). Meanwhile, the use of $InBr_3$ instead of $AgBF_4$ results in the formation of *threo* isomers **62** as the major products in good yields.[71]

Scheme 33

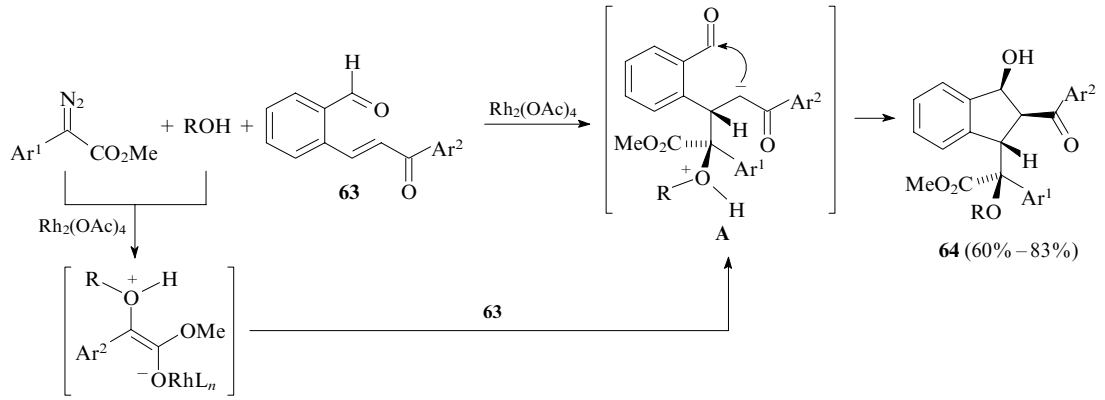


threo-**62** (58%–76%, *dr* = 96:4)

Ar^3 = Ph, XC_6H_4 (X = 3-Me, 4-Cl, *etc.*)

The Rh^{II}-catalyzed three-component cascade of reactions, involving the nucleophilic 1,4-addition of oxonium ylide to the double bond of (*E*)-2-(3-aryl-3-oxopropen-1-yl)benzaldehyde **63** followed by the intramolecular cyclization of the resulting zwitterion **A** (Scheme 34), can be considered as a prominent result in research on the reactions of oxonium ylides with α,β-unsaturated carbonyl

Scheme 34

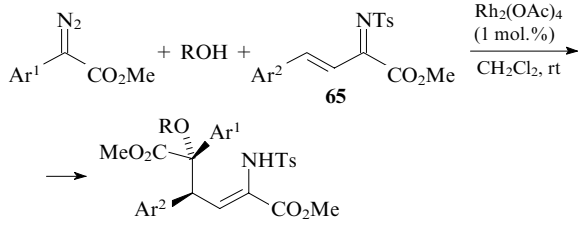


Ar^1 = Ph, PMP, 4-MeC_6H_4, *etc.*; Ar^2 = Ph, XC_6H_4 (X = 4-F, 3-Cl, 4-O_2N, *etc.*); R = Bn, Me, Et, Pr^i, *etc.*

compounds. This reaction produces methyl 2-alkoxy-2-aryl-2-(2-acyl-3-hydroxy-2,3-dihydro-1*H*-inden-1-yl)acetates **64** in good yields (see Scheme 34).[74]

In addition to β,γ-unsaturated α-keto esters,[71] the reactions of oxonium ylides were studied also with the use of *N*-tosylimino esters — (3*E*)-methyl 4-aryl-2-(tosylimino)-but-3-enoates **65** — as electrophilic reagents (Scheme 35).[75]

Scheme 35



66 (56%–95%, *dr* > 95 : 5)

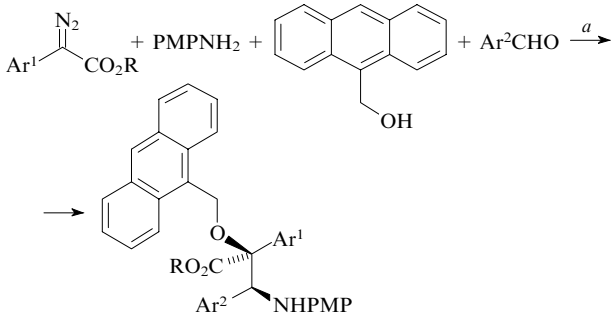
Ar^1 = Ph, XC_6H_4 (X = 4-Cl, 3-Br, 4-MeO, *etc.*);
Ar^2 = YC_6H_4 (Y = 4-Cl, 4-Me, 4-O_2N, *etc.*);
R = Bn, 4-$O_2NC_6H_4CH_2$, Et, Pr^i, *etc.*

It was found that the Rh^{II}-catalyzed decomposition of α-aryldiazoacetates in the presence of alcohols and sulfonylimines **65** gives (4*S**,5*S**,*Z*)-dimethyl 5-alkoxy-4,5-diaryl-2-[(4-methylphenyl)sulfonylamido]hex-2-enedioates **66** in high yields with excellent diastereoselectivity (*anti*:*syn* > 95 : 5) (see Scheme 35).[75]

IV.6. Four-component reactions of oxonium ylides

As shown above, three-component reactions of oxonium ylides with imines provide an efficient approach to β-amino-α-hydroxy ester derivatives.[58, 60, 61, 63, 64, 67, 69, 70] To reduce the total number of reaction steps, a procedure was developed for the synthesis of (2*S*,3*S*)-2-(anthracen-9-ylmethoxy)-2,3-diaryl-3-[(4-methoxyphenyl)amino]propanoates **41** by means of the catalytic four-component reaction (4MCR) of α-aryldiazoacetates, aromatic aldehydes, amines and alcohols. This reaction is based on the simultaneous *in situ* generation of oxonium ylides and imines in the reaction medium (Scheme 36).[76] In this reaction, Brønsted acid (R_a)-**10c** used as the co-catalyst plays a dual role: on the one hand, it catalyzes the formation of imine from amine and aldehyde; on the other hand, it activates imine making it more electrophilic in the subsequent reaction with oxonium ylide. The reaction was tested with a series of α-aryldiazoacetates and the *in situ* generated imines. In most cases, the reaction gave only the *syn* isomer of β-amino-α-hydroxy esters **41** with enantioselectivity >90% in good yields (see Scheme 36).[76]

Scheme 36

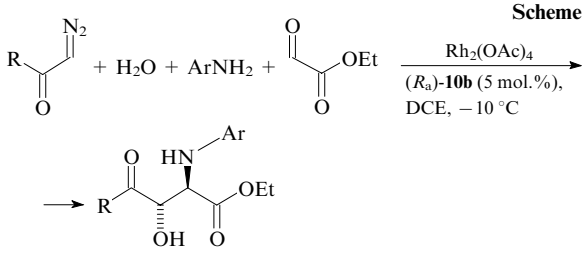


41 (58%–90%, 87%–97% *ee*, *dr* > 99 : 1)

Ar^1 = PMP, XC_6H_4 (X = 2-Br, 3-Cl, *etc.*); R = Me, Et;
Ar^2 = Ph, YC_6H_4 (Y = 4-Cl, 4-Br, 4-Me, *etc.*);
(*a*) $Rh_2(OAc)_4$, (R_a)-**10c** (2 mol.%), CH_2Cl_2, −20 °C

A procedure was developed for the synthesis of β-amino-α-hydroxy esters **67** containing the tertiary carbon atom in the α position with respect to the amino group, fragments of which are often present in natural compounds, based on the Rh^{II}-catalyzed four-component reaction of diazoacetophenones, aromatic amines, water and glyoxylate (Scheme 37).[78] The reaction produces β-amino-α-hydroxy ester derivatives **67** in yields of up to 88% with good

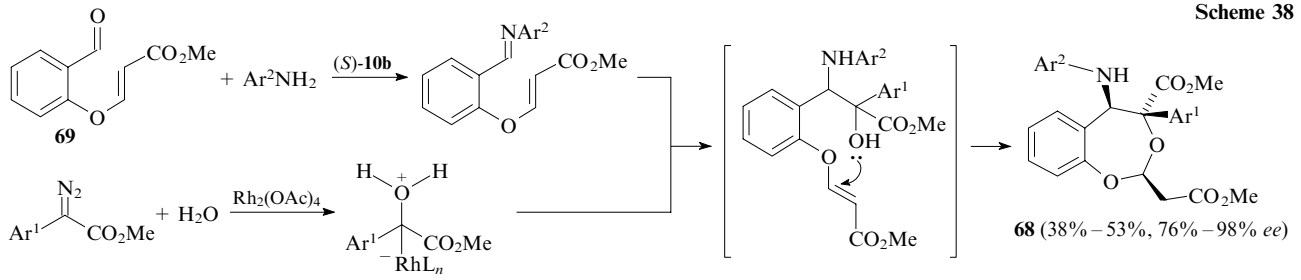
Scheme 37



67 (61%–88%, 85%–96% *ee*, *dr* ⩽ 89 : 11)

R = Ph, XC_6H_4 (X = 4-MeO, 4-Br, 4-Me, *etc.*);
Ar = Ph, YC_6H_4 (Y = 4-Cl, 4-Br, 4-Me, *etc.*);
DCE is 1,2-dichloroethane

Scheme 38



Ar^1 = Ph, XC_6H_4 (X = 4-Me, 4-Cl, 2-MeO, *etc.*); Ar^2 = YC_6H_4 (Y = 4-Br, 4-Cl, 3-Cl, *etc.*)

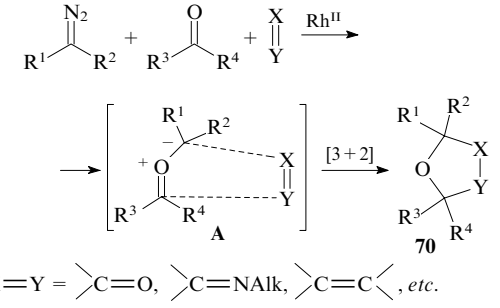
diastereo- and enantioselectivity (*anti* : *syn* ⩽ 89 : 11) (see Scheme 37).[78]

In continuation of research on multicomponent reactions, an ingenious scheme of the synthesis of (2*S*,4*R*,5*R*)-methyl 4-aryl-5-arylamino-2-(2-methoxy-2-oxoethyl)-4,5-dihydrobenzo[*d*][1,3]dioxepine-4-carboxylate **68** was developed based on the four-component process, involving the Mannich reaction followed by the intramolecular cyclization of the resulting unsaturated hydroxy esters (Scheme 38).[79] For instance, the $Rh_2(OAc)_4$-catalyzed reaction of α-aryldiazoacetates with (*E*)-methyl 3-(2-formylphenoxy)acrylate (**69**), water and aromatic amines in the presence of chiral phosphate (*S*)-**10b** as the co-catalyst affords the corresponding O,O-acetals **68** in low yields but with excellent enantioselectivity (*ee* ⩽ 98%) (see Scheme 38).[79]

V. Reactions of carbonyl ylides

The catalytic decomposition of diazocarbonyl compounds in the presence of substrates containing the C=O group is one of the commonly accepted procedures for the generation of carbonyl ylides.[4] In these reactions, electrophilic Rh carbenoids interact with the oxygen lone pair of the carbonyl group resulting in the formation of reactive carbonyl ylides of type **A** (Scheme 39). The latter are active 1,3-dipoles and readily enter into inter- and intramolecular cycloaddition reactions with different dipolarophiles to form various cyclic adducts **70**.[80–120]

Scheme 39

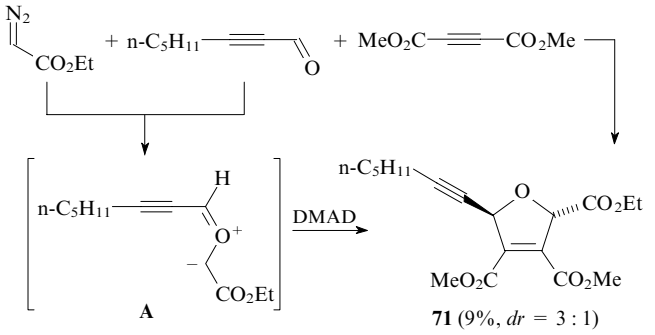


In this section, we consider examples of intermolecular three-component reactions of diazocarbonyl compounds that occur through the intermediate formation of carbonyl ylides, as well as some intramolecular two-component reactions, which formally can be referred to as three-component processes.

V.1. Three-component reactions

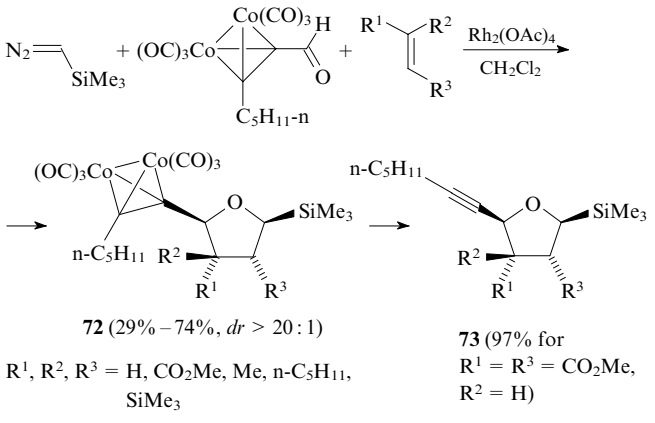
The catalytic decomposition of diazoacetic ester in the presence of oct-2-ynal and dimethyl acetylenedicarboxylate (DMAD) affords 5-(hept-1-yn-1-yl)-2,5-dihydrofuran-2,3,4-tricarboxylate **71** in low yield with low diastereoselectivity (isomer ratio *trans* : *cis* = 3 : 1) through the cycloaddition of the *in situ* generated carbonyl ylide **A** to the acetylenic dipolarophile (Scheme 40).[80] The low efficiency of the process is attributed to the fact that the triple bond of octynal can act as a dipolarophile to give [3 + 2]-cycloadducts with ethyl diazoacetate.[80]

Scheme 40



Both parameters of the process can be optimized by protecting the triple bond of acetylenic aldehyde by means of cobalt carbonyl $Co_2(CO)_6$. In this case, the yields of cycloadducts **72** in reactions with different dipolarophiles, including DMAD, are substantially higher, the diastereoselectivity of the process being also increased (*cis* : *trans* > 20 : 1) (Scheme 41). The best results were achieved in these reactions with the use of alkenes bearing electron-withdrawing substituents as dipolarophiles.[80]

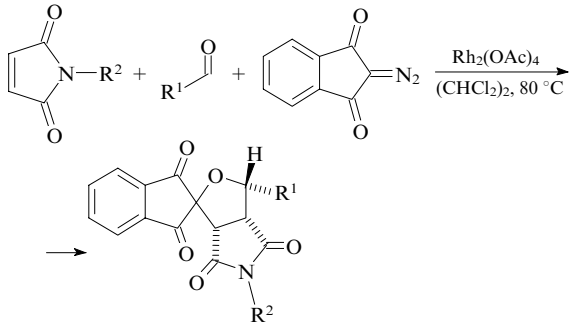
Scheme 41



The cobalt carbonyl protecting group can be easily removed with molecular iodine, which provides an efficient route to 3,4,4-trisubstituted 5-(hept-1-yn-1-yl)-2-trimethylsilyltetrahydrofurans **73** (see Scheme 41).[80]

The three-component reaction involving the cycloaddition of carbonyl ylides, which are generated from diazoindane-1,3(2*H*)-dione and aromatic aldehydes, to N-substituted maleimides proved to be a convenient method for the synthesis of analogues of the tRNA synthetase inhibitor — 3,3a-dihydrospiro(furo[3,4-*c*]pyrrole-1,2′-indene)-1′,3′,4,6(5*H*,6a*H*)-tetraones **74** (Scheme 42).[81] The reaction produces spirocyclic fused tetrahydrofurans **74** in good yields with the *endo* isomers predominating (shown in Scheme 42).[81]

Scheme 42

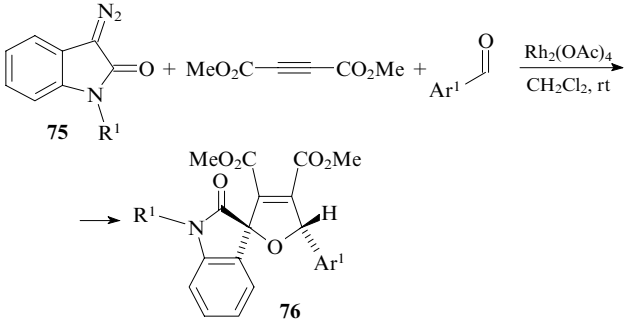


74 (47% – 78%, *dr* ⩽ 80 : 20)

R^1 = Ar, (*E*)-styryl; R^2 = Ar, Alk

The reaction of intermediate carbonyl ylides, which are formed through the decomposition of N-substituted 3-diazoindolin-2-ones by dirhodium tetraacetate **75** in the presence of aromatic aldehydes, with DMAD gives dimethyl 2′-oxo-5*H*-spiro(furan-2,3′-indoline)-3,4-dicarboxylates **76** in good and even high yields (Scheme 43). The best results were achieved using aldehydes as dipolarophiles with electron-excessive substituents in the aromatic nucleus (Ar^1 = PMP, 3-MeO-4-HOC_6H_3).[82, 83]

Scheme 43

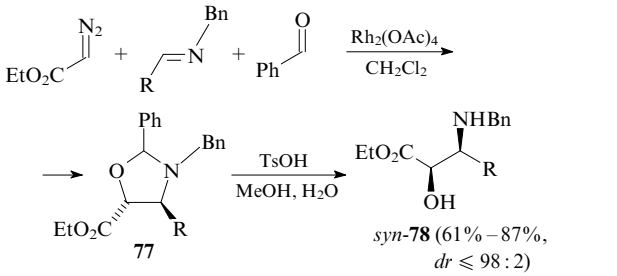


75 **76**

R^1 = Alk, Bn, All, *etc.*; Ar^1 = Ph (yield of **77** is 50% – 64%), PMP, 3-MeO-4-HOC_6H_3 (yield of **77** is 70% – 96%)

In addition to alkenes and DMAD, imines with aromatic substituents at the carbon atom (R = Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, 2-naphthyl, 2-furyl) can also efficiently trap carbonyl ylides in these reactions.[84] For instance, the dirhodium tetraacetate-catalyzed three-component reaction of ethyl diazoacetate with imines and benzaldehyde gives ethyl (4*S**,5*R**)-2,4-diaryl-3-benzyloxazolidine-5-carboxylates **77**, which are key intermediates in the synthesis of ethyl 3-aryl-3-benzylamino-2-hydroxypropanoates **78** (Scheme 44).[84] The latter are formed in good yields with high diastereoselectivity by the treatment of cycloadducts **77** with *p*-toluenesulfonic acid.[84]

Scheme 44



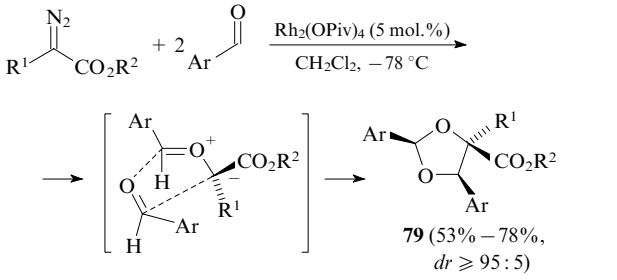
77

syn-**78** (61% – 87%, *dr* ⩽ 98 : 2)

R = Ph, XC_6H_4 (X = 4-O_2N, 4-F, 4-MeO, 4-Me, *etc.*)

In the reactions under consideration, aldehydes often not only act as the carbonyl component of C=O-ylides but also react with these intermediates as dipolarophiles according to [3 + 2]-cycloaddition pattern to form 1,3-dioxolanes.[4] Thus, the Rh^{II}-catalyzed reaction of α-alkyldiazoacetates with aromatic aldehydes gave 4-alkyl-2,5-diaryl-1,3-dioxolane-4-carboxylates **79** in good yields with high diastereoselectivity [isomer ratio (2*R*,4*R*,5*R*) : (2*R*,4*S*,5*R*) > 95 : 5] (Scheme 45).[85]

Scheme 45



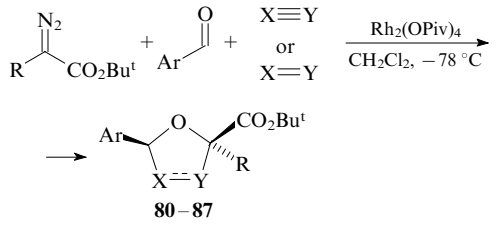
79 (53% – 78%, *dr* ⩾ 95 : 5)

Ar = Ph, XC_6H_4 (X = 4-F, 4-Cl, 4-O_2N, *ect.*);
R^1 = Me, Et, Bn, *ect.*; R^2 = Et, Bu^t; PivO is pivalate

The reactions involving α-alkyldiazoacetates are accompanied by the noticeable competing 1,2-hydride shift in intermediate Rh carbenoid.[12] However, this undesirable intramolecular process giving α,β-unsaturated esters can be suppressed to a considerable extent and the reaction can be directed *via* an intermolecular pathway using $Rh_2(OPiv)_4$ as the catalyst at reduced temperature (CH_2Cl_2, −78 °C).[85] For example, the $Rh_2(OPiv)_4$-catalyzed decomposition of α-alkyldiazoacetates in the presence of aromatic aldehydes and different dipolarophiles at −78 °C affords the corresponding tetrahydro- and dihydrofurans **80** – **86**, as well as oxadiazole **87** in high yields (up to 97%); under these conditions, the reaction occurs with excellent diastereoselectivity [isomer ratio (2*R*,5*R*) : (2*S*,5*R*) reaches > 95 : 5] (Scheme 46; the major isomers are shown).[86]

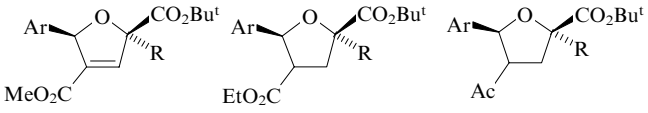
High yields of adducts **80** – **87** in the reactions under consideration are apparently due to high reactivity at low temperatures of C=O-ylides generated from α-alkyldiazoacetates compared with α-aryl diazoacetates or unsubstituted diazoacetates. The selectivity of the process

Scheme 46

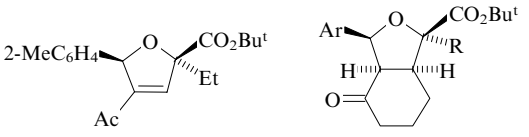


80–87

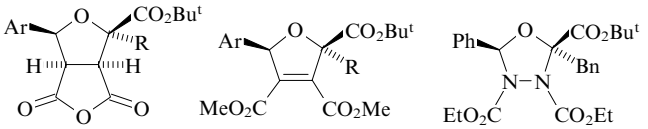
Ar = Ph, ZC_6H_4 (Z = 4-F, 2-Me, *ect.*); R = Me, Et, Bn, Bu^n, *ect.*



80 (76%–97%, *dr* > 88 : 12) **81** (59%–73%, *dr* = 88 : 12) **82** (51%–80%, *dr* > 95 : 5)



83 (90%, *dr* > 95 : 5) **84** (63%–77%, *dr* > 95 : 5)

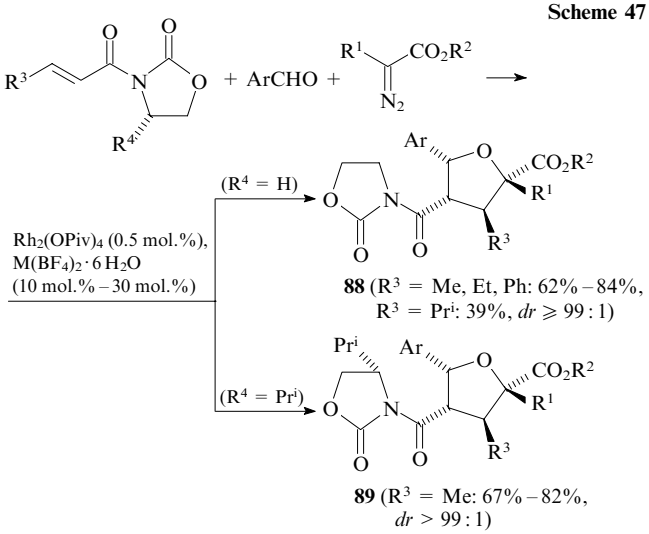


85 (68%–73%, *dr* > 91 : 9) **86** (63%–99%, *dr* > 95 : 5) **87** (57%)

substantially decreases with an increase in the temperature of the reaction medium.[86]

The addition of Co^{II}, Ni^{II} or Ag^{I} tetrafluoroborate as the co-catalyst is another way to minimize the side reaction producing dioxolanes in the three-component reaction of 2-diazoacetates with aromatic aldehydes and 3-(alk-2-enoyl)oxazolidin-2-ones (Scheme 47).[87] The co-catalyst not only suppresses the competitive reaction producing dioxolanes but also causes a substantial increase in the yield of target 2,3,5-trisubstituted 4-(2-oxooxazolidinocarbonyl)tetrahydrofuran-2-carboxylates **88** (up to 84%).[87]

Scheme 47



88 (R^3 = Me, Et, Ph: 62%–84%, R^3 = Pr^i: 39%, *dr* ⩾ 99 : 1)

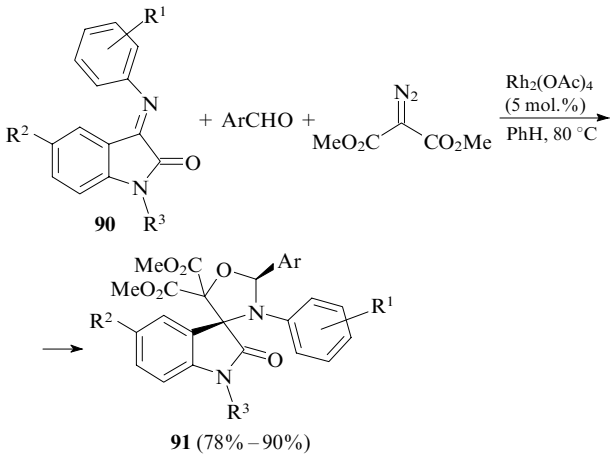
89 (R^3 = Me: 67%–82%, *dr* > 99 : 1)

R^1 = Et, Bu^i, Bn; R^2 = Me, Et, Bu^t; R^3 = Me, Et, Pr^i, Ph;
Ar = Ph, XC_6H_4 (X = 4-Me, 4-Cl, 4-O_2N, *etc.*)

The employment of chiral dipolarophiles — (*S*)-3-crotonoyl-4-isopropyloxazolidin-2-ones — in this reaction in the presence of Co^{II} or Ni^{II} tetrafluoroborate as the co-catalyst results in the formation of chiral 2,3,5-trisubstituted (2*S*,3*S*,4*S*,5*R*)-4-[(*S*)-4-isopropyl-2-oxooxazolidinocarbonyl]tetrahydrofuran-2-carboxylates **89** in yields from moderate to good with excellent diastereoselectivity [(2*S*,3*S*,4*S*,5*R*) : (2*R*,3*S*,4*S*,5*R*) > 99 : 1] (see Scheme 47).[87]

The Rh^{II}-catalyzed reaction of diazomalonate with aromatic aldehydes and 1,5-disubstituted (*E*)-3-(arylimino)indolin-2-ones **90** gave 1,5-disubstituted 2′,3′-diaryl-2-oxospiro(indoline-3,4′-oxazolidine)-5′,5′-dicarboxylates **91** in high yields (Scheme 48).[88] In this case, the absence of competing formation of 1,3-dioxolanes was apparently due to higher dipolarophilic activity of the C=N bond of imines in reactions with carbonyl ylides compared with the C=O bond of aromatic aldehydes.[88]

Scheme 48

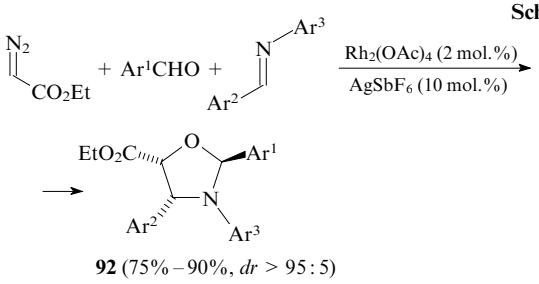


91 (78%–90%)

R^1 = H, 3-Cl, 4-Me, 4-Br, *etc.*; R^2 = H, Me, Br, Cl, NO_2;
R^3 = Me, Bn *etc.*); Ar = Ph, YC_6H_4 (Y = 4-O_2N, 4-NC, 4-Me, 4-Br, *etc.*)

The application of co-catalysts in the three-component reaction of ethyl diazoacetate with aromatic aldehydes and imines also makes it possible to avoid the competing formation of dioxolanes and prepare target 2,3,4-triaryloxazolidine-5-carboxylates **92** in high yields with excellent diastereoselectivity [isomer ratio (2*S*,4*R*,5*R*) : (2*S*,4*S*,5*R*) > 95 : 5] (Scheme 49).[89] The compound $AgSbF_6$ proved to be the co-catalyst of choice, whereas the use of Yb^{III}, Zn^{II} and Sc^{III} triflates resulted in low yields (27%–38%) of the target cycloaddition products of C=O-ylides and low

Scheme 49



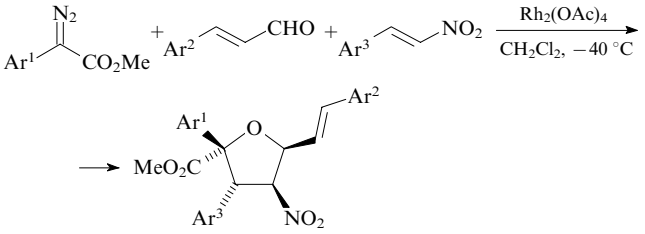
92 (75%–90%, *dr* > 95 : 5)

Ar^1 = 4-BrC_6H_4; Ar^2 = Ph, XC_6H_4 (X = 4-Br, 4-MeO, 4-Me, *etc.*);
Ar^3 = Ph, PMP, 4-ClC_6H_4

diastereoselectivity of the reaction [(2*S*,4*R*,5*R*) : (2*S*,4*S*,5*R*) ⩽ 63 : 37].[89]

The introduction of the conjugated C=C bonds into the aldehyde molecule has almost no effect on the selective interaction of intermediate carbonyl ylides with the dipolarophilic component. For instance, the Rh^{II}-catalyzed three-component reaction of α-aryl-substituted diazoacetates with α,β-unsaturated aldehydes and nitro-substituted alkenes in dichloromethane at −40 °C gives cycloaddition products of carbonyl ylides to the C=C bond of the dipolarophile — the corresponding methyl 2,3-diaryl-4-nitro-5-[(*E*)-styryl]tetrahydrofuran-2-carboxylates **93** — in yields of up to 90% with high diastereoselectivity [isomer ratio (2*S*,3*S*,4*S*,5*S*) : (2*S*,3*R*,4*R*,5*S*) ⩽ 95 : 5] (Scheme 50).[90]

Scheme 50



93 (*dr* ⩽ 95 : 5)

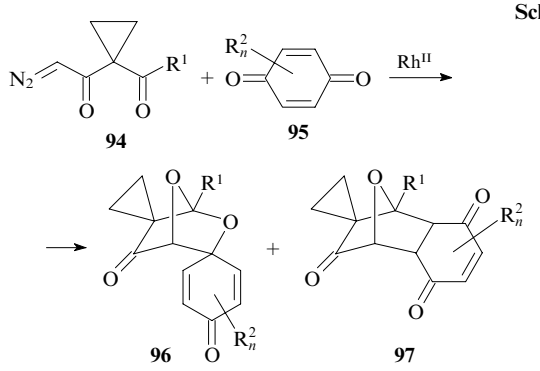
Ar^1 = Ph, PMP, 4-$HalC_6H_4$; Ar^2 = Ar^3 = Ph (yield of **94** is 65% – 90%),
Ar^2 = PMP, Ar^3 = XC_6H_4 (X = 4-O_2N, 4-Br, 2-Br, 2-MeO)
(yield of **94** is 43% – 58%)

V.2. Two-component reactions of cyclic carbonyl ylides

As mentioned in the beginning of the Section, the reactions of cyclic carbonyl ylides containing an additional C=O group can also formally be classified as three-component processes because they actually involve the following three components: the diazo substrate and the ylide and dipolarophilic carbonyl groups. The recent examples of such reactions are summarized below.

Since spirocyclopropanes are significant structural elements of many biologically active compounds, the development of an efficient strategy for the synthesis of these compounds based on the methodology under consideration is an important problem of the chemistry of Rh carbenoids.[4] The studies showed that the Rh^{II}-catalyzed decomposition of α-diazodicarbonyl compounds of type **94** in the presence of *p*-quinones **95** affords target polycyclic adducts **96** and **97** containing the spirocyclopropane moiety in good yields (Scheme 51).[91]

Scheme 51



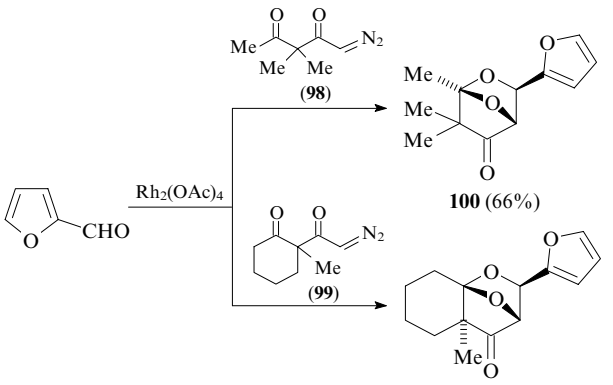
(61% – 81%, **96** : **97** from 100 : 0 to 0 : 100)

R^1 = Me, OAlk; R^2_n = H, 2,5-Me_2, 2,6-$(MeO)_2$, 2,5-Cl_2, benzo

It was found that the reaction pathway depends on the structures of the starting components. Thus, the reactions of diazo ketone **94a** (R^1 = Me) with 2,6-dimethoxy- and 2,5-dichlorobenzoquinones produce exceptionally cycloadducts **96**, which are formed through the cycloaddition of C=O-ylide to the quinone carbonyl group.[91] Meanwhile, the use of naphthoquinone in this reaction results in the cycloaddition of carbonyl ylides to the quinone double C=C bond to form cycloadducts **97**.[91]

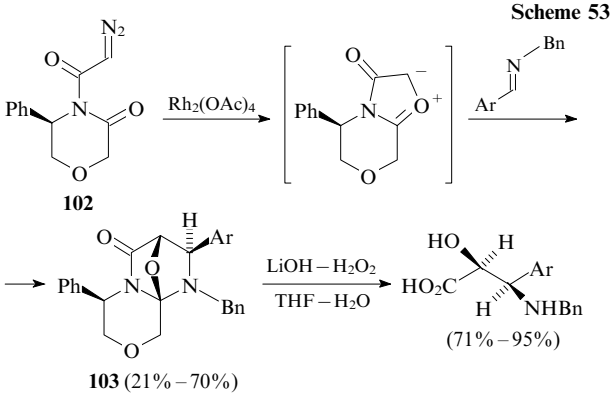
The carbonyl group of furan-2-carbaldehyde is also efficiently involved in the reaction with cyclic carbonyl ylides generated from 1-diazo-3,3-dimethylpentane-2,4-dione (**98**) and 2-(2-diazoacetyl)-2-methylcyclohexanone (**99**) to give 1,6,6-trimethyl-3-(2-furyl)-2,7-dioxabicyclo[2.2.1]heptan-5-one (**100**) and 4a-methyl-2-(2-furyl)hexahydro-3,8a-epoxychromen-4(4a*H*)-one (**101**) in good yields (Scheme 52).[92]

Scheme 52



The cycloaddition of cyclic carbonyl ylides to various dipolarophiles can be successfully used in the synthesis of enantiomeric β-amino-α-hydroxycarboxylic acids.[93] Thus, (2*R*,3*S*,6*R*,9a*R*)-2-aryl-1-benzyl-6-phenyltetrahydro-1*H*-3,9a-epoxypyrimido[2,1-*c*]oxazin-4(9*H*)-ones **103** were synthesized in good yields with excellent diastereoselectivity by the reaction of aryl-substituted imines with cyclic carbonyl ylide generated from (*R*)-4-(2-diazoacetyl)-5-phenylmorpholin-3-one (**102**) (Scheme 53). The cleavage of products

Scheme 53



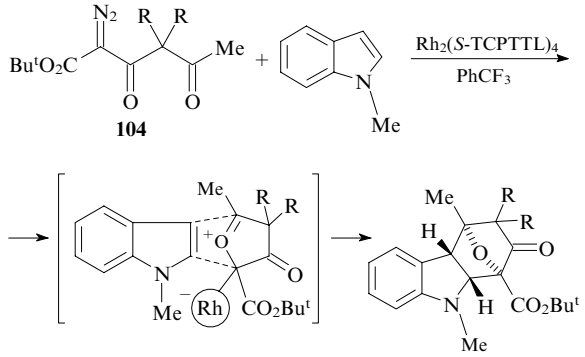
103 (21% – 70%)

Ar = Ph, 4-XC_6H_4 (X = Cl, MeO, Me_2N, O_2N)

103 by the $LiOH-H_2O_2$ system gives rise to substituted enantiomerically pure amino acids in high yields.[93]

Chiral Rh^{II} carboxylates provide high stereoselectivity of the cycloaddition of carbonyl ylides generated from α,γ-dioxodiazo esters to indoles.[94] For example, the reaction of 4,4-disubstituted *tert*-butyl 3,5-dioxodiazohexanoates **104** with *N*-methylindole catalyzed by $Rh_2(S\text{-TCPTTL})_4$ (see structures **4**) gives 3,3-disubstituted (1*R*,4*S*,4a*S*,9a*R*)-*tert*-butyl 4,9-dimethyl-2-oxo-2,3,4,4a,9,9a-hexahydro-1*H*-1,4-epoxycarbazole-1-carboxylates (*exo*-**105**) as the major products in yields of up to 88% and the isomer ratio *exo* : *endo* from 87 : 13 to 99 : 1 (Scheme 54).[94] The enantioselectivity of the reaction depends on the nature of the substituents R in diazodiketo ester **104**; *ee* varies from 50% to 92%.[94]

Scheme 54

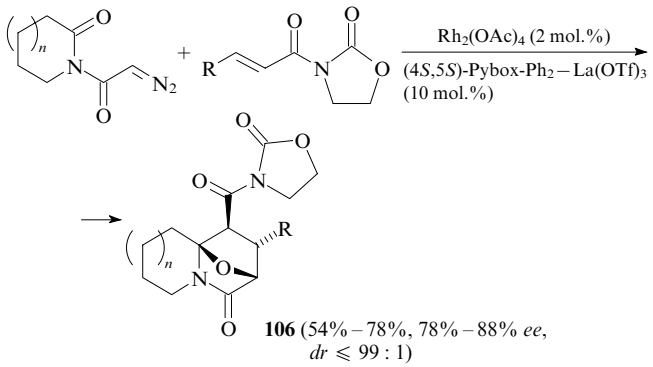


exo-**105** (40%–88%, *ee* 50%–92%, *dr* ⩽ 99 : 1)

R = Me; R–R = CH_2CH_2

The lanthanum complex with the ligand (4*S*,5*S*)-Pybox-Ph_2 as the co-catalyst proved to be very useful in providing high diastereo- and enantioselectivity of the Rh^{II}-catalyzed reactions of *N*-(diazoacetyl)lactams with 3-(alk-2-enoyl)oxazolidin-2-ones (Scheme 55).[95] The products of cycloaddition of carbonyl ylides to the C=C bond of oxazolidinones — cycloadducts **106** — are obtained in good yields with high diastereo- and enantioselectivity (*exo* : *endo* ⩽ 99 : 1).[95]

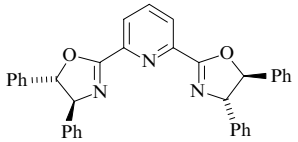
Scheme 55



106 (54%–78%, 78%–88% *ee*, *dr* ⩽ 99 : 1)

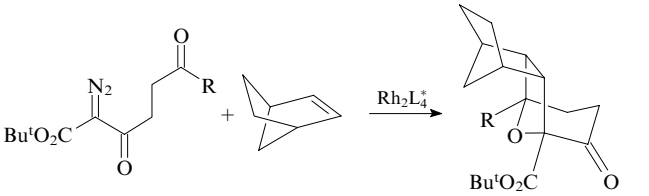
n = 1, 2; R = H, Me, Et, Pr, OAc;

(4*S*,5*S*)-Pybox-Ph_2 =



The catalytic decomposition of 2-diazo-3,6-diketo esters with the chiral rhodium complex $Rh_2(S\text{-DOSP})_4$ (see structures **4**) or dirhodium tetrakis[(*R*)-6,6′-didodecylbinaphthyl-2,2′-phosphate] ($Rh_2L_4^*$) in the presence of norbornene produces adducts **107** of intermediate C=O-ylide with the double bond of bicycloalkene in good yields with good enantioselectivity (Scheme 56).[96]

Scheme 56

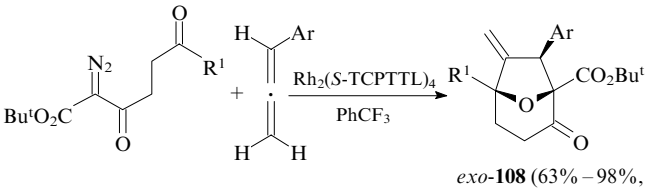


107 (34%–83%, 41%–92% *ee*)

R = Me, Pr^i, n-C_6H_{13}, Ph

The similar Rh^{II}-catalyzed reaction of 2-diazo-3,6-diketo esters with 1-(aryl)allenes affords exceptionally 5,7-disubstituted (1*R*,5*R*,7*R*)-6-methylidene-2-oxo-8-oxabicyclo[3.2.1]octane-1-carboxylates (*exo*-**108**) in high yield with high enantioselectivity (Scheme 57).[97]

Scheme 57



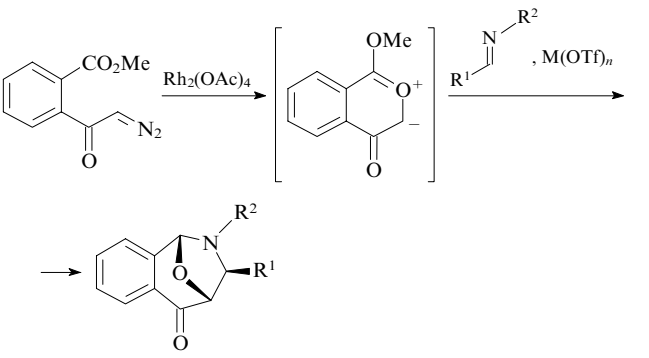
exo-**108** (63%–98%, 83%–99% *ee*)

R^1 = H, Me, Ph;

Ar = Ph, XC_6H_4 (X = 4-Me, 4-MeO, 4-F_3C, 2-Me, *etc.*)

Lewis acids (Mg^{II}, Yb^{III}, Ho^{III}, *etc.* triflates) can serve as efficient co-catalysts for the reactions of 2-(diazoacetyl)-benzoate with imines.[98] For example, 2,3-disubstituted 3,4-dihydro-1*H*-1,4-epoxybenzo[*c*]azepin-5(2*H*)-ones **109** were prepared in good yields with high diastereoselectivity (*exo* : *endo* ⩽ 94 : 6) by the cycloaddition of intermediate cyclic C=O-ylide to the imine C=N bond (Scheme 58).[98]

Scheme 58



109 (⩽94, *dr* ⩽ 94 : 6)

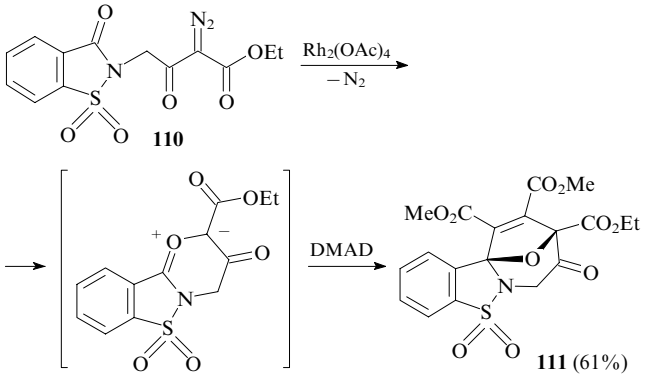
R^1 = Ph, XC_6H_4 (X = 2-BnO, 2-MeO, 4-MeO, *etc.*);

R^2 = Ph, PMP, 4-ClC_6H_4, *etc.*; M = Mg, Yb, Ho; *n* = 2, 3

The catalytic decomposition of the diazo derivative of saccharine **110** by dirhodium tetraacetate gives cyclic carbonyl ylide, which reacts with DMAD to form the cyclo-

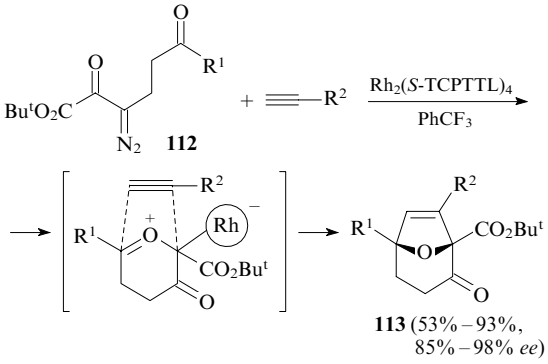
adduct of 9-ethyl-10,11-dimethyl-8-oxo-8,9-dihydro-7*H*-9,11a-epoxybenzo[4,5]isothiazolo[2,3-*a*]azepine-9,10,11-tricarboxylate 5,5-dioxide (**111**) in good yield (Scheme 59).[99, 108]

Scheme 59



The application of chiral Rh^{II} carboxylates provides high enantioselectivity of the intermolecular cycloaddition of carbonyl ylides to terminal alkynes. The complex Rh_2(*S*-TCPTTL)$_4$ (see structures **4**) proved to be one of the most efficient and selective catalysts.[100, 101] (1*R*,5*R*)-*tert*-Butyl 2-oxo-8-oxabicyclo[3.2.1]oct-6-ene-1-carboxylates **113** were prepared in good yields with good enantioselectivity by the decomposition of 3-diazo-2,6-dioxo ester **112** by Rh_2(*S*-TCPTTL)$_4$ in the presence of alkynes (Scheme 60).[101]

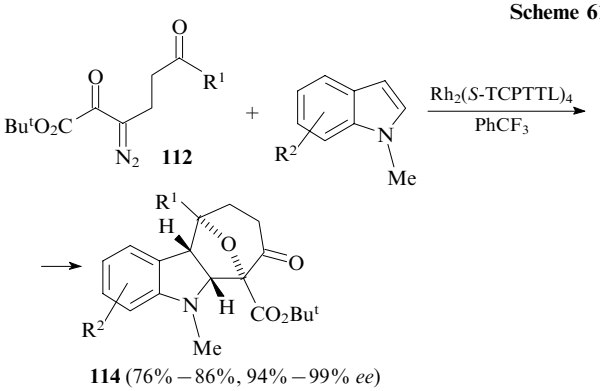
Scheme 60



R^1 = Me, Ph, 4-ClC_6H_4, 4-MeC_6H_4; R^2 = Ph, OEt, PMP, *etc.*

The analogous reaction of 3-diazo-2,6-dioxo ester **112** with N-substituted indoles as dipolarophiles affords 5,10-disubstituted (5a*R*,6*R*,10*R*,10a*S*)-*tert*-butyl 7-oxo-5,5a,6,7,8,9,10,10a-octahydro-6,10-epoxycyclohepta[*b*]indole-6-carboxylates **114** in good yields with high enantioselectivity (Scheme 61, the position of R^2 in the starting indole is indicated).[94]

Scheme 61



R^1 = Me, Ph; R^2 = H, 4-Me, 7-Me, 5-Br, 5-Me, 5-MeO

The results of recent studies considered in the present review show that Rh^{II}-catalyzed multicomponent reactions of aliphatic diazo compounds provide a powerful tool for targeted organic synthesis. These reactions allow researchers to perform the three- or four-component processes as one-pot procedures and prepare complex organic molecules, biologically active and natural compounds with high diastereo- and enantioselectivity.

Noteworthy are successful attempts to use co-catalysts in order to increase the efficiency and stereoselectivity of the transformations under consideration. This is a new area of the chemistry of metal complex-catalyzed reactions of ADC and an efficient tool, which can be employed to change the reaction pathway and substantially increase the selectivity of multicomponent processes.

Although the reactions of diazo compounds catalyzed by transition metal complexes have been extensively studied for many years, this area of the chemistry of ADC is undoubtedly far from being exhausted and new discoveries will be expected in the future.

References

1. R Huisgen *Angew. Chem.* **67** 439 (1955)
2. I A D'yakonov *Alifaticheskie Diazosoedineniya* (Aliphatic Diazo Compounds) (Leningrad: Leningrad State University, 1958)
3. *The Chemistry of Diazonium and Diazo Groups* (Ed. S Patai) (Chichester: Wiley, 1978)
4. M Regitz, G Maas *Diazo Compounds. Properties and Synthesis* (London: Academic Press, 1986)
5. E A Shapiro, A B Dyatkin, O M Nefedov *Diazoefiry* (Diazo Esters) (Moscow: Nauka, 1992)
6. H Zollinger *Diazo Chemistry II. Aliphatic, Inorganic and Organometallic Compounds* (Weinheim: Wiley-VCH, 1995)
7. G Maas *Top. Curr. Chem.* **137** 75 (1987)
8. O M Nefedov, A I Ioffe, L G Menchikov *Khimiya Karbenov* (The Chemistry of Carbenes) (Moscow: Khimiya, 1990)
9. A Padwa, S F Hornbuckle *Chem. Rev.* **91** 263 (1991)
10. H M L Davies, E G Antoulinakis *Org. React.* **57** 1 (2001)
11. M P Doyle, M A McKervey, T Ye *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides* (New York: Wiley, 1998)
12. *Modern Rhodium-Catalyzed Organic Reactions* (Ed. P A Evans) (Weinheim: Wiley-VCH, 2005)
13. H M L Davies, R E Beckwith *Chem. Rev.* **103** 2861 (2003)
14. H Lebel, J-F Marcoux, C Molinaro, A B Charette *Chem. Rev.* **103** 977 (2003)
15. H M L Davies, S J Hedley *Chem. Soc. Rev.* **36** 1109 (2007)
16. J Hansen, H M L Davies *Coord. Chem. Rev.* **252** 545 (2008)
17. Z Zhang, J Wang *Tetrahedron* **64** 6577 (2008)
18. H M L Davies, J R Manning *Nature (London)* **451** 417 (2008)
19. M P Doyle, R Duffy, M Ratnikov, L Zhou *Chem. Rev.* **110** 704 (2010)
20. P Herrmann, T Bach *Chem. Soc. Rev.* **40** 2022 (2011)
21. F Collet, C Lescot, P Dauban *Chem. Soc. Rev.* **40** 1926 (2011)
22. H M L Davies, D Morton *Chem. Soc. Rev.* **40** 1857 (2011)
23. M L Rosenberg, A Krivokapic, M Tilset *Org. Lett.* **11** 547 (2009)

24. M L Rosenberg, K Vlašaná, N S Gupta, D Wragg, M Tilset *J. Org. Chem.* **76** 2465 (2011)
25. M L Rosenberg, E Langseth, A Krivokapic, N S Gupta, M Tilset *New J. Chem.* **35** 2306 (2011)
26. M L Rosenberg, A Krapp, M Tilset *Organometallics* **30** 6562 (2011)
27. W-W Chan, S-F Lo, Z Zhou, W-Y Yu *J. Am. Chem. Soc.* **134** 13565 (2012)
28. T K Hyster, K E Ruhl, T Rovis *J. Am. Chem. Soc.* **135** 5364 (2013)
29. Z Shi, D C Koester, M Boultadakis-Arapinis, F Glorius *J. Am. Chem. Soc.* **135** 12204 (2013)
30. X Yu, S Yu, J Xiao, B Wan, X Li *J. Org. Chem.* **78** 5444 (2013)
31. J Shi, Y Yan, Q Li, H E Xu, W Yi *Chem. Commun.* **50** 6483 (2014)
32. A DeAngelis, O Dmitrenko, J M Fox *J. Am. Chem. Soc.* **134** 11035 (2012)
33. N R Candeias, P M P Gois, C A M Afonso *J. Org. Chem.* **71** 5489 (2006)
34. S Chamni, Q-L He, Y Dang, S Bhat, J O Liu, D Romo *ACS Chem. Biol.* **6** 1175 (2011)
35. Y Lian, H M L Davies *Org. Lett.* **14** 1934 (2012)
36. S A Bonderoff, A Padwa *Org. Lett.* **15** 4114 (2013)
37. D Gillingham, N Fei *Chem. Soc. Rev.* **42** 4918 (2013)
38. P Müller, Y F Allenbach, S Chappellet, A Ghanem *Synthesis* 1689 (2006)
39. V N G Lindsay, A B Charette *ACS Catal.* **2** 1221 (2012)
40. A F Trindade, J A S Coelho, C A M Afonso, L F Veiros, P M P Gois *ACS Catal.* **2** 370 (2012)
41. Y Wang, Z Chen, A Mi, W Hu *Chem. Commun.* 2486 (2004)
42. H Huang, Y Wang, Z Chen, W Hu *Adv. Synth. Catal.* **347** 531 (2005)
43. Y Zhu, C Zhai, L Yang, W Hu *Eur. J. Org. Chem.* 1113 (2011)
44. Y Wang, Y Zhu, Z Chen, A Mi, W Hu, M P Doyle *Org. Lett.* **5** 3923 (2003)
45. Y Zhu, C Zhai, Y Yue, L Yang, W Hu *Chem. Commun.* 1362 (2009)
46. J Jiang, H-D Xu, J-B Xi, B-Y Ren, F-P Lv, X Guo, L-Q Jiang, Z-Y Zhang, W-H Hu *J. Am. Chem. Soc.* **133** 8428 (2011)
47. C Jing, D Xing, Y Qian, T Shi, Y Zhao, W Hu *Angew. Chem., Int. Ed.* **52** 9289 (2013)
48. J Jiang, X Ma, S Liu, Y Qian, F Lv, L Qiu, X Wu, W Hu *Chem. Commun.* **49** 4238 (2013)
49. C Wang, S Liu, D Xing, X Wang, X Wu, W Hu *Tetrahedron* **69** 11203 (2013)
50. L Qiu, D Wang, F Lv, X Guo, W Hu, L Yang, S Liu *Tetrahedron* **70** 1471 (2014)
51. X Zhang, J Ji, Y Zhu, C Jing, M Li, W Hu *Org. Biomol. Chem.* **10** 2133 (2012)
52. C-Y Zhou, J-C Wang, J Wei, Z-J Xu, Z Guo, K-H Low, C-M Che *Angew. Chem., Int. Ed.* **51** 11376 (2012)
53. L Ren, X-L Lian, L-Z Gong *Chem. – Eur. J.* **19** 3315 (2013)
54. S G Dawande, V Kanchupalli, B S Lad, J Rai, S Katukojvala *Org. Lett.* **16** 3700 (2014)
55. S R Hansen, J E Spangler, J H Hansen, H M L Davies *Org. Lett.* **14** 4626 (2012)
56. C Jing, D Xing, W Hu *Chem. Commun.* **50** 951 (2014)
57. A Viso, R Fernández de la Pradilla, A Garcta, A Flores *Chem. Rev.* **105** 3167 (2005)
58. Z Guo, T Shi, J Jiang, L Yang, W Hu *Org. Biomol. Chem.* **7** 5028 (2009)
59. X-Y Guan, L-P Yang, W Hu *Angew. Chem., Int. Ed.* **49** 2190 (2010)
60. Y Qian, X Xu, L Jiang, D Prajapati, W Hu *J. Org. Chem.* **75** 7483 (2010)
61. Y Qian, C Jing, T Shi, J Ji, M Tang, J Zhou, C Zhai, W Hu *ChemCatChem* **3** 653 (2011)
62. C Wang, D Xing, D Wang, X Wu, W Hu *J. Org. Chem.* **79** 3908 (2014)
63. C-D Lu, H Liu, Z-Y Chen, W-H Hu, A-Q Mi *Org. Lett.* **7** 83 (2005)
64. H Huang, X Guo, W Hu *Angew. Chem., Int. Ed.* **46** 1337 (2007)
65. X Guo, H Huang, L Yang, W Hu *Org. Lett.* **9** 4721 (2007)
66. X Zhang, H Huang, X Guo, X Guan, L Yang, W Hu *Angew. Chem., Int. Ed.* **47** 6647 (2008)
67. W Hu, X Xu, J Zhou, W-J Liu, H Huang, J Hu, L Yang, L-Z Gong *J. Am. Chem. Soc.* **130** 7782 (2008)
68. B Alcaide, P Almendros, C Aragoncillo, R Callejo, M P Ruiz, M R Torres *J. Org. Chem.* **74** 8421 (2009)
69. Z Guo, M Cai, J Jiang, L Yang, W Hu *Org. Lett.* **12** 652 (2010)
70. X Xu, Y Qian, L Yang, W Hu *Chem. Commun.* **47** 797 (2011)
71. J Ji, X Zhang, Y Zhu, Y Qian, J Zhou, L Yang, W Hu *J. Org. Chem.* **76** 5821 (2011)
72. X Han, L Jiang, M Tang, W Hu *Org. Biomol. Chem.* **9** 3839 (2011)
73. B Alcaide, P Almendros, C Aragoncillo, R Callejo, M P Ruiz, M R Torres *Eur. J. Org. Chem.* 2359 (2012)
74. J Jiang, X Guan, S Liu, B Ren, X Ma, X Guo, F Lv, X Wu, W Hu *Angew. Chem., Int. Ed.* **52** 1539 (2013)
75. L Qiu, L Gao, J Tang, D Wang, X Guo, S Liu, L Yang, J Li, W Hu *J. Org. Chem.* **79** 4142 (2014)
76. X Xu, J Zhou, L Yang, W Hu *Chem. Commun.* 6564 (2008)
77. S Muthusamy, J Krishnamurthi *Tetrahedron Lett.* **48** 6692 (2007)
78. Y Qian, C Jing, S Liu, W Hu *Chem. Commun.* **49** 2700 (2013)
79. L Qiu, X Guo, C Ma, H Qiu, S Liu, L Yang, W Hu *Chem. Commun.* **50** 2196 (2014)
80. A J Skaggs, E Y Lin, T F Jamison *Org. Lett.* **4** 2277 (2002)
81. C-D Lu, Z-Y Chen, H Liu, W-H Hu, A-Q Mi M P Doyle *J. Org. Chem.* **69** 4856 (2004)
82. S Muthusamy, C Gunanathan, M Nethaji *J. Org. Chem.* **69** 5631 (2004)
83. S Muthusamy, R Ramkumar, A K Mishra *Tetrahedron Lett.* **52** 148 (2011)
84. S Torssell, M Kienle, P Somfai *Angew. Chem., Int. Ed.* **44** 3096 (2005)
85. A DeAngelis, P Panne, G P A Yap, J M Fox *J. Org. Chem.* **73** 1435 (2008)
86. A DeAngelis, M T Taylor, J M Fox *J. Am. Chem. Soc.* **131** 1101 (2009)
87. Y Hashimoto, K Itoh, A Kakehi, M Shiro, H Suga *J. Org. Chem.* **78** 6182 (2013)
88. T Rajasekaran, G Karthik, B Sridhar, B V S Reddy *Org. Lett.* **15** 1512 (2013)
89. X Xu, X Guo, X Han, L Yang, W Hu *Org. Chem. Front.* **1** 181 (2014)
90. L Qiu, X Guo, J Zhou, S Liu, L Yang, X Wu, W Hu *RCS Adv.* **3** 20065 (2013)
91. M C Pirrung, K P Kaliappan *Org. Lett.* **2** 353 (2000)
92. S Muthusamy, S A Babu, C Gunanathan, B Ganguly, E Suresh, P Dastidar *J. Org. Chem.* **67** 8019 (2002)
93. Y Gan, L M Harwood, S C Richards, I E D Smith, V Vinader *Tetrahedron: Asymmetry* **20** 723 (2009)
94. N Shimada, T Oohara, J Krishnamurthi, H Nambu, S Hashimoto *Org. Lett.* **13** 6284 (2011)
95. H Suga, Y Hashimoto, S Yasumura, R Takezawa, K Itoh, A Kakehi *J. Org. Chem.* **78** 10840 (2013)
96. D M Hodgson, T Brückl, R Glen, A H Labande, D A Selden, A G Dossetter, A J Redgrave *Proc. Natl. Acad. Sci. USA* **101** 5450 (2004)
97. J Krishnamurthi, H Nambu, K Takeda, M Anada, A Yamano, S Hashimoto *Org. Biomol. Chem.* **11** 5374 (2013)
98. H Suga, Y Ebiura, K Fukushima, A Kakehi, T Baba *J. Org. Chem.* **70** 10782 (2005)

99. Vs V Nikolaev, I S Krylov, B Schulze, L L Rodina *Russ. J. Org. Chem.* **41** 784 (2005) [*Zh. Org. Khim.* **41** 798 (2005)]
100. J L G Ruano, A Fraile, M R Marttn, A Núñez *J. Org. Chem.* **71** 6536 (2006)
101. N Shimada, M Anada, S Nakamura, H Nambu, H Tsutsui, S Hashimoto *Org. Lett.* **10** 3603 (2008)
102. C Bolm, S Saladin, A Kasyan *Org. Lett.* **4** 4631 (2002)
103. D M Hodgson, R Glen, A J Redgrave *Tetrahedron Lett.* **43** 3927 (2002)
104. G Mehta, S Muthusamy *Tetrahedron* **58** 9477 (2002)
105. D M Hodgson, R Glen, G H Grant, A J Redgrave *J. Org. Chem.* **68** 581 (2003)
106. A P Molchanov, V V Diev, J Kopf, R R Kostikov *Russ. J. Org. Chem.* **40** 431 (2004) [*Zh. Org. Khim.* **40** 458 (2004)]
107. A Padwa *J. Organomet. Chem.* **690** 5533 (2005)
108. Vs Nikolaev, L Hennig, J Sieler, L Rodina, B Schulze, V A Nikolaev *Org. Biomol. Chem.* **3** 4108 (2005)
109. S Muthusamy, B Gnanaprakasam, E Suresh *Org. Lett.* **7** 4577 (2005)
110. Vs V Nikolaev, H Heimgartner, A Linden, I S Krylov, V A Nikolaev *Eur. J. Org. Chem.* 4737 (2006)
111. Vs V Nikolaev, L Hennig, H Heimgartner, B Schulze, V A Nikolaev *Tetrahedron Lett.* **47** 2643 (2006)
112. H Suga, D Ishimoto, S Higuchi, M Ohtsuka, T Arikawa, T Tsuchida, A Kakehi, T Baba *Org. Lett.* **9** 4359 (2007)
113. B Shi, S Merten, D K Y Wong, J C K Chu, L L Liu, S K Lam, A Jäger, W-T Wong, P Chiu, P Metz *Adv. Synth. Catal.* **351** 3128 (2009)
114. L R Domingo, J A Svez *J. Org. Chem.* **76** 373 (2011)
115. S Muthusamy, T Karikalan, E Suresh *Tetrahedron Lett.* **52** 1934 (2011)
116. A Padwa *Tetrahedron* **67** 8057 (2011)
117. M Terada, Y Toda *Angew. Chem., Int. Ed.* **51** 2093 (2012)
118. M Enßle, S Buck, R Werz, G Mass *ARKIVOC* (iii) 149 (2012)
119. S Muthusamy, T Karikalan *Tetrahedron* **68** 1443 (2012)
120. S Muthusamy, M Sivaguru *Tetrahedron Lett.* **54** 6810 (2013)