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Novel Multicomponent Reactions via Trapping of Protic Onium Ylides with Electrophiles

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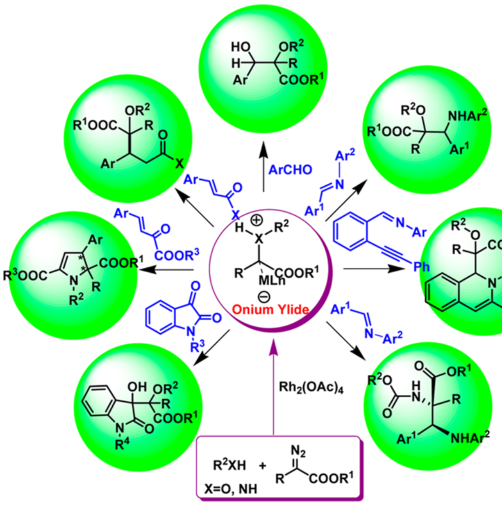

Multicomponent reactions (MCRs) are one-pot processes in which three or more starting materials form a product that incorporates the structural features of each reagent. These reactions date back to the mid-19th century, when Strecker first prepared α-aminonitriles through the condensation of aldehydes with ammonia and hydrogen cyanide. In addition to affording products with structural complexity and diversity, MCRs offer the advantages of simplicity, synthetic efficiency, synthetic convergence, and atom economy. Therefore, they have played an important role in modern synthetic organic chemistry and drug-discovery research.

The irreversible trapping of an active intermediate generated from two components by a third one offers an effective way to discover novel MCRs. In cases where the intermediate from the first two components is reactive enough to generate a two-component byproduct, it becomes challenging to control of the chemoselectivity of these MCRs over the side reaction. For example, researchers had expected that ammonium/oxonium ylides, high energy intermediates that have acidic protons and basic carbanions attached to adjacent carbons, would be too reactive to be intercepted by external electrophiles. Instead, a very fast 1,2-proton transfer would neutralize the charge separation, resulting in a stable N−H/O−H insertion product.

In this Account, we present our efforts toward the development of novel MCRs via trapping of the active ammonium/oxonium ylide intermediates with a number of electrophiles. In these reactions, a "delayed proton transfer" that occurs after the trapping process produces novel multicomponent coupling products. Thus, transition-metal-catalyzed MCRs of diazocarbonyl compounds, anilines/alcohols, and electrophiles efficiently afford polyfunctional molecules such as α-amino-β-hydroxy acids, α-hydroxy-β-amino acids, α,β-diamino acids, and α,β-dihydroxy acid derivatives. We have also applied a cooperative catalysis strategy to some of these MCRs leading to reactions with high chemo-, diastereo-, and enantioselectivity. These MCRs also provide solid experimental evidence for the existence of the active protic onium ylides.

1. Introduction

By generating structural complexity in a single operation from three or more reactants, MCRs provide efficient and atom-economic routes for the synthesis of target compounds.[1] They have played important roles in modern synthetic organic chemistry including drug-discovery research.[2] Considerable effort has been devoted to improving known MCRs and developing new ones on the basis of diversity- and complexity-generating strategies for the synthesis of small molecules.

Irreversible trapping of an active intermediate **1** generated from two components by a third one is an effective strategy for the discovery of novel MCRs (Scheme 1). However, control of the chemoselectivity of the MCRs over 2CRs is challenging, especially when the intermediate tends to be transformed into a stable product **2** that does not react with the remaining components.

Since the discovery of the Wittig reaction in 1953, the chemistry of ylides has grown rapidly, and become a powerful and versatile tool in organic synthesis.[3] An attractive

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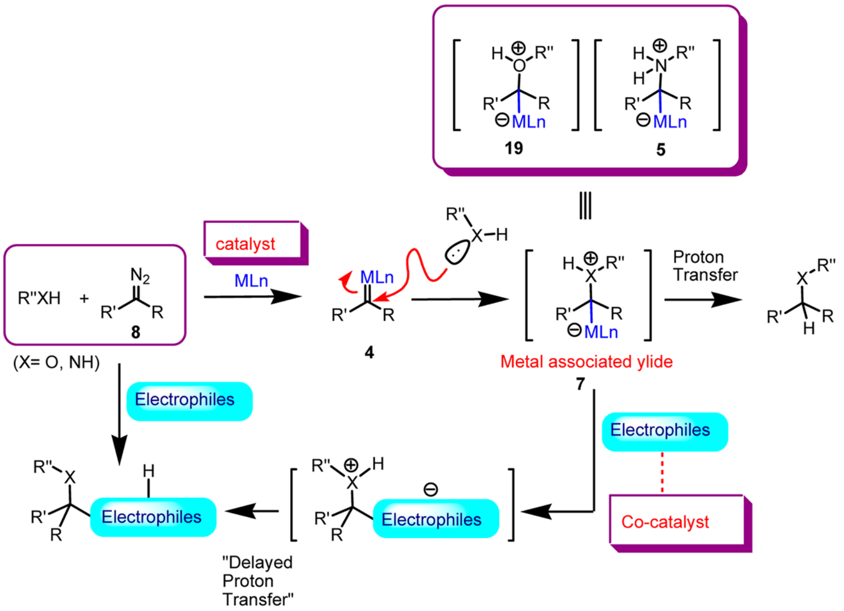
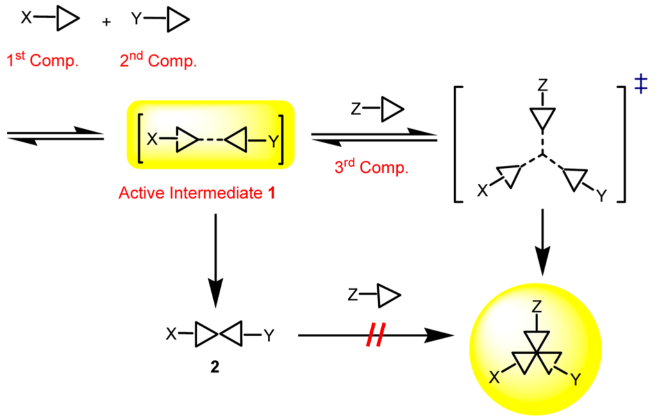
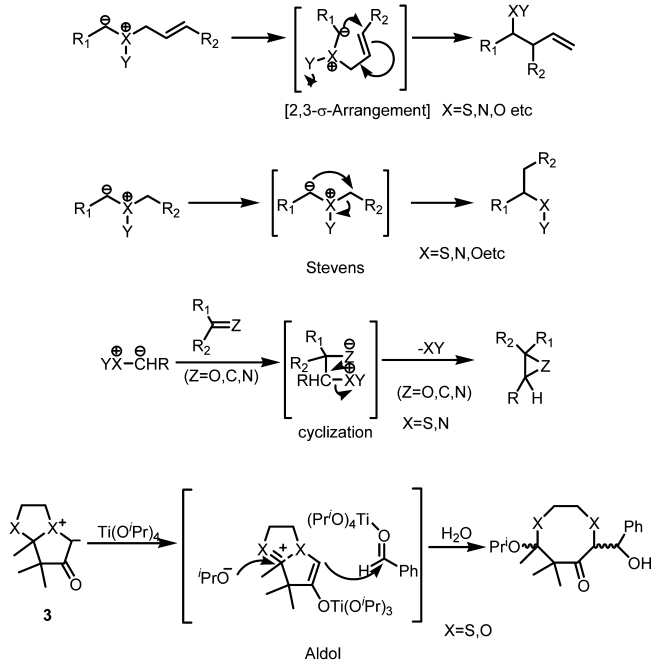


FIGURE 1. Trapping of protic onium ylides with electrophiles.

SCHEME 1. MCRs Involving Trapping of Active Intermediates



SCHEME 2. Traditional Reaction Pathways of Onium Ylides



method for ylide formation involves the interaction of free carbenes or metal carbenes with the unshared electronic pairs of heteroatoms. [1,2]-Dipolar onium ylides formed from sulfur, ethers, or tertiary amines typically undergo three types of reactions (Scheme 2): (1) [2,3]-sigmatropic rearrangement; (2) 1,2-shift (Stevens rearrangement); and (3) nucleophilic addition to the C═Z bond (Z = C, N, O) and subsequent cyclization to a three-membered ring (epoxidation, cyclopropanation, or aziridination) or rings of other sizes. Recently, ethereal or thioethereal ylides **3** have been reported to undergo nucleophilic addition to aldehydes without elimination of the onium moiety, giving expanded oxygen/sulfur-containing rings and a hydroxyl alkyl ether moiety.[4]

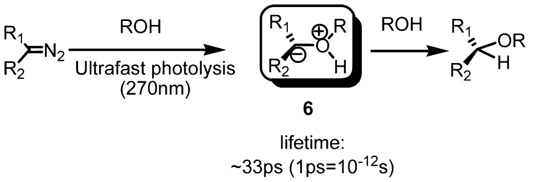
The N–H/O–H insertions, in which carbenes or metal carbenes **4** react with the protic amino groups (including amines, amides, ammonium hydroxide, and carbamates) or hydroxyl groups (including alcohols, phenols, carboxylic acids, and water), form C–N/C–O bonds directly (Figure 1).[5] A [1,2]-dipolar metal-associated or free protic ammonium ylide **5** has been proposed as the intermediate for N–H insertion (Scheme 4),[3a,b] while the intermediates for the O–H insertions are still a subject of debate.[6] Recently, direct observations of the formation and decay of a carbene-alcohol ylide **6** were reported for the O–H insertion, and the lifetime of the ylide was extremely short (Scheme 3).[7]

This class of onium ylides **7** with acidic protons and basic carbanions in vicinal proximity are of high energy, and they were formerly thought to be too reactive to be intercepted by external electrophiles. However, we discovered that the active onium ylides can be trapped by electrophiles to achieve novel bond formation (Figure 1). Thus, the transition-metal-catalyzed MCRs of diazocompounds **8** and anilines/alcohols with electrophiles not only provide a novel approach for the efficient construction of polyfunctional molecules, but also provide solid experimental evidence for the existence of the protic onium ylide intermediates. In this account, we present our efforts in the development of these novel MCRs, the control of their chemo- and stereoselectivities, and the application of the method in the convergent construction of polyfunctional molecules including α-amino-β-hydroxy acids, α-hydroxy-β-amino acids, α,β-diamino acids, α,β-dihydroxy acid derivatives, and heterocycles.

2. Trapping of Ammonium Ylide

2.1. Mannich-Type Reactions. The initial discovery of the three-component reaction (3CR) was a consequence of a reaction that was overlooked during research into the dirhodium(II)-catalyzed aziridination of aryldiazoacetates with aryl imines (path A). The aziridination was proposed to proceed through an intramolecular ring closure of an azomethine ylide **9**.[8] For the examination of the correlation between the electronic effect of the imine and the diastereoselectivity, an imine derived from *para*-nitro benzaldehyde and *para*-nitro aniline was employed. To our surprise, an α,β-diamino ester **10** (path B), which incorporated the structural features of the diazo compound, the imine, and the aniline, was isolated in the reaction (Scheme 4).[9] For the determination of what should account for the three-component coupling product, the purity of the starting materials was first checked. It was identified that the imine contained a significant amount of unreacted *para*-nitro aniline, which was not removed during the imine purification process. It was an oversight to use the impure imine, but without it, such an experiment to explore the 3CR would not have been designed.

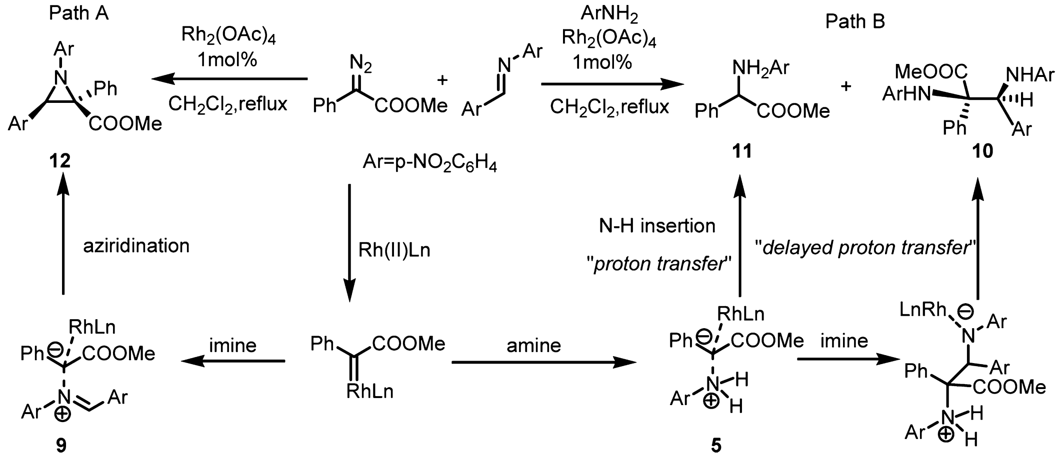
SCHEME 3. Observation of the Formation and Decay of a Carbene-Alcohol Ylide



The reaction scope was explored next. Electron-deficient anilines and imines favored the 3CR. In addition, a higher imine concentration was beneficial for the 3CR. Although the diastereoselectivity was high (up to 95:5), the application of this 3CR was limited by the narrow substrate scope as well as the difficulty of further derivatization of the coupling product.

The reaction can be rationalized to proceed via initial formation of a protic ammonium ylide **5** (Scheme 4), which then undergoes product formation through two competitive reaction pathways: (1) proton transfer to give the N$-$H insertion product **11**; and (2) nucleophilic addition to the imine and subsequent "delayed proton transfer" to give the coupling product **10**. In the current reaction, the inherent reaction kinetics do not favor the aziridination process,

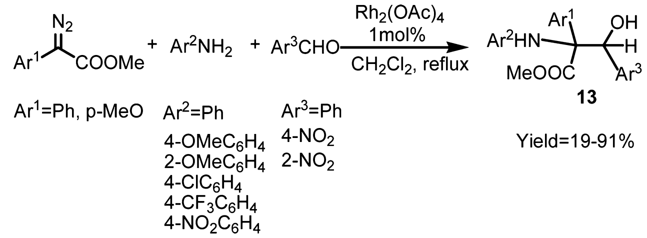
SCHEME 4. Trapping of Ammonium Ylides with Imines



indicating that the 4-π electronic ring closure is relatively slow compared to the C–C bond formation or proton transfer. Control experiments excluded the formation of the coupling product either from **11** or from the aziridination product **12**. The coupling product can only be formed when the three starting materials coexist in the presence of the catalyst.

2.2. Aldol-Type Reactions. The reactivity of this ammonium ylide was explored further by expanding the electrophile scope from imines to aldehydes (Scheme 5).[10] In the rhodium(II)-catalyzed 3CR of aryldiazoacetates, anilines, and aromatic aldehydes, no epoxidation from aldehydes was observed.[8,11] Only β-hydroxy-α-amino esters **13** were obtained in competition with the N–H insertion product. Electron-deficient arylaldehydes, electron-rich anilines, and aryl diazoacetates favored the 3CR. However, the diastereoselectivity was generally poor.

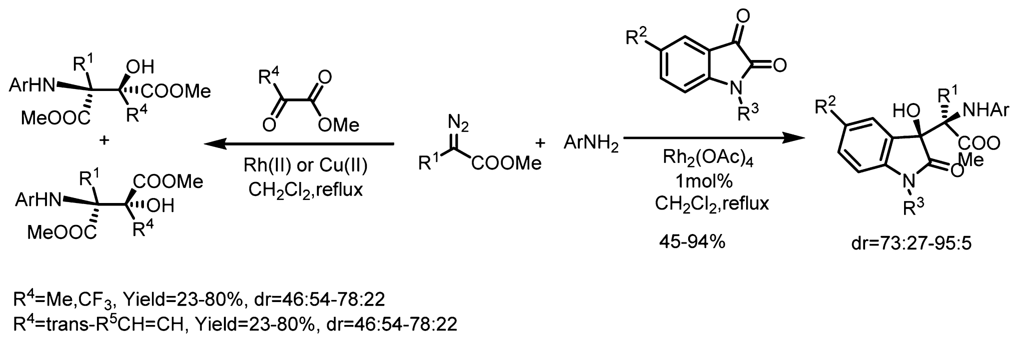
SCHEME 5. Trapping of Ammonium Ylides with Aldehydes



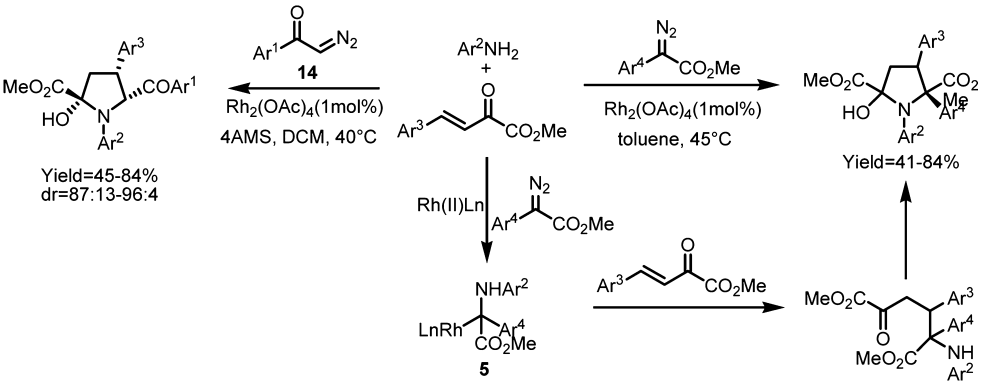
Other electrophilic carbonyl compounds were also employed as the ylide-trapping reagents. The reaction of isatins afforded α-amino-β-hydroxy esters bearing the 3-substituted 3-hydroxyindolin-2-one moiety and vicinal quaternary carbon centers in one step with high chemo- and diastereoselectivity (Scheme 6). Extension of the reaction to methyl pyruvates afforded succinic acid derivatives in moderate yield and diastereomeric ratio (dr).[12] β,γ-Unsaturated α-ketoesters were also used successfully in the Cu(OTf)$_2$-catalyzed 3CRs of acceptor-substituted or α-alkyl-substituted diazoacetates with anilines, affording densely functionalized β-hydroxy α-amino acid derivatives in a regiospecific 1,2-addition manner with high yield (71–94%) and dr.[13]

2.3. Tandem Michael Addition-Cyclization Reactions. In the rhodium(II)-catalyzed 3CRs of aryldiazoacetates, anilines, and β,γ-unsaturated α-ketoesters, pyrrolidine derivatives with three stereocenters were produced with low dr (Scheme 7).[14] The reaction was proposed to proceed through trapping of the ammonium ylide intermediates in a 1,4-addition manner with subsequent cyclization. Through

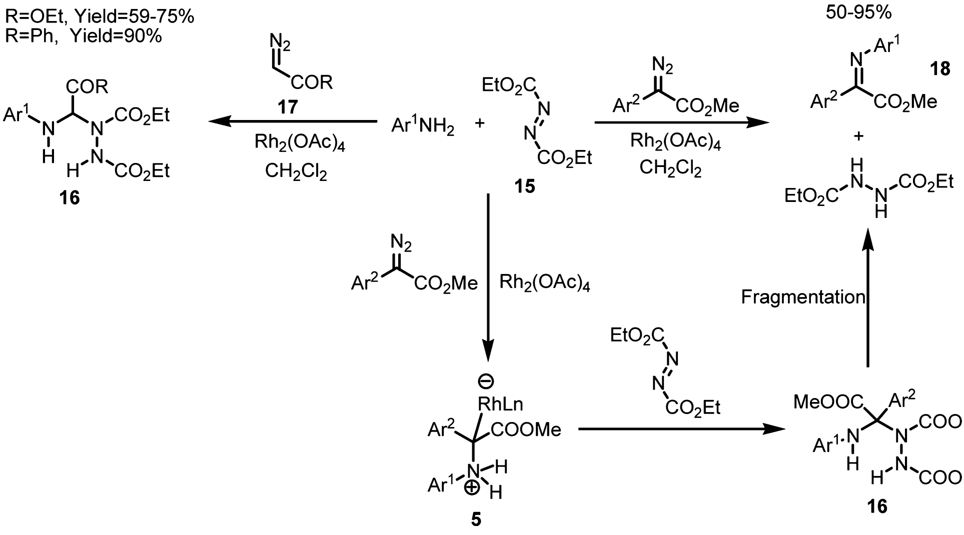
SCHEME 6. Trapping of Ammonium Ylides with Activated Ketones



SCHEME 7. Trapping of Ammonium Ylides with β,γ-Unsaturated α-Ketoesters



SCHEME 8. Trapping of Ammonium Ylides with Azodicarboxylates



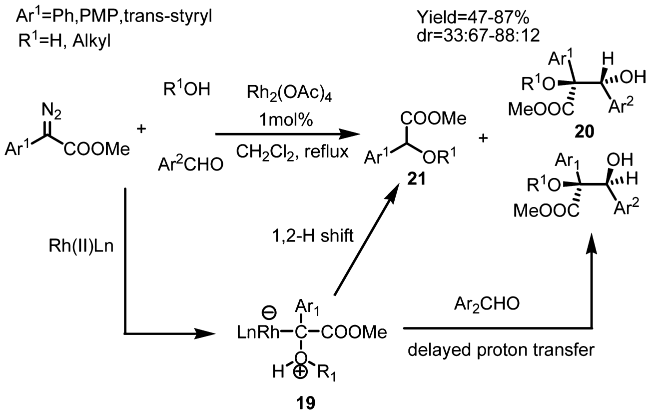
dehydration under acidic conditions, a facile synthesis of 2,3-dihydropyrrole derivatives was achieved in moderate to good yields in a one-pot fashion. The diastereoselectivity was found to be dependent on the electronic nature of the diazo compounds. When a diazoacetophenone **14** was used instead of an aryl diazoacetate, multisubstituted pyrrolidine derivatives were afforded in good yield and high dr.[15]

2.4. C–N Bond-Forming Reactions. Since azodicarboxylates have been reported as excellent electrophiles, diethyl azodicarboxylate (DEAD) **15** was employed to trap the protic ammonium ylides (Scheme 8).[16] Unsymmetrical aminals **16** were obtained in good yield when acceptor-substituted diazo compounds such as ethyl diazoacetate (EDA) **17** or diazoacetophenone **14** were used. In the case of aryldiazoacetates, only aryl α-imino esters **18** were produced as a result of fragmentation from corresponding aminals.[17]

3. Trapping of Oxonium Ylide

3.1. Aldol-Type Reactions. Inspired by the successful trapping of protic ammonium ylides, we designed novel transformations based on the trapping of the protic oxonium ylides **19**. Thus, alcohols were used instead of anilines in the rhodium(II)-catalyzed 3CRs of aryldiazoacetates with aromatic aldehydes to give α-alkoxyl-β-hydroxyl esters **20** in good yield (Scheme 9).[18] Control experiments indicated that the product formation comes neither from ring-opening of the epoxide with the alcohols nor from the aldol-type addition from the O–H insertion product **21**.

SCHEME 9. Trapping of Protic Oxonium Ylides with Aldehydes



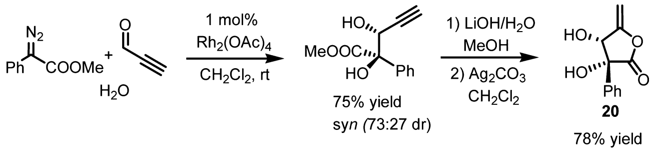
Similar to the ammonium ylide trapping process, electron-deficient aryl aldehydes and electron-rich aryldiazoacetates gave the desired three-component products in moderate to good yields. Water also served as a hydroxy donor to afford **20** in moderate yield. The reaction pathway is proposed as follows: (1) formation of metal-associated protic oxonium ylide **19** by the attack of the metal carbenes to the electronic lone pair of alcohol/water; (2) nucleophilic attack of the ylide to the aldehyde, followed by "delayed proton transfer." The successful trapping process also provides experimental evidence for the existence of the protic oxonium ylide.

The substrate scope of the 3CR was extended to 2-alkynals to afford β-alkynyl-α,β-dihydroxy acid derivatives in good yield and with high dr (Scheme 10).[19] The synthetic utility of the reaction was demonstrated through the conversion of the versatile alkynyl functionality to other synthetically useful compounds such as enelactones **20**.

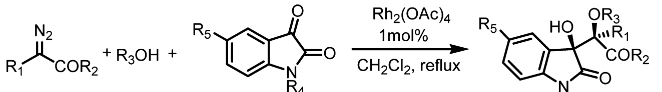
High levels of chemo- and stereoselectivity were obtained in the 3CR of diazoacetates, alcohols, and isatins, from which highly functionalized 3-substituted 3-hydroxyindolin-2-ones with two vicinal quaternary stereocenters were constructed efficiently (Scheme 11).[20] This reaction can be extended to acceptor-substituted α-diazocarbonyl compounds such as EDA and diazoacetophenones, giving moderate product yields.

Alcaide et al. successfully applied optically pure azetidine-2,3-diones as electrophiles to trap protic oxonium ylides derived from EDA and alcohols for the synthesis of 3-hydroxy-β-lactam derivatives (Scheme 12). Moderate to good stereoselectivity of 3-substituted-3-hydroxy-β-lactams bearing two new adjacent stereogenic centers was obtained.[21]

SCHEME 10. Trapping of Oxonium Ylides with 2-Alkynals

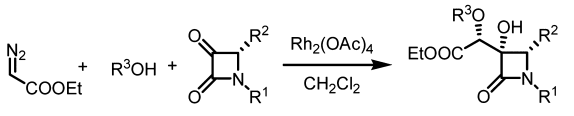


SCHEME 11. Trapping of Hydroxyl Oxonium Ylides with Isatins



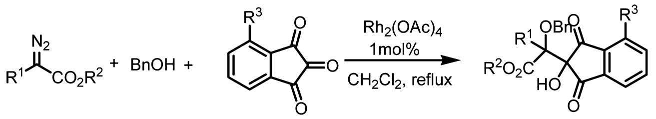
R_1=Ar, R_2=Me, R_3=Alkyl, Yield=72-95%, dr=92:8-99:1
R_3=H, Yield=96%, dr=63:37
R_1=H, R_2=OEt, Ph, R_3=Bn, Yield=89%, 88%, dr=54:46,60:40

SCHEME 12. Trapping of Oxonium Ylides with Azetidine-2,3-diones



Yeld=54-88%
syn:*anti*=65:35- 90:10

SCHEME 13. Trapping of Oxonium Ylides with Indane-1,2,3-triones



R^1=Ar, H, R^2=Me,Et

R^3=H,F,Cl,Br,Me

Yield=21-65%

An indane-1,2,3-trione was also used in the reaction to afford 2-substituted-2-hydroxyindane-1,3-diones in moderate yield (Scheme 13).[22]

Copper salts were also found to be suitable catalysts in the oxonium ylide trapping process. For example, $CuPF_6\cdot(CH_3CN)_4$-catalyzed 3CRs of methyl phenyldiazoacetate with an alcohol and an aldehyde or an α-ketoester gave the corresponding α-alkoxy-β-hydroxy esters in good yields (Scheme 14).[23] It is noteworthy that α-ketoesters, electron-rich aromatic aldehydes, and some aliphatic aldehydes, which are poor substrates in rhodium(II)-catalyzed 3CRs,[18] worked well in the copper-catalyzed reaction. We assumed that $CuPF_6\cdot(CH_3CN)_4$ acted both as a diazo-decomposing metal and as a Lewis acid to activate the carbonyl electrophiles.

3.2. Mannich-Type Reactions.

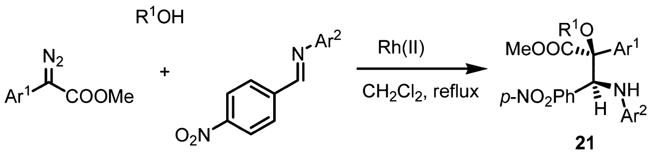
The 3CRs of diazoesters, alcohols, and aldimines gave α-alkoxy-β-amino esters **21** in moderate to good yields and with moderate diastereoselectivity (Scheme 15).[18]

When imines **22** derived from 2-aminophenol were used, high chemo- and diastereoselectivity were observed (Scheme 16).[24] The reactions worked well with both electron-rich and electron-deficient imines and alcohols. The imines were assumed to be more electrophilic as a result of self-activation by the phenol functionality through intramolecular hydrogen bonding.

The reaction was successfully extended to EDA or α-alkyl diazoacetates when water was used as a matched

SCHEME 15. Trapping of Oxonium Ylides with Imines

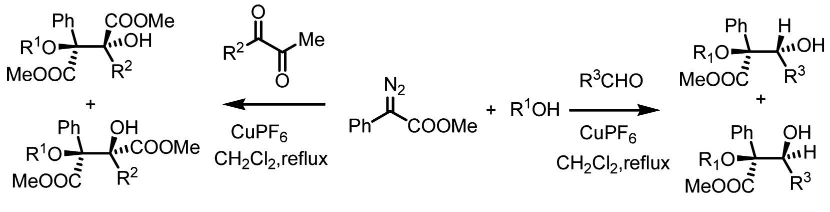
R^1=Bn, PMB



Ar^1,Ar^2=Ph, PMP

Yield=29-81%
dr=68:32-85:15

SCHEME 14. $CuPF_6\cdot(CH_3CN)_4$-Catalyzed Aldol-type Trapping of Oxonium Ylides



R^1=Bn,Me,Et,
R^2=Aryl,(*E*)-styryl,Me
Yield=40-80%, dr=50:50-22:78

R^1=Bn, R^3=Aryl, Alkyl
Yield=38-85%, dr=27:73 -83:17

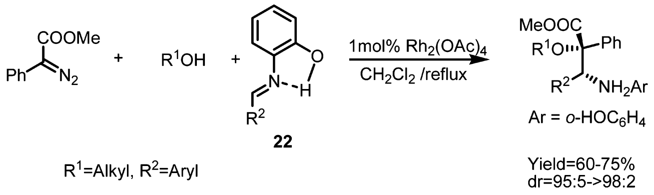
component, affording β-aryl isoserine derivatives in good yield and with high diastereoselectivity (Scheme 17).[25]

3.3. Michael-Type Reactions. Compared to $Rh_2(OAc)_4$, copper catalysts showed superior chemo- and diastereoselectivity in the 3CRs of aryl diazoacetates, alcohols, and chalcones (Scheme 18).[26] The resulting coupling adducts **23** can be converted easily into furan-containing oligoaryls **24**, tetrahydrofuran **25**, and 2,3-dihydrofuran derivatives **26**.

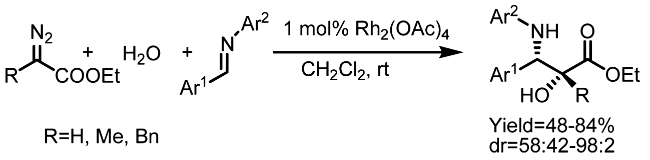
The $Rh_2(OAc)_4$-catalyzed 3CRs of diazo compounds, alcohols, and benzylidene Meldrum's acids **27**/4-oxo-enoates **28** gave the corresponding α-alkoxy esters in good yield and with high to excellent dr (Scheme 19).[27] The synthetic utility of this method was demonstrated by conversion of the addition products to γ-butyrolactones **29** through simple procedures.

3.4. C−N Bond-Formation Reactions. The rhodium(II)-catalyzed 3CR of a variety of aryldiazoacetates with H_2O and DEAD gave aryl α-ketoesters **30** in high yield (Scheme 20).[28] A study of the reaction pathways through ^1H NMR monitoring indicated that the formation of the ketoesters occurred via the fragmentation of the three-component intermediate **31**, while the oxidation of the O−H insertion product was also observed as a minor process.

SCHEME 16. Trapping of Oxonium Ylides with Imines Derived from 2-Aminophenol



SCHEME 17. 3CRs of EDA or α-Alkyl Diazoacetates, Water, and Imines



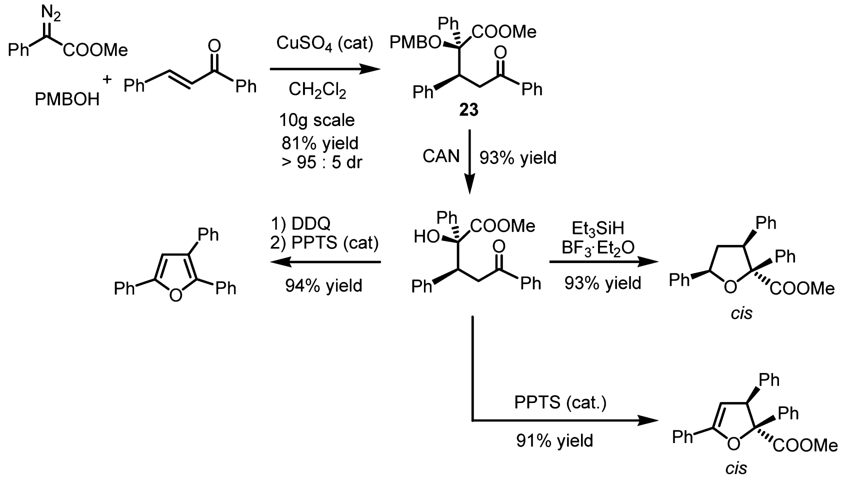
3.5. [2,3]-Sigmatropic Rearrangement of Alcoholic Oxonium Ylides. Davies and Li reported that the rhodium(II)-catalyzed reaction of racemic allyl alcohols and donor/acceptor-substituted diazoacetates results in a tandem protic oxonium ylide (**31**) formation/[2,3]-sigmatropic rearrangement process (Scheme 21).[29] This process competes favorably with the more conventional O−H insertion as long as donor/acceptor diazoacetates and highly substituted allyl alcohols are used. When the reactions are catalyzed by $Rh_2(S\text{-DOSP})_4$ (**32**), tertiary α-hydroxyesters **33** with two adjacent quaternary centers are produced with high enantioselectivity (79−98% *ee*), indicating that a metal-associated ylide intermediate **31** is probably involved in this case.

4. Asymmetric MCRs

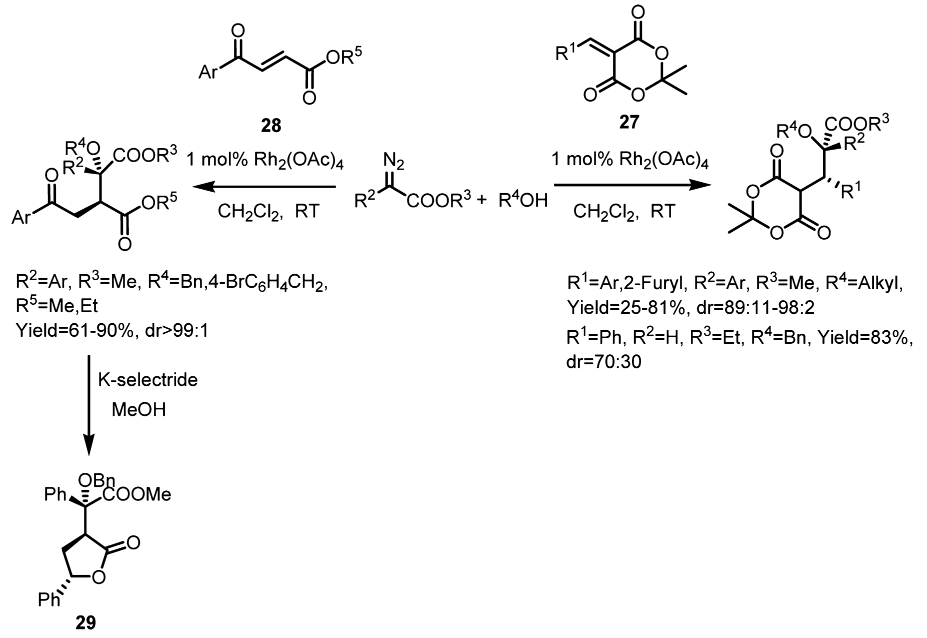
4.1. Chiral Reagent Induction. The asymmetric synthesis of amino acid derivatives with quaternary carbon centers is challenging. *N*-(*tert*-Butylsulfinyl) imines **34** have been used widely as chiral reagents for the preparation of optically active amines.[30] We found that high dr values were observed in the 3CRs of diazoacetates, alcohols, and electron-deficient *N*-(*tert*-butylsulfinyl) imines (Scheme 22).[24] The protecting groups can be removed readily to give optically active β-amino-α-hydroxy esters in moderate yield.

4.2. Enantioselective Catalysis via Chiral Metal-Associated Ylide. Che et al. have recently developed a highly enantioselective metal-catalyzed three-component coupling reaction

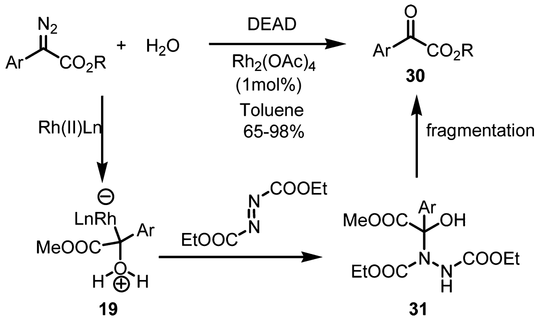
SCHEME 18. Trapping of Oxonium Ylides with Chalcones Catalyzed by Copper Catalysts



SCHEME 19. Michael-Type Trapping of Oxonium Ylides



SCHEME 20. 3CRs of Diazoacetates, Water, and DEAD for the Synthesis of α-Ketoesters

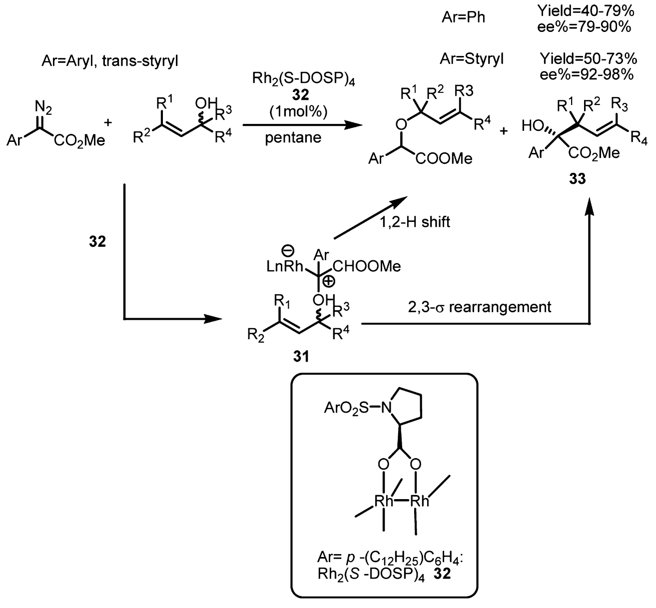


of diazophosphonates **35**, anilines, and electron-deficient aldehydes (Scheme 23).[31] Catalyzed by chiral rhodium(II)-carboxylates such as $Rh_2(S\text{-PTAD})_4$ (**36**) or $Rh_2(S\text{-PTTL})_4$ (**37**), a series of α-amino-β-hydroxy phosphonates **38** were obtained in good yields and with high enantioselectivities. The high level of enantiocontrol provides evidence for the intermediacy of a metal-associated ammonium ylide **39** in the nucleophilic addition step.

5. Synergistic Catalysis

Synergistic catalysis, in which the nucleophile and electrophile are activated by two different catalysts at the same time, has emerged as a powerful strategy in organic synthesis (Figure 2).[32] This new concept has led to the achievement of organic transformations that cannot be accessed by single specific catalytic systems.

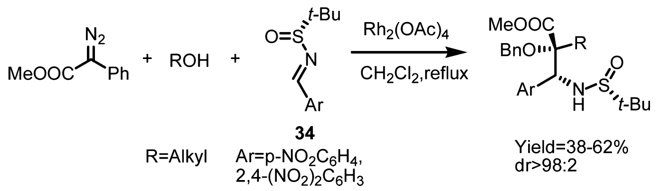
SCHEME 21. [2,3]-Sigmatropic Rearrangement of Protic Oxonium Ylides



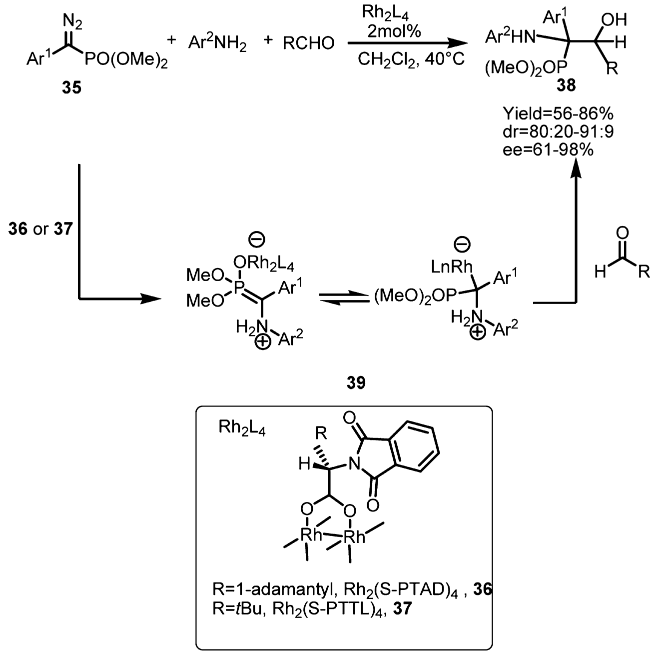
5.1. Combination of Transition Metal and Lewis Acid Catalysts.

The dual-metal catalysis strategy was first introduced in the 3CRs of diazoacetates, alcohols, and aldehydes.[18] Similarly to the copper-catalyzed 3CRs,[23] the combination of $Rh_2(OAc)_4$ and $Ti(OBu^t)$ allowed the inclusion of electron-rich aldehydes as reactive electrophiles. When a less sterically hindered titanium(IV) alkoxide **40** was used as a reagent, the α-alkoxy-β-hydroxy ester **41** was given in moderate to good yield (Scheme 24).[33] Satisfactory yields

SCHEME 22. Trapping of Oxonium Ylides with *N*-(*tert*-Butylsulfinyl) Imines



SCHEME 23. Chiral Dirhodium(II)-Catalyzed Trapping of Ammonium Ylides with Electron-Deficient Aldehydes



have been obtained from both aromatic and aliphatic aldehydes. The reaction is likely to proceed through nucleophilic addition of an oxonium ylide generated from the rhodium carbenoid and an alkoxyl group of the titanium(IV) alkoxide to the titanium-activated aldehydes **42**.

Muthusamy and Krishnamurthi reported that this titanium-associated oxonium ylide could also be trapped by p-benzoquinones (Scheme 25).[34] Depending on the nature of the diazo compounds, the reaction could involve a 1,2- or 1,4-addition process.

In the three-component aldol-type reactions of aryldiazoacetates, alcohols, and β,γ-unsaturated α-ketoesters, higher 3CR yields were achieved when combinations of $Rh_2(OAc)_4$ and Lewis acids were used instead of $Rh_2(OAc)_4$ alone. A switch in the diastereoselectivity was also observed when $InBr_3$ was used as a cocatalyst (Scheme 26).[35] We assumed that in the transition states **43** and **44**, the ylide proton complexed with the carbonyl oxygen of the electrophiles in the background reaction, while $InBr_3$, with strong Lewis acidity, coordinated with those of the diazoesters and the electrophiles, leading to the switch in diastereoselectivity.

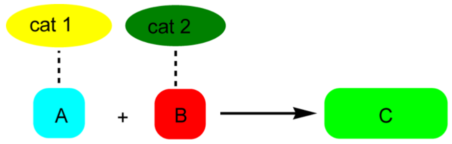
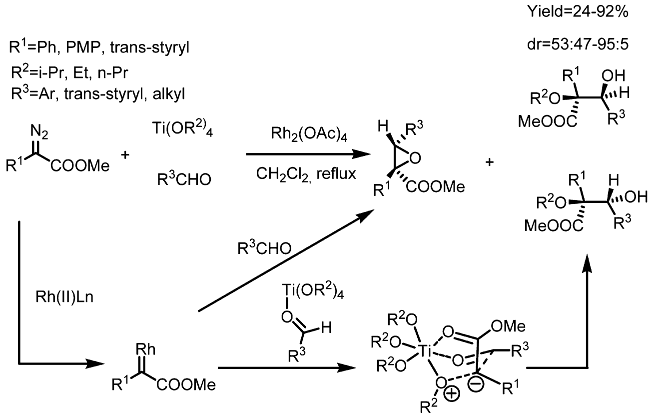


FIGURE 2. Synergistic catalysis.

SCHEME 24. Trapping of Oxonium Ylides Derived from Titanium Alkoxides with Aldehydes



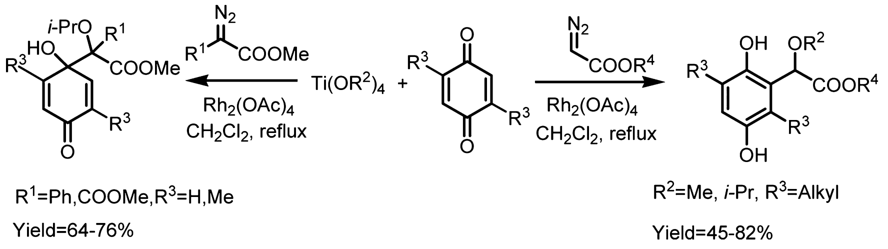
The successful activation of carbonyl compounds and Michael acceptors with Lewis acids encouraged us to apply chiral Lewis acids to achieve an asymmetric version of these reactions. The zirconium–BINOL–molecular-sieve system developed by Kobayashi and co-workers[36] provided efficient catalysis of the 3CRs of aryldiazoacetates, alcohols, and aromatic aldehydes with high diastereoselectivity and enantioselectivity (Scheme 27).[37]

The combination of $Rh_2(OAc)_4$ and AgOTf was found to catalyze a tandem cyclization/3CR of 2-alkynylarylaldimines **45** with diazo compounds and alcohols/water to afford 1,2-dihydroisoquinoline derivatives **46** in high yields (Scheme 28).[38] The reaction is proposed to proceed through addition of the oxonium ylide to an AgOTf-bound isoquinolinium ion intermediate **47**.

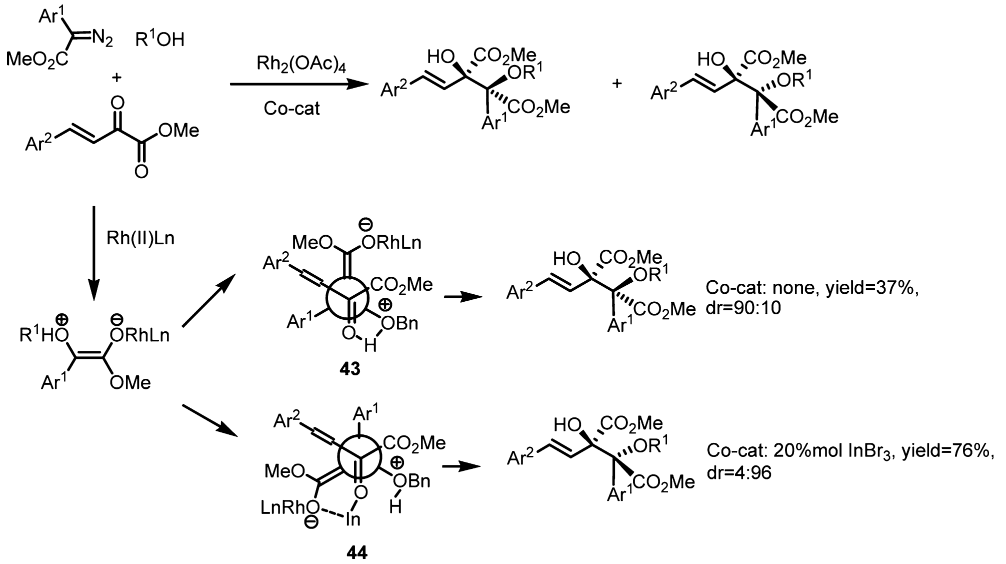
The dual-metal catalysis strategy was also applied to an enantioselective three-component Michael-type reaction (Scheme 29).[39] The catalyst combination of $Rh_2(OAc)_4$-(*S*)-*t*-Bu-BOX-$Zn(OTf)_2$-TsOH was applied successfully to the 3CRs of aryldiazoacetates, water, and acyl imidazoles **48** to produce γ-hydroxy acid derivatives **49** with excellent diastereo- and enantioselectivity.

5.2. Combination of Transition Metals and Brønsted Acids. In the Mannich-type 3CRs catalyzed by rhodium(II)

SCHEME 25. Trapping of Oxonium Ylides Derived from Titanium Alkoxides with *p*-Benzoquinones



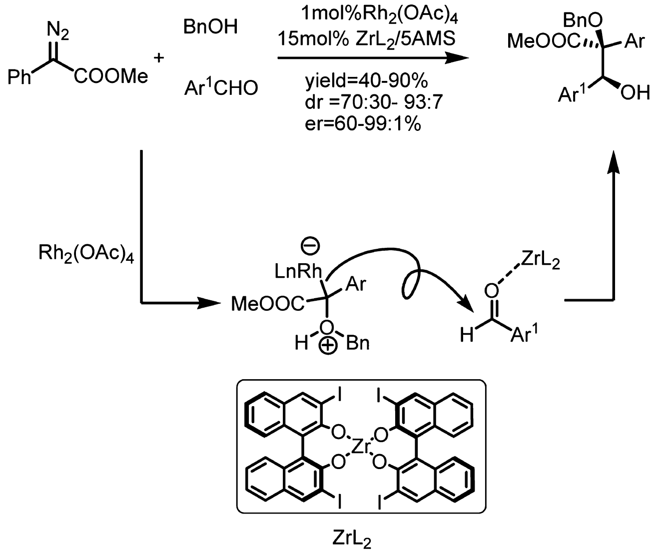
SCHEME 26. Diastereoselectivity-Switchable Aldol-Type Trapping of Oxonium Ylides Cocatalyzed by Rh(II) and Lewis Acids



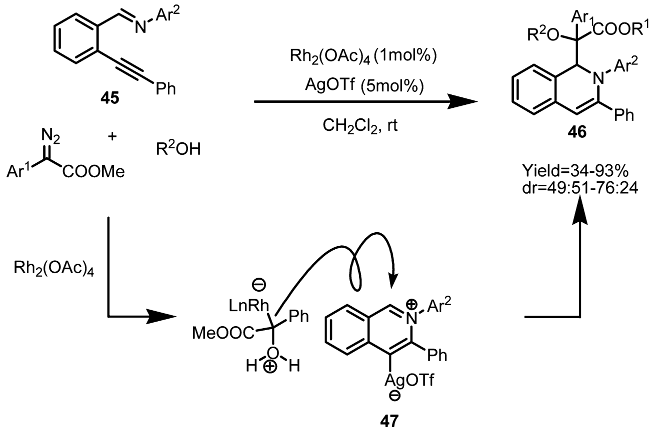
catalysts alone, the reaction scope was limited to highly electron-deficient imines and those derived from 2-aminophenol.[18,24] Inspired by the success of the synergistic catalysis of transition metals and Brønsted acids in other asymmetric reactions[40] and the compatibility of diazo compounds and phosphoric acids,[41] we explored the 3CRs of diazoacetates with a variety of imines and alcohols catalyzed by a combination of $Rh_2(OAc)_4$ and a chiral phosphoric acid **50**. *syn*-β-Amino-α-alkoxyesters were constructed with high yields, dr, and *ee* (Scheme 30).[42] The catalyst loadings could be decreased to 2 mol % without any deleterious effect on the reaction yield or selectivity. This protocol was also extended to water as a hydroxy donor, producing unprotected *syn*-β-amino-α-hydroxy esters **51** in good yields and with high selectivities.[43]

In this synergistic catalytic system, $Rh_2(OAc)_4$ catalyzed the formation of a metal-associated protic oxonium ylide **19** in a controllable fashion. In the transition state **52**, the bifunctional phosphoric acid **50** acted both as a Brønsted acid to activate the imine through iminium ion formation, and as a base to interact with the acidic proton of the ylide intermediate (Scheme 31). Without sufficient activation of the imine, the oxonium ylide may undergo an undesired 1,2-proton transfer, lowering the yield of the desired coupling product dramatically.

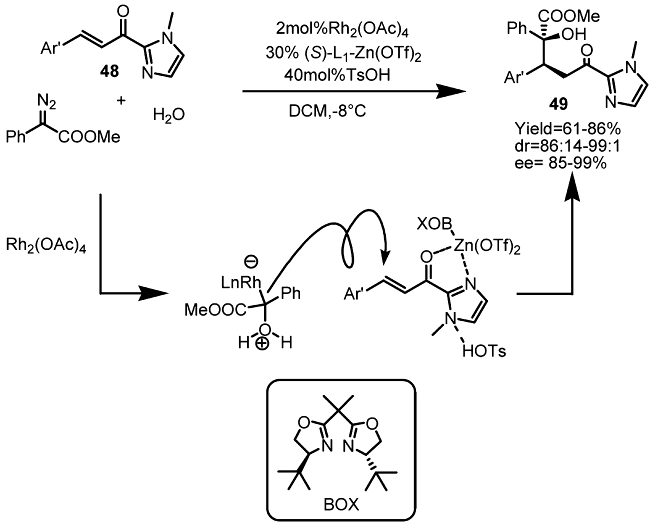
SCHEME 27. Enantioselective Aldol-Type Trapping of Oxonium Ylides



SCHEME 28. Tandem Cyclization/3CR of 2-Alkynylarylaldimines

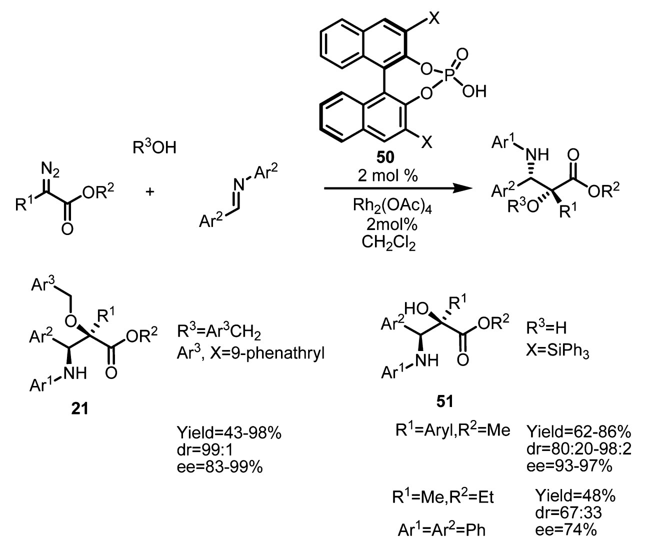


SCHEME 29. Enantioselective Michael-Type Trapping of Oxonium Ylides

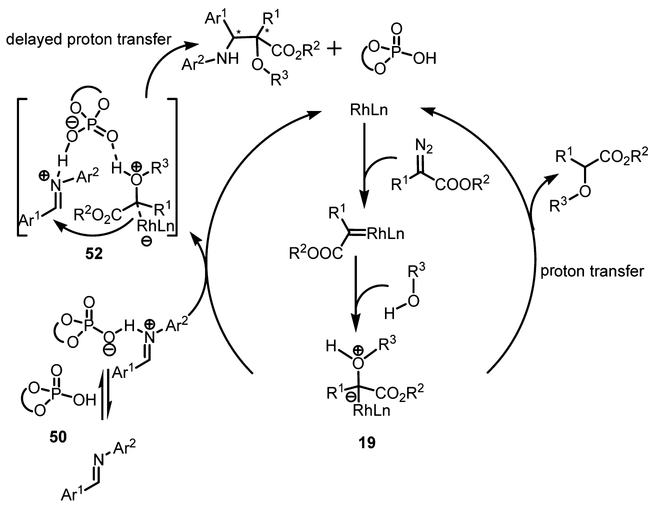


Since phosphoric acids may also promote iminium ion formation directly from aldehydes and anilines, an enantioselective 4CR was designed under the synergistic catalytic conditions. The 4CR proceeded smoothly under similar conditions, leading to chiral β-amino-α-alkoxyesters from simple starting materials in high yields and with good selectivities (Scheme 32).[44]

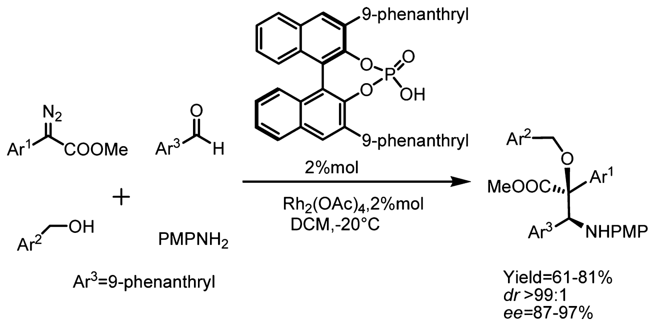
SCHEME 30. Enantioselective Mannich-Type Trapping of Oxonium Ylides



SCHEME 31. Mechanism of the 3CR of Diazoacetates, Alcohols, and Imines Cocatalyzed by Rhodium(II) and Brønsted Acids



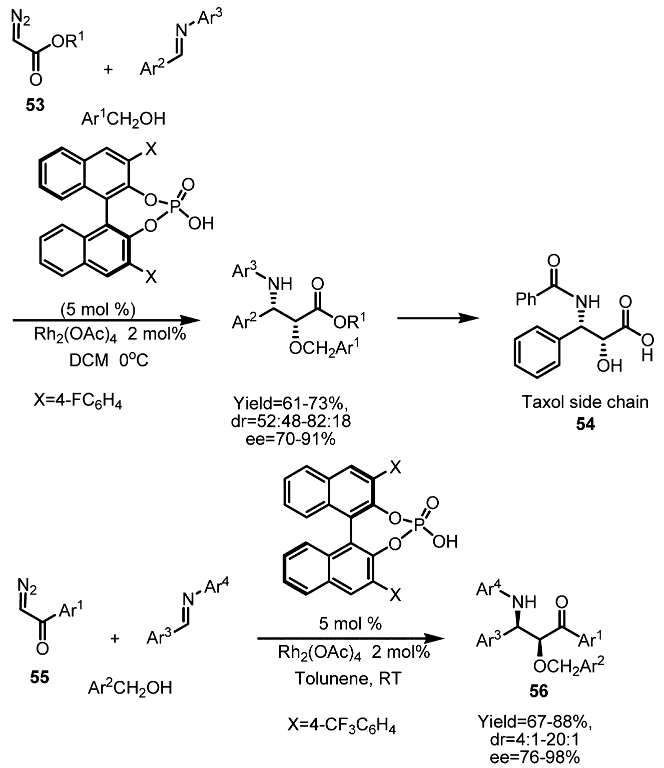
SCHEME 32. Enantioselective 4CR of Alcohols, Anilines, Aldehydes, and Diazoacetates



The substrate scope of diazo compounds was extended from aryldiazoacetates to acceptor-substituted diazocarbonyls. For example, diazoacetates **53** were employed in the 3CR to give optically active β-amino-α-alkoxy esters with moderate dr and good *ee* (Scheme 33).[45] This methodology was applied in the efficient synthesis of a taxol side chain **54** and (−)-epicytoxazone. Diazoacetophenones **55** were also suitable substrates in the 3CR, affording β-amino-α-hydroxyl ketones **56** in good yield with excellent diastereo- and enantioselectivity.[46]

This robust synergistic catalytic system was also applied successfully in the 3CR of diazoacetates, carbamates **57**, and imines, producing α,*β*-diamino acid derivatives **58** in high yield with excellent diastereo- and enantioselectivity via an analogous ammonium ylide trapping process (Scheme 34).[47] Initially, the basic diamine products appeared to poison the phosphoric acid catalyst through bidentate coordination. The addition of tartaric acid alleviated this effect by neutralizing the basic diamine product and regenerating the chiral phosphoric acid. The switch in diastereoselectivity was observed when the substitution of the BINOL-based phosphoric acid was altered; thus, each possible enantiomer could be obtained simply by changing the combination of catalysts.

SCHEME 33. Enantioselective 3CR of Alcohols, Imines, and Acceptor-Substituted Diazo Compounds

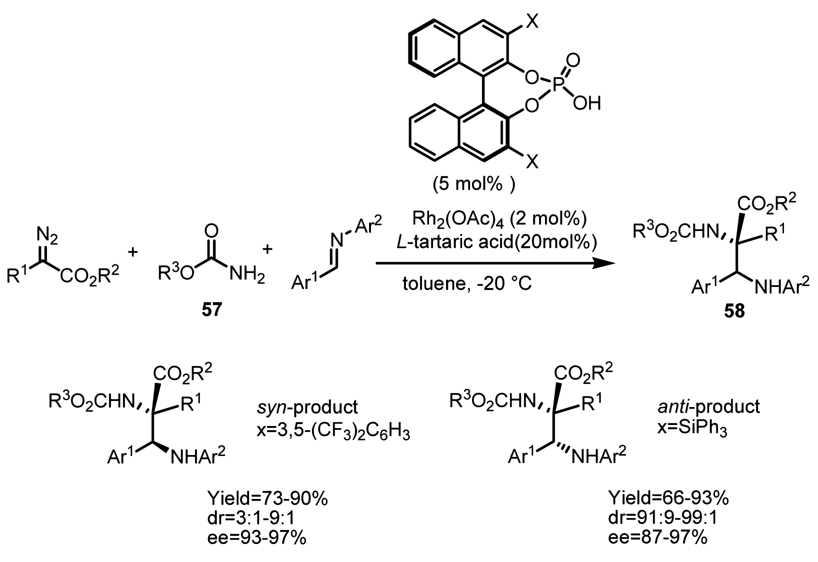


During the preparation of this Account, Gong et al. applied this strategy to enable an enantioselective three-component aldol-type reaction of 3-diazo oxindoles and anilines with glyoxylates to give highly functionalized and structurally diverse 3-amino oxindoles in high stereoselectivity (>20:1 dr, 99% *ee*).[48]

6. Conclusions and Outlook

In conclusion, we have developed novel MCRs of diazocarbonyls, anilines/alcohols, and electrophiles, which provide experimental evidence for the existence of protic onium ylides, as well as efficient methods for the construction of polyfunctional molecules. We have also applied the strategy of synergistic catalysis in the MCRs to achieve good control of the chemo-, diastereo-, and enantioselectivity. The efficiency of the MCRs lies not only in the formation of multiple bonds in one operation, but also in the extremely high reaction rate. However, the scope of the electrophiles and diazo compounds needs to be extended further for wide applicability. Future efforts will be devoted to the development of more efficient catalytic systems to extend the substrate scope, and to the combination of MCRs and cascade processes for the construction of diversified complex frameworks from simple starting materials.

SCHEME 34. Enantioselective Mannich-Type Trapping of Carbamate Ammonium Ylides



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BIOGRAPHICAL INFORMATION

Xin Guo received his B.S. in chemistry from Nanjing University in 2003 and his Ph. D. from Chengdu Institute of Organic Chemistry (CIOC), Chinese Academy of Sciences in 2008 with Prof. Wenhao Hu. He continued his research in the same group at Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development (SERCMTNDD), East China Normal University (ECNU), Shanghai, China as a research associate. His research focuses on development of novel multicomponent reactions and asymmetric catalysis.

Wenhao Hu received a B.S. in chemistry from Sichuan University (1987), M.S. from CIOC (1990), and Ph.D. from Hong Kong Polytechnic University with Professor Albert S. C. Chan (1998). He became a postdoctoral fellow at the University of Arizona with Professor Michael P. Doyle. In 2002−2006, he worked as a medicinal chemist at Genesoft in South San Francisco and a process chemist at Bristol-Myers Squibb in New Jersey. In 2006 he joined ECNU, where he is a professor of Chemistry, and head of SERCMTNDD. He received National Natural Science Funds for Distinguished Young Scholar (2011). His research interests include synthetic methodology, MCRs, and medicinal and process chemistry.

FOOTNOTES

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The authors declare no competing financial interest.

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