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EMERGING AREA

A one-pot catalysis: the strategic classification with some recent examples

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In this "Emerging Area", the strategic classification of one-pot catalysis, *i.e.* cooperative, relay and sequential catalysis, is described. In order to illustrate this classification, we take the readers through a series of recent examples which utilize either metal-metal, metal-organo and organo-organo catalysts. The compilation clearly demonstrates the explosive growth and power of this field, which has become, in the last few years, an important technique particularly in the case of enantioselective catalysis.

1. Introduction

Transition metal-mediated reactions for the formation of carbon-carbon (C–C) and carbon-heteroatom (C–X) bonds have revolutionized the field of organic synthesis. In the study of the evolution of metal catalysis, one can quickly judge that many C–C and C–X bond-forming processes have been developed and found extensive relevance in the synthesis of natural products and privileged structures. Traditionally, it is assumed that catalysis has been the realm of metals.

In recent years, organocatalysis, *i.e.* the use of small organic molecules to catalyze organic transformations, has emerged as a new area. These new organocatalysts offer new reactivities and most importantly the properties of them can be tuned according to the need and design of molecular structure. Now it is widely accepted that organocatalysis is one of the main branches of

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Nitin T. Patil was born in Jalgaon (Maharashtra), India, in 1975. He completed his doctoral study at University of Pune in 2002 under the supervision of Prof. D. D. Dhavale. After working as a post-doc at Goettingen with Professor Christoph Schneider, he moved to Tohoku University, Japan, as a JSPS fellow. Later, in April 2005, he was appointed as Assistant Professor in Prof. Yoshinori Yamamoto's laboratory. In June 2006, he joined Prof. K. C. Nicolaou's laboratory (PI: Prof. David Chen) at Singapore, and later at The Scripps Research Institute, USA. He began his independent career in September 2008 at IICT, Hyderabad, India. He has been the recipient of INSA Young Scientist Medal-2010 and Alkyl Amines-ICT Foundation Day Young Scientist Award-2010. He has also been elected as "Young Associate" of the Indian Academy of Sciences, Bangalore in 2010. His broad research interests include development of metal-, organo- and metaloorgano-catalyzed enantioselective methods and total synthesis of natural products.

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Valmik S. Shinde was born in 1982 in Ahmednagar (Maharashtra), India. He completed his M.Sc. (2006) in organic chemistry from Department of Chemistry, University of Pune. Later, he joined Lupin Pharmaceuticals Ltd., Pune, and worked for about three years in R & D division as a research associate. In 2009, he joined Dr Nitin T. Patil's research group at IICT Hyderabad where he is currently pursuing his Ph.D. studies.

synthetic organic chemistry for the creation of new C–C and C–X bonds.

Increased focus has recently been placed on the development of multiple-catalyst systems for organic transformations that allow rapid construction of highly functionalized molecules from simple and readily available starting materials. The reaction catalyzed by two different catalysts (metal-metal, metal-organocatalyst and organo-organocatalyst) at the same time can provide access to reactivity and selectivity of the reaction otherwise not possible by a single catalyst alone. Clearly, such a reaction can provide a powerful tool to synthesise highly complex molecules preserving energy and resources. The main problem that everyone has to face in these reactions is to find the proper catalyst which should not only be compatible with other catalysts but also tolerates all reagents and intermediates generated during the course of the reaction. Unlike biological processes, where nature takes advantage of enzyme architecture to facilitate a multiple reaction manifold, it is very difficult to exploit on such process in a flask. The important feature of this type of multiple catalysis lies in a fact that there are number of ways to make the reaction enantioselective either by using a single chiral catalyst or by using both chiral catalysts synergistically. However, coordination between the two catalysts is always not possible and therefore this event is occasionally avoided by addition of catalysts during the course of reaction.

To analyze the state of art of this important field, we decided to consider these reactions as a point of review as well as classification using known literature data. Many of these reactions have been compiled in the form of highlights,[1] concepts[2] and reviews.[3] However, most of them are too general. In this manuscript, we aim to focus on the most significant reactions catalyzed by metal-metal, metal-organocatalyst and organo-organocatalyst binary catalytic systems, based on a classification proposed by us. While it is beyond the scope of this review to comprehensively describe the literature, we have endeavoured to provide a brief overview on the most recent results.

2. One-pot catalysis: a classification

The development of one-pot processes that allows many reactions to occur in a single flask has a significant impact in the synthesis of fine chemicals and drugs. One-pot catalysis avoids the time, labour and yield losses associated with the isolation and purification of intermediates in multistep sequences. The classification of one-pot catalysis has been reported by Fogg and Santos in 2004 (Fig. 1).[4] However, the classification is very broad and is not well suited to describe the examples of recent literature in a precise manner. Hence, we propose a new classification (Fig. 2) that encompasses the recent examples and we believe that this classification may find extensive application for precisely understanding the type of catalysis (Fig. 3–5). Since the classification proposed in Fig. 2 is self explanatory, the authors have preferred to discuss the contents directly without definition.

Balakrishna Gajula

Balakrishna Gajula was born in Karimnagar (Andhra Pradesh), India, in 1985. He completed his graduation at Kakatiya University in 2006. Later, he joined as project assistant in IICT, Hyderabad, and worked for two years. From 2009, he has worked as a technical assistant and is presently associated with Dr Nitin T. Patil's research group.

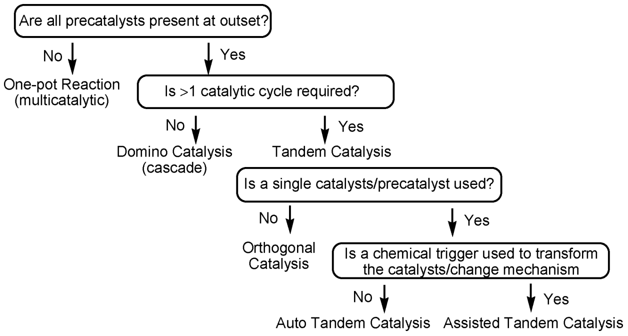
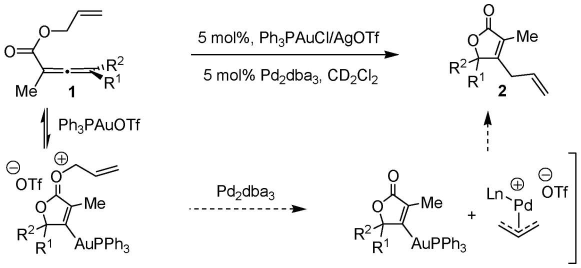


Fig. 1 Classification of catalysis by Fogg and Santos reported in 2004.

3. Cooperative catalysis

3.1. Metal and metal catalysts

Blum and coworkers investigated the cooperative catalytic process consisting of carbophilic Lewis acidic Au-catalyst and Lewis basic Pd-catalyst that afforded substituted butenolides **2** from allenoate **1** (Scheme 1).[5] The proposed mechanism involves Au(I)-catalyzed intramolecular oxy-auration in allenoate that produce allyl oxonium ion intermediate which undergoes deallylation by Pd(0) towards the allylic substrate bearing cationic leaving groups. The subsequent transmetallation between neutral vinyl gold complex and π-allyl Pd complex followed by C–C bond-forming reductive elimination affords substituted butenolides **2**. In yet another example, Cheng *et al.* reported a cooperative Pd(0) and CuI catalyzed highly regio- and chemoselective three-component coupling reaction of benzyne, generated from **3**, terminal alkynes and 2-vinyloxirane to afford products **4** in moderate to good yields (Scheme 2).[6]



Scheme 1

Hu and coworkers reported an enantioselective three component coupling reaction of conjugated enone **5**, water and

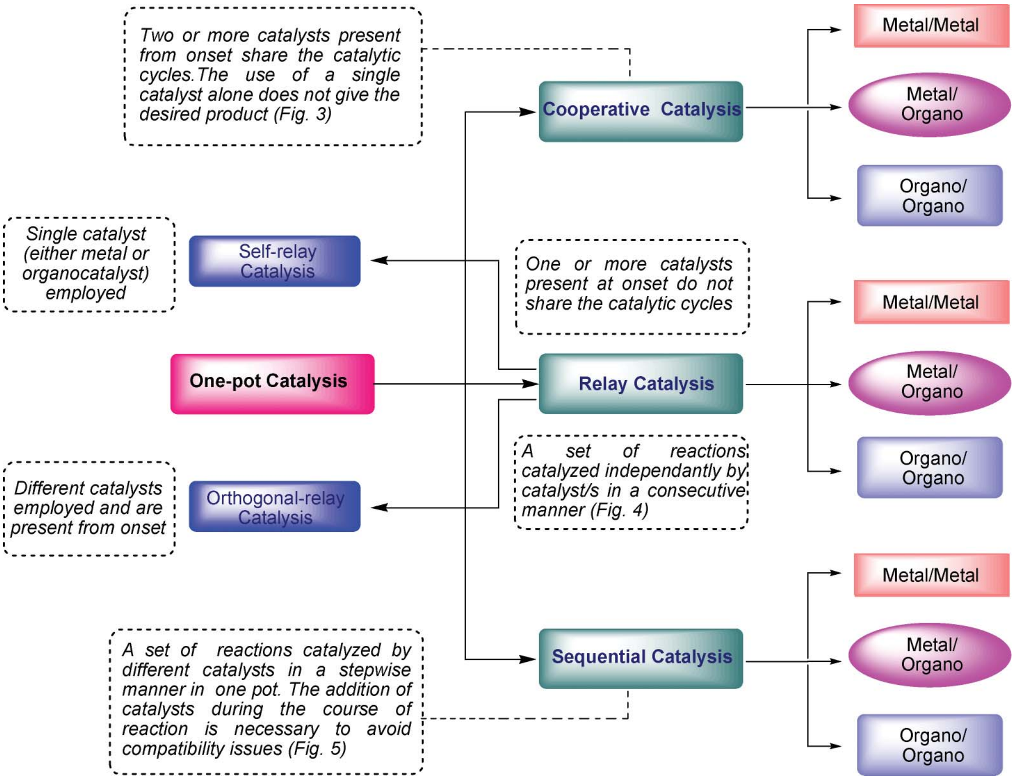


Fig. 2 Various modes of catalysis.

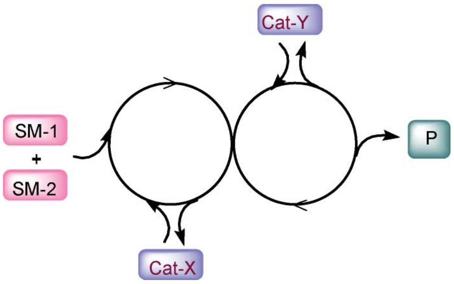


Fig. 3 Cooperative catalysis.

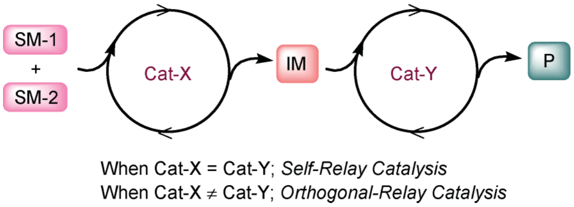


Fig. 4 Relay catalysis.

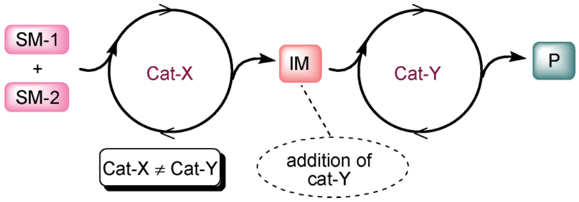
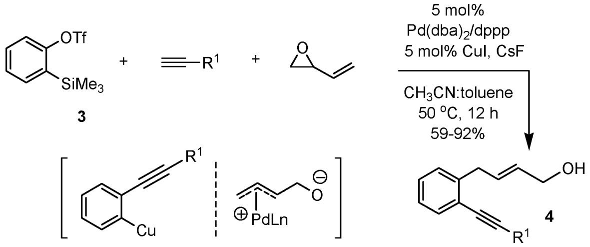


Fig. 5 Sequential catalysis.



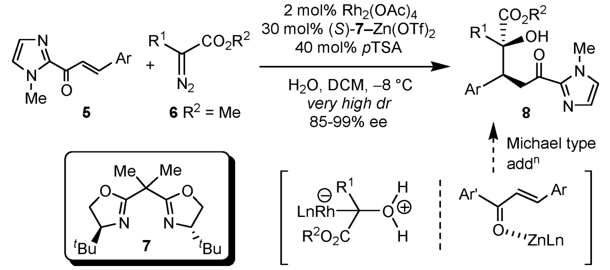
Scheme 2

α-diazoester **6** using the cooperative catalytic system consisting 2 mol% $Rh_2(OAc)_4$ and 30 mol% (*S*)-^{t}Bu-box-Zn$(OTf)_2$ to give γ-hydroxyketones **8** in good yields and with excellent enantioselectivities 85–99% (Scheme 3).[7] Later the same group extended this concept of cooperative catalysis to the reaction of α-diazoester **6** with 2-alkynylarylaldimines **9** and alcohol to afford 1,2-dihydroisoquinolines **10** using 1 mol% $Rh_2(OAc)_4$ and 5 mol% AgOTf (Scheme 4).[8]

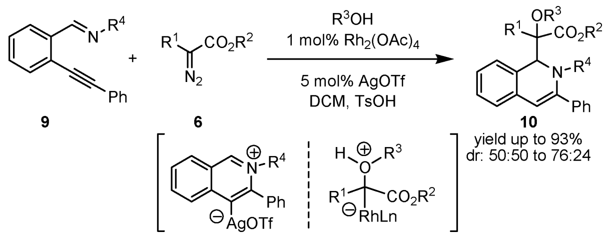
Very recently, Trost and Luan established a novel catalytic cooperative system by combination of vanadium-catalyzed 1,3-transposition of propargyl alcohols **11** (Meyer–Shuster rearrangement) and a palladium-catalyzed alkylation of allylic carbonates **12** (Scheme 5).[9] The authors had shown the formation of products **15** from two highly reactive catalytic intermediates **13** and **14** by overcoming the other possible competing side reactions. The success of such a reaction shows the power of cooperative catalysis.

3.2. Metal and organo catalysts

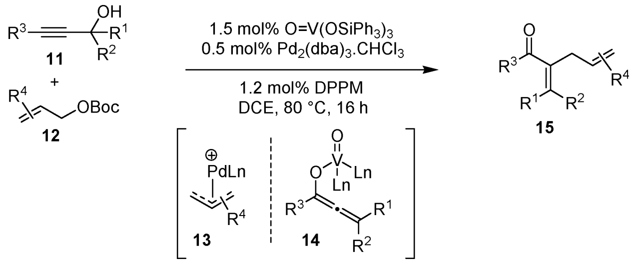
Saicic and coworkers reported an intramolecular Tsuji–Trost-type cyclization to construct five and six-membered ring compounds



Scheme 3

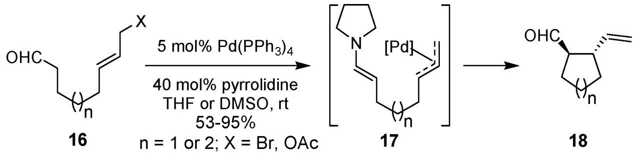


Scheme 4



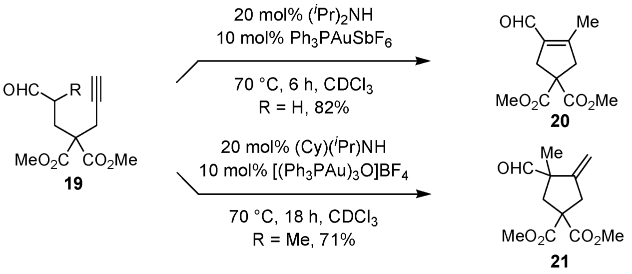
Scheme 5

using $Pd(PPh_3)_4$ and pyrrolidine cooperative catalytic system (Scheme 6).[10] From the proposed mechanism, the cooperativity between two catalysts can be understood by the formation of an active intermediate **17** that led to the formation of 2-vinyl-cycloalkanecarbaldehyde **18**. In the same publication, the authors had demonstrated the catalytic enantioselective version of this reaction using chiral (*R*)-(BINAP)Pd complex and pyrrolidine. The principle of mutual cooperativity between Au(I) complexes and secondary amine was used for direct intramolecular C–C bond formation using alkynals **19** by Kirsch *et al.* (*cf.* **20**/**21**) (Scheme 7).[11] A similar type of carbocyclization using $InCl_3$/(Cy)(^{i}Pr)NH catalytic system has also been reported recently (*cf.* **22**→**24**) that proceeded through intermediate **23** (Scheme 8).[12]

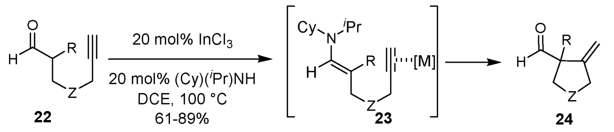


Scheme 6

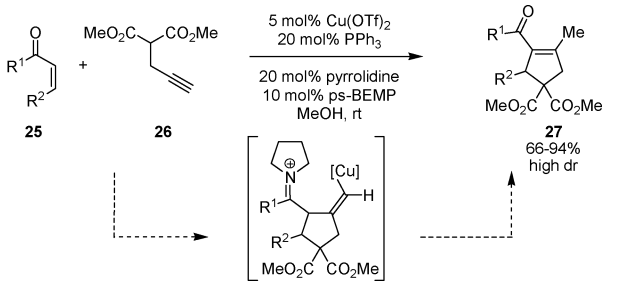
The use of a combination of $Cu(OTf)_2$-PPh_3 and pyrrolidine as catalysts for the synthesis of substituted cyclopentenes **27** from α,β-unsaturated ketones **25** and dimethyl propargylmalonate **26** was reported by Dixon and coworkers (Scheme 9).[13] The group of Córdova developed a highly enantioselective domino oxa-Michael/carbocyclization strategy that utilizes propargyl alcohols and enals under the catalysis of $PdCl_2$ and proline derived catalysts **28** (Scheme 10).[14]



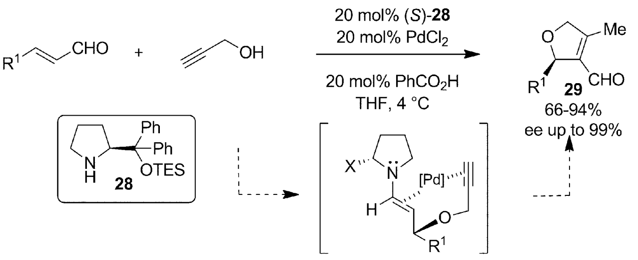
Scheme 7



Scheme 8



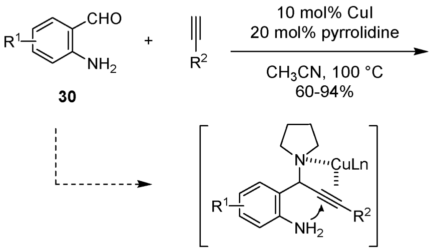
Scheme 9



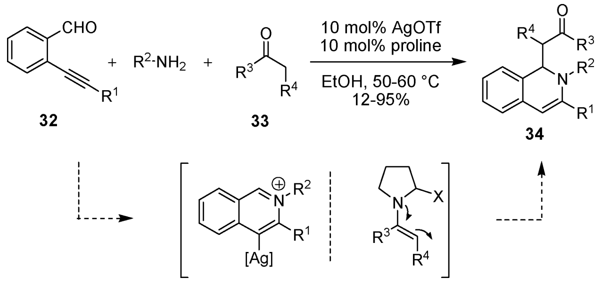
Scheme 10

Recently, our group developed a cooperative catalytic system consisting of CuI and pyrrolidine for regioselective synthesis of 2-substituted quinolines **31** from 2-aminobenzaldehydes **30** and terminal alkynes (Scheme 11).[15] Similarly, the combination of AgOTf and proline is known to catalyze the three component reaction between, 2-alkynylbenzaldehydes **32**, ketones **33** and amines to afford 1,2-dihydroisoquinolines **34** (Scheme 12).[16]

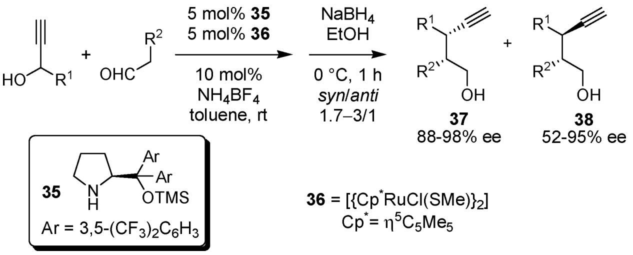
Ikeda, Miyake and Nishibayashi demonstrated that ruthenium complex **36** and secondary amine **35** cooperatively catalyzes the enantioselective α-alkylation of aldehydes (Scheme 13).[17] The ruthenium complex and secondary amine activate the propargylic alcohol and aldehyde respectively, resulting in a mixture of two diastereomers, each with high enantioselectivity and good yields. The same group extended the protocol to propargylic esters utilizing chiral secondary amine and Cu-complex (*cf.* **39**→**41**/**42**) (Scheme 14).[18]



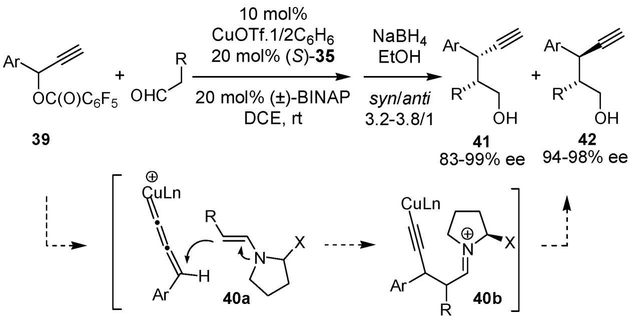
Scheme 11



Scheme 12

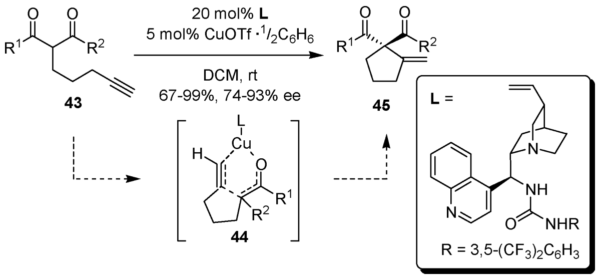


Scheme 13

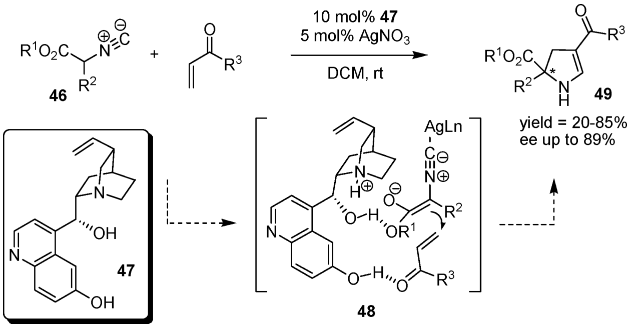


Scheme 14

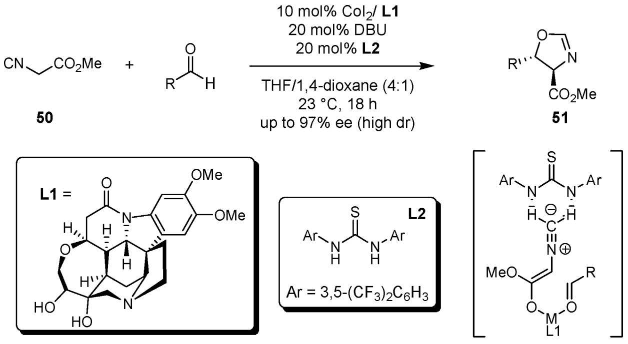
Dixon and coworkers developed an enantioselective Conia–Ene reaction of **43** utilizing Cu(OTf)·1/2C$_6$H$_6$ and cinchona-based catalyst **L** (Scheme 15).[19] The reaction proceeded through intermediacy of a ligated copper enolate **44** which undergoes *syn* carbocupration to furnish cyclized products **45** in good yields 67–99% with ee ranging from 74–93%. The formal [3 + 2] cycloaddition reaction catalyzed by AgNO$_3$ and cupreiene **47** has recently appeared in the literature (Scheme 16).[20] The protocol provides enantiopure 2,3-dihydropyrroles **49** from isocyanoacetates **46** and α,β-unsaturated ketones. A bifuctional cupreiene catalyst is responsible for the dual activation through hydrogen bonding interactions as shown in **48**. Kim and Oh described a cooperative catalyst system consisting of chiral cobalt catalyst and an achiral organocatalyst for the highly diastereo- and enantioselective catalytic aldol reaction of methyl α-isocyanoacetates **50** that provided product **51** (Scheme 17).[21] As mentioned by the authors, the success of this stereocontrolled reaction probably lies in strong anion-binding interaction between isocyanides and thioureas.



Scheme 15



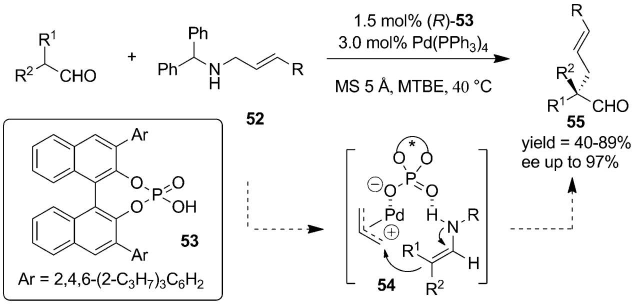
Scheme 16



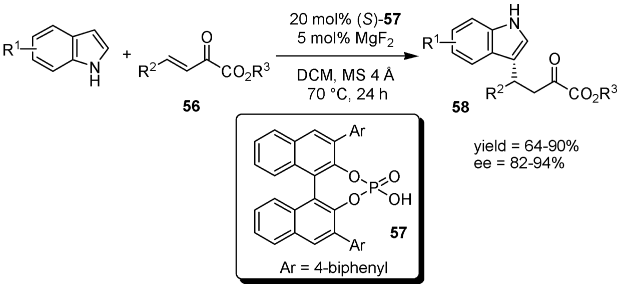
Scheme 17

Mukherjee and List presented an example of cooperative catalysis wherein Pd(0) and chiral phosphoric acid **53** catalyze the highly enantioselective α-allylation of α-branched aldehydes (Scheme 18).[22] A proposed mechanism involved a phosphoric acid catalyzed condensation of amines **52** with aldehydes to give an enamonium salt which reacts with Pd(0) species producing the cationic π-allyl-Pd-complex **54** that leads to the formation of α-allylated aldehydes **55** in good yields and enantioselectivities. As depicted in Scheme 19, Luo *et al.* developed asymmetric Friedel–Crafts alkylation of phenols and indoles with β,γ-unsaturated α-ketoesters **56** by employing MgF$_2$/chiral phosphoric acid **57** metallo-organocatalytic system to obtain **58** with high level of enantioselectivities (Scheme 19).[23]

Hu, Gong and coworkers described a cooperative catalyst system consisting of Rh$_2$(OAc)$_4$ and (*R*)-**60** that provides enantiopure β-amino-α-hydroxyl esters **62** by three component coupling of

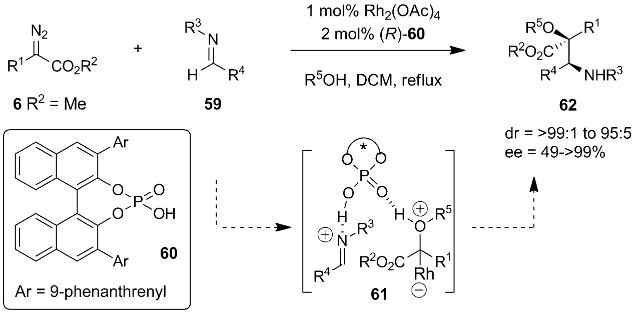


Scheme 18



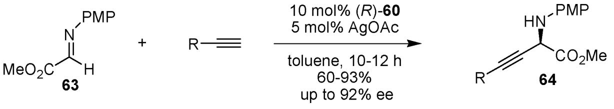
Scheme 19

α-diazoesters **6**, alcohols and imines **59** (Scheme 20).[24] The reaction proceeds through intermediate **61** generated from $Rh_2(OAc)_4$-initiated oxonium ylide intermediate and Brønsted acid activation of imine. The method has been utilized for synthesis of Taxol side chain and (–)-*epi*-cytoxazone.[25]

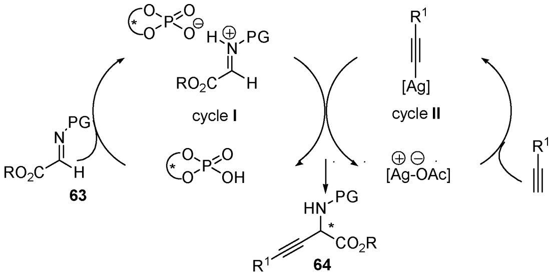


Scheme 20

Rueping, Antonchick and Brinkmann investigated the combination of silver(I) and Brønsted acid catalyst (*R*)-**60** for the alkynylation of α-imino ester **63** that led to α-alkynylated amino ester **64** in yields ranging from 73 to 93% and ee's up to 96% (Scheme 21).[26] The mechanism of this reaction is shown in Scheme 22. A similar reaction was also reported by using $CuPF_6$ and α-amino acids combined catalyst system.[27]

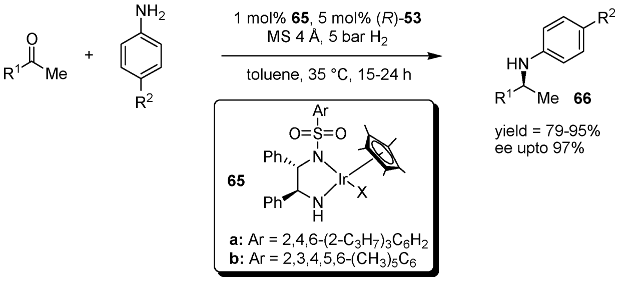


Scheme 21

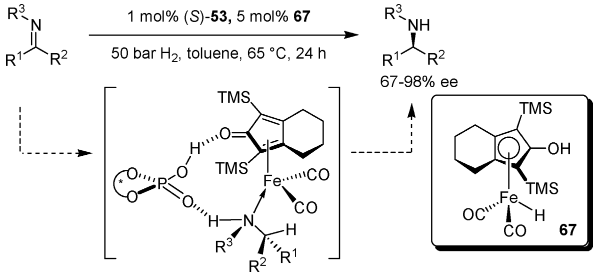


Scheme 22

Xiao and coworkers described an Ir-complex **65**/(*R*)-**53** cooperative catalytic system for direct asymmetric reductive amination of ketones with anilines that provides chiral amines **66** in good yields (up to 88–94%) with high enantioselectivities (81–97%) (Scheme 23).[28] The Ir-complex reduces the *in situ* generated iminium cation *via* ionic hydrogenation and phosphoric acid aiding enantioselective hydrogen transfer *via* ion pairing of its conjugate base with iminium ion. Likewise, Beller and coworkers also performed an enantioselective reduction of imines by using Fe-complex **67** with (*S*)-TRIP phosphoric acid **53** (Scheme 24).[29]

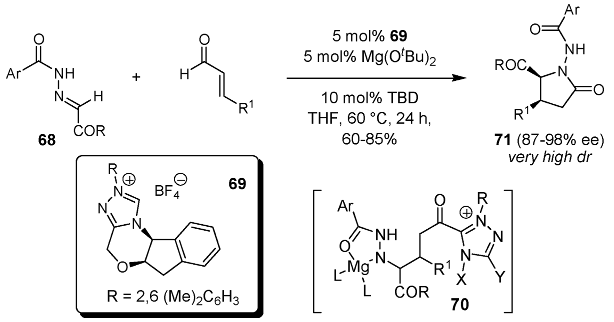


Scheme 23

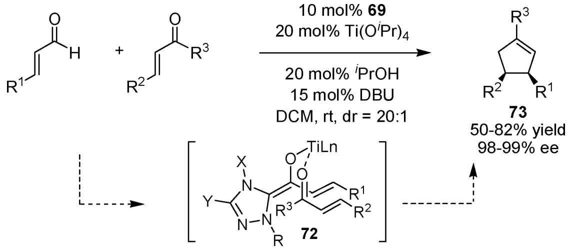


Scheme 24

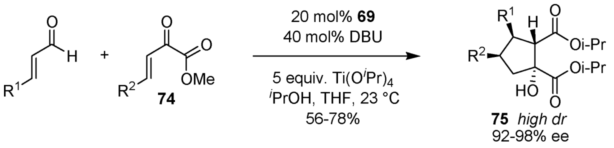
Although a large number of transformations exist for NHC catalysis, until recently there was no knowledge about the compatibility of metal (Lewis acid) and NHC (Lewis base) as catalysts and their workability in presence of each other. Scheidt and coworkers reported the first enantioselective cooperative catalytic system consisting of $Mg(O^tBu)_2$ and chiral NHC **69** for the stereoselective and enantioselective synthesis of γ-lactams **71** from N-acyl hydrazones **68** and α,β-unsaturated aldehydes (Scheme 25).[30] The key behind the success is the reversible magnesium-NHC interaction. The report from the same group disclosed an enantioselective cooperative catalytic system that utilizes $Ti(O^iPr)_4$ catalysis and NHC catalysis to provide access to substituted cyclopentenes **73** from α,β-unsaturated aldehydes and α,β-unsaturated ketones (Scheme 26).[31] They further extended this protocol for homoenolate addition to β,γ-unsaturated α-ketoesters **74** that afforded substituted cyclopentanols **75** (Scheme 27).[32]



Scheme 25



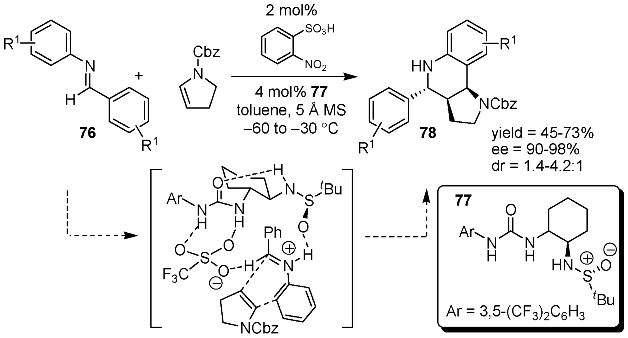
Scheme 26



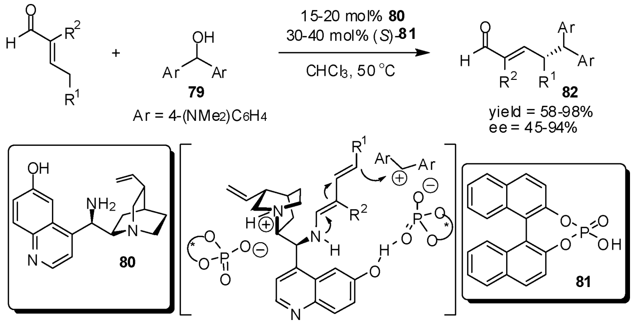
Scheme 27

3.3. Organo and organo catalysts

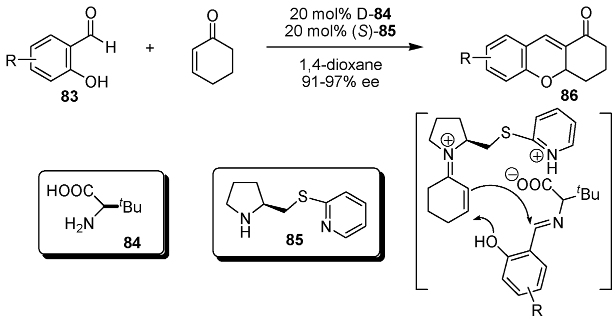
In 2010, Jacobsen and coworkers reported an interesting example of cooperative organo-catalysis of strong Brønsted acid (*o*-nitrobenzene sulfonic acid) and chiral urea **77** for enantioselective Povarov reaction between electron-rich alkenes and imines **76** that furnished adducts **78** (Scheme 28).[33] Bergonzini, Vera and Melchiorre established the possibility of cooperative organocatalytic system involving quinidine derivative **80** and (*S*)-**81** as catalysts that provide functionalized compounds **82** from enals and **79** (Scheme 29).[34] Xia *et al.* presented an efficient approach for the enantioselective oxa-Michael–Mannich reaction of salicylaldehydes **83** with cyclohexenones using organocatalytic ion pair assemblies consisting of pyrrolidine **85** and amino acid *t*-Leu **84** that works cooperatively to obtain tetrahydroxanthenones **86** (Scheme 30).[35]



Scheme 28



Scheme 29

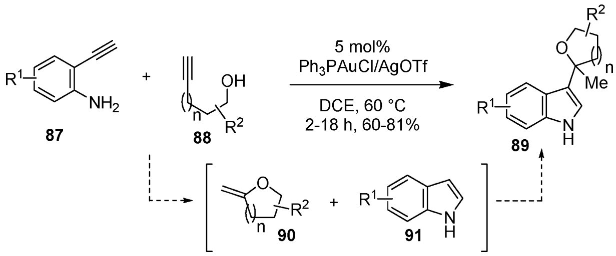


Scheme 30

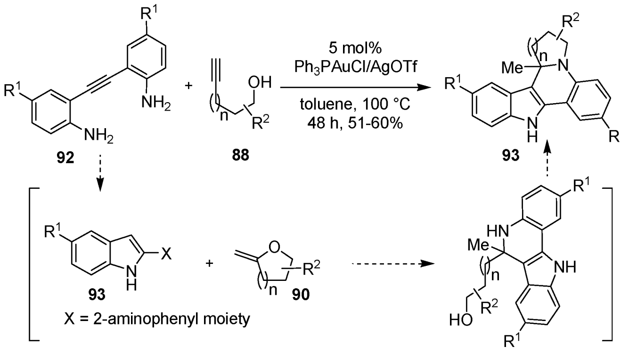
4. Relay catalysis

4.1. Self-relay catalysis

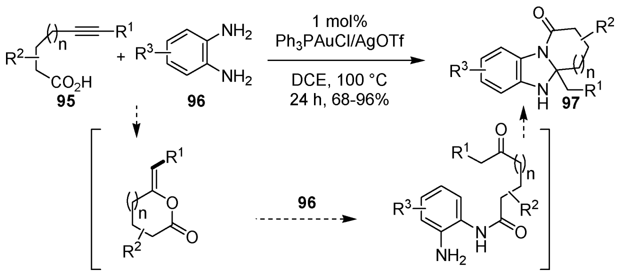
4.1.1. Metal and metal catalysts. Our group established a gold(I)-catalyzed self-relay catalytic approach to the C-3 functionalized indoles **89** starting from 2-alkynylanilines **87** and alkynols **88** (Scheme 31).[36] The Au(I) catalyst is capable of catalyzing three different reactions, *i.e.* hydroalkoxylation (*cf.* **90**), hydroamination (*cf.* **91**) and hydroarylation, in a one-pot. Later, we reported a PtCl$_4$-catalyzed reaction, namely "hydroamination-triggered cyclization", to synthesize biologically important fused heterocycles.[37] For instance, the multistep one-pot reaction between symmetrical diamines **92** and alkynols **88** furnished indolo[3,2-*c*]quinolines **93** in good yields (Scheme 32). In a similar context, Au(I)-catalyzed self-relay catalytic process involving formal double hydroamination of alkynes **95** with diamines **96** that affords fused dihydrobenzimidazoles **97** was also reported by us (Scheme 33).[38] Very recently, we have investigated



Scheme 31



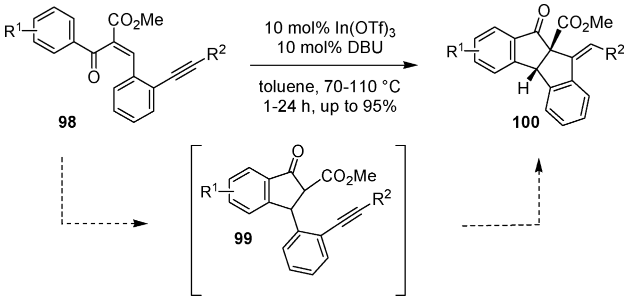
Scheme 32



Scheme 33

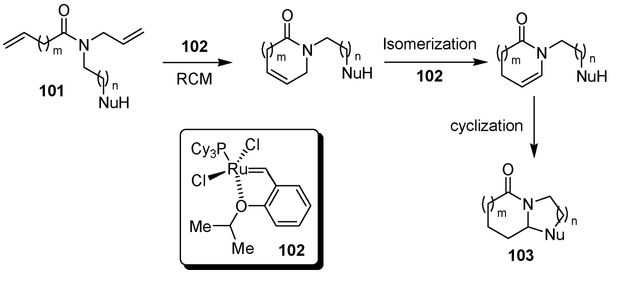
Zn(II)-catalyzed self-relay catalytic process for the synthesis of pyrazolines from 1,3-enynes with aryl hydrazines.[39]

Liu *et al.* found that 10 mol% In(OTf)$_3$ effectively catalyzes both reactions, *i.e.* Nazarov cyclization and 5-*exo-dig* Conia-ene reaction, in a one-pot. For instance, the alkynyl β-ketoesters **98** under the established reaction conditions afforded bicyclic scaffolds **100** through the intermediacy of **99** (Scheme 34).[40] Recently, Ascic, Jensen and Nielsen investigated self-relay catalytic approach to the fused cyclic compounds **103**. The reaction utilizes diene **101** as a starting material, Hoveyda–Grubbs I **102** as a catalyst (Scheme 35).[41]

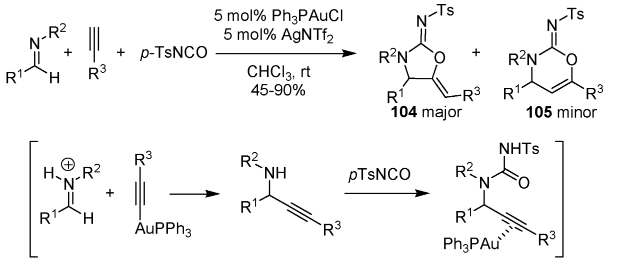


Scheme 34

Recently, Campbell and Toste presented an interesting example of self-relay catalysis where they identified a system in which a single Au(I)-complex catalyzes both alkynylation of aryl imines and 5-*exo-dig* cyclization of corresponding acyclic urea to furnish cyclic carbamimidates **104**/**105** (Scheme 36).[42] The authors also explored the enantioselective version of this process using chiral Au(I)-complex that provided the carbamimidates in moderate to high enantioselectivities.

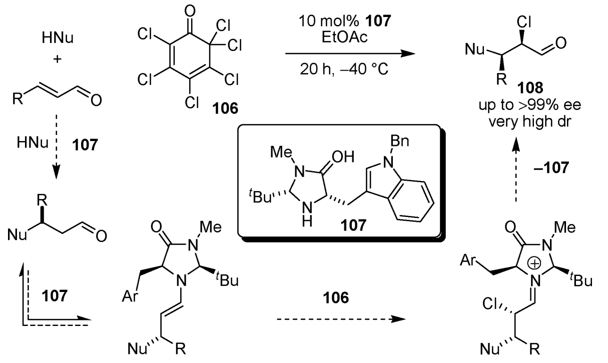


Scheme 35



Scheme 36

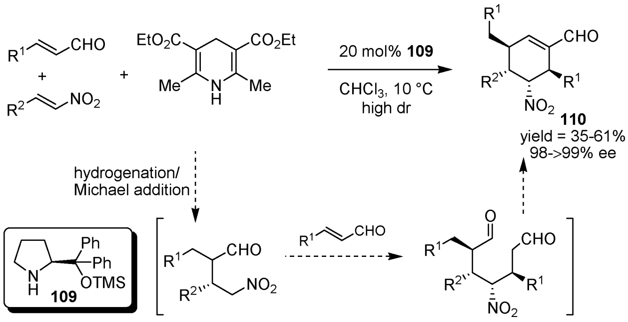
4.1.2. Organo and organo catalysts. The MacMillan group has developed a new organo self-relay catalytic strategy which allows access to 3′-substituted 2-chloropropanals **108** from α,β-unsaturated aldehydes, chlorinated quinone reagent **106** and various nucleophiles (Scheme 37).[43] In this transformation imidazolinone-based catalyst **107** catalyzes both the iminium and enamine activation catalytic pathways. In an attempt to design biologically inspired multi-component cascade reactions, Rueping *et al.* investigated an enantioselective process that represents an example of self-relay catalysis by secondary amine **109**. Overall, the reaction involves catalyzed iminium-enamine-iminium-enamine activation sequence to furnish products **110** in good yields and with high ee's (Scheme 38).[44] Very recently, Loh *et al.* reported a phosphine-catalyzed self-relay catalytic protocol for the isomerisation of 3-alkynoates into allenes followed by its reaction with imines to obtain highly functionalized pyrrolines in one-pot.[45]



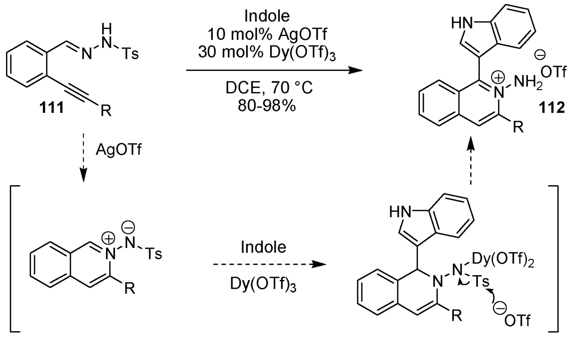
Scheme 37

4.2. Orthogonal-relay catalysis

4.2.1. Metal and metal catalysts. Wu and coworkers reported orthogonal relay catalytic system consisting of AgOTf and Dy(OTf)$_3$ to catalyse reaction between alkynyl hydrazide **111** and indole to afford isoquinolinium triflates **112** in good yields (Scheme 39).[46] The catalyst AgOTf was responsible for the

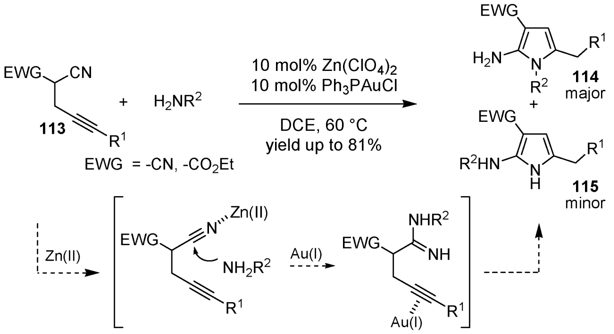


Scheme 38



Scheme 39

generation of isoquinolinium-2-yl amide while Dy(OTf)$_3$ catalysed the subsequent reaction with indoles. A report from Demir *et al.* revealed that Au(I) complex and Zn(II) catalysts act in a relay sequence to catalyze hydroamination/annulation reaction to furnish 2-aminopyrroles **114**/**115** (Scheme 40).[47] The experiment showed that Zn(II) salts catalyzes the formation of imidates while Au(I) salts catalyze the hydroamination reaction.

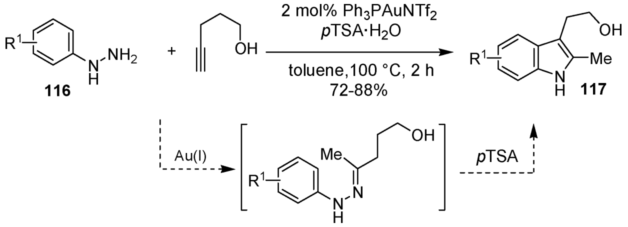


Scheme 40

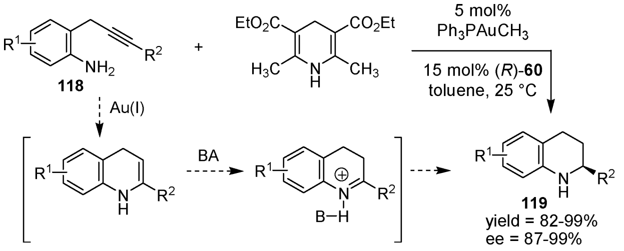
4.2.2. Metal and organo catalysts.

Recently, our group investigated gold and *p*TSA catalyzed hydrohydrazination-Fischer indolization reaction between aryl hydrazines **116** and alkynol that afforded 2,3-substituted indoles **117** in one-pot (Scheme 41).[48] The Ph$_3$PAuNTf$_2$ catalyzes hydrohydrazination reaction while *p*TSA·H$_2$O aids in catalyzing Fischer indolization process.

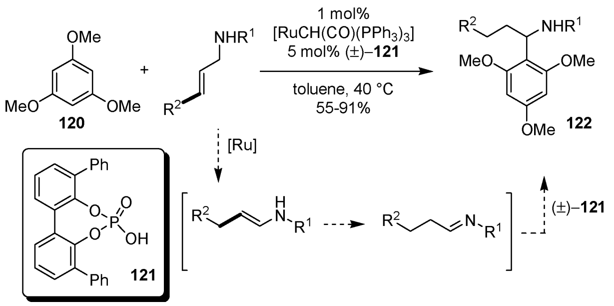
Gong and coworkers reported an intramolecular hydroamination/enantioselective transfer hydrogenation reaction of 2-(2-propynyl)-anilines **118** under orthogonal-relay catalysis of an achiral gold complex and chiral Brønsted acid binary system to afford tetrahydroquinolines **119** (Scheme 42).[49] In yet another example, Terada and Sorimachi reported an orthogonal-relay catalytic system involving Ru-complex and phosphoric acid (±)-**121** for isomerization/C–C bond formation sequence (*cf.* **120**→**122**) (Scheme 43).[50]



Scheme 41



Scheme 42

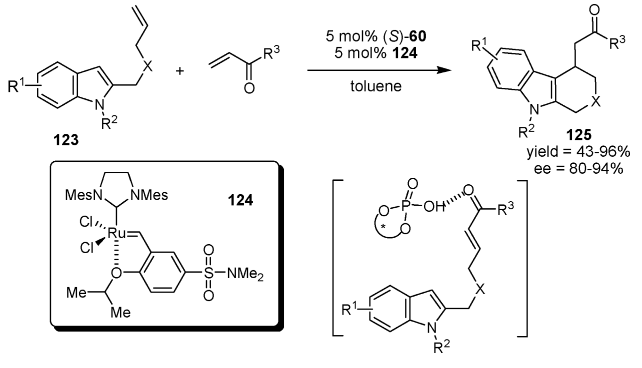


Scheme 43

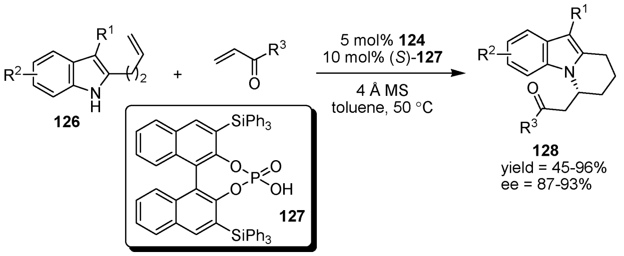
You and coworkers investigated the orthogonal-relay catalysis that involves two distinct catalytic processes: olefin metathesis of indolyl allyl ether **123** catalyzed by Ru-complex **124**, and an enantioselective intramolecular Friedel–Crafts alkylation catalyzed by a chiral phosphoric acid (*S*)-**60** to provide polycyclic indole derivatives **125** in good yields and ee's (Scheme 44).[51] Interestingly, when they used indolyl olefin **126** and α,β-unsaturated enones in the presence of 5 mol% Ru-complex **124** and (*S*)-**127**, regioisomeric fused indoles **128** were obtained (Scheme 45).[52] Jørgensen and coworkers reported metal-organo orthogonal-relay catalytic system for the synthesis of cyclopentene carbaldehydes **129** (Scheme 46).[53]

4.2.3. Organo and organo catalysts.

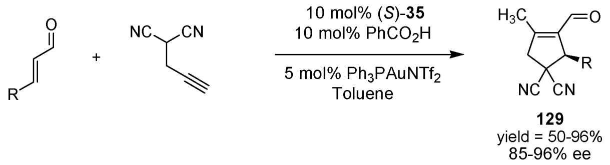
Xu, Dixon and coworkers[54] developed a chemo-, diastereo- and enantioselective three-component organo-relay cascade catalyzed by two organocatalysts to afford fully substituted piperidines **131**. From the proposed mechanism, the activation of aldehyde by catalyst **28** facilitates the Michael-type addition to nitroalkenes which after *in situ* hydrolysis would afford nitro-aldehyde. The nitro-aldehyde intermediate under catalysis of **130** would undergo nitro-Mannich reaction/cyclization to afford piperidines **131** (Scheme 47).



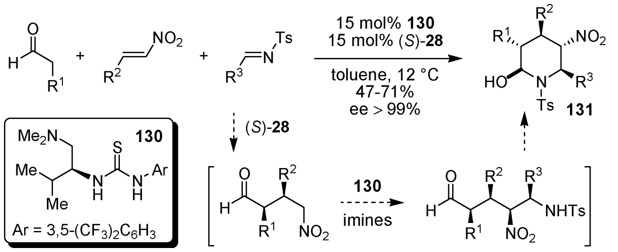
Scheme 44



Scheme 45



Scheme 46



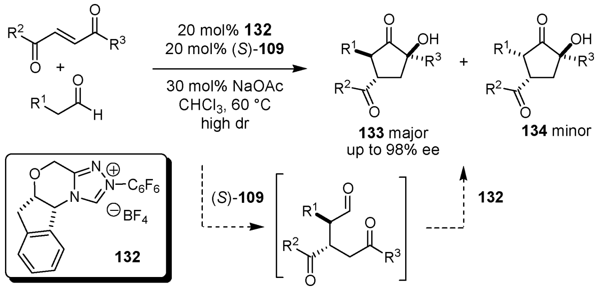
Scheme 47

Filloux, Lathrop and Rovis developed a protocol for the synthesis of cyclopentanone derivatives **133**/**134** from aliphatic aldehydes and activated Michael acceptors using NHC **132** and secondary amine **109** (Scheme 48).[55] The authors also reported an enantioselective Michael/Stetter reaction between salicylaldehydes and electron-deficient alkynes *via* DABCO-catalyzed Michael addition followed by NHC-promoted Stetter reaction in one pot to furnish benzofuranones **135** (Scheme 49).[56]

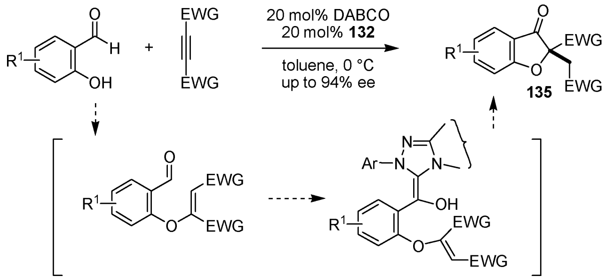
5. Sequential catalysis

5.1. Metal and metal catalysts

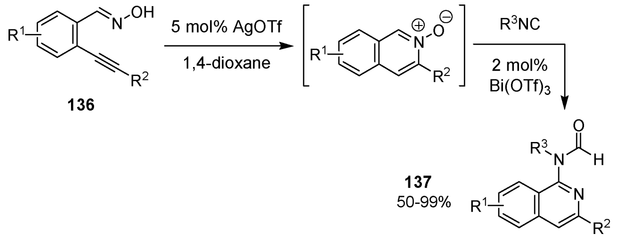
Wu and co-workers reported the synthesis of *N*-(isoquinoline-1-yl)formamides **137** that involves AgOTf catalyzed isoquinoline-*N*-oxide formation from 2-alkynyl benzaldoximes **136** followed by subsequent reaction triggered by nucleophilic addition of isocyanide, catalyzed by 2 mol% Bi(OTf)$_3$ in one pot (Scheme 50).[57] Giacomina, Riat and Alexakis developed a new strategy to access highly enantioselective cyclopentenes **140** using ω-ethylenic allylic substrates **138** through a one-pot enantioselective allylic alkylation and ring-closing metathesis reaction (Scheme 51).[58] The asymmetric allylic alkylation was performed using 3 mol% copper-thiophene carboxylate (CuTC), 3.3 mol% of chiral phosphoramidite ligand **139** and 1.3 equivalents of Grignard reagent in DCM at −78 °C, while ring closing metathesis was performed by the addition of Grubbs-II catalyst in the same pot. Ackermann *et al.* demonstrated a sequential catalysis protocol for synthesis of indoles **142**/**143** utilizing Ti-catalyzed regioselective hydroamination and 5-*endo* Heck reaction starting from 2-choloroanilines **141** (Scheme 52).[59]



Scheme 48



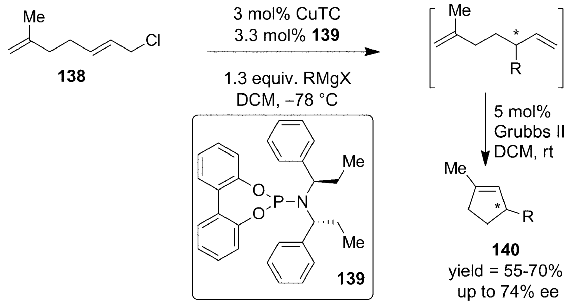
Scheme 49



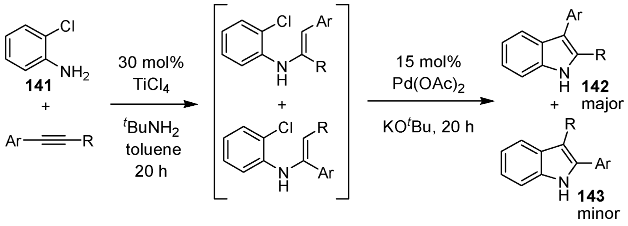
Scheme 50

5.2. Metal and organo catalysts

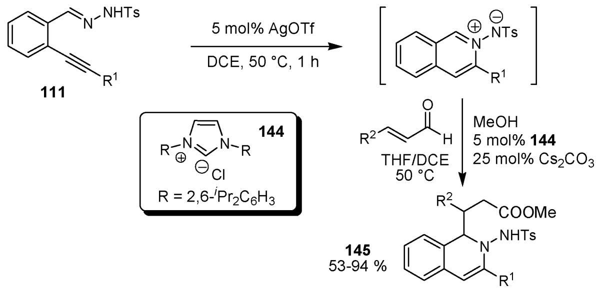
Wu and coworkers shown that AgOTf and NHC **144** catalyze a three-component reaction of *N*′-(2-alkylbenzylidene)-hydrazide **111** and methanol with α,β-unsaturated aldehydes that afforded 2-amino-1,2-dihydroisoquinolines **145** in good yields (Scheme 53).[60] Krause, Alexakis and coworkers developed a one-pot strategy that consists of an enantioselective organocatalytic Michael addition to a nitroenyne **146** catalyzed by secondary amine **109**, to afford intermediate **147** followed by gold-catalyzed acetalization/cyclization



Scheme 51

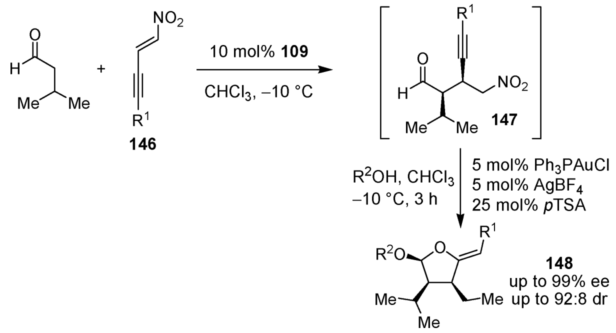


Scheme 52

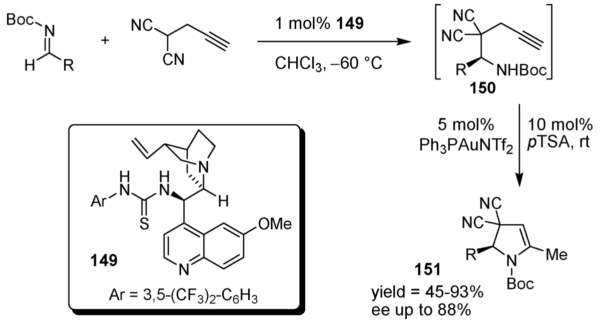


Scheme 53

(Scheme 54).[61] Importantly, in all the cases tetrahydrofuranyl ethers **148** were obtained in better yields with almost same diastereoselectivities compared to that obtained in stepwise reaction sequences.

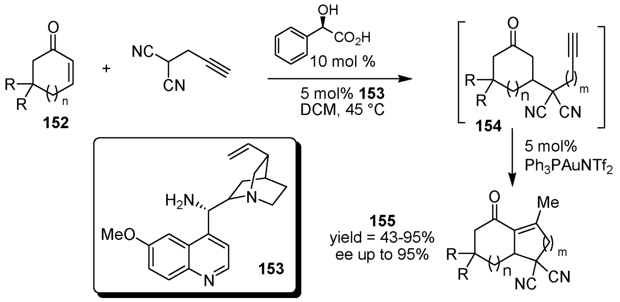


Scheme 54



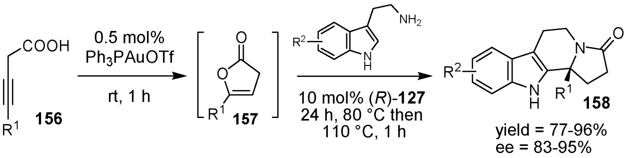
Scheme 55

Jørgenson and coworkers demonstrated a novel synthetic approach towards optically pure dihydropyrroles **151**.[62] The protocol involves organocatalyst **149**-catalyzed Mannich reaction (*cf.* **150**) and subsequent gold-catalyzed alkyne hydroamination/isomerization in one pot (Scheme 55). In yet another example, the authors developed a one-pot procedure for the synthesis of functionalized bicyclic enones. The organocatalyst **153**-catalyzed Michael addition reaction between α,β-unsaturated ketones **152** and propargylated malanonitrile gives intermediate **154**, which on subsequent Au(I)-catalyzed *exo-dig* cyclization/isomerization furnished functionalized bicyclic enones **155** (Scheme 56).[63] Recently Ramachary and co-workers developed a one-pot sequential protocol for synthesis of functionalized indenes and 1,2,3-triazoles utilizing L-proline and CuI combined catalytic system.[64]



Scheme 56

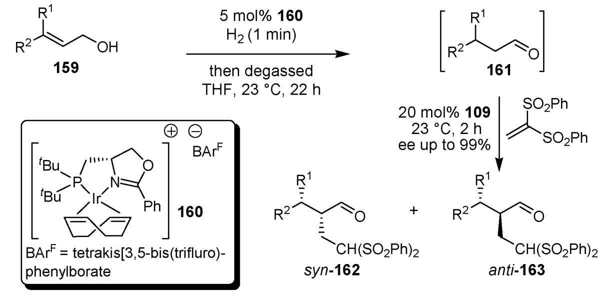
The Dixon group described an example of enantioselective gold(I) and chiral Brønsted acid-catalyzed sequential reaction to give enantioenriched indole containing tetracyclic products **158** (Scheme 57).[65] In this process, first gold(I)-catalyzed cycloisomerization of alkynoic acid **156** took place to generate enol lactone **157** that subsequently undergoes further reaction after addition of tryptamines and (*R*)-**127** to give products **158** in one-pot.



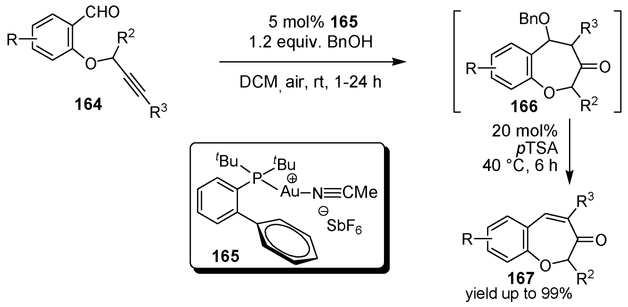
Scheme 57

Very recently, Quintard, Alexakis and Mazet developed a sequential reaction that exploits the compatibility between cationic iridium catalyst **160** and secondary amine catalyst **109**. The role of catalyst **160** was proposed to isomerize primary alcohols **159**, while catalyst **109** catalyzes α-functionalization of aldehydes to obtain **162**/**163** *via* intermediate **161** (Scheme 58).[66]

Recently, Chan and coworkers described a one-pot strategy to benzo[*b*]oxepin-3(2*H*)-ones **167** by utilizing Au-complex **165**-catalyzed heterocyclization/Petasis-Ferrier rearrangement of 2-(prop-2-ynyloxy)benzaldehydes **164** to produce intermediate **166** (Scheme 59).[67] The second catalyst *p*TSA was added to the



Scheme 58

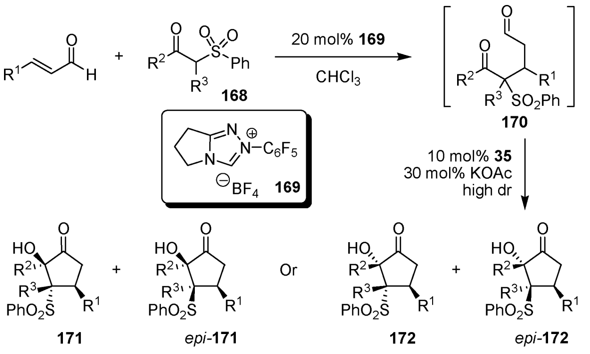


Scheme 59

same pot after completion of the first reaction to promote debenzoxylation.

5.3. Organo and organo catalysts

Very recently, Enders *et al.* developed a protocol for sequential organocatalytic cascade reaction between enals and oxosulfones **168** by utilizing a secondary amine/NHC (**35**/**169**) catalytic system to provide polyfunctionalized cyclopentanones **171**/**172** (Scheme 60).[68] Notably, three contiguous stereo-centres are formed in this reaction with good yields and moderate to good diastereoselectivities.



Scheme 60

Scope and limitations

The classification proposed in this article will help the readers in categorising catalytic one-pot processes in a precise manner. The two catalyst systems (particularly in case of cooperative and orthogonal-relay catalysis) operate concurrently giving rise to products which are not in the reach of either catalyst alone; undoubtedly this indicates the importance of such processes in synthetic organic chemistry. Further opportunities for extension of this chemistry could include the development of novel compatible catalytic systems. Since there are several metal salts available and several organocatalysts can be structurally tuned, the combination of them appears to be huge and therefore a number of new reactions are expected to appear using these types of catalysts in the near future.

Although we attempted to provide a classification that is universal and can be applied to any given reaction sequence, some disadvantages still exists. When two catalysts are simultaneously employed in a given transformation, it is observed that the sense of one of the catalytic cycles essentially depends upon the new catalyst generated from both the catalysts. For instance, an example from our laboratory showed an enantioselective catalytic process consisting of two different catalysts; cat X and cat Y (Scheme 61).[69] Controlled experiments revealed that the intermediate (IM) forming process is catalyzed by only cat X while final product formation from IM is catalyzed by cat X–Y, which is generated *in situ* from cat X and cat Y. At the present moment, we refer this reaction as cooperative catalysis, although this example clearly does not fit in any of the types proposed in this article. To account for this type, we propose herein the definition of principal catalyst for the one whose role is major and can invert the absolute configuration of the product, whereas the secondary catalyst is the catalyst that has the minor role.

$$\mathrm{A} + \mathrm{B} \xrightarrow{\mathrm{X}} \mathrm{IM} \xrightarrow{\mathrm{X\text{-}Y}} \mathrm{A\text{-}B}\ \text{(product)}$$

Reaction Conditions: cat X, cat Y, solvent, rt

Scheme 61

In some organic transformations, two metal catalysts are known to be used; however, the role of one catalyst is to activate another. Example includes $Ph_3PAuCl/AgOTf$, $AuCl_3/AgOTf$, $AuCl/AgOTf$, $PtCl_2/AgOTf$, $PtCl_2/AgSbF_6$, $K_2PtCl_4/AgOTf$, $IrCl_3/AgOTf$, $RuCl_3/AgOTf$, $[\{Rh(C_2H_2)_2Cl\}_2]/AgOTf$, $[Cp^*RhCl_2]_2/AgSbF_6$, *etc.*[70] Therefore, these types of catalyses are not clearly falling in the proposed categories.

Since the field of one-pot catalysis is continuously growing, we anticipate that many new reactions which would not obey the present classification would appear and accordingly a closer classification of one-pot catalysis might be necessary in the future.

Conclusions and future outlook

In general, purification processes are time-consuming, cost-demanding and waste-producing manual operations. Therefore, the one-pot process has long been adapted as an effective means of reducing time, cost and waste generation. In this Emerging Area, we have proposed the strategic classification of one-pot catalysis into three categories, *i.e.* cooperative, relay and sequential catalysis. We have reviewed the most significant reactions catalyzed by metal-metal, metal-organocatalyst and organo-organocatalyst binary catalytic system on the basis of proposed classification. The possible future developments and perspectives in this field are also discussed.

It is the authors' personal experience that some say organocatalysis is dominating metal catalysis. They have said that the common drawbacks associated with metal catalysis are their moisture sensitivity, recoverability and toxicity, particularly for heavy metals. While the statement above may be true, the question is not whether which type of catalysis (metal- or organo-) is superior but how new reactivities could be found. Although metal and organocatalysis individually will always have their own place in synthetic organic chemistry, increasingly there is a need to search for a dual catalyst system. The two-catalyst system where the products obtained are not accessible by using one of the catalysts alone clearly reflects the new type of reactivities exhibited in those reactions.

Acknowledgements

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