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Auto-Tandem Catalysis: Activation of Multiple, Mechanistically Distinct Process by a Single Catalyst

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Key Topic

>Auto-Tandem Catalysis

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>Auto-tandem catalysis methods allow for the rapid synthesis of complex molecules. These processes, in which on catalyst promotes multiple mechanistically distinct reactions in a single reactor, can also minimise waste in terms of time, cost and to the environment. This review covers recent advances in this powerful methodology.

Key words – auto-tandem catalysis, catalysis, metal catalysis heterocycles, carbocycles

Abstract

Auto-tandem catalysis (ATC) is a powerful method for the synthesis of heterocycles and carbocycles as well as acyclic compounds. The process is defined as a single reagent catalysing multiple, mechanistically distinct processes of a chemical reaction. In this review recent advances in ATC using transition metal catalysts is described. In particular, the use of different catalytic systems for the controlled synthesis of the desired product, enantioselective synthesises in which multiple bonds are formed and mechanistic investigations are illustrated with applications to the synthesis of heterocycles and carbocycles as well as acyclic compounds. New approaches that use earth abundant catalysts, greener solvents or increased catalyst efficiency are highlighted. Examples of ATC reaction development are also included. In addition, ATC processes are used as key steps in the synthesis of natural products as well as biologically active compounds.

Introduction

The catalysis of multiple, mechanistically distinct processes in a synthetic sequences was defined by Fogg and dos Santos as auto-tandem catalysis (Figure 1).[1,2] Whilst this process has been described by a number of different names through the years, such as: (a) single-pot catalysis,[3] (b) domino-catalysis,[4] (c) one-pot catalysis,[5] (d) tandem-catalysis,[6] (e) dual catalysis[7] and (f) multifaceted catalysis,[8] the emphasis on the development of novel, convergent synthetic methods has remained consistent. ATC is

a powerful approach towards the synthesis of heterocycles and carbocycles as well as acyclic compounds. A number of important synthetic transformation, including: electrocyclisation / rearrangement, ene-reaction, RCM / cross-metathesis, cycloaddition, transfer hydrogenation and atom transfer radical cyclisation, have been used as part of an ATC process. Of the transition metals used for ATC reactions, palladium, gold and ruthenium are the most common with iron, platinum and copper have also been investigated.
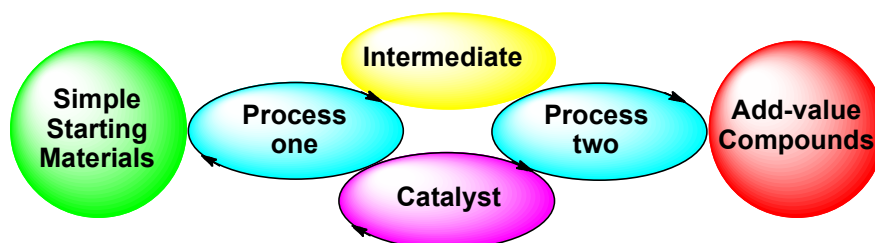

Figure 1. Overview of auto-tandem catalysis (ATC)

## Auto-Tandem Catalysis Approaches to Heterocycles

5-Membered Rings

One of the most popular uses of the auto-tandem catalysis (ATC) approach has been in the synthesis of 5-membered heterocycles.[9] Recently, Blanc et al. reported the synthesis of substituted pyrroles and furans **4** from alkynyl aziridine and epoxides, **1**, via a gold-catalysed ATC process (Scheme 1).[10] Gold activation of alkynes **1** allowed for intramolecular 5-endo-dig cyclisation of the pendant acetate to afford oxoniums **2** Intermolecular ring opening of oxoniums **2** by an alcohol gave substituted allenes **3**. Gold-catalysed activation of allene **3** allowed for an intramolecular 5-endo-dig cyclisation of the pendant amine or alcohol, which after tautomerisation gave the desired pyrroles or furans **4** in moderate to good yield.
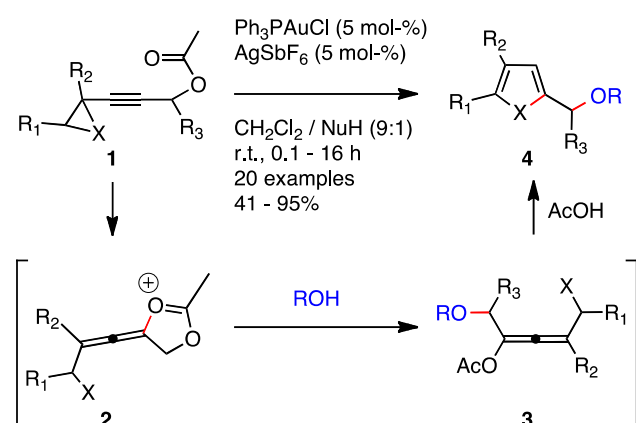
Scheme 1. ATC approach to substituted furans, thiophenes and pyrroles.

We also developed a gold-catalysed synthesis of highly substituted pyrroles **4** (Scheme 2).[11,12] Starting from oximes **5**, activation of either ethylpropiolate (**6**) or dimethylacetylene decarboxylation (**7**) with the in situ formed cationic gold species allowed for facile formation of *O*-vinyloximes **8**. Gold-catalysed tautomerisation of

O-vinyloximes **8** to dienes **9** followed by a [3,3]-sigmatropic rearrangement afforded imino-aldehydes/ketones **10**. Cyclodehydration of the imino-carbonyls **10** followed by tautomerisation gave the desired pyrroles **11** in moderate to good yields. These sorts of processes were used for the synthesis novel cytotoxic agents against leukemia.[13]
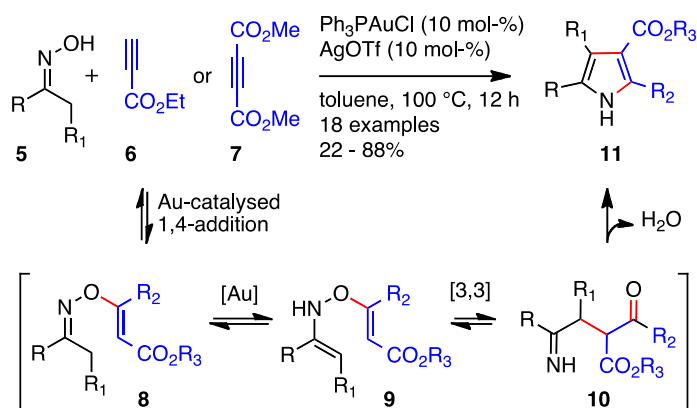
Scheme 2. Gold-ATC approach to substituted *NH*-pyrroles

Drive et al. reported the synthesis of substituted indoles **14** from arylazides **12** using an iron catalyst (Scheme 3).[14] Reduction of arylazides **14** by iron(II) bromide[15] formed an iron-nitrene species that promoted intramolecular hydride transfer to form an oxonium species. Addition of the pendant aniline to the oxonium gave indolenes **13**. Iron-catalysed iminium formation from aminals **13** allowed for the migration of the alkyl or carbocyclic group to form indoles **14** in moderate to excellent yields.
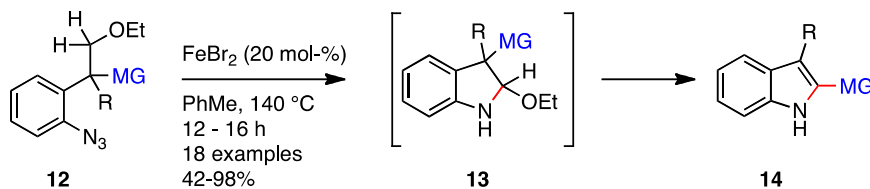
MG - migrating group = alkyl or carbocyclic

Scheme 3. Use of iron catalysis in the synthesis of indoles.

A copper-catalysed ATC process has been used for the synthesis of benzoxazoles **17** directly from dihaloarenes **15** (Scheme 4).[16] Xie et al. subjected dihaloarenes **15** and amides **16** to the reaction conditions in the presence of a CuI / methyl 2-methoxybenzoate catalytic system to cleanly form both the C-N and C-O bonds of benzoxazoles **17** in moderate to good yields. An alternative ATC method for the synthesis of benzoxazoles from trichloroacetonitrile and 2-aminophenols used platinum (IV) chloride to catalyse multiple mechanistically distinct steps of the process.[17]
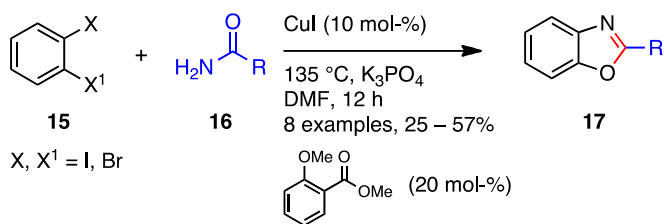
Scheme 4. Copper-catalysed ATC process to benzoxazoles.

He et al. recently reported a novel ATC method for the synthesis of 3-pyrazolines **21** (Scheme 5).[18] Gold activation of diaziridines **18** promoted ring opening to form ylids **19**. Insertion of the terminal alkyne to form a carbon-carbon bond gave 1,1-disubstituted cyclohexanes **20**. Gold-catalysed intramolecular hydroamination of alkynyl-hydrazines **20** afforded the desired 3-pyrazolines **21** in good to excellent yields.
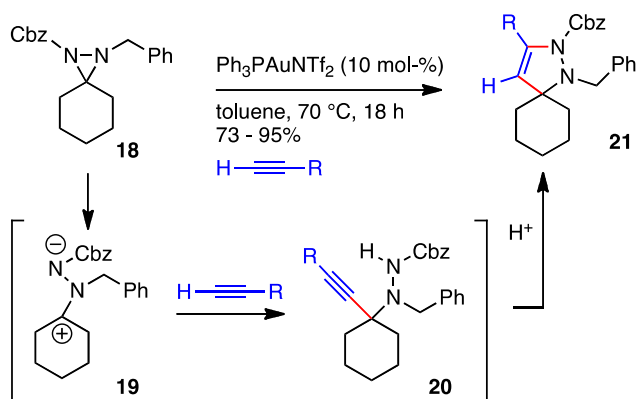

Scheme 5. 3-Pyrazolines via a gold-ATC approach.

Unsaturated 5-membered heterocycles have also been accessed via an auto-tandem catalysis approach. For example, Komeyama et al. developed a novel bismuth-catalysed methodology for the synthesis of substituted pyrrolidines (Scheme 6).[19] A bismuth-catalysed[20] ene-reaction between alkene **22** and secondary alcohols **23** gave alkenes **24**. The bismuth then catalysed the intramolecular hydroamination of amino-alkenes **24** to afford the desired pyrrolidines **25** in moderate to good yields. A related ATC process was reported by France et al. who used a palladium catalyst for the heteroallyation of unactivated alkenes and also illustrated the utility of this novel route in a synthesis of the antidepressant citalopram.[21]
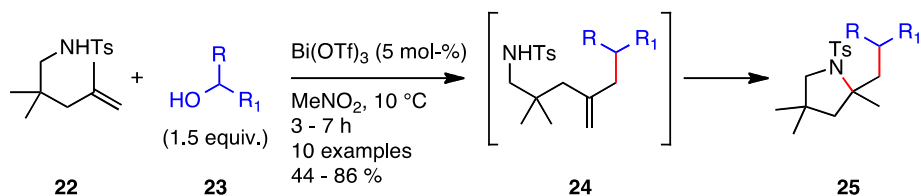

Scheme 6. Bismuth-catalysed methodology for the synthesis of substituted pyrrolidines.

A gold-catalysed cyclisation / nucleophilic substitution reaction was recently used by Blanc et al. for the synthesis of *N*-sulfonylpyrroin-4-ones **29** (Scheme 7).[22] Subjection of ynone-azetidines **26** to the reaction condition allowed for an intramolecular cyclisation to form azetidinium intermediates **28**. Nucleophilic ring opening of azetidiniums **28** gave the desired *N*-sulfonylpyrroin-4-ones **29** in moderate to excellent yields. Importantly, water, alcohols and indoles were all competent nucleophiles in this process. Recently it was shown that phenols on the other hand resulted in desulfonylation of intermediate **28** to give azabicyclo(3.2.0)alkane derivatives.[23]
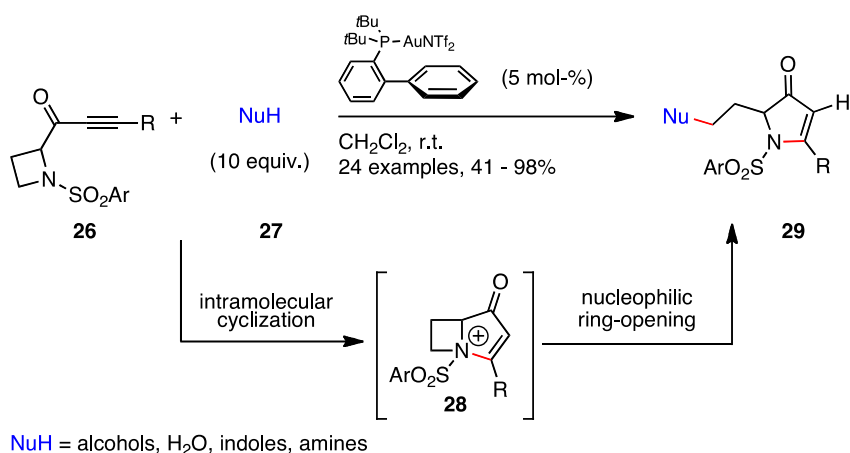

Scheme 7. Gold-catalysed ATC approach to *N*-sulfonylpyrroin-4-ones.

One of the key early examples of an auto-tandem catalysis approach was the use of ruthenium catalysts by Grubbs et al. for a ring-closing metathesis / hydrogenation process. [24] A number of researchers subsequently built on this research for the development of tandem ring-closing metathesis or cross-metathesis processes as one of the ATC steps.[25] Important recent advances in this area have lead to some of the first asymmetric ATC approaches towards the synthesis of 5-membered heterocycles. Okamura et al. used a ruthenium-ATC approach for the synthesis of enantiomerically enriched γ-lactams **33** (Scheme 8).[26] Asymmetric allylic substituted of allylchlorides **30** by α-haloamides **31** catalysed by the planar-chiral ruthenium complex **34** gave allylamides **32**. Atom transfer radical cyclisation[27] catalysed by the same ruthenium complex afforded *anti*-substituted γ-lactams **33** in good yields and ee's.
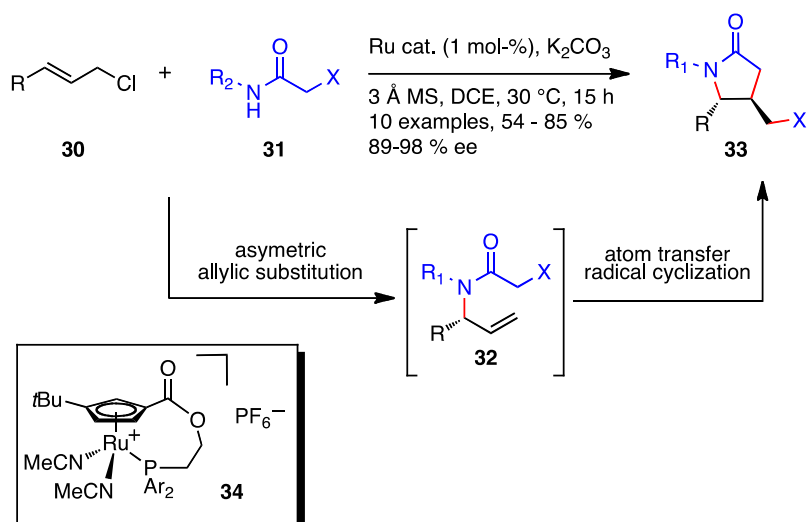
Scheme 8. Enantioselective ruthenium-catalysed approach to γ-lactams

Another example of the utility of chiral ruthenium catalysts in asymmetric ATC process was recently reported by Trost et al. (Scheme 9).[28] Ruthenium-catalysed redox isomerisation of propargyl alcohols **35** gave ruthenium carbenoids **36**. In the asymmetry inducing step, ruthenium-catalysed [2+2]-cycloaddition afforded ruthenocycles **37**, which after reductive elimination gave the desired [3.1.0]-bicycles **38** in moderate to good yields and enantiomeric ratios.
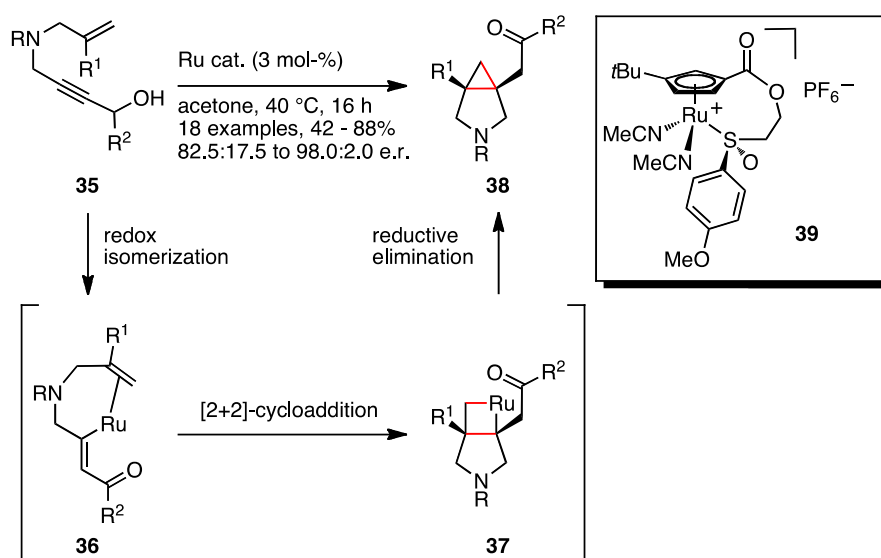
Scheme 9. Enantioselective ATC approach to fused bicycles.

6-Membered Heterocycles

Six-membered heterocycles have also been synthesised via auto-tandem catalysis processes.[29] Ruthenium catalysts can also be used as Lewis acids for the promotion of one of the steps of an auto-tandem catalysis process. For example, Fuwa et al. synthesised tetrahydopyran derivatives **42** using a ruthenium ATC process (Scheme 10).[30] Cross-metathesis of type I alkenes **40** with type II enones **41** in the presence of the Hoveyda-Grubbs II catalyst (**43**) afforded a homologated alkene. Ruthenium then

acted as a Lewis acid to activate the enone towards an intramolecular oxa-conjugate cyclisation to afford 2,6-*cis*-tetrahydropyrans **42** in moderate to good yields. This process has been used for a number of total syntheses of natural products, including: cyanolide A by Krische et al.[31] and (-)-exiguolide by Fuwa et al.[32] In addition, related ATC processes have been developed for the synthesis of nitrogen heterocycles.[33]
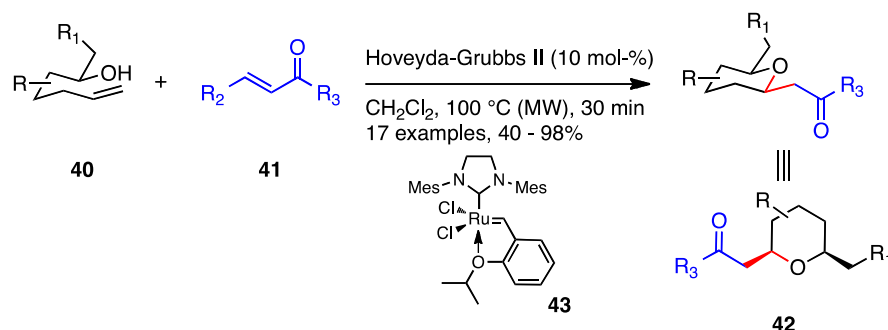
Scheme 10. Ruthenium-catalysed ATC approach to the synthesis of 2,6-*cis*-tetrahydropyrans.

Wu et al. used a relatively cheap copper catalyst for the synthesis of pyrido-pyrmidinones **48** in an ATC process (Scheme 11).[34] Copper-catalysed conjugate addition of 2-aminopyridine **45** to activated 1,4-enediones **44** gave amines **46**. Copper then catalysed both the aerobic oxidation of tricarbonyls **45** to enone **47** as well as the subsequent intramolecular amide formation to afford 4*H*-pyrido[1,2-a]-pyrimidin-4-ones **48** in moderate to good yield. A related study by Jaenicke et al. showed that BiCl₃ was also an effective catalyst for the synthesis of pyrido-pyrmidinones via an ATC process.[35]
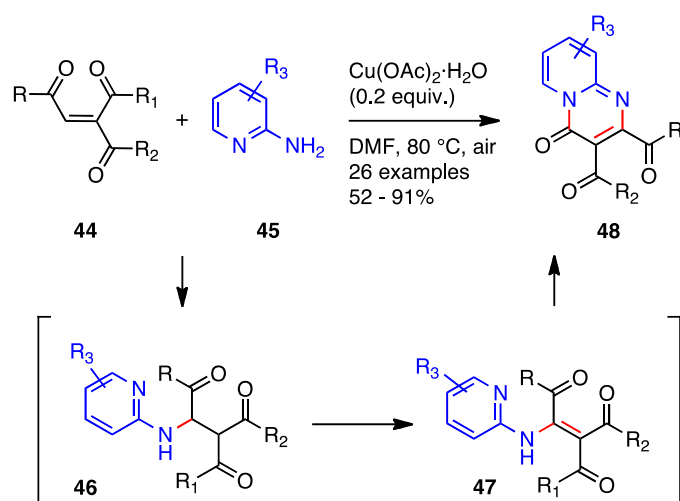
Scheme 11. Copper ATC method for the synthesis of pyrido-pyrmidinones.

Gold catalysts have also proved popular in auto-tandem catalysts methods for the synthesis of 6-membered heterocycles. Schreiber et al. disclosed an ATC method for the synthesis of α-pyrones **54** using a cationic gold catalyst (Scheme 12).[36] Cationic gold activation of electron rich alkynes **50** promoted intermolecular nucleophilic addition of propiolic acids **49** to form vinyl-gold propiolates **51**. Proto-deauration to form vinylpropiolates **52** followed by gold-catalysed 6-endo-dig cyclisation gave

oxocarbeniums **53**. Tautomerisation and proto-deauration afforded the desired α-pyrones **54** in moderate to excellent yields. Schreiber's method as well as related gold-catalysed syntheses of α-pyrones have been applied towards the total syntheses of natural products including the podolactones, [37] (+)-violapyrone C [38] and neurymenolide A.[39]
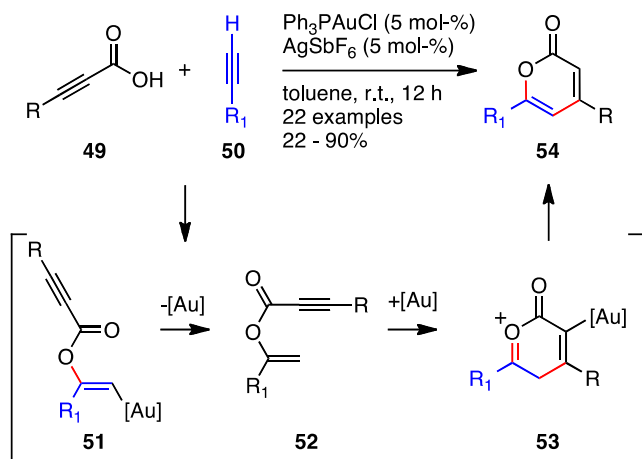
Scheme 12. Synthesis of α-pyrones via an ATC process.

Fustero et al. recently used a gold-catalysed ATC process for the synthesis of dihydropyridinones **57** (Scheme 13).[40] Gold promoted intramolecular cyclisation of homo-propargy alcohols **55** gave oxazines **56**, which subsequently underwent proto-deauration. A gold-catalysed Petasis-Ferrier rearrangement[41] of the oxazine afforded the desired 2,3-dihydropyridin-4(1*H*)-ones **57** in good to excellent yields.
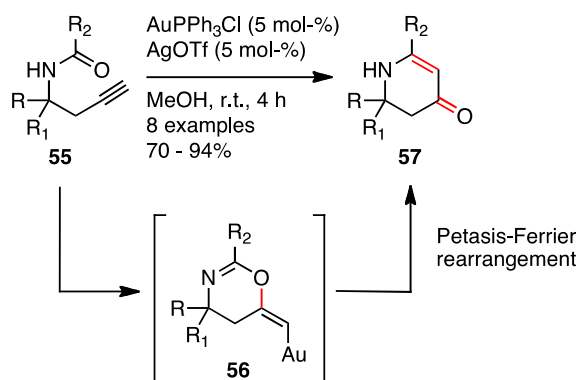
Scheme 13. Gold-catalysed ATC process for the synthesis of dihydropyridinones.

Liang et al. used a gold catalyst with an imidazolium ligand for the synthesis of fused 6-membered carbo- and heterocycles, **61**, (Scheme 14). [42] The cationic gold-imidazolium complex [BMIM = 1-butyl-3-methylimidazolium (**62**)] promoted the intramolecular 5-exo-dig cyclisation of hydroxyl-enynes **58** to afford vinyl ethers **59**. Isomerisation to isobenzofurans **60** followed by an intramolecular [4+2] cyclisation gave an oxanorbornene. Gold-catalysed ring opening then gave the substituted naphthalenes **61** in poor-good yields.
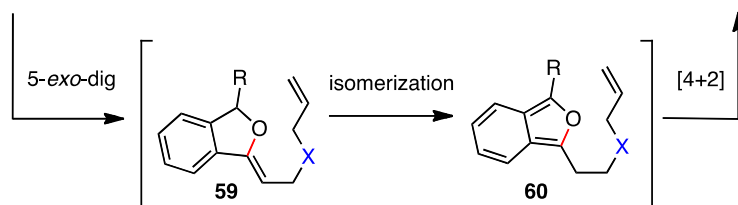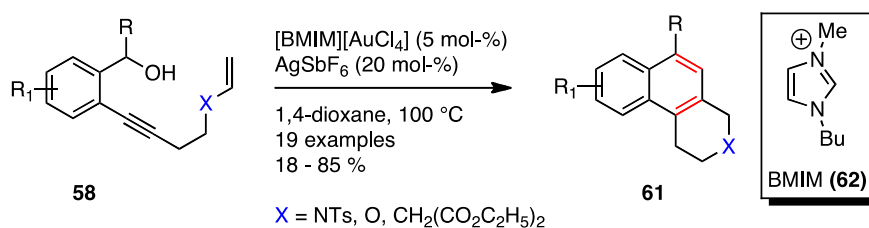
Scheme 14. Gold-catalysed ATC synthesis of naphthalenes.

Barluenga et al. used a palladium species for the catalyst of multiple mechanistically distinct processes in a single reactor for the synthesis of substituted phenanthridines **66** (Scheme 15).[43] Subjection of β-amino-tosylhydrazides **63** to basic conditions formed a diazo species in situ, which was intercepted by the palladium catalyst to form a vinyl-palladium compound.[44] The vinyl-palladium then underwent an intermolecular carbon-carbon cross-coupling process with the bromine of halogens of *o*-bromochloroarenes **64** to give bicycles **65**. Palladium-catalysed carbon-nitrogen bond formation afforded the desired phenanthridines **66** in poor-excellent yield depending on the substitution pattern. This powerful method was used for the synthesis of a series of human CCR2 chemokine receptor antagonists.[45]
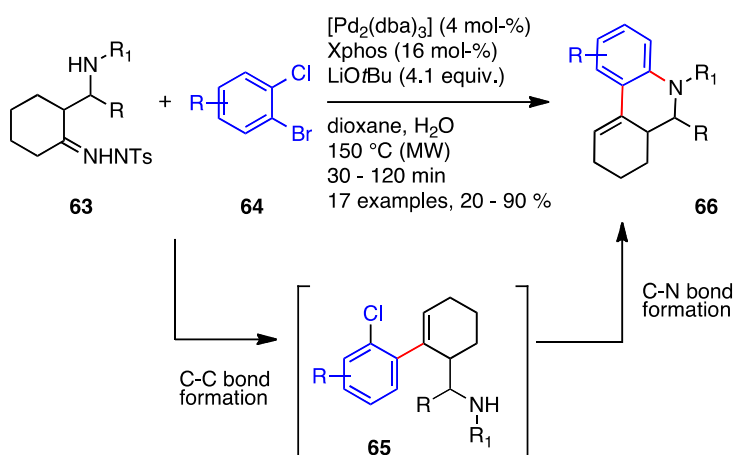

Scheme 15. An ATC process via a vinyl-palladium intermediate.

Auto-Tandem Catalysis Approaches to Carbocycles

5-Membered Carbocycles

Carbocycles have also been synthesised using an auto-tandem catalysis approach.[46] One of the most common metals for the synthesis of 5-membered carbocycles via ATC processes is palladium.[47] Garbriele et al. recently used a palladium ATC method

for the synthesis of substituted indanes **71** (Scheme 16). [48] Palladium-catalysed reaction of phenylacetylenes **67** with amines **68** in the presence of carbon monoxide lead to a carbamoylation reaction that afforded propargyl-amides **69**. *syn*-Carbocyclisation of alkynes **69** via intramolecular attack of palladium stabilised enolates **70** afforded, after proto-depalladation, (*E*)-indanes **71** in moderate to good yields. A related ATC method for the synthesis of 8-membered lactam derivatives was used by Gabriele et al. for the synthesis of antitumor compounds. [49]
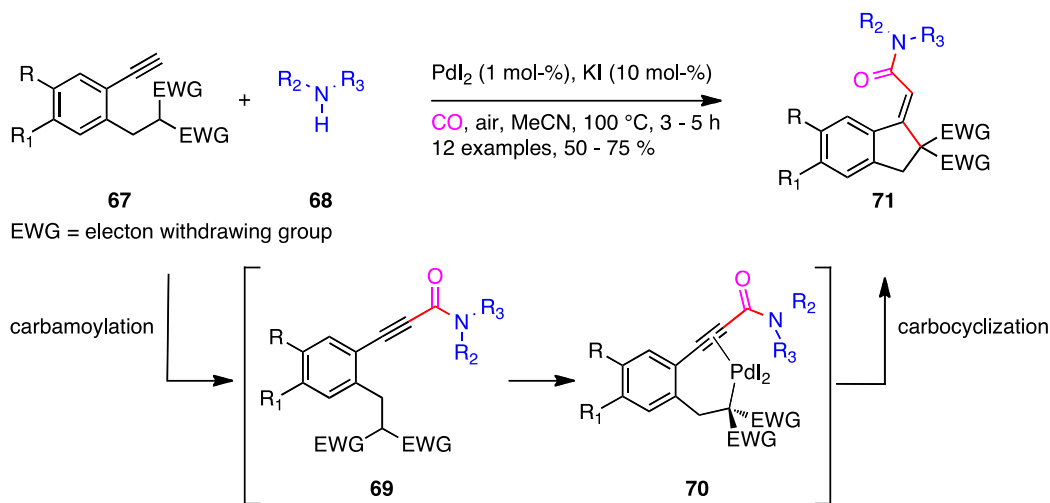
Scheme 16. Palladium ATC method for the synthesis of substituted indanes.

In a report analogous to that of Barluenga et al. outlined above (*cf.* Scheme 15), Valdés et al. recently disclosed the synthesis of spirocycles **75** utilising a palladium mediated ATC process (Scheme 17). [50] Thus, intermolecular cross-coupling between tosylhydrazones **72** and 2,2'-dibromobephenyls **73** gave vinyl adducts **74**. A further palladium-catalysed intramolecular Heck reaction afforded the desired spirocycles **75** in poor to excellent yields. The researchers plan to use this method for the development of novel optoelectronic materials.
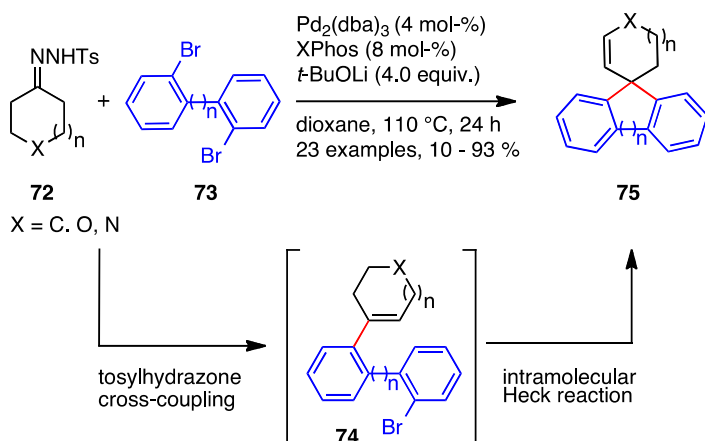
Scheme 17. Palladium mediated ATC method to spirocycles.

An alternative to palladium catalysts was recently disclosed by Prajapati et al. who showed that carbocycles can also be easily accessed using an auto-tandem catalysis

approach. For example, a novel indium mediated ATC process for the synthesis of indanones **79** was developed (Scheme 18).[51] In their method, an indium species catalysed both the intermolecular Nakamura reaction[52] between 1,3-dicarbonyls **76** and phenyl acetylenes **77** to give enones **78** as well as the subsequent hydroarylation and decarboxylation processes. The result of these multiply transformation in a single reactor is the formation of substituted indanones **79** in poor-good yields.
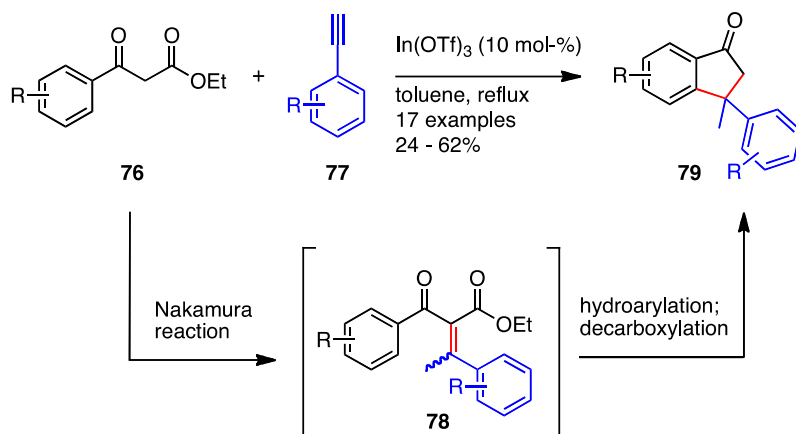
Scheme 18. Indium-catalysed synthesis of substituted indanones.

*6-Membered Carbocycles*

Six-membered carbocycles have also been synthesised utilising an auto-tandem catalysis approach. Greaney et al. showed that annulated indoles **83** were accessible via a palladium mediated ATC process in which a SIMes (1,3-dimesityl-4,5-dihydroimidazol-2-ylidene) salt was used as a ligand (Scheme 19).[53] Subjection of alkynyl-indoles **80** to the reaction conditions resulted in an intramolecular 6-exo-dig alkyne carbopalladation reaction to give vinyl-palladium intermediates **82**. The process is mainly *syn*-selective, which sets the stereochemistry of the next step of the reaction. Arylation of the vinyl-palladium species **82** by diaryl iodonium salts **81** proceeds with retention to afford the desired annulated indoles **83** in moderate to excellent yields.
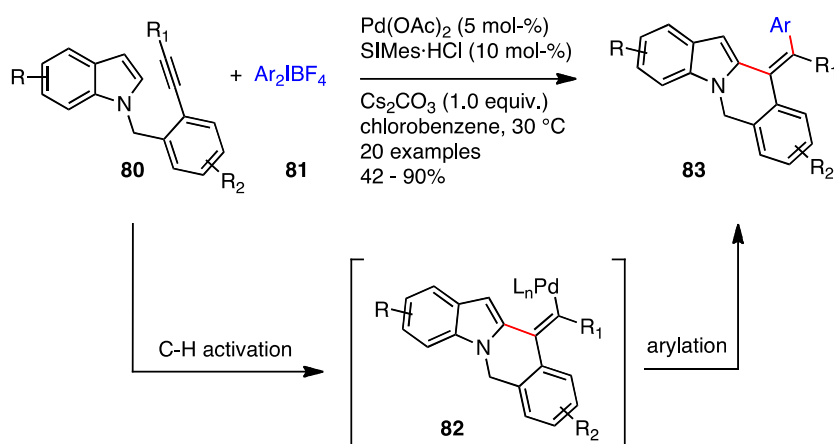
Scheme 19. ATC approach to annulated indoles.

Rodríguez et al. recently reported the synthesis of substituted cyclohexanes **85** from acyclic precursors via an ATC process (Scheme 20).[54] Platinum-catalysed hydration of enynes **84** followed by intramolecular enol addition, also catalysed by the platinum complex, afforded cyclohexanes **85** after proto-deplatinisation. The observed *anti*-selectivity is believed to come from the adoption of cyclic transition state **86** during the cyclisation process, which is purportedly stabilised by the two pseudo-axial hydroxyl groups (alcohol and enol ether). The products were isolated in moderate to good yields with high diastereomeric ratios.
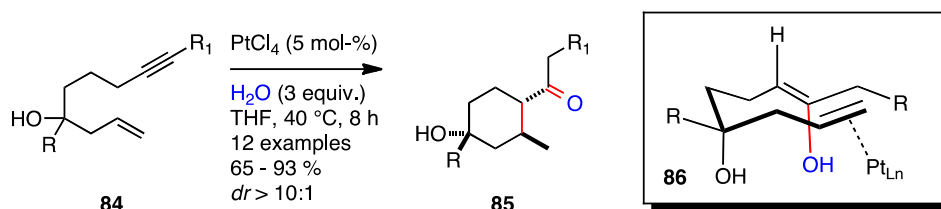

Scheme 20. Platinum-catalysed synthesis of cyclohexanes via an ATC process.

Auto-Tandem Catalysis Approaches to Acyclic Compounds

Acyclic systems can also be easily accessed via an auto-tandem catalysis approach. For example, in work related to their synthesis of pyrido-pyrmidinones **48** (*cf.* Scheme 11), Wu et al. recently reported a copper-catalysed method for the synthesis of tetrasubstituted alkenes **88** (Scheme 21).[55] Copper-catalysed addition of amines **87** to 1,4-enediones **44** afforded an alkane intermediate that subsequently underwent aerobic oxidation promoted by the same copper catalyst. The products of this one reactor transformation were the desired tetrasubstituted alkenes **88**, which were isolated in moderate to excellent yields.
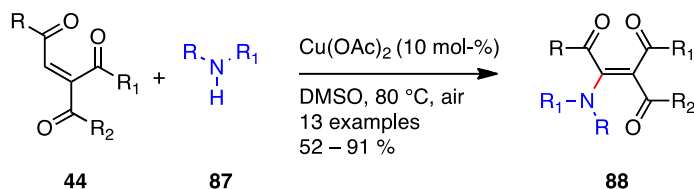
Scheme 21. ATC approach to tetrasubstituted alkenes

We recently used an ATC approach towards the direct synthesis of halogenated allylic amides **93** from allylic alcohols **89** (Scheme 22).[56] Platinum activation of halo-nitriles **90** allowed for facile addition of allylic alcohols **89**. The same catalyst then promoted the subsequent [3,3]-sigmatropic rearrangement of imidates **91** to afford the desired halogenated allylic alcohols **92** in moderate to good yields. Importantly, this method mitigates the need to preform and isolate the intermediate imidate, as is done traditionally in the Overman rearrangement sequence.[57]
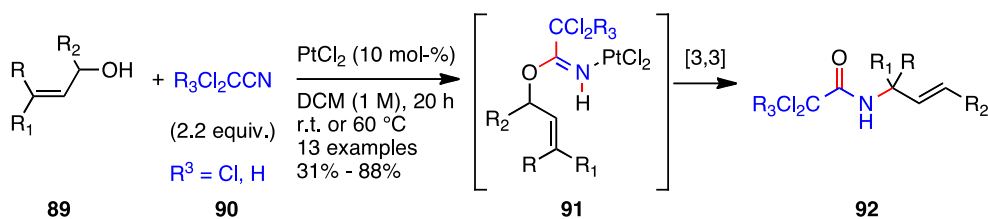
Scheme 22. Direct synthesis of halogenated allylic amides from allylic alcohols.

Hamze et al. recently disclosed a three-component ATC process in which the palladium catalyst is promoting a number of mechanistically distinct steps (Scheme 23).[58] In situ formation of the vinyl-palladium species, via the palladium carbenoid, from hydrazines **93** was initiated by the excess base in the reaction. The vinyl-palladium species can then undergo an intermolecular cross-coupling reaction with dihaloarenes **94** to afford a tetrasubstituted alkene. The haloarene product can then undergo an intermolecular amination reaction with amines **95** catalysed by the palladium species, which afforded the desired tetrasubstituted alkenes **96** in moderate to excellent yields. Hamze et al. were able to further extend this ATC process to include Suzuki couplings in place of the final amination[59] as well as to the synthesis of amino-*N*-vinylindoles, whose antiproliferative activity against human colon carcinoma cells was probed.[60]
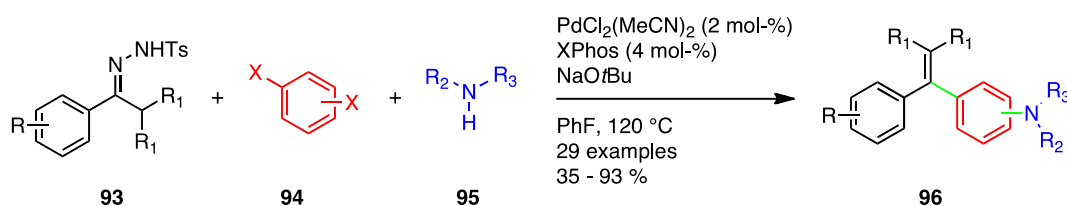
Scheme 23. Palladium-catalysed ATC process to tetrasubstituted alkenes.

Huang et al. recently disclosed an ATC method for the formation of α,β-diamines **103** from aminals **97** (Scheme 24).[61] It is proposed that this transformation proceeds via initial oxidative addition of the palladium species into the aminals **97** to give palladicycles **99**. Carbenoid formation from reaction of the palladicycles **99** and α-diazoacetates **98** afforded palladium carbenoids **100**. Migratory insertion then gave intermediates **101** to which the initially displaced amine added to form palladium-amine intermediates **102**. Reductive elimination of intermediates **102** afforded the desired α,β-diamines **103** in moderate to excellent yields. This group was able to further develop this ATC method for the enantioselective aminomethylaminations of conjugated dienes[62] and the synthesis of aminomethyl substituted allylic sulfones.[63]
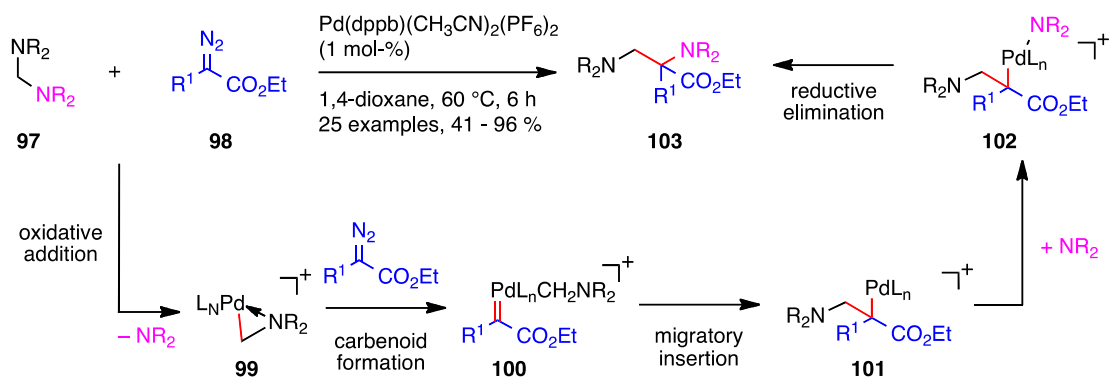
Scheme 24. Synthesis of α,β-diamines from α,α-diamines.

Recently Li and Herzon disclosed a novel concept that should aid in the development of auto-tandem catalysis methodology, temporal separation. Temporal separation seeks to allow a catalyst to perform multiple mechanistically distinct steps of a process sequentially, by ensuring that an individual process is completed before the next one is begun.[64] For example, they showed that terminal alkynes **104** could be converted to alcohols **106** via a ruthenium-catalysed ATC process (Scheme 25). Thus, 2-fluorophenylacetylenes **104** underwent anti-Markovnikov hydration to afford aldehydes **105**. The same ruthenium catalyst then promoted a transfer hydrogenation reaction for the reduction of aldehydes **105** to the desired alcohols **106** in good to excellent yields. Importantly, the researchers were able to monitor the progress of the reaction using F^{19} NMR and showed that the reduction of aldehydes **105** only occurred after all of the starting material acetylenes **104** was consumed. Further advancements using this concept allowed for the synthesis of alcohols,[65] 1,3-amino alcohols, 1,3-diols, amines and carboxylic acids from terminal alkynes[66] as well as the total synthesis of the natural product (+)-batzelladine B.[67]
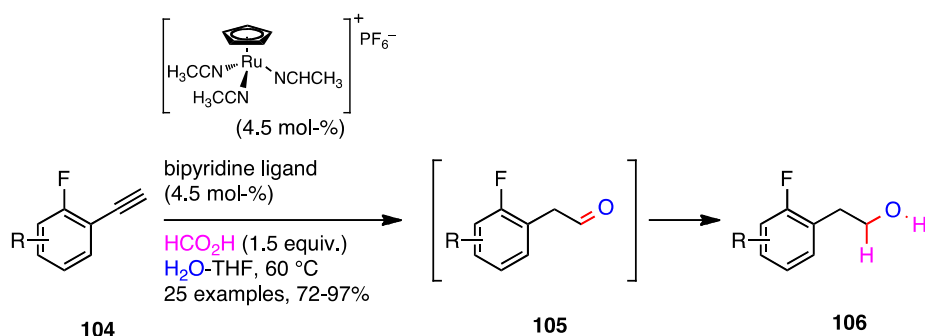
Scheme 25. Application of temporal separation to an ATC process.

Conclusions

The ability to catalyse multiple mechanistically distinct processes in a reaction, auto-tandem catalysis, is a powerful approach to the synthesis of the small molecules on which we all depend. This approach has been used to make a variety of important heterocycles, carbocycles and acyclic systems. Furthermore, the utility of this approach has been demonstrated in the total synthesis of natural products and the synthesis of novel, biologically active compounds. Significant progress has been made in the area of ATC, specifically in the rapid development of novel processes and

the application of these new methods to complex synthesis. Despite the recent advances, there is still plenty of opportunity in the field of ATC, especially in the areas of reaction design, mechanistic understanding and the development of greener, more sustainable processes.

Biography

Jason E. Camp obtained his PhD from The Pennsylvania State University under the supervision of Prof. Steven Weinreb working on the total synthesis of the chartellamide and chartelline family of marine natural products. He then was a postdoctoral fellow working with Prof. Donald Craig (Imperial College London) before obtaining lectureships at the University of Nottingham and Queen Mary University of London. He is currently a senior lecturer at the University of Huddersfield working on the development of novel auto-tandem catalysis methods as well as sugar-powered catalysis protocols.

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