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Advancement in Cascade [1,n]-Hydrogen Transfer/Cyclization: A Method for Direct Functionalization of Inactive C(sp^3)–H Bonds

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Abstract: The cascade [1,n]-hydrogen transfer/cyclization, recognized one century ago, has received considerable interest in recent decades and great achievements have been made. This cascade process can functionalize C(sp^3)–H bonds directly into C–C, C–N, C–O bonds under the catalysis by Lewis acids, Brønsted acids or organocatalysts, and even under thermal conditions. This methodology has shown preeminent power to construct 5- or 6-membered heterocyclic as well as all-carbon rings. In this review, various hydrogen donors and hydrogen acceptors are categorized and discussed.

Abbreviations: Cbz: benzyloxycarbonyl; Cod: 1,5-cyclooctadiene; CSA: camphorsulfonic acid; DCE: 1,1-dichloroethane; DFT: density function theory; DMF: *N,N*-dimethylformamide; DNBS: 2,4-dinitrobenzenesulfonic acid; DPP: diphenyl phosphate; ERC: electrocyclic ring closure; Fmoc: 9-fluorenylmethoxycarbonyl; HT: hydrogen transfer; IBX: *ortho*-iodoxybenzoic acid; *m*-CPBA: *meta*-chloroperbenzoic acid; MW: microwave; MS: molecular sieves; Pg: protecting group; *p*-TSA: *para*-toluenesulfonic acid; r.t.: room temperature; TCE: 1,1,2-trichloroethane; TFA: trifluoroacetic acid; TMS: trimethylsilyl.

Keywords: C–H activation; C(sp^3)–H bonds; cyclization; hydride transfer; *tert*-amino effect

1 Introduction

Over the past decades, tremendous progress has been made in C–H functionalization in accord with the demands for green and sustainable chemistry.[1] The fast development of this vigorous field arises from the recognition by the chemical community that such methodologies are able to streamline synthetic routes and facilitate the direct formation of C–C bonds and C–Z bonds (Z = O, N, B, Si, etc.) without prefunctionalization of C–H bonds to C–X bonds (X = halogens, OTf, etc.). In this context, a large number of innovative and efficient synthetic methodologies has been developed, thus offering intriguing opportunities for the rapid build-up of molecules with complex architectures. Among these methodologies, the transition metal-catalyzed C(sp^2)–H bond activation has dominated this area and the direct functionalization of

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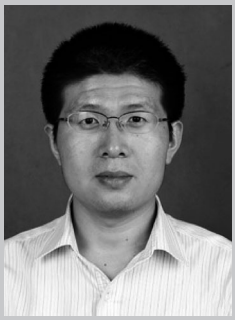


Jian Xiao was born in Shandong province in 1981 and received his PhD degree from Nanyang Technological University under the guidance of Prof. Teck-Peng Loh in 2009. After one more year as postdoc in the same group, he joined the Dalian Institute of Chemical Physics, Chinese Academy of Sciences as an associate professor (2010–2012). In 2012, he was appointed as a full professor at Qingdao Agricultural University. In 2013–2014, he worked as a research associate in the Scripps Research Institute with Prof. Carlos F. Barbas III. His research interest is new synthetic methodology involving organocatalysis and asymmetric catalysis, focusing on organocatalytic C–H activation and cycloaddition reactions.

inert C(sp^3)–H bonds still remains a great challenge owing to the high bond dissociation energy of C(sp^3)–H bonds. Just recently, some promising catalytic processes for the selective functionalization of C(sp^3)–H bonds have been reported, such as palladium- and rhodium-catalyzed reactions.[2] Despite the numerous challenges posed by direct C(sp^3)–H bond activation, the cascade [1,n]-hydrogen transfer/cyclization process opens new avenues and provides unusual solutions to many of these synthetic obstacles.[3] This fascinating intramolecular redox, neutral process was initially discovered in 1895 and termed as "*tert*-amino effect" by Meth-Cohn and Suschitzky in 1972,[4] and since then has been recognized as an efficient and powerful method for selective activation and direct functionalization of inactive C(sp^3)–H bonds. This cascade process represents an intriguing sequential C-(sp^3)-H activation/C–C, C–N or C–O bond formation process and proves to be a versatile protocol to construct 5-, 6- or 7-membered hetero, spiro, or fused cycles, as well as full-carbon cycles, such as tetrahydroquinolines,[5] chromans,[6] spiro-ethers[7] and tetrahydropyrans,[8] which are common moieties in biologically important natural products and pharmaceuticals.

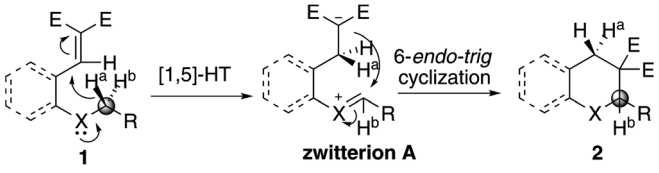
Some reputable groups such as those of Sames, Seidel, Akiyama, Vidal, Liu and Gagosz have shown preeminent applications of this methodology to build various heterocyclic or all-carbon spirocycles and fused rings. In the following, these elegant findings will be categorized according to the types of hydride donors [*tert*-amino effect, C(sp^3)–H bonds α to ethereal oxygen and sulfur, benzylic C(sp^3)–H bonds, non-benzylic C(sp^3)–H bonds] and the types of hydrogen acceptors (benzylidenemalonates, transition metal-activated alkynes or allenes, enals or enones, aldehydes or imines, ketenimines/carbodiimides). This review provides elementary insights into these cascade reactions concerning the mechanism, the reactivity of hydrogen donors and acceptors, as well as migration modes of hydrogen.

2 Mechanistic Insights into [1,5]-Hydrogen Transfer/Cyclization

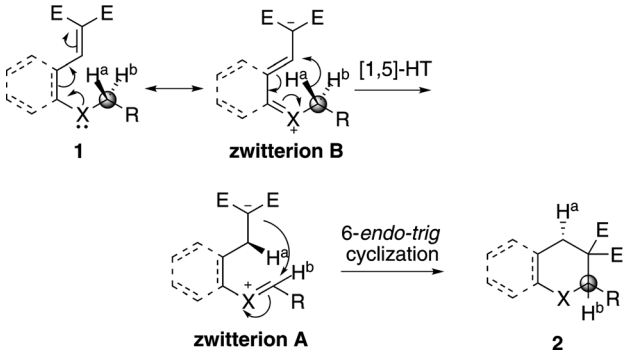
The [1,5]-hydrogen transfer was selected as a model reaction for discussing the mechanism since it is the most common migration mode. However, other modes of migration have also been reported such as [1,4] and [1,6] hydrogen transfer.

2.1 Possible Reaction Pathways

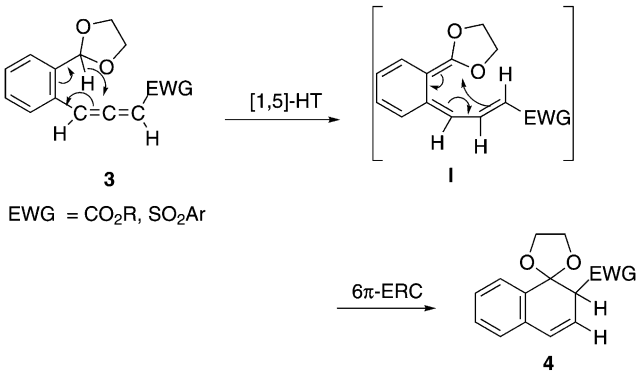
The exact nature of the hydrogen transfer is still a matter of debate in the scientific community. Some argue that it is transferred *via* a sigmatropic shift, whereas others believe that the migration of hydrogen to the acceptor occurs in the form of a hydride anion.[9] A plausible mechanism of this transformation is depicted in Scheme 1. The zwitterion **A** is generat-



Scheme 1. The transfer of ionic hydride through space.



Scheme 2. The transfer of sigmatropic hydrogen.



Scheme 3. Cascade [1,5]-hydride transfer/6π-electrocyclic ring closure.

ed from **1** *via* [1,5]-suprafacial hydrogen transfer from the carbon α to heteroatom **X** to the electrophilic hydrogen acceptor in the form of a hydride, followed by a subsequent intramolecular 6-*endo-trig* cyclization (or nucleophilic attack), giving rise to the heterocycle **2**.[3c,10]

This cascade process can also be rationalized in an alternative way (Scheme 2). Initially, substrate **1** resonates to give zwitterion **B**, and subsequent [1,5]-suprafacial hydrogen transfer in the form of a sigmatropic hydrogen transfer results in zwitterion **A**. A consecutive intramolecular nucleophilic attack affords the final cyclic product **2**.[11] DFT calculations show that [1,5]-hydride (or hydrogen) transfer is the rate-determining step and the energy barrier of the subsequent cyclization step is very low.[12]

The final cyclization can also proceed in the manner of a 6π-electrocyclic ring closure (6π-ERC) (Scheme 3). After a [1,5]-hydride transfer, the conjugated 1,3,5-hexatriene intermediate **I** can be produced, which undergoes subsequent 6π-ERC to give the cyclized product **4**. Thus the formation of unstable zwitterionic intermediate **A** with charge separation is omitted.[12c,13]

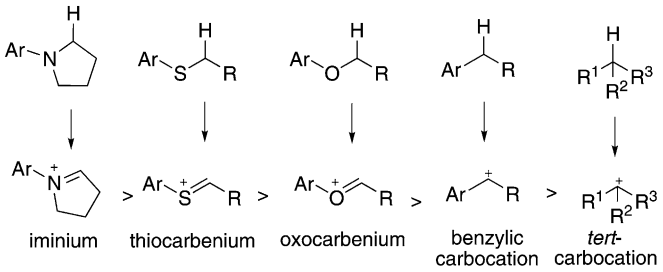


Figure 1. Stability comparison of different cations.

2.2 Reactivities of Different Hydrogen Donors

Heteroatoms, such as nitrogen, oxygen and sulfur can facilitate the hydride migration, as also do aryl groups and alkyl groups. The heteroatoms adjacent to hydrogen donors (methylene or methine) play a dual role, one of which is to polarize and weaken the C–H bond, which increases the negative charge density at the hydrogen atom *via* hyper-conjugative interaction, thus facilitating hydride abstraction.[14] The other is to stabilize *in situ* generated cations upon hydride migration (e.g., iminium, oxocarbenium, thiocarbenium) *via* *p–p* conjugation with the heteroatoms' lone pair electrons. In contrast with the iminium ion, oxocarbenium and thiocarbenium ions are less stable and more difficult to generate, not to mention the benzylic carbocation and *tert*-carbocation (Figure 1). DFT calculations and experimental results show that the thiocarbenium ion exhibits a slightly higher stability than the oxocarbenium species.[15] The aromatic or alkyl substituents on the hydrogen donors can also stabilize the cations *via* π-*p* conjugation or σ-*p* hyperconjugation. The primary C–H bond is rarely exploited as hydrogen donor except for Zhang's and Chatani's reports.[9d,16] In addition to the above-mentioned hydride donors, acetal and dithioacetal C–H bonds can also work as the hydride donors.[12c,14]

2.3 Activation Mode of Hydride Acceptors

The types of hydride acceptors are limited to alkylidenemalonates, carbophilic transition metal-activated alkynes or allenes, enal or enone species, aldehydes/ketones, imines, ketenimines/carbodiimides, metal carbenoids, as well as alkynes carrying electron-withdrawing groups (Figure 2).

It can be imagined that there is competition between the cations and electrophilic hydride acceptors for the hydride after cleavage of the inert C(sp^3)–H bond (Figure 2). If the hydride acceptor is electrophilic enough, it can "snatch" the hydride to give the zwitterion **A**, followed by an intramolecular nucleophilic attack to give the cyclized product **2**

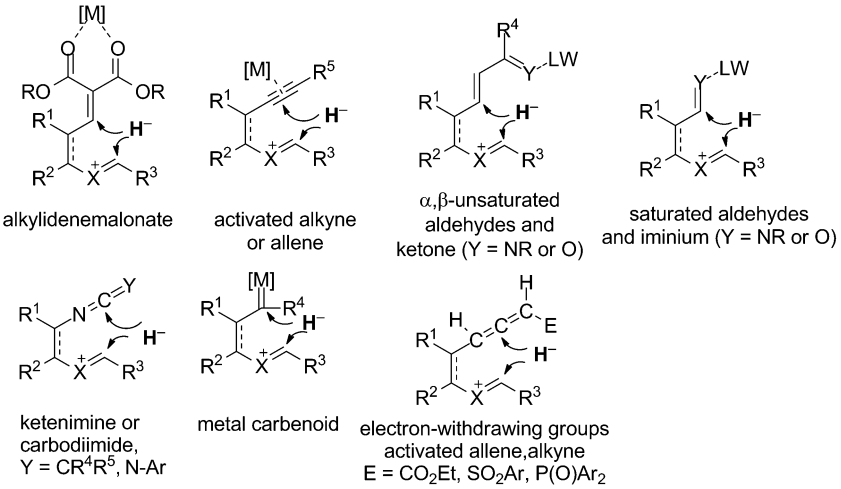


Figure 2. Different types of hydride acceptors and activation modes.

(Scheme 1); whereas if not, the cations will "retrieve" the hydride and no reaction will occur. Therefore two strategies are applicable to facilitate the cascade process: increasing the electrophilicity of the hydride acceptor or increasing the stability of the cations generated upon hydride migration.

The nature of hydrogen to be transferred strongly depends on the characteristics of hydrogen acceptors. Hydrogen can be transferred not only in the form of a hydride anion, but also in the form of a proton. If the hydrogen acceptor is a relatively strong nucleophile, hydrogen will be abstracted by the acceptor in the form of a proton.[13a,16b,17] The hydrogen can be transferred not only in a [1,5]-manner, but also in [1,4][18] or [1,6][9c,17c,19] manners. If the hydride donor and acceptor are active enough, the hydride migration may occur through space, giving rise to a zwitterionic intermediate. Only when the nucleophile and electrophile in the zwitterionic intermediate are located in proper geometric positions will the intramolecular nucleophile attack occur and result in 5-,[19b,c] 6-, or 7-membered[9e,20] products. When the nucleophile is unavailable or cyclization was blocked because of steric hindrance, the hydride will simply work as a reductant[21] or unwanted side products will be produced.[19d]

3 C(sp^3)–H Bonds Adjacent to *tert*-Amino Moieties (*tert*-Amino Effect)

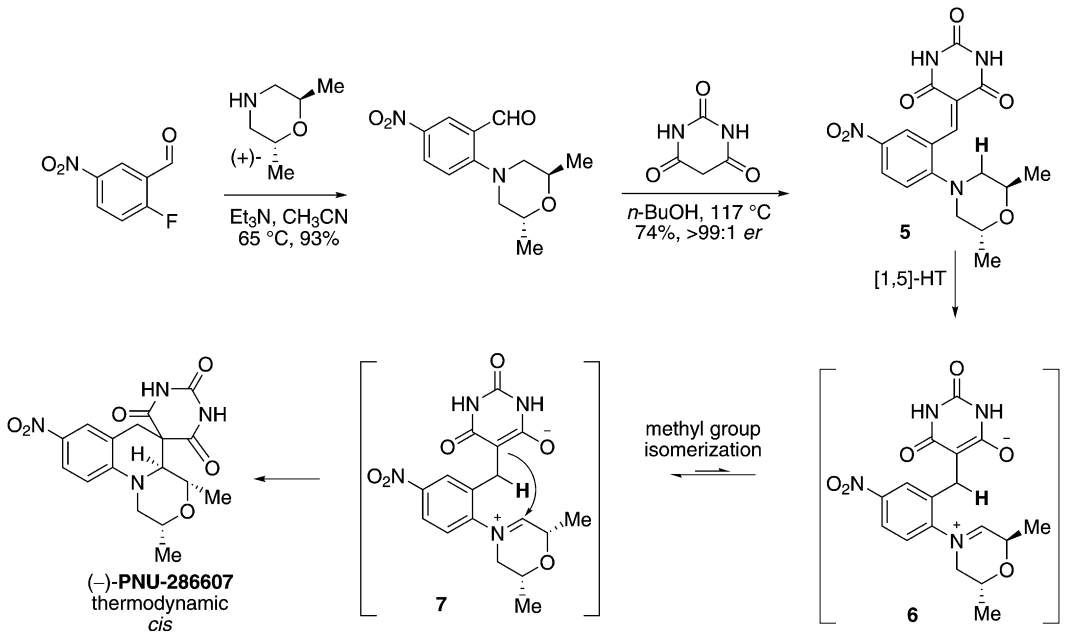
The term "*tert*-amino effect" is used to describe ring-closure of *N,N*-dialkyl-substituted anilines with an unsaturated electrophilic *ortho* substituent to afford fused tetrahydroquinolines[5] or nitrogen hetereocycles.[3a–g] The *tert*-amino effect has been widely utilized in the synthesis of pyridine, pyrimidine and pyridazine derivatives, which has been well reviewed by Mátyus and co-workers.[3e]

3.1 Benzylidenemalonates as Hydride Acceptor

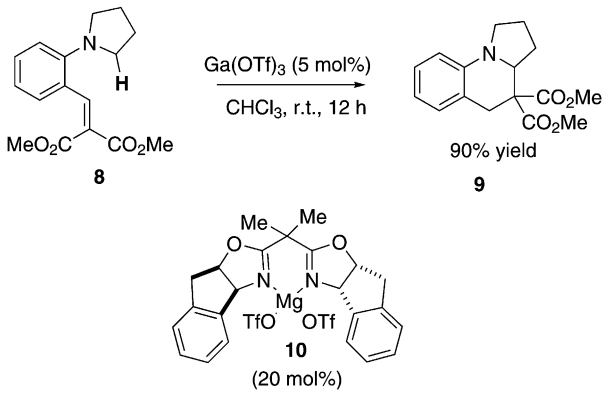
In 2009, Hurd and co-workers elegantly elaborated this methodology in the key step of a total synthesis of PNU-286607 which possesses whole cell antibacterial activity (Scheme 4).[22] The key benzylidene intermediate **5** was prepared *in situ* and [1,5]-hydride migration readily proceeded under thermal conditions to give zwitterionic intermediate **6**. With reversal of the configuration of the methyl group, the zwitterion **6** was isomerized to the thermodynamically favorable zwitterion **7**, and a subsequent intramolecular equatorial attack of the enolate on the iminium furnished *cis* (−)-PNU-286607 in 74% yield and >99:1 *er*.

For a long time, thermal or even harsher conditions were needed to overcome the high energy barrier of the [1,5]-hydride transfer/cyclization, which limited the application of this methodology. In 2009, Seidel and co-workers employed $Ga(OTf)_3$ to catalyze the cascade process of **8**, *via* which the products **9** could be furnished in 90% yield within 15 min at room temperature (Scheme 5).[23] The chiral bisoxazoline magnesium complex **10** catalyzed the asymmetric version of this reaction to furnish the product **9** in 74% yield and 30% *ee*, which represented the first report of the enantioselective cascade [1,5]-hydride transfer/cyclization.

In 2011, Akiyama and co-workers disclosed a chiral phosphoric acid **13**-catalyzed asymmetric cascade [1,5]-hydrogen transfer/cyclization of substrate **11**, affording tetrahydroquinolines **12** with good to excellent enantioselectivity (Scheme 6).[24] The benzylidenemalonate subunit forms a hydrogen bond with the proton of the phosphoric acid **13**, which not only



Scheme 4. Elegant elaboration of the cascade 1,5-HT/cyclization in the total synthesis of (−)-PNU-286607.

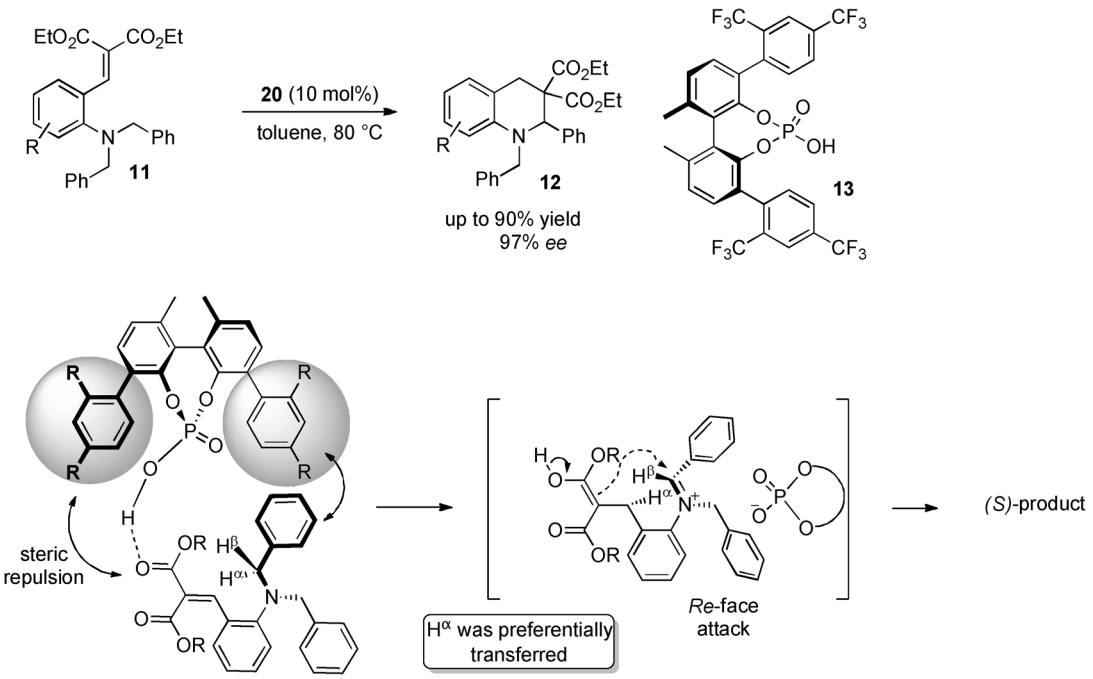


Scheme 5. Lewis acid-catalyzed formation of tetrahydroquinolines.

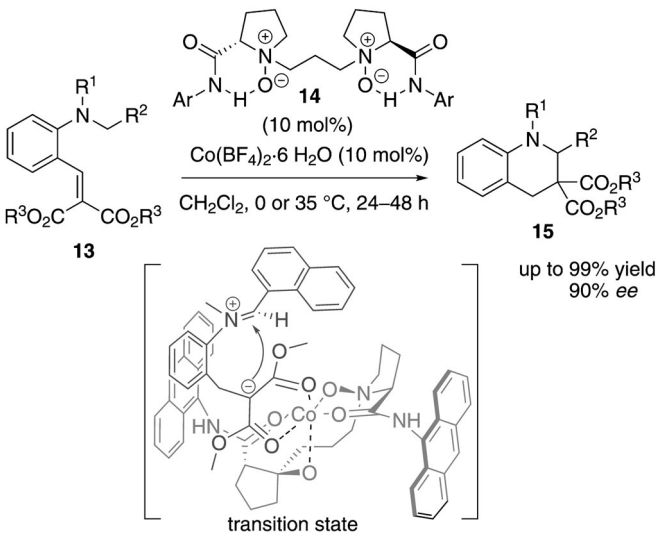
increased the electrophilicity of hydride acceptor, but also governed the asymmetric process. Akiyama and co-workers argue that the stereoselectivity is mostly controlled at the hydride shift process and the enantiotopic hydrogen is selectively activated by a chiral phosphoric acid. Due to the steric repulsion between the aromatic ring of the *N*-benzyl group and the aromatic group at the 3 or 3′ position of the catalyst, the benzyl group is located on the opposite side (β-side) relative to the aromatic ring at the 3 or 3′ position. Thus H^{β} is too far away to be transferred to the olefinic carbon and H^{α} migrates preferentially. A subsequent highly stereoselective cyclization affords (*S*)-**12** as the major enantiomer.

One more asymmetric version of cascade [1,5]-hydride transfer/cyclization was reported in 2011 by Feng and co-workers using a chiral *N*,*N*′-dioxide-Co(II) complex **14** as catalyst. The optically active tetrahydroquinolines **15** were obtained in excellent yields and high enantioselectivities (Scheme 7).[25] The central metal can bind dicarbonyl groups of substrates **13**, resulting in more electrophilic alkenes. In the proposed transition state model, the oxygen atoms of *N*,*N*′-dioxide, amide, and the benzylidenemalonate are coordinated to cobalt(II) in a hexadentate manner. The carbanion prefers to attack the *Re* face rather than the *Si* face of the iminium because the latter is strongly shielded by the nearby anthracenyl ring, resulting in the (*S*)-configured product.

In 2012, Luo and co-workers exploited an intriguing binary catalytic system involving $Mg(BF_4)_2$ and phosphoric acid **18** to facilitate the cascade reaction of **16**, affording the enantioenriched products **17** in high yields and enantioselectivities (Scheme 8).[12b] Both H^a and H^b on the isoquinoline methylene carbon atom may participate in [1,5]-hydride transfer, requiring two different helical conformations **I** and **II**. Due to the suprafacial constraint, **I** is more favorable than **II** owing to its space tolerance. The selective activation in complex **I** initiates an enantiotopic [1,5]-H^b transfer, leading to the chiral helical zwitterionic intermediate. After a small conformational change, the C–C bond can be formed spontaneously with preserved stereochemistry.



Scheme 6. Chiral phosphoric acid-catalyzed asymmetric synthesis of tetrahydroquinolines.



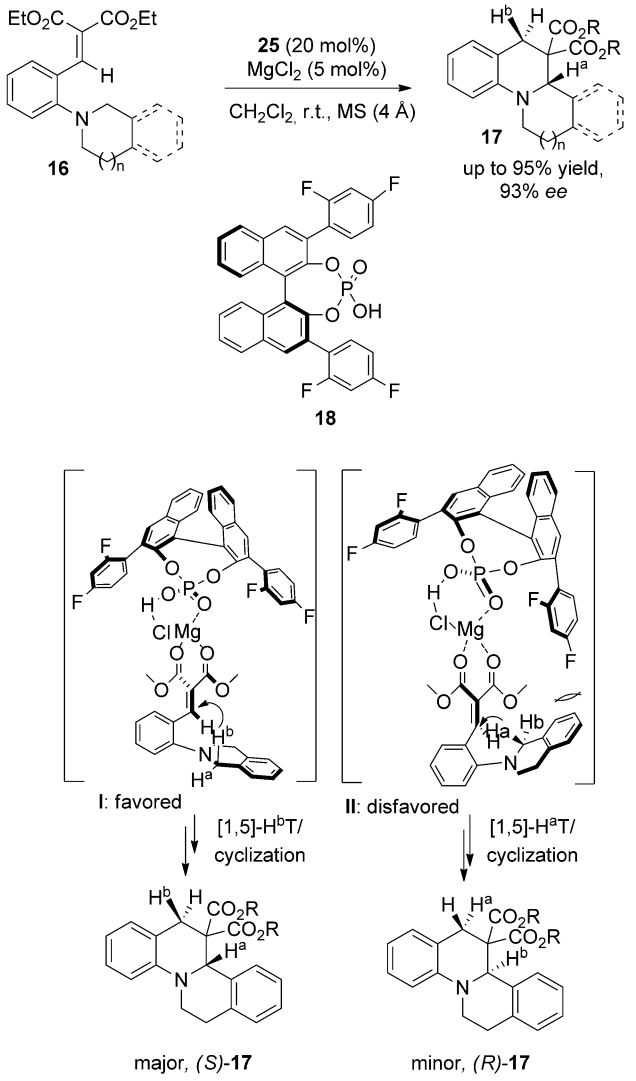
Scheme 7. Chiral complex of *N*,*N*′-dioxide and cobalt(II)-catalyzed synthesis of tetrahydroquinolines.

3.2 Activated Alkynes as Hydride Acceptor

In 2008, Barluenga and co-workers described a [1,5]-hydride transfer/cyclization process of an alkynyl Fischer carbene complexes **19**, leading to 1,2-dihydroquinolynyl carbene complexes **20** (Scheme 9).[12a] The alkyne moiety in **19** activated by electrophilic Fischer carbene is a good hydride acceptor. Theoretically, migration of hydride from the benzylic methylene to the highly electrophilic β carbon of the triple bond generates zwitterionic intermediate **I** and a subsequent cyclization leads to the new carbene complex **20** which can be further elaborated.[12a,26] The presence of the strong electron-withdrawing chromium pentacarbonyl moiety is crucial to trigger the energy-demanding [1,5]-hydride transfer. When alkynyl carbene complex **21** was heated with 4 equivalents of 1-hexyne **22**, 5,6-dihydrophenanthridine derivative **23** could be prepared.

The alkynes activated by alkynophilic metals such as platinum and ruthenium are good hydride acceptors for the cascade [1,5]-hydride transfer/cyclization process. Chatani and co-workers employed alkynophilic metal salts $PtCl_2$ and $[RuCl_2(CO)_3]_2$ to catalyze the cycloisomerization of 9-carbazolyl-substituted 1-alkyl-2-ethynylbenzene **24** to produce substituted indene **25** under mild conditions (Scheme 10).[9d] Basically, the metal-vinylidene complex **I** is formed initially *via* π-activation of the alkyne moiety, then the benzylic hydride is delivered in a [1,5]-manner to the most electrophilic α-carbon of the metal vinylidene, resulting in the formation of zwitterionic intermediate **II**. The metal carbenoid intermediate **III** generated *via* resonance of intermediate **II** undergoes 6π-electrocyclization to give intermediate **IV**. A final reductive elimination gives rise to the cyclized product **32**.

The methylene adjacent to a protected secondary amine can also be exploited as the hydride donor. In 2009 Sames and co-workers reported a PtI_4-catalyzed α-alkenylation of protected cyclic secondary amines **26** to afford the annulation products **27** (Scheme 11).[9c] Because of the electron-withdrawing nature of carbamates, electron density on the nitrogen

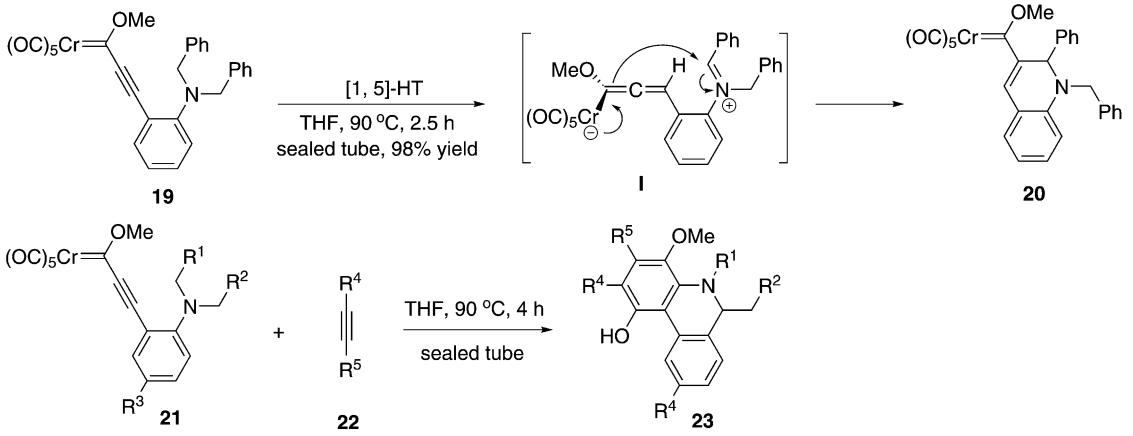


Scheme 8. Catalytic enantioselective *tert*-amino cyclization by asymmetric binary acid catalysis.

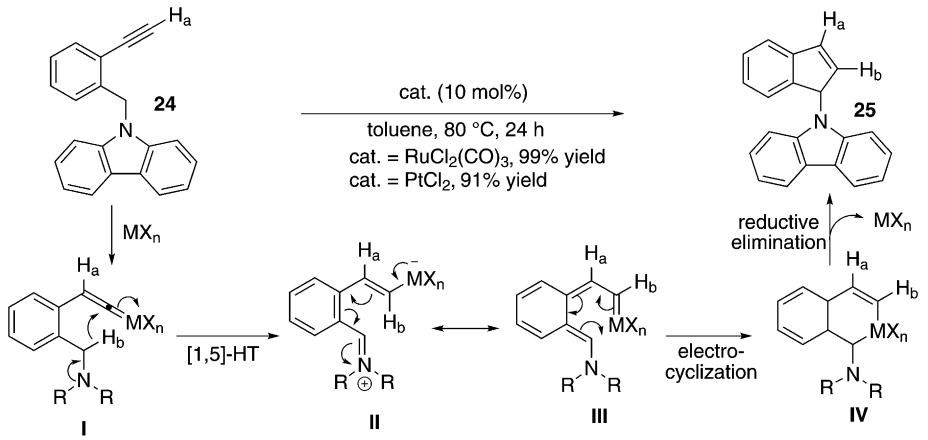
atom was decreased, resulting in comparative difficulty in forming an alkoxycarbonyl-iminium intermediate which is less stable than that generated from a *tert*-amine. Spirocyclization products **29** could also be furnished in good yield *via* the cascade protocol if the terminal alkyne was substituted at C-2 of cyclic amine **28**. Theoretically, the platinum vinylidene **I** is formed *via* π-activation of the alkyne moiety, followed by [1,6]-hydride transfer through space to afford intermediate **II**, in which the nucleophilic vinyl-platinum attacks the electrophilic alkoxycarbonyl-iminium to give the intermediate **III**. A final platinum salt elimination gives rise to the fused products **27** or **29**.

In 2011, Liang and co-workers described a palladium-catalyzed cascade [1,5]-hydrogen transfer/cyclization involving propargylic esters **30** to construct substituted naphthylamines **31** (Scheme 12).[13a] Notably, propargylic esters with electron-rich aryl groups which led to electron-rich allenyl-palladium at the propargylic position always gave better yields than the ones with electron-withdrawing substituents and the electron-withdrawing acyl or sulfonyl group on the nitrogen was crucial to the reaction. These clues indicate that the hydrogen is abstracted in a [1,5]-manner by nucleophilic allenyl-palladium in the form of a proton. Mechanistically, the nucleophilic allenyl-palladium intermediate **II** is generated from the propargylic compound **I** under the catalysis of Pd(0), then [1,5]-proton transfer affords the intermediate **III**, the direct 6π-electrocyclic ring closure (ERC) of which leads to the intermediate **IV**. Afterwards, **IV** undergoes [1,3]-H shift and hydrogen elimination to afford the final product **31** (path **A**). Alternatively, the intermediate **VI** may also be formed after a [1,3]-palladium shift of the intermediate **III**. The following insertion of the C–Pd bond and hydrogen elimination afford the product **31** (path **B**).

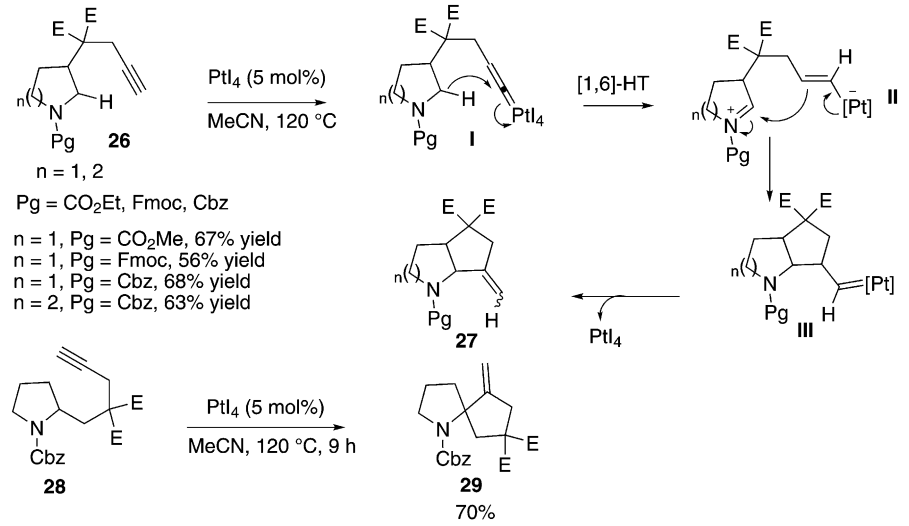
In 2012, the same group reported a $PtCl_2$-catalyzed hydro-functionalization reaction of allenes formed *in*



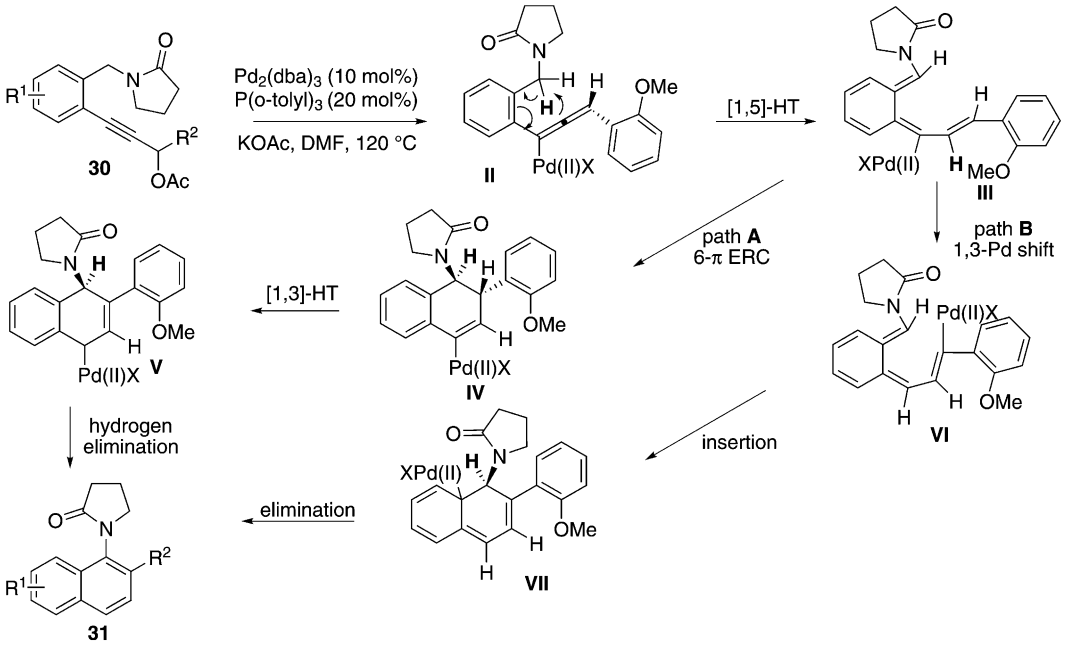
Scheme 9. Synthesis of 1,2-dihydroquinolinyl carbene complexes *via* [1,5]-HT/cyclizations.



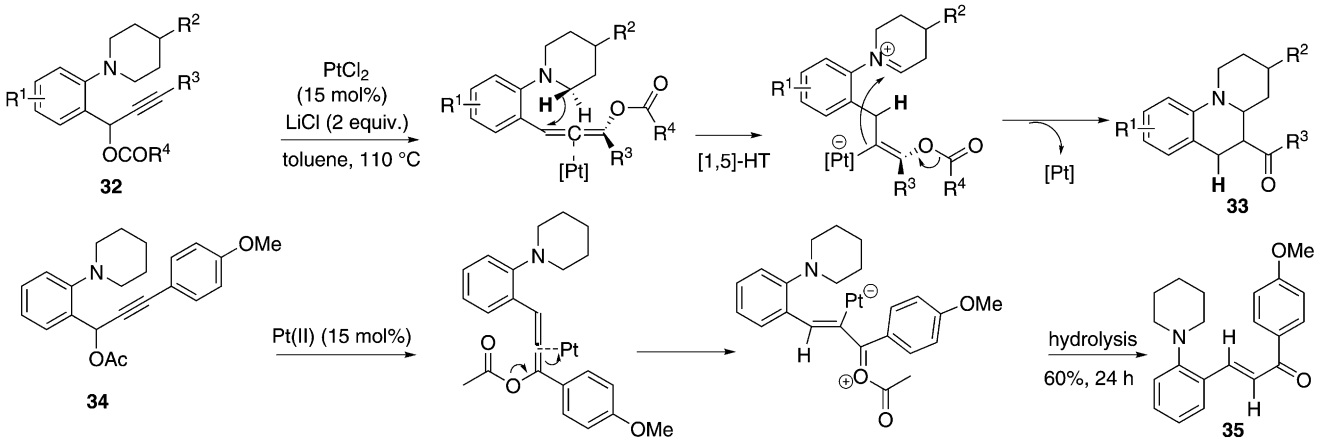
Scheme 10. Platinum- and ruthenium-catalyzed cycloisomerization of 1-alkyl-2-ethynylbenzenes.



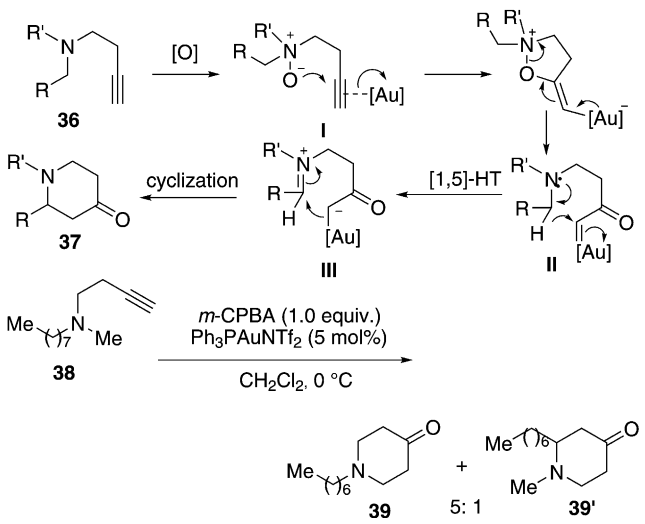
Scheme 11. Platinum-catalyzed *N*-alkenylation *via* [1,6]-HT/cyclization.



Scheme 12. Palladium-catalyzed [1,5]-proton migration of propargylic esters toward substituent naphthylamines.



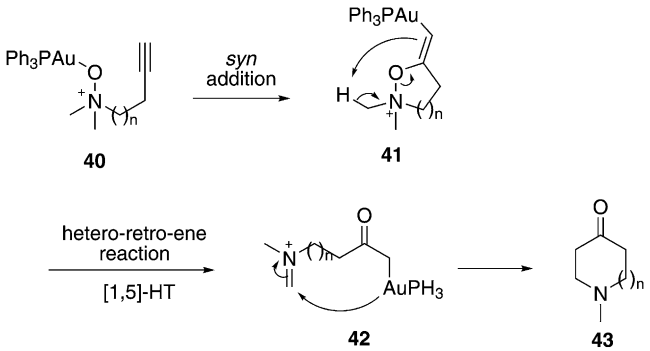
Scheme 13. Platinum-catalyzed synthesis of ring-fused tetrahydroquinolines.



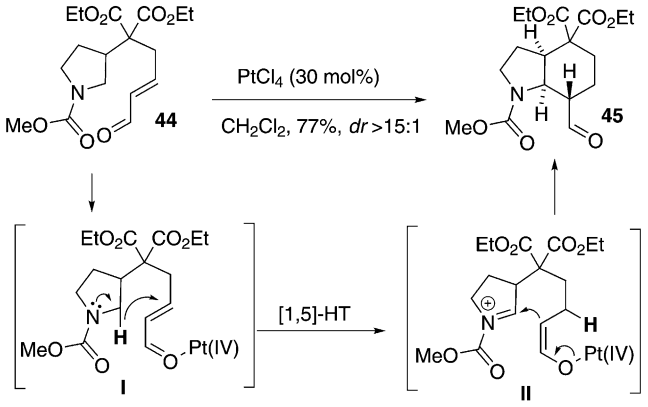
Scheme 14. Formal [4+2] approach toward piperidin-4-ones *via* Au catalysis.

situ from propargylic esters **32**, furnishing multi-functionalized tetrahydroquinoline **33** (Scheme 13).[9f] If R^3 is an electron-withdrawing group, the formation of products **33** is favored. Mechanistically, hydride is delivered initially to the C-1 carbon of platinum-activated allene intermediate **I** formed *via* platinum-catalyzed [1,3]-OAc migration. The resulting vinyl-platinum species **II** then attacks the iminium to furnish the ring fused tetrahydroquinoline **33**. A completely different transformation occurred in the case of propargylic ester **34** bearing a strong electron-donating, 4-$MeOC_6H_5$ group, as R^3 and an α,β-unsaturated ketone **35** was formed, suggesting that in this case the electron-donating 4-$MeOC_6H_5$ group in R^3 decreases the electrophilicity of C-1, thus the hydration of allene will be preferential over the [1,5]-hydride shift.

Zhang and co-workers reported an efficient synthesis of piperidin-4-ones based on gold-catalyzed intramolecular alkyne oxidation in 2009 (Scheme 14).[16a] One-pot sequential *m*-CPBA oxidation and gold catalysis with $Ph_3PAuNTf_2$ led to an excellent yield of piperidin-4-one **37**. This chemistry allowed the facile preparation of 5-, 6- and 7-membered ring-fused or spiro-piperidin-4-ones. Initially, Zhang et al. speculated that tertiary aliphatic amine *N*-oxide **I** which was readily generated from tertiary amine **36** might undergo gold-catalyzed intramolecular alkyne oxidation,[27] leading to α-oxo gold carbene **II**; the α-hydride in **II** could migrate to the electrophilic gold carbene, leading to zwitterion **III** containing an electrophilic iminium and a nucleophilic gold enolate. A subsequent intramolecular cyclization led to the piperidin-4-one **37**. Notably, the less-substituted methyl in amine **38** was preferentially involved in the ring formation with serviceable regioselectivities (5:1). In all the substrates whose *tert*-amine moieties are unsymmetrical, the chemistry behavior of the hydrogen donor was rather unusual: the poor hydride donors are more active than good hydride donors, for example, methyl > methylene and benzylic methylene, methylene > methine, electron-rich benzylic methylene ≈ electron-deficient benzylic methylene. Although the proposed mechanism could account for the formation of product **39** and **39′**, it failed to explain the regiose-



Scheme 15. Mechanism of Au(I)-catalyzed rearrangements of acetylenic amine *N*-oxides.



Scheme 16. $PtCl_4$-catalyzed hydroalkylation of α,β-unsaturated aldehydes.

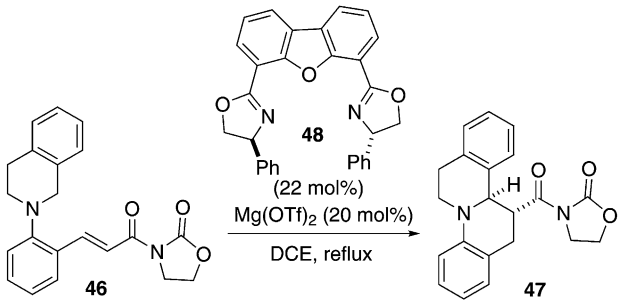
lectivity. Thus the initially proposed mechanism of [1,5]-hydride transfer/cyclization is quite questionable.

In 2012, based on DFT calculations and a variety of experiments, Zhang and Houk et al. argued that the mechanism involving the sequential ring opening and [1,5]-proton shift is energetically more favorable (Scheme 15).[16b] The first step is the *syn* addition of the gold-coordinated *N*-oxide **40** to alkyne, resulting in the formation of intermediate **41** which undergoes the hetero-retro-ene ([1,5]-proton **s**hift) to furnish intermediate **42**, thus the formation of gold-carbenoid intermediate **III** is avoided altogether. The final step is the cyclization of **42** to yield the piperidin-4-one derivatives **43** and regeneration of the catalyst, which was calculated to be the rate-determining step. In **41**, the phosphine ligand makes the adjacent carbon more nucleophilic, thus proton transfer is favored and the proton is abstracted from the least sterically hindered amine substituent.

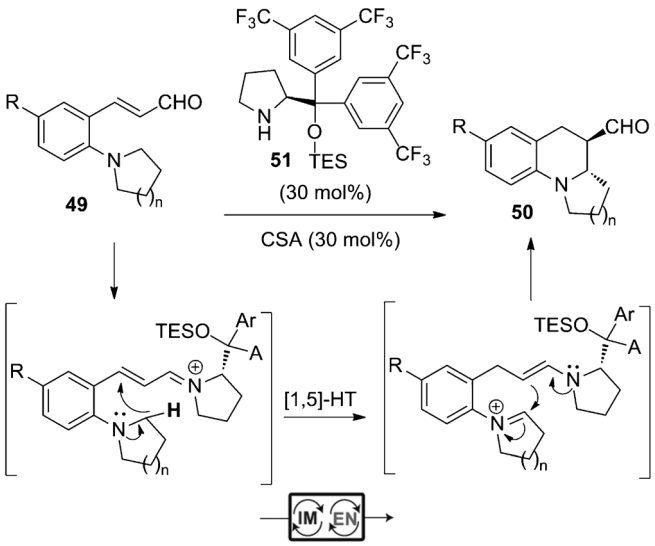
3.3 α,β-Unsaturated Aldehydes and Acyloxazolidinones as Hydride Acceptor

In 2005, Sames and co-workers reported a $PtCl_4$-catalyzed α-alkylation of protected pyrrolidine **44**, furnishing the fused cycles **45** in good yield and high diastereoselectivity ($dr > 15:1$) (Scheme 16).[28] Notably, the malonate moiety in the substrate **44** can increase the conformational rigidity of the substrate **44**, resulting in a more reactive hydride acceptor.[29] Because the electron-withdrawing nature of carbamates could destabilize the corresponding iminium **II** and the secondary C–H bond is a less reactive hydride donor than a tertiary C–H bond, a large amount of highly active $PtCl_4$ (30 mol%) was necessary to activate the hydride acceptor.

In 2009, Seidel and co-workers exploited the complex of $Mg(OTf)_2$ and chiral bisoxazoline **48** to catalyze the cascade reaction of substrates **46** carrying



Scheme 17. Chiral Mg complex-catalyzed intramolecular redox reactions *via* [1,5]-HT/cyclization.

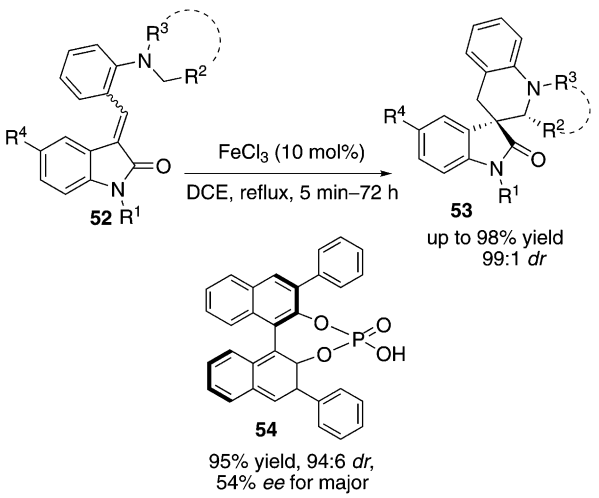


Scheme 18. Organocatalyzed enantioselective C–H bond functionalization *via* cascade [1,5]-HT/ring closure.

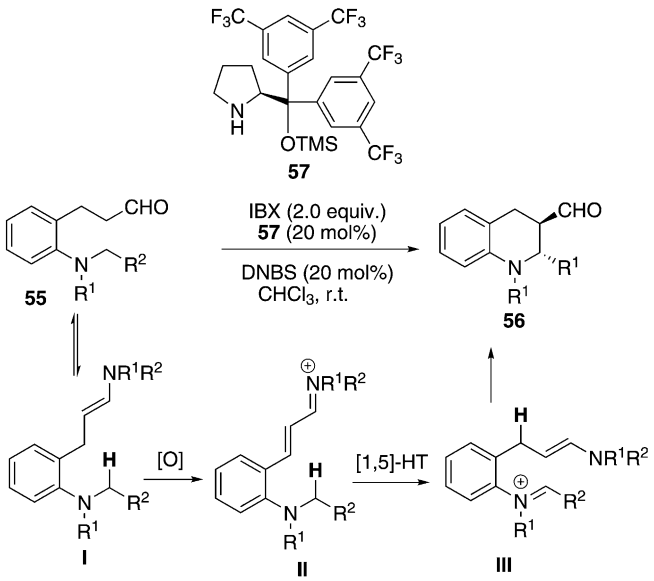
α,β-unsaturated acyloxazolidinone, producing chiral tetrahydroquinolines **47** in good yields and high enantioselectivities (Scheme 17).[30] The use of nickel perchlorate in combination with ligand **48** also led to the formation of **47** in good diastereo- and enantioselectivity.

In 2010, Kim and co-workers utilized the Jørgensen catalyst **51** successfully to catalyze the cascade [1,5]-hydride transfer/ring closure sequences of *ortho*-*N*-pyrrolidinyl-substituted cinnamaldehydes **49** *via* sequential iminium and enamine activation, affording chiral tetrahydroquinolines **50** in high enantioselectivities (Scheme 18).[31] Products which incorporated 7- to 9-membered azacycles could also be formed with excellent enantioselectivities.

In 2012, Yuan and co-workers reported an $FeCl_3$-catalyzed stereoselective cascade [1,5]-hydride transfer/ring closure of **52**, furnishing structurally diverse spirocyclic oxindole tetrahydroquinolines **53** in high yields and good diastereoselectivities (Scheme 19).[32] The asymmetric reaction could be catalyzed by chiral phosphoric acid **54** (20 mol%) and the enantioen-



Scheme 19. $FeCl_3$-catalyzed synthesis of spirooxindole tetrahydroquinolines.



Scheme 20. Cascade organocatalytic oxidative enamine catalysis/[1,5]-HT/cyclization sequences.

riched tetrahydroquinoline could be achieved in 95% yield, 94:6 *dr* and 54% *ee* ($R^1 = CO_2Et$, R^2, R^3 = butylene, $R^4 = H$).

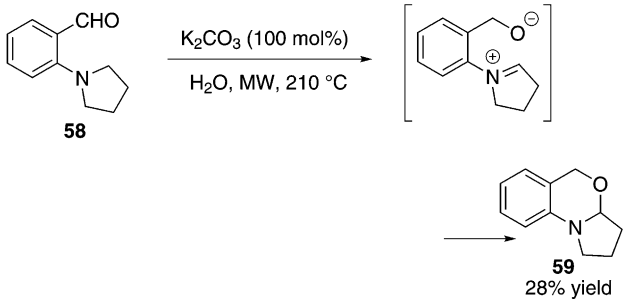
In 2013, Kim and co-workers disclosed a Jørgensen catalyst **57**-catalyzed enantioselective 3-step cascade reaction of substrate **55** involving enamine oxidation/[1,5]-hydride transfer/ring closure, which furnished ring-fused tetrahydroquinolines **56** in moderate yields, moderate to high diastereoselectivities and excellent enantioselectivities (Scheme 20).[33] Basically, enamine **I** is converted to iminium ion **II** under oxidative conditions,[34] afterwards the nucleophilic enamine generated after hydride migration is trapped by the electrophilic iminium before it is reoxidized to iminium ion, resulting in the enantioenriched product **56**.

3.4 Saturated Aldehydes and Imines as Hydride Acceptor

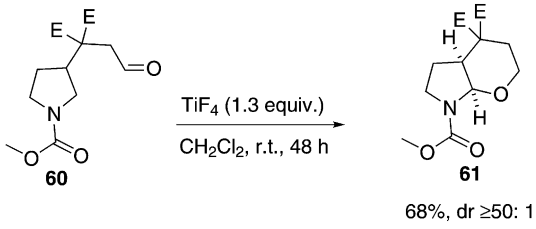
The C–H bond can be functionalized not only into a C–C bond, but also into a C–O bond and a C–N bond *via* cascade reactions. In 2004, Mátyus and co-workers reported a microwave-assisted synthesis of tricyclic angularly annulated aminal **59** from *ortho*-dialkylaminobenzaldehdyde **58** with H_2O as solvent (Scheme 21).[35] The transformation was accomplished at 210 °C for 50 min and stoichiometric K_2CO_3 was exploited, resulting in the formation of aminal **59** in low yield. According to the report by Maulide and co-workers, Lewis acidic condition should be beneficial to the yield of the transformation[36] which was not investigated in Mátyus' report.

Sames and co-workers reported a highly active TiF_4-catalyzed intramolecular hydro-*O*-alkylation of aldehyde substrate **60** in 2005 (Scheme 22), *via* which the N-protected pyrrolidine substrate **60** was transformed into the *cis*-fused bicyclic aminal **61** as a single diastereomer.[9a] Because of the electron-withdrawing nature of carbamate and the lesser activity of the secondary C–H bond, the reaction was promoted by highly active and oxophilic TiF_4 (1.3 equiv.) at 50 °C, resulting in the formation of fused aminal in 68% yield and good disastereoselectivity (≥50:1).

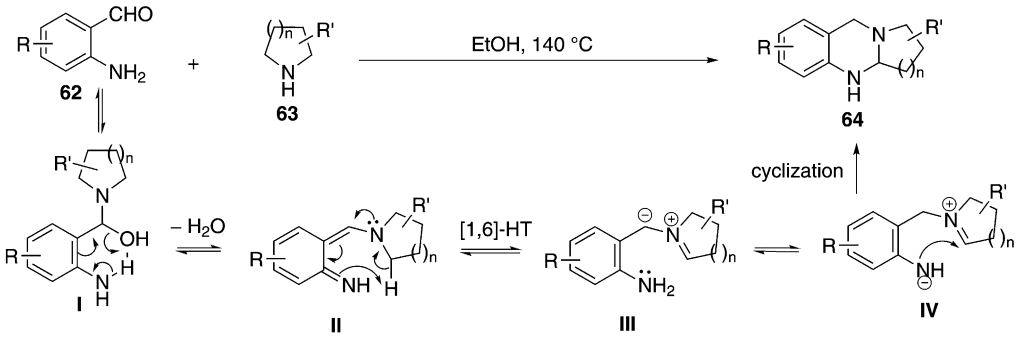
In 2008, Seidel and co-workers reported a metal-free one-pot α-amination of cyclic secondary amines **63** with 2-aminobenzaldehyde **62**, efficiently furnishing ring-fused aminal **64** in good yields (Scheme 23).[17a,b,c] Both the electronic structure and



Scheme 21. Microwave-assisted synthesis of tetrahydroquinoline applying the *tert*-amino effect.



Scheme 22. TiF_4-catalyzed hydro-*O*-alkylation of aldehydes *via* cascade [1,5]-HT/cyclization.



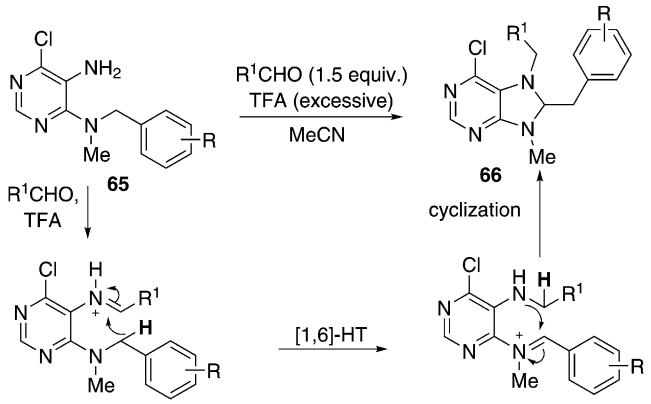
Scheme 23. Synthesis of ring-fused aminals *via* cascade [1,6]-proton transfer/cyclization.

the geometry of the amines have profound effects on reactivities and yields. *Via* an extensive exploration of possible pathways using DFT calculations based on the original experimental results, Seidel and Houk proposed an unusual mechanism involving cascade [1,5]-proton transfer/cyclization.[17c] Initially the aminobenzaldehye reacts with secondary amine **63** to furnish hemiaminal **I** which undergoes subsequent dehydration to give quinoidal intermediates **II**. The nucleophilic imine abstracts a proton from the methylene adjacent to the *tert*-amine ([1,6]-proton shift), resulting in azomethine ylide **III** which is rapidly protonated by ethanol. A subsequent deprotonation of the primary amino moiety by the coordinated ethoxide furnishs **IV**. Finally ring-fused aminal **64** is formed by intramolecular nucleophilic attack. Dang and Bai et al. also reported a similar cascade process in 2008 for preparation of tetrahydropyrimido[4,5-*d*]pyrimidine.[37] In 2008, the same group reported a trifluoroacetic acid-catalyzed cascade [1,6]-hydride transfer/cyclization of **65** to synthesize 7,8,9-trisubstituted dihydropurine derivatives **66** (Scheme 24).[19c] TFA plays two roles in this process: (i) promotion of imine formation and (ii) acceleration of the hydride shift process. Meth-Cohn and Volochnyuk et al. reported similar reactions in 1967[19a] and 2007, respectively.[19b]

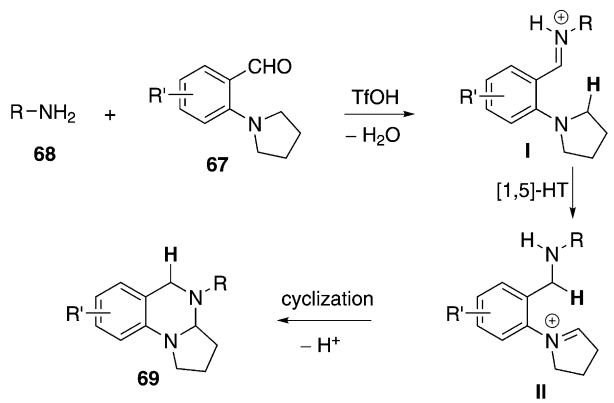
In 2009 Seidel and co-workers described a TfOH-catalyzed one-pot synthesis of aminals **69** from *ortho*-aminobenzaldehydes **67** and primary aromatic or aliphatic amines **68** (Scheme 25).[38] The protonated imine **I** worked as the hydride acceptor. Almost at the same time, Akiyama and co-workers reported a similar catalytic approach to synthesize quinazolines by exploiting the *tert*-amino effect and $TsOH{\cdot}H_2O$ was shown to be the best catalyst.[39]

In 2011 Gong and co-workers reported a chiral Brønsted acid **73**-catalyzed asymmetric cascade [1,5]-hydride transfer/cyclization of 2-pyrrolidinyl phenyl keto esters **70** with anilines **71** to produce the enantioenriched cyclic aminals **72** (Scheme 26).[40] Theoretically, this reaction proceeds initially through the condensation of *ortho*-aminobenzo ketone **70** with aniline **71** in the presence of **73** to generate iminium intermediate **I**, which undergoes an asymmetric [1,5]-hydride shift followed by ring closure to give enantioenriched **72**.

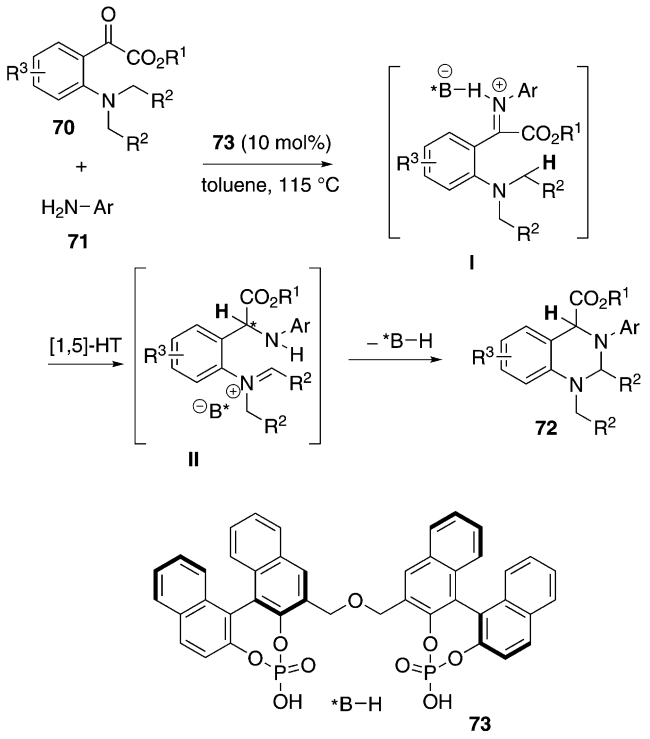
In 2012, Maulide and co-workers described a $Sc(OTf)_3$-catalyzed one-pot C–H functionalization of cyclic tertiary amines **74**, in which the sacrificial reduction of a neighboring carboxaldehyde group directed the addition of Grignard reagents and lithium alkynyltrifluoroborates to the α-position of the amine



Scheme 24. Synthesis of 7,8,9-trisubstituted dihydropurine derivatives *via tert*-amino effect cyclization.



Scheme 25. Synthesis of cyclic aminals *via* cascade 1,5-hydride transfer/cyclization.



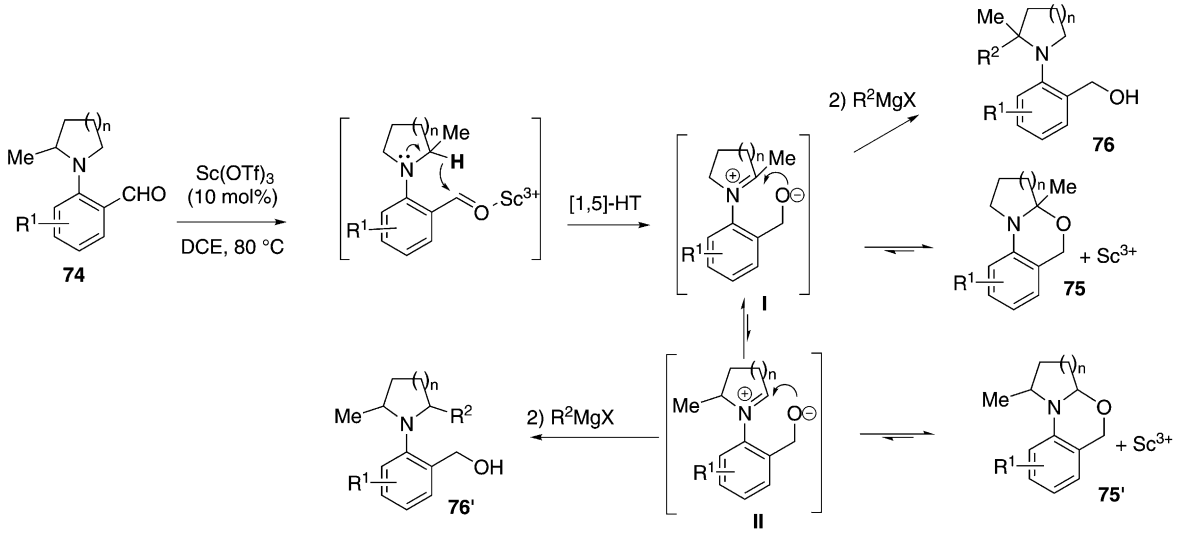
Scheme 26. Asymmetric sp^3 C–H functionalization *via* a chiral Brønsted acid-catalyzed redox reaction.

moiety, resulting in the formation of the corresponding α-functionalized products **76** and **76′** bearing a wide range of appendages in good to excellent yields. (Scheme 27).[36] Basically, the formation of **75**/**75′** from **74** is under thermodynamic control, with **75** being the thermodynamically favored product; the aminals **75** and **75'** are comparatively unstable species which can be reversed to intermediate **I** and **II**, thus there exists an equilibrium for interconversion between **75** and **75′**. The more favorable iminium intermediate **I** (stabilized by more substituents) and less favorable iminium intermediate **II** can be trapped by more nucleophilic reagents, leading to the final stable products **76** and **76′,** respectively.

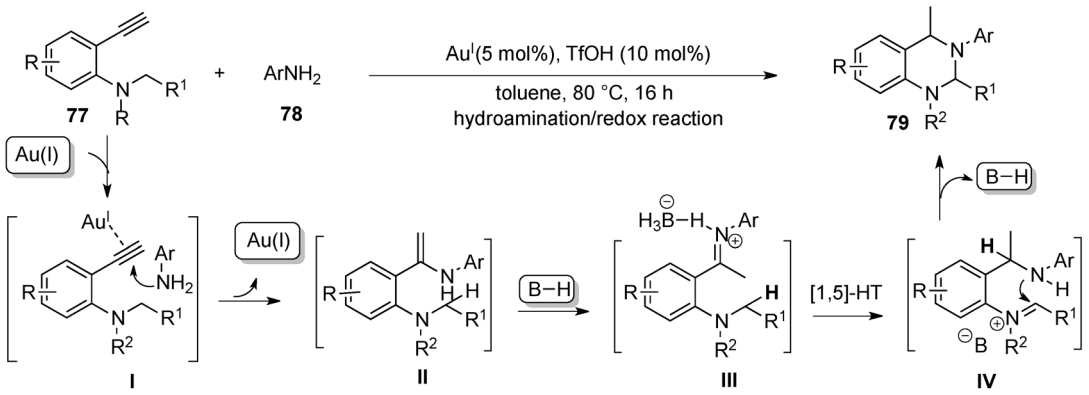
In 2013, Gong and co-workers disclosed a catalytic domino hydroamination/redox reaction which could directly assemble the tertiary amine-substituted 3-en-1-yne derivatives **77** and various amines **78** into cyclic aminals **79** in excellent yields and moderate to high diastereoselectivities by using the combination of gold(I) complex and TfOH (Scheme 28).[41] Theoretically, the terminal alkyne **77** undergoes gold(I)-catalyzed intermolecular hydroamination of aniline **78** to give imine intermediate **II** which is protonated by Brønsted acid to give an electrophilic iminium species **III**; this intermediate then undergoes a subsequent [1,5]-hydride transfer to generate a transient intermediate **IV** which ultimately suffers an intramolecular nucleophilic attack to afford **79**. The asymmetric version could be facilitated by overstoichiometric chiral phosphoric acid and 5 mol% $Ph_3PAuNTf_2$, giving rise to enantioenriched **79** in high yield and excellent enantioselectivity.

3.5 Metal Carbenoids as Hydride Acceptor

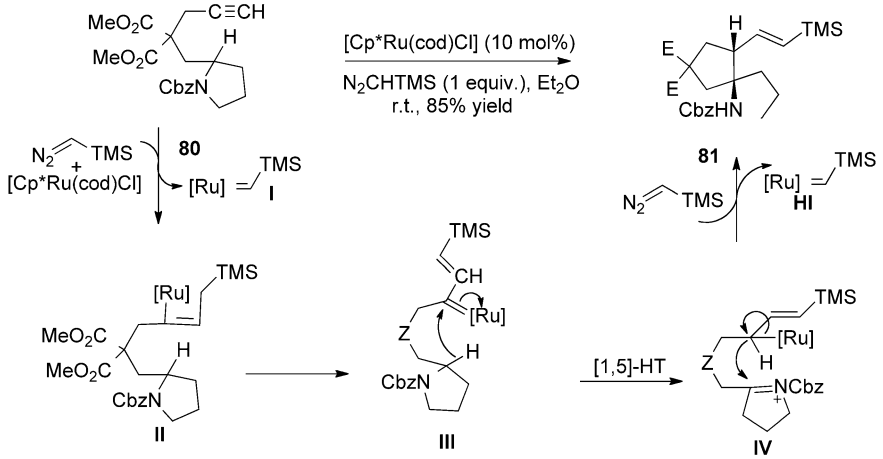
In 2012, Saa and co-workers elegantly demonstrated a [Cp*Ru(cod)Cl]-catalyzed cyclization of protected alkynylpyrrolidine **80**, furnishing 1-azaspiro[4,4]-nonane **81** carrying the versatile TMS moiety as a single diastereomer in rather good yield (Scheme 29).[19f] Mechanistically, the complex [Cp*Ru(cod)Cl] reacts with N_2CHTMS to furnish ruthenium carbenoid **I** which undergoes oxidative coupling with **80** to give metallacyclobutene **II**. A sub-



Scheme 27. $Sc(OTf)_3$-catalyzed intramolecular redox-triggered C–H functionalization.



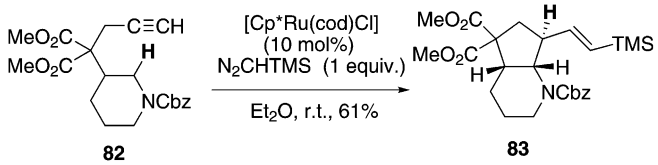
Scheme 28. Catalytic enantioselective *tert*-aminocyclization by asymmetric binary acid catalysis.



Scheme 29. Intramolecular α-alkylation of C-2 linked pyrrolidine by catalytic ruthenium carbene insertion.

sequent ring opening of **II** leads to the electrophilic Ru-vinyl carbene **III** which suffers [1,5]-hydride shift to furnish intermediate **IV**. Ultimately an intramolecular nucleophilic attack of alkyl ruthenium gives rise to the spiro compound **81**.

The C-3 linked piperidine **82** was also readily cyclized under the optimal conditions with less reactive secondary C–H bonds α to protected secondary amine as the hydride donor, furnishing the fused bicyclic piperidine **83** in good yields (Scheme 30).

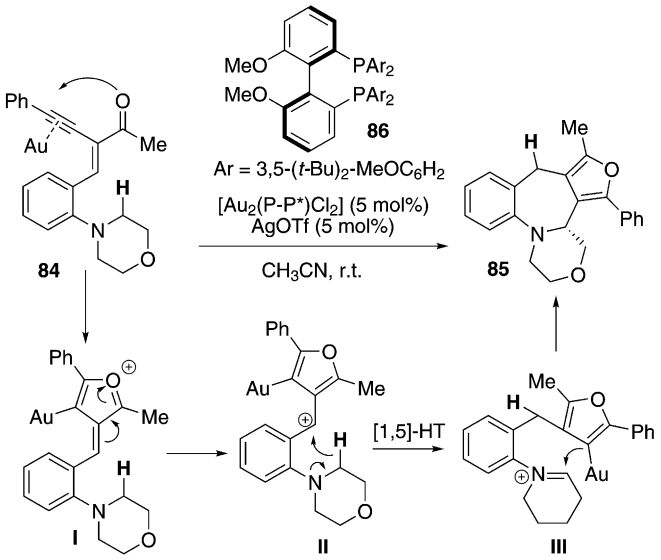


Scheme 30. Intramolecular α-alkylation of C-3 linked pyrrolidine by catalytic ruthenium carbene insertion.

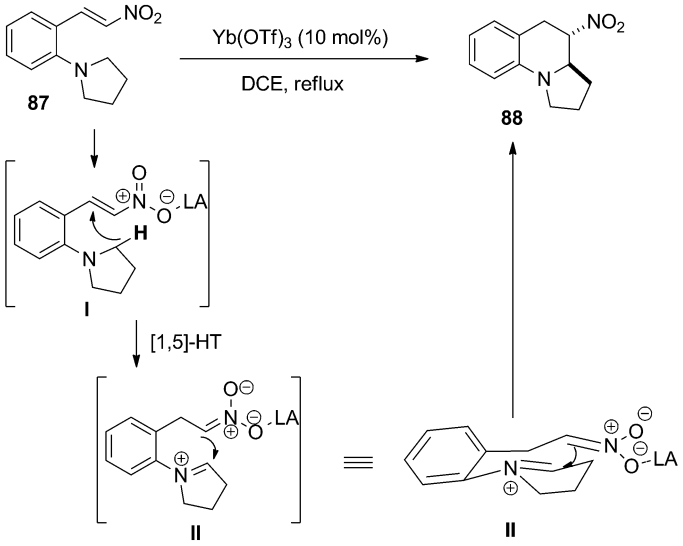
3.6 Other Electrophiles as Hydride Acceptor

In 2010 Zhang and co-workers reported an enantioselective catalytic intramolecular redox reaction of yneenones **84** in the presence of an Au(I) catalyst and chiral ligand **86**, affording 7-membered tetrahydroazepines **85** in high yield and with high to excellent enantioselectivity. (Scheme 31).[9e,20a] Compared with the relatively inactive C–H bond α to a *tert*-amine, the oxygen of a carbonyl is more nucleophilic and ready to attack the electrophilic alkyne activated by Au(I) catalyst. Basically, the alkynophilic Au(I) catalyst triggers a heterocyclization (first cyclization) by activation of the alkyne to generate the furanyl intermediate **II** involving a reactive carbocation which is exploited as hydride acceptor; a subsequent [1,5]-hydride shift leads to the intermediate **III** and ring closure ensues (second cyclization) to produce polycyclic tetrahydroazepines **85**.

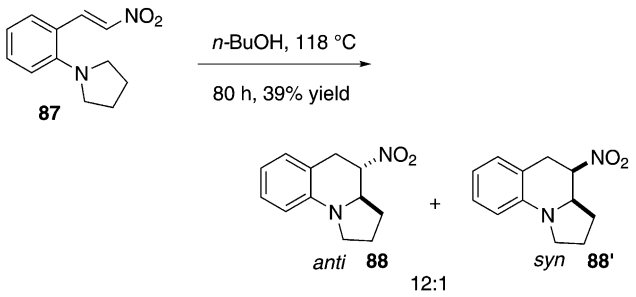
The nitroalkene is a versatile electron-deficient olefin and might be exploited as the hydride acceptor as well. In 2008, the cascade process was investigated by Jordis and co-workers with (*E*)-1-[2-(2-nitrovinyl)-



Scheme 31. Enantioselective Au-catalyzed selective formation of ring-fused tetrahydroazepines.



Scheme 33. Lewis acid-catalyzed synthesis of nitro-substituted tetrahydroquinolined *via* [1,5]-HT/cyclization.



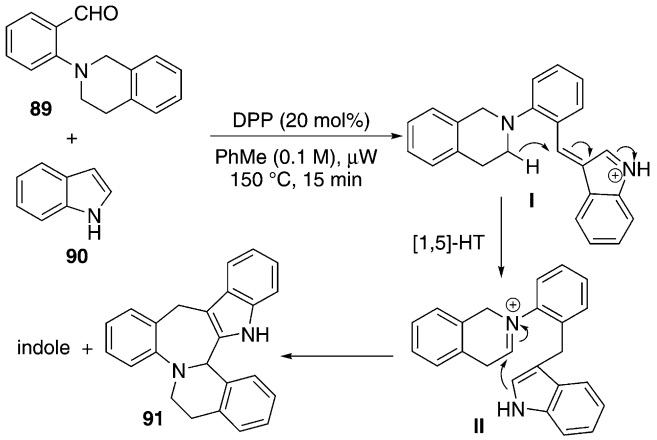
Scheme 32. Synthesis of nitro-substituted tetrahydroquinolines *via* [1,5]-HT/cyclization under thermal conditions.

phenyl]pyrrolidine **87** as the substrate (Scheme 32).[42] This transformation could be accomplished under thermal conditions (118 °C) in 80 h, leading to the cyclized product **88** and **88′** in 39% yield (*syn/anti* = 12:1).

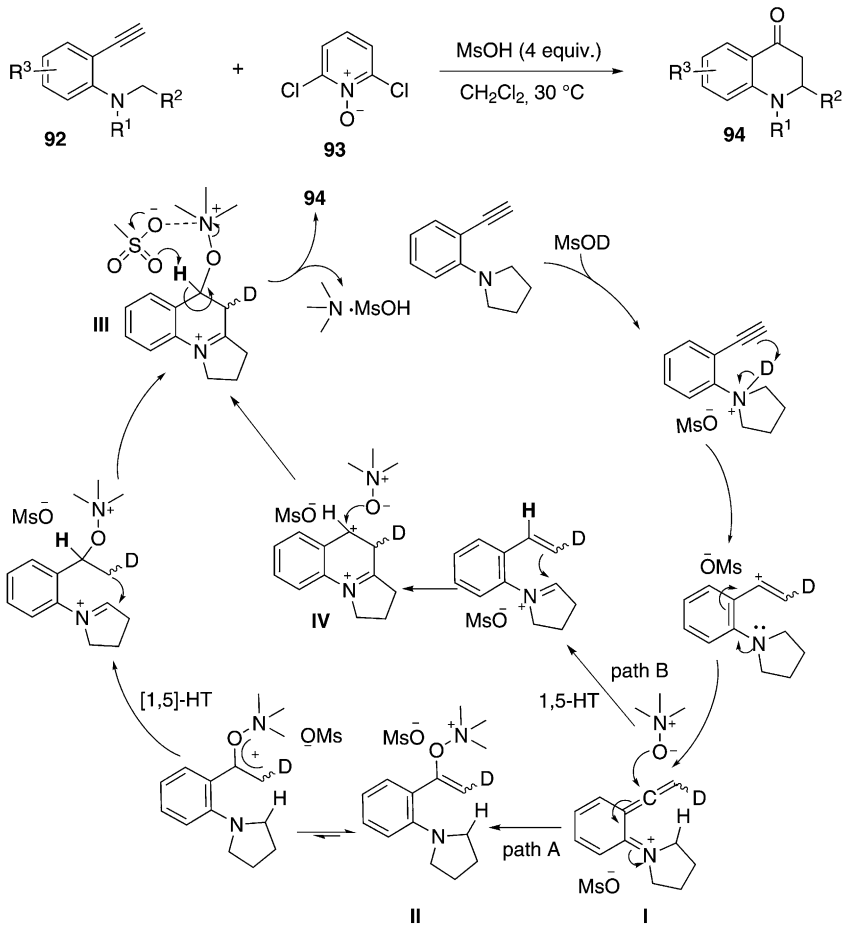
The nitroalkene could also be activated by Lewis acids, for example, $Sc(OTf)_3$, $Yb(OTf)_3$, $Zn(OTf)_2$ to increase its electrophilicity. According to unpublished results of the Pfaltz group, the cascade process could be facilitated by $Yb(OTf)_3$ and the cyclized product **88** could be furnished in 60% yield at 80 °C within 12 h (Scheme 33). The transformation was diastereospecific and only the *anti* diastereomer was observed. The diastereoselectivtiy can be explained through Traxler–Zimmer transition state **II** in which the orientation of substituents would be pseudo-equatorial, leading to the *anti*-product *via* intramolecular nucleophilic attack.

In 2011, Seidel and co-workers reported a diphenyl phosphate (DPP)-catalyzed cascade [1,5]-hydride shift/cyclization with the doubly nucleophilic indole **90** and aminobenzaldehydes **89** as substrates, ultimately giving rise to 7-membered rings **91** in good to excellent yields. (Scheme 34).[20b] Mechanistically, the acid-catalyzed reaction of aldehyde **89** with indole **90** initially furnishes the electrophilic vinylogous iminium **I**. A subsequent intramolecular [1,5]-hydride transfer leads to the electrophilic iminium **II** which traps the nucleophilic C-2 of indole, giving rise to the product **91**.

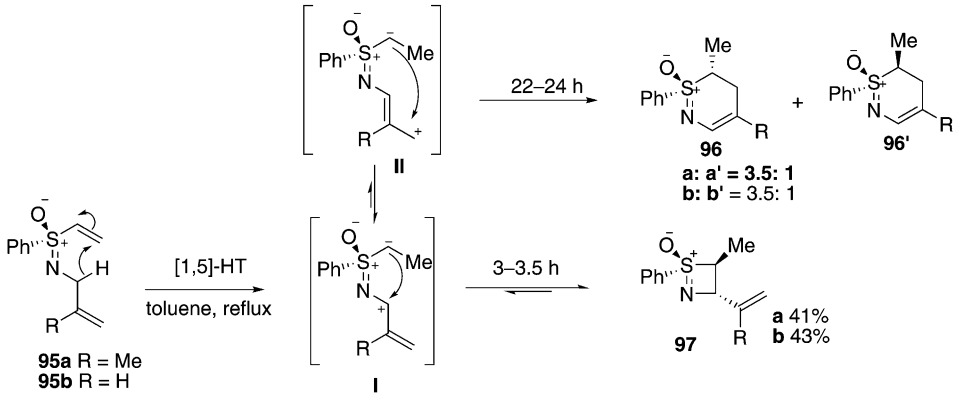
In 2012, Gong and co-workers discovered an MsOH-catalyzed cascade oxidation/C(sp^3)–H functionalization of unactivated terminal alkynes **92** with **93** as the oxidant, yielding 2,3-dihydroquinolin-4(1*H*)-ones **94** (Scheme 35).[43] Mechanistically, the nucleophilic nitrogen atom initially captures a proton which is delivered to the alkyne subsequently. Intermediate **I** is formed by dearomatization of the styrene cation.



Scheme 34. Brønsted acid-catalyzed redox-neutral indole annulation cascades.



Scheme 35. Metal-free oxidation/C(sp^3)–H functionalization of unactivated alkynes.

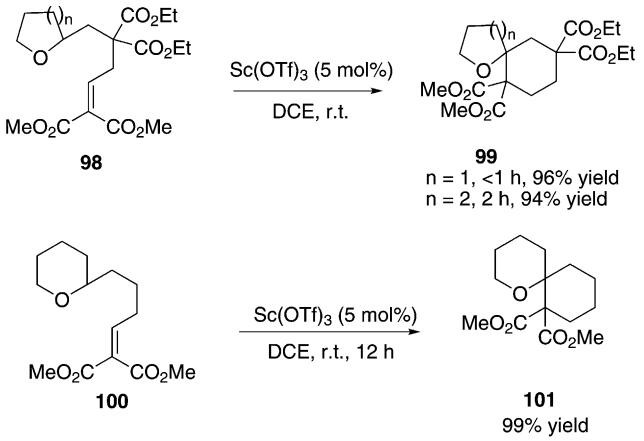


Scheme 36. C–H activation in *S*-alkenyl sulfoximines.

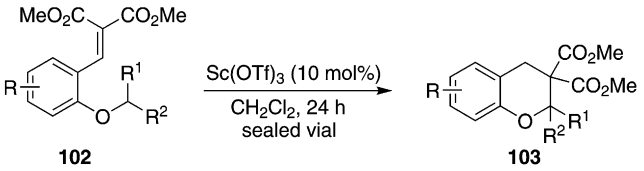
Afterwards two possible pathways can rationalize the formation of the final products. In path **A**, the nucleophilic attack of pyridine *N*-oxide onto intermediate **I** generates enolate **II**, which undergoes a subsequent [1,5]-hydride transfer/ring-closure process and the process is probably promoted by delocalization of **II**. In a final intermediate **III**, the interaction between methanesulfonic anion and pyridine cation facilitates C–H and N–O bond cleavage. In path **B**, the hydride of intermediate **I** migrates preferentially, which is followed by cyclization and nucleophilic attack of pyridine *N*-oxide onto benzylic cation **IV**, resulting in the formation of intermediate **III**.

In 2012, Harmata and co-workers discovered an intramolecular redox C–H activation process of alkenyl sulfoximines (**95**) to synthesize 4- and 6-membered

heterocycles **97** and **96** (Scheme 36).[44] The terminal alkene activated by sulfoximines worked as a hydride acceptor and the allylic C–H bond was exploited as hydride donor. Notably, the reaction time strongly influenced the formation of the final products. When **95** was refluxed in toluene for 3.5 h, the 4-membered cyclic species **97** could be obtained in 41% yield as the major product; whereas if the reaction was refluxed for around 24 h, 6-membered thiazines **96** were isolated as a mixture of diastereomers in 40% yield. Mechanistically, an intramolecular [1,5]-hydride migration operates initially, leading to zwitterionic intermediate **I**. Subsequent ring closure can be formulated as the intramolecular collapse of the zwitterionic intermediate **I** or **II**. The formation of 4-membered product **97** might be kinetically favorable and reversible. Although intermediate **II** might be less stable than intermediate **I** for the reason that the allylic positive charge in intermediate **I** can be dispersed by more substituents, the conversion of 4-membered **97** to **96** is thermodynamically favorable and the driving force might be the release of cyclic strain of **97**.



Scheme 37. $Sc(OTf)_3$-catalyzed C–H functionalization of cyclic ether *via* [1,5]-HT/cyclization.



Scheme 38. $Sc(OTf)_3$-catalyzed hyrodroalkylation *via* [1,5]-HT/cyclization.

4 C(sp^3)–H Bonds Adjacent to Ethereal Oxygen

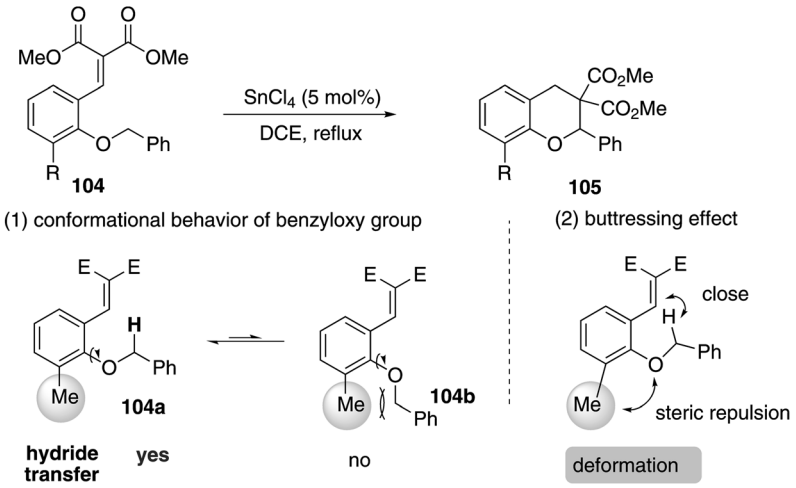
A methylene (or methane) adjacent to an ethereal oxygen working as a hydride donor was first disclosed by Sames in 2005.[28] As discussed in the part on mechanistic insights, the C–H bond adjacent to an ethereal oxygen is less reactive than that adjacent to a *tert*-amine, thus more reactive hydride acceptors are required.

4.1 Benzylidenemalonates as Hydride Acceptor

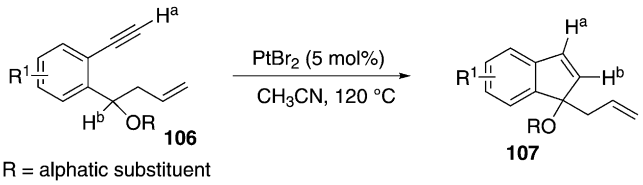
In 2005 Sames and co-workers reported an $Sc(OTf)_3$-catalyzed intramolecular hydroalkylation of isolated electron-deficient olefins (Scheme 37).[28] A tetrahydropyran or tetrahydrofuran carrying a C-2 linked, α,β-unsaturated malonate side chain, **98** and **100**, was employed as substrate and the respective spiroether products **99** and **101** could be produced in excellent yields in short reaction times. Thus a relatively reactive tertiary C–H bond was directly transformed into a heteroatom-substituted quaternary center. Notably, germinal substitution along the olefin tether was not required for efficient annulation for the reason that benzylidenemalonates activated by $Sc(OTf)_3$ were reactive enough, thus higher conformational rigidity to increase the reactivity of hydride acceptor was not indispensable.[29]

In 2009, Sames and co-workers also reported an $Sc(OTf)_3$-catalyzed [1,5]-hydride transfer/cyclization of *ortho*-vinylaryl alkyl ethers **102**, *via* which the highly substituted dihydrobenzopyran **103** could be prepared concisely in excellent yields (Scheme 38).[45] The cyclic and acyclic aliphatic ethers **102** substituted with phenyl or vinyl were well tolerated and a strong substituent effect on the reactivity was observed.

In 2010, Akiyama and co-workers described an $SnCl_4$-catalyzed highly efficient synthesis of a benzopyran skeleton **105** from benzyloxybenzylidenemalonate **104** (Scheme 39).[46] Notably, the methyl *ortho* to the alkoxy group or the benzylidene moiety could enhance the reactivity drastically compared with the non-substituted substrate. This remarkable enhancement of the reactivity could be well rationalized by the following two factors: (i) the conformational behavior of the benzyloxy group and (ii) the "*buttressing effect*". In the case of **104** having an *ortho*-methyl group, the conformational equilibrium largely shifted to the left conformer **104a** because of the severe steric repulsion. Furthermore, the "*buttressing effect*" between the methyl group and the benzyloxy group made the hydrogens on the benzyl group much closer to the electrophilic benzylidene carbon. As a result of the synergetic effect of these two factors, hydride can be delivered more readily to the acceptor, thus both catalyst loading and reaction time could be dramatically reduced.



Scheme 39. Remarkable enhancement of reactivity by an *ortho* substituent.



Scheme 40. $PtBr_2$-catalyzed cyclization of allyl(*ortho*-ethynylaryl)carbinol derivatives.

4.2 Activated Alkynes and Allenes as Hydride Acceptor

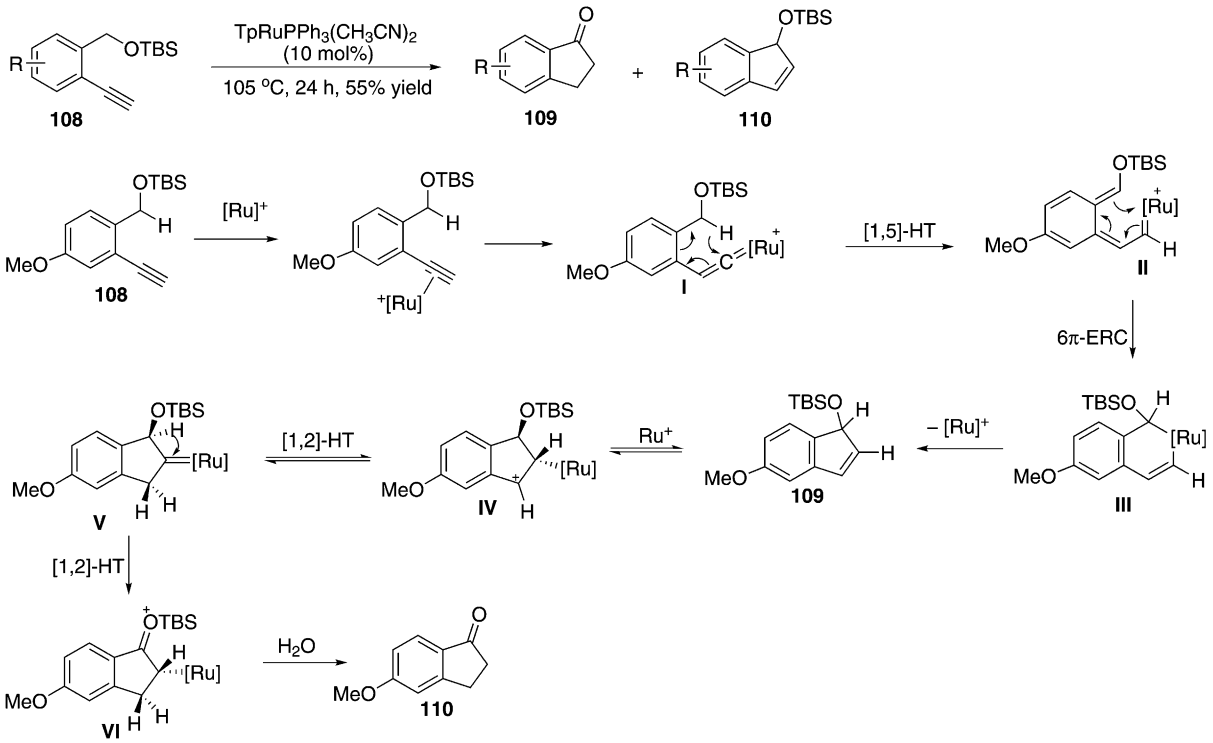
In 2006, Yamamoto and co-workers reported a $PtBr_2$-catalyzed cyclization of 1-ethynyl-2-(1-alkoxybut-3-enyl)-benzenes **106** and functionalized indenes **107** were furnished in good to acceptable yields (Scheme 40).[47] The allyl substituted at the benzylic position played a critical role for the success of this cyclization without which the reaction did not work at all. This observation suggests that the coordination of olefin to platinum at a right position/geometry might be essential for the indene formation.

In 2007, Liu and co-workers reported a $TpRuPPh_3(CH_3CN)_2SbF_6$-catalyzed cyclization of 2-alkyl-1-ethynylbenzenes **108** bearing a siloxy group, affording synthetically valuable 1-indanone products **109** or 1*H*-1-indenols **110** in reasonable yields and in short times (Scheme 41).[11b] Basically, the terminal alkyne is transformed to ruthenium-vinylidene species **I** initially, which undergoes a [1,5]-hydride shift to give ruthenium-containing 1,3,5-hexatriene **II**. A subsequent 6π-electrocyclization of species **II** furnishes ruthenium-containing cyclohexadiene **III** which suffers reductive elimination to produce the observed 1-substituted-1*H*-indene **109**. Afterwards the cationic ruthenium catalyst attacks on the indene C-2 carbon to form benzyl cation **IV**. Subsequently a [1,2]-hydride shift operates in this intermediate, resulting in ruthenium cyclopentylidene species **V**. Ultimately the 1-indanone **110** is produced after a second hydride shift and hydrolysis.

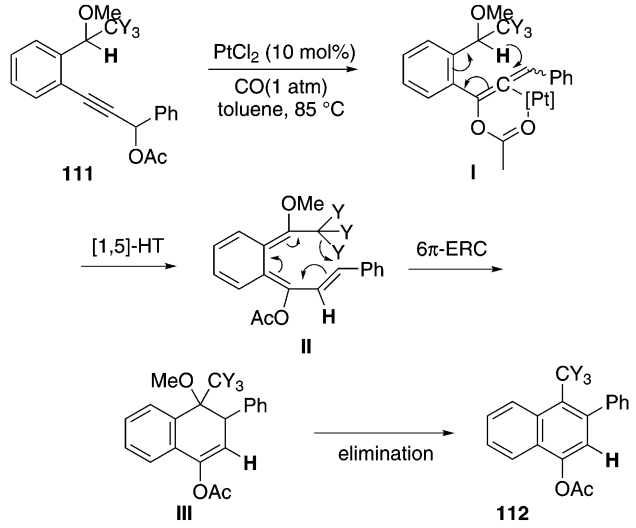
In 2008, Liang and co-workers reported a $PtCl_2$-catalyzed transformation of 3-(2-alkyl)phenylpropynyl acetate **111** to naphthalenyl acetate **112** (Scheme 42).[11c] The electrophilic Pt-allene complexes formed *in situ* worked as hydride acceptors. Mechanistically, the Pt(II)-promoted [1,3]-OAc shift leads to the formation of platinum-activated allenyl ester **I**, which undergoes a [1,5]-hydride shift to form 1,3,5-hexatriene **II**. A subsequent 6π-electroncyclic ring closure affords intermediate **III** which further eliminates a methoxy group to rearomatize, giving rise to **112**.

In 2008, Liu and co-workers reported a $PPh_3AuCl/AgSbF_6$-catalyzed cycloisomerization of allene acetal functionality **113**, *via* which bicyclo[3.2.1]oct-6-en-2-ones **114** were prepared in high yields, high chemoselectivities and high stereoselectivities (Scheme 43).[48] In most cases only one single stereoisomer was formed for the resulting cyclized products despite their molecular complexities. Mechanistically, substrate **113** initially undergoes Au(I)-catalyzed allene cyclization to give electrophilic Au(I)-alkenyl carbenoid **I**, which abstracts an acetal hydride through [1,5]-hydride transfer, leading to Au(I)-η^1-allyl species **II** containing a dimethoxymethyl cation. A subsequent S_E2' addition of Au(I)-η^1-allyl functionality at this oxocarbenium opposite the neighboring methyl group affords tricyclic species **III** with its methyl group on the same side as the adjacent hydrogen and ethyl group. A final acid-catalyzed deprotection leads to **114**.

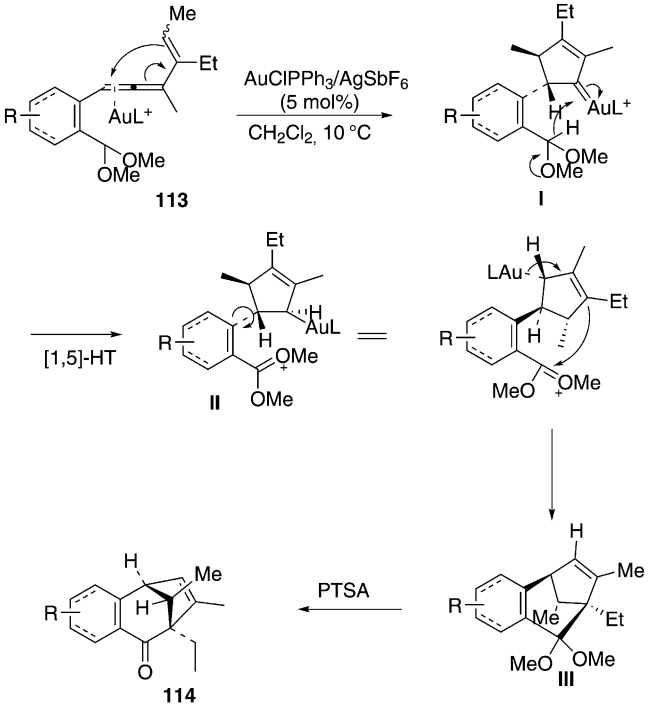
In 2009, Chatani and co-workers employed other alkynophilic metals such as $PtCl_2$, $PtCl_4$ and $[RuCl_2(CO)_3]_2$ to catalyze the cyclization of non-allyl-



Scheme 41. Ruthenium-catalyzed cyclization of 2-alkyl-1-ethynylbenzene carrying a silyl ether.



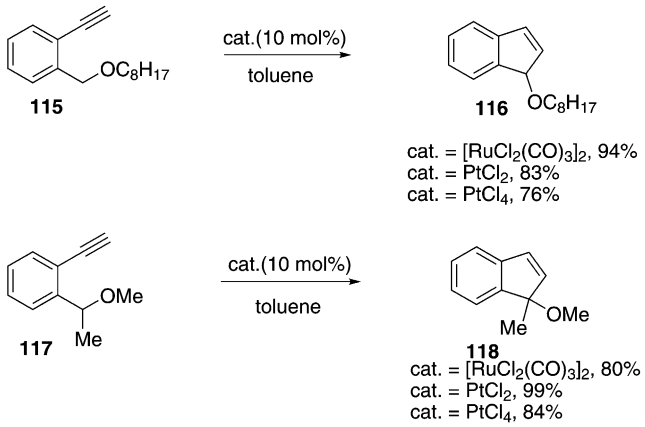
Scheme 42. Synthesis of naphthalenyl acetate from propargylic esters *via* Pt-catalyzed [1,5]-HT/cyclization.



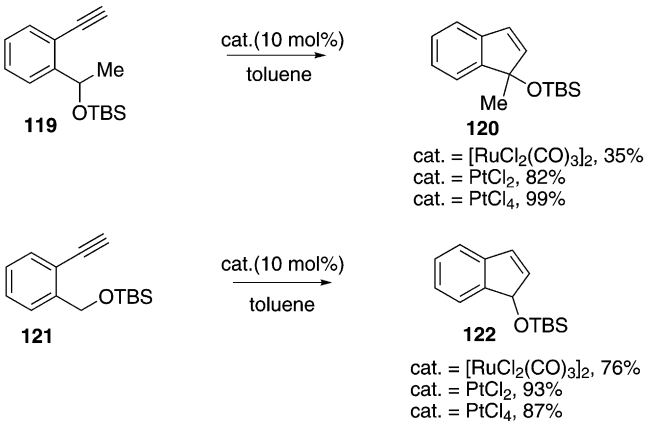
Scheme 43. Gold-catalyzed stereoselective synthesis of bicyclo[3.2.1]oct-6-en-2-ones.

substituted 1-ethynyl-2-(1-alkoxyalkyl)benzenes **115** and **117** under mild conditions, affording the desired indenes **116** and **118** in high yields (Scheme 44).[9d] In contrast to Yamamoto's results,[47] the substrates in Chatani's report lacked an allyl group but still worked well.

Chatani and co-workers also investigated the catalytic cyclization of 2-alkyl-1-ethynylbenzene derivatives carrying a silyl ether, **119** and **121**, which are similar to Liu's substrates (Scheme 45).[9d] In contrast to Liu's result,[11b] when silyl ether-substituted 2-methyl-1-ethynylbenzene was subjected to the reac-



Scheme 44. Alkynophilic metal-catalyzed cyclization of non-allyl substituted 1-ethynyl-2-(1-alkoxyalkyl)benzenes.

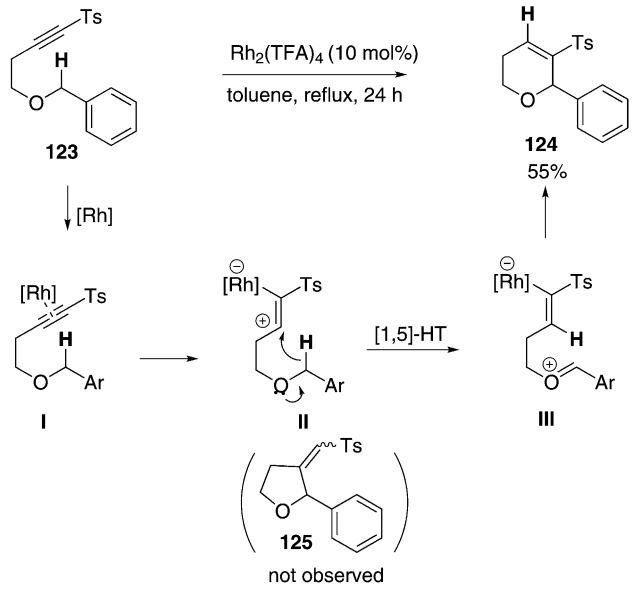


Scheme 45. Catalytic cyclization of 2-alkyl-1-ethynylbenzene derivatives carrying a silyl ether to indene.

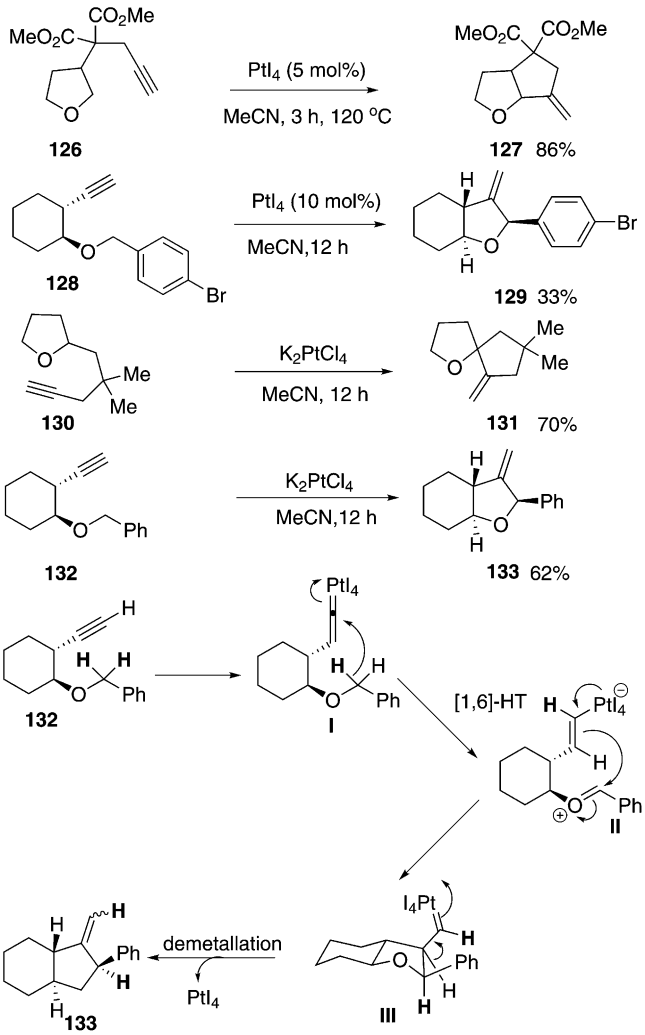
tion, only silyl ether-substituted indenes **120** and **122** were afforded in good to excellent yields.

In 2009, Urabe and co-workers described an $Rh_2(TFA)_4$-catalyzed cyclization of alkynyl ethers **123**, affording dihydropyrans **124** in good yields (Scheme 46).[49] Ring closure proceeded in a highly regioselective manner, and no isomeric five-membered product **125** was detected. The sulfonyl moiety is critical for the success of this reaction. Mechanistically, initial coordination of the Rh metal to the alkyne generates a cationic carbon β to the sulfonyl group which abstracts a hydride from a methylene α to the ethereal oxygen, generating a zwitterionic intermediate **III**. A final intramolecular nucleophilic attack furnishes the product **124**.

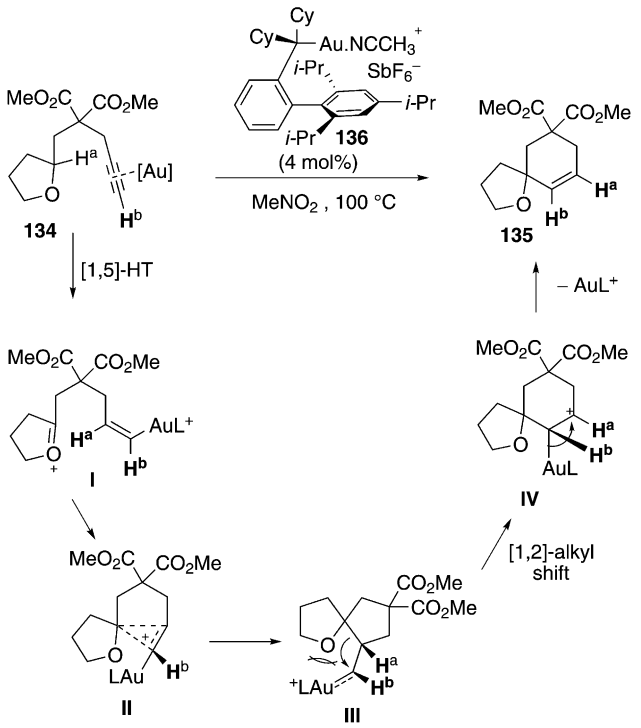
In 2009, Sames and co-workers described an α-alkenylation of cyclic ethers to synthesize both annulation and spirocyclization products (Scheme 47).[9c] Four types of electronically diverse hydride donors were investigated. The selection of suitable catalysts was crucial to the success of the cascade process. As to the



Scheme 46. Rhodium-catalyzed intramolecular redox reaction of alkynyl ethers.



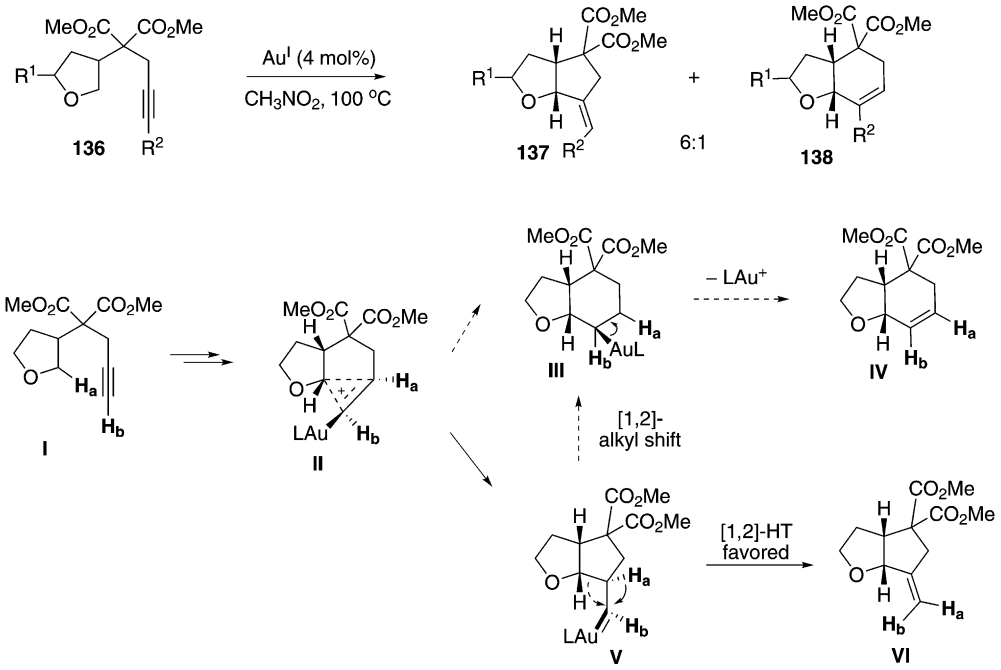
Scheme 47. Platinum-catalyzed α-alkenylation of cyclic ethers based on cascade [1,5]-HT/cyclization.



Scheme 48. Gold(I)-catalyzed *a*-alkylation of C-2 linked terminal alkynyl ethers.

substrate **126**, the relatively unreactive secondary C–H bond was exploited as the hydride donor and no aromatic group was present to stabilize the oxocarbenium generated upon [1,5]-HT. Hypervalent platinum catalyst PtI_4 was the optimal catalyst which effected complete conversion of **126** to furnish the product **127** in 86% yield. In contrast, PtI_4 only led to complete decomposition of **130** despite the higher reactivity of its tertiary C–H bond. Less active platinum catalyst K_2PtCl_4 was the optimal catalyst to produce spirocycles **131** in 70% isolated yield. With K_2PtCl_4 as catalyst, substrate **132** could also be transformed into product **133** in 62% yield. Although the hydride donor in **132** was a less active secondary C–H bond, the oxocarbenium generated upon [1,5]-HT could be stabilized by adjacent phenyl group, thus less active K_2PtCl_4 could facilitate the conversion well. The brominated derivative **128** gave a lower yield of compound **129** (33%) even when highly active PtI_4 was employed, showing the sensitivity of this reaction to electron-withdrawing substituents, particularly in the *para*- and *ortho*-positions due to their destabilization of the oxocarbenium intermediates. Theoretically, the platinum vinylidene **I** is formed initially, followed by the through-space [1,6]-hydride transfer to produce zwitterionic intermediate **II**, which affords the final product *via* the sequence of C–C bond formation and platinum salt elimination.

In addition to rhodium, ruthenium and platinum, gold salts can also be exploited to activate the alkyne moieties for hydride abstraction. In 2010, Gagosz and co-workers reported that Au(I) catalyst **136** catalyzed the alkylation of alkynyl ethers to produce cyclohexane **135** as the major product (Scheme 48).[50] Theoretically, the electrophilic activation of the alkyne **134** by Au(I) can induce a [1,5]-hydride shift to furnish oxocarbenium ion **I**. Interaction of this cationic spe-

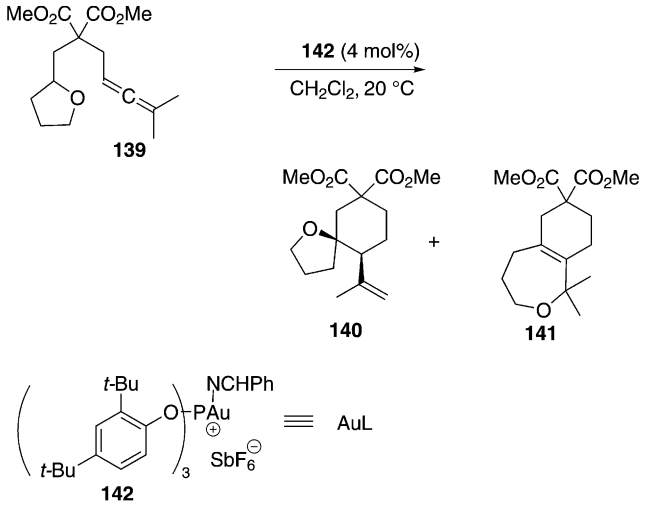


Scheme 49. Gold(I)-catalyzed α-alkylation of C-3 linked terminal alkynyl ethers.

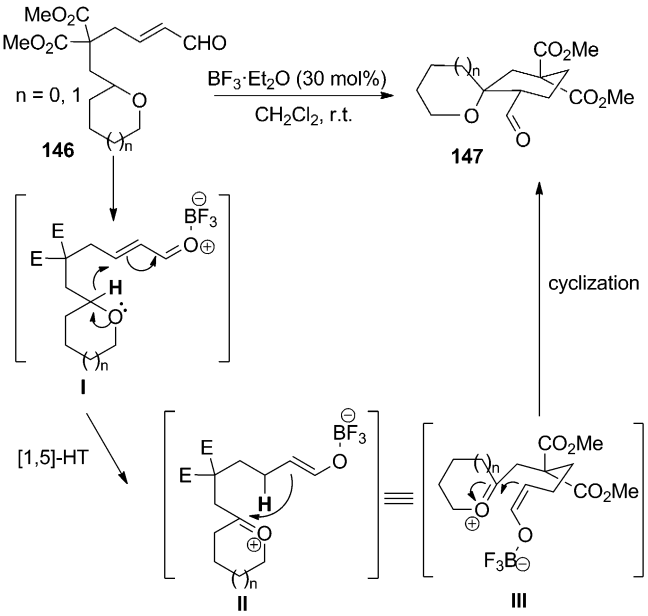
cies with the pendant nucleophilic vinyl-gold moiety might afford cyclopropenium intermediate **II**. Carbocation **IV** which would finally collapse into cyclohexene **135** after elimination of the gold(I) catalyst might be generated in a stepwise fashion *via* a [1,2]-alkyl shift on Au-carbene intermediate **III**.

In contrast to C-2 linked terminal alkynes **134**, gold-catalyzed alkylation of C-3 linked THF carrying terminal alkynes **136** mainly led to the formation of the major product, *exo*-methylenecyclopentane **137**, and minor product **138** (Scheme 49). This reversed selectivity might be explained by considering the relative stability of intermediates **III** and **V**. Steric constraints should be weaker for the fused bicyclic intermediate **V** (in Scheme 52) than intermediate **III** (in Scheme 51), thus allowing a rapid [1,2]-hydride shift which leads to **VI** rather than a [1,2]-alkyl shift which leads to **III**.

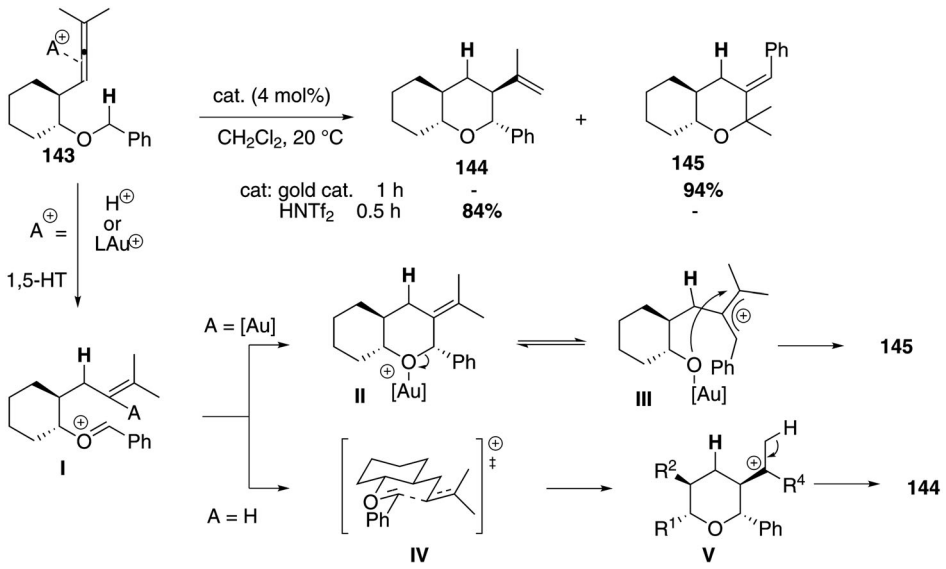
Gold-activated allene can also be employed as hydride acceptor. In 2011, Gagosz and co-workers demonstrated a phosphite gold complex **142**-catalyzed intramolecular hydroalkylation of allenes **139**, affording the spiro compound **140** and undesired fused bicyclic compound **141** in 30% and 61% yields respectively (Scheme 50).[51] The selectivity could be reversed when $HNTf_2$ was exploited. Under Brønsted acidic conditions, the transformation was slower but furnished exclusively the desired spiro compound **140** in



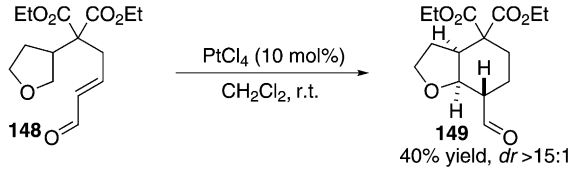
Scheme 50. Gold- and Brønsted acid-catalyzed hydride shift onto allenes.



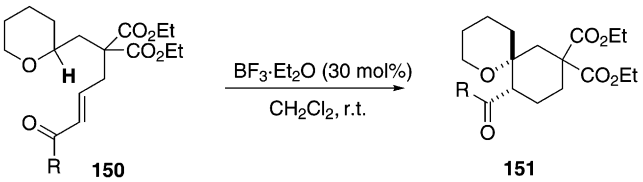
Scheme 52. $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydroalkylation of isolated α,β-enals.



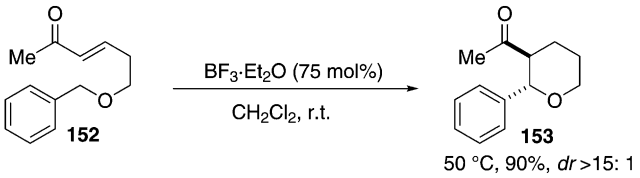
Scheme 51. Gold- and Bronsted acid-catalyzed α-alkylation of benzyl ether.



Scheme 53. $PtCl_4$-atalyzed intramolecular hydroalkylation of isolated α,β-enals.



Scheme 54. $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydroalkylation of isolated α,β-unsaturated ketones.



Scheme 55. $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydroalkylation of α,β-unsaturated ketones.

an excellent yield. The two reactions under Au(I) or Brønsted acid catalysis proceeded under very mild conditions in a stereoselective manner and two new contiguous asymmetric centers, one of which is quaternary, were formed during the process.

A similar complete divergence in product selectivity was observed when the substrates **143** possessing a benzyl ether moiety were treated with either gold complex **142** or $HNTf_2$ (Scheme 51).[51] Under gold catalysis, tetrahydropyran 1**45** was obtained in 94% yield, while tetrahydropyran **144** was produced in 84% yield with $HNTf_2$ as the catalyst. The stereoselective formation of compound **144** can be explained by considering the highly ordered chair-like transition state **IV** leading to carbocation **V** from oxocarbenium **I**. The relative *trans* relationship between the phenyl and isopropenyl substituents in product **144** results from the pseudo-equatorial orientation of the phenyl and isopropylidene group in transition state **IV**. An analogous disposition explained the *cis* relationship between the phenyl group and the alkyl substituent at carbon C-6.

4.3 α,β-Unsaturated Aldehydes and Ketones as Hydride Acceptor

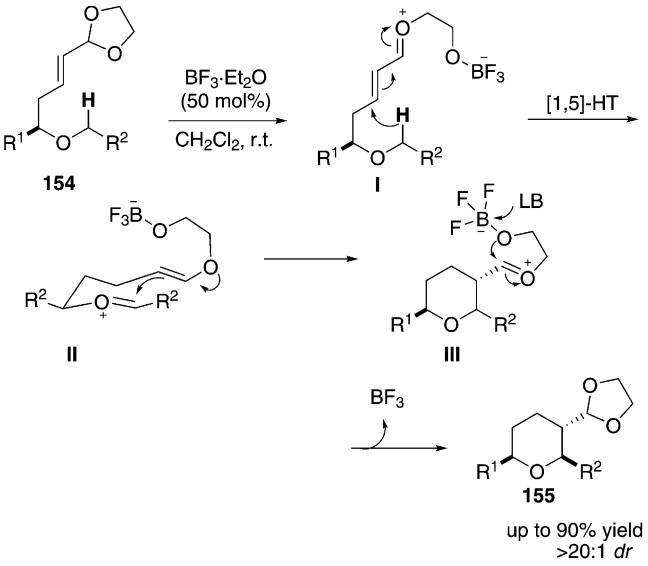
In 2005, Sames and co-workers described a $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydroalkylation reaction of α,β-enal 1**46**, *via* which the desired spirocycles **147** could be furnished in good yields at ambient temperature as a mixture of diastereomers (Scheme 52).[28]

In addition to tertiary C–H bonds, secondary C–H bonds could also be directly functionalized (Scheme 53).[28] Compared with tertiary C–H bonds, the secondary C–H bond is less reactive, therefore a more active Lewis acid, $PtCl_4$ (10 mol%), was employed to facilitate the hydroalkylation of enal **148**, giving rising to the fused annulation product **149** in 40% yield and good diasteroselectivity ($dr > 15{:}1$).

In addition to the more active α,β-enals, the hydroalkylation of less active enones **150** also proceeded smoothly (Scheme 54).[28] Under the action of 30 mol% of $BF_3{\cdot}Et_2O$ and with comparatively active tertiary C–H as hydride donor, the substrate **150a** or **150b** carrying an α,β-unsaturated methyl ketone or a phenyl ketone, respectively, was efficiently transformed into the corresponding spirocycle products **151a** and **151b**, respectively, in excellent yields and moderate diastereoselectivities.

The 2,3-disubstituted tetrahydropyran **153** could be obtained in high diastereoselectivity *via* treatment of acyclic ether **152** with a substoichiometric amount of $BF_3{\cdot}Et_2O$ at elevated temperature (Scheme 55).[28] The less active secondary C–H bond acted as the hydride donor and the less active methyl ketone was employed as hydride acceptor. Because the oxocarbenium could be stabilized by the adjacent phenyl group, the relatively mild Lewis acid $BF_3{\cdot}Et_2O$ (75 mol%) was active enough to promote the cascade process efficiently, resulting in the desired product **153** in high yield (90%) and good diastereoselectivity ($dr > 15{:}1$).

A simple and economical intramolecular hydroalkylation of olefins was elegantly demonstrated by Sames and co-workers in 2009 based on the generation of highly activated alkenyl-oxocarbenium intermediates **I** *in situ* from acetals (Scheme 56).[9b] $BF_3{\cdot}Et_2O$ was the optimal catalyst under the action of which the acetal **154** could be consumed within 1 hour, leading to the cyclic product **155** in good yield and diastereoselectivity. Direct comparison of **154** to the corresponding unprotected aldehyde showed a drastic increase in both reactivity and chemical yield, as well as an improvement in diastereoselectivity. Theoretically, $BF_3{\cdot}Et_2O$ opens the cyclic acetal **154** generating the oxocarbenium intermediate **I** which activates the conjugated double bond for the subsequent hydride abstraction. After hydride transfer, the resulting oxocarbenium-enol ether intermediate **II** undergoes rapid C–C bond formation and the acetal can be reformed from the new oxocarbenium

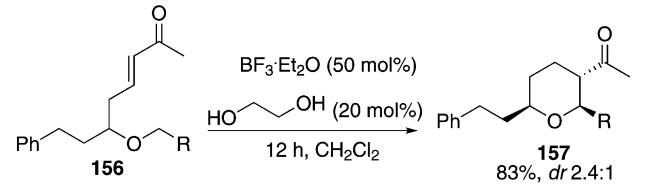


Scheme 56. $BF_3{\cdot}Et_2O$-catalyzed alkylation through highly activated alkenyl-oxocarbenium intermediates.

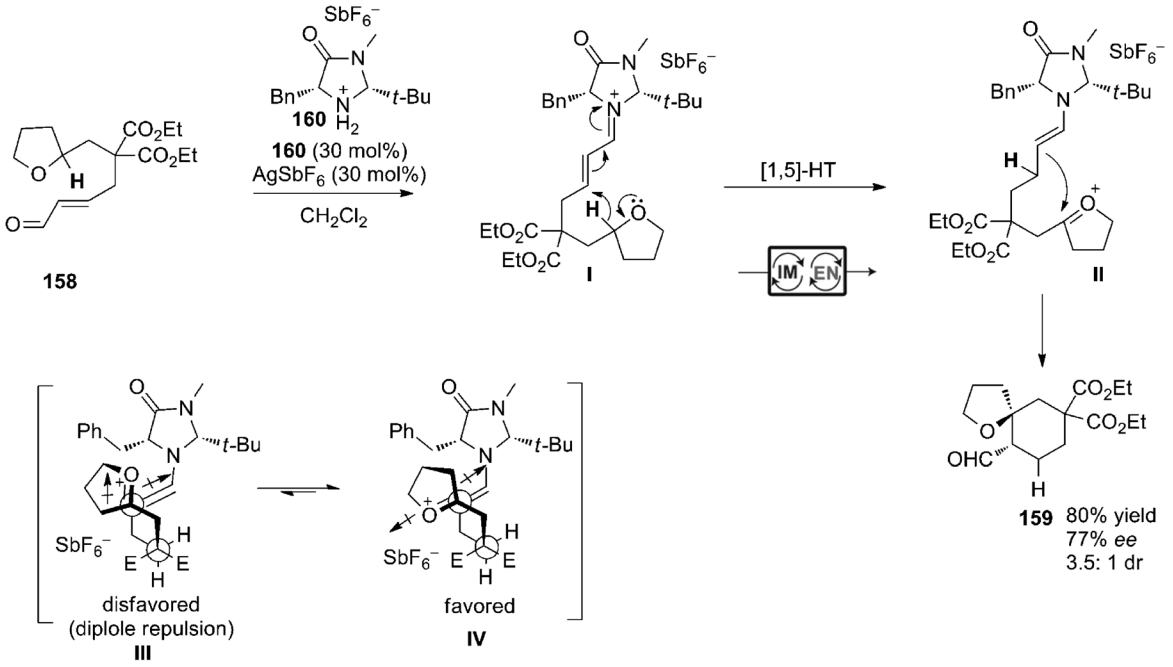
species **III**, producing **155**. The observed high stereoselectivity can be explained by the favorable transition state **II** in which all substituents are in equatorial positions.

This strategy could also be exerted on the intramolecular hydroalkylation of enones. (Scheme 57).[9b] Addition of ethylene glycol had a dramatic effect on the reaction rate as demonstrated in the cyclization of enones **156**; the reaction could be completed within 12 h, furnishing the cyclized products **157** in good yields but with low diastereoselectivities. This strategy can not only drastically increase reaction rate, but also improve the isolated yields and stereoselectivities.

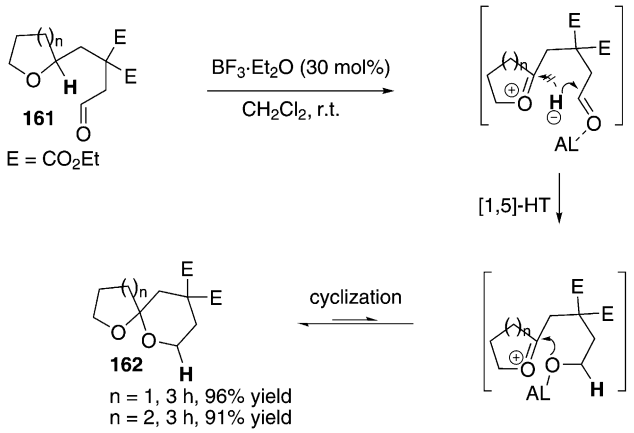
In 2012, Tu and co-workers reported a Macmillan catalyst **160**-catalyzed asymmetric α-alkylation of tetrahydrofuran **158** containing an α,β-unsaturated aldehyde to construct the chiral spiroether **159** (Scheme 58).[52] The sequential [1,5]-hydride transfer/cyclization was facilitated *via* a cascade iminium/enamine activation. The presence of a strong acid was required to ensure that the iminium ion would be of sufficient electrophilicity. Theoretically, substrate **161** reacts with **160** to give iminium **I**. Owing to the steric interaction of the bulky *tert*-butyl group, the *E* enamine **II** is formed preferentially upon [1,5]-hydride transfer, and exists in two possible conformers **III** and **IV**. Because of the repulsion of dipoles of the cyclic-oxocarbenium and enamine moieties in conformer **III**, **IV** is the more favored conformer which undergoes intramolecular C–C bond formation to afford the final **159**.



Scheme 57. $BF_3{\cdot}Et_2O$-catalyzed C–H bond functionalization with enone as hydride acceptors.



Scheme 58. Organocatalyzed asymmetric direct C(*sp*3)–H functionalization of cyclic ethers.

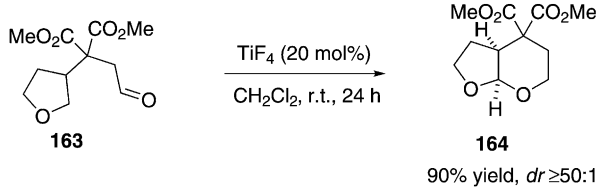


Scheme 59. $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydro-*O*-alkylation of C-2 linked aldehydes.

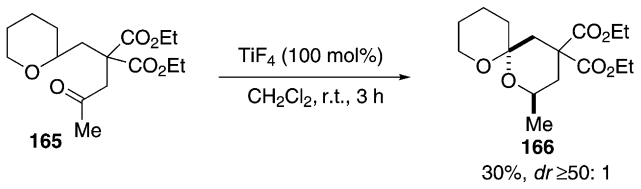
4.4 Saturated Aldehydes and Ketones as Hydride Acceptor

In 2005, Sames and co-workers described a $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydro-*O*-alkylation of aldehyde substrates **161** which led to spiroketal products **162** (Scheme 59).[9a] Because the oxocarbenium generated upon hydride migration is also a highly electron-deficient species which would compete with aldehyde for the hydride, the task of how to deliver the hydride to the acceptor is challenging. Same's protocol to address this problem was to employ $BF_3{\cdot}Et_2O$ (30 mol%) for activation of the carbonyl of **161**, rendering the hydride acceptor more electrophilic in competing for the hydride. Tetrahydropyran substrate **161** (n = 2) could be converted to the spiroketal **162** in 91% isolated yield at ambient temperature within 3 h. Remarkably, the final cyclization step is a reversible process which is under thermodynamic control, thus the cascade process is highly diastereoselective. Both 6,6-scaffolds and 5,6 spiroketals could be obtained in excellent yields.

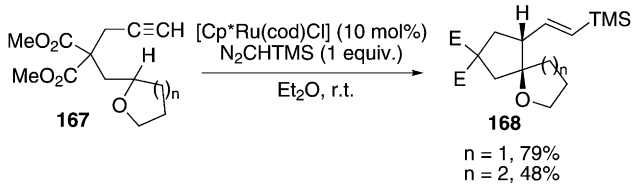
The *cis*-fused bicyclic acetal **164** could also be afforded as a single diastereomer using this strategy with **163** as the substrate (Scheme 60).[9a] $BF_3{\cdot}Et_2O$ was inactive and only the strong oxophilic Lewis acid TiF_4 (20 mol%) could facilitate the transformation for the reason that the secondary C–H is less reactive than the tertiary C–H bond.



Scheme 60. TiF_4-catalyzed intramolecular hydro-*O*-alkylation of C-3 linked aldehydes.



Scheme 61. TiF_4-catalyzed intramolecular hydro-*O*-alkylation of C-2 linked methyl ketones.



Scheme 62. Intramolecular α-alkylation of C-2 cyclic ethers.

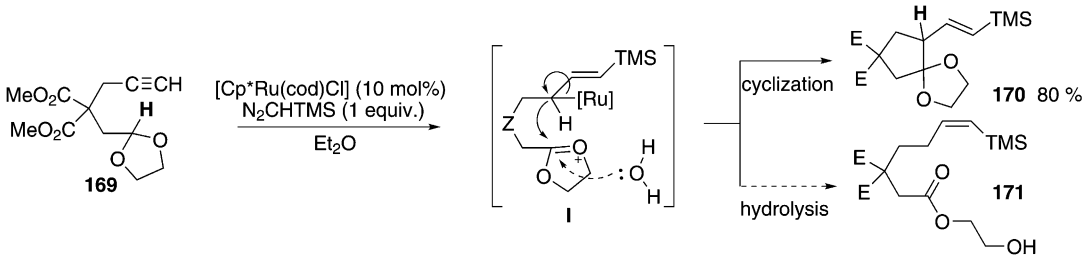
In addition to aldehyde substrates, the less electrophilic ketone **165** could be converted into the spiroketal **166** in 30% yield and excellent diastereoselectivity under the mediation of stoichiometric TiF_4 (Scheme 61).[9a] $BF_3{\cdot}Et_2O$ was not active enough to promote this hydro-*O*-alkylation.

4.5 Metal Carbenoids as Hydride Acceptor

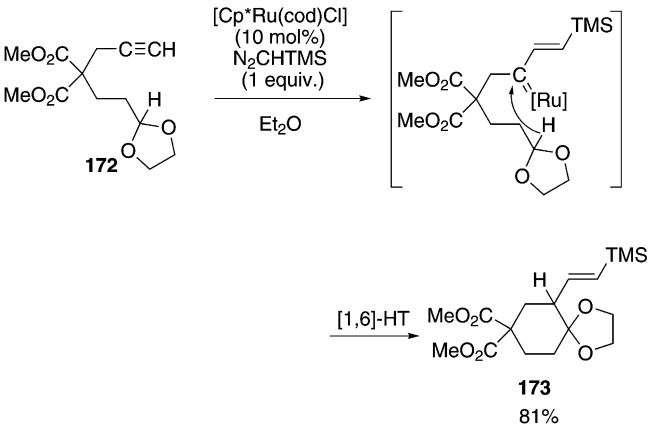
In 2012, Saa and co-workers discovered a ruthenium-catalyzed diastereoselective cyclization of linear alkynyl ether **167** involving cyclic and acyclic ethers, which produced complex spirocycles **168** smoothly in fairly good yields (Scheme 62).[19f] The ring size of the cyclic ether has a dramatic effect on the reaction time. The mechanism is the same as that of Scheme 29.

Saa and co-workers also investigated the ruthenium-catalyzed cyclization of linear alkynyl acetals **169**, affording complex spirobicycles **170** (Scheme 63).[19f] The acetal C–H bond was exploited as hydride donor and the desired spiro compound **170** could be furnished in fairly good yield, although with formation of the linear hydroxy ester **171** which was generated by hydrolysis of intermediate **I**. Notably, the rigid cyclic acetal afforded a higher yield of spiro compound in comparison to the linear acetals.[29]

A [1,6]-hydride shift/cyclization process could occur when specially designed dioxolane substrate **172** was subjected to the reaction and 5,6-spirocyclic product **173** could be afforded in excellent yield (Scheme 64).[19f] The examples showed again that the hydride could be delivered through space and the distance between hydride donor and acceptor was not an issue. A comparison of the cyclizations of dioxolanes **169** and **172** shows the easier formation of the 1,4-



Scheme 63. Intramolecular alkylation of dioxolane by catalytic ruthenium carbene insertion.



Scheme 64. Intramolecular alkylation of dioxolane *via* cascade [1,6]-HT/cyclization.

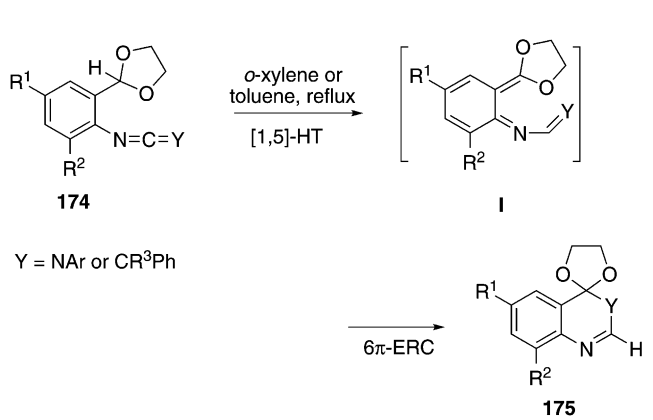
dioxaspiro[4,5]decane **173** *versus* 1,4-dioxaspiro-[4,4]nonane **170**; this result clearly indicated that the conformation of the metallic intermediate played a definitive role during the course of the reaction.

Fukuyama and co-workers exploited the highly reactive rhodium carbenoid generated from a diazoester as hydride acceptor to construct tetrahydrofuran moieties in his total syntheses many times. The mechanism should be the cascade [1,5]-Hydride migration/cyclization, whereas Fukuyama and co-workers argued that their reactions proceeded *via* a metal carbene C–H insertion reaction.[53]

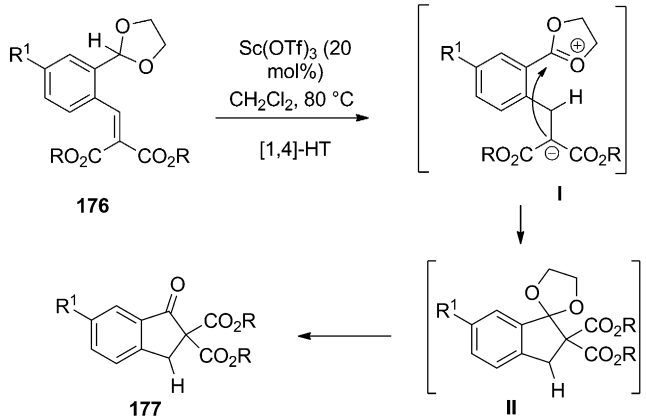
4.6 Ketenimines and Carbodiimides as Hydride Acceptor

In 2006, Alajarin and Vidal et al. discovered that dihydroquinolines and spirocyclic dioxolanoquinazolines **175** could be readily accessed *via* cascade [1,5]-hydride transfer/6π-ERC under mild thermal conditions (Scheme 65).[14b] With active ketenimine or carbodiimide as hydride acceptor, whose central carbon atom is highly electrophilic, the cascade process is facilitated by the hydricity of the acetal C–H bonds in **174**. After hydride migration, the 1,3,5-conjugated hexatriene **I** can be generated which has a long conjugate system and can be stabilized to a large extent. The formation of a zwitterion could be avoided and the activation energy would be much lower than that with charge separation. Both dihydroquinolines and spirocyclic dioxolanoquinazolines **175** could be produced in moderate to good yields.

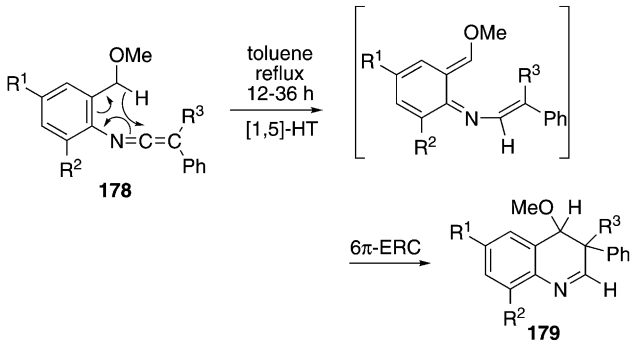
In 2011, Alajarin, Vidal and co-workers described an $Sc(OTf)_3$-catalyzed 3-step cascade reaction of **176** involving hydride shift/cyclization/hydrolysis to produce indanones **177** (Scheme 66).[18b] Hydride was delivered to the acceptor in an uncommon [1,4]-manner, followed by a [1,5]-cyclization. Lewis acid activation



Scheme 65. Hydricity-promoted [1,5]-HT/cyclization in acetal ketenimines and carbodiimides.



Scheme 66. $Sc(OTf)_3$-catalyzed cascade [1,4]-HT/cyclization/hydrolysis.

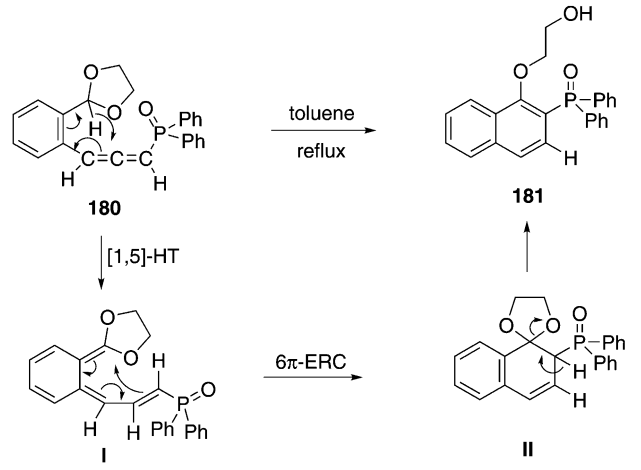


Scheme 67. Synthesis of quinolones *via* [1,5]-HT/6π-ERC.

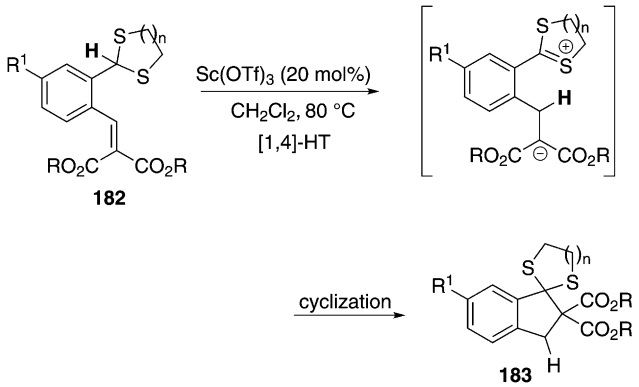
was indispensable. $Sc(OTf)_3$ was the only Lewis acid that could catalyze the cascade process. Because of the oxophilicity of $Sc(OTf)_3$, it not only catalyzed the cascade process, but also promoted the hydrolysis of the acetal function.

In 2012, Alajarin and Vidal et al. discovered that ketenimines **178** bearing an ether moiety could be transformed exclusively into dihydroquinolines **179** (Scheme 67).[13d] Thermal conditions could successfully promote the cascade process.

Allenes could be activated not only by carbophilic transition metals, but also by electron-withdrawing groups at the terminal carbon atom. In 2013, Alajarin, Sanchez-Andrada and Vidal et al. disclosed that 2-(1,3-dioxolan-2-yl)phenylallenes **180** containing a range of electron-withdrawing substituents such as phosphinyl, alkoxycarbonyl, sulfonyl at the cumulenic C-3 position could be converted into the 1-(2-hydroxy)-ethoxy-2-substituted naphthalenes **181** under thermal conditions (Scheme 68).[12c] Mechanistically, an initial [1,5]-hydride shift of the acetalic H atom onto the central cumulene carbon atom affords the conjugated 1,3,5-hexatriene **I**; a subsequent 6π-electrocyclic ring-closure of **I** gives rise to spirocycle intermediate **II**; and a final aromatization step with concomitant ring opening of the 1,3-dioxolane fragment produces the substituted naphthalenes **181**.



Scheme 68. Hydricity-promoted intramolecular hydroalkylation of electron-deficient allenes.



Scheme 69. Cascade [1,4]-HT/cyclization with dithioacetal C–H as hydride donor.

5 C(sp^3)–H Bonds Adjacent to Sulfur

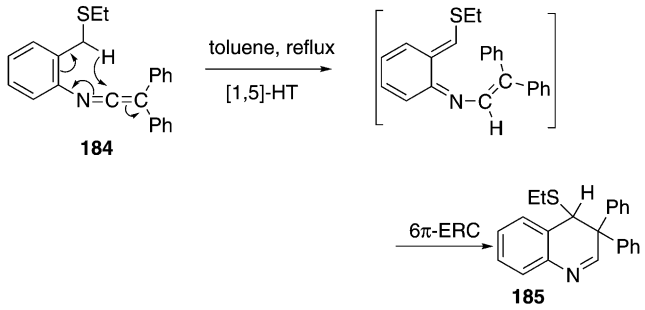
The methylene (or methane) adjacent to a sulfur atom can also work as a hydride donor. With reactive electrophilic moieties as hydride acceptors, the cascade [1,5]-hydride transfer/cyclization can occur to give thio-heterocycles.

In 2011, Alajarin and Vidal et al. described an $Sc(OTf)_3$-catalyzed cascade [1,4]-hydride shift/cyclization of substrate **182** carrying a 1,3-dithiolane which produced spirocyclic products **183** in medium to good yields (Scheme 69).[18b] The tertiary C–H bond in the 1,3-dithiolane worked as hydride donor. Because $Sc(OTf)_3$ is oxophilic, not thiophilic, the dithiolane moiety remained intact after the cascade [1,4]-hydride shift/cyclization. Compared with substrate **178** carrying 1,3-dioxolane, the disturbing hydrolysis of the acetal function was thoroughly suppressed.

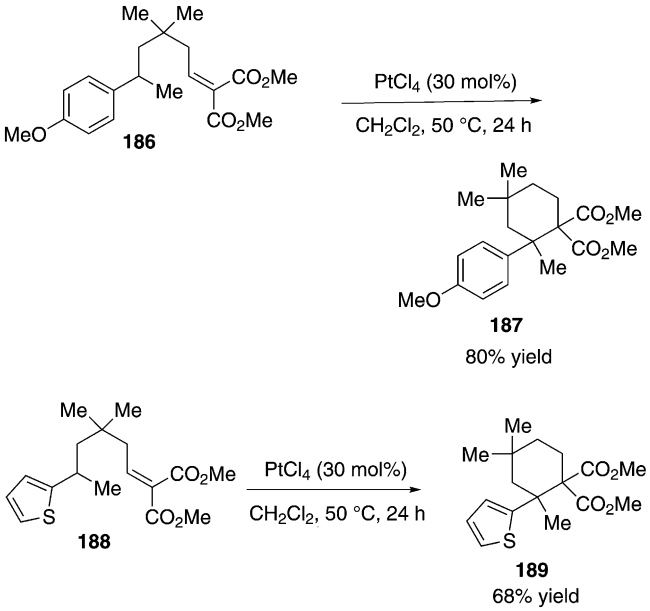
In 2012, Alajarin and Vidal et al. discovered that under thermal conditions (reflux in toluene), the single thioether **194** carrying a ketenimine moiety could be transformed into 4-ethylthio-3,4-dihydroquinoline **195** in good yield *via* a cascade [1,5]-hydride transfer/6π-ERC (Scheme 70).[13d] Similar to oxoethers, the methylene adjacent to a single thioether function is a good hydride donor.

6 Benzylic C(sp^3)–H Bonds

A range of cascade reactions of heteroatom-containing substrates (X=NR, O or S) has been described, whereas the corresponding carbon analogues (X=CH_2 or CHR) had been overlooked until 2005. This is due to the difficulties posed by the rate-determining step of [1,5]-hydride transfer without the assistance of



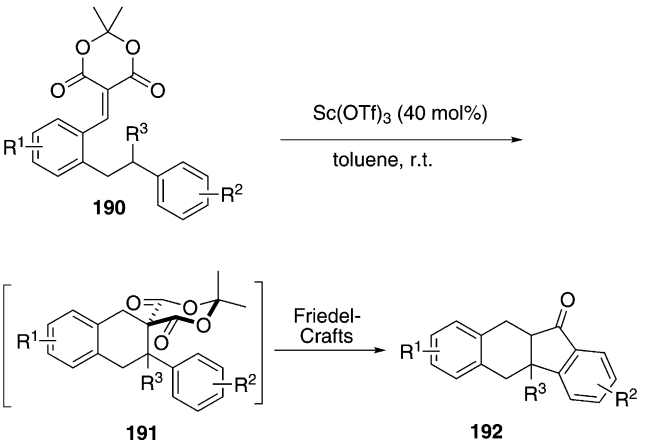
Scheme 70. Cascade [1,5]-HT/6π-ERC to synthesize 3,4-dihydroquinolines.



Scheme 71. $PtCl_4$-catalyzed direct C(sp^3)–H functionalization of benzylic methines.

an adjacent heteroatom. For the first time Sames et al. disclosed that the secondary and tertiary benzylic C–H bonds without an adjacent heteroatom could also be exploited as hydride donor. After [1,5]-hydride transfer, the cation that develops on the benzylic position can be stabilized by adjacent electron-rich aromatic groups and alkyl groups *via* π–*p* conjugation and hyperconjugation, respectively.

In 2005, Sames and co-workers elegantly demonstrated a $PtCl_4$-catalyzed cascade process involving benzylic methines that lack the stabilization of an α-heteroatom (Scheme 71).[28] The aryl substrate **186** and thiophene substrate **188** were consumed within 24 h at 50 °C. Although the electrophilic alkene is activated by two electron-withdrawing carboxylate groups and the cation generated upon [1,5]-hydride trasnsfer can be stabilized by the adjacent aromatic group, $PtCl_4$ is still indispensable for the transformation, under the catalysis of which the hexasubstituted



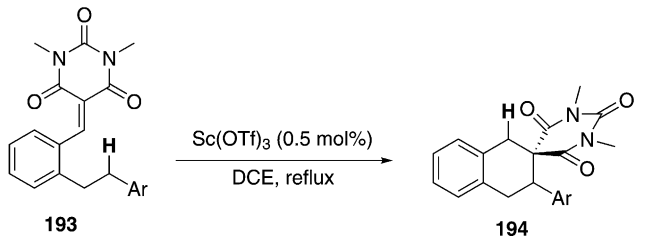
Scheme 72. $Sc(OTf)_3$-catalyzed synthesis of tetrahydrobenzo[*b*]fluoren-11-ones.

cyclohexanes **187** and **189** could be obtained in moderate to good yield.

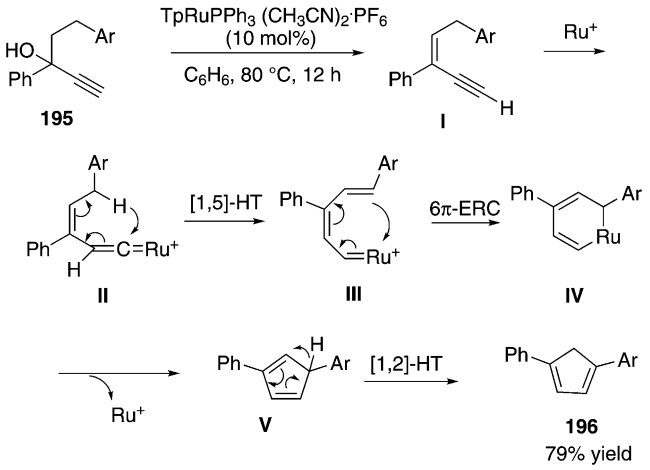
In 2009, Fillion and co-workers reported a convenient one-pot construction of tetrahydrobenzo[*b*]fluoren-11-ones **192** under $Sc(OTf)_3$ catalysis (Scheme 72).[54] Three new bonds: a C–H and two C–C bonds were formed in the cascade process. The substrates **190** involving highly electrophilic benzylidene Meldrum's acids and benzylic methylene or methine functions could undergo a cascade [1,5]-hydride shift/cyclization to afford intermediate spirocycles **191**, which suffered subsequent intramolecular Friedel–Crafts acylation to generate tetracycles **192**.

In 2011, Akiyama and co-workers reported an $Sc(OTf)_3$-catalyzed concise construction of the 3-aryltetralin skeleton **194** from simple phenethyl derivatives **193** (Scheme 73).[14c] The electronic and steric properties of the aromatic ring adjacent to the C–H bond significantly influenced the reactivity of this transformation.

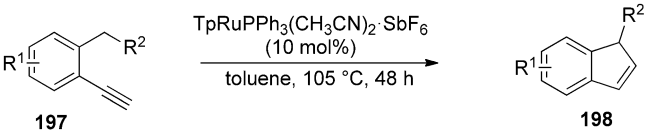
In 2005, Liu and co-workers reported on the $TpRuPPh_3(CH_3CN)_2{\cdot}PF_6$-catalyzed cycloisomerization of *cis*-3-en-1-ynes **I** or the precursor alcohol **195**, affording cyclopentadiene **196** (Scheme 74).[11a] Mechanistically, the alcohol undergoes ruthenium-catalyzed dehydration to afford the real substrates *cis*-3-en-1-



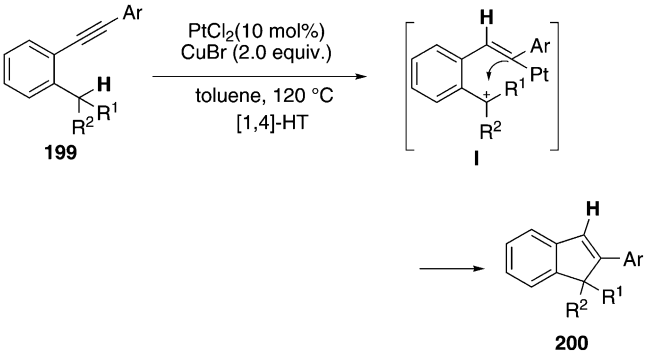
Scheme 73. Synthesis of 3-aryltetralin skeleton *via* cascade [1,5]-HT/cyclization.



Scheme 74. Ruthenium-catalyzed cycloisomerization of *cis*-3-en-1-ynes to cyclopentadienes.



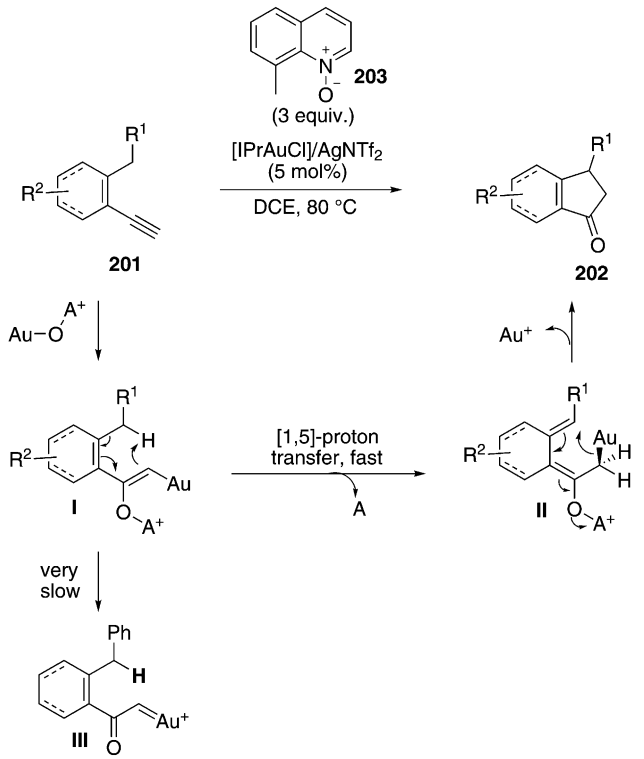
Scheme 75. Ruthenium-catalyzed cyclization of 2-alkyl-1-ethynylbenzenes.



Scheme 76. $PtCl_2$-catalyzed intramolecular cyclization of *ortho*-substituted arylalkynes *via* [1,4]-HT/cyclization.

ynes **I** which are converted into ruthenium-vinylidene intermediate **II** *via* a [1,2]-shift of the alkynyl hydrogen. A [1,5]-hydride shift ensues to generate ruthenium hexa-1,3,5-triene **III** which undergoes 6π-electrocyclic ring closure and reductive elimination to furnish cyclopentadiene **IV**. Ultimately the most stable regioisomer **196** is yielded *via* a [1,2]-hydrogen shift.

In 2007, Liu and co-workers reported a cyclization of 2-alkyl-1-ethynylbenzene derivatives **197** catalyzed by $TpRuPPh_3(CH_3CN)_2{\cdot}SbF_6$ (10 mol%), affording 1-substituted-1*H*-indene products **198** in moderate to good yields (Scheme 75).[11b] Counterions were critical to the success of the reaction and the mechanism of this reaction is the same as that of Scheme 41.

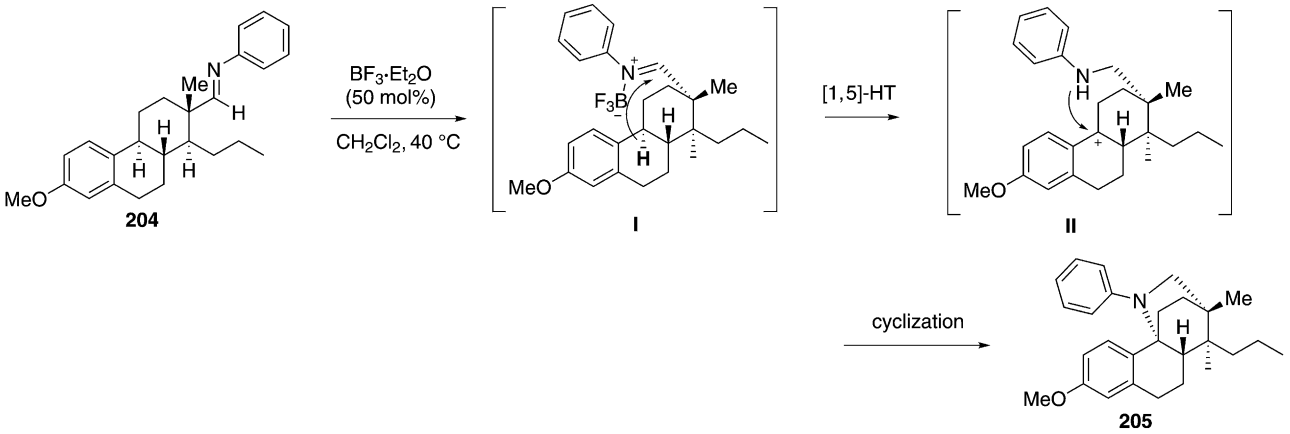


Scheme 77. Gold-catalyzed oxidative cyclizations of *cis*-3-en-1-ynes.

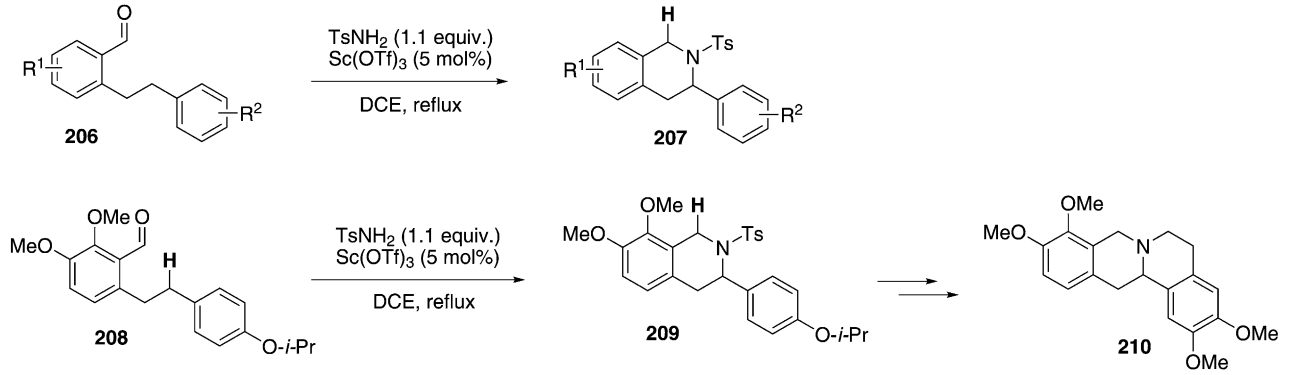
In 2009, He and co-workers described a $PtCl_2$-catalyzed intramolecular cyclization of *ortho*-isopropyl- or *ortho*-benzylarylalkynes **199**, furnishing functionalized indenes **200** (Scheme 76).[18a] In contrast to a previous report,[11b] the terminal of the alkyne is substituted with an aryl substituent. CuBr (2.0 equiv.) was indispensable to achieve high yield. Theoretically, a mechanism involving an unusual cascade [1,4]-hydride migration/cyclization should operate. Initially, the platinum(II)-activated electrophilic alkyne abstracts a hydride from the benzylic C–H to generate a benzylic carbocation **I**, which subsequently intercepts the nucleophilic alkenyl-platinum(II) to afford the 5-membered ring.

Chatani and co-workers reported a cycloisomerization of 1-alkyl-2-ethynylbenzenes catalyzed by $PtCl_2$, $PtCl_4$ and $[RuCl_2(CO)_3]_2$ under relatively mild reaction conditions to prepare the substituted indene in 2009.[9d] Remarkably, the benzylic primary C–H bond could participate in this cascade process to afford indene in 44% yield. In contrast to Zhang's report,[16a] it is the hydride that transfers in a [1,5]-manner this time.

In 2012, Liu and co-workers described an [IPrAuCl]/$AgNTf_2$-catalyzed oxidative cyclization of cis-3-en-1-ynes **201** with 8-methylisoquinoline oxide **203** as the oxidant, giving rise to cyclopentenone skeletons **202** (Scheme 77).[17d] Basically, the initially formed gold-containing enol ether **I** has a high energy



Scheme 78. $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydro-*N*-alkylation of phenylimine.



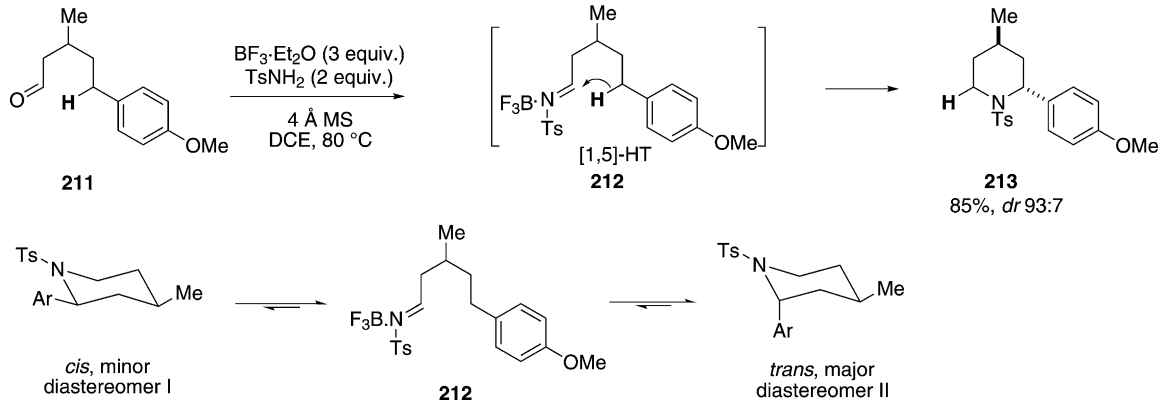
Scheme 79. $Sc(OTf)_3$-catalyzed hydro-*N*-alkylation of tosylimines to form 3-arylisoquinolines.

barrier to overcome to form the hypothetical carbenoid **III**. Instead, **I** undergoes a rapid [1,5]-hydrogen shift to generate the species **II**. The hydrogen is transferred in the form of a proton because hydrogen is captured by the electron-rich gold-alkenyl moiety and the electron-withdrawing substituent in the benzylic position is beneficial to the cascade process. A subsequent cyclization of **II** leads to the observed product **202**. This proposed mechanism explains the observation that an acidic C–H bond can accelerate this oxidative cyclization. The similar mechanisms of transferring a proton in a [1,5]-manner have been described by Zhang, Seidel, Houk et al.[16b,17a–c]

In the total synthesis of D-homosteroid, Tietze and co-workers in 1999 reported a $BF_3{\cdot}OEt_2$-catalyzed cascade [1,5]-hydride transfer/cyclization of **204** to give the unusual novel bridged steroid alkaloid **205** in 85% yield at room temperature for 24 h (Scheme 78).[55] Although the benzylic methine and imine in **204** are comparatively inactive hydride donor and acceptor, respectively, with the assistance of an electron-donating methoxy group at *para*-position and activation by $BF_3{\cdot}OEt_2$, hydride could migrate to imine moiety readily. A subsequent nucleophilic attack of the amino group on the carbocation of **II** led to the formation of the bridged steroidal azacycles **205**.

In addition to phenyl-substituted imine, hydrazones and oxime ethers could also work as hydride acceptors in the presence of a Lewis acid. In 2009, Frank and co-workers described a similar $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydro-*N*-alkylation of hydrazones and oxime ethers.[56]

In 2012, Akiyama and co-workers described an expeditious $Sc(OTf)_3$-catalyzed reaction to access the isoquinoline skeleton **207** (Scheme 79).[57] The tosylimine formed *in situ* and the benzylic methylene worked as hydride acceptor and donor, respectively. $Sc(OTf)_3$ plays dual roles in the process, one of which is to promote the condensation of benzaldehyde **206** and tosyl amide. Because the hydride donor in the reaction is an inactive benzylic methylene, the electron-withdrawing tosyl group is indispensable to increase the electrophilicity of the C=N bond and $Sc(OTf)_3$ is also required to further activate the imide. The methodology was elegantly elaborated in the formal synthesis of racemate tetrahydropalmatine **210**.



Scheme 80. $BF_3{\cdot}Et_2O$-catalyzed stereoselective intramolecular amination of benzylic C(sp^3)–H bonds.

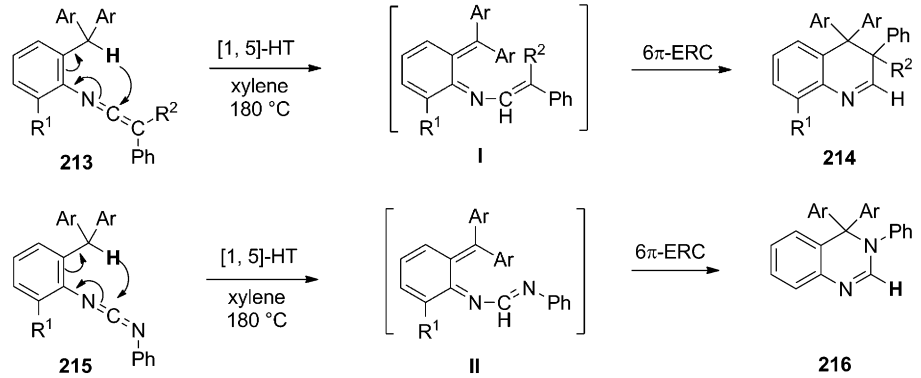
In 2012, Sames and co-workers demonstrated a highly stereoselective intramolecular amination of benzylic C(sp^3)–H bonds *via* the cascade [1,5]-hydride transfer/cyclization of *N*-tosylimines **212** formed *in situ* from aliphatic aldehyde **211** to construct 2-arylpiperidines **213** and 3-aryl-1,2,3,4-tetrahydroisoquinolines (Scheme 80).[29] The conformational freedom of the substrates has a profound influence on the chemical behavior of the hydride acceptors and those substrates with high conformational rigidity have higher reactivity than those with high conformational freedom. The cascade [1,5]-hydride transfer/cyclization is a highly stereoselective process which can be rationalized by the reversibility of the cyclization step. The high stereoselectivity results from thermodynamic control and the aryl ring prefers to adopt an axial position in diastereomer **II** in the chair of the piperidine ring to avoid the steric interaction (pseudo-allylic strain) with the sulfonamide group in diastereomer **I**.

In 2010, Alajarin and co-workers described a concise protocol for the synthesis of 3,4-dihydroquinolines **214** and 3,4-dihydroquinazolines **216** (Scheme 81).[13c] Triphenyl-substituted methines and electrophilic ketenimine/carbodiimide worked as hydride donors and acceptors, respectively. Because of the high electrophilicity of ketenimine and carbodiimide, and the highly stabilizing effect of the adjacent three aromatic groups, thermal conditions alone could efficiently facilitate the cascade process, under which **213** and **215** could be transformed into 3,4-dihydroquinolines **214** and 3,4-dihydroquinazolines **216**, respectively, in moderate to good yield. Mechanistically, the C–H bond of the triarylmethane fragment is cleaved *via* a [1,5]-hydride shift to give the intermediate conjugated 1,3,5-hexatriene **I** or **II** which suffers a subsequent 6π-electrocyclic ring closure to produce the sterically congested **214** and **216**.

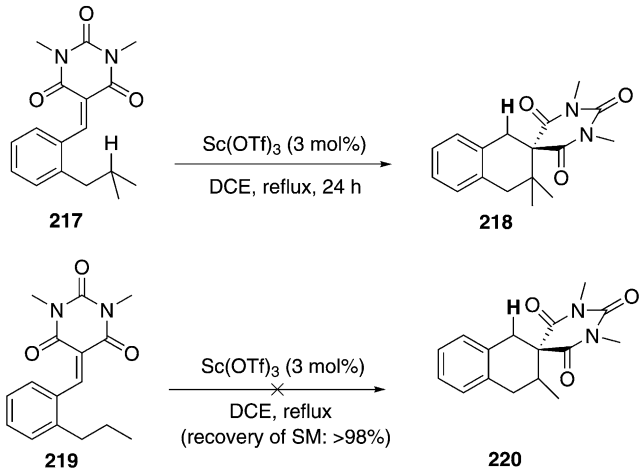
7 Non-Benzylic C(sp^3)–H Bonds

The cascade [1,5]-hydride transfer/cyclizations reported to date have entailed the electronic assistance of an adjacent heteroatom or aromatic group for stabilizing the carbocation formed upon hydride shift. However, hydride abstraction from an aliphatic, non-benzylic position is still a challenging task, and its realization would improve the usefulness of the cascade process in synthetic organic chemistry.

Because of the lack of electronic assistance of an adjacent heteroatom or aromatic group, the bond dissociation energy of the C–H bond in an aliphatic



Scheme 81. Direct C(sp^3)–H functionalization of tri(di)arylmethanes.

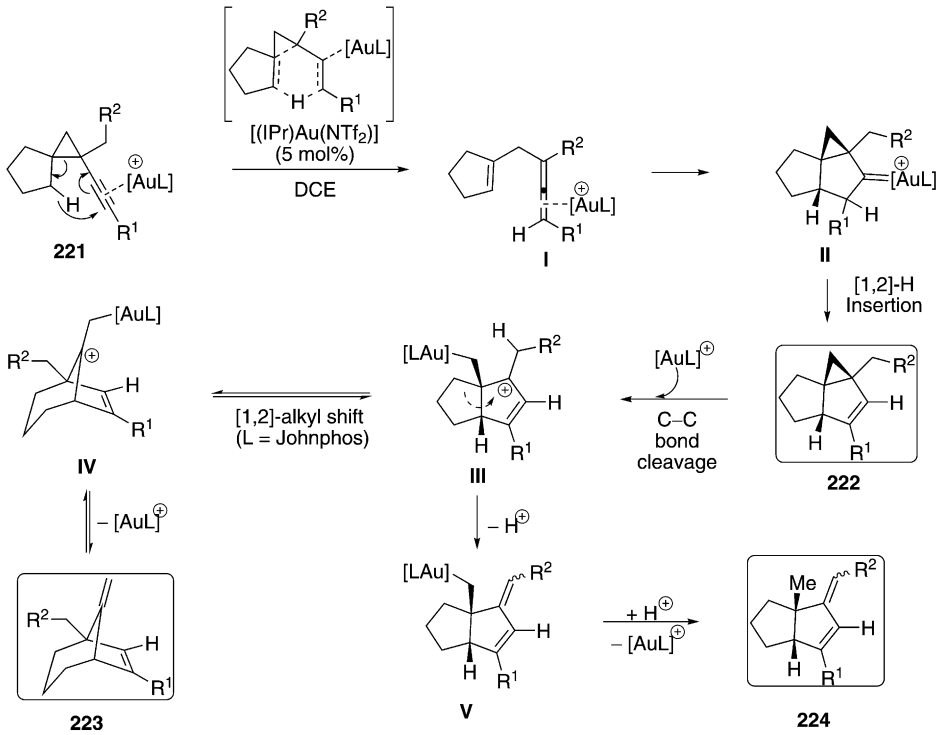


Scheme 82. $Sc(OTf)_3$-catalyzed direct functionalization of aliphatic tertiary C(sp^3)–H bond.

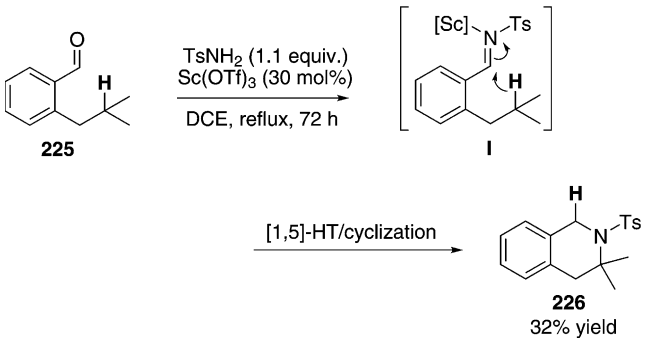
non-benzylic position is quite high. It was not until 2011 that Aikyama et al. managed to employ non-benzylic methylene as the hydride donor in a cascade reaction.

In 2011, Akiyama and co-workers first discovered an unprecedented cascade [1,5]-hydride transfer/cyclization with non-benzylic methine as hydride donor (Scheme 82).[19d] This reaction represented the first example of a hydride shift occurring from an aliphatic, non-benzylic position in the internal redox process. Treatment of benzylidenebarbituric acid **217** with 3 mol% $Sc(OTf)_3$ in refluxing $ClCH_2CH_2Cl$ for 24 h could furnish the desired tetraline **218** in excellent yield. Notably, the substrate with a linear side chain **219** did not give the desired product **220**, even with a catalyst loading of 30 mol%. This result suggests that the substituent effect is crucial for the success of the cascade process.

In 2012, Barluenga and co-workers elegantly demonstrated an intriguing manifold reactivity of alkynylcyclopropanes **221** that bear a spirane core (Scheme 83).[58] Remarkably, a comparatively inactive non-benzylic secondary C–H bond could work as hydride donor. The cyclopropane ring in the substrate was crucial for the success of the cascade process, which could bring an inactive methylene group close to the alkyne moiety. Thus the proximate hydride could be readily abstracted by the electrophilic alkyne activated by a gold catalyst. The diverse fate of the resulting cationic gold species could be efficiently controlled by simply selecting the appropriate catalyst {either [(JohnPhos)Au(MeCN)][SbF_6] or [(IPr)Au-(NTf_2)]} and reaction temperature. A range of cyclic structures, for example, pentalene derivatives **222** and **224**, and bicycles **223** can be accessed with complete selectivity. Mechanistically, the gold-alkyne coordination triggers the [1,5]-hydride transfer with concomitant ring opening of the cyclopropane. The generated 1,4-enallenyl gold intermediate **I** might then undergo a cyclization *via* intermediate **II** to afford tricycle **222**. The subjection of **222** to harsher



Scheme 83. Gold-catalyzed direct functionalization of secondary non-benzylic C(sp^3)–H bonds.



Scheme 84. $Sc(OTf)_3$-catalyzed hydro-*N*-alkylation with aliphatic tertiary C(sp^3)–H bond as hydride donor.

reaction conditions leads to the formation of **223** and **224**, and **III** might be their common intermediate – formed by regioselective gold-catalyzed C–C bond cleavage. The formation of **223** can be rationalized by a [1,2]-alkyl migration of **III** and metal elimination of **IV**. Alternatively, deprotonation of **III** and a subsequent protodemetallation of **V** would provide the pentalene **224**.

One more example with an aliphatic non-benzylic methine as hydride donor was also reported by Akiyama and co-workers in 2012, in which the tosylimine **I** generated *in situ* from **225** was employed as hydride acceptor (Scheme 84).[57] Three-step cascade transformations involving imine formation/[1,5]-hydride shift/cyclization occurred to afford isoquinoline with $Sc(OTf)_3$ as catalyst. In order to get a decent yield, a 30 mol% catalyst loading was employed and the tetraline **226** was obtained only in 32% yield even with a prolonged reaction time (72 h).

8 Conclusions and Perspectives

In this review we have highlighted the recent advances of cascade [1,n]-hydrogen transfer/cyclization as a versatile protocol to directly functionalize inactive C(sp^3)–H bonds into C–C, C–N and C–O bonds in an atom-economical manner. A variety of hydrogen donors and acceptors has been well categorized and different activation modes of hydrogen acceptors have been discussed. This methodology has proved powerful in delivering molecular complexity, especially in the synthesis of a variety of useful and pharmaceutically important heterocycles, for example, 5-, 6-, 7-membered heterocyclic, carbon-fused or spirocyclic species. The facile construction of C–C, C–N and C–O bonds and ring skeletons renders it an attractive method to access value-added molecules from readily available starting materials.

Despite the significant developments in recent years, there is still much left to do in the future. For instance, the types of hydride donors and acceptors are still rather limited. More C(sp^3)–H bonds α to heteroatoms which have lone pairs, for example, phosphorus, bromine, chlorine etc. are likely to be exploited as hydrogen donors and more diverse electron-deficient species can be employed as hydrogen acceptors. Furthermore, complex domino reactions involving the generation of hydrogen acceptors *in situ* with subsequent hydrogen migration/cyclization can also be designed to construct more complex ring skeletons.

Another clear frontier in this area is the asymmetric catalytic version of this reaction, especially under organocatalysis. Although this methodology has shown an appealing potential to construct complex moieties, it has been seldom exploited in total syntheses. The synthetic scope of this methodology in natural product synthesis has to be further exploited.

Finally, the mechanistic pathway behind this reaction should be studied in-depth and some problems need to be addressed such as the influencing factors of the hydride transfer and the essence of the hydrogen transferred. On the basis of the above clarifications and deeper understanding of these transformations, discovery of new highly active and selective catalysts for this reaction and development of novel reactions are to be expected in the future.

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