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REVIEW

Hydrogen-Atom Transfer Reactions

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Abstract The cascade [1,*n*]-hydrogen transfer/cyclization, recognized as the *tert*-amino effect one century ago, has received considerable interest in recent decades, and great achievements have been made. With the aid of this strategy, the inert C(sp^3)–H bonds can be directly functionalized into C–C, C–N, C–O bonds under catalysis of Lewis acids, Brønsted acids, as well as organocatalysts, and even merely under thermal conditions. Hydrogen can be transferred intramolecularly from hydrogen donor to acceptor in the form of hydride, or proton, followed by cyclization to furnish the cyclic products in processes featuring high atom economy. Methylene/methine adjacent to heteroatoms, e.g., nitrogen, oxygen, sulfur, can be exploited as hydride donor as well as methylene/methine without heteroatom assistance. Miscellaneous electrophilic subunits or intermediates, e.g., alkylidene malonate, carbophilic metal activated alkyne or allene, α,β-unsaturated aldehydes/ketone, saturated aldehydes/iminium, ketenimine/carbodiimide, metal carbenoid, electron-withdrawing groups activated allene/alkyne, in situ generated carbocation, can serve as hydride acceptors. This methodology has shown preeminent power to construct 5-, 6-, or 7-membered heterocyclic as well as carbon rings. In this chapter, various hydrogen donors and acceptors are adequately discussed.

Keywords Hydrogen transfer · Hydrogen donors · Hydrogen acceptors · C(sp^3)–H functionalization · Heterocycles

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Abbreviations

Cbz	Benzyloxycarbonyl
Cod	1,5-Cyclooctadiene
CSA	Camphorsulfonic acid
DCE	1,1-Dichloroethane
DFT	Density functional theory
DMF	*N,N*-dimethylformamide
DNBS	2,4-Dinitrobenzensulfonic acid
DPP	Diphenyl phosphate
ERC	Electrocyclic ring closure
Fmoc	9-Fluorenylmethoxycarbonyl
HT	Hydrogen transfer
IBX	*O*-iodoxybenzoic acid
m-CPBA	*meta*-Chloroperbenzoic acid
MW	Microwave
MS	Molecular sieves
Pg	Protecting group
*P*TSA	*p*-Toluenesulfonic acid
RT	Room temperature
TCE	1,1,2-Trichloroethane
TFA	Trifluoroacetic acid
TMS	Trimethylsilyl

1 Introduction

When talking about hydride donors, undoubtedly miscellaneous metal hydrides serving as reducing agents should be mentioned first, e.g., $NaBH_4$, $LiAlH_4$, Red-Al, selectride, etc. In addition, organic molecules can also play the role of hydride donors, which could be retrospected to 1853 when Cannizzaro reported base-mediated disproportionation of benzaldehyde into benzyl alcohol and benzoic acid via intermolecular hydride transfer from a deprotonated hemiacetal intermediate onto an aldehyde [1–3]. The Tishchenko reaction may be considered as the seminal example of a reaction proceeding by an intramolecular hydride shift. Evans et al. further developed this reaction to diastereoselectively construct β-hydroxy ketones, which is known as the Evans–Tishchenko reaction [4]. Similarly, by changing the redox state of the reactants in the Tishchenko reaction, the alcohol can be readily oxidized to aldehyde via the Meerwein–Pondorf–Verley (MPV) reduction [5–7], and aldehyde can be reduced to alcohol via the reverse Oppenauer oxidation, which operate by means of an identical Al^{3+}-preorganized intramolecular 1,5-hydride shift [8–10].

Over the past decades, tremendous progress has been made in functionalization of inert C–H with the demand of green and sustainable chemistry [11–14]. The fast development of this vigorous research 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 inert C–H bonds to C–X bonds (X = halogens, OTf, etc.). In this context, a large number of innovative and efficient synthetic methodologies have been developed, thus offering chemists powerful tools for the rapid buildup 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 inert C(sp^3)–H bonds still remains a great challenge owing to the high bond dissociation energy of C(sp^3)–H bonds. Only recently, some promising catalytic processes for the selective functionalization of C(sp^3)–H have been reported with noble metal salts, e.g., Pd, Rh as catalysts. Despite numerous challenges posed by direct C(sp^3)–H bond activation, the cascade [1,*n*]-hydrogen transfer/cyclization process opens new avenues, which provides organic chemists unusual solutions to address their synthetic challenges [15–20]. This fascinating chemistry was discovered in 1895, which was initially termed as '*tert-amino effec*t' by Meth-Cohn and Suschitzky in 1972 [21]. This name refers to the tendency of substituted *N*,*N*-dialkylanilines to undergo unusually facile ring-closing reactions involving various groups at the *ortho* position. However, the tertiary amine group is neither necessary nor sufficient to guarantee a successful reaction for a particular substrate.

The substrate requires a hydride acceptor proximal to a C–H bond serving as hydride donor, and the reaction is initiated by a hydride shift (or related H-atom-transfer step), which formally oxidizes the carbon donor and reduces the hydride acceptor. The new C–X bond will be formed at the hydride-donor atom, after the hydride shift takes place. The defining characteristic for these reactions is the functionalization of a C–H bond concurrent with a hydride shift. The names proposed by Sames ("HT-cyclization") and Akiyama ("Internal Redox Cascade") would seem more appropriate if focusing more on the unique hydride-shift mechanism that draws together a diverse group of substrates, at least for intramolecular examples.

This cascade process has been recognized as an efficient and powerful method for selective activation and direct functionalization of inactive C(sp^3)–H bonds. It represents an intriguing sequential C(sp^3)–H activation/C–C, C–N or C–O bonds formation process and proves to be a versatile protocol to construct 5-, 6-, or 7–membered hetero/carbon spiro or fused cycles, such as tetrahydroquinolines [22], chromans [23–25], spiroethers [26–30], and tetrahydropyrans [31–36], which are common moieties in biologically important natural products and pharmaceuticals.

A series of significant review papers have been published on this chemistry [15–18] and we aim to cover the progress in this field since 2006. Some reputable groups such as Sames, Seidel, Akiyama, Vidal, Liu, and Gagosz showed preeminent applications of this methodology to build various hetero/carbon spirocycles and fused rings. In the following, these elegant findings will be categorized according to the types of hydride donors (i.e., *tert*-amino effect, C(sp^3)–H bonds α to ethereal oxygen and sulfur, benzylic C(sp^3)–H bond, non-benzylic C(sp^3)–H bond) and the types of hydrogen acceptors (benzylidene malonate, transition metal activated alkyne or allene, enal or enone, aldehyde or

imine, ketenimine/carbodiimide). This review will provide elementary insight into these cascade reactions concerning the mechanism, the reactivity of hydrogen donor and acceptor, migration modes of hydrogen, etc.

2 Mechanistic Insight into [1,5]-Hydrogen Transfer

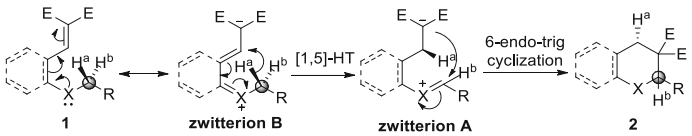
[1,5]-Hydrogen transfer is selected as a model reaction for discussing the mechanism as it is the most common mode of hydrogen migration.

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 hydrogen 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 [37–42]. A plausible mechanism of this transformation is depicted in Scheme 1. Initially, **1** and zwitterion **B** form a resonance hybrid. Subsequently **B** undergoes [1,5]-hydrogen transfer in the form of a sigmatropic hydrogen, resulting in zwitterion **A**. A consecutive intramolecular nucleophilic attack affords the final cyclic product **2** [43–45].

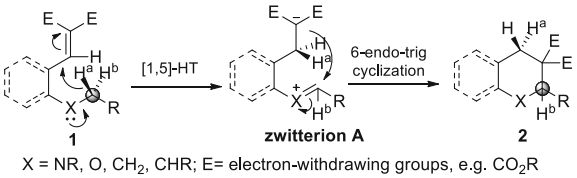
This cascade process can also be rationalized in an alternative way (Scheme 2). The zwitterion **A** is generated from **1** via [1,5]-hydrogen transfer from the carbon α to heteroatom **X** to the electrophilic acceptor in the form of hydride anion, followed by an intramolecular 6-*endo-trig* cyclization (or intramolecular nucleophilic attack), giving rise to the heterocycle **2** [46–48]. 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 [49–52]. Generally speaking, the second theoretical explanation is more reasonable because the aromatic ring is dispensable and the cascade HT-cyclization can proceed smoothly within many aliphatic substrates.

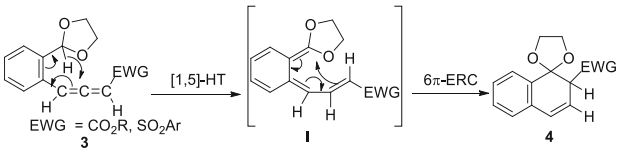
The final cyclization can also proceed in the manner of a 6π-electrocyclic ring closure (6π-ERC) (Scheme 3). After a [1,5]-hydride transfer, the conjugated 1,3,5-hexatriene intermediate **I** can be produced, which undergoes subsequent 6π-ERC to give the cyclized product **4**. Thus, the formation of unstable zwitterionic intermediate **A** (Schemes 1, 2) with charge separation is avoided [52–56].



Scheme 1 The sigmatropic transfer of hydrogen

Scheme 2 The transfer of hydride anion through space





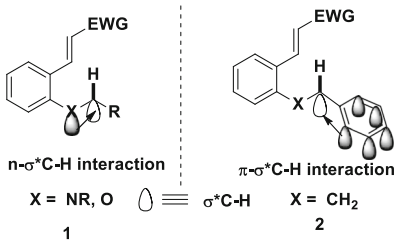
Scheme 3 Cascade [1,5]-hydride transfer/6π-electrocyclic ring closure

2.2 Reactivity of Different Hydrogen Donors

Heteroatoms, e.g., nitrogen, oxygen, and sulfur, adjacent to hydrogen donors (methylene or methine) can facilitate the hydride migration, so do aryl groups and alkyl groups. Theoretically, the heteroatoms play three roles. Firstly, heteroatoms with high electronegativities will polarize the C–X bond, causing the weakening of the C–H bond. Secondly, the hyperconjugation effect of σ^*C–H orbital with a neighboring atom lone pair or π-orbital promotes the hydride shift (Fig. 1) [57–59]. This effect not only weakens the C(sp^3)–H bond but also increases the negative charge density of the hydrogen atom.

Thirdly, the carbocationic intermediate generated upon hydride migration, with which iminium, oxocarbenium, and thiocarbenium can form resonance hybrids, would be stabilized by adjacent heteroatoms via *p–p* conjugation. Consequently, the rate of C(sp^3)–H bond cleavage is closely associated with the stability of cationic intermediate, thus any factor that can stabilize this intermediate will dramatically promote this process, while the groups destabilizing it will retard the proximal C(sp^3)–H bond cleavage. In contrast to iminium cation, which has considerable stability, oxocarbenium- and thiocarbenium ions are less stable and more difficult to generate, not to mention benzylic and *tert*-alkyl carbocation (Fig. 2). DFT calculations and experimental results show that the thiocarbenium ion exhibits a little bit higher stability than the oxocarbenium species [60]. The cationic

Fig. 1 The electronic assistance from heteroatom and aryl group



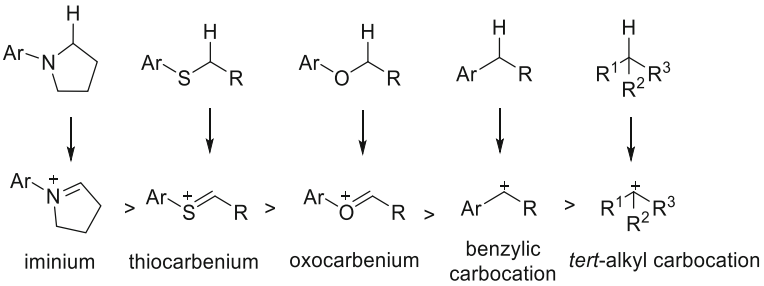


Fig. 2 Stability comparison of different cations

intermediate can also be stabilized by the aromatic or alkyl substituents on the hydrogen donors via π–p conjugation or σ–p hyperconjugation, respectively. Primary C–H bond is rarely exploited as hydrogen donor except in Zhang's and Chatani's reports [40, 61, 62]. In addition to the above-mentioned hydride donors, acetalic and dithioacetalic C–H bonds can also work as the hydride donors [52, 57–59].

2.3 Activation Mode of Hydride Acceptors

Almost all the electrophilic groups or electrophilic intermediates can be employed as the hydride acceptors, e.g., alkylidene malonates, carbophilic transition metals activated alkynes or allenes, enal/enones, aldehyde/ketones, imines, ketenimine/carbodiimides, metal carbenoids, alkynes carrying electron-withdrawing groups, as well as in situ-generated carbocations (Fig. 3).

The feasibility of hydrogen transfer strongly depends on the natures of hydrogen acceptors and donors. It can be imagined that there is competition between the transient cationic subunits and the electrophilic hydride acceptors for the hydride after cleavage of the inert C(sp^3)–H bond (Fig. 3). If the hydride acceptor is

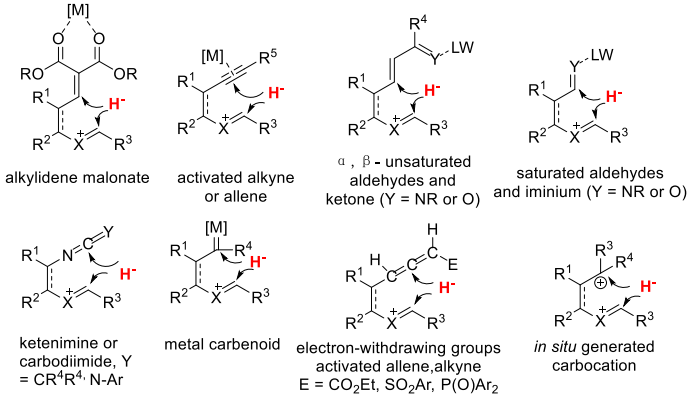


Fig. 3 Different types of hydride acceptors and activation modes

electrophilic enough, it can "snatch" hydride to give the zwitterion **A**, followed by an intramolecular nucleophilic attack to give the cyclized product **2** (Scheme 2); whereas if not, the cationic subunit will "retrieve" hydride and no reaction will occur. Therefore, two strategies are applicable to facilitate the cascade process, i.e., increasing the electrophilicity of the hydride acceptor or increasing the stability of the cationic subunit generated in situ upon hydride migration. Remarkably, hydrogen can be transferred not only in the form of hydride anion but also in the form of protons and hydrogen atoms [63]. If the hydrogen acceptor is a relatively strong nucleophile, hydrogen will be abstracted by the acceptor in the form of a proton [53, 62, 64–68], and if the hydrogen acceptor is a free radical, the C–H of hydrogen donator will be homolyzed to give the hydrogen atom, which is then transferred to the hydrogen acceptor [63]. The hydrogen can be transferred not only in [1,5]-manner but also in the manners of [1,4]-[69, 70] [1,6]-[39, 66, 71–77], and [1,9]-manner [78]. If the hydride donor and acceptor are active enough, the hydride migration may occur through space, giving rise to a zwitterionic intermediate. Only if the nucleophile and electrophile in the zwitterionic intermediate are located in proper geometric positions, the subsequent intramolecular nucleophilic attack will occur, resulting in the formation of 5- [72, 73], 6-, or 7- [41, 79, 80] membered products. If no nucleophile is available or cyclization was blocked by steric hindrance, hydride will merely serve as reductant [81–84] or unwanted side products will be produced [74].

3 C(sp^3)–H Bond Adjacent to *Tert*-Amino Moieties as Hydride Donor (*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 [22] or other *N*-heterocycles [15, 19, 20, 46, 85–87]. The *tert*-amino effect has been widely utilized in the synthesis of pyridine, pyrimidine, and pyridazine derivatives, which has been well reviewed by Mátyus et al. [15].

3.1 Electrophilic Benzylidene Malonates as the Hydride Acceptors

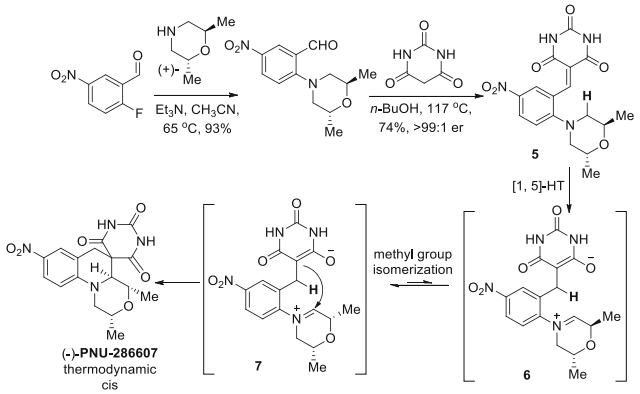
Hurd et al. elegantly elaborated this methodology in the key step of total synthesis of PNU-286607 (Scheme 4) [88]. The benzylidene intermediate **5** was prepared in situ and [1,5]-hydride migration readily proceeded under thermal conditions to give zwitterionic intermediate **6**. Via *trans–cis* isomerization of methyl group, the zwitterion **6** was converted to thermodynamically more favorable zwitterion **7**, and a subsequent intramolecular equatorial attack of the enolate on the iminium subunit furnished *cis* (−)-PNU-286607 in 74 % yield and >99:1 er.

For a long time, harsh thermal conditions were always needed to overcome the high energy barrier of [1,5]-hydride transfer, which severely limited the application of this strategy. Seidel et al. employed $Ga(OTf)_3$ to catalyze the cascade process of **8**, via which tetrahydroquinolines **9** could be furnished in 90 % yield within 15 min at room temperature (Scheme 5) [89]. Meanwhile, the chiral bisoxazoline

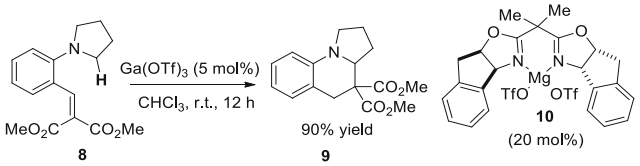
magnesium complex **10** was employed to catalyze the asymmetric version of this reaction, furnishing the enantio-enriched product **9** in 74 % yield and 30 % ee, which presented the first report of enantioselective cascade [1,5]-HT/cyclization.

Akiyama et al. disclosed a chiral phosphoric acid **13**-catalyzed asymmetric cascade [1,5]-HT/cyclization of **11**, which afforded tetrahydroquinolines **12** with good to excellent enantioselectivity (Scheme 6) [90]. The benzylidene malonate subunit forms hydrogen bonds with the proton of phosphoric acid **13**, which not only increased the electrophilicity of hydride acceptor but also governed the asymmetric step. Presumably, the stereoselectivity is mostly controlled at the hydride shift step and the enantiotopic hydrogen is selectively activated by chiral phosphoric acid **13**.

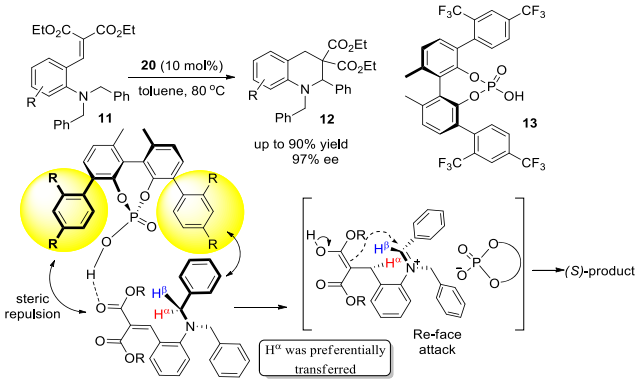
One more asymmetric version of cascade [1,5]-hydride transfer/cyclization was reported by Feng et al. using his well-known chiral *N*, *N*′-dioxide-Co(II) complex **14** as catalyst. The optically active tetrahydroquinolines **15** were obtained in excellent yields and high enantioselectivities (Scheme 7) [91]. Theoretically, the oxygen atoms of *N*, *N*′-dioxide, amide, and the benzylidene malonate are coordinated to cobalt(II) in a hexadentate manner, hence 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, furnishing the (*S*)-configured products.



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

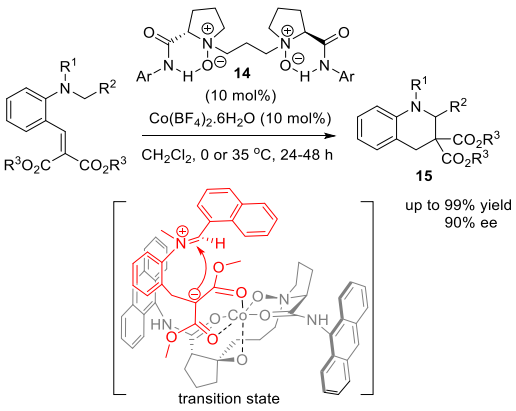


Scheme 5 Lewis acid-catalyzed formation of tetrahydroquinolines



Scheme 6 Chiral phosphoric acid-catalyzed asymmetric synthesis of tetrahydroquinoline

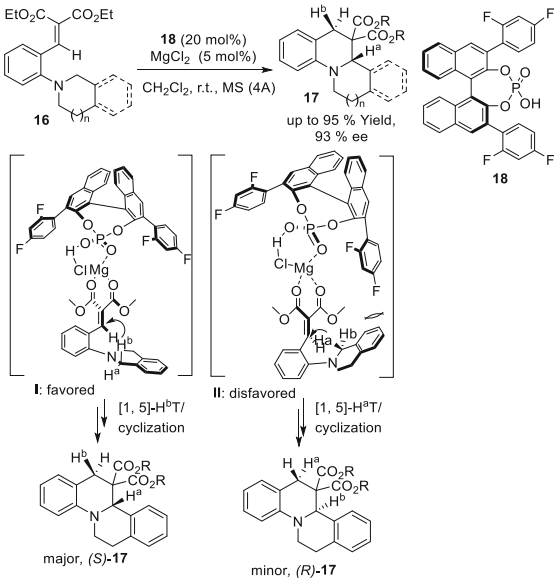
Scheme 7 Chiral complex of *N*,*N*′-dioxide and cobalt(II)-catalyzed synthesis of tetrahydroquinolines



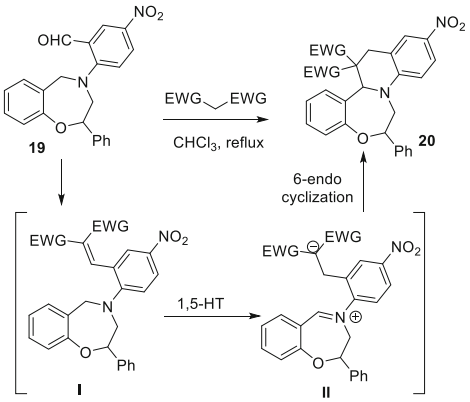
Luo et al. exploited a binary catalytic system, which involved $Mg(BF_4)_2$ and chiral phosphoric acid **18** to facilitate the cascade reaction of **16**, furnishing the enantio-enriched products **17** in high yields and enantioselectivities (Scheme 8) [49, 50]. Both H^a and H^b on the isoquinoline methylene carbon atom may participate in [1,5]-hydride transfer, requiring two different helical conformations **I** and **II**. Due to the suprafacial constraint, however, **I** is more favorable than **II** owing to its space tolerance. Therefore, the selective activation in complex **I** initiates enantiotopic [1,5]-H^b transfer, leading to the chiral helical zwitterionic intermediate. Finally, the C–C bond can be formed spontaneously with preserved stereochemistry after a small conformational change.

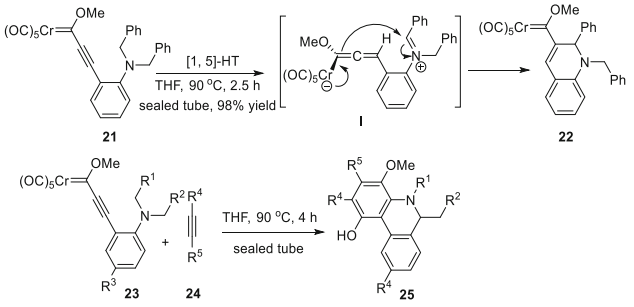
Matyus et al. described a cascade Knovenagel/1,5-hydride transfer/cyclization reactions of 4-aryl-2-phenyl-1,4-benzoxazepine derivatives **19**, which furnished fused *O*,*N*-heterocycles **20** containing tetrahydro-1,4-benzoxazepine and tetrahydroquinoline moieties with high yields and diastereoselectivity (Scheme 9) [92]. Basically, under thermal conditions, the benzylidene intermediate **I** generated in situ

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



Scheme 9 Synthesis of 1,4-benzoxazepines by domino Knoevenagel–[1,5]-hydride shift cyclization reaction





Scheme 10 Synthesis of 1,2-dihydroquinolinyl carbene complexes via [1,5]-HT/cyclizations

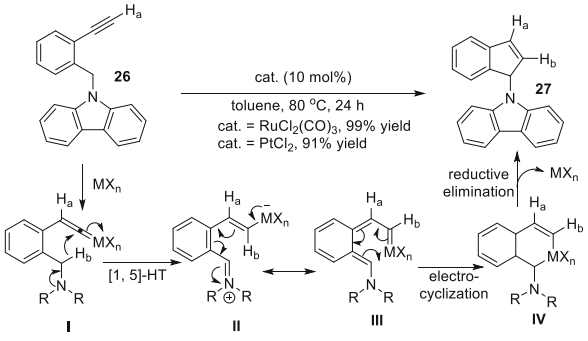
underwent sequential 1,5-hydride shift and intramolecular 6-endo cyclization readily to furnished **20**.

3.2 Electrophilic Activated Alkyne as the Hydride Acceptor

Electron-deficient alkyne can also serve as an ideal hydride acceptor. Barluenga et al. described a [1,5]-hydride transfer/cyclization process of alkynyl Fischer carbene complexes **21**, which afforded 1,2-dihydroquinolynyl carbene complexes **22** (Scheme 10) [51]. The alkyne moiety in **21** activated by electrophilic Fischer carbene was 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 **22**, which can be further elaborated [51, 93]. The presence of strong electron-withdrawing chromium pentacarbonyl moiety is crucial to trigger the energy-demanding [1,5]-hydride transfer. When alkynyl carbene complex **23** was heated with four equivalents of 1-hexyne **24**, 5,6-dihydrophenantridine derivative **25** could be afforded.

The alkynes activated by alkynophilic metals, e.g., platinum and ruthenium, are considerably electrophilic, which can be employed as good hydride acceptors for the cascade [1,5]-HT/cyclization process. Chatani et al. reported a cycloisomerization of 9-carbazolyl substituted 1-alkyl-2-ethynylbenzene **26** catalyzed by alkynophilic metal salts $PtCl_2$ and $[RuCl_2(CO)_3]_2$ under mild conditions, which produced substituted indene **27** (Scheme 11) [40]. Basically, the metal-vinylidene complex **I** is formed initially via π-activation of alkyne moiety, then benzylic hydride is delivered in [1,5]-manner to the most electrophilic α-carbon of metal vinylidene, resulting in zwitterionic intermediate **II**. Afterwards, the metal carbenoid intermediate **III** generated via resonance of intermediate **II** undergoes 6π-electrocyclization to give intermediate **IV** and a final reductive elimination gives rise to the cyclized product **27**.

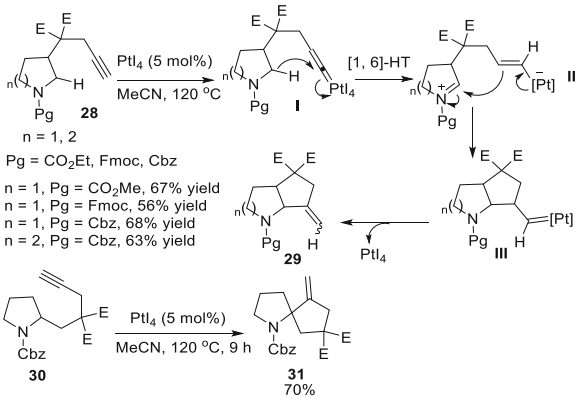
A methylene group adjacent to a protected secondary amine, e.g., carbamate, could also be exploited as hydride donor. Remarkably, as the lone pair of nitrogen was partially transferred to carbonyl group via *p*–π conjugation, the electron-donating ability of nitrogen was significantly decreased and the negative charge



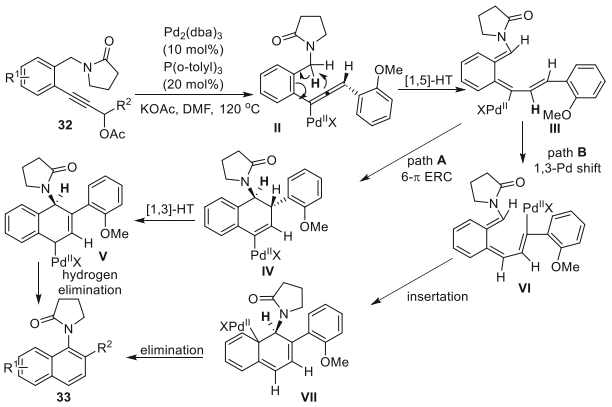
Scheme 11 Platinum and ruthenium-catalyzed cycloisomerization of 1-alkyl-2-ethynylbenzenes

density of the hydrogen atom could only be partially increased by nitrogen via hyper-conjugative interaction compared with *tert*-amine. Therefore, high valent metal salts owning stronger activation ability should be employed to facilitate the cascade process. Additionally, because of the electron-withdrawing nature of carbamates, electron density on the nitrogen atom was decreased, resulting in comparative difficulty in forming alkoxycarbonyl-iminium intermediate, which is less stable than that generated from *tert*-amine. Sames et al. reported a PtI_4-catalyzed α-alkenylation of protected cyclic secondary amines **28**, which afforded annulation products **29** (Scheme 12) [39]. 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 **30**. 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 fragment to give the intermediate **III**. A final platinum salt elimination gives rise to the fused products **29** or **31**.

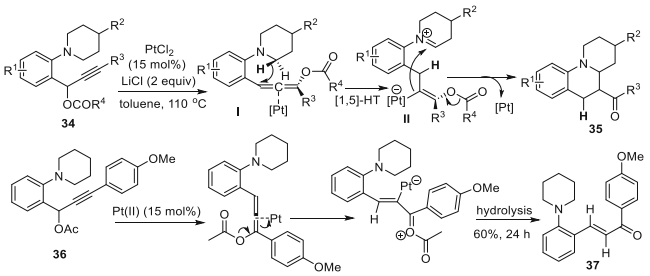
Liang et al. described a palladium-catalyzed cascade [1,5]-HT/cyclization of propargylic esters **32** to construct substituted naphthylamines **33** (Scheme 13) [53]. Notably, propargylic esters substituted with electron-rich aryl groups, which led to electron-rich allenyl-palladium complex at the propargylic 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 indicated the hydrogen was abstracted by nucleophilic allenyl-palladium in the form of proton. Mechanistically, the nucleophilic allenyl-palladium intermediate **II** is generated from the propargylic compound **32** under the catalysis of Pd(0), then [1,5]-proton transfer follows to afford the intermediate **III**, the direct 6π-electrocyclic ring closure (ERC) of which leads to the intermediate **IV**. Afterwards, **IV** undergoes [1,3]-hydrogen shift and elimination to afford the final product **33** (path A). Alternatively, the intermediate **VI** may also be formed via a [1,3]-palladium shift of the intermediate **III**. The following insertion of the C-Pd bond and hydrogen elimination afford the product **33** (path B).



Scheme 12 Platinum-catalyzed *N*-alkenylation via [1,6]-HT/cyclization



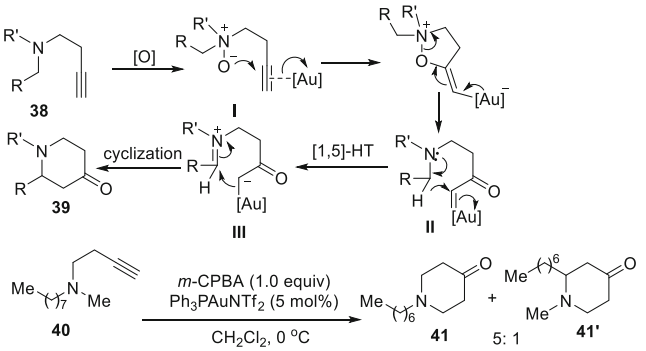
Scheme 13 Palladium-catalyzed [1,5]-proton migration of propargylic esters toward substituted naphthylamines



Scheme 14 Platinum-catalyzed synthesis of ring-fused tetrahydroquinolines

The same group also reported a $PtCl_2$-catalyzed hydro-functionalization reaction of allenes formed in situ from propargylic esters **34**, which furnished multi-functionalized tetrahydroquinolines **35** (Scheme 14) [42]. If R^3 is an electron-withdrawing group, the formation of products **35** is favored. Mechanistically, hydride is delivered initially to 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 fused tetrahydroquinoline **35**. A completely different transformation occurred in the case of propargylic ester **36** bearing a strong electron-donating 4–$MeOC_6H_5$ group in R^3, furnishing an α, β-unsaturated ketone **37**, which suggested that electron-donating 4–$OMeC_6H_5$ group in R^3 decreased the electrophilicity of C(1), and the hydration of allene would be more favored than [1,5]-hydride shift.

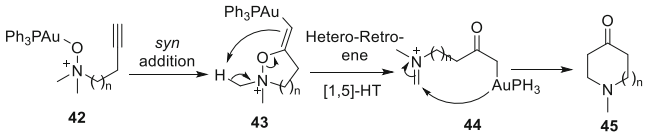
Zhang et al. reported an efficient synthesis of piperidin-4-ones based on gold-catalyzed cascade process (Scheme 15) [61, 68]. One-pot sequential *m*-CPBA oxidation and gold-catalysis with $Ph_3PAuNTf_2$ led to an excellent yield of piperidin-4-one **39**. This chemistry allowed facile preparation of 5-, 6-, and 7-membered ring-fused or spiro-piperidin-4-ones. Initially, Zhang et al. speculated that tertiary



Scheme 15 Formal [4 + 2] approach toward piperidin-4-ones via Au catalysis

aliphatic amine *N*-oxide **I** generated via *m*-CPBA oxidation of tertiary amine **38** might undergo gold-catalyzed intramolecular alkyne oxidation [94] to furnish α-oxo gold carbene **II**, in which α-hydride would migrate to the electrophilic gold carbene, leading to the formation of zwitterion **III** containing an electrophilic iminium and a nucleophilic gold-enolate. A subsequent intramolecular cyclization furnished piperidin-4-one **39**. Notably, the less-substituted methyl in amine **40** 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 hydrogen donors was rather unusual, i.e., the poor hydride donors were more active than good hydride donors, e.g., 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 **41** and **41′**, it failed to explain the regioselectivity. Thus, the initially proposed mechanism of [1,5]-hydride transfer/cyclization is quite questionable.

Based on DFT calculation and a variety of control experiments, Zhang and Houk et al. argued that the mechanism involving the sequential ring opening and [1,5]-proton **s**hift was energetically more favorable (Scheme 16) [62]. Presumably, the first step is a *syn* addition of gold-coordinated *N*-oxide **42** to alkyne, resulting in the formation of intermediate **43**, which undergoes a hetero-retro-ene ([1,5]-proton **s**hift) to furnish intermediate **44**, thus the formation of gold-carbenoid intermediate **III** is avoided. The final step is a cyclization of **44** to yield piperidin-4-one derivatives **45** and regenerate the catalyst, which was calculated to be the rate-determining step. In **43**, phosphine ligand makes the adjacent carbon more



Scheme 16 Mechanism of Au(I)-catalyzed rearrangements of acetylenic amine-*N*-oxides

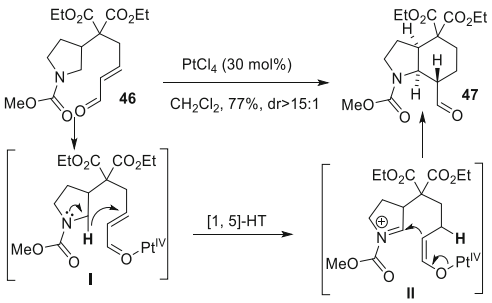
nucleophilic, thus the proton is abstracted from the least sterically hindered amine-substituent.

3.3 Electrophilic α,β-Unsaturated Aldehyde and Acyl Oxazolidinone as the Hydride Acceptors

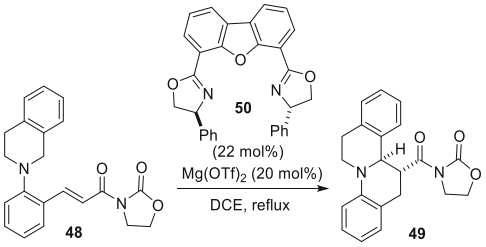
Sames et al. reported a $PtCl_4$-catalyzed α-alkylation of protected pyrrolidine **46**, via which the fused cycles **47** was furnished in good yield and high diastereoselectivity (dr > 15:1) (Scheme 17) [95]. Notably, the conformational rigidity of the substrate **46** could be increased significantly by the malonate moiety, which led to a more reactive hydride acceptor [96]. Because the iminium subunit in intermediate **II** could be significantly destabilized by carbamate, which rendered secondary C–H bond in intermediate **I** serving as hydride donor less reactive, high catalyst loading (30 mol%) of highly active $PtCl_4$ was indispensable to get decent yield (77 %).

Seidel et al. exploited the complex of $Mg(OTf)_2$ and chiral bisoxazoline **50** to catalyze the cascade reaction of substrates **48** carrying α, β-unsaturated acyl oxazolidinone, which produced chiral tetrahydroquinolines **49** in good yields and high enantioselectivities (Scheme 18) [97]. The employment of nickel perchlorate in combination with ligand **50** also furnished **49** in good diastereo- and enantioselectivity.

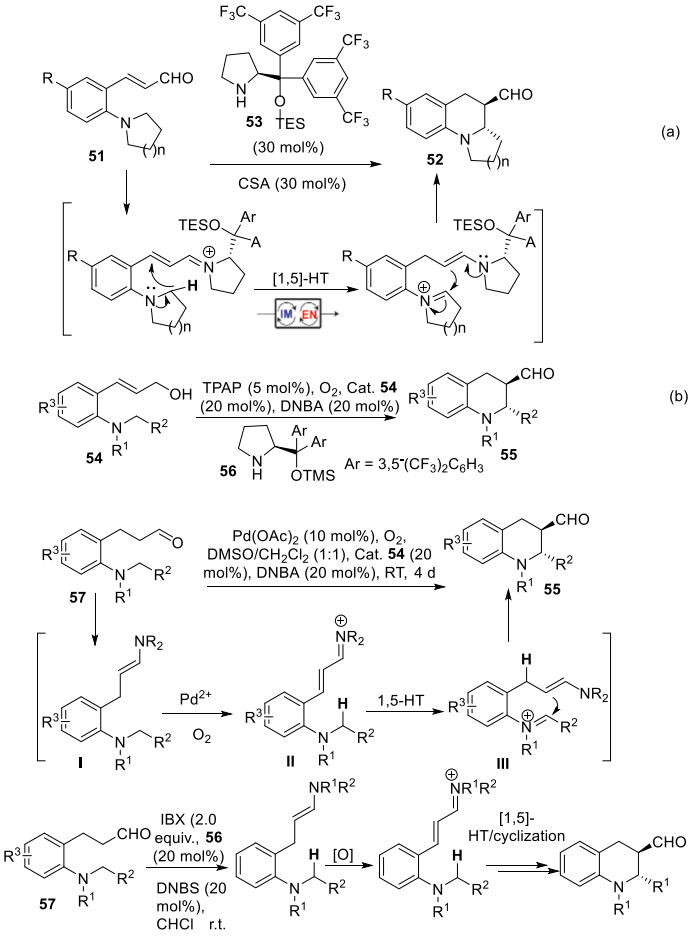
Chiral secondary amine could be employed to catalyze this cascade process. Kim et al. utilized Jørgensen catalyst **53** successfully to catalyze the cascade [1,5]-HT/ring closure sequences of *o*-*N*-pyrrolidinyl-substituted cinnamaldehydes **51** via sequential iminium and enamine activation, affording chiral tetrahydroquinolines **52** in high enantioselectivities (Scheme 19, a) [98]. Products incorporated with 7- to



Scheme 17 $PtCl_4$-catalyzed hydroalkylation of α, β-unsaturated aldehydes

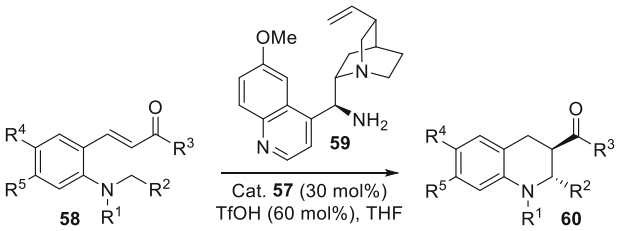


Scheme 18 Chiral Mg-bisoxazolidine complex-catalyzed intramolecular redox reactions via [1,5]-HT/cyclization

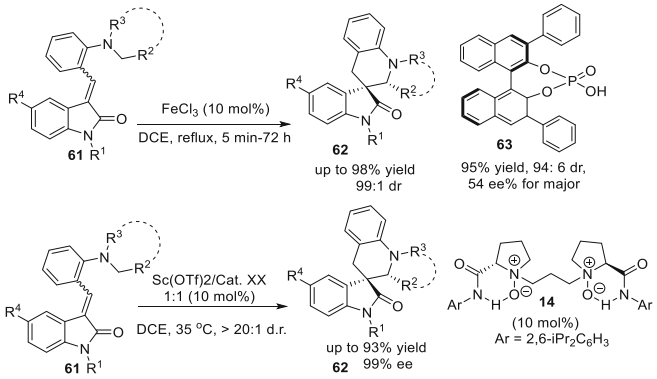


Scheme 19 Organocatalyzed enantioselective C–H bond functionalization via cascade [1,5]-HT/ring closure

9-membered azacycles could also be formed with excellent enantioselectivities. The enal could also be furnished in situ via aerobic oxidation of allylic alcohol. The same group described a one-pot transformation of 3-arylprop-2-en-1-ol derivatives **54** into tetrahydroquinolines **55** via a sequence of Ru(VII)-catalyzed aerobic oxidation/1,5-hydride transfer/cyclization (Scheme 19, b) [99], in which an in situ generated enal served as hydride acceptor. TMS substituted prolinol ether **56** was exploited as chiral catalyst, achieving high levels of enantioselectivity. Additionally, the saturated aldehyde **57** could be employed as the precursor of hydride acceptor, which was transformed in situ to α,β-unsaturated iminium **II** via Pd(II)-catalyzed aerobic oxidation (Scheme 19, c). Via a cascade Saegusa-type oxidative enamine catalysis/1,5-HT/cyclization sequences, which was catalyzed by Pd(II) and prolinol ether **56** in a relay style [100], tetrahydroquinolines **55** was prepared in



Scheme 20 Chiral primary amine-catalyzed asymmetric synthesis of tetrahydroquinolines via 1,5-HT/cyclization



Scheme 21 $FeCl_3$-catalyzed synthesis of spirooxindole tetrahydroquinolines

moderate yields and high levels of enantioselectivity. Furthermore, the electrophilic α,β-unsaturated iminium **II** could also be generated under metal-free oxidation condition (Scheme 19, d) [101]. The same group reported a Jørgensen catalyst **56**-catalyzed enantioselective three-step cascade reaction of substrate **57** involving oxidation/[1,5]-hydride transfer/ring closure, [102] in which IBX was exploited as oxidative agent to transform enamine to hydride acceptor **II**, furnishing tetrahydroquinolines **58** in moderate yields, moderate-to-high diastereoselectivities and excellent enantioselectivities.

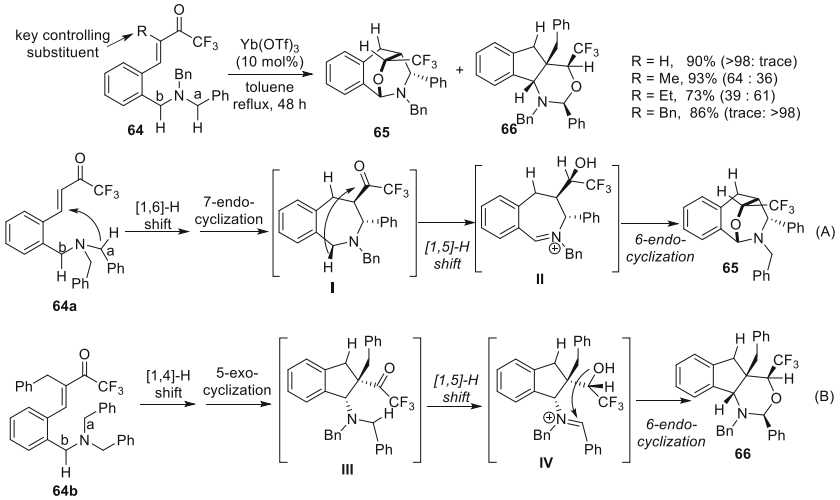
A similar reaction could also be implemented with enone **58** as hydride acceptor. This time, Kim et al. employed chiral primary amine **59** as chiral catalyst to prompt the cascade process [103], affording tetrahydroquinine derivatives **60** in moderate yields and with high enantioselectivities (up to 97 % ee) (Scheme 20).

Yuan et al. reported a $FeCl_3$-catalyzed stereoselective cascade [1,5]-HT/ring closure of **61**, furnishing structurally diverse spirocyclic oxindolyl tetrahydroquinolines **62** bearing contiguous quaternary or tertiary stereogenic carbon centers in high yields and with good diastereoselectivities (Scheme 21) [104]. The asymmetric reaction could be catalyzed by chiral phosphoric acid **63** (20 mol%), affording the enantio-enriched tetrahydroquinoline in 95 % yield, 94:6 dr and 54 % ee ($R^1 = CO_2Et$, R^2, R^3 = butylene, $R^4 = H$). The same reaction was further

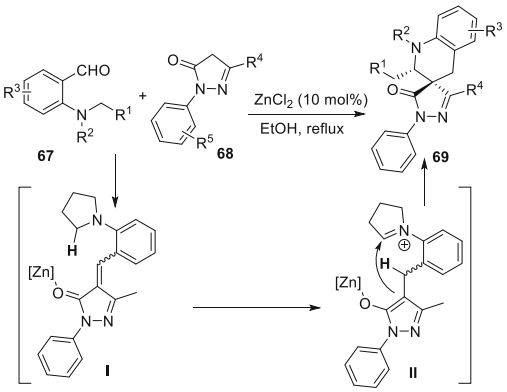
investigated by Feng et al. with his well-known chiral *N*, *N*′-dioxide-scandium complex **14** [105], resulting in the optically active spirooxindolyl tetrahydroquinolines **62** in good yields (up to 97 %) with excellent diastereoselectivities (>20:1) and enantioselectivities (up to 94 % ee). Strong chiral memory effect was found using a chiral substrate.

If two or more hydride donators and acceptors are available in the substrate, multiple cascade processes will occur to furnish complex cyclic products. Akiyama et al. reported a fascinating $Yb(OTf)_3$-catalyzed double $C(sp^3)$–H bond functionalizations of benzylamine derivative **64** through a sequential dual hydride shift/cyclization process, which carries two potential hydrogen donors, i.e., methylene **a** and methylene **b** (Scheme 22) [106]. The key feature was the initial hydride shift ([1,4]- or [1,6]-hydride shift), which was completely controlled by the bulkiness of α substituent of trifluoromethyl ketone. Through variation of the R group of ketone, the sequence of functionalization of two potential hydrogen donors could be totally reversed. A bicyclo[3.2.2]nonane skeleton **65** afforded from the substrate **64a** with *trans*-α,β-unsaturated trifluoroacetyl group (R^1=H) by a sequential [1,6]-and [1,5]-hydride shift process (equation A). On the other hand, a [1,4]- and [1,5]-hydride shift occurred successively in the substrate **64b** with a benzyl group α to a trifluoroacetyl group, resulting in the formation of bicyclic product **66** (equation B). The regioselectivity of initial $C(sp^3)$–H activation was elegantly rationalized by Akiyama via DFT calculation and theoretical studies revealed that the resonance stabilization in the benzylidene carbonyl moiety and the steric repulsion of the α-substituent (R) were the key to change the reaction course.

The enone could be prepared in situ via Knoevenagel condensation. Wang et al. reported a $ZnCl_2$-catalyzed tandem Knoevenagel condensation/1,5-hydride shift/cyclization of *o*-aminiobenzaldehyde **67** with substrate **68** carrying reactive methylene



Scheme 22 Double $C(sp^3)$–H bond functionalization mediated by sequential hydride shift/cyclization process for construction of polyheterocycles



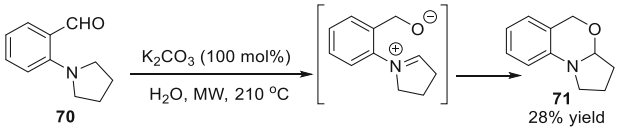
Scheme 23 $ZnCl_2$-catalyzed construction of spiropyrazolo-tetrahydroquinolines via cascade [1,5]-HT cyclization sequence

(Scheme 23) [107], which produced spiropyrazolo-terahydroquinoline derivatives **69** in good to high yields with good to excellent diastereoselectivities (up to 95 % yield, >95:5 dr). The strong Lewis acid, i.e., $ZnCl_2$, could not only facilitate the formation of enone **I** and enolate **II** but also increase the electrophilicity of enone by chelation of the carbonyl of enone to promote 1,5-hydride shift.

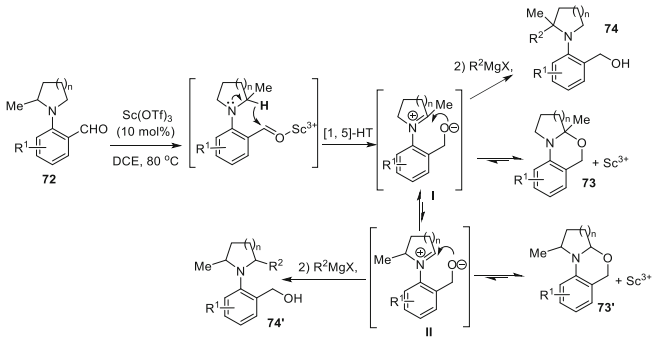
3.4 Saturated Aldehydes and Imines as the Hydride Acceptors

The C–H bond can be functionalized not only into C–C bond but also into C–O bond and C–N bond via similar cascade processes. Mátyus et al. reported a microwave-assisted synthesis of tricyclic angularly annulated aminal **71** from *ortho*-dialkylaminobenzaldehdyde **70** with H_2O as solvent (Scheme 24) [108, 109]. Even though the reaction was conducted under harsh conditions, i.e., at 210 °C for 50 min and employment of stoichiometric K_2CO_3, aminal **71** could only be obtained in low yield. According to the report by Maulide et al., Lewis acidic condition should be beneficial to the transformation [110], which was not investigated in Mátyus' report

The annulated aminal can be employed as unstable intermediate for further C–H functionalization of tertiary amines. Maulide et al. described a $Sc(OTf)_3$-catalyzed one-pot C–H functionalization of cyclic tertiary amines **72**, in which the sacrificial reduction of a neighboring carboxaldehyde group directed addition of Grignard reagents and lithium alkynyl trifluoroborates to the α-position of amine moiety, resulting in the corresponding α-functionalized products **74** and **74′** bearing a wide range of appendages in good to excellent yields. (Scheme 25) [110]. Basically, the formation of **73/73′** from **72** is under thermodynamic control and **73** is the

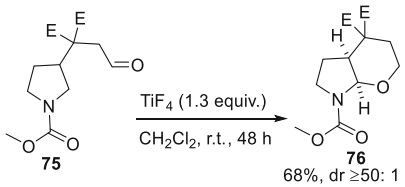


Scheme 24 Microwave-assisted synthesis of tetrahydroquinoline applying the *tert*-amino effect



Scheme 25 $Sc(OTf)_3$-catalyzed intramolecular redox-triggered C–H functionalization

Scheme 26 TiF_4-catalyzed hydro-*O*-alkylation of aldehydes via cascade [1,5]-HT/cyclization



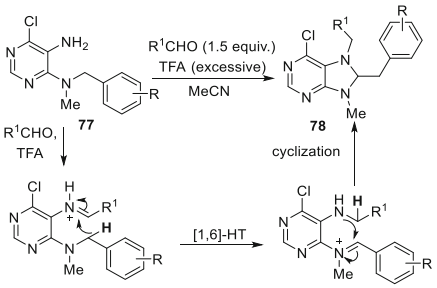
thermodynamically favored product. The aminals **73** and **73′** can be reversed to intermediate **I** and **II**, thus an equilibrium for interconversion exists between **73** and **73′**. The more favorable iminium intermediate **I** (stabilized by more substituents) and less favorable iminium intermediate **II** can be trapped by more nucleophilic reagents, leading to the final stable products **74** and **74′**, respectively.

Sames et al. reported a highly active TiF_4-catalyzed intramolecular hydro-*O*-alkylation of aldehyde substrate **75** (Scheme 26), via which the *N*-protected pyrrolidine substrate **75** was transformed into a *cis*-fused bicyclic aminal **76** as a single diastereomer [37]. Because of the electron-withdrawing nature of carbamate and less activity of secondary C–H bond, the employment of highly active and oxophilic TiF_4 with high catalyst loading (1.3 eq) was crucial for successful transformation, which resulted in the fused aminal in 68 % yield and good diastereoselectivity (≥50:1).

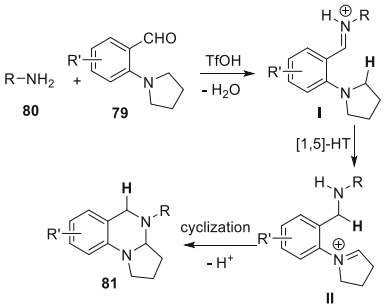
The in situ-generated iminium could also be exploited as hydride acceptor, via which inert $C(sp^3)$–H bond could be functionalized to C–N bond efficiently. Seidel et al. reported a trifluoroacetic acid-catalyzed cascade [1,6]-hydride transfer/cyclization of **77** to synthesize 7,8,9-trisubstituted dihydropurine derivatives **78** (Scheme 27) [73]. TFA plays two roles in this process: (1) promotion of imine formation and (2) protonation of imine for acceleration of the hydride shift process. Meth-Cohn and Volochnyuk et al. reported similar reactions in 1967 [71] and 2007, respectively [72].

The same group also described a TfOH-catalyzed one-pot synthesis of aminals **81** from *o*-aminobenzaldehydes **79** and primary aromatic or aliphatic amines **80** (Scheme 28) [111]. The protonated imine **I** worked as hydride acceptor. Almost at

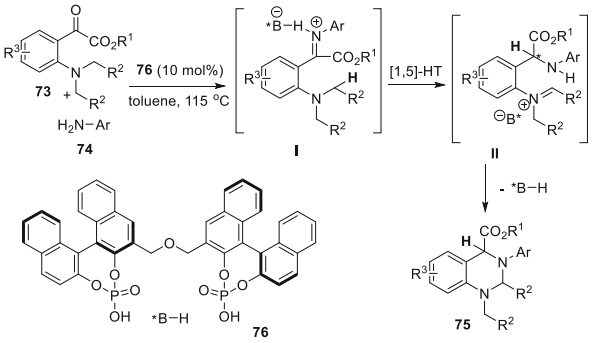
Scheme 27 Synthesis of 7,8,9-trisubstituted dihydropurine derivatives via *tert*-amino effect cyclization



Scheme 28 Synthesis of cyclic aminals via cascade 1,5-hydride transfer/cyclization



Scheme 29 Asymmetric sp^3 C–H functionalization via a chiral Brønsted acid-catalyzed redox reaction



the same time, Akiyama et al. reported a similar catalytic approach to synthesize quinazolines and $TsOH{\cdot}H_2O$ was identified as the optimal catalyst [112].

Ketoesters could be exploited to generate iminium intermediate employed as hydride acceptor. Gong et al. reported a chiral Brønsted acid **85**-catalyzed asymmetric cascade [1,5]-hydride transfer/cyclization of 2-pyrrolidinyl phenyl ketoesters **82** with anilines **83**, which produced the enantio-enriched cyclic aminals **84** (Scheme 29) [113]. The iminium subunit in intermediate **I** served as hydride acceptor, which was generated in situ through the condensation of *o*-aminobenzoketone **82** with aniline **83** in the presence of **85**.

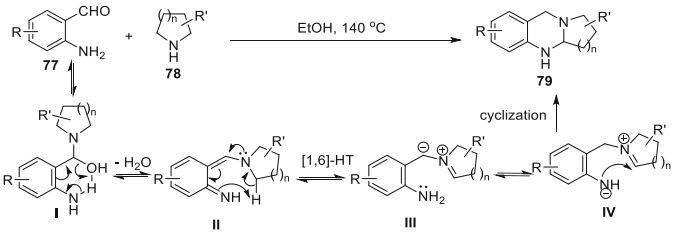
Seidel et al. also reported a metal-free one-pot α-amination of cyclic secondary amines **78** with 2-aminobenzaldehyde **77**, which efficiently furnished ring-fused

aminals **79** in good yields (Scheme 30) [64–66]. Both the electronic structure and 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 [66]. Initially amino-benzaldehyde **77** reacts with secondary amine **78** to furnish hemi-aminal **I**, which undergoes subsequent dehydration to give quinoidal intermediates **II**. The nucleophilic imine subunit then abstracts a proton from the methylene adjacent to *tert*-amine moiety ([1,6]-proton shift), resulting in azomethine ylide **III**, which is rapidly protonated by ethanol. Subsequently, **IV** is furnished via internal proton transfer and finally ring-fused aminal **79** is formed by intramolecular nucleophilic attack. Dang and Bai et al. also reported a similar cascade process for preparation of tetrahydro-pyrimido[4,5-*d*]pyrimidine [114].

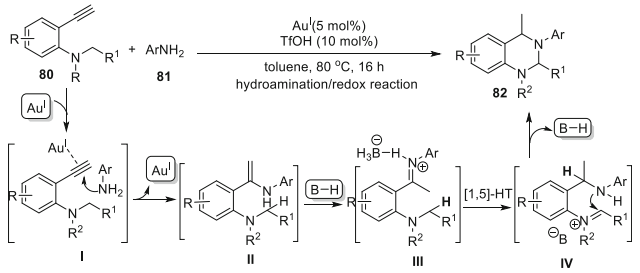
The electrophilic iminium could also be prepared in situ from alkyne via gold catalysis. Gong et al. disclosed a catalytic domino hydroamination/redox reaction, which could directly assemble the tertiary amine substituted 3-en-1-yne derivatives **80** and various amines **81** into cyclic aminals **82** in excellent yields and moderate to high diastereoselectivities by using the combination of gold(I) complex and TfOH (Scheme 31) [115]. Theoretically, terminal alkyne **80** undergoes gold(I)-catalyzed intermolecular hydroamination with aniline **81** to give imine intermediate **II**, which is protonated by Brønsted acid to give 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 **82**. The asymmetric version could be facilitated by over-stoichiometric chiral phosphoric acid and 5 mol% $Ph_3PAuNTf_2$, giving rise to enantio-enriched **82** in high yield and excellent enantioselectivity.

3.5 Electrophilic Metal Carbenoids as the Hydride Acceptors

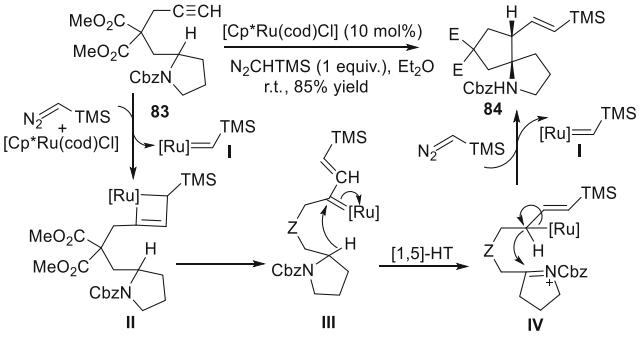
As an electrophilic species, metal carbenoid can also serve as an ideal hydride acceptor. Saa et al. elegantly demonstrated a [Cp*Ru(cod)Cl]-catalyzed cyclization of protected alkynyl pyrrolidine **83**, which furnished 1-Azaspiro[4,4]-nonane **84** carrying versatile TMS moiety as a single diastereomer in good yield (Scheme 32) [76]. Mechanistically, the ruthenium carbenoid **I** is afforded from N_2CHTMS and [Cp*Ru(cod)Cl], which undergoes cycloaddition with **83** to give



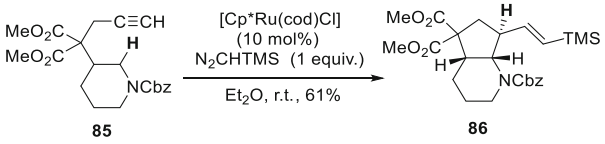
Scheme 30 Synthesis of ring-fused aminals via cascade [1,6]-proton transfer/cyclization



Scheme 31 Catalytic enantioselective *tert*-aminocyclization by asymmetric binary acid catalysis



Scheme 32 Intramolecular α-alkylation of C(2)-linked pyrrolidine by catalytic ruthenium carbene insertion



Scheme 33 Intramolecular α-alkylation of C(3)-linked pyrrolidine by catalytic ruthenium carbene insertion

metallacyclobutene **II**. A subsequent ring opening of **II** leads to the electrophilic Ru-vinyl carbenoid **III**, which suffers [1,5]-hydride shift to furnish intermediate **IV**. Ultimately, an intramolecular nucleophilic attack gives rise to the spiro product **84**.

C3-linked piperidine **85** was also readily cyclized under the optimal condition with less reactive secondary C–H bonds α to protected secondary amine as the hydride donor, furnishing the fused bicyclic piperidine **86** in good yields (Scheme 33).

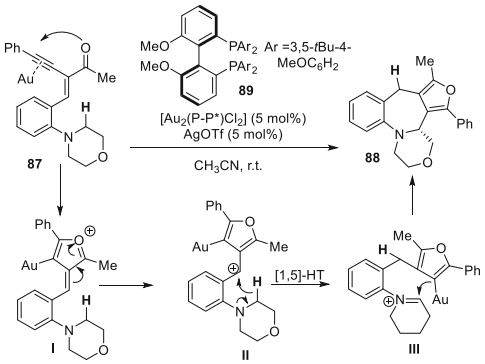
3.6 Other Electrophiles as the Hydride Acceptors

The in situ-generated carbocation can be exploited as a good hydride acceptor. Zhang et al. reported an enantioselective catalytic intramolecular redox reaction of yne-enones **87** in the presence of Au(I) catalyst and chiral ligand **89**, affording 7-membered tetrahydroazepines **88** in high yield and with high to excellent enantioselectivity (Scheme 34) [41, 79]. Compared with relatively inactive C–H bond α to *tert*-amine, oxygen of carbonyl is more nucleophilic and ready to attack the electrophilic alkyne activated by Au(I) catalyst. Basically, alkynophilic Au(I) catalyst triggers a heterocyclization (first cyclization) by activation of the alkyne to generate the furanyl carbocationic subunit in intermediate **II**, which is exploited as the hydride acceptor.

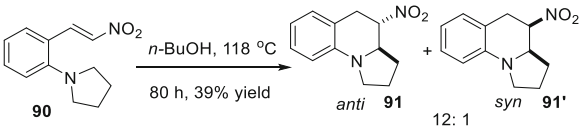
Nitroalkene is a versatile electron-deficient olefin, which might be exploited as the hydride acceptor as well. The cascade process was investigated by Jordis et al. with (*E*)-1-(2-(2-nitrovinyl)phenyl)pyrrolidine **90** as the substrate (Scheme 35) [116]. This transformation could be accomplished under thermal conditions (118 °C) in 80 h, leading to the cyclized product **91** and **91′** in 39 % yield (*syn*/*anti* = 12: 1).

Nitroalkene could also be activated by Lewis acids, e.g., $Sc(OTf)_3$, $Yb(OTf)_3$, and $Zn(OTf)_2$ to increase its electrophilicity. According to the unpublished result in Pfaltz group, the cascade process could be facilitated by $Yb(OTf)_3$, which furnished the cyclized product **91** in 60 % yield at 80 °C within 12 h (Scheme 36). The transformation was diastereospecific and only *anti* diastereomer was observed. The diastereoselectivity can be explained through Zimmer–Traxler transition state **II** in which the orientation of substituents would be pseudoequatorial, leading to the *anti*-product via intramolecular nucleophilic attack.

The electrophilic vinylogous iminium could also be exploited as hydride acceptor. Seidel et al. reported a diphenyl phosphate (DPP)-catalyzed cascade [1,5]-hydride shift/cyclization with doubly nucleophilic indole **93** and *o*-aminobenzaldehydes **92** as substrates, which gave rise to 7-membered rings **94** in good to excellent yields (Scheme 37) [80]. Mechanistically, the acid-catalyzed reaction of aldehyde **92** with indole **93** initially furnishes the electrophilic vinylogous iminium **I** via

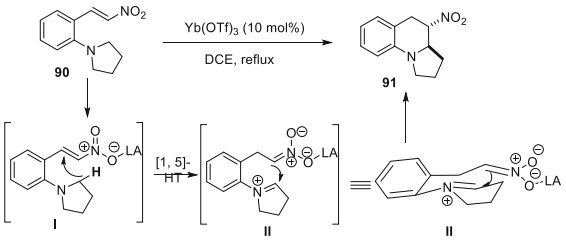


Scheme 34 Enantioselective Au-catalyzed selective formation of ring-fused tetrahydroazepines

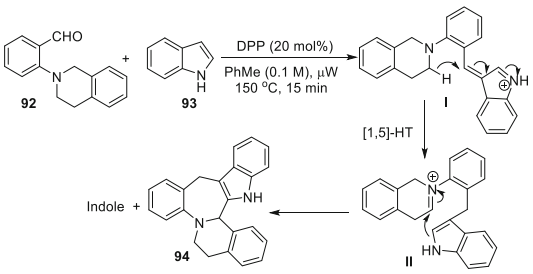


Scheme 35 Synthesis of nitro-substituted tetrahydroquinoline via [1,5]-HT/cyclization under thermal conditions

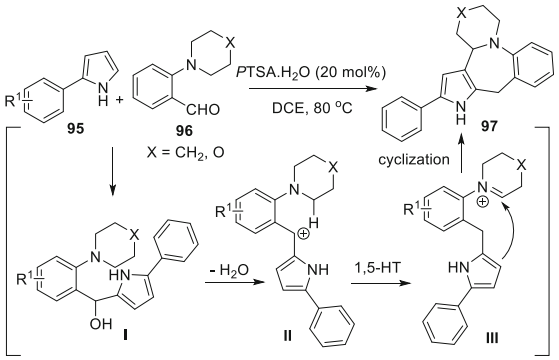
Scheme 36 Lewis acid-catalyzed synthesis of nitro-substituted tetrahydroquinoline via [1,5]-HT/cyclization



Scheme 37 Brønsted acid-catalyzed redox-neutral indole annulation cascades



Scheme 38 Brønsted acid-catalyzed synthesis of 1,2-pyrrole-annulated benzazepines through a redox-neutral domino reaction



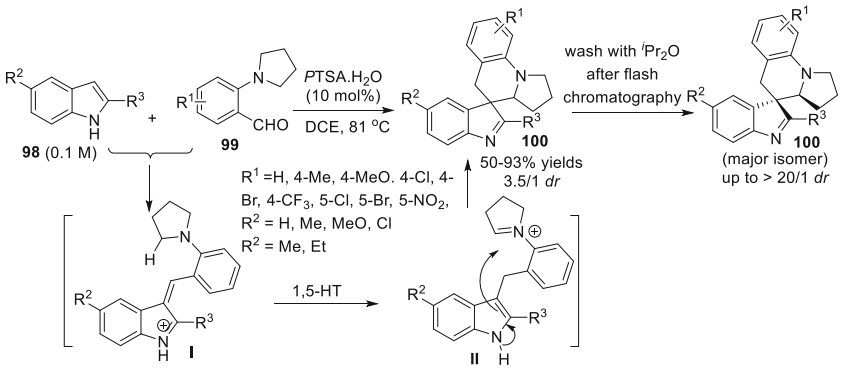
sequential Friedel–Crafts reaction and dehydration. A subsequent intramolecular [1,5]-hydride transfer leads to electrophilic iminium **II**, which traps nucleophilic C2 of indole to afford 7-membered product **94**.

Sun and Xu et al. reported a Brønsted acid-catalyzed cascade dehydration/1,5-hydride shift/cyclization of 2-arylpyrroles **95** and 2-(pyrrolidin-1-yl)-, 2-(piperidin-

1-yl), or 2-morpholinobenzaldehydes **96** (Scheme 38) [117], which produced structurally diverse 7-membered 1,2-pyrrole-annulated benzazepines **97** in yields of 25–65 %. Both the initial Friedel–Crafts reaction and subsequent dehydration were promoted by *P*TSA, resulting in the carbocationic intermediate **II**, which served as hydride acceptor.

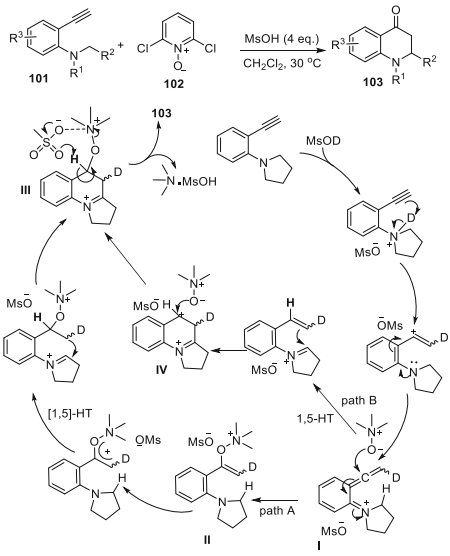
The same group also reported a *P*TSA-catalyzed synthesis of spiroindolenines **100** from 2-substituted (Me, Et) indoles **98** and 2-(pyrrolidin-1-yl)benzaldehydes **99** via a [1,5]-hydride shift/cyclization sequence with good to excellent yields and moderate diastereoselectivity (dr 3.5:1)(Scheme 39) [118]. The major diastereoisomer product could be readily obtained with up to >20/1 d.r. by simple washing with isopropyl ether after flash chromatography. Similar to Seidel's report, the in situ-generated vinylogous iminium intermediate **I** served as the hydride acceptor, which underwent subsequent [1,5]-hydride transfer and cyclization to furnish spiroindolenines **100**. As C2 of indole moiety was substituted by an alkyl group, the more nucleophilic C3 will attack the iminium moiety instead, resulting in the dearomatization of indole subunit.

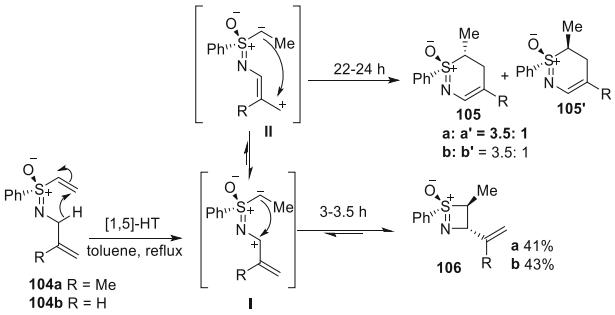
Gong et al. discovered a MsOH-catalyzed cascade oxidation/C(sp^3)–H functionalization of unactivated terminal alkynes **101** with **102** as the oxidant, which yielded 2,3-dihydroquinolin-4(1H)-ones **103** (Scheme 40) [119]. Mechanistically, the nucleophilic nitrogen atom initially captures a proton that is delivered to alkynes subsequently. Intermediate **I** is formed by dearomatization of styrene cation. Afterwards, two possible pathways might operate to afford the final products. In path **A**, the nucleophilic attack of pyridine-*N*-oxide onto intermediate **I** generates enolate **II**, which undergoes sequential delocalization and [1,5]-hydride transfer/ring-closure to furnish a final intermediate **III**. The interaction between methanesulfonic anion and pyridine cation in **III** facilitates C–H and N–O bonds cleavage to afford **103**. 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 intermediate **III**.



Scheme 39 Brønsted acid-catalyzed synthesis of spiroindolenines via [1,5]-hydride shift/cyclization sequence

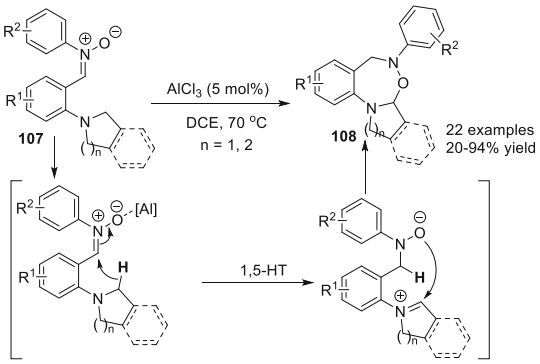
Scheme 40 Metal-free oxidation/C(sp^3)–H functionalization of unactivated alkynes





Scheme 41 C–H activation in *S*-alkenyl sulfoximines

Harmata et al. developed an intramolecular redox C–H activation process of alkenyl sulfoximines to synthesize 4- and 6-membered heterocycles **106** and **105** (Scheme 41) [120]. Terminal alkene activated by sulfoximines worked as hydride acceptor and allylic C–H bond served as hydride donor. Notably, the reaction time strongly influenced the formation of final products. When **104** was refluxed in toluene for 3.5 h, the 4-membered cyclic species **106** could be obtained in 41 % yield as the major product; whereas if the reaction was refluxed for around 24 h, 6-membered thiazines **105** 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 **106** might be kinetically favorable and reversible. Although intermediate **II** might be less stable than intermediate **I** for the reason that the allylic



Scheme 42 Construction of oxadiazepines via Lewis acid-catalyzed tandem 1,5-HT/cyclization

positive charge in intermediate **I** can be dispersed by more substituents, the conversion of 4-membered **106** to **105** is thermodynamically favorable and the driving force might be the release of cyclic strain of **106**.

Nitrones have been widely exploited in various cycloaddition reactions. Intriguingly, these electrophilic species can also serve as the hydride acceptors. Sun and Xu et al. reported an expeditious access to structurally diverse oxadiazepines **108** via 1,5-hydride shift/cyclization of pyrrolidine- or tetrahydroisoquinoline-containing nitrones **107** with nitrones as hydride acceptors and $AlCl_3$ was exploited as Lewis to promote the cascade process (Scheme 42) [121]. Furthermore, the nitrone **107** could be furnished in situ, which underwent subsequent 1,5-hydride shift, and ring cyclization through a one-pot process to afford **108** in good yields.

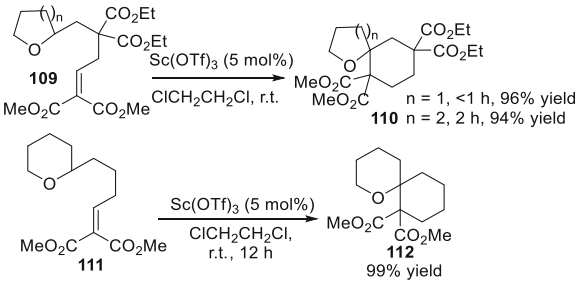
4 C(sp^3)–H Bond Adjacent to Ethereal Oxygen as The Hydride Donors

In addition to the C–H bond adjacent to *tert*-amino moieties, methylene (or methine) adjacent to ethereal oxygen could also be employed as hydride donor. As discussed in the section of mechanistic insight, the C–H bond adjacent to ethereal oxygen is less reactive than that adjacent to *tert*-amine, thus more reactive hydride acceptors are required.

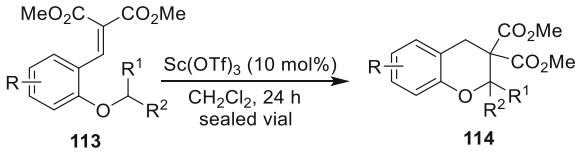
4.1 Electrophilic Benzylidene Malonates and Their Derivatives as the Hydride Acceptors

Sames et al. reported a $Sc(OTf)_3$-catalyzed intramolecular hydroalkylation of isolated electron-deficient olefins (Scheme 43) [95]. Tetrahydropyrans or tetrahydrofurans carrying C(2)-linked α, β-unsaturated malonate side chain **109** and **111** were employed as substrate to furnish the spiroether product **110** and **112** in excellent yields. Notably, germinal substitution along the olefin tether was not required for efficient annulation for the reason that benzylidene malonate activated by $Sc(OTf)_3$ were reactive enough, thus higher conformational rigidity to increase the reactivity of hydride acceptor was not indispensable [96].

Scheme 43 $Sc(OTf)_3$-catalyzed C–H functionalization of cyclic ether via [1,5]-HT/cyclization



Scheme 44 $Sc(OTf)_3$-catalyzed hyrdroalkylation via [1,5]-HT/cyclization



The same group also reported a $Sc(OTf)_3$-catalyzed [1,5]-hydride transfer/cyclization of *ortho*-vinylaryl alkyl ethers **113**, via which highly substituted dihydrobenzopyran **114** could be prepared in excellent yields (Scheme 44) [122].

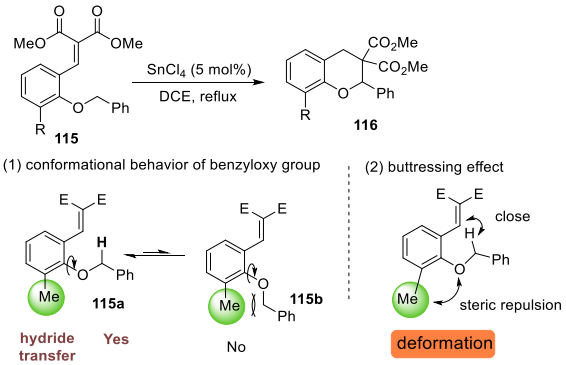
$SnCl_4$ could also be employed as Lewis acid to efficiently catalyze the cascade process for synthesis of a benzopyran skeleton **116** from benzyloxy benzylidene malonate **115** (Scheme 45) [123]. Notably, the methyl *ortho* to the alkoxy group or the benzylidene moiety could enhance the reactivity drastically compared with non-substituted substrate. This remarkable enhancement of the reactivity could be well rationalized by following two factors: (1) the conformational behavior of the benzyloxy group and (2) the "*buttressing effect*". In the case of **115** having an *o*-methyl group, the conformational equilibrium largely shifted to the left conformer **115a** because of the severe steric repulsion. As a consequence, the "*buttressing effect*" between the methyl group and the benzyloxy group made the hydrogens on the benzyl group much closer to benzylidene electrophilic 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.

4.2 Electrophilic Activated Alkyne and Allene as the Hydride Acceptors

Yamamoto et al. reported a $PtBr_2$-catalyzed cyclization of 1-ethynyl-2-(1-alkoxy-but-3-enyl)-benzenes **117**, which furnished functionalized indenes **118** in good to allowable yields (Scheme 46) [124]. Notably, the allyl group substituted at benzylic position was indispensable 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.

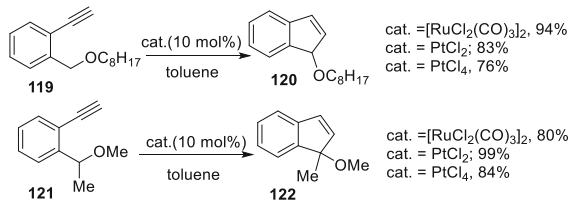
Chatani et al. employed other alkynophilic metals such as $PtCl_2$, $PtCl_4$, and $[RuCl_2(CO)_3]_2$ to catalyze the cyclization of non-allyl substituted 1-ethynyl-2-(1-

Scheme 45 Remarkable enhancement of reactivity by an *ortho* substituent



Scheme 46 $PtBr_2$-catalyzed cyclization of allyl(o-ethynylaryl) carbinol derivatives

Scheme 47 Alkynophilic metal-catalyzed cyclization of non-allyl substituted 1-ethynyl-2-(1-alkoxyalkyl)-benzenes

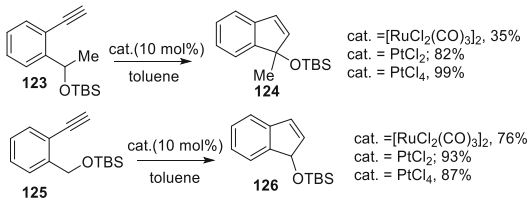


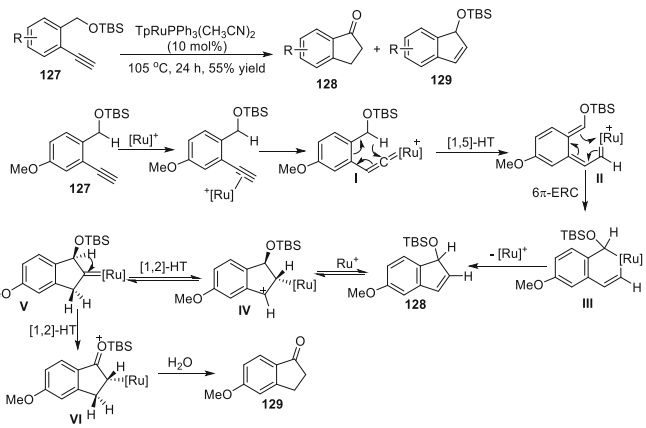
alkoxyalkyl) benzenes **119** and **121** under mild condition, via which the desired indenes **120** and **122** were furnished in high yields (Scheme 47) [40]. In contrast to Yamamoto's results [124], the substrates without allyl group still worked well.

The same group also investigated catalytic cyclization of 2-alkyl-1-ethynylbenzene derivatives carrying silyl ether groups as in **123** and **125** (Scheme 48) [40]. In contrast to Liu's result [44], when silyl ether-substituted 2-methy-1-ethynylbenzene was subjected to the reaction, only silyl ether-substituted indenes **124** and **126** were afforded in good to excellent yields.

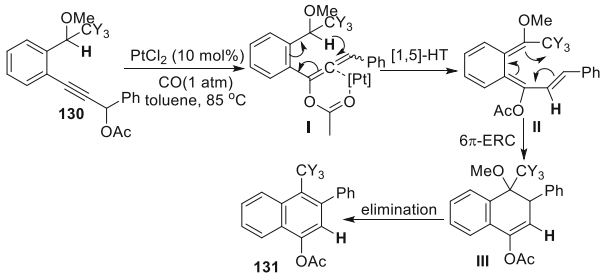
Liu et al. also reported a $TpRuPPh_3(CH_3CN)_2{\cdot}SbF_6$-catalyzed cyclization of 2-alkyl-1-ethynylbenzenes **127** bearing a siloxy group, which produced synthetically valuable 1-indanones **128** or 1*H*-1-indenols **129** in reasonable yields and in short periods (Scheme 49) [44]. Basically, terminal alkyne subunit is transformed to ruthenium-vinylidene **I** initially, which undergoes a [1,5]-hydride shift to give ruthenium-containing 1,3,5-hexatriene **II**. A subsequent 6π-electrocyclization of intermediate **II** furnishes ruthenium-containing cyclohexadiene **III**, which suffers reductive elimination to produce 1-substituted-1*H*-indene **128**. Afterwards, the cationic ruthenium catalyst attacks C(2) carbon of indene to form benzyl cation **IV**,

Scheme 48 Catalytic cyclization of 2-alkyl-1-ethynylbenzene derivatives carrying silyl ether groups to indenes





Scheme 49 Ruthenium-catalyzed cyclization of 2-alkyl-1-ethynylbenzene carrying a silyl ether group



Scheme 50 Synthesis of naphthalenyl acetate from propargylic esters via Pt-catalyzed [1,5]-HT/cyclization

followed by [1,2]-hydride shift to afford ruthenium cyclopentylidene **V**. Ultimately, 1-indanone **129** is produced via a second hydride shift and hydrolysis.

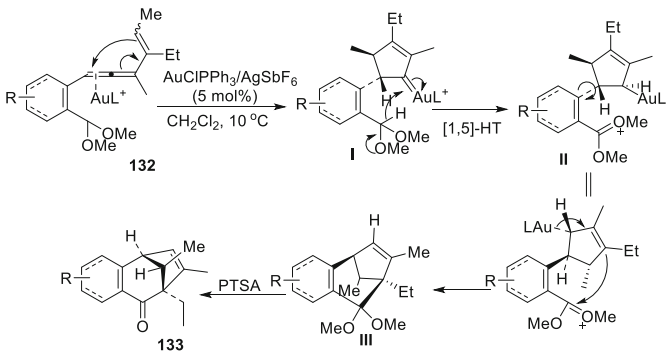
Liang et al. reported a $PtCl_2$-catalyzed transformation of 3-(2-alkyl)phenyl-propynyl acetate **130** to prepare naphthalenyl acetate **131** (Scheme 50) [45]. The electrophilic Pt–allene complexes formed in situ worked as hydride acceptors. Mechanistically, the Pt(II)-promoted [1,3]-OAc shift leads 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-electrocyclic ring closure affords intermediate

III, which further eliminates the methoxy group, resulting in rearomatization to afford **131**.

Liu et al. reported a $PPh_3AuCl/AgSbF_6$-catalyzed cycloisomerization of allenene acetal functionality **132**, via which bicyclo[3.2.1]oct-6-en-2-ones **133** were prepared in high yields, high chemoselectivities, and high stereoselectivities (Scheme 51) [125]. In most cases, only one single stereoisomer of the resulting cyclic products was formed despite their molecular complexities. Mechanistically, substrate **132** initially undergoes Au(I)-catalyzed allene cyclization to give electrophilic Au(I)-alkenyl carbenoid **I**, which abstracts acetalic hydride through [1,5]-hydride transfer, leading to the formation of 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 oxocarbeniums 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 **133**.

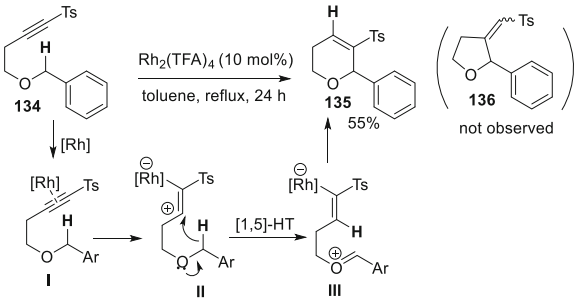
Urabe et al. described a $Rh_2(TFA)_4$-catalyzed cyclization of alkynyl ethers **134**, which afforded dihydropyrans **135** in good yield (Scheme 52) [126]. Ring closure proceeded in a highly regioselective manner, and no isomeric five-membered product **136** was detected. Notably, the sulfonyl moiety was critical for the success of this reaction. Mechanistically, initial coordination of Rh(II) to alkyne subunit generates a cationic carbon β to sulfonyl group, which abstracts a hydride from methylene α to ethereal oxygen, generating a zwitterionic intermediate **III**. A final intramolecular nucleophilic attack furnishes the product **135**.

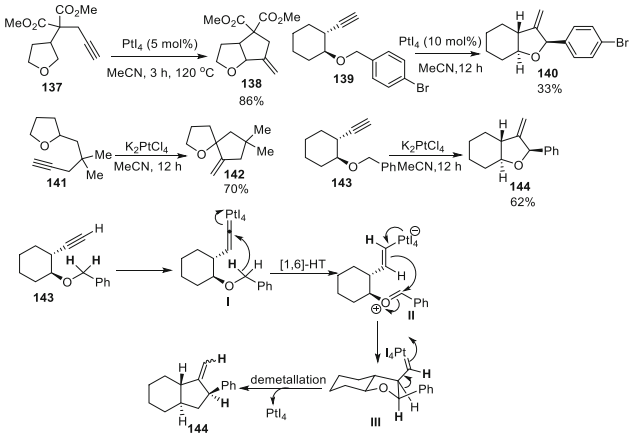
Sames et al. developed an α-alkenylation of cyclic ethers to synthesize both annulation and spirocyclization products (Scheme 53) [39]. Four types of electronically diverse hydride donors were investigated and remarkably the selection of suitable catalysts was crucial to the success of cascade processes. As to substrate **137**, in which relatively unreactive secondary C–H bond was exploited as hydride donor, no aromatic group was available to stabilize the oxocarbenium generated via [1,5]-HT. Hypervalent platinum catalyst PtI_4 was the optimal catalyst, which affected complete conversion of **137** to furnish the product **138** in 86 % yield, whereas PtI_4 only led to complete decomposition of **141** despite higher reactivity of



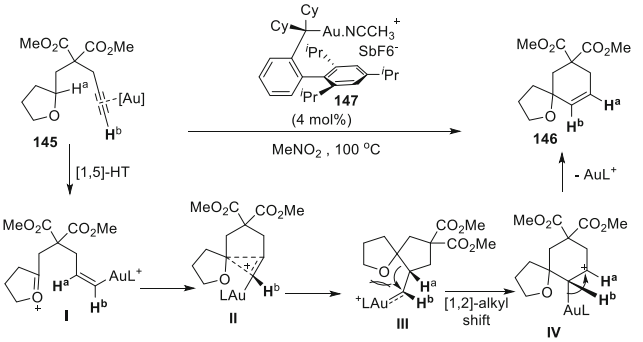
Scheme 51 Gold-catalyzed stereoselective synthesis of bicyclo[3.2.1]oct-6-en-2-ones

Scheme 52 Rhodium-catalyzed intramolecular redox reaction of alkynyl ethers





Scheme 53 Platinum-catalyzed α-alkenylation of cyclic ethers based on cascade [1,5]-HT/cyclization



Scheme 54 Gold(I)-catalyzed *a*-alkylation of C(2)-linked terminal alkynyl ethers

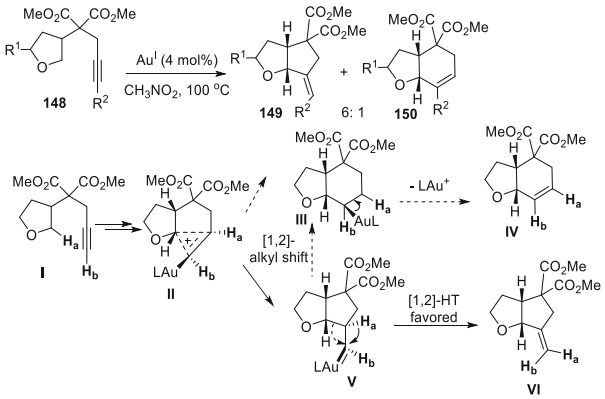
its tertiary C–H bond. Less active platinum catalyst K_2PtCl_4 was the optimal catalyst to produce spirocycles **142** in 70 % isolated yield. With K_2PtCl_4 as catalyst, substrate **143** could also be transformed into fused product **144** in 62 % yield. Although hydride donor in **143** was a less 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. The brominated derivative **139** gave a lower yield of compound **140** (33 %) even though highly active PtI_4 was employed, showing a considerable sensitivity of this reaction to electron-withdrawing substituents, particularly in *para*- and *ortho*-position due to their destabilization of oxocarbenium intermediates. Theoretically, the platinum vinylidene **I** is formed initially, followed by through-space [1,6]-hydride transfer to produce zwitterionic intermediate **II**, which affords the final product via a sequential C–C bond formation and platinum salt elimination.

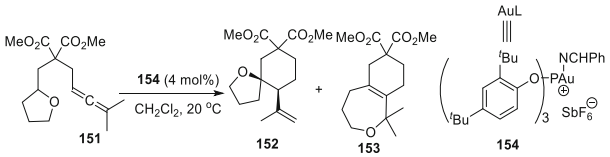
Gagosz et al. reported Au(I) catalyst **147**-catalyzed alkylation of alkynyl ethers which produced cyclohexane **146** as major product (Scheme 54) [127]. Theoretically, the electrophilic activation of the alkyne **145** by Au(I) initiates a [1,5]-hydride shift to furnish oxocarbenium ion **I**, interaction of which with the pendant nucleophilic vinyl-gold moiety affords cyclopropenium intermediate **II**. Carbocation **IV,** which would finally collapse into cyclohexene **146** after elimination of the gold(I) catalyst might be generated via a [1,2]-alkyl shift on Au-carbene intermediate **III**.

In contrast to C(2)-linked terminal alkynes **145**, gold-catalyzed alkylation of C(3)-linked tetrahydrofurans bearing terminal alkyne functions **148** mainly led to the formation of major product *exo*-methylene cyclopentanes **149** and minor products **150** (Scheme 55). This reversed selectivity might be explained by the relative stability of intermediates **III** and **V**. Steric constrains should be weaker for the fused bicyclic intermediate **V** (in Scheme 55) than intermediate **III** (in Scheme 54), thus allowing a rapid [1,2]-hydride shift, which leads to **VI** rather than a [1,2]-alkyl shift, which leads to **III**.

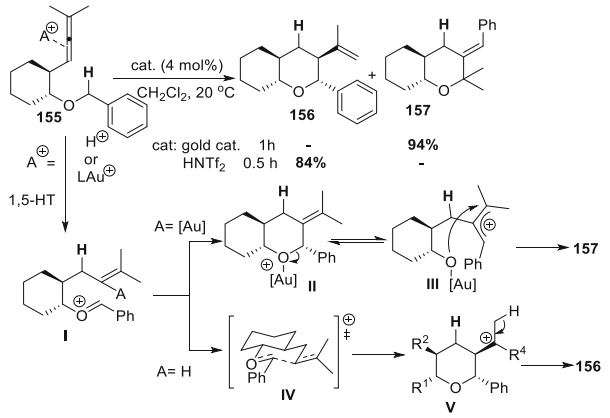
Gold-activated allene can also be employed as hydride acceptor. Gagosz et al. demonstrated that a phosphite gold complex **154**-catalyzed intramolecular hydroalkylation of allenes **151**, which afforded the spiro compound **152** and undesired fused bicyclic compound **153** in 30 and 61 % yields, respectively (Scheme 56) [128]. The selectivity could be reversed if $HNTf_2$ was exploited.



Scheme 55 Gold(I)-catalyzed α-alkylation of C(3)-linked terminal alkynyl ethers



Scheme 56 Gold and Brønsted acid-catalyzed hydride shift onto allenes



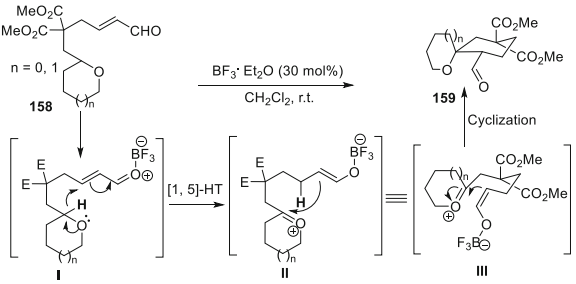
Scheme 57 Gold and Brønsted acid-catalyzed α-alkylation of benzyl ether

Under Brønsted acidic condition, the transformation was slower but furnished exclusively the desired spiro compound **152** in 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 were formed.

A similar complete divergence in product selectivity was observed when the substrates **155** possessing a benzyl ether moiety were treated with either gold complex **154** or $HNTf_2$ (Scheme 57) [128]. Under gold catalysis, tetrahydropyran **157** was obtained in 94 % yield, while tetrahydropyran **156** was produced in 84 % yield with $HNTf_2$ as the catalyst. The stereoselective formation of compound **156** can be explained by the highly ordered chair-like transition state **IV**, which leads to carbocation **V** from oxocarbenium **I**. The relative *trans* relationship between the phenyl and isopropenyl substituents in product **156** results from the pseudoequatorial 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 C(6).

4.3 Electrophilic α, β-Unsaturated Aldehydes and Ketones as the Hydride Acceptors

The electrophilicity of alkene subunit of α, β-unsaturated aldehydes can be dramatically increased if activated by $BF_3{\cdot}Et_2O$, which serves as an ideal hydride



Scheme 58 $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydroalkylation of isolated α,β-enals

acceptor. Sames et al. described a $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydroalkylation reaction of α, β- unsaturated aldehydes 1**58**, via which spirocycles **159** could be furnished in good yields at ambient temperature as a mixture of diastereomers (Scheme 58) [95].

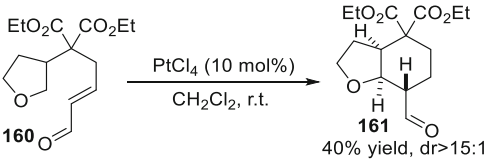
In addition to tertiary C–H bonds, secondary C–H bonds could also be directly functionalized (Scheme 59) [95]. Compared with tertiary C–H bond, secondary C–H bond was less reactive, therefore more active Lewis acid, i.e., $PtCl_4$ (10 mol%) was employed to facilitate hydroalkylation of enal **160**, giving rising to the fused annulation product **161** in 40 % yield and good diastereoselectivity (dr >15: 1).

In addition to the more active α, β-enal, hydroalkylation of less active enones **162** also proceeded smoothly (Scheme 60) [95]. Under the catalysis of 30 mol% of $BF_3{\cdot}Et_2O$ and with comparatively active tertiary C–H as hydride donor, the substrate **162a** or **162b** carrying α, β-unsaturated methyl and phenyl ketone units were efficiently transformed into spirocycles **163a** and **163b**, respectively, in excellent yields and moderate diastereoselectivities.

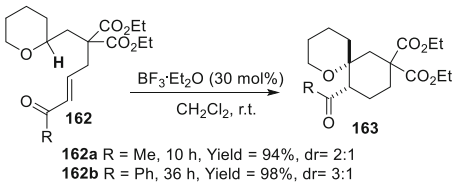
The 2,3-disubstituted tetrahydropyran **165** could be obtained in high diastereoselectivity via treatment of acyclic ether **164** with a substoichiometric amount of $BF_3{\cdot}Et_2O$ at elevated temperature (Scheme 61) [95]. The less active secondary C–H bond acted as hydride donor and less active methyl ketone was employed as hydride acceptor. Because the oxocarbenium could be stabilized by adjacent phenyl group, relatively mild Lewis acid $BF_3{\cdot}Et_2O$ (75 mol%) was active enough to promote the cascade process efficiently, resulting in the formation of desired product **165** in high yield (90 %) and good diastereoselectivity (dr >15: 1).

A simple and economical intramolecular hydroalkylation of olefins was elegantly demonstrated by Sames et al. based on the generation of highly reactive alkenyloxocarbenium intermediates **I** in situ from acetals (Scheme 62) [38]. Under the catalysis of $BF_3{\cdot}Et_2O$, the cyclic product **167** could be obtained in good yield and diastereoselectivity from acetal **166** within 1 h. Direct comparison of **166** 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 cyclic acetal **166** to generate oxocarbenium intermediate **I**, which activates conjugated alkene moiety for 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 species **III**, producing **167**. The observed high stereoselectivity can

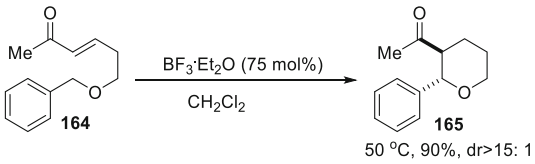
Scheme 59 $PtCl_4$-catalyzed intramolecular hydroalkylation of isolated α, β-enals



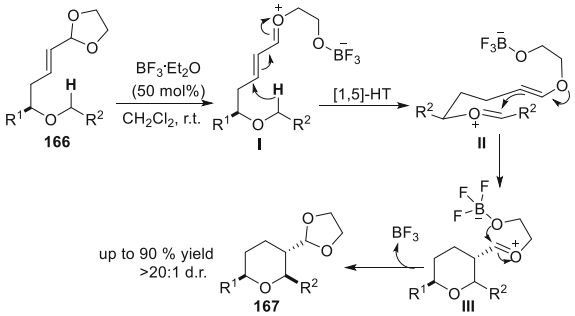
Scheme 60 $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydroalkylation of isolated α,β-unsaturated ketones



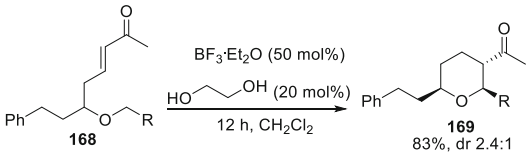
Scheme 61 $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydroalkylation of α,β-unsaturated ketones



Scheme 62 $BF_3{\cdot}Et_2O$-catalyzed alkylation through highly activated alkenyl-oxocarbenium intermediates



Scheme 63 $BF_3{\cdot}Et_2O$-catalyzed C–H bond functionalization with enone as hydride acceptors



be explained by the favorable transition state **II** in which all the substituents are in equatorial positions.

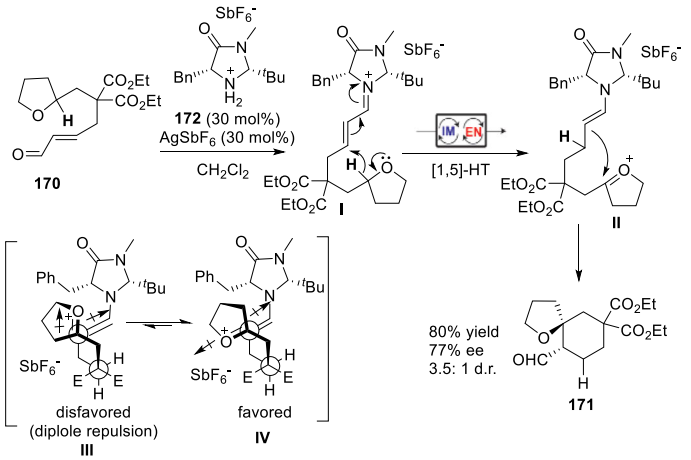
The intramolecular hydroalkylation of enones could be readily implemented as well via this strategy (Scheme 63) [38]. The addition of ethylene glycol had a dramatic effect on the reaction rate as demonstrated in the cyclization of enones **168**; the reaction could be completed within 12 h, furnishing the cyclized products

169 in good yields but with low diastereoselectivities. This strategy could not only drastically increase the reaction rate but also improve the isolated yields and stereoselectivities.

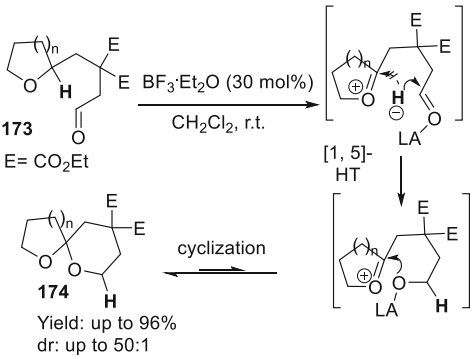
Tu et al. reported a Macmillan's catalyst **172**-catalyzed asymmetric α-alkylation of tetrahydrofuran **170** containing an α,β-unsaturated aldehyde, via which chiral spiroether **171** could be prepared (Scheme 64) [129]. The sequential [1,5]-hydride transfer/cyclization was facilitated via cascade iminium/enamine activation. The presence of strong acid was indispensable to ensure sufficient electrophilicity of the iminium intermediate. Theoretically, substrate **170** reacts with **172** to give iminium intermediate **I**. Owing to the steric interaction of the bulky *tert*-butyl group, the *E* enamine **II** is formed preferentially upon [1,5]-HT, which exists in two possible conformers **III** and **IV**. Because of dipole repulsion between 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 product **171**.

4.4 Saturated Aldehyde and Ketone as the Hydride Acceptors

Sames et al. described a $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydro-*O*-alkylation of aldehyde substrates **173**, which led to spiroketal products **174** (Scheme 65) [37]. Because oxocarbenium generated upon hydride migration is also a highly electron-deficient species, which would compete for hydride with aldehyde, thus how to deliver hydride to acceptor is challenging. Sames' protocol to address this problem was to employ $BF_3{\cdot}Et_2O$ (30 mol%) for activation of carbonyl of **161**, rendering hydride acceptor more electrophilic to "snatch" hydride. Tetrahydropyran substrate **173** could be converted to spiroketal **174** in high isolated yield at ambient temperature. Remarkably, the final cyclization step was a reversible process, which was under thermodynamic control, thus the cascade process was highly



Scheme 64 Organocatalyzed asymmetric direct C(sp^3)–H functionalization of cyclic ethers



Scheme 65 $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydro-*O*-alkylation of C(2)-linked aldehydes

diastereoselective. Both 6, 6-scaffolds and 5, 6 spiroketals could be obtained in excellent yields.

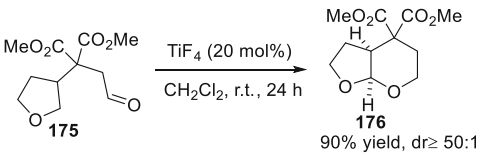
The *cis*-fused bicyclic acetal **176** could also be afforded as a single diastereomer via this strategy with **175** as the substrate (Scheme 66) [37]. Mild Lewis acid, e.g., $BF_3{\cdot}Et_2O$, was inactive and only the stronger oxophilic Lewis acid TiF_4 (20 mol%) could facilitate the transformation for the reason that secondary C–H was less reactive than the tertiary C–H bond in **173**.

In addition to aldehyde substrates, less electrophilic ketone **177** could also be converted into spiroketal **178** in 30 % yield and excellent diastereoselectivity under the mediation of stoichiometric TiF_4 (Scheme 67) [37]. $BF_3{\cdot}Et_2O$ was not active enough to promote this hydro-*O*-alkylation, which might be ascribed to the poor reactivity of methyl ketone.

4.5 Electrophilic Metal Carbenoid as the Hydride Acceptors

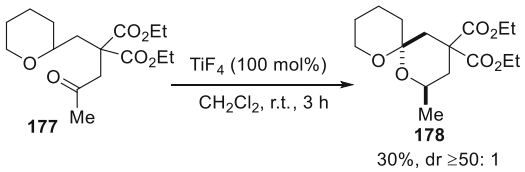
Saa et al. discovered a ruthenium-catalyzed diastereoselective cyclization of linear alkynyl ether **179** involving cyclic and acyclic ethers, which produced spirocycles **180** in fairly good yields (Scheme 68) [76]. The ring size of the cyclic ether had a dramatic effect on the reaction time and yields.

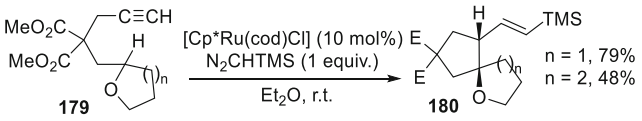
Similarly, acetalic C–H bond could be exploited as hydride donor as well, and via ruthenium-catalyzed cyclization of linear alkynyl acetals **181**, spirobicycles **182** could be furnished in fairly good yield (Scheme 69) [76], along with the formation of linear hydroxyester **183**, which was generated by hydrolysis of intermediate **I**. Notably, rigid cyclic acetal afforded a higher yield of spiro compound in comparison to the linear acetals [96].



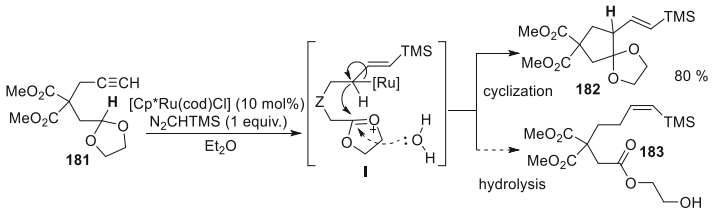
Scheme 66 TiF_4-catalyzed intramolecular hydro-*O*-alkylation of C(3)-linked aldehydes

Scheme 67 TiF_4-catalyzed intramolecular hydro-*O*-alkylation of C(2)-linked methyl ketone

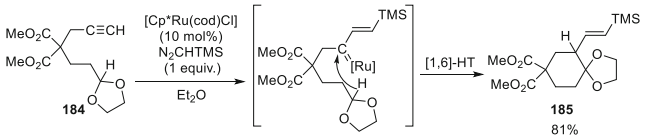




Scheme 68 Intramolecular α-alkylation of C(2)-cyclic ether



Scheme 69 Intramolecular alkylation of dioxolane by catalytic ruthenium carbene insertion



Scheme 70 Intramolecular alkylation of dioxolane via cascade [1,6]-HT/cyclization

[1,6]-hydride shift/cyclization process could occur when specially designed dioxolane substrate **184** was subjected to the reaction, affording 5,6-spirocyclic product **185** in excellent yield (Scheme 70) [76]. The examples showed again 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 **181** and **184** shows the more rapid formation of the 1,4-dioxaspiro[4,5]decane **185** versus 1,4-dioxaspiro[4,4] nonane **182**, which clearly indicated that the conformation of metallic intermediate played a definitive role during the course of the reaction.

Fukuyama et al. exploited highly reactive rhodium carbenoids as hydride acceptors to construct tetrahydrofuran moieties in his total syntheses for many times. The mechanism should be the cascade [1,5]-Hydride migration/cyclization, whereas Fukuyama et al. argued that their reactions proceed via metal carbene C–H insertion reactions [130–135].

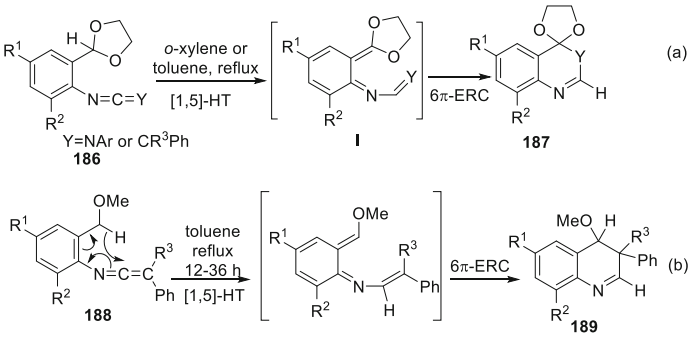
4.6 Ketenimines and Carbodiimides as Hydride Acceptors

Alajarin and Vidal et al. discovered dihydroquinolines and spirocyclic dioxolanoquinazolines **187** could be readily accessed via cascade [1,5]-hydride transfer/6π-ERC under thermal conditions (Scheme 71, a) [58]. Basically, 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 acetalic C–H bonds in **186**. After hydride migration, the 1,3,5-conjugated hexatriene **I** can be generated, which had a long conjugate system and can be stabilized to a large extent. The ketenimines **188** bearing ether moiety could also be transformed exclusively into dihydroquinolines **189** (Scheme 71, b) [56].

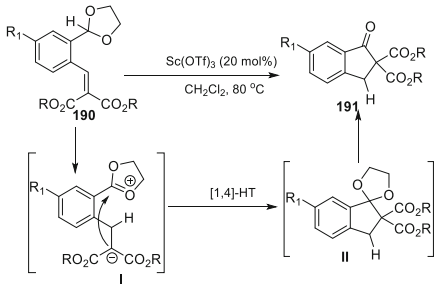
The same group described a $Sc(OTf)_3$-catalyzed three-step cascade reaction of **190** involving hydride shift/cyclization/hydrolysis as well, which produced indanones **191** (Scheme 72) [70]. Hydride was delivered to acceptor in an uncommon [1,4]-manner and Lewis acid activation was indispensable. $Sc(OTf)_3$ was the preferable 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 acetalic function.

4.7 Electron-Withdrawing Group Activated Allene as Hydride Acceptor

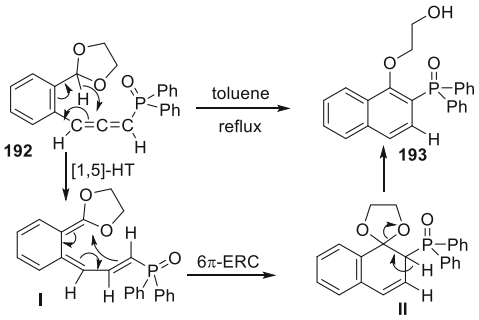
Allene could be activated not only by carbophilic transition metals but also by electron-withdrawing groups at the terminal carbon atom. Alajarin, Sanchez-Andrada, and Vidal et al. disclosed that 2-(1,3-dioxolan-2-yl)phenylallenes **192** containing a range of electron-withdrawing substituents such as phosphinyl, alkoxycarbonyl, sulfonyl at the cumulenic C3 position could be converted into 1-(2-hydroxy)-ethoxy-2-substituted naphthalenes **193** under thermal conditions (Scheme 73) [52]. 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**, which undergoes a subsequent 6π-electrocyclic ring-closure of **I** to furnish spirocycle intermediate **II**. A final aromatization step with concomitant ring opening of 1,3-dioxolane fragment produces the substituted naphthalenes **193**.



Scheme 71 Hydricity-promoted [1,5]-HT/cyclization in acetalic/ethereal ketenimines and carbodiimides



Scheme 72 $Sc(OTf)_3$-catalyzed cascade [1,4]-HT/cyclization/hydrolysis



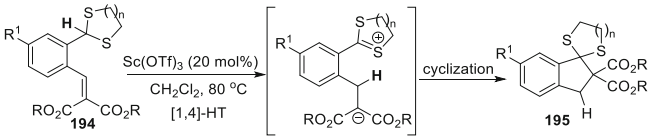
Scheme 73 Hydricity-promoted intramolecular hydroalkylation of electron-deficient allene

5 C(sp^3)–H Bond Adjacent to Sulfur as the Hydride Donor

The methylene (or methine) adjacent to sulfur atom can also work as hydride donor. With reactive electrophilic moieties as hydride acceptors, the cascade [1,5]-hydride transfer/cyclization can occur to give thio-heterocycles. Alajarin and Vidal et al. contributed much to this chemistry.

5.1 1,3-Dithiolane as the Hydride Donor and Benzylidene Malonate as the Hydride Acceptors

Alajarin and Vidal et al. described a $Sc(OTf)_3$-catalyzed cascade [1,4]-hydride shift/cyclization of substrate **194** carrying 1,3-dithiolane, which produced spirocyclic products **195** in moderate to good yields (Scheme 74) [70]. Tertiary C–H bond in 1,3-dithiolane worked as hydride donor. Because $Sc(OTf)_3$ is not thiophilic but oxophilic, the dithiolane moiety could remain intact after the cascade [1,4]-



Scheme 74 Cascade [1,4]-HT/cyclization with dithioacetalic C–H as hydride donor

hydride shift/cyclization. Compared with substrate **190** carrying 1,3-dioxolane, the disturbing hydrolysis of the acetalic function was thoroughly suppressed.

5.2 Ketenimine and Carbodiimide as the Hydride Acceptors

Alajarin and Vidal et al. discovered that under thermal conditions (refluxed in toluene), the single thioether **196** carrying ketenimine moiety could be transformed into 4-ethylthio-3,4-dihydroquinoline **197** in good yield via cascade [1,5]-hydride transfer/6π-ERC (Scheme 75) [56].

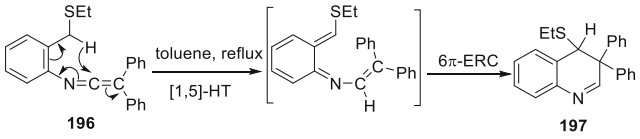
6 Benzylic C(sp^3)–H Bond as the Hydride Donors

Although a range of cascade reactions of heteroatom-containing substrates (X = NR, O, or S) have been described, their corresponding carbon analogues (X = CH_2 or CHR) have been rarely investigated, which might be ascribed to difficulties posed by the rate-determining step of [1,5]-hydride transfer without the assistance of adjacent heteroatom. Sames et al. disclosed that the secondary and tertiary benzylic C–H bond without an adjacent heteroatom could also be exploited as hydride donor. After [1,5]-hydride transfer, the carbocation that develops on benzylic carbon can be stabilized by adjacent electron-rich aromatic groups and alkyl groups via π–*p* conjugation and hyperconjugation, respectively.

6.1 Electrophilic Benzylidene Malonates and Their Derivatives as the Hydride Acceptors

Sames et al. elegantly demonstrated a $PtCl_4$-catalyzed cascade process involving benzylic methines that lacked the stabilization of α-heteroatom (Scheme 76) [95]. The aryl substrate **198** and thiophene substrate **200** were consumed up within 24 h at 50 °C. Although the electrophilic alkene was activated by two electron-withdrawing carboxylate groups and the cation generated upon [1,5]-hydride transfer could be stabilized by adjacent aromatic group, high-valent $PtCl_4$ was still indispensable for successful transformation, under the catalysis of which hexa-substituted cyclohexanes **199** and **201** could be obtained in moderate to good yield.

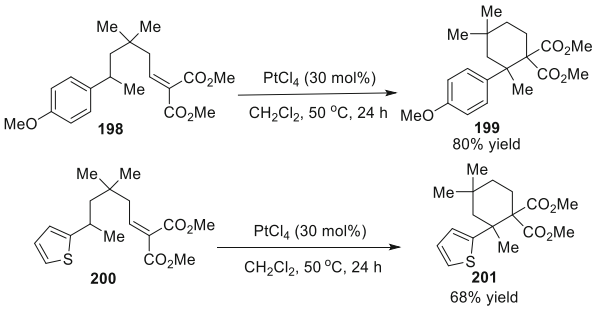
Fillion et al. reported a one-pot construction of tetrahydrobenzo-[*b*]fluoren-11-ones **204** under the catalysis of $Sc(OTf)_3$ (Scheme 77) [136]. The substrates **202** carrying highly electrophilic benzylidene Meldrum's acids and benzylic methylene or methine functions could undergo a cascade [1,5]-hydride shift/cyclization to

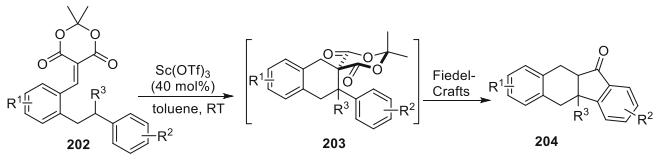


196 197

Scheme 75 Cascade [1,5]-HT/6p-ERC to synthesize 3,4-dihydroquinoline

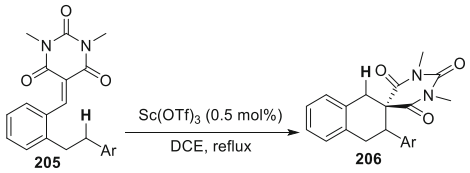
Scheme 76 $PtCl_4$-catalyzed direct C(sp^3)–H functionalization of benzylic methines





Scheme 77 $Sc(OTf)_3$-catalyzed synthesis of tetrahydro-benzo[*b*]fluoren-11-ones

Scheme 78 Synthesis of 3-aryltetralin skeleton via cascade [1,5]-HT/cyclization



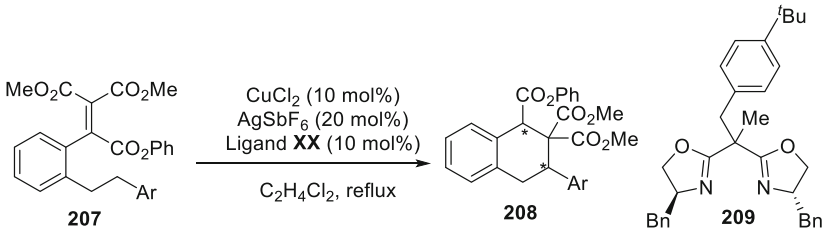
afford spirocycles **203**, which suffered subsequent intramolecular Friedel–Crafts acylation to generate tetracycles **204**.

Akiyama et al. reported a $Sc(OTf)_3$-catalyzed construction of 3-aryltetralin skeleton **206** from simple phenethyl derivatives **205** (Scheme 78) [59]. The electronic and steric properties of the aromatic ring adjacent to C–H bond serving as hydride donor significantly influenced the reactivity of this transformation.

Yu and Luo et al. reported a catalytic enantioselective benzylic C(sp^3)–H functionalization of **207** via a [1,5]-hydride transfer/cyclization sequence with the chiral complex of copper(II) and side-armed bisoxazoline **209** as catalyst, which provided tetrahydronaphthalene derivatives **208** in moderate to high yield with up to 69 % ee (Scheme 79).

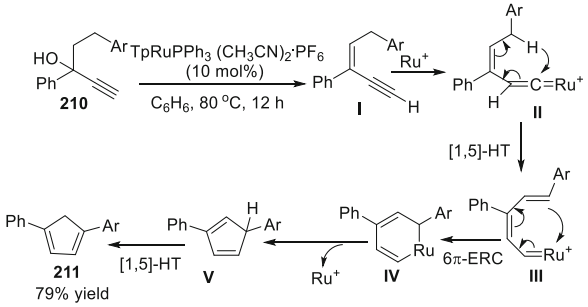
6.2 Activated Alkynes as the Hydride Acceptors

Liu et al. reported a $TpRuPPh_3$ $(CH_3CN)_2{\cdot}PF_6$-catalyzed cycloisomerization of *cis*-3-en-1-ynes **I** or their precursor alcohols **210**, which afforded cyclopentadiene **211** (Scheme 80) [43]. Mechanistically, **210** undergoes ruthenium-catalyzed dehydration to afford the real substrates *cis*-3-en-1-ynes **I**, which is converted into ruthenium-vinylidene intermediate **II** via [1,2]-shift of alkynyl hydrogen. A [1,5]-

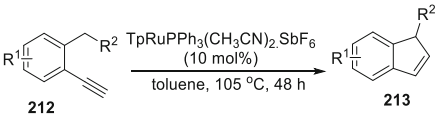


Scheme 79 Catalytic enantioselective C(sp3)–H functionalization via [1,5]-HT/cyclization

Scheme 80 Ruthenium-catalyzed cycloisomerization of *cis*-3-en-1-ynes to cyclopentadienes



Scheme 81 Ruthenium-catalyzed cyclization of 2-alkyl-1-ethynyl-benzenes

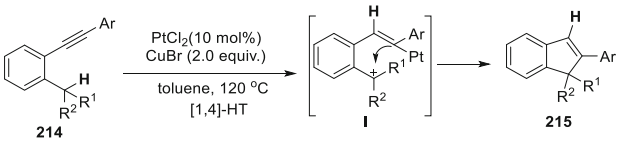


Hydride shift ensues to generate ruthenium haxa-1,3,5-triene **III**, which undergoes 6π-electrocyclic ring closure and reductive elimination to furnish cyclopentadiene **IV**. Ultimately, the most stable regioisomer **211** is yielded via a [1,5]-hydrogen shift.

Liu et al. reported a $TpRuPPh_3(CH_3CN)_2SbF_6$ (10 mol%)-catalyzed cyclization of 2-alkyl-1-ethynylbenzene derivatives **212**, which yielded 1-substituted-1*H*-indene products **213** in moderate to good yields (Scheme 81) [44]. The counterions were critical to the success of the reaction.

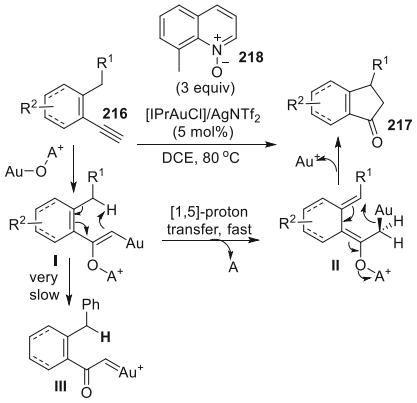
He et al. described a $PtCl_2$-catalyzed intramolecular cyclization of *o*-isopropyl or *o*-benzyl arylalkynes **214**, which yielded functionalized indenes **215** (Scheme 82) [69]. In contrast to a previous report [44], the terminal carbon of alkyne in this reaction was substituted with aryl substituent. Notably, CuBr (2.0 equiv.) was indispensable to achieve high yield. Theoretically, platinum(II)-activated electrophilic alkyne initially abstracts a hydride from benzylic C–H in [1,4]-manner to generate a benzylic carbocation **I**, which subsequently intercepts nucleophilic alkenyl-platinum(II) to afford the 5-membered ring.

Chatani et al. reported a cycloisomerization of 1-alkyl-2-ethynylbenzenes catalyzed by $PtCl_2$, $PtCl_4$, and $[RuCl_2(CO)_3]_2$ for preparing substituted indenes



Scheme 82 $PtCl_2$-catalyzed intramolecular cyclization of *ortho*-substituted aryl alkynes via [1,4]-HT/cyclization

Scheme 83 Gold-catalyzed oxidative cyclizations of *cis*-3-en-1-ynes

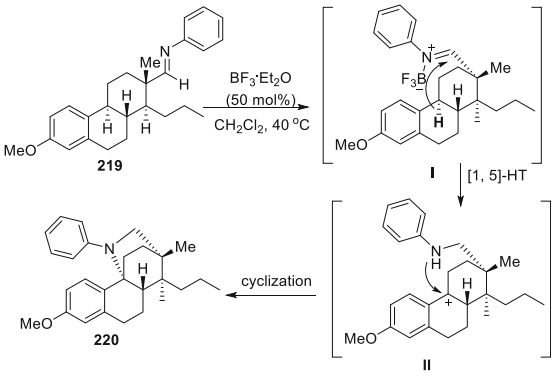


[40]. Remarkably, the benzylic primary C–H bond could participate in this cascade process to afford indene in 44 % yield. In contrast to Zhang's report [61], it is the hydride that transfers in [1,5]-manner this time.

Liu et al. described a [IPrAuCl]/$AgNTf_2$-catalyzed oxidative cyclizations of *cis*-3-en-1-ynes **216** with 8-methylisoquinoline oxide **218** as oxidant, which gave rise to cyclopentenone skeletons **217** (Scheme 83) [67]. Basically, the initially formed gold-containing enol ether **I** has a high energy barrier to overcome to form hypothetical carbenoid **III**. Instead, **I** undergoes a rapid [1,5]-hydrogen shift to generate intermediate **II**. Remarkably, hydrogen is transferred in the form of proton because hydrogen is captured by electron-rich gold-alkenyl subunit and the electron-withdrawing substituent in the benzylic position is beneficial to the cascade process. Afterwards, a subsequent cyclization of **II** leads to **217**. This proposed mechanism explains the observation that an acidic C–H bond can accelerate this oxidative cyclization. Similar mechanisms of transferring proton in [1,5]-manner have also been described by Zhang et al. [62, 64–66].

6.3 Electrophilic Imine, Hydrazone, Oxime Ester as the Hydride Acceptors

In the total synthesis of D-Homosteroid, Tietze et al. reported a $BF_3{\cdot}OEt_2$-catalyzed cascade [1,5]-hydride transfer/cyclization of **219**, which produced an unusually bridged steroid alkaloid **220** in 85 % yield at room temperature (Scheme 84) [137–139]. Although benzylic methine and imine in **219** are comparatively inactive hydride donor and acceptor, with the assistance of electron-donating methoxy group

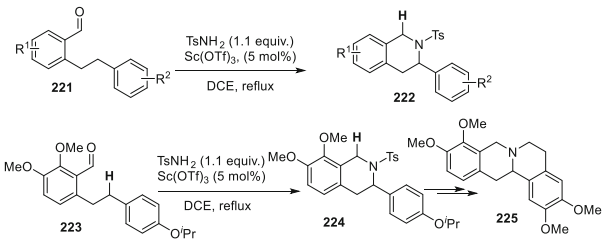


Scheme 84 $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydro-*N*-alkylation of phenyl imine

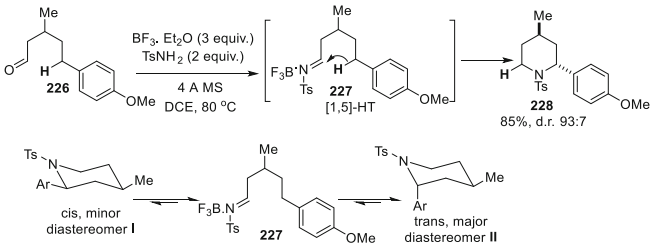
at *para*-position and activation by $BF_3{\cdot}OEt_2$, hydride could migrate to imine moiety readily. A subsequent nucleophilic attack of amino group on carbocation on **II** led to the formation of bridged steroidal azacycles **220**. In addition to phenyl substituted imine, hydrazones and oxime ethers could also work as hydride acceptor in the presence of Lewis acid. Frank et al. described a similar $BF_3{\cdot}Et_2O$-catalyzed intramolecular hydro-*N*-alkylation of hydrazones and oxime ethers [140].

Akiyama et al. described a $Sc(OTf)_3$-catalyzed reaction to access isoquinoline skeleton **222** (Scheme 85) [141]. The tosyl imine formed in situ and benzylic methylene worked as hydride acceptor and donor, respectively. $Sc(OTf)_3$ played dual roles, one of which was to promote the condensation of benzaldehyde **221** and tosylamide. Because the hydride donor in the reaction was inactive benzylic methylene, electron-withdrawing tosyl group was indispensable to increase the electrophilicity of C=N bond, additionally $Sc(OTf)_3$ could further activate the imine. The methodology was elegantly elaborated in the formal synthesis of (±)-tetrahydropalmatine **225**.

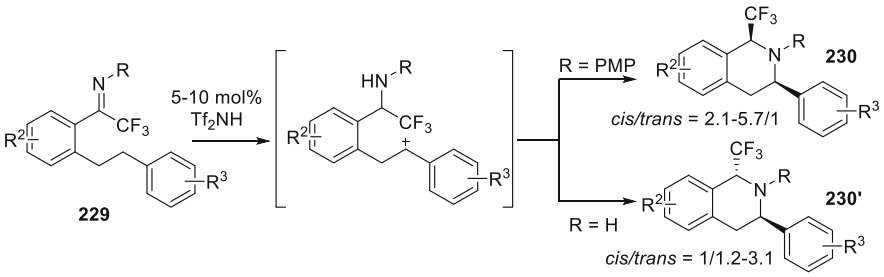
Sames et al. reported a highly stereoselective intramolecular amination of benzylic $C(sp^3)$–H bonds via cascade [1,5]-HT/cyclization of *N*-tosylimine **227** generated in situ from aliphatic aldehyde **226**, which constructed 2-arylpiperidines **228** and 3-aryl-1,2,3,4-tetrahydroisoquinolines (Scheme 86) [96]. Remarkably, the conformational freedom of substrates had a profound influence on the chemical behaviors of hydride acceptors: the substrates with high conformational rigidity had



Scheme 85 $Sc(OTf)_3$-catalyzed hydro-*N*-alkylation of tosyl imines to form 3-arylisoquinolines



Scheme 86 $BF_3{\cdot}Et_2O$-catalyzed stereoselective intramolecular amination of benzylic C(sp^3)–H bonds



Scheme 87 Brønsted acid-catalyzed C(sp^3)–H bond functionalization for synthesis of 3-aryl-1-trifluoromethyltetrahydroisoquinolines

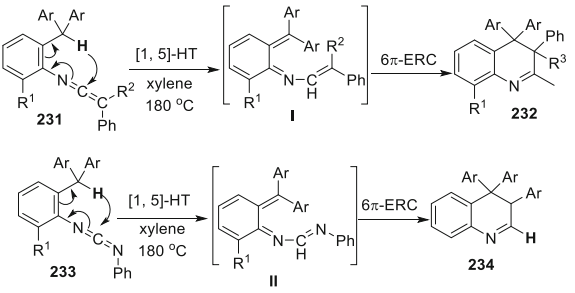
higher reactivities than those with high conformational freedom. The cascade [1,5]-HT/cyclization was highly stereoselective, which could be rationalized by the reversible cyclization step. The high stereoselectivity resulted from thermodynamic control and the aryl ring preferred to adopt an axial orientation in diastereomer **II** to avoid the steric interaction (pseudo-allylic strain) with the sulfonamide group in diastereomer **I**.

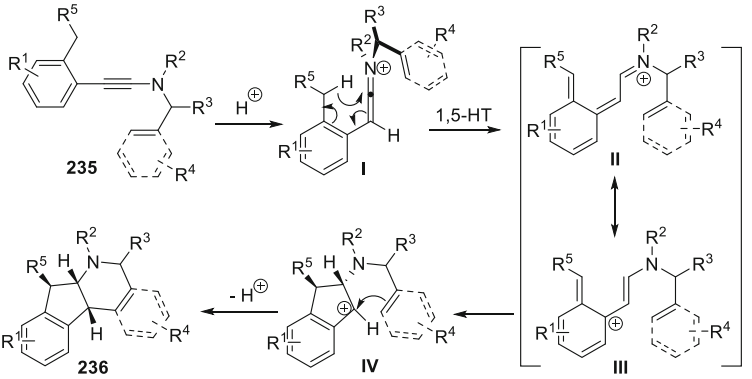
Akiyama et al. reported a Brønsted acid-catalyzed synthesis of 3-aryl-1-trifluoromethyltetrahydroisoquinolines **230** and **230′** by a benzylic [1,5]-hydride shift-mediated C–H bond functionalization (Scheme 87) [142], which features the diastereo-divergent synthesis of 3-aryl-1-trifluoromethyltetrahydroisoquinolines **230** and **230′** by tuning the substituents on nitrogen atom. The trifluoromethylketimine derived from *para*-anisidine and activated by Tf_2NH served as hydride acceptor and the substituents on ketimines had dramatic impacts on the diastereoselectivities: *cis*-product **230** could be furnished as major product when R was PMP group, whereas the diastereoselectivity was reversed with R as hydrogen.

6.4 Ketenimine and Carbodiimide as Hydride Acceptors

Alajarin et al. described a concise protocol for synthesis of 3,4-dihydroquinolines **232** and 3,4-dihydroquinazolines **234** (Scheme 88) [55]. Triphenyl substituted methines and electrophilic ketenimine/carbodiimide worked as hydride donors and acceptors, respectively. Because of the high electrophilicity of ketenimine and

Scheme 88 Direct C(sp^3)–H functionalization of tri(di)arylmethane





Scheme 89 Keteniminium ion-initiated cascade cationic polycyclization

carbodiimide, and highly stabilizing effect of adjacent three aromatic groups, thermal conditions alone could efficiently facilitate the cascade process, under which **231** and **233** could be transformed into **232** and **234**, 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 conjugated 1,3,5-hexatriene **I** or **II**, which suffers subsequent 6π-electrocyclic ring closure to produce the sterically congested **232** and **234**.

Thibaudeau and Evano et al. reported a TfOH or Tf_2NH-catalyzed keteniminium-initiated cationic polycyclization of ynamides **235** (Scheme 89) [143], which provided a straightforward access to polycyclic nitrogen heterocycles **236** possessing up to three contiguous stereocenters and seven fused cycles. Basically, the reaction is initiated by protonation of electron-rich alkyne of ynamide **XX**, yielding a highly reactive *N*-tosyl- or *N*-acyl-keteniminium ion **I**, which served as hydrogen acceptor. A [1,5]-sigmatropic hydrogen shift would then ensue to generate conjugated iminium **II** (in resonance with the bis-allylic carbocationic form **III**). The first cycle would be formed by a 4π conrotatory electrocyclization, producing **IV** in the manner of Nazarov reaction. Finally, a second cyclization between the benzylic carbocation **IV** and the arene/alkene subunit leads to the formation of polycycle **236**.

7 Non-benzylic C(sp^3)–H Bonds as the Hydride Donors

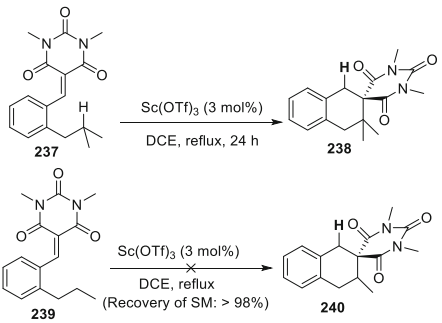
The cascade [1,5]-hydride transfer/cyclization summarized above have entailed the electronic assistance of adjacent heteroatoms or aromatic groups for stabilizing the carbocation formed upon hydride shift. However, hydride abstraction from an aliphatic, non-benzylic position is still a challenging task, and its realization would improve the usefulness of the cascade strategy in synthetic organic chemistry. Because of the lack of electronic assistance from adjacent heteroatom or aromatic group, the dissociation energy of C–H bond in aliphatic non-benzylic position is quite high. It was not until 2011 that Akiyama et al. managed to employ non-benzylic methylene as the hydride donor.

7.1 Electrophilic Benzylidene Malonates and Their Derivatives as the Hydride Acceptors

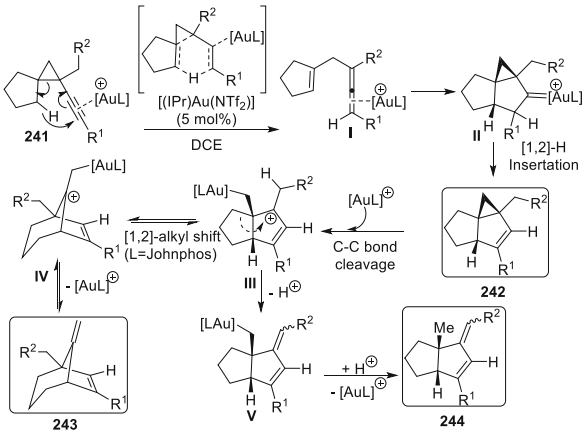
Akiyama et al. first reported an unprecedented cascade [1,5]-hydride transfer/cyclization with non-benzylic methine as hydride donor (Scheme 90) [74]. Treatment of benzylidene barbituric acid **237** with 3 mol% $Sc(OTf)_3$ in refluxing $ClCH_2CH_2Cl$ for 24 h could furnish the desired tetraline **238** in excellent yield. Notably, the substrate with a linear side chain **239** did not give the desired product **240**, even with a catalyst loading of 30 mol%. This result suggested that the substitution degree at the hydride-releasing carbon atom was crucial for the success of the cascade process.

7.2 Gold-Activated Alkynes as the Hydride Acceptors

Barluenga et al. elegantly demonstrated an intriguing manifold reactivity of alkynylcyclopropanes **241** bearing a spirane core (Scheme 91) [144]. Remarkably, comparatively inactive non-benzylic secondary C–H bond could work as hydride donor. The cyclopropane moiety was crucial for the success of the cascade process, which rendered inactive methylene group closer to electrophilic alkyne moiety. Thus, the proximate hydride could be readily abstracted by electrophilic alkyne activated by gold catalyst. The diverse fate of the resulting cationic gold species could be efficiently controlled by simple option of appropriate catalyst (either



Scheme 90 $Sc(OTf)_3$-catalyzed direct functionalization of aliphatic tertiary C(sp^3)–H bond

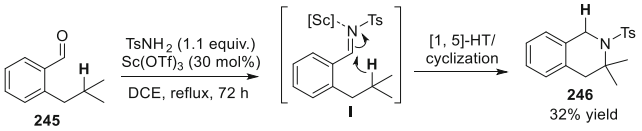


Scheme 91 Gold-catalyzed direct functionalization of secondary non-benzylic C(sp^3)–H bonds

[(JohnPhos)Au(MeCN)]-[SbF_6] or [(IPr)Au-(NTf_2)]) and reaction temperature. A range of cyclic structures, e.g., pentalene derivatives **242** and **244**, and bicycles **243** could be accessed with complete selectivity. Mechanistically, the gold-alkyne coordination triggers a [1,5]-hydride transfer with concomitant ring opening of cyclopropane. The generated 1,4-enallenyl gold intermediate **I** might then undergo a cyclization via intermediate **II** to afford tricycle **242**. The subjection of **242** to harsher reaction conditions leads to the formation of **243** and **244**, and **III** might be their common intermediate, which is formed by regioselective gold-catalyzed C–C bond cleavage. The formation of **243** 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 pentalene **244**.

7.3 Electrophilic Imine as the Hydride Acceptor

One more example of using aliphatic non-benzylic methine as hydride donor was also reported by Akiyama et al. in which the tosyl imine **I** generated in situ from **245** was employed as hydride acceptor (Scheme 92) [141]. 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 decent yield, 30 mol% catalyst loading was employed, whereas the tetraline **246** was obtained only in 32 % yield even with a prolonged reaction time (72 h).



Scheme 92 $Sc(OTf)_3$-catalyzed hydro-*N*-alkylation with aliphatic tertiary C(sp^3)–H bond as hydride donor

8 Conclusions and Perspectives

In this review, we have introduced the recent advances of cascade [1,*n*]-hydrogen transfer/cyclization as a versatile protocol to directly functionalize inactive C(sp^3)–H bond into C–C, C–N, and C–O bonds in an atom-economic manner. A variety of hydrogen donors and acceptors as well as different activation modes of hydrogen acceptors have been well organized and discussed. This methodology has proven to be powerful in delivering molecular complexity, especially in the synthesis of a variety of useful and pharmaceutically important heterocycles, e.g., 5-, 6-, 7-membered fused or spiro-hetero, or full carbon cycles. The facile construction of C–C, C–N, and C–O bonds and ring skeletons renders this strategy attractive to access value-added molecules from readily available starting materials. In addition to the benefit of atom-economy, the reaction conditions are mild, and expensive transition metal catalysts are not required in many cases.

Despite the significant developments in recent years, there is still much left to do in this chemistry, for instance, the types of hydride donors and acceptors are still rather limited. More C(sp^3)–H α to heteroatoms, which have lone pairs, e.g., phosphorus, bromine, chlorine, etc., are likely to be exploited as hydrogen donors and more diverse electron-deficient species can be employed as hydrogen acceptors.

Another hot research topic in this area is the asymmetric catalytic version of this reaction, and more efficient and selective catalytic systems needs to be developed. Although this methodology has shown an appealing application to construct complex moieties, it has been rarely exploited in total syntheses and the synthetic potential 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 methodology and development of novel reactions are expected in the future.

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