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Silver-catalyzed enantioselective functionalizations of alkenes and alkynes: A short review

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Transition metal-catalyzed asymmetric transformations of alkenes and alkynes can upgrade readily available unsaturated compounds to valuable building blocks for organic synthesis. Late transition metals supported by asymmetric ligands, particularly palladium, rhodium, and iridium, have traditionally been employed for enantioselective functionalization of alkenes and alkynes, but these precious metals are costly. Silver is a much less expensive late transition metal with good Lewis acidity that can accommodate diverse ligands and coordination geometries. Silver(I) complexes are also capable of engaging in non-covalent interactions with alkenes and alkynes to drive selectivity in reactions at both the unsaturated bond, as well as at an adjacent activated allylic or propargylic C–H bond. This short review summarizes recent developments in asymmetric silver-catalyzed reactions of alkene-containing and alkyne-containing compounds. Direct enantioselective transformations of the alkene/alkyne π bond are described, as well as examples where the site of unsaturation drives functionalization at an adjacent C–H bond.

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Introduction

Transition metal-catalyzed transformations of compounds containing π-donors, including alkenes and alkynes [1–6], represent a powerful way to access highly functionalized and valuable synthetic building blocks. A host of metals have been employed in this regard, particularly palladium, rhodium, and iridium [7–9], but there has been a recent resurgence of interest in the use of less expensive metals, including silver [10,11]. Silver(I) is among the softest Lewis acids and can interact with both π-donors and n-donors, as exemplified by alkenes, alkynes, allenes, carbonyls, and imines [12]. Other advantages of this metal include versatility in its coordination ability with a variety of N-donor and P-donor ligands, unique redox chemistry and high oxidizing power, and the ability to catalyze both intramolecular and intermolecular reactions of alkenes and alkynes with high degrees of stereoselectivity and regioselectivity.

In terms of the historical development of silver catalysts, early advances focused mainly on the Lewis acidic properties of the metal. One of the most common modes of reactivity of silver catalysts involves activation of a C–C π bond by the Lewis acidic metal, followed by trapping of the complex with a variety of nucleophiles, resulting in the formation of diverse C–X bonds (X = C, N, O, P, halogen) [13,14]. Asymmetric silver-catalyzed reactions have traditionally involved additions to C = X π bonds, highlighted by examples of enantioselective aldol reactions, 1,3-dipolar cycloadditions, and asymmetric allylations [15–19]. However, several enantioselective functionalizations of alkynes and alkenes *en route* to the synthesis of bioactive [20–23] molecules have been reported in the past two years. This short review highlights selected examples that furnish enantioenriched alkaloid scaffolds, fused carbocycles, pyrrolidines, other heterocycles, and propargylamines.

Enantioselective functionalization of the π bond of alkynes and alkenes

Alkynes are more readily activated by silver as compared to alkenes; thus, most efforts toward enantioselective transformations involve this functional group. For example, silver-catalyzed cyclizations have been employed to form polycyclic cores that are present in a number of bioactive natural products, including the akuammiline alkaloids [24–26]. The Unsworth group recently investigated an Ag(I)-catalyzed enantioselective dearomatization of the indole ring of **4** to form the alkaloid scaffold **6** (Figure 1a). The precursor ynone-tethered indoles **4** are easily accessible via radical alkylations of commercially available indoles **1** with various xanthate derivatives **2** and alkyne Grignard reagents **7**. Unsworth and coworkers also achieved enantioselective dearomatizations utilizing (R)-SPINOL CPA-H **3** as the ligand in combination with a silver salt to furnish **6** in up to 96% *ee* (Figure 1a). Ynone derivatives facilitated the reaction under mild conditions, due to the binding of the carbonyl group to the Lewis acidic silver catalyst. A wide range of related enantioselective dearomatizative cyclizations was performed on

diverse substrates to give **6** in high yields and stereoselectivities in most cases [24,27,28].

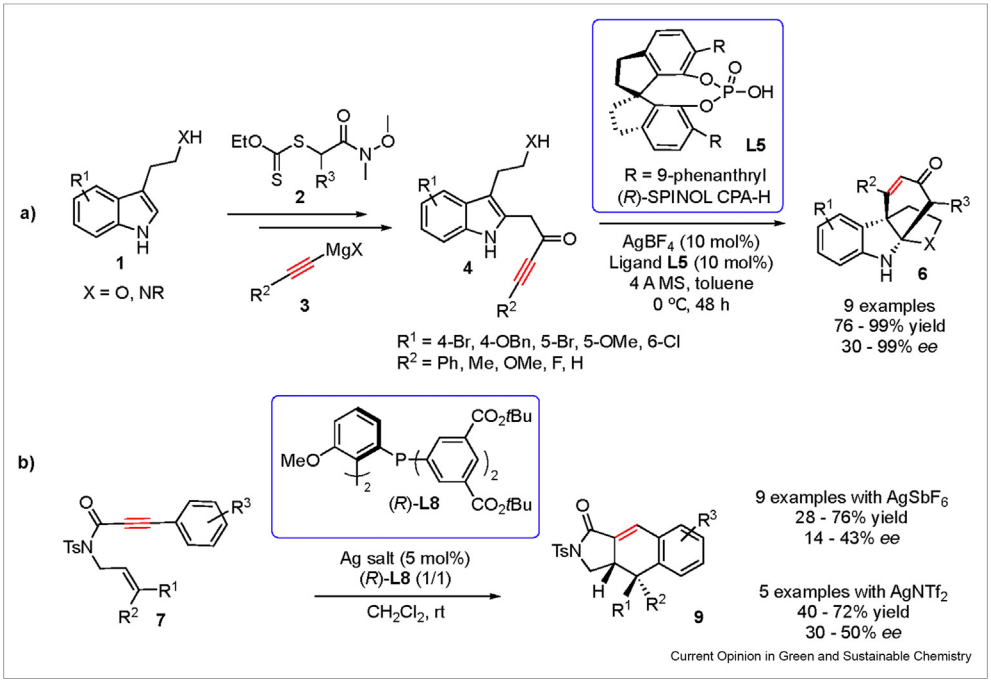
The Michelet group recently reported that ynone derivatives of form **7** (Figure 1b) can be cyclized in high *ee* via intramolecular, silver-catalyzed [4 + 2] cycloadditions. This chemistry delivers enantioenriched carbo- and heterocyclic motifs that are present in several bioactive natural products [29]. After evaluating several ligands for the asymmetric [4 + 2] cycloadditions of **7**, a chiral phosphine (R)-L**8** was found to give **9** in yields of 28–76% and *ee* of up to 50% (Figure 1b) [29]. Although these results are promising, further ligand screening is required to improve the low-to-moderate *ee*.

Ishihara and coworkers reported the first example of an asymmetric one-pot Michael addition/Conia-ene cyclization of enones and propargylamines via synergistic Fe(III)/Ag(I) catalysis to furnish enantioenriched pyrrolidines (Figure 2a), which are useful synthons for the preparation of a variety of natural products and bioactive molecules [30]. Optimal conditions employed a Fe(III)/Ag(I) cooperative catalyst supported by the ligand **L12** to couple enone derivatives **10** with propargylic sulfamates **11** to form pyrrolidine scaffolds **13** (Figure 2a) in up to 98% yield and 91% *ee*. The success of this approach was rationalized through the initial activation of the alkyne by the silver complex to facilitate the subsequent iron-catalyzed Conia-ene reaction. The ligand is proposed to predominantly coordinate to the iron center, with the major role of the silver simply to activate the triple bond.

Silver-catalyzed strategies to access other attractive nitrogen-containing scaffolds in enantioenriched form have also been recently developed by the groups of Che and Ma [31,32]. In 2019, Che and coworkers investigated the transformation of enantioenriched propargylamines of form **14** (Figure 2b), readily prepared using (*S*)-prolinol as a chiral auxiliary, to axially chiral vinyl allenes **15** in good yields and excellent *ee* up to 99%. Technically, this is not an asymmetric reaction; however, the excellent fidelity in the transfer of point-to-axial chirality from **14** to **15**, which can bear diverse electron-donating and withdrawing groups, is noteworthy. The utility of the chiral vinyl allenes **15** was further highlighted in subsequent (hetero)-Diels–Alder reactions with both azodicarboxylates **16** and maleimides **18** in the presence of water. These reactions also displayed excellent axial-to-point chirality transfer to give the heterocyclic products **17** and **19** in up to 99% *ee* [31,33].

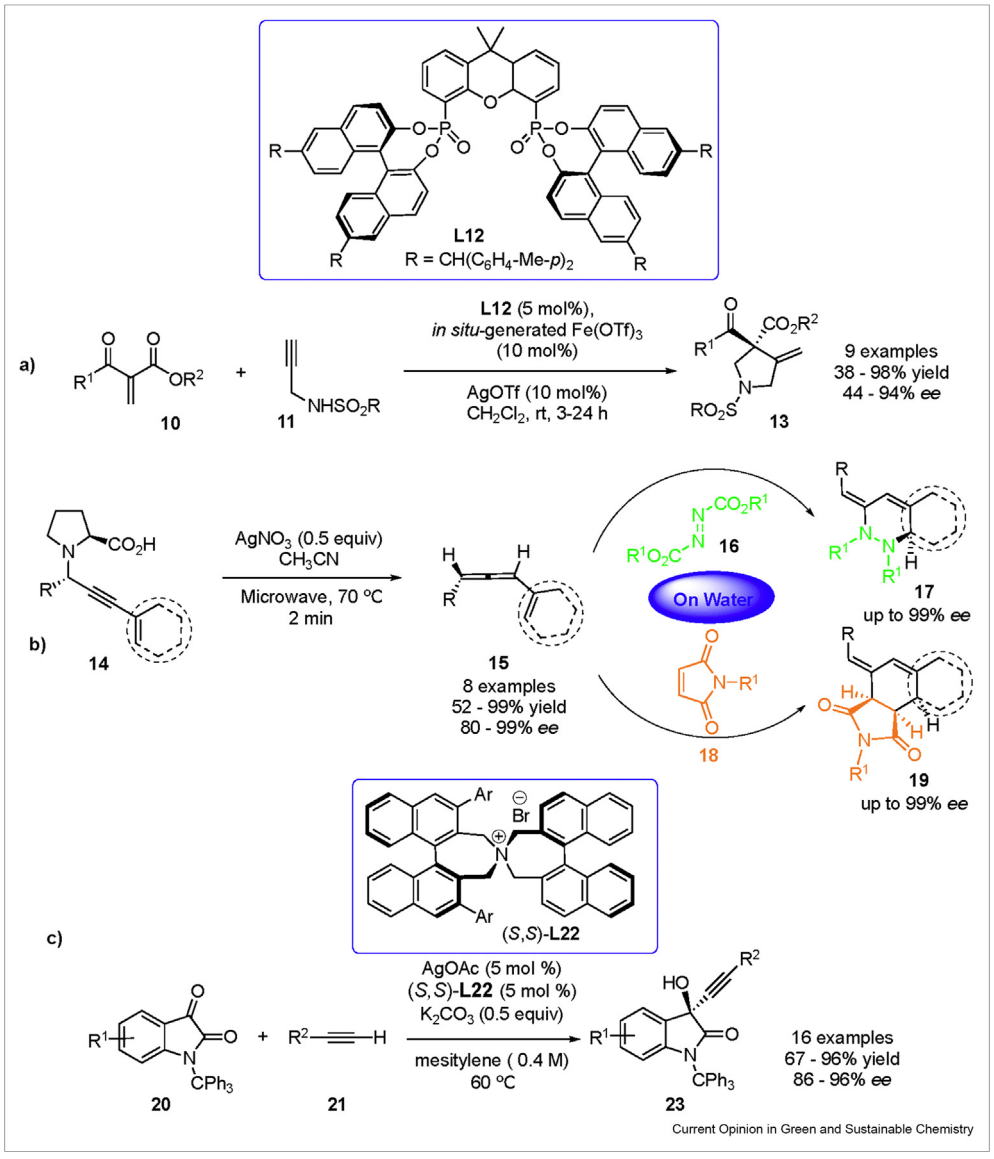
In recent years, the combination of chiral phase-transfer and transition-metal catalysis has been widely utilized for the preparation of chiral alkynes that comprise

Figure 1



(a) Silver-catalyzed asymmetric indole dearomatization of **4** to furnish alkaloid scaffolds **6**. **(b)** Silver-catalyzed enantioselective intramolecular [4 + 2] cycloadditions of enynes **7**.

Figure 2

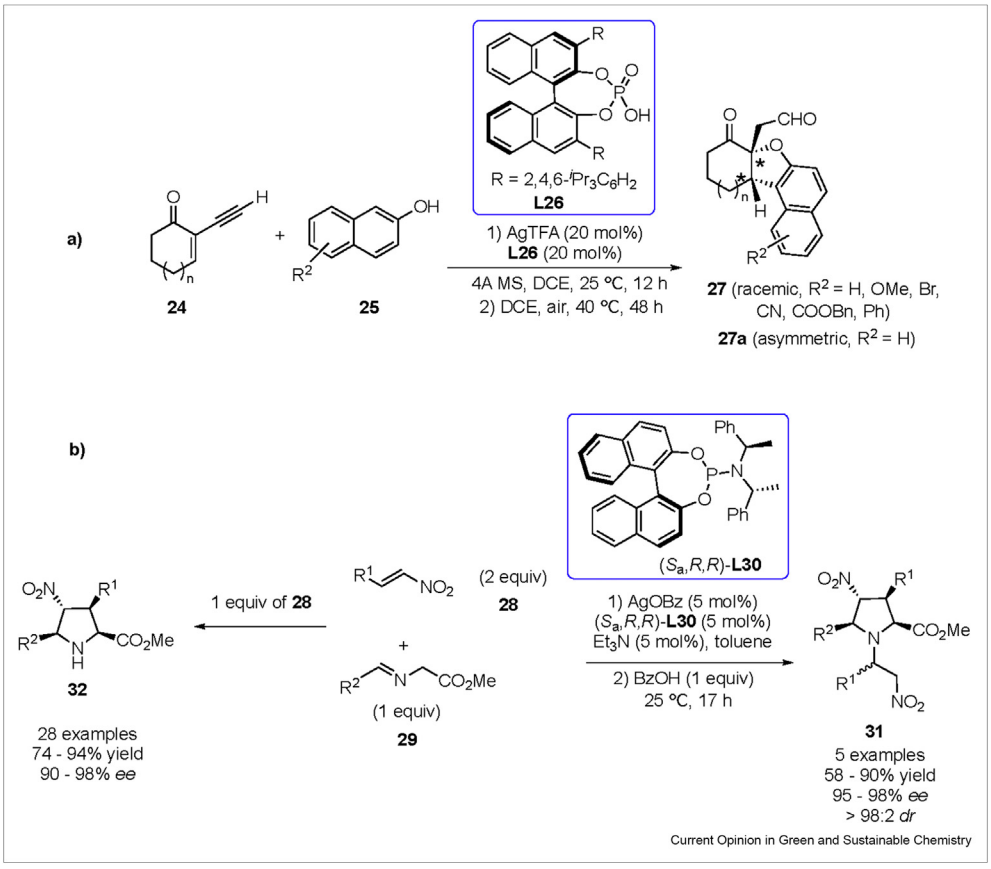


(a) One-pot asymmetric tandem Michael addition/Conia-ene cyclization via cooperative Fe(III)/Ag(I) catalysis. **(b)** $AgNO_3$-mediated synthesis of axially chiral vinyl allenes and use in hetero-Diels–Alder reactions. **(c)** Enantioselective, silver-catalyzed alkynylations of ketones.

valuable synthetic building blocks [34]. In this context, Maruoka and colleagues in 2019 investigated the asymmetric, silver-catalyzed alkynylation of imines to furnish chiral propargylic alcohols. While this has been accomplished using other late transition metals, the successful use of silver would provide a much less expensive route [34,35]. The formation of the alkyne nucleophile **21** was achieved in presence of a silver catalyst formed *in situ* from AgOAc and a chiral (*S*,*S*)-**L22** ligand. This enantioenriched phase-transfer catalyst was able to discriminate between the two enantiotopic faces of **20** during nucleophilic addition of alkyne **21** to furnish alcohol **23** in high yield and *ee* of up to 96%. The addition of K_2CO_3 as the base and careful control of the temperature proved essential for the success of this reaction. A wide range of amines **20** and alkyne derivatives **21** was well-tolerated under the reaction conditions (Figure 2c) [34,36,37].

An efficient approach toward the silver-catalyzed functionalization of 2-(1-alkynyl)-2-alken-1-ones **24** with 2-naphthols **25** has been recently disclosed by Ren and coworkers (Figure 3a). A previously reported silver catalyst gives highly regioselective and diastereoselective reactions between **24** and **25** to form racemic fused tetracyclic furan derivatives of form **27** [25]. The

Figure 3



(a) Enantioselective silver-catalyzed cascade reaction of 2-(1-alkynyl)-2-alken-1-ones with 2-naphthols. **(b)** Catalytic, asymmetric silver-catalyzed formation of nitropyrrolidines.

scope and generality of this cascade reaction was also investigated, showing that a broad range of substrates bearing functionalities such as halides, cyanide, and esters, on the naphthalene ring was tolerated to deliver products of form **27** in up to 84% yield. The use of AgTFA resulted in only one isolable diastereomer **27** in a significantly enhanced yield. Other silver catalysts, including AgOAc and Ag2CO3, were not effective; thus, the choice of silver salt is critical. [25, 38, 39] In addition, the group developed an asymmetric version of the reaction, employing silver trifluoroacetate supported by a chiral phosphoric acid **26**. The heterocyclic product **27a** was furnished in 72% yield and 71:29 er.

Chiral pyrrolidines bearing nitro groups are of interest due to their bioactivity, which includes potential as anti-adhesives and significant inhibitory activity toward various skin cancers [40]. The nitro group can also be transformed into other functional groups of great utility in organic synthesis; in addition, its presence imparts a unique conformation to the five-membered ring of the pyrrolidine that is of benefit for the biological activity [40]. An asymmetric synthesis of nitropyrrolidines **31** (Figure 3b) was achieved through a regioselective and diastereoselective Michael addition of **29** to **28**, controlled by the chiral phosphoramidite-silver-benzoate complex **30** [40,41]. When one equivalent of both **28** and **29** was employed, nitroprolinates **32** were formed via the expected catalytic [3 + 2] cycloaddition (Figure 3b) [42,43]. As a further extension of this chemistry, a one-pot reaction utilizing one equivalent of imine **29** and 2 equivalents of the nitroalkene **28** was envisaged to furnish **31**. The sequence proceeds via an asymmetric [3 + 2] cycloaddition catalyzed by **L30**, followed by a Michael addition, to give **31** in good yield and up to 95% dr and 99% *ee*. The benzoic acid additive aids in the activation of **28** toward the Michael addition [21,40,44].

Enantioselective functionalization of C–H bonds adjacent to the π bond of alkenes and alkynes

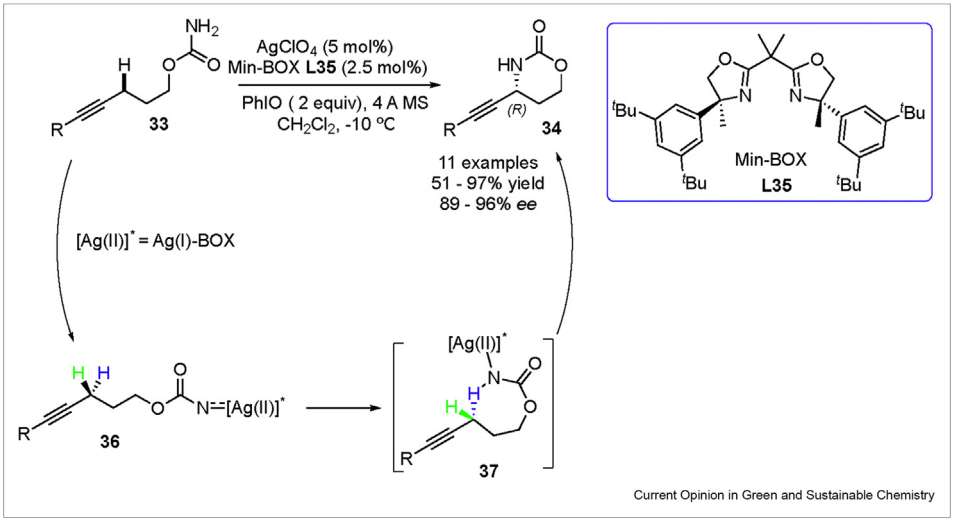
The π bond of an alkyne can also be engaged to activate the adjacent propargylic C–H bond

toward silver-catalyzed nitrene transfer to form a new carbon-nitrogen bond. The Schomaker group recently reported the design of a novel ligand for silver-catalyzed asymmetric aminations of the propargylic C–H bond in **33** to ultimately furnish γ-amino alcohol motifs **34** (Figure 4) [45,46]. The ligand design was critical to achieving both good site-selectivity between competing β-C(sp^3)–H bonds or γ-C(sp^3)–H bonds, as well as high enantioselectivity [45,47]. Various ligand designs were evaluated to assess the effects of electronics, steric bulk, substrate-ligand π–π, and metal–ligand cation–π interactions on site-selectivity and enantioselectivity. The ligand optimization studies culminated in the design of Min-BOX L35, where key features important to consistently high *ee* include the aryl substitution, bulk at the 3- and 5-positions of the aromatic ring, and a quaternary stereodefined carbon bearing a methyl group. Much lower *ee* was observed using BOX ligands lacking the fully substituted carbon center. Both the steric bulk and the introduction of the α-Me group substitution on the BOX ligand **35** are hypothesized to minimize rotation around the Ar–C bond of the ligand, leading to a more restricted conformation in the transition state and enhancing the enantioselectivity. Alkynes **33** containing bulky alkyl or aryl substituents at the distal alkyne carbon gave the highest *ee*, but a variety of electron-donating and electron-withdrawing substituents, regardless of sterics, were well-tolerated, as were alkynes bearing heterocycles, such as furan and thiophene [46]. The mechanism is proposed to involve formation of an intermediate iminoiodinane from the reaction of the alkyne precursor with PhIO. Subsequent transfer to the chiral Ag(I) catalyst furnishes the silver-nitrene complex **36**. The nitrogen of the metal-supported nitrene, believed to be an Ag(II) radical anion, abstracts one of the prochiral propargylic hydrogens in an H-atom transfer (HAT) step, as depicted in transition state **37**. Rapid radical recombination yields the desired product **34** with high enantioselectivity. Further applications of this chemistry will enable the formation of valuable building blocks for bioactive molecules and synthetic containing 1,3-aminoalcohol functionality [11,45,48,49].

Concluding remarks

This review addresses recent developments in the application of silver catalysis to the enantioselective functionalization of alkenes and alkynes. These powerful transformations are capable of forming a variety of useful compounds, including enantioenriched alkaloid scaffolds, fused carbocycles, pyrrolidines, diverse heterocycles, and propargylamines. These motifs occur in many molecules with potential bioactivity and are of significant interest to synthetic and medicinal chemists alike. The practicality of these methods is demonstrated by their generally broad substrate scope, excellent functional group compatibility, and high yields and enantioselectivity. In particular, the low cost and toxicity of silver catalysts, coupled with their versatile coordination with diverse classes of chiral ligands, will increase interest in the future design and applications of new asymmetric silver catalysts.

Figure 4



Enantioselective silver-catalyzed propargylic C–H bond amination with $AgClO_4$ supported by a new MinBOX ligand.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that influence the work reported in this paper.

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