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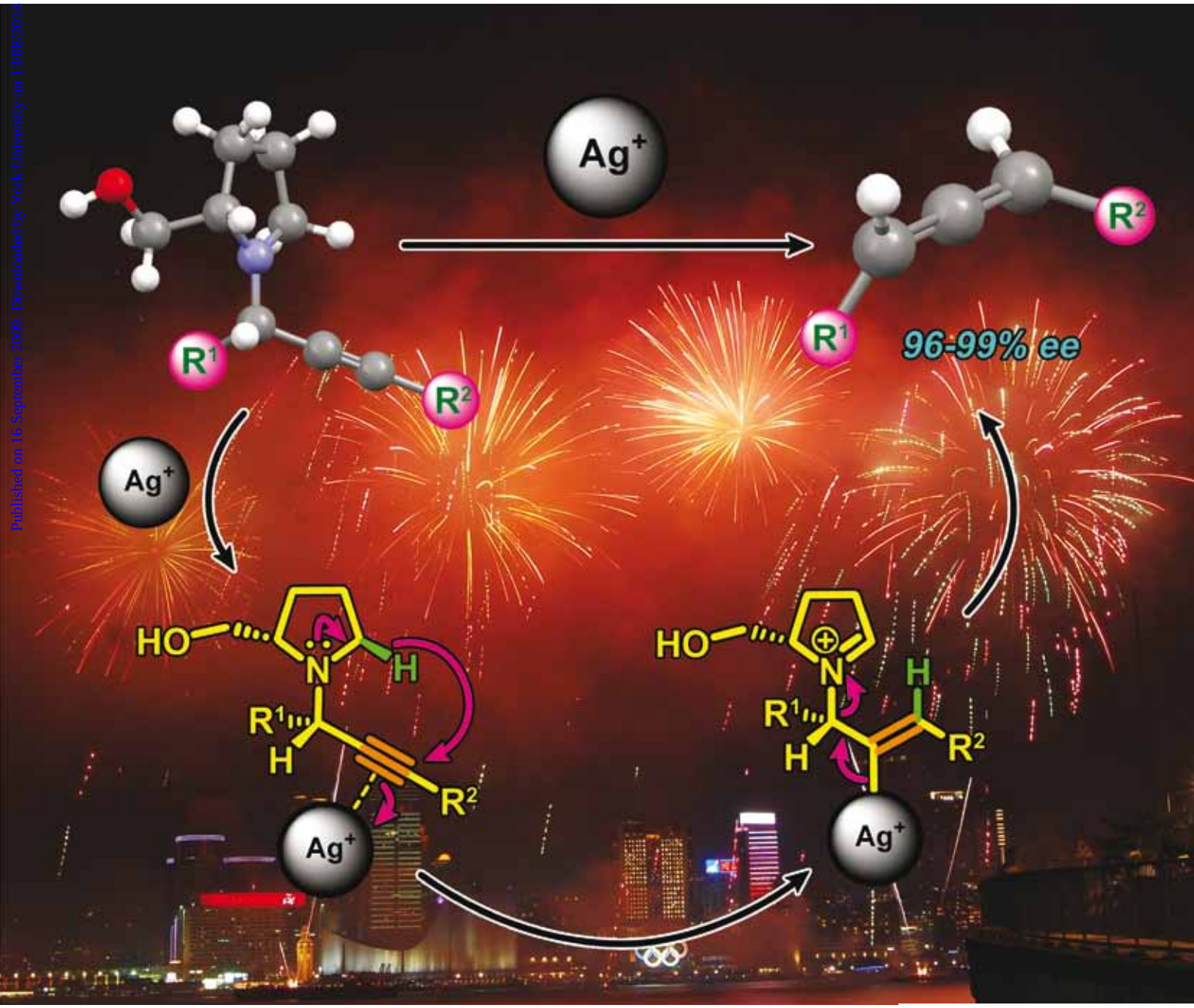

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Silver(I)-mediated highly enantioselective synthesis of axially chiral allenes under thermal and microwave-assisted conditions†‡

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Silver(I) salts mediated stereospecific transformation of optically active propargylamines to axially chiral allenes with excellent enantioselectivities (17 examples with 96–99% ee; one substrate with 91% ee) without subsequent racemization.

Axially chiral allenes are important structural motifs present in biologically active natural products,[1] and are versatile synthons featuring excellent axis-to-center chirality transfer.[1b,2] The synthesis of chiral allenes mainly relies on S_N2' displacement reactions of chiral propargylic compounds by organometallic reagents, 3,3-sigmatropic rearrangement of propargyl alcohols, and asymmetric catalysis with chiral metal complexes as catalysts.[1b,3] Recently, we reported a gold-catalyzed synthesis of axially chiral allenes from optically active propargylamines.[4] Although this method is tolerant to a variety of functional groups, the substrate scope was confined to 1,3-diarylallenes, and the enantiomeric excess of the allene products was found to be dependent on the electronic effect of substrates (Scheme 1); for example, electron-rich propargylamines led to corresponding allenes with low enantioselectivities. This result was explained by coordination of the gold catalyst to axially chiral allenes that subsequently leads to racemization.[5] Thus there is a need to search for other metal catalysts for highly enantioselective synthesis of axially chiral allenes from optically active propargylamines. The criterion is that such a metal catalyst is active for the transformation (Scheme 1) but would not racemize allenes.

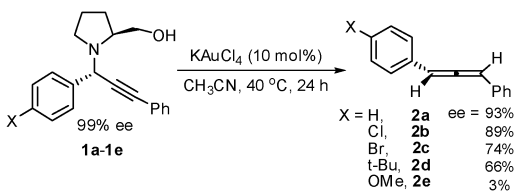
We are attracted to silver(I) compounds that are known to activate alkynes for nucleophilic attack, and there are many examples revealing that the chirality of allenes could be preserved in silver(I)-mediated organic transformations.[6] Here we report a silver(I)-mediated reaction of optically active propargylamines to form a wide range of axially chiral allenes with enantiomeric excess values, with the exception of one example, being 96–99%. To our knowledge, applications of silver compounds in highly enantioselective organic synthesis are sparse. Among them, a notable example is enantioselective allylation and Mukaiyama aldol reaction catalyzed by Yamamoto and Yanagisawa's BINAP–Ag(I) system.[7]

At the outset, we examined the catalytic activities of different silver(I) salts towards the transformation of propargylamine **1a** to allene **2a**, and the results are depicted in Table 1.

The initial experiment was conducted with $AgNO_3$. Treatment of propargylamine **1a** (99% ee)[8] with $AgNO_3$ (10 mol%) in CH_3CN (2 mL) at 40 °C for 24 h in the dark led to (*R*)-1,3-diphenylpropa-1,2-diene **2a** in 90% yield and 98% ee based on 39% substrate conversion (entry 1); no racemization of the resulting allene was observed. Increasing the silver(I) loading could improve the substrate conversion. When 50 mol% of $AgNO_3$ was used, the substrate conversion reached 91% (entry 3), while no further significant improvement was observed when a stoichiometric amount of $AgNO_3$ was used (entry 4). The substrate conversion was reduced to 50% when the reaction was performed in the presence of light (entry 5), and this is attributed to the fact that most silver(I) compounds are light-sensitive.

The activities of other silver(I) salts were examined. $AgBF_4$ was also effective to convert propargylamine **1a** to allene **2a** with 99% ee and with substrate conversion and product yield comparable to those of the reaction mediated by $AgNO_3$ (entry 6). AgOTf, $Ag(OOCCF_3)$ and $Ag(OOCCH_3)$ can also mediate this transformation with lower product yields (entries 7–9). AgCl, AgBr and AgI were found to be inactive under similar conditions (entries 10–12). Since $AgNO_3$ is non-hygroscopic, air-stable and inexpensive, the protocol with 50 mol% of $AgNO_3$ and reaction time of 24 h under 40 °C was employed for subsequent studies.

With the optimized conditions, a variety of axially chiral allenes were synthesized in high product yields (up to 95%) and high enantioselectivities (98–99% ee with the exception of product **2e** being obtained in 91% ee). In all cases, no racemization of the resulting allenes was observed. The results are listed in Table 2. This protocol allows the synthesis of a variety of 1,3-diarylallenes having different aryl moieties from corresponding propargylamines in a stereospecific manner (entries 1–9).



Scheme 1 Electronic effect on enantiomeric excess of allenes from gold-catalyzed reaction of optically active propargylamines.

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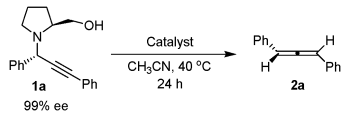
‡ Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data and supports for mechanistic studies. See DOI: 10.1039/b914516h

Table 1 Conditions for optimization



Entry	Catalyst	mol%	Conv. (%)[a]	Yield (%)[b]	Ee[c]
1	$AgNO_3$	10	39	90	98
2	$AgNO_3$	30	55	99	99
3	*$AgNO_3$*	*50*	*91*	*74*	*99*
4	$AgNO_3$	100	90	73	98
5[d]	$AgNO_3$	50	50	84	99
6	$AgBF_4$	50	92	79	99
7	AgOTf	50	96	61	99
8	$Ag(OOCCF_3)$	50	96	67	99
9	$Ag(OOCCH_3)$	50	38	95	85
10	AgCl	50	0	—	—
11	AgBr	50	0	—	—
12	AgI	50	0	—	—

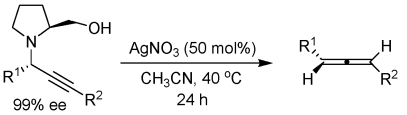
[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield based on conversion. [c] Determined by HPLC using Chiralcel-OD column. [d] Reaction performed in the presence of light.

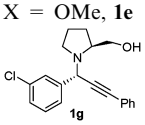
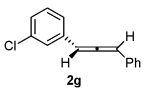
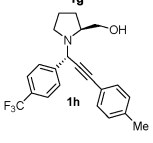
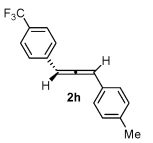
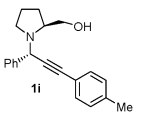
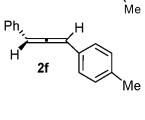
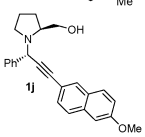
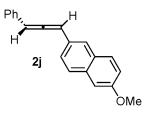
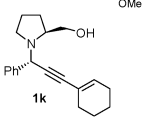
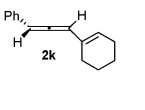
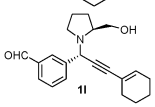
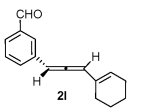
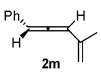
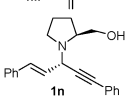
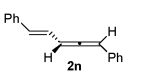
Vinylallenes are versatile intermediates for the construction of organic compounds with complexity through [4 + 2] cycloaddition.[9] In this work, axially chiral vinylallenes can be synthesized stereospecifically *via* silver(I)-mediated transformation of optically active propargylamines bearing an alkene moiety at a terminal or α position of the alkyne (entries 10–13). As an example, the reaction of propargylamine **1k** bearing a cyclohexenyl group led to vinylallene **2k** in 80% yield with 99% ee (entry 10). However, when $KAuCl_4$ was used as the catalyst, **2k** was obtained with 50% ee under the same conditions. Propargylamine **1n** having a cinnamyl moiety at the α position of the alkyne gave the corresponding vinylallene **2n** in 74% yield based on 95% conversion and with 99% ee (entry 13).

It is well-known that microwave irradiation can accelerate transition metal-catalyzed reactions.[10] Recently, we reported that the reaction time of gold-catalyzed hydroamination and hydroarylation of alkenes could be significantly shortened by microwave irradiation.[11] In this work, we also investigated microwave-assisted silver(I)-mediated transformation of propargylamines to allenes.

It was found that considerably shorter reaction times of around 20 min were achieved for the $AgNO_3$-mediated transformation of propargylamines to allenes, affording corresponding products in good yields and with excellent enantioselectivities. The results are depicted in Table 3. As an example, the reaction of propargylamine **1a** mediated by $AgNO_3$ was completed under microwave irradiation in 20 min, leading to **2a** in 80% yield based on 100% conversion and with 99% ee (entry 1). This protocol is useful for the synthesis of axially chiral 1,3-alkylarylallenes from corresponding propargylamines, affording products in high yields (up to 85%) with almost complete chirality transfer (entries 2–5). In contrast, when using the conventional thermal conditions a long reaction time was needed, resulting in products in low yields.[4] This protocol under microwave irradition also allowed the synthesis of 1,3-dialkylallene in high enantioselectivity (entry 6).

Table 2 $AgNO_3$-mediated synthesis of axially chiral allenes from propargylamines[a]



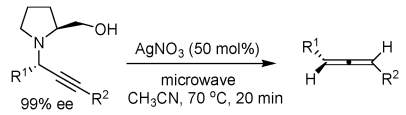
Entry	Substrate	Product	Conv. (%)[b]	Yield (%)[c]	ee (%)[d]
1	X = H, **1a**	**2a**	91	74	99
2	X = Br, **1c**	**2c**	68	91	98
3	X = *t*-Bu, **1d**	**2d**	80	78	98
4	X = Me, **1f**	**2f**	87	73	99
5	X = OMe, **1e**	**2e**	71	84	91
6			92	75	99
7			49	95	98
8			86	70	99
9			70	61	98
10			100	80	99
11			77	64	99
12			70	90	98
13			95	74	99

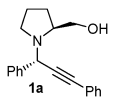
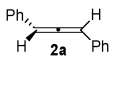
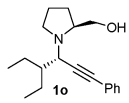
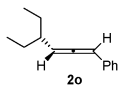
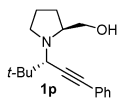
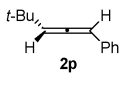
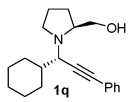
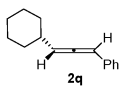
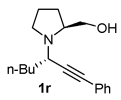
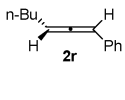
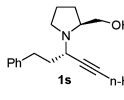
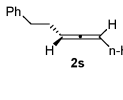
[a] Substrate : $AgNO_3$ = 1 : 0.5, ee of substrates = 99%. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield based on conversion. [d] Determined by HPLC using Chiralcel-OD column.

A proposed reaction mechanism is depicted in Scheme 2. Silver(I) ion coordinates to the alkyne moiety of the propargylamine to give intermediate **I**. An intramolecular hydride transfer converting intermediate **I** to intermediate **II**, followed by β-elimination gives the allene product in a stereospecific manner.

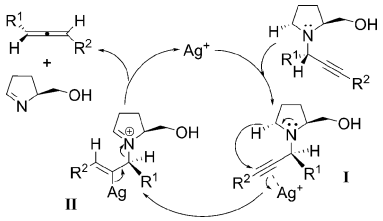
ESI-MS analysis of a reaction mixture of **1a** and $AgNO_3$ (50 mol%) after stirring for 1 h in CH_3CN at room temperature showed peaks centered at m/z 398, which is attributed to the adduct between **1a** and silver(I) ion (see supporting information‡). The isotopic pattern of the adduct

Table 3 Microwave-assisted $AgNO_3$-mediated synthesis of axially chiral allenes[a]



Entry	Substrate	Product	Conv. (%)[b]	Yield (%)[c]	ee (%)[d]
1			100	80	99
2			74	69	98
3			100	78	96[e]
4			65	85	97
5[f]			100	77	97
6			63	63	97

[a] Substrate : $AgNO_3$ = 1 : 0.5, ee of substrates = 99%. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Isolated yield based on conversion. [d] Unless otherwise specified, determined by HPLC using Chiralcel-OD column. [e] Determined by GC using Cyclodex-β column. [f] Substrate : $AgNO_3$ = 1 : 1.

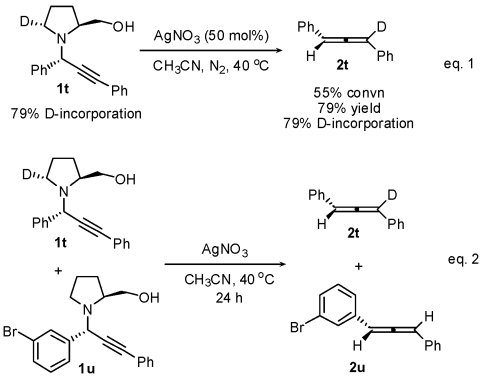


Scheme 2 Tentative mechanism for silver-mediated synthesis of axially chiral allenes from optically active propargylamines.

is in accordance with the formulation of silver(I)-coordinated intermediate **I**.

The reaction of deuterium-labeled propargylamine **1t** (79% deuterium incorporation) in the presence of $AgNO_3$ in CH_3CN under N_2 at 40 °C for 24 h gave deuterium-labeled **2t** in 79% yield with 79% deuterium incorporation (Scheme 3, eqn (1)). As no crossover of deuterium was observed in the allenes by GC-MS analysis of the reaction mixture using a 1 : 1 ratio of **1t** and **1u** (eqn (2)), the proposed hydride transfer from **I** to **II** could occur in an intramolecular manner.

In summary, we have developed a silver(I)-mediated highly enantioselective synthesis of a wide range of axially chiral allenes from optically active propargylamines under mild conditions. The use of microwave irradiation allows completion



Scheme 3 Deuterium-labeling experiment.

of the reaction in a much shorter time than that required under conventional thermal conditions.

We are grateful for the financial support of The University of Hong Kong (University Development Fund), Hong Kong Research Grant Council (HKU 7052/07P), and the Areas of Excellence Scheme established under the University Grants Committee of the Hong Kong Special Administrative Region, China (AoE/P-10/01).

Notes and references

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