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Enantioselective Tandem Cyclization of Alkyne-Tethered Indoles Using Cooperative Silver(I) and Chiral Phosphoric Acid Catalysis

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Abstract

We report the enantioselective synthesis of tetracyclic indolines using cooperative silver(I) and chiral phosphoric acid catalysis. A variety of alkyne-tethered indoles are suitable for this process. Mechanistic studies suggest that the in situ-generated silver(I) chiral phosphate activates both the alkyne and the indole nucleophile in the initial cyclization step through an intermolecular hydrogen bond and the phosphate anion promotes proton transfer. In addition, further modifications of the cyclization products enabled stereochemistry-function studies of a series of bioactive indolines.

Graphical abstract

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Dual functions in dual catalysis. Highly enantioselective synthesis of tetracyclic indolines was realized using cooperative silver(I) and chiral phosphoric acid catalysis. Mechanistic studies identified dual roles of the chiral phosphate.

Keywords

asymmetric catalysis; cyclization; density functional calculations; cooperative catalysis; polycyclic indoline

Carbophilic catalysts,^[1] such as gold and platinum, can selectively activate π -bonds and in turn trigger a variety of transformations under mild conditions,^[2] enabling rapid constructions of a wide range of complex molecules.^[3] Although a large number of gold-catalyzed reactions involving alkynes have been developed, only a portion of these have been rendered enantioselective.^[4] This is mainly due to the linear coordination geometry of ligand–Au–alkyne and the anti-addition of Au and a nucleophile across the alkyne. To address this problem, both well-defined large chiral ligands^[5] and the use of chiral counter anions have been studied with some success.^[6] Some of these reactions were rendered enantioselective by using other carbophilic catalysts, such as iridium,^[7] platinum,^[5c,8] palladium,^[9] and copper.^[10] However, these strategies can only be applied to a limited number of transformations. Alternative approaches for highly enantioselective synthesis of complex carbo- and heterocyclic compounds are still in high demand.

Inspired by indole alkaloids^[11] (see representatives in Figure 1a), our group has developed a series of cationic gold(I) complex-catalyzed cyclizations of alkyne-tethered indoles (e.g., **1**→**2**, Figure 1b) to access tetracyclic scaffolds often found in akuammiline alkaloids.^[12] The cyclization products were further modified, leading to the discovery of two indolines, **3** and **4** (Figure 1b), that re-sensitize methicillin-resistant *Staphylococcus aureus* (MRSA) to β -lactam antibiotics, and **5** (Figure 1b) as a novel antibacterial agent.^[13] To prepare enantiomerically pure indolines for biological studies and complex indole alkaloid syntheses, we decided to develop an asymmetric cyclization. Herein, we report highly enantioselective tandem cyclizations of alkyne-tethered indoles **1** (Figure 1b) using a cooperative silver(I) and chiral phosphoric acid catalysis approach.

The silver(I)/chiral Brønsted acid dual catalysis system has been demonstrated as effective in asymmetric catalysis.^[4b,14] However, as carbophilic catalysts, silver species are

understudied, mainly due to their significantly lower reactivity than related gold complexes.^[15] Silver chiral phosphates have been reported as effective catalysts in asymmetric transformations.^[16] However, the origin of the enantioselectivity is unclear.

We envisioned that silver-catalyzed tandem cyclization of alkyne-tethered indoles could be accelerated by the addition of a Brønsted acid, a common means to accelerate gold catalysis.^[17] A readily available alkyne-tethered indole, **6a**, was selected as the model substrate to explore the reaction conditions (Table 1). As expected, silver(I) salts alone, such as AgBF₄, do not catalyze the transformation at 4 °C. A series of chiral phosphoric acids (Table 1, entries 1–6) were next evaluated as additives to the reaction. Gratifyingly, the expected product, **7a**, was produced. Among chiral phosphoric acids bearing the binol backbone, both diphenyl substituted acids, HX¹ and HX², gave low yields of **7a** with poor enantioselectivity (Table 1, entries 1 and 2). Switching the phenyl substitutions to larger aromatic substitutions on the binaphthyl backbone significantly enhanced both the yields and enantioselectivity. Chiral acid bearing anthracenyl substitutions, HX⁴, afforded **7a** in 99% yield with an excellent enantiomeric ratio of 98:2 (Table 1, entry 4). Chiral phosphoric acids bearing alternative backbones were also evaluated, yet with unsatisfactory results (Table 1, entries 5 and 6).^[18] Under similar gold catalysis conditions, the reaction proceeded much faster, yet with poor enantioselectivity (Table 1, entry 7). The reaction is compatible with most non-polar solvents, such as chloroform and benzene. Silver sources containing various counter anions were next investigated. Only AgX⁴ gave similar results (Table 1, entry 11), and the reaction does not proceed in the absence of silver salts. AgX⁴ was also able to catalyze the reaction (Table 1, entry 12); however, slower reaction rate was observed (*vide supra*). Combinations of AgX⁴ with achiral Brønsted acids all resulted in significantly lower enantioselectivity. Further comparison of two best silver sources, on additional substrates showed that the results were almost always identical. Hence, AgBF₄ was used in our standard conditions due to its commercial availability and affordable price.

Carbamates on the side chain of the substrates are well tolerated in this reaction. Replacing the methoxycarbonyl group with benzyloxycarbonyl (Cbz) or 2,2,2-trichloroethoxycarbonyl (Troc) has only minimal impact on the reaction. Both **6b** and **6c** (Table 2, entries 2–3) furnished the desired products in excellent yields and high enantioselectivity. Sulfonamides **6d** and **6e** (Table 2, entries 4–5) also provided the desired products in excellent yields and stereoselectivity. Indoles bearing no methyl groups (**6f**, Table 2, entry 6) or one methyl group, **6g–h** (Table 2, entries 7 and 8), all cyclized smoothly and gave the desired products in high yields and good enantioselectivity. Interestingly, much slower reactions were observed for substrates bearing either an electron-donating or -withdrawing group on the indole (Table 2, entries 9–12). Gratifyingly, the yields were significantly improved by conducting these reactions at higher concentration and room temperature, although the enantioselectivity decreased slightly. Most substrates were insensitive to water. In the cases of less reactive substrates, **6i–l**, the addition of molecular sieves to the reaction was critical to prevent hydration of alkyne. Internal alkynes failed to produce any products under these conditions.

To investigate the reaction mechanism, we first used ¹H NMR to monitor cyclization of sulfonamide **6d** to avoid complication due to carbamate rotamers of the cyclization product.

In the reaction using $\text{AgBF}_4/\text{HX}^4$, only **6d** and **7d** were observed. In the reaction catalyzed by only AgBF_4 , an additional species, **7d-H⁺**, was observed with a maximum yield equivalent to the loading of AgBF_4 (Figure S1), suggesting that the phosphate anion accelerates the reaction by promoting proton transfer. Comparison of the initial rates of the reaction further confirmed that HX^4 accelerated the reaction by 8.3 folds (Figure S2, *vide infra*), and 1:1 ratio of AgBF_4 and HX^4 is optimal (Figure S3). ^{31}P NMR spectrum of $\text{AgBF}_4/\text{HX}^4$ indicates partial formation of AgX^4 (Figure S4).

While no reaction intermediates were observable by ^1H NMR, we next pursued a computational approach at the M06-L level of density functional theory (DFT). Both AgBF_4 - and AgX^4 -catalyzed cyclizations of **6a** were calculated. A hydrogen bond was identified in the complex of AgX^4 and **6a** involving a phosphate oxygen of X^4 and the N^{in} -H of **6a** (Figure 2a).^[19] This hydrogen bond appears to significantly lower the energy of the transition state in the initial cyclization (**TS-I**, Figure 2b), presumably by increasing both the nucleophilicity of indole and the carbophilicity of silver(I). The involvement of this hydrogen bond could account for the observed modest kinetic isotope effect (KIE: 2.1), which was derived from initial rates of reactions conducted in the presence of H_2O or D_2O (Figure S5). Comparison of the computed pathways (Figure 2a) suggests that the initial cyclization is catalyzed by AgX^4 and (*R*)-**8X⁴** is the favored product, because **TS-I** is more stable than **TS-I'** by 2.4 kcal/mol. This agrees with the observed enantioselectivity. Detailed analysis indicates more significant Ag-C non-bonded van der Waals repulsions exist in **TS-I'**.^[20]

To verify the proposed mechanism, an N^{in} -methylated substrate **6m** was prepared to block the key hydrogen bond. When subjected to the dual catalysis conditions, **6m** cyclized qualitatively significantly more slowly than **6a**, and only gave product **3** in 32% yield and reduced enantioselectivity of 86:14. In this reaction, phosphate only serves as a X-type ligand to silver(I) and would decrease its carbophilicity.

(1)

In addition, this asymmetric method does not appear to be limited to the formation of fused ring systems. For example, alkyne-tethered indole **9** (Eq. 1) also cyclized under dual catalysis conditions and produced spirocyclic indoline **10a** in 65% yield. Its enantiomeric ratio was determined based on its sulfonamide derivative **10b** as 93:7.

To demonstrate the utility of this method, we prepared indolines **3–5** (Figure 1b) from their corresponding cyclization products^[13] and evaluated their biological activity (see results in Table S1). For tetracyclic indoline **3**, only the (2*S*,3*R*)-stereoisomer re-sensitizes MRSA to ceftazolin, and its enantiomer has no observable activity. However, the absolute stereochemistry of tricyclic indolines **4** and **5** is not critical to their biological activity.

In conclusion, we have developed a highly enantioselective tandem cyclization of alkyne-tethered indoles using commercially available AgBF₄ and chiral phosphoric acid HX⁴ as the catalysts. Mechanistic studies suggest dual roles for the chiral phosphoric acid. First, it generates silver(I) chiral phosphate in situ that catalyzes the initial cyclization enantioselectively. Secondly, the phosphate anion accelerates the reaction by promoting proton transfer. This method also enabled stereochemistry-function relationship studies of a variety of bioactive polycyclic indolines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Representative natural and synthetic polycyclic indolines. a) Structures of representative natural indoline alkaloids. b) Our previous gold approach to diverse bioactive polycyclic indolines.

Figure 2. Density functional calculation results. a) Energy diagram of the first cyclization beginning with **6a**. Numbers are free energies in kcal mol⁻¹. b) Optimized structures of **TS-I** and **TS-I'**. Most H atoms are omitted for clarity. All inter-atomic distances are in Å. Tol=toluene.

Table 1

Optimization of reaction conditions.

Entry	Catalyst	Acid	T [°C]	Yield [%] ^[a]	er ^[b]
1	AgBF ₄	HX ¹	4	20	58:42
2	AgBF ₄	HX ²	4	48	60:40
3	AgBF ₄	HX ³	4	61	92:8
4	AgBF ₄	HX ⁴	4	99	98:2
5	AgBF ₄	HX ⁵	4	34	54:46
6	AgBF ₄	HX ⁶	4	41	56:44
7	Ph ₃ PAuBF ₄	HX ⁴	-30	40	56:44
8	AgSbF ₆	HX ⁴	4	88	96:4
9	AgOTf	HX ⁴	4	92	83:17
10	AgBAF ₄	HX ⁴	4	80	53:47
11	AgX ⁴	HX ⁴	4	98	98:2
12	AgX ⁴	-	4	96	98:2

^[a] Isolated yields.

^[b] Enantioselective ratio (er) determined by HPLC.

Table 2

Scope studies.

Entry	6	R	Z	7	Yield [%] ^a	er ^b
1	6a	4,6-Me ₂	COOMe	7a	99%	98:2
2	6b	4,6-Me ₂	Cbz	7b	93%	97:3
3	6c	4,6-Me ₂	Troc	7c	98%	96:4
4	6d	4,6-Me ₂	SO ₂ PhCl	7d	88%	97:3
5	6e	4,6-Me ₂	Ts	7e	84%	95:5
6	6f	H	COOMe	7f	95%	93:7
7	6g	5-Me	COOMe	7g	90%	95:5
8	6h	7-Me	COOMe	7h	95%	91:9
9 ^c	6i	5-MeO	COOMe	7i	85%	89:11
10 ^c	6j	5-Cl	COOMe	7j	94%	94:6
11 ^c	6k	5-Cl	Cbz	7k	95%	91:9
12 ^c	6l	5-Br	SO ₂ PhCl	7l	62%	86:14

^[a] Average isolated yields of at least two runs.

^[b] er determined by HPLC.

^[c] 0,10 M, 25 °C. Absolute configuration of **7d** was determined as (2*R*,3*S*) by single-crystal X-ray diffraction. All other products were assigned by analogy.