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Au-Catalyzed [2 + 3] Annulation of Enamides with Propargyl Esters: Total Synthesis of Cephalotaxine and Cephalezomine H

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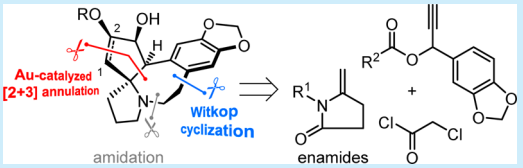
Supporting Information

ABSTRACT: A novel Au-catalyzed [2 + 3] annulation reaction of enamides with propargyl esters has been developed, providing a new method for expeditious assembly of synthetically useful functionalized 1-azaspiro[4.4]nonane building blocks. Based on this key annulation, strategic installation of the pivotal azaspirocyclic core, followed by constructing the benzazepine unit via Witkop cyclization, led to the divergent total syntheses of cephalotaxine and cephalezomine H.



Cephalotaxine possessing an aza-quaternary scaffold (Figure 1) was first isolated from *Cephalotaxus drupacea* and *Cephalotaxus fortunei* by Paudler in 1963,[1] and its stereochemistry was entirely established using X-ray analysis by Powell in 1974.[2] Generally, cephalotaxine represents the parent polycyclic core of a series of *Cephalotaxus* alkaloids. Despite the inactivity of cephalotaxine alone, homoharringtonine as one of its esters has been approved by the FDA for treatment of chronic myeloid leukemia since 2012.[3] Due to the intriguing polycyclic architecture as well as the pharmaceutical potential, *Cephalotaxus* alkaloids have attracted significant attention in synthetic community[4,5] since the chemical synthesis of cephalotaxine by Weinreb and Semmelhack in 1972.[6]

Structurally, *Cephalotaxus* alkaloids are characterized with a 1-azaspiro[4.4]nonane ring system featuring a crucial aza-quaternary carbon center (Figure 1), which also constitutes an important architectural subunit in stemonamine-type *Stemona* alkaloids.[7] Synthetically, a diversity-oriented assembly of such a functionalized azaspirocyclic nucleus is of major importance in the expeditious synthesis of related natural products and their analogues. Focusing on the construction of the 1-azaspiro[4.4]-nonane ring system driven by the synthesis of cephalotaxine-type alkaloids, we have recently explored a novel Au-catalyzed [2 + 3] annulation reaction of enamides with propargyl esters (Scheme 1). To our knowledge, this [2 + 3] annulation has not been thoroughly explored in the enamide chemistry and the gold-catalyzed propargyl chemistry.[8−12] Herein we wish to present our preliminary results on this annulation reaction as well as its application in the total synthesis of cephalotaxine and its congener cephalezomine H.

A retrosynthetic analysis of cephalotaxine and cephalezomine H (Scheme 2) strategically features a design for the assembly of ring E through a novel catalytic [2 + 3] annulation of enamides **V** with propargyl esters **VI**, wherein the densely functionalized 1-azaspiro[4.4]nonane synthon **IV** could be envisioned to incorporate the tetracyclic ring system (rings A, B, D, and E) embedded in our target alkaloids. As for constructing ring C, a Witkop photocyclization of the synthon **III** bearing a 4,5-*trans* configuration, which would be chemically derived from the stepwise reduction of **IV** followed by haloacetamidation, could be conceived to form the C11−C12 bond in pentacyclic synthon **II**. Logically, the late-stage functional group transformations directed to cephalotaxine and cephalezomine H would be available through the common synthon **I**.

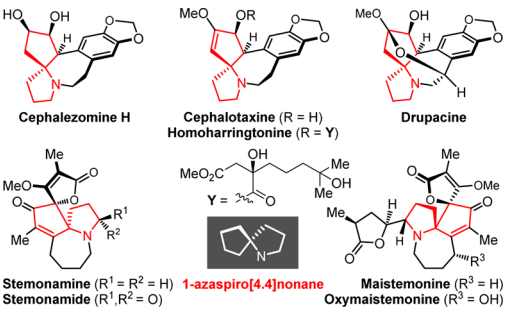
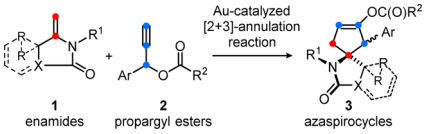


Figure 1. Selected alkaloids containing 1-azaspiro[4.4]nonane unit.

Scheme 1. Au-Catalyzed Annulation Reaction



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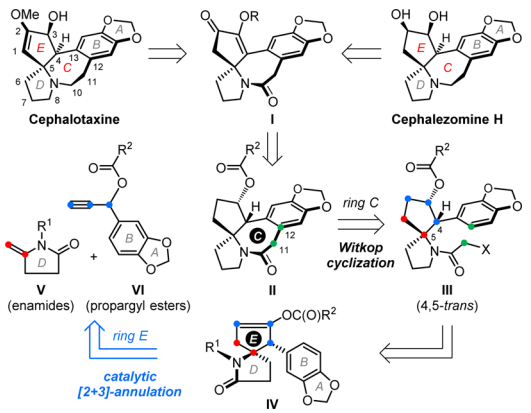
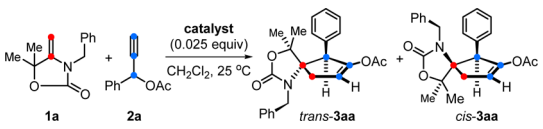
Scheme 2. Retrosynthetic Analysis



Based on the above synthetic consideration, a model using enamide **1a** and propargyl acetate **2a** was initially investigated for the key catalytic [2 + 3] annulation reaction. Inspired by the pioneering exploration of propargyl chemistry under gold catalysis,[12] *N*-heterocyclic carbene (NHC) gold(I) catalyst combined with a series of silver salts was first examined in our model. As tabulated in Table 1, IPrAuCl as a weak-acidic catalyst

Table 1. Catalyst Optimization for [2 + 3]-Annulation[a]



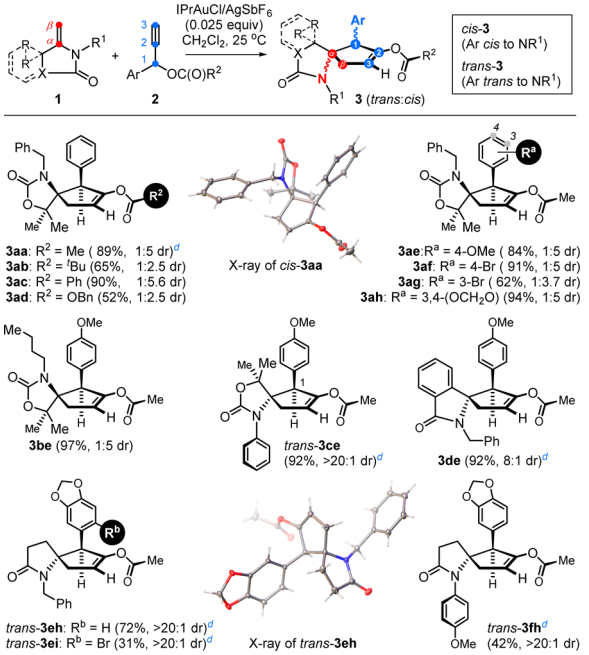
entry	catalyst	time (h)	yield[b] (%)	dr[c] (*trans*/*cis*)
1	IPrAuCl	50	NR	
2	IPrAuCl/$AgNTf_2$	0.25	82	1:5
3	IPrAuCl/$AgBF_4$	0.25	90	1:5
4	**IPrAuCl/$AgSbF_6$**	**0.25**	**92**	**1:5**
5	IPrAuCl/AgOAc	50	NR	
6	IPrAuCl/AgOTf	50	*d*	
7	$Ph_3PAuCl/AgSbF_6$	24	70	1:3
8	$[IPrAu]^+[SbF_6]^-$	8	NR	
9	$[IPrAu]^+[SbF_6]^-/AgSbF_6$	0.25	86	1:5
10	$AgSbF_6$	50	*d*	

[a]Performed with **1a** (0.12 mmol), **2a** (0.10 mmol), and the catalyst (0.0025 mmol) in CH_2Cl_2 (1.0 mL) at 25 °C. [b]Isolated yield. [c]Determined by ^1H NMR. [d]A complex mixture observed on TLC. NR = no reaction.

could not promote the title reaction (entry 1), mostly due to the strong coordination of the chloride ion with gold(I). Interestingly, it was found that an *in situ* formed catalytic system resulting from the combination of IPrAuCl and $AgNTf_2$ (entry 2) could effectively enable the expected annulation of **1a** with **2a** in CH_2Cl_2 at 25 °C, affording the desired [2 + 3]-annulated product **3aa** in 82% yield with 1:5 dr. Stereochemically, the relative configuration of major isomer *cis*-**3aa** was unambiguously assigned by X-ray crystallographic analysis.[13] Compared with the reaction efficiency using $AgBF_4$ as an additive (90% yield, 1:5 dr; entry 3), the silver salt $AgSbF_6$ combined with IPrAuCl could give the optimal result in CH_2Cl_2 (15 min, 92% yield, 1:5 dr; entry 4). Surprisingly, AgOAc (entry 5) or AgOTf (entry 6) as an additive in this model led to either no reaction or a complex mixture. In addition to the above carbene-ligated gold(I) catalyst (IPrAuCl), phosphane gold(I) chloride combined with silver salt $AgSbF_6$ was also examined, but the decreased reactivity and selectivity were observed (24 h, 70% yield, 1:3 dr; entry 7). Notably, in contrast to the fact that no reaction was observed in a controlled experiment using the catalyst $[IPrAu]^+[SbF_6]^-$ (entry 8), which was individually prepared from IPrAuCl and $AgSbF_6$,[14] this [2 + 3] annulation reaction could proceed with analogous efficiency (15 min, 86% yield, 1:5 dr; entry 9) after adding $AgSbF_6$ into the above controlled reaction using $[IPrAu]^+[SbF_6]^-$ as a catalyst (entry 8). It is noteworthy that $AgSbF_6$ itself could not effectively promote this transformation (entry 10). Importantly, these facts (entries 8−10) indicate that a positive silver effect is involved in the current [2 + 3] annulation reaction.[15]

With the optimized reaction conditions in hand, the generality of this annulation was preliminarily explored (Scheme 3). A

Scheme 3. Reaction Generality[a,b,c,d]



[a]For experimental details, see the Supporting Information. [b]Major isomer indicated, and the dr (*trans*/*cis*) determined by ^1H NMR. [c]Isolated yield. [d]The relative configuration was determined by X-ray analysis.

variety of propargyl esters **2** with a different ester group (−OC(O)R^2) and aryl group (Ar) were first investigated in combination with enamide **1a** as a two-carbon component. For example, propargyl esters **2a−2d** (Ar = Ph, R^2 = Me, *t*-Bu, Ph, OBn) were subjected to the standard conditions, and desired products **3aa−3ad** could be obtained in moderate to good yields (52% to 90%) with modest to moderate diastereoselectivities (1:2.5 to 1:5.6 dr), wherein the negative influence of a bulky (R^2 = *t*-Bu) or electron-rich (R^2 = OBn) ester group on the annulation reactivity was observed. Besides, propargyl esters **2e−2h** (R^2 = Me, Ar = 4-OMe-C_6H_4, 4-Br-C_6H_4, 3-Br-C_6H_4, 3,4-(OCH_2O)-C_6H_3) bearing different substituents on the phenyl ring were also examined, affording products **3ae−3ah** in 62% to 94% yields with 1:3.7 to 1:5 dr. To probe the influence of *N*-substituents (R^1) in enamides **1**, two substrates **1b** (R^1 = *n*-Bu) and **1c** (R^1 = Ph) were evaluated for this annulation by using **2e** as a three-carbon component. Compared with *N*-Bn enamide **1a** (R^1 = Bn), *N*-butyl enamide **1b** (R^1 = *n*-Bu) gave product **3be** with similar reactivity (97% yield) and stereoselectivity (1:5 dr). In contrast to the

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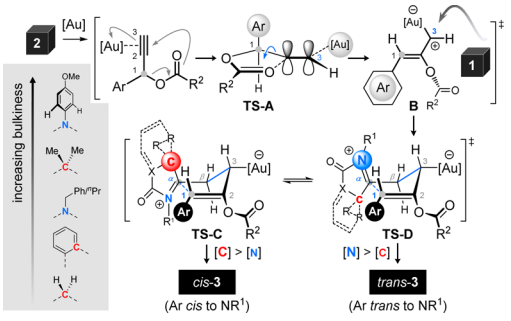
preferential *cis*-selectivity observed in **3aa**−**3ah** and **3be**, interestingly, the [2 + 3] annnulation reaction of *N*-phenyl enamide **1c** (R^1 = Ph) with **2e** proceeded in an entirely reversed diastereoselectivity, leading to the formation of the sole product *trans*-**3ce** (>20:1 dr, 92% yield). The stereochemistry of *trans*-**3ce** was clearly determined by X-ray crystallographic analysis.[13] Notably, as seen from its X-ray structure, the observed *trans*-selectivity is consistent with the fact that the opposite orientation of the *N*-phenyl and C1-aryl group in the spirocyclic skeleton of **3ce** could minimize the potential steric repulsion.

To further investigate the structural effect of substrates without a *gem*-dimethyl group and carbamate moiety, the isoindolinone-containing enamide **1d** was then employed (Scheme 3). Upon treatment of **1d** with **2e** under the standard conditions, the product **3de** could be afforded readily (92% yield, 8:1 dr), and the preferential *trans*-selectivity was assigned by X-ray crystallographic analysis of separable major isomer *trans*-**3de**,[13] to some extent indicating that the planar isoindolinyl ring is less bulky than the exocyclic *N*-benzyl group. Moreover, two pyrrolidinonyl-containing enamides **1e** (*N*-benzyl)[16] and **1f** (*N*-(4-methoxyphenyl))[16] were additionally used in the reaction with **2h**, and the expected products *trans*-**3eh** and *trans*-**3fh**, structurally confirmed by X-ray crystallographic analysis,[13] were obtained with high stereoselectivity (>20:1 dr). While using **1e**[16] with propargyl ester **2i** having a sterically unfavorable *ortho*-substituted aromatic ring (R^b = Br), the crystallographically determined *trans*-**3ei** could be yielded with analogous stereoselectivity (>20:1 dr),[13] but in a low yield (31% yield).

To gain preliminary insight into the interesting *cis*- and *trans*-selectivity observed in this annulation, possible rationale is proposed on the basis of a stepwise annulation mechanism (Scheme 4).[17] First, the propargyl esters **2** undergo a 1,2-acyl shift

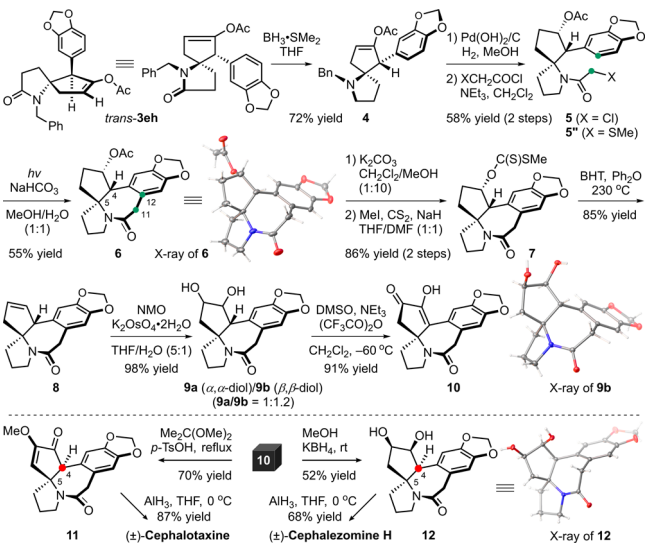
Scheme 4. Proposed Mechanism for [2 + 3] Annulation



through **TS-A** under gold catalysis, leading to the zwitterionic resonance species **B** as one of the main resonance contributors. Following the nucleophilic attack of enamides **1** to the more electrophilic C3-position of **B**, two presumable transition states **TS-C** and **TS-D**, which could deliver *cis*-**3** and *trans*-**3**, respectively, might be involved in a thermodynamically controlled pathway for five-membered ring spiro-annulation. Notably, the minimal steric hindrance between the bulky *α*-[C] or *α*-[N] substituent and the C1−Ar group in **TS-C** or **TS-D** could mostly account for the stereopreference at the final iminium cyclization step, wherein the observed diastereoselectivity (Scheme 3) is consistent with an approximate order of increasing bulkiness of the [C] and [N] substituents on the spirocyclic quaternary carbon center.

Having developed this Au-catalyzed method for the construction of azaspirocycles, we then focused our attention toward exploring such target-oriented synthesis (Scheme 5).[18] As shown in Scheme 5, reductive treatment of *trans*-**3eh** with BH_3·SMe_2

Scheme 5. Synthesis of Cephalotaxine and Cephalezomine H



gave tertiary amine **4** in 72% yield, and then a subsequent one-pot *N*-debenzylation/enol-acetate hydrogenation, followed by acylation of the resultant secondary amine, delivered the chloroacetamide **5** (X = Cl) in 58% yield over two steps. To access the benzazepine ring system, Witkop photocyclization[19] of **5** (X = Cl) with a high-pressure mercury vapor lamp in aqueous MeOH in the presence of $NaHCO_3$ was performed to afford the desired pentacyclic product **6** in 55% yield, and its stereochemistry with retention of C4−C5 *trans*-configuration was confirmed by X-ray crystallographic analysis.[13] Particularly noteworthy is that Pummerer rearrangement of the sulfoxide resulting from the oxidation of **5**″ (X = SMe), which was successfully used to form the C11−C12 bond of the benzazepine unit by Ikeda,[20] was ineffective in this case. A two-step protocol involving acetate hydrolysis and xanthate formation gave xanthogenate ester **7** in 86% yield, which subsequently underwent Chugaev elimination to afford olefin **8** in 85% yield. Upon treating **8** with K_2OsO_4·$2H_2O$ and NMO, *cis*-dihydroxylation afforded chromatographically separable diols **9a** and **9b** in 98% yield, wherein the configuration of isomer **9b** was determined by X-ray crystallographic analysis.[13] Swern oxidation of **9a** and **9b** could deliver *α*-enolone **10** in 91% yield.

With the common building block **10** in hand, as described in Scheme 5, regioselective etherification with dimethoxypropane in the presence of *p*-TsOH afforded the enol ether **11** with C4−C5 *cis*-configuration in 70% yield, and subsequent reduction with alane furnished the synthesis of (±)-cephalotaxine in 87% yield. Divergently, a diastereoselective KBH_4 reduction of the enolone motif in **10** could deliver *β*,*β*-diol **12** in 52% yield, wherein *cis*-configuration at C-4 and C-5 was confirmed by its X-ray structure.[13] Following further alane reduction of the amide moiety, the synthesis of (±)-cephalezomine H was achieved in 68% yield, and its NMR spectroscopic data are identical to those from a previous synthesis.[21]

In conclusion, driven by the total synthesis of *Cephalotaxus* alkaloids, a novel NHC-Au(I)/Ag(I)-catalyzed [2 + 3] annulation of enamides with propargyl esters has been developed, leading to an effective construction of the crucial aza-quaternary carbon center embedded in a highly functionalized 1-azaspiro[4.4]-

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nonane system. Based on this key annulation as well as a Witkop cyclization, total syntheses of (±)-cephalotaxine and (±)-cephalezomine H were accomplished divergently. The present studies not only chemically enrich the methodology design for constructing synthetically useful functionalized azaspirocycles in gold catalysis but also strategically illustrate the potential of enamide chemistry in the total synthesis of natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01202.

Experimental procedures and spectra data (PDF)
X-ray data for *cis*-**3aa** (CIF)
X-ray data for *trans*-**3ce** (CIF)
X-ray data for *trans*-**3de** (CIF)
X-ray data for *trans*-**3eh** (CIF)
X-ray data for *trans*-**3ei** (CIF)
X-ray data for *trans*-**3fh** (CIF)
X-ray data for **6**(CIF)
X-ray data for **9b** (CIF)
X-ray data for **12** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) CCDC 1523168 (*cis*-**3aa**), CCDC 1523169 (*trans*-**3ce**), CCDC 1536571 (*trans*-**3de**), CCDC 1536570 (*trans*-**3eh**), CCDC 1523172 (*trans*-**3ei**), CCDC 1523171 (*trans*-**3fh**), CCDC 1523173 (**6**), CCDC 1523174 (**9b**), and CCDC 1523175 (**12**) contain the supplementary crystallographic data (Supporting Information, SI).
(14) $[IPrAu]^+[SbF_6]^-$ was prepared by mixing IPrAuCl and $AgSbF_6$ in CH_2Cl_2 after gravity filtration through celite, and its purity without silver was confirmed by XPS analysis. For details, see the SI.
(15) For selected examples on silver effect in Au-catalyzed reactions, see: (a) Weber, D.; Gagné, M. R. *Org. Lett.* **2009**, *11*, 4962. (b) Patrick, S. R.; Boogaerts, I. I. F.; Gaillard, S.; Slawin, A. M. Z.; Nolan, S. P. *Beilstein J. Org. Chem.* **2011**, *7*, 892. (c) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012.
(16) Partial isomerization of exocyclic double bond in **1e** and **1f** to endocyclic occurs under standard conditions, leading to the aza-fused annulation products **4eh** (23% yield), **4ei** (28% yield), and **4fh** (42% yield). For details, see the SI.
(17) An alternative pathway involving [2 + 1] cycloaddition, followed by vinylcyclopropane rearrangement or cyclopropane ring opening/cyclization, could not be ruled out at this stage.
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