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Counteranion-Controlled Unprecedented Diastereo- and Enantioselective Tandem Formal Povarov Reaction for Construction of Bioactive Octahydro-Dipyrroloquinolines

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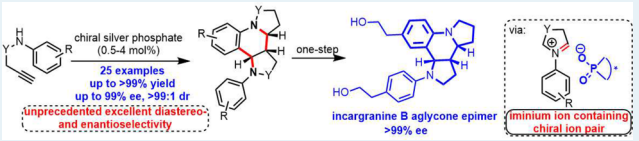
Supporting Information

ABSTRACT: The asymmetric inverse-electron-demand hetero-Diels–Alder (IEHDA) reactions of imines and dienophiles have emerged as an attractive tool for derivatizing optically active complex azaheterocycles. In comparison, such reactions involving iminium ions remain great challenges because of low association of iminium ions with neutral catalytic centers. To overcome this, we report a metal-phosphate-catalyzed asymmetric tandem hydroamination/formal Povarov reaction of secondary aminoalkynes via a chiral counteranion-controlled iminium ion intermediate strategy. Critical to the success of this challenging strategy was chiral phosphate as an ion pair to achieve counteranion-controlled asymmetric reaction of in situ-generated iminium ions. This method enables a convenient, powerful, and atom-economical access to tetracyclic octahydro-dipyrroloquinoline frameworks bearing multiple contiguous stereogenic centers in good yields with diastereo- and enantioselectivities, from acyclic starting materials, and the catalyst loadings could be as low as 1 mol %. The asymmetric cross-coupling reaction of different aminoalkynes has further been demonstrated with good results. Furthermore, this methodology was applied to enantioselective synthesis of incargranine B aglycone epimer in only two steps. The reaction is demonstrated to proceed through a stepwise process for formal Povarov reaction.



KEYWORDS: *asymmetric, counteranion, hydroamination, octahydro-dipyrroloquinoline, Povarov reaction, phosphate*

INTRODUCTION

Asymmetric Povarov and inverse-electron-demand hetero-Diels–Alder (IEHDA) reactions[1] of preformed or in situ-generated imines (2-azadienes) and dienophiles catalyzed by chiral Lewis acids[2] or chiral Brønsted acids[3] are among the most powerful in organic chemistry, providing an atom-economical method for the synthesis of enantioenriched complex azaheterocycles (Scheme 1a). Despite their widespread utility and applications, catalytic enantioselective Povarov reactions involving iminium ions are much scarcer (Scheme 1a). This could be attributed in part to the low association of the intermediate iminium ions with neutral catalytic centers, therefore rendering it difficult to induce high enantioselectivity in subsequent transformations. Thus, the development of novel catalytic system to realize asymmetric iminium ion cyclization reactions has long been recognized as a preeminent goal for organic synthesis. Only recently, Seidel and co-workers achieved a significant breakthrough by using conjugate-base-stabilized Brønsted acids to enable enantioselective Povarov reaction involving iminium ions, which were in situ-generated from the reaction of secondary anilines and aldehydes with 20 mol % of catalytic loadings.[4] Therefore, the exploration of more atom-economical and convenient asymmetric complementary strategies tolerating a wide substrate scope with low catalyst loadings remains a formidable challenge for synthetic chemists.

It is well-known that the octahydro-dipyrroloquinoline framework with multiple stereogenic centers is a unique motif found in a wide range of biologically active alkaloid natural products, such as incargranine B[5a,6g] and seneciobipyrrolidine (Figure 1).[5b] Moreover, the octahydro-dipyrroloquinoline derivatives have been successfully applied as a key intermediate in the synthesis of martinellic acid and martinelline as BK receptor antagonists (Figure 1).[5c] Therefore, great endeavors have been devoted to various nonasymmetric approaches to access the tetracyclic amine core of these alkaloids for many years.[6] In this regard, more recently, our research group have also successfully developed a gold(I)-catalyzed tandem process of 1,4-aminoalkynes via hydroamination/formal Povarov pathways through an iminium ion intermediate, providing access to octahydro-dipyrroloquinoline frameworks in good yields.[7] However, the poor diastereoselectivity was observed in the presence of both gold catalyst and dual gold/diphenyl phosphate catalyst in all cases for 1,4-aminoalkyne substrates (Scheme 1b). In spite of these attractive racemic attributes, the

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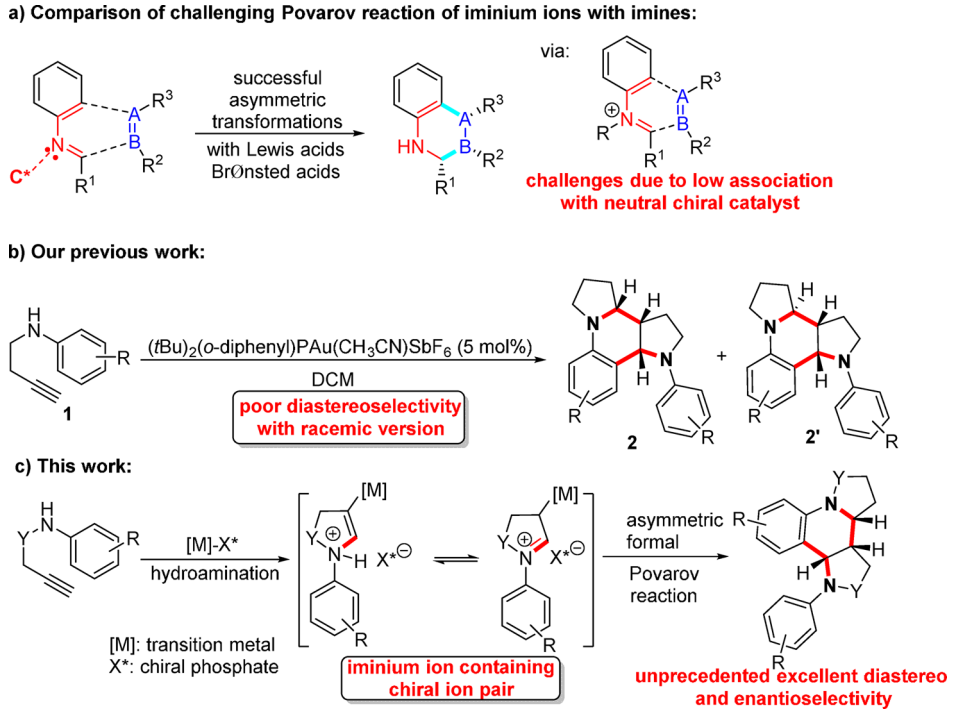
Scheme 1. Strategy for Asymmetric Formal Povarov Reaction of Iminium Ions



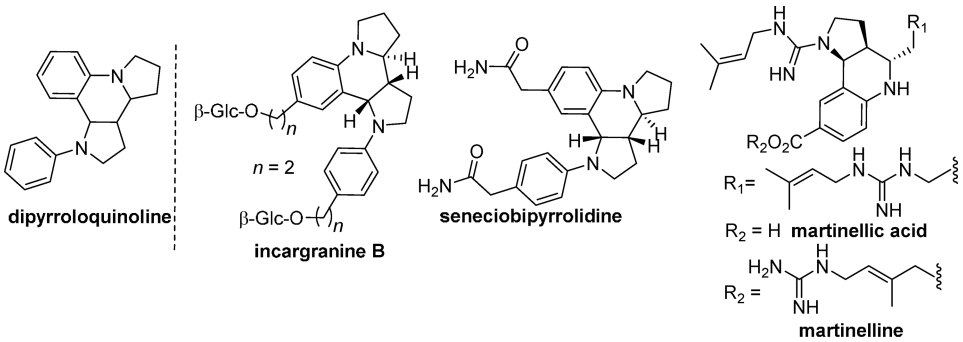


Figure 1. Natural octahydro-dipyrroloquinoline alkaloids and derivatives.

development of a catalytic enantioselective approach for the construction of octahydro-dipyrroloquinoline frameworks remains an unaddressed formidable challenge. Therefore, the invention of novel asymmetric systems capable of constructing structurally diverse octahydro-dipyrroloquinoline skeletons in a highly enantioselective and straightforward way from readily available starting materials is highly desirable and will be of great synthetic importance.

Stimulated by the challenge of asymmetric version for the construction of octahydro-dipyrroloquinoline skeletons, we became interested in developing an asymmetric tandem hydroamination/formal Povarov reaction of secondary 1,4-aminoalkynes (Scheme 1c). To fulfill this, several considerable challenges need to be addressed: (1) the control of diastereoselectivity of three stereogenic centers is particularly challenging because the poor diastereoselectivity has already been observed in our previous racemic version catalyzed by metal catalyst.[7] (2) The rational design of appropriate catalytic system to efficiently control enantioselectivity would also be a great challenge due to the nature of the in situ-generated iminium ion intermediate involving the low association with neutral catalytic centers. Recently, chiral metal phosphate catalysis has been demonstrated as a powerful strategy for the development of asymmetric transformations involving cationic intermediates to form a tight ion pair with the chiral counteranion, since the pioneering studies carried out by Toste, List, Rueping, and others.[8−10] On the basis of this strategy and in our continuous efforts in hydroamination and asymmetric hydrogen-bond and counteranion catalysis,[11] we envisioned that a chiral metal phosphate might be able to catalyze asymmetric tandem hydroamination/formal Povarov reaction of secondary aminoalkynes, in which in situ-generated metal-containing iminium ions would interact with chiral phosphate as an ion pair to achieve counteranion-controlled asymmetric formal Povarov reaction, thus providing a convenient and powerful access to enantioenriched octahydro-dipyrroloquinolines with excellent diastereo-/enantioselectivity control (Scheme 1c). Herein, we disclose the details of this new reaction system with unprecedented excellent diastereo- and enantioselectivity and its application in the first enantioselective synthesis of the incargranine B aglycone epimer. To our knowledge, the asymmetric tandem process reported herein not only represents the first highly enantioselective construction of synthetic challenging enantio-

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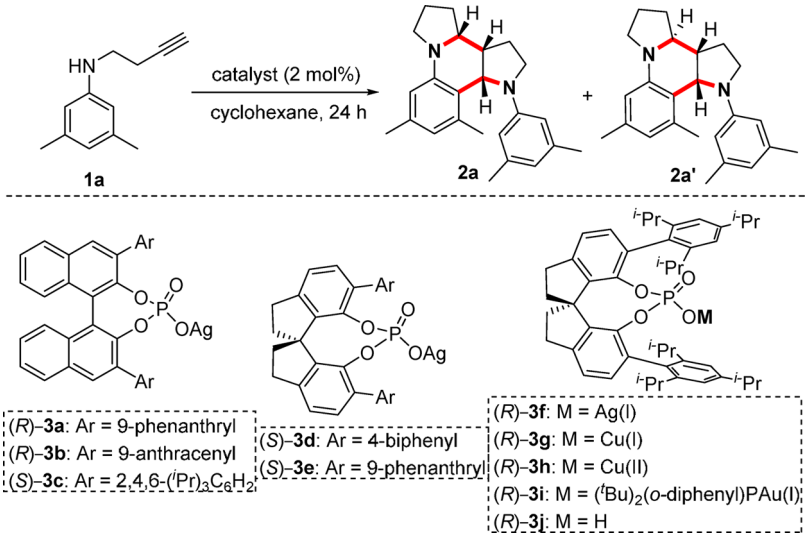
Table 1. Evaluation of Chiral Metal Phosphates and Optimization of Reaction Conditions



entry	catalyst	solvent	temp (°C)	conversion (%)[a]	dr[b]	ee (%)[c]
1	(*R*)-**3a**	cyclohexane	60	100	5:1	−32
2	(*R*)-**3b**	cyclohexane	60	100	2:1	0
3	(*S*)-**3c**	cyclohexane	60	100	>20:1	80
4	(*S*)-**3d**	cyclohexane	60	80	>20:1	−26
5	(*S*)-**3e**	cyclohexane	60	100	>20:1	−36
6	(*R*)-**3f**	**cyclohexane**	**60**	**100(95)**[g]	**>20:1**	**96**
7	(*R*)-**3f**	*n*-heptane	60	100	>20:1	92
8	(*R*)-**3f**	toulene	60	100	>20:1	90
9	(*R*)-**3f**	DCM	60	100	>20:1	54
10	(*R*)-**3f**	cyclohexane	20	30	>20:1	89
11	(*R*)-**3f**	cyclohexane	40	63	>20:1	94
12	(*R*)-**3f**	cyclohexane	80	100	>20:1	95
13	(*R*)-**3g**	cyclohexane	60	60	>20:1	89
14	(*R*)-**3h**	cyclohexane	60	57	>20:1	92
15	(*R*)-**3i**	cyclohexane	60	7	>20:1	92
16[d]	(*R*)-**3f**	cyclohexane	60	100	>20:1	93
17[e]	(*R*)-**3f**	cyclohexane	60	100	>20:1	95
18[f]	(*R*)-**3f**	cyclohexane	60	100	>20:1	95
19	(*R*)-**3j**	cyclohexane	60	trace		

[a]Estimated from ^{1}H NMR of the crude product. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Determined by chiral HPLC. [d](*R*)-**3f** (5 mol %). [e](*R*)-**3f** (1 mol %). [f](*R*)-**3f** (0.5 mol %), solvent (2.0 mL). [g]Value in parentheses reflects isolated yield.

pure octahydro-dipyrroloquinoline skeletons but also provides a particularly advantageous alternative to the asymmetric Povarov reactions of iminium ions.[4]

RESULTS AND DISCUSSION

Optimization of Reaction Conditions with Chiral Metal Phosphate Catalysts. The initial investigation to validate our hypothesis started with the designed tandem reaction with linear aminoalkyne **1a** as the model substrate for the optimization of reaction conditions (Table 1). Since silver phosphate catalysts have been proved not only as excellent π-Lewis acid catalysts to activate unactivated alkynes[12] but also as chiral counteranion catalyst for a diverse range of asymmetric reactions,[9] a BINOL-based chiral silver phosphate (*R*)-**3a** was first examined in this reaction. To our surprise, in the presence of only 2 mol % of (*R*)-**3a**, the reaction of **1a** proceeded smoothly to give the corresponding *endo* octahydro-dipyrroloquinoline **2a** in almost quantitative yield, albeit with moderate diastereoselectivity (5:1) and poor enantioselectivity (32% ee) (entry 1). This is in sharp contrast to the gold-catalyzed racemic tandem process with poor diastereoselectivity.[7] The comparison of the present result with that observed for our previous racemic work with gold catalysis clearly indicated that the chiral bulky phosphate counteranion plays a crucial role in the control of diastereo- and enantioselectivity. To further improve the stereoselectivity, we screened other BINOL-derived chiral silver phosphates **3b** and **3c** and found that 2,4,6-triisopropylphenyl-BINOL-derived (*S*)-**3c** gave both an excellent yield and an excellent diastereoselectivity (>20:1 dr), albeit with 80% ee (entries 2 and 3). Then, the evaluation of SPINOL-derived catalysts **3d**−**3f** was conducted, and (*R*)-**3f** was the most effective one, giving **2a** in 95% yield and 96% ee along with >20:1 dr (entries 4−6). Furthermore, a solvent effect was observed, and the best results were obtained with cyclohexane as the solvent (entries 6−9). Among the reaction temperatures examined, the reaction at 60−80 °C gave the best results (entries 10−12). However, the corresponding copper(I),[10a] copper(II),[10a] and gold phosphates[10b] gave lower reactivity albeit with excellent stereoselectivity, presumably

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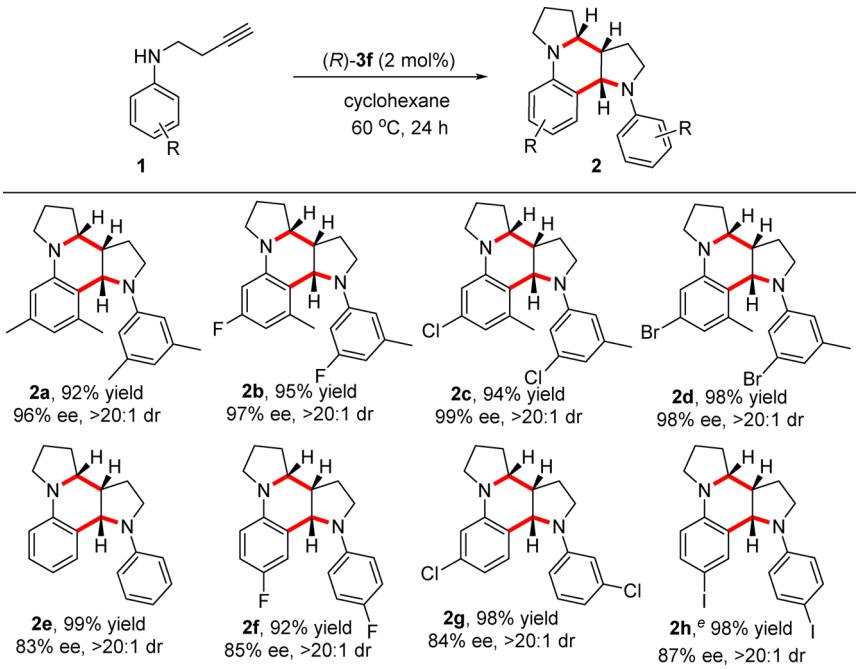
Table 2. Reaction Scope with Respect to the Linear Aminoalkyne[a,b,c,d]



[a]All the reactions were conducted on a 0.1 mmol scale. [b]Isolated yield. [c]The ee were determined by HPLC analysis. [d]The dr was determined by ^{1}H NMR of the crude reaction mixture. [e]The reaction time was 48 h.

due to the low catalytic reactivity for these chiral metal catalysts (entries 13−15). It should be noted that the catalyst loading could be reduced from 5 to even 0.5 mol % without affecting the reaction efficiency and stereoselectivity (entries 16−18), which is unusual with such catalytic loadings in the asymmetric Povarov reactions.[1−4] A control experiment indicated that none of the desired product was observed in the presence of chiral phosphoric acid **3j**, which unambiguously revealed that the metal phosphate is essential for this reaction.

Substrate Scope. With the optimized conditions established, the substrate scope and the generality of the current method with respect to linear aminoalkyne were next investigated. A wide range of substrates with different substituents at different positions all reacted smoothly to afford the corresponding products as a single diastereoisomer with excellent efficiency and good to excellent enantioselectivities (Table 2). For example, substrates **1** bearing disubstituted groups of the aryl ring reacted efficiently to give **2a−2d** in excellent yields (92−98%) and excellent stereoselectivities (>20:1 dr, 96−99% ee) along with exclusive regioselectivities. It was revealed that with monosubstituted groups on the phenyl ring the octahydro-dipyrroloquinolines (**2f−2h**) were obtained as a single diastereoisomer in excellent yields and good enantioselectivities (83−87% ee). The structure of **2h** was confirmed by X-ray diffraction analysis of its single crystals, and the absolute configuration was assigned to be (3a*R*,3b*S*,11b*R*) (Figure 2).

Having succeeded in the asymmetric reaction of linear aminoalkynes, we then focused our attention on C-tethered aminoalkynes to allow structurally diverse modifications. As shown in Table 3, a variety of propargylic amino ester, bearing electron-neutral (H), electron-donating (Me, Et, OMe, CH_2CO_2Me) or electron-withdrawing (F, Cl) groups at the *para* or *meta* positions of the phenyl ring, and disubstituted groups on the phenyl ring, proved to be viable substrates for this process, affording the desired products **5a−5j** in 80−99%

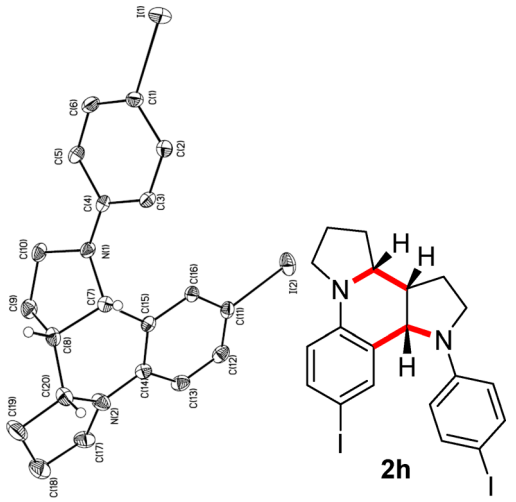


Figure 2. X-ray structure of **2h**.

yields with excellent diastereoselectivities (>17:1−20:1 dr) and enantioselectivities (86−98% ee). Gratifyingly, when the *meta*-substituted substrates **4k** and **4l** were used in this reaction, the 6-position C−H bond with less steric hindrance was selectively activated to afford the corresponding products **5k** and **5l** as a single diastereoisomer in 91% yield and 92% and 90% ee along with 3.8:1 and >20:1 rr (regioisomeric ratio), respectively, thus exhibiting not only excellent stereoselectivity but also good to excellent regioselectivity for such a reaction. Meanwhile, changing methyl ester to other esters, such as ethyl (**4m−4o**), *iso*-propyl (**4p**), and benzyl (**4q**) group had no significant influence on the reaction to give **5m−5q** as a single diastereoisomer in 93−99% yields and 92−99% ee.

To further evaluate the practicality of this methodology, we performed this reaction on a gram scale with even only 1 mol % of catalyst loading. The reaction afforded **5o** in 96% yield and

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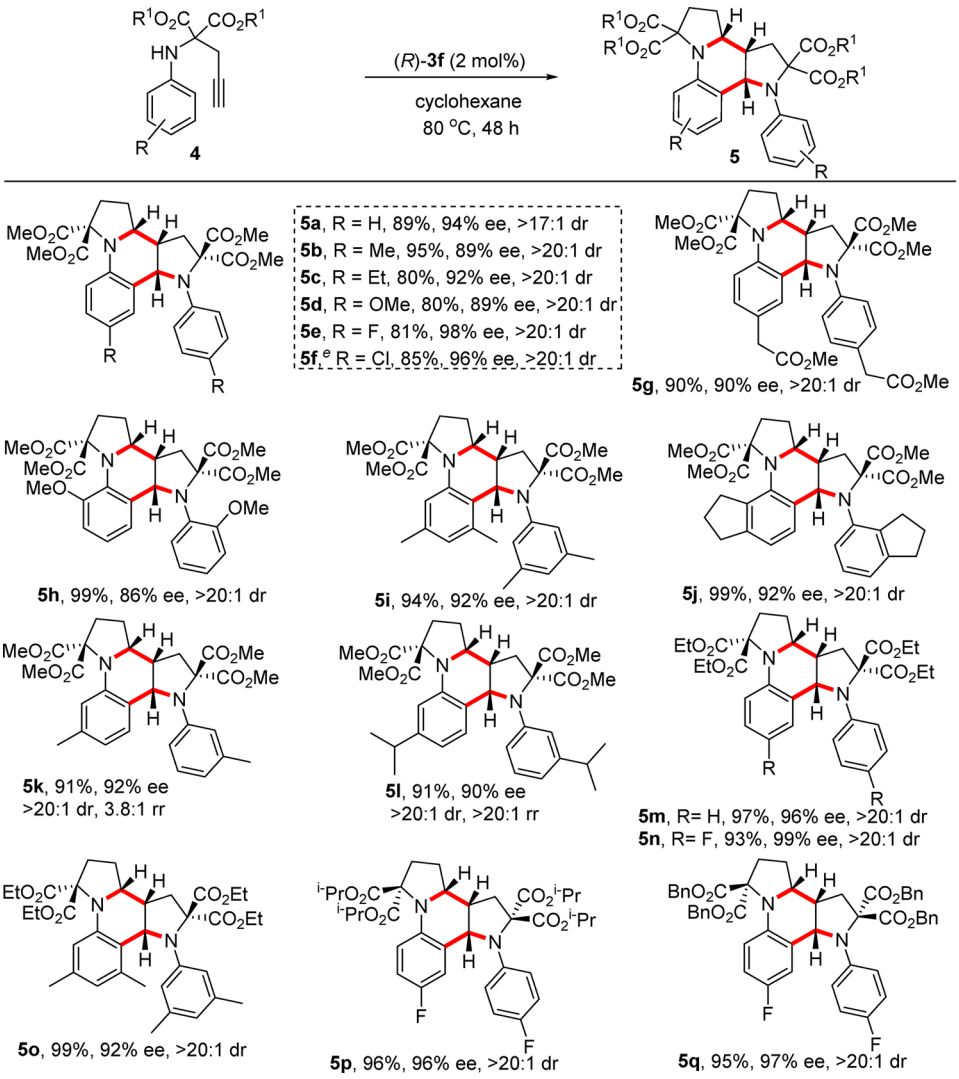
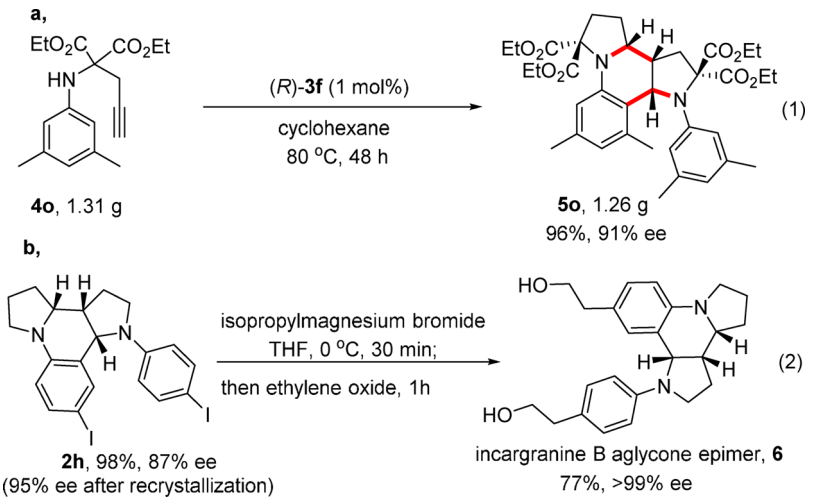
Table 3. Reaction Scope with Respect to Propargylic Amino Ester[a,b,c,d]



[a]All the reactions were conducted on a 0.1 mmol scale. [b]Isolated yield. [c]The ee was determined by HPLC analysis. [d]The dr and rr were determined by ^{1}H -NMR of the crude reaction mixture. [e]4 mol % of catalyst.

Scheme 2. Gram Scale and Synthesis of Incargranine B Aglycone Epimer 6



91% ee (Scheme 2, eq 1). For the purpose of accessing enantioenriched incargranine B aglycone epimer, whose structure has been revised by Lawrence and co-workers,[6g] we conducted the reaction of **1h** under the standard conditions on

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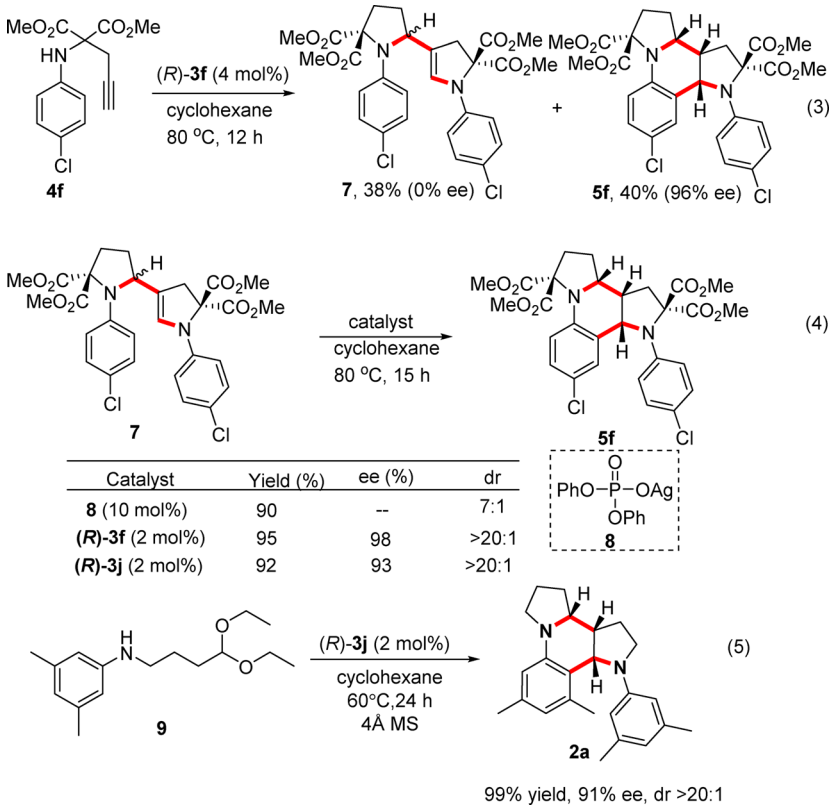
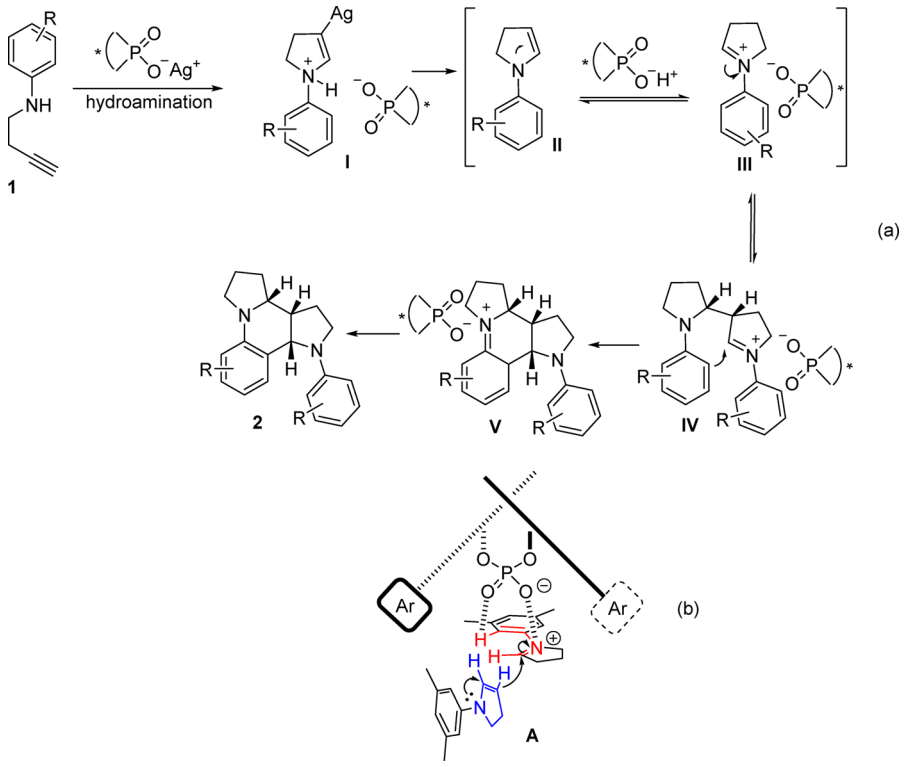
Scheme 3. Control Experiments



Scheme 4. Proposed Mechanism and Proposed Transition State



a gram scale to give **2h** in 98% yield and 87% ee (95% ee after a single recrystallization process). Next, treatment of 95% ee of **2h** with isopropylmagnesium bromide solution, followed by the addition of ethylene oxide, afforded incargranine B aglycone epimer **6** in 77% yield with >99% ee (Scheme 2, eq 2). *The structure resemblance with a variety of biologically active compounds also encouraged us to evaluate the biological activity of our products. Our preliminary biological studies revealed that*

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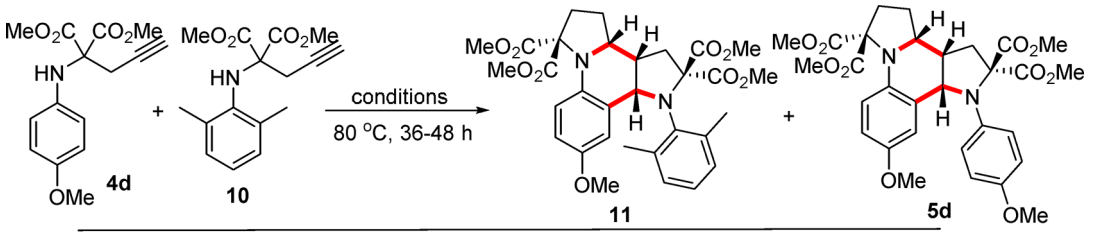
Scheme 5. Cross-Coupling Reaction



Conditions	11:5d	Yield for 11 (%)	ee for 11 (%)	dr for 11 (%)
$AuCl_3$ (6 mol%), $HOP(O)(OPh)_2$ (8 mol%), DCE	7.1:1.0	74	0	1.9:1.0
$Pd(OAc)_2$ (5 mol%), (*R*)-**3j** (7.5 mol%), cyclohexane	1.3:1.0	42	62	9.0:1.0

randomly selected enantioenriched compounds ***2a*** *and* ***5o*** *exhibited good cytotoxicities against PC3 cancer cell lines with* IC_{50} *values of 38.6 and 12.4 μM, respectively, suggesting a potential application of this class of chiral octahydro-dipyrroloquinolines in anticancer studies.*

Mechanistic Investigations and Cross-Coupling Reaction. Because the Povarov reaction could proceed in a stepwise manner or via a concerted IEHDA mechanism,[13] a series of control experiments were conducted to rationalize the current reaction process and its stereochemistry. Fortunately, the Mannich adduct **7**[14] was obtained in 38% yield, along with the final product **5f** (40% yield), when substrate **4f** bearing Cl substituent was used under otherwise identical conditions with only 12 h (Scheme 3, eq 3). This result indicated a stepwise mechanism of our subsequent enantioselective formal Povarov reaction is feasible. Subsequent treatment of the Mannich adduct **7** at 80 °C for 15 h in the presence of (*R*)-**3f**, (*R*)-**3j**, or achiral **8** gave **5f** in excellent yield via an intramolecular aza-Friedel−Crafts (FC) reaction, further demonstrating a stepwise Mannich/aza-FC process for this reaction. However, with chiral (*R*)-**3f** or (*R*)-**3j** as catalyst, the corresponding product **5f** was obtained as a single diastereomer with 98% or 93% ee, while with achiral **8**, a 7:1 mixture of diastereomers was obtained (Scheme 3, eq 4). These observations indicated that the Mannich reaction is a reversible step. On the other hand, the desired product **2a** was obtained in 99% yield with 91% ee as a single diastereomer when *N*-(4,4-diethoxybutyl)-3,5-dimethylaniline **9** was treated with a catalytic amount of chiral phosphoric acid (*R*)-**3j** (2 mol %) in the presence of 4 Å MS in cyclohexane at 60 °C for 24 h (Scheme 3, eq 5). This result, along with the high diastereo- and enantioselectivity of **5f** by treatment of the intermediate **7** with phosphoric acid (*R*)-**3j** (Scheme 3, eq 4), indicated that the silver catalyst is not necessary for enantiocontrol.

On the basis of the above observations and by considering previous works on silver-catalyzed hydroamination reactions,[12] a reaction mechanism is proposed as depicted in Scheme 4. Intramolecular hydroamination of **1** catalyzed by chiral silver phosphate could generate the silver-enamine intermediate **I** that is protonated to give enamine intermediate **II**. On the other hand, intermediate **II** could undergo tautomerization with chiral phosphoric acid[15] to form iminium cation intermediate **III**,[7,9f] wherein chiral phosphate anion could be coordinated as a counteranion to the iminium part.[16,17] The subsequent reversible Mannich reaction of intermediate **III** and **II** followed by the aza-FC cyclization yields an intermediate **V**, in which the chiral counteranion could induce the high diastereo- and enantioselectivity. The aromatization and protonation of intermediate **V** would give the final *endo* product **2**. To further rationalize the observed stereochemistry for this reaction, an interaction transition state based on Simon and Goodman's model[18] and Terada's DFT calculation[19a] was proposed (Scheme 4), in which chiral phosphate anion interacts with the iminium ion through not only electrostatic interactions but also a C−H···O hydrogen bond interaction[19] to form a tight ion pair **A**. Due to the steric effect of the bulky substituent and the SPINOL framework, the enamine, which acts as the nucleophile, is forced to selectively attack the iminium ion from only one side of the iminium ion, thus inducing *endo* diastereoselectivity, which is in accordance with the experimental findings.

Considering the possibility that the Mannich reaction is a reversible step for this tandem process (Scheme 4), we hypothesized that a cross-coupling reaction with two different aminoalkynes could be realized under an appropriate catalytic reaction system. As expected, our preliminary result showed that racemic product **11** was obtained in 74% yield with 7.1:1.0 product ratio (**11**/**5d**), albeit with 1.9:1.0 dr for the reaction of **10** and **4d** with $AuCl_3$ (6 mol %) and diphenyl phosphate (8 mol %). Furthermore, enantioenriched product **11** was obtained in 42% yield and 62% ee along with 9.0:1.0 dr with 1.3:1.0 product ratio (**11**/**5d**) with $Pd(OAc)_2$ (5 mol %) and (*R*)-**3j** (7.5 mol %) as the catalyst after the systematic optimization of different reaction parameters (Scheme 5 and Table S1 in SI). Clearly, there is still room for improvement of the result of such reaction.

CONCLUSIONS

We have successfully developed a first chiral metal-phosphate-catalyzed asymmetric tandem hydroamination/formal Povarov reaction of aminoalkynes via a chiral counteranion-controlled iminium ion intermediate strategy to enable a straightforward and efficient synthesis of biologically important tetracyclic octahydro-dipyrroloquinolines bearing multiple contiguous stereogenic centers in excellent yield with unprecedented high levels of regio-, diastereo-, and enantioselectivity from readily available starting materials at catalytic loadings even as low as 1 mol %. Furthermore, this methodology allows for the first synthesis of incargranine B aglycone epimer. Mechanistic studies suggest that the key step of cyclization reaction proceeds via a stepwise process, in which both diastereoselectivity and enantioselectivity are controlled by a chiral phosphate counteranion. Further investigation of the corresponding cross-coupling reaction with expected excellent

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results is ongoing in our laboratory. Considering the broad utility for this new counteranion-controlled asymmetric protocol, we further anticipate that this efficient strategy may has the potential to open the door for developing asymmetric inverse-electron-demand hetero-Diels–Alder reaction of different types of iminium ions and dienophiles for other classes of useful enantiopure complex azaheterocycles through metal phosphate catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b01492.

Experimental procedures and characterization of all new compounds (PDF)

X-ray data of **2h** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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