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Organocatalytic Formal (3 + 2) Cycloaddition toward Chiral Pyrrolo[1,2-*a*]indoles via Dynamic Kinetic Resolution of Allene Intermediates

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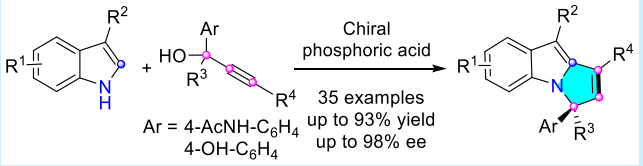
ABSTRACT: We report the chiral phosphoric acid catalyzed formal (3 + 2) cycloaddition of 3-substituted 1*H*-indoles and propargylic alcohols containing a functional directing group (*p*-NHAc or *p*-OH). This work represents a straightforward method to synthesize chiral pyrrolo[1,2-*a*]indole bearing a tetrasubstituted carbon stereocenter. The reaction proceeds smoothly with a wide array of substrate tolerance to deliver various chiral pyrrolo[1,2-*a*]indoles in up to 93% yield and 98% ee. The utility of this method is highlighted by the diverse transformations of the products into various indole derivatives.



Chiral pyrrolo[1,2-*a*]indole scaffolds are key skeletons found in a range of natural products and pharmaceuticals.[1] As representative examples shown in Figure 1, such

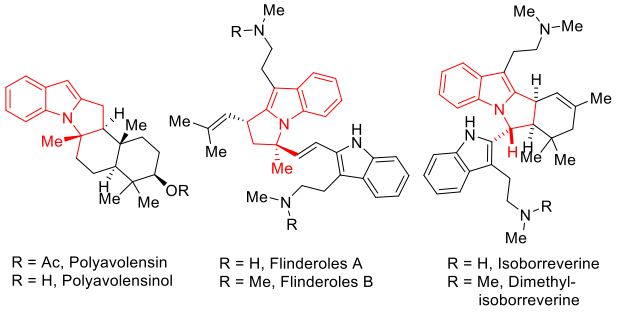


Figure 1. Representative examples of natural and biologically active products containing the pyrrolo[1,2-*a*]indole core.

compounds exhibit antitumor, analgetic, or anticancer properties and have attracted much attention in medicinal chemistry.[2] Thus, developing efficient catalysis methodologies for enantioenriched pyrrolo[1,2-*a*]indoles is highly desirable. In recent decades, a number of seminal studies were conducted for the construction of chiral pyrrolo[1,2-*a*]indoles, including cyclization of *N*-substituted indoles, (3 + 2) cycloaddition of nitrovinylindoles or 1*H*-indole-2-carbaldehyde, and a C-2 functionalization and annulation sequence of indoles.[3,4] Despite the significance of these approaches, most of these strategies utilize prefunctionalized substrates or require multiple steps, and the direct asymmetric catalytic functionalizations of indoles to pyrrolo[1,2-*a*]indoles bearing the tetrasubstituted carbon stereocenter remains rare.

It is generally considered that indoles are nucleophilic at the C3, C2, and N1 positions, and this unique property provides the possibility to regioselectively functionalize indole-containing substrates by cascade reaction sequences, thus resulting in chiral polycyclic indole derivatives.[5] Clearly, the key to synthesize pyrrolo[1,2-*a*]indoles directly from indoles is to rationally employ proper electrophiles, which could regioselectively react with the C2- and/or N1-position of indoles. In 2013, Xiao et al. reported a Cu-catalyzed asymmetric Friedel–Crafts alkylation/*N*-hemiacetalization cascade reaction between 3-substituted indoles and *β*,*γ*-unsaturated *α*-ketoesters (Scheme 1a).[4b] The process enables the efficient construction of diversely functionalized pyrrolo[1,2-*a*]indoles with a *N*-hemiacetal group. Shortly thereafter, Wang et al. described a Pd-catalyzed cascade reaction of 3-alkylindoles with oxindolyl *β*,*γ*-unsaturated *α*-ketoesters to synthesize various spiro-polycyclic indole derivatives (Scheme 1b).[4h] In light of the importance of pyrrolo[1,2-*a*]indoles with a tetrasubstituted carbon stereocenter, it is still highly desirable and challenging to develop methods for rapid construction of pyrrolo[1,2-*a*]indole skeletons with novel and complex structures under mild conditions.

On the other hand, propargylic alcohols are easily available building blocks and have been extensively applied in the construction of heterocyclic compounds.[6] However, it remains difficult to control the enantioface selection of propargylic

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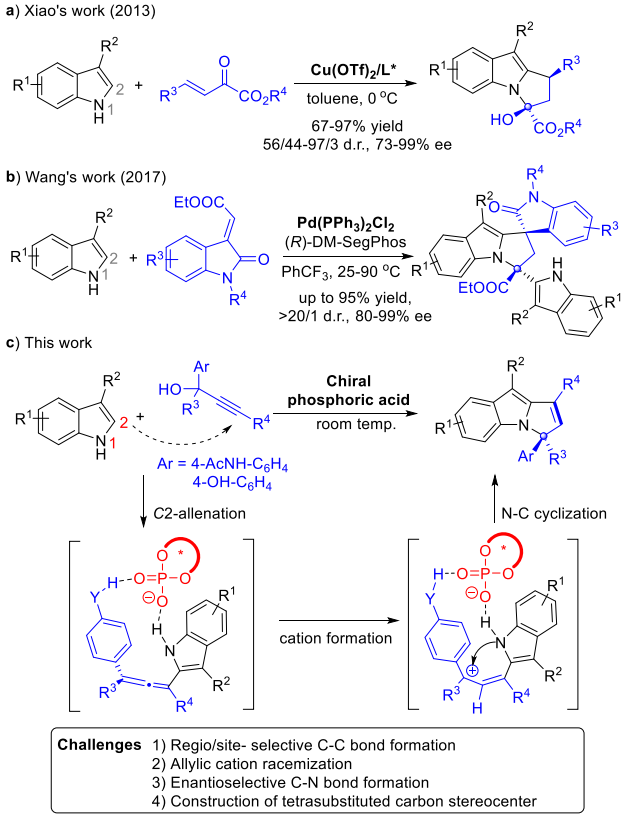
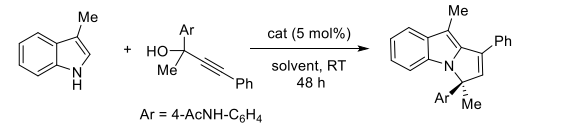
Scheme 1. Asymmetric Synthesis of Pyrrolo[1,2-*a*]indoles Bearing the Tetrasubstituted Carbon Stereocenter

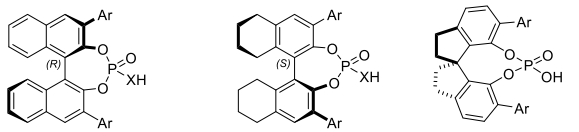


cation species which are generated *in situ* by elimination of the hydroxy group, *leaving catalytic asymmetric cycloaddition of propargylic alcohols to indoles uncertain*. On the basis of our continuing interest in asymmetric synthesis, herein we report an organocatalytic enantioselective synthesis of chiral pyrrolo-[1,2-*a*]indoles using 3-substituted 1*H*-indoles and propargylic alcohols containing functional directing groups (NHAc or OH; Scheme 1).[7,8] Therefore, the stereochemistry of the propargylic carbocation intermediate could be controlled via hydrogen bonding of the *p*-acetamido/hydroxy group with a chiral Brønsted acid catalyst.

We initiated our investigation by using 3-methyl-1*H*-indole **1a** and propargylic alcohol **2a** as model substrates, with 5 mol % of chiral phosphoric acids or phosphoramides as catalyst.[9] Gratifyingly, the reaction proceeded smoothly in dichloromethane at room temperature in the presence of catalyst **4a**, and the desired pyrrolo[1,2-*a*]indole **3a** was obtained in 51% yield with 41% ee (Table 1, entry 1). Screening of other catalysts with different backbones and steric environments (Table 1, entries 2−11) showed that catalyst **5c** with chiral spirocyclic skeleton was suitable, affording **3a** in 78% yield with 87% ee (Table 1, entry 10). Therefore, we chose **5c** as the catalyst for further optimizations. The addition of 4 Å molecular sieves improved the enantioselectivity, albeit with a slightly lower yield (Table 1, entry 12). Furthermore, solvent screening was carried out in the hope of improving the reaction yield. Disappointingly, no better results were obtained (Table 1, entries 13−17). Different Brønsted acids with varying acidity were also evaluated as additives (Table 1, entries 18−19; for more examples, see the Supporting Information (SI)).[10] While stronger acids led to lower enantioselectivities, boronic acids

Table 1. Optimization of the Reaction Conditions[a]





4a: Ar = 3,5-$(CF_3)_2C_6H_3$, X = O
4b: Ar = 9-phenanthryl, X = O
4c: Ar = 9-anthryl, X = O
4d: Ar = 2,4,6-$(i\text{Pr})_3C_6H_2$, X = O
4e: Ar = 2,4,6-$(i\text{Pr})_3C_6H_2$, X = NTf
4f: Ar = 2,4,6-$(i\text{Pr})_3C_6H_2$, X = O
4g: Ar = 2,4,6-$(i\text{Pr})_3C_6H_2$, X = NTf
5a: Ar = 2,4,6-$(i\text{Pr})_3C_6H_2$
5b: Ar = 2,4,6-$Me_3C_6H_2$
5c: Ar = 9-anthryl
5d: Ar = 1-pyrenyl

Entry	Catalyst	Solvent	Yield (%)[b]	ee (%)[c]
1	**4a**	CH_2Cl_2	51	−41
2	**4b**	CH_2Cl_2	70	−66
3	**4c**	CH_2Cl_2	16	−51
4	**4d**	CH_2Cl_2	65	−77
5	**4e**	CH_2Cl_2	75	−17
6	**4f**	CH_2Cl_2	70	81
7	**4g**	CH_2Cl_2	79	22
8	**5a**	CH_2Cl_2	42	24
9	**5b**	CH_2Cl_2	75	77
10	**5c**	CH_2Cl_2	78	87
11	**5d**	CH_2Cl_2	72	84
12[d]	**5c**	CH_2Cl_2	73	90
13[d]	**5c**	$CHCl_3$	61	81
14[d]	**5c**	toluene	69	86
15[d]	**5c**	C_6H_5Cl	73	90
16[d]	**5c**	$C_6H_5CF_3$	78	87
17[d]	**5c**	CH_3CN	51	3
18[d,e]	**5c**	CH_2Cl_2	81	90
19[d,f]	**5c**	CH_2Cl_2	83	90
20[d,f,g]	**5c**	C_6H_5Cl/CH_2Cl_2	85	91
21[d,f]	**4f**	$CHCl_3$	86	90

[a]Use of **1a** (0.06 mmol), **2a** (0.066 mmol), a catalyst (0.003 mmol), and a solvent (0.6 mL), room temperature (RT), 48 h. [b]Determined by ^{1}H NMR with 1,2-dichloroethane as internal standard. [c]Determined by chiral HPLC. [d]4 Å Molecular sieves (50 mg) was used. [e]Phenylboronic acid (20 mol %) was used. [f]4-Fluorophenylboronic acid (20 mol %) was used. [g]C_6H_5Cl/CH_2Cl_2 = 0.4/0.2 mL.

with weaker acidity appear to be suitable and act as a hydrogen bond donor providing enhanced reactivity without detrimental effect on enantioselectivity. To our delight, the addition of 4-fluorophenylboronic acid increased the yield of **3a** to 83% with 90% ee (Table 1, entry 19). Subsequently, it was found the optimized reaction conditions required catalyst **5c** (5 mol %), 4-fluorophenylboronic acid (20 mol %), and 4 Å molecular sieves in C_6H_5Cl/CH_2Cl_2 mixed solvents (Table 1, entry 20). In addition, with H8-BINOL-derived catalyst **4f** in $CHCl_3$, the product **3a** could also be obtained in similar yield and enantioselectivity (Table 1, entry 21 vs 20; see the SI for details).

With the optimized conditions in hand, the reaction scope was initially assessed using a range of 3-substituted 1*H*-indoles **1** with propargylic alcohol **2a** (Scheme 2, **3a**−**3o**). All 3-methyl-1*H*-indoles showed excellent reactivity with either electron-withdrawing groups (Cl or Br) or electron-donating groups (Me or OMe) on the phenyl ring, generating the products in 64−81% yields with 87−98% ee (**3b**−**3m**).

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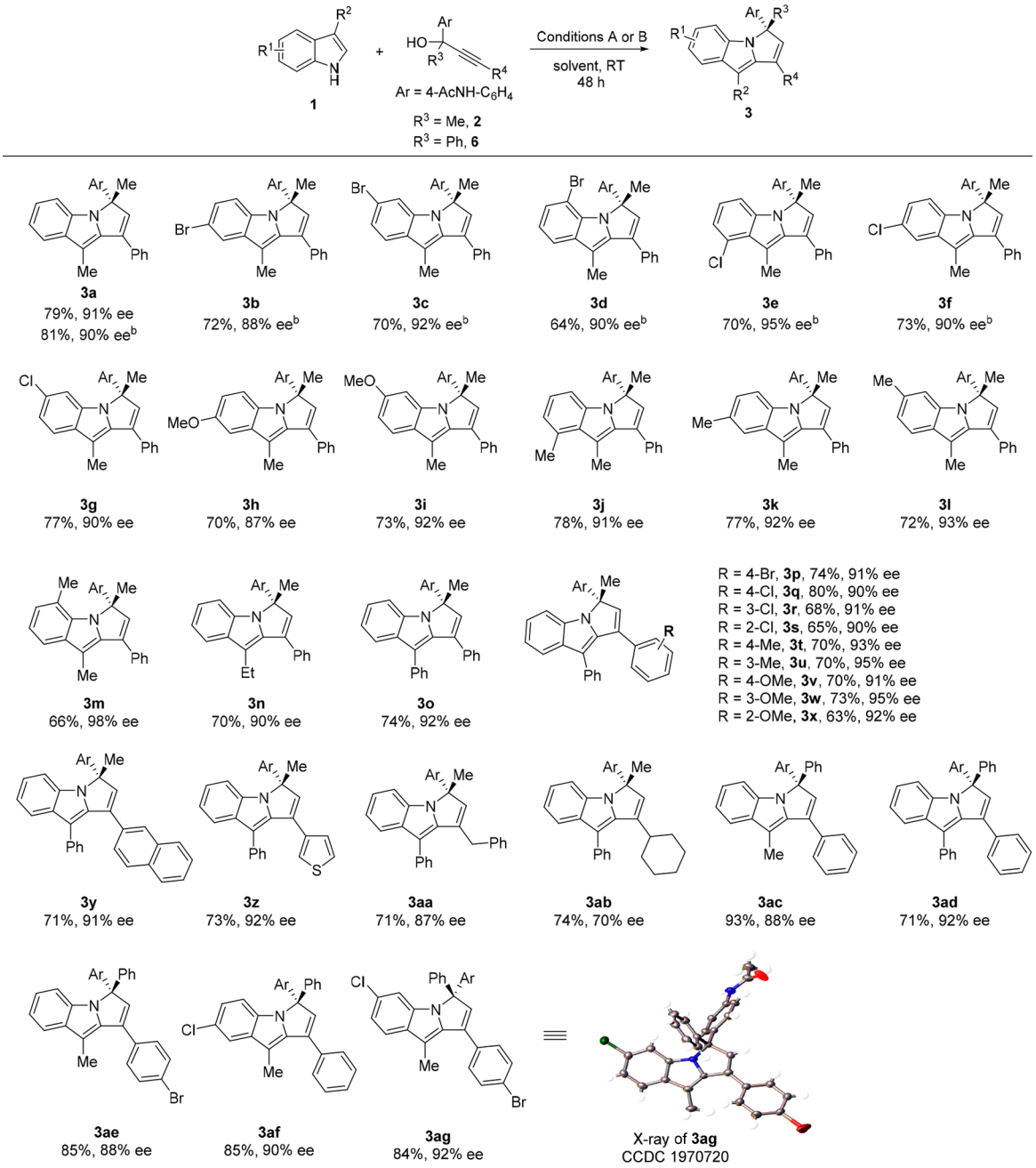
Scheme 2. Scope of 3-Substituted 1*H*-Indoles and Propargylic Alcohols[a]



[a]Conditions A: Use of indole **1** (0.13 mmol), propargylic alcohol **2** or **6** (0.12 mmol), **5c** (0.006 mmol), 4-F-$C_6H_4B(OH)_2$ (0.024 mol), and 4 Å molecular sieves (100 mg) in C_6H_5Cl/CH_2Cl_2 (0.8/0.4 mL) at RT for 48 h. Yields of isolated products are reported. The enantiomeric excess was determined by chiral HPLC methods. [b]Conditions B: Use of **1** (0.13 mmol), propargylic alcohol **2** or **6** (0.12 mmol), **4f** (0.006 mmol), 4-F-$C_6H_4B(OH)_2$ (0.024 mmol), and 4 Å molecular sieves (100 mg) in $CHCl_3$ (1.2 mL) at RT for 48 h.

However, 7-bromo and 7-methyl substituted 1*H*-indoles reacted with relatively lower yields due to steric hindrance (**3d** and **3m**). The 3-substituted group of 1*H*-indole appears to have less effect on the reaction, and both 3-ethyl and 3-phenyl 1*H*-indoles afforded the cyclic adduct **3** in good yields and enantioselectivities (**3n**−**3o**). Next, we explored the scope of propargylic alcohols. A number of propargylic alcohols **2** having aryl, heteroaryl, and alkyl groups were well tolerated under optimized conditions (Scheme 2, **3p**−**3ab**). In addition, the electronic properties of the substituents on terminal aryl groups of alkynes have little effect on the reaction. Both electron-withdrawing (Br or Cl) and electron-donating (Me or OMe) groups were compatible, and the reactions produced the desired products in moderate to good yields (63−80%) and high enantioselectivities (90−95% ee, **3p**−**3x**). Propargylic alcohols with a 2-naphthyl or 3-thienyl group also gave good yields (71−73%) and excellent enantioselectivities (91−92% ee, **3y**−**3z**). In addition, alkyl (R^4 = benzyl and cyclohexyl) substituted propargylic alcohols **2** proceeded smoothly to afford the desired products in moderate yields and relatively low enantioselectivities (**3aa**−**3ab**). Encouraged by these results, propargylic alcohols **6** (R^3 = Ph) with pronounced

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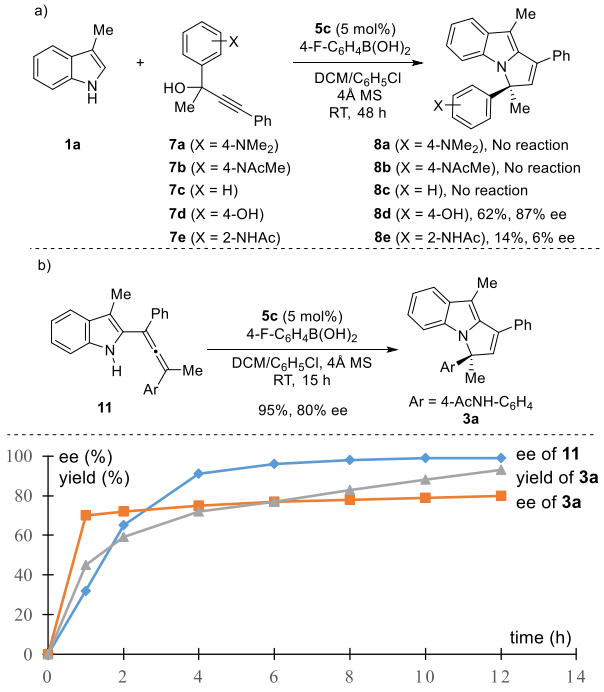
steric hindrance were also investigated. The reaction gave desired adducts in higher yields compared with propargylic alcohol **2** (**3ac**−**3ag**). Various substituted 1*H*-indoles reacted with propargylic alcohols **6** and afforded cyclic products in good to excellent yields (71−93%) and enantioselectivities (88−92% ee). The absolute configuration of **3ag** was determined to be (*R*) by X-ray crystallographic analysis, and the configuration of other pyrrolo[1,2-*a*]indoles **3** were assigned by analogy.

To probe the reaction mechanism, several control experiments were carried out (Scheme 3). *N*-Methylated propargylic

Scheme 3. Several Control Experiments



alcohols (**7a** and **7b**) and 2,4-diphenylbut-3-yn-2-ol (**7c**) reacted with indole **1a** giving no adducts **8** under the optimized conditions (Scheme 3a). The application of the present method to a propargylic alcohol with a *p*-hydroxyphenyl substituent (**7d**) also provided the desired product in 62% yield and 87% ee. The reaction of propargylic alcohol **7e** with the acetamido group at the *ortho*-position gave cyclic product **8e** in 14% yield and 6% ee. These results indicate that a hydrogen-bond donor at the *para*-position of propargylic alcohols is essential for activation and chiral induction.

With respect to the mechanism of formation of pyrrolo[1,2-*a*]indole skeletons, we considered that it may proceed through two pathways: the first pathway could involve the attack of aza-quinone methides (aza-*p*-QMs) by the C2 of indoles through 1,8-addition to generate allene followed by intramolecular N−C bond formation, while the second pathway is the attack of *N* in indoles to aza-*p*-QMs through 1,6-addtion to generate *N*-propargyl indole followed by intramolecular C−C bond formation. To better understand the reaction pathway, density functional theory (DFT) calculations were carried out, which revealed that the 1,8-addition to generate tetrasubstituted allene has a lower energy barrier than 1,6-addition (5.5 vs 19.8 kcal/mol; for details see SI).[11] In order to validate the mechanism on the generation of tetrasubstituted allene intermediates, the racemic allene **11** was synthesized and fully characterized. It was further discovered that, in the presence of catalyst **5c** under optimized reaction conditions, **11** was smoothly converted into the corresponding product **3a** in 95% yield and 80% ee, and the ee of **11** continued to increase to >99% as the reaction proceeded further (Scheme 3b).

Based on these results and previous reports, we proposed the following plausible reaction mechanism for the formation of **3ac** (Figure 2). Firstly, the *in situ* dehydration of the

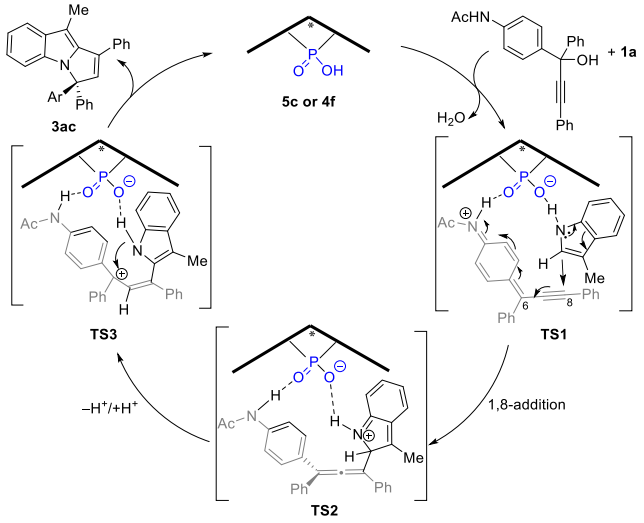


Figure 2. Plausible reaction mechanism.

propargylic alcohol generates the aza-*p*-QMs intermediate in the presence of chiral phosphoric acid (CPA). CPA serves as a bifunctional catalyst to activate both the aza-*p*-QMs intermediate and **1a** by hydrogen bonding (**TS1**). Due to the steric hindrance of aza-*p*-QMs at the 6-position, the reaction prefers kinetically the 1,8-conjugate addition of the C2-position of indole **1a** to generate the chiral tetrasubstituted allene (**TS2**). Finally, the hydrogen-bonded chiral allene is protonated to generate the benzylic cation (**TS3**),[12] which undergoes intramolecular cyclization to provide the cyclic product **3ac**. The presence of the N−H moiety in propargylic alcohols is pivotal, which not only accelerates the dehydration of propargylic alcohol to form aza-*p*-QMs but also interacts with the catalyst to control chiral induction during dynamic kinetic resolution of the allene intermediate.

To demonstrate the synthetic value of these pyrrolo[1,2-*a*]indole derivatives, further transformations of **3a** were carried out (Scheme 4).[13,14] Dihydropyrroloindole **9a** was formed by hydroboration of **3a** followed by oxidation in good yield (71%) with excellent diastereoselectivity (d.r. > 20/1). This sequence provided an expeditious access to indole derivatives possessing three contiguous stereocenters.[13a] The brominated product **9b** could be obtained in 84% yield by the reaction of **3a** with bromine, which can be used as a versatile intermediate for further modifications. The acetamido group of **3a** was hydrolyzed to an amino group after being treated with 4 N HCl,[8g] and the amine was further converted into the corresponding halide derivative **9c** in 82% yield.[13b] In addition, indole **1p** reacted smoothly with propargylic alcohol **10** under the optimized conditions to give pyrrolo[1,2-*a*]indole **9d** in 47% yield with 94% ee.[14]

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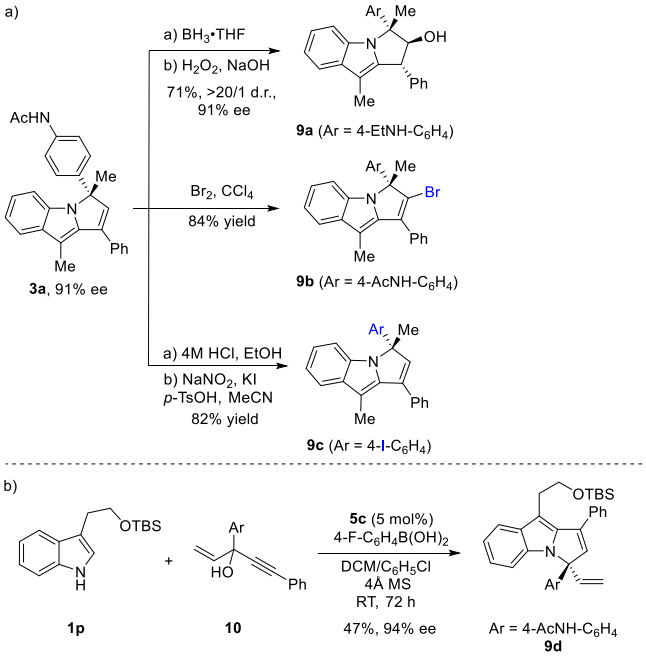
Scheme 4. Synthetic Applications



In conclusion, we have developed the first organocatalytic asymmetric formal (3 + 2) cycloaddition of 3-substituted 1*H*-indoles with readily available propargylic alcohols containing a functional directing group (*p*-NHAc or *p*-OH). Under mild reaction conditions, a variety of valuable chiral pyrrolo[1,2-*a*]indoles bearing the tetrasubstituted carbon stereocenter were conveniently constructed with excellent reactivity, regioselectivity, and enantioselectivity. In this system, an acetamido group that acts as both the activating and directing group is crucial for the cycloaddition and favorable for hydrogen bonding and chiral induction with chiral phosphoric acid catalysts. Besides, chiral pyrrolo[1,2-*a*]indoles were amenable to further transformations and enabled convenient synthesis of indole derivatives. This protocol provided a potentially effective method for the construction of various chiral cyclic compounds from propargylic alcohols. Further studies of this process with respect to other nucleophiles are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01812.

Experimental procedures, characterization of new compounds, crystallographic data for **3ag**, density functional theory (DFT) calculations, NMR and HPLC spectra (PDF)

Accession Codes

CCDC 1970720 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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