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Stereoselective Total Synthesis of KAE609 via Direct Catalytic Asymmetric Alkynylation to Ketimine

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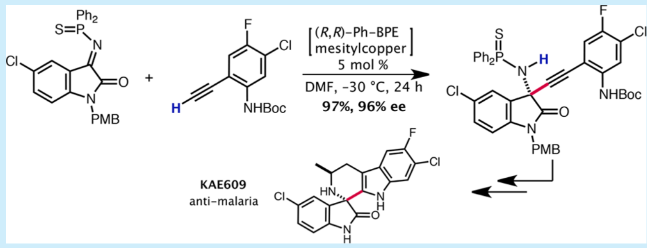
Supporting Information

ABSTRACT: A direct catalytic asymmetric alkynylation protocol is applied to provide the requisite enantioenriched propargylic α-tertiary amine, allowing for the stereoselective total synthesis of KAE609 (formerly NITD609 or cipargamin).



Malaria is a life-threatening infectious disease that remains a persistent global health concern. In 2013 alone, malaria caused ~584,000 deaths, mostly among African children.[1] Malaria is caused by protozoan parasites, *Plasmodium falciparum* and *Plasmodium vivax*, causing acute flu-like symptoms. Currently, the primary treatment of malaria infection is artemisinin-containing combination therapies, but the recent emergence of artemisinin-resistant strains has led to an urgent demand for new antimalarial drug candidates.[2−4] The Novartis Institute of Tropical Diseases discovered a new spiroindolone entity by high-throughput screening, KAE609 (formerly NITD609 or cipargamin), that exhibits novel and potent antimalarial activity (Figure 1).[5−7] Under the growing

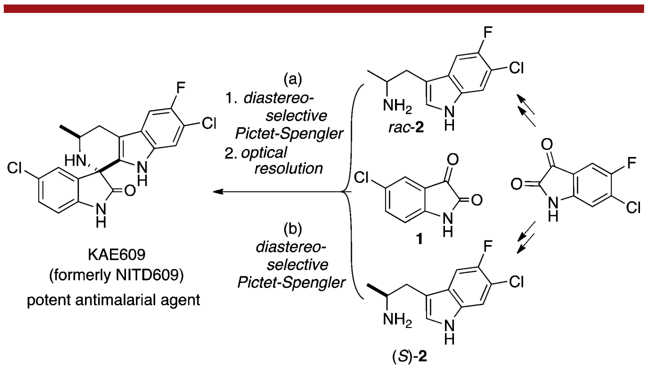


Figure 1. Structure of KAE609 and its synthetic approach.

threat of artemisinin resistance, clinical development of KAE609 is now underway (phase II) with promising prospects. KAE609 is characterized by a tetrasubstituted stereogenic spiro carbon at the junction of an oxindole unit and an indole-fused piperidine unit with an additional chiral center. The three halogen atoms present necessitate prefunctionalization of the synthetic units. All four stereoisomers were synthesized and separated by HPLC (Figure 1a), and KAE609 was identified as the most active compound (Figure 1).[5] The Pictet−Spengler reaction of 5-chloroisatin (**1**) and α- methyltryptamine (**2**) preferentially afforded the desired diastereomer,[8,9] and a more efficient synthetic approach via enantioenriched (*S*)-**2** was extensively studied using engineered enzymes for large scale production of KAE609.[10] The amine-containing tetrasubstituted stereogenic center of KAE609 and its favorable promise as a novel treatment for malaria led us to examine the potential of our asymmetric catalysts to furnish this fascinating molecule. We anticipated that direct catalytic asymmetric alkynylation of ketimines,[11,12] which was recently developed in our group,[13] would be feasible for use with a functionalized terminal alkyne to construct the requisite tetrasubstituted stereogenic center (Scheme 1). The halogenated *o*-alkynylaniline moiety of the resulting adduct is a direct precursor of an indole unit, and

Scheme 1. Retrosynthetic Analysis of KAE609

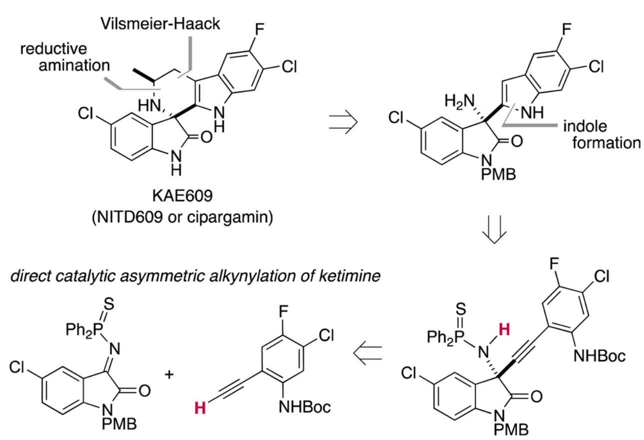


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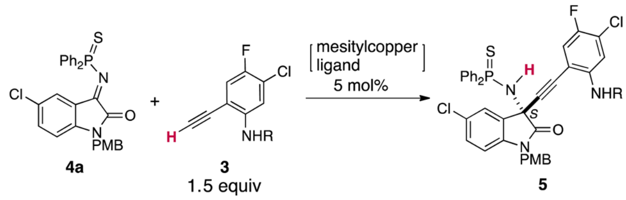
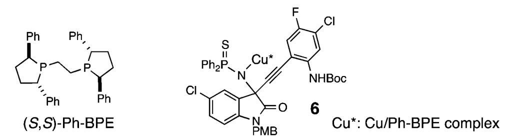
Table 1. Direct Catalytic Asymmetric Alkynylation Functionalized Terminal Alkyne 3 to *N*-(Diphenylthiophosphinoyl)ketimine 4[a]



entry	alkyne 3 R =		ligand	solvent	product config		temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	H	**3a**	(*S*,*S*)-Ph-BPE	THF	**5a**		−78	18	79	73
2	CF_3CO	**3b**	(*S*,*S*)-Ph-BPE	THF	**5b**		−78	21	—	—
3	Cbz	**3c**	(*S*,*S*)-Ph-BPE	THF	**5c**		−78	18	38	81
4	Fmoc	**3d**	(*S*,*S*)-Ph-BPE	THF	**5d**		−78	24	98	40
5	Boc	**3e**	(*S*,*S*)-Ph-BPE	THF	**5e**	*R*	−78	18	87	87
6[d]	Boc	**3e**	(*R*,*R*)-Ph-BPE	DMF	**5e**	*S*	−30	24	97	96

[a]**3**: 0.075 mmol. **4a**: 0.05 mmol. [b]Isolated yield. [c]Determined by chiral-stationary-phase HPLC. [d]3.1 g of **4a** was used. 1.2 equiv of **3e** was used.



subsequent introduction of an acetonyl group at C3 of the indole followed by intramolecular reductive amination would afford KAE609.

The synthesis of KAE609 was initiated by direct catalytic asymmetric alkynylation of functionalized terminal alkyne **3** to *N*-(diphenylthiophosphinoyl(thioDpp))ketimine **4a** derived from 5-chloroisatin (Table 1).[14,15] Based on our previous communication documenting the alkynylation of *N*-thioDpp-ketimines derived from aryl alkyl ketones (e.g., acetophenones), we applied a catalyst comprising mesitylcopper/(*S*,*S*)-Ph-BPE for the alkynylation using terminal alkyne **3a** with the requisite halogen substituents and a free amino group (entry 1). In contrast to the reaction using *N*-thioDpp-ketimines derived from normal ketones, **4a** exhibited much higher reactivity and the reaction proceeded even at −78 °C, affording **5a** in 79% yield with 73% ee. Mesitylcopper ligated with Ph-BPE initially generated a Cu-alkynylide from a terminal alkyne that was sufficiently nucleophilic toward **4a**, which was also activated by a Cu/Ph-BPE complex through a soft−soft interaction. The thus-generated intermediate **6** deprotonated **3** and drove the following catalytic cycle with concomitant liberation of product **5a**. A protecting group on the nitrogen modulated the reaction profile. Whereas alkyne **3b** with a trifluoroacetyl protecting group gave a complicated mixture (entry 2), *N*-Cbz, -Fmoc, and -Boc protected alkynes **3c−e** afforded the desired products (entries 3−5). **3d** exhibited superior reactivity (entry 4), but based on enantioselectivity, **3e** (Boc) was selected as the best substrate (entry 5). Unexpectedly, the absolute configuration of the alkynylated product **5e** was the undesired *R*. Based on a previous observation that alkynes approached from the upper prochiral face of ketimines derived from aryl alkyl ketones (e.g., acetophenone **4b**) using (*S*,*S*)-Ph-BPE (Figure 2a), we anticipated that ketimine **4a** would react in a similar manner in an essentially identical catalytic system. In contrast to our expectation, however, the manner of approach for **4a** was the opposite; **3e** approached from the lower prochiral face of **4a** (Figure 2b), presumably due to the different orientation of the thioDpp group, which would determine the stereochemical

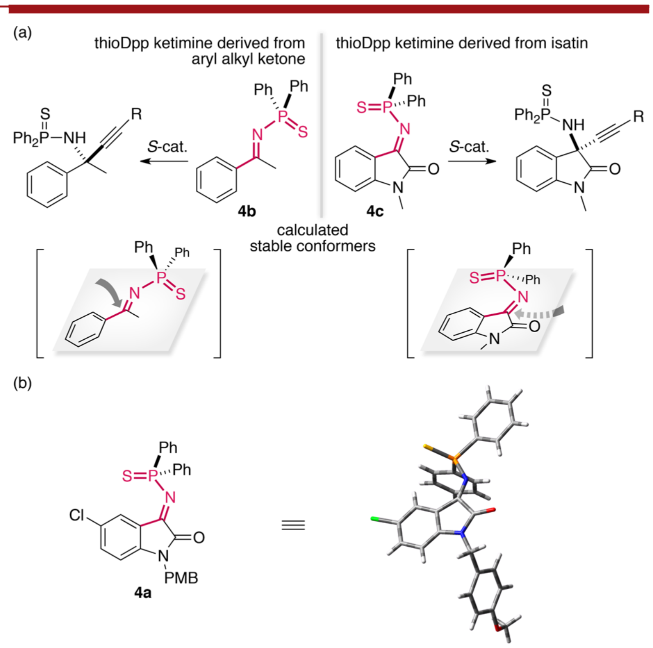


Figure 2. (a) Structures of stable conformers of ketimines **4b** and **4c** and stereochemical course of asymmetric alkynylation using (*S*,*S*)-Ph-BPE. (b) Crystal structure of **4a**. White, hydrogen; gray, carbon; blue, nitrogen; red, oxygen; orange, phosphorus; yellow, sulfur; green, chlorine.

course in the present Cu(I) catalysis. The optimized structures were computed for **4b** and simplified isatin-derived ketimine **4c** using the 6-31G+(d,p) basis set at the B3LYP level of theory (Figure 2a).[16] Whereas the thioDpp group was located on the side opposite that of the aromatic group of **4b**, it occupied the same side relative to the aromatic ring of **4c**, likely due to electronic repulsion with the neighboring carbonyl. Indeed, X-ray crystallographic analysis of **4a** revealed the expected geometry (Figure 2b). The different orientation might be responsible for the opposite stereochemical course. Use of

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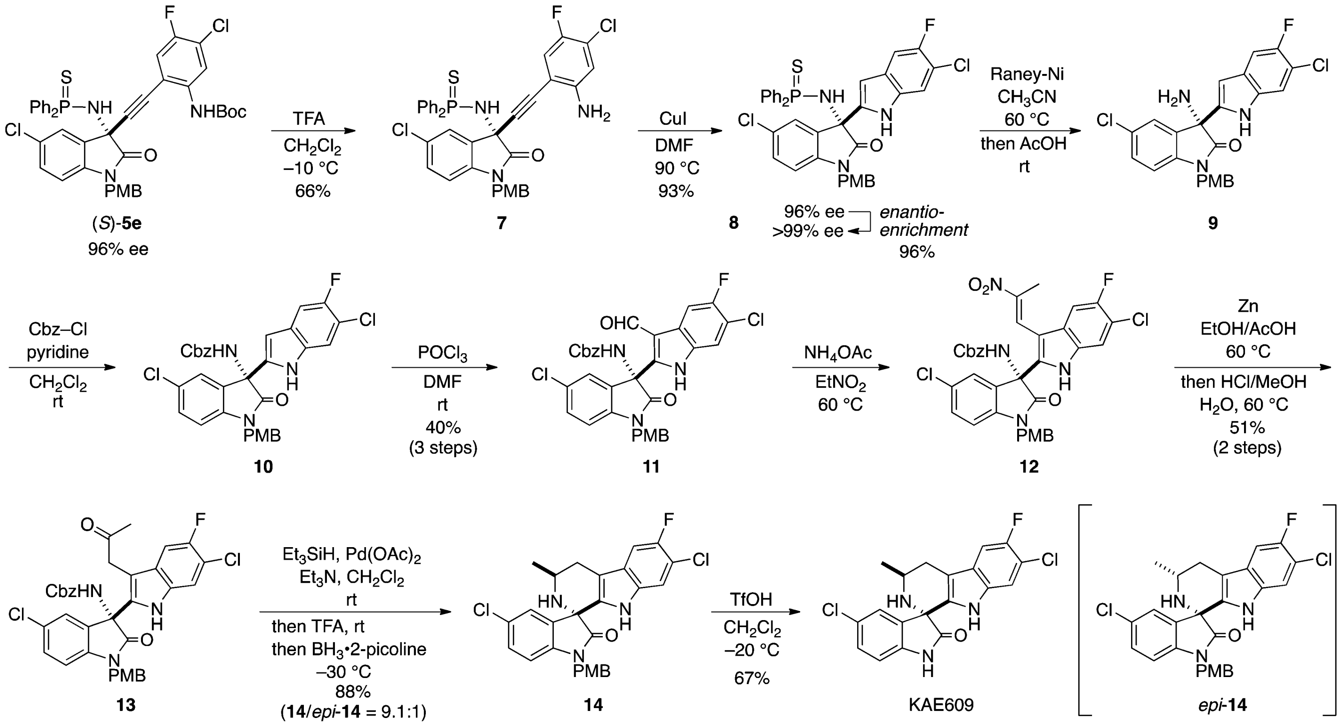
Scheme 2. Synthesis of KAE609



DMF as a solvent improved the enantioselectivity, and the desired (*S*)-**5e** was obtained on a greater than 3-g scale in 97% yield with 96% ee using (*R*,*R*)-Ph-BPE (entry 6).

Synthesis of KAE609 from key intermediate (*S*)-**5e** is illustrated in Scheme 2. After removing the Boc group of (*S*)-**5e** by TFA, Cu(I) catalyzed intramolecular hydroamination of the alkyne furnished the requisite indole unit to give **8** in 93% yield.[17] Racemic (±)-**8** was preferentially recrystallized from EtOAc/*n*-hexane, and the mother liquor was enriched to afford enantiomerically pure **8**, from which we removed the *N*-thioDpp group. Acidic conditions are generally applied to remove the protecting group, but acidic treatment of **8** gave a mixture of unidentified compounds. Alternatively, the thiophosphinoyl group was desulfurinated by Raney-Ni and the thus-generated trivalent aminophosphine was hydrolyzed under the mild acidic conditions of AcOH to give **9**. Before manipulation of the indole ring, the free amine was protected by a Cbz group, and various conditions were evaluated to directly provide **13** bearing an acetonyl unit at the 3-position of indole, which were unsuccessful. Therefore, a stepwise approach to **13** was adopted and the C1-unit was initially introduced by a Vilsmeier−Haack reaction to deliver 3-formylated indole **11**.[18] A nitroaldol/*β*-elimination sequence with nitroethane gave nitroolefin **12**, and subsequent reduction of the nitro group mediated by Zn followed by acidic hydrolysis gave **13**, which was a key substrate for the crucial diastereoselective intramolecular reductive amination. The Cbz group was resistant to removal under conventional conditions, and only specific conditions of $Et_3SiH/Pd(OAc)_2$ were effective in giving a transient triethylsilyl carbamate.[19] Addition of TFA triggered the decomposition of the silyl carbamate to expose a free amine, affording a cyclic ketimine intermediate. Because the attempts to isolate the cyclic ketimine led to undesired benzylic oxidation, the ketimine was directly subjected to reducing conditions using BH_3·picoline,[20] which preferentially furnished desired diastereomer **14** with the requisite spiroindole core. Final removal of the *N*-PMB group on the oxindole of isolated diastereomer **14** was achieved by TfOH, affording KAE609, whose spectroscopic data were consistent with previously reported data.

In conclusion, KAE609 (formerly NITD609 or cipargamin), a potent antimalaria drug under Phase II clinical trials by Novartis, was synthesized in an optically pure form. Direct catalytic asymmetric alkynylation of ketimine was applied as a key step to generate the requisite tetrasubstituted stereogenic center. Asymmetric alkynylation to ketimines using a catalytic amount of metal remains challenging, and the synthesis presented here showcases the synthetic utility of this elusive reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02300.

Experimental procedures and characterization of new compounds (PDF)
X-ray data for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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