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Letter

Asymmetric Synthesis of 3-Methyleneindolines via Rhodium(I)-Catalyzed Alkynylative Cyclization of *N*-(*o*-Alkynylaryl)imines

Shi-Yi Yuan, Qi-Qi Yan, Dan Wang, Ting-Ting Dan, Long He, Cheng-Yu He,* Wen-Dao Chu,* and Quan-Zhong Liu*

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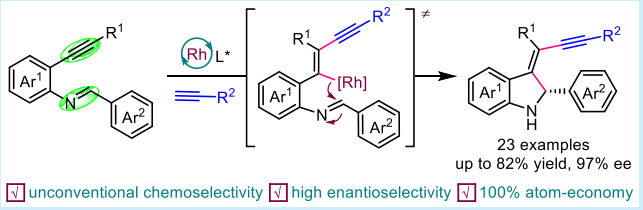
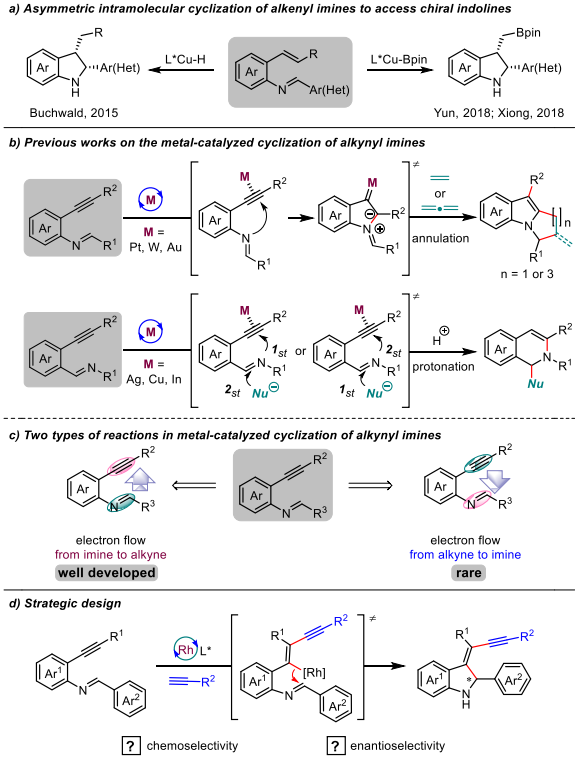
ABSTRACT: The first asymmetric synthesis of 3-methyleneindolines from alkynyl imines has been developed via a rhodium-catalyzed tandem process: regioselective alkynylation of the internal alkynes and subsequent intramolecular addition to the imines. The reaction proceeded with unconventional chemoselectivity and provided 3-methyleneindolines with good yields (up to 82% yield) and high enantioselectivities (up to 97% ee). Moreover, this transformation also features mild reaction conditions, perfect atom economy, and a broad substrate scope.



Chiral indoline scaffolds are found in numerous biologically active molecules and have a broad application in pharmaceutical chemistry. As a result, many asymmetric synthetic approaches have been developed to generate such ring systems.[1] Among them, transition-metal-catalyzed intramolecular tandem cyclization of unsaturated hydrocarbons and imines is an efficient way to access the substituted chiral indoline. In 2015, Buchwald et al. reported the first copper-catalyzed asymmetric cyclization of alkenyl imines to construct 2,3-disubstituted indolines via enantioselective Cu−H addition to aryl olefins and subsequent nucleophilic addition of in situ generated organocopper to imines (Scheme 1a).[2] In 2018, Yun and Xiong reported independently the copper-catalyzed intramolecular borylative cyclization of alkenyl imines for the synthesis of enantioenriched boron-containing 2,3-disubstituted indolines (Scheme 1a).[3] However, a study in which alkynyl imines were applied to catalytically synthesize chiral indolines has not been disclosed so far.[4] There are mainly two types of reactions in the metal-catalyzed cyclization of alkynyl imines (Scheme 1b): (1) the nucleophilic *endo*-attack of nitrogen of *N*-(*o*-alkynylaryl)imines to an *o*-alkynyl group to form the metal-bound azomethine ylides and then cycloaddition with electron-rich alkenes or *N*-allenamides to give the corresponding polycyclic indole derivatives;[5] (2) the nucleophilic *endo*-attack of nitrogen of aryl aldimines to an *o*-alkynyl group to form electropositive imine intermediates that were subsequently tripped by nucleophiles to afford dihydroisoquinolines or the imine group undergoes nucleophilic addition first to form electronegative amino intermediates, which were then trapped by alkynyl.[6] Under both of the reaction platforms of metal-catalyzed cyclization of alkynyl imines, the electrons all transferred from imines to alkynes in the tandem process, and the reaction in which the electrons flow from alkynes to imines is rare (Scheme 1c).[7] As a part of

Scheme 1. Previous Works and Reaction Design



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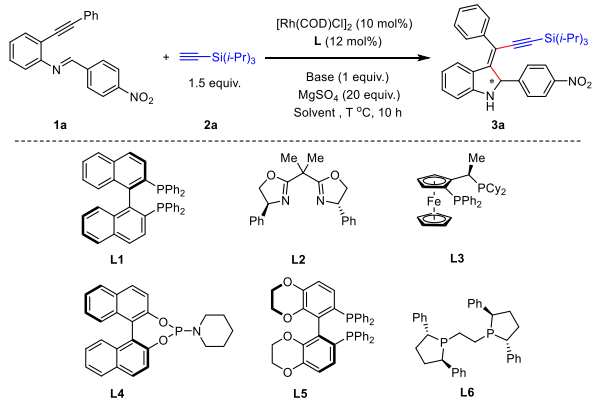
our continuous efforts on the addition reactions of imines and unsaturated imines,[8] we envisioned that the opposite chemoselectivity, i.e., the organometal species reacted with alkynes first rather than imines, might be realized under a carefully optimized asymmetric reaction system.

The carbon−carbon triple bond is a versatile functional group that has abundant derivatization possibilities.[9] The transition-metal-catalyzed hydroalkynylation of internal alkynes with terminal alkynes has been extensively studied for its perfect atom economy in the synthesis of functionalized alkynes.[10] Due to the wealth of carbo- and heterocycles in natural products, it is of great importance to develop efficient asymmetric annulation protocols; however, the synthesis of enantioenriched heterocycles via transition-metal-catalyzed alkynylative tandem reactions of alkynes is quite limited.[11] Consequently, we proposed the rhodium-catalyzed enantioselective alkynylative cyclization of *N*-(*o*-alkynylaryl)imines, even though several challenges were encountered in this process (Scheme 1d). The first issue is the unconventional chemoselectivity: the rhodium acetylide complex should undergo cross addition with aryl alkynes rather than imines. The second issue is the enantioselectivity: a suitable catalytic system should be found to effectively distinguish the prochiral imines during the intramolecular addition of alkenyl rhodium. If successful, this could be an efficient path to the construction of enantioenriched 3-methyleneindolines.[12]

With these considerations in mind, we initiated our investigation by searching for a suitable chiral ligand for the alkynylative cyclization reaction of alkynyl imine **1a** and (triisopropylsilyl)acetylene **2a** using $[Rh(COD)Cl]_2$ as the catalyst and $MgSO_4$ as the additive to prevent hydrolysis of the imine substrates. A screening of frequently used ligands (**L1**−**L4**) indicated that the efficiency was extremely low for our desired reaction (Table 1, entries 1−4), and the major side product was the N-substituted indole **3a′** derived from the opposite chemoselectivity. (*S*)-SYNPHOS (**L5**) could promote this transition with a higher yield but showed almost no enantioselectivity (entry 5). To our delight, the desired product **3a** was obtained with a much higher yield and moderate enantioselectivity when (*R*,*R*)-Ph-BPE (**L6**) was applied as the chiral ligand (entry 6). Then, we examined the solvent effects and found that tetrahydrofuran was privileged in the promotion of both reactivity and enantioselectivity (71% yield, 77% ee, entry 7). After evaluation of a series of bases, Cs_2CO_3 was proved to be vital to this transformation; other bases such as its homologue K_2CO_3 only led to 14% yield and 27% ee (entry 8). This finding suggested that the cesium ion may play a role in the enantioselective addition step via coordination with imine. Decreasing the reaction temperature resulted in an enhancement of enantioselectivities but a large erosion of the yields (entries 9−11). Applying 1.5 equiv of Cs_2CO_3 gave an improved yield to 60% (entry 12). Notably, in the absence of $MgSO_4$, the reaction was obviously inhibited to give 8% yield (entry 13), and the addition of 4 Å molecular sieve led no reaction as well (entry 14). These results indicated that $MgSO_4$ played an important role in the cascade reaction indeed, but not the initially supposed role of dehydration. We suspected that a trace amount of hydrate water in the $MgSO_4$ may accelerate the reaction, so 20 equiv water was applied instead of $MgSO_4$. Gratifyingly, the addition of free water significantly promoted the reactivity and afforded the product **3a** with satisfactory yield and enantioselectivity (83% yield and 91% ee, entry 15). However, applying a stoichiometric amount of water to the model reaction only led to 27% NMR yield, which indicates that the equivalent of water has an important influence on the reaction.

Table 1. Optimization of the Reaction Conditions



entry[a]	L	solvent	T (°C)	conv[b] (%)	yield[b] (%)	ee[c] (%)
1	**L1**	1,4-dioxane	60	76	15	27
2	**L2**	1,4-dioxane	60	56	13	24
3	**L3**	1,4-dioxane	60	35	6	22
4	**L4**	1,4-dioxane	60	55	19	5
5	**L5**	1,4-dioxane	60	77	47	2
6	**L6**	1,4-dioxane	60	100	62	50
7	**L6**	THF	60	100	71	77
8[d]	**L6**	THF	60	45	14	27
9	**L6**	THF	40	92	61	82
10	**L6**	THF	30	87	56	83
11	**L6**	THF	25	53	24	86
12[e]	**L6**	THF	30	85	60	88
13[f]	**L6**	THF	30	18	8	
14[g]	**L6**	THF	30	<5		
15[h]	**L6**	THF	30	100	83	91
16[i]	**L6**	THF	30	38	27	

[a]Reactions were performed under an Ar atmosphere. [b]Determined by ^{1}H NMR analysis of unpurified mixtures. [c]Determined by HPLC analysis. [d]K_2CO_3 was applied instead of Cs_2CO_3. [e]1.5 equiv of Cs_2CO_3 was used. [f]Mg_2SO_4 was not added. [g]50 mg of 4 Å MS was applied instead of Mg_2SO_4. [h]20 equiv of H_2O was applied instead of Mg_2SO_4. [i]1 equiv of H_2O was applied instead of Mg_2SO_4.

With the optimal reaction conditions established, the scope of the *N*-(*o*-alkynylaryl)imines **1** was examined (Scheme 2). We found that substrates derived from various aryl aldehydes worked well in this reaction. The para-substituted and meta-substituted phenyl substrates, including those with electron-deficient substituents (NO_2, F, Cl, Br) as well as electron-rich substituents (Me, CH_2Cl, Ph), were all converted smoothly into the corresponding chiral indolines with moderate to good yields and high ee values (52−80% yield, 77−92% ee, **3a**−**3i**). Pyridine-substituted alkynyl imine also gave the desired cyclization product **3j**, albeit with slightly lower ee value (76% ee). A variety of substrates bearing electron-withdrawing and electron-donating groups at the 4/5-position of the aryl nucleus of *N*-(*o*-alkynylaryl)imines underwent the reaction with high efficiency (62−82% yield, 82−94% ee, **3k**−**3o**). As for the alkynyl motif in the alkynyl imines, the substrate with an electron-donating group (Me) at the 4-position of phenylacetylene reacted smoothly under the standard conditions to afford the corresponding chiral indoline with 67% yield and 86% ee (**3r**). However, substrate with an electron-

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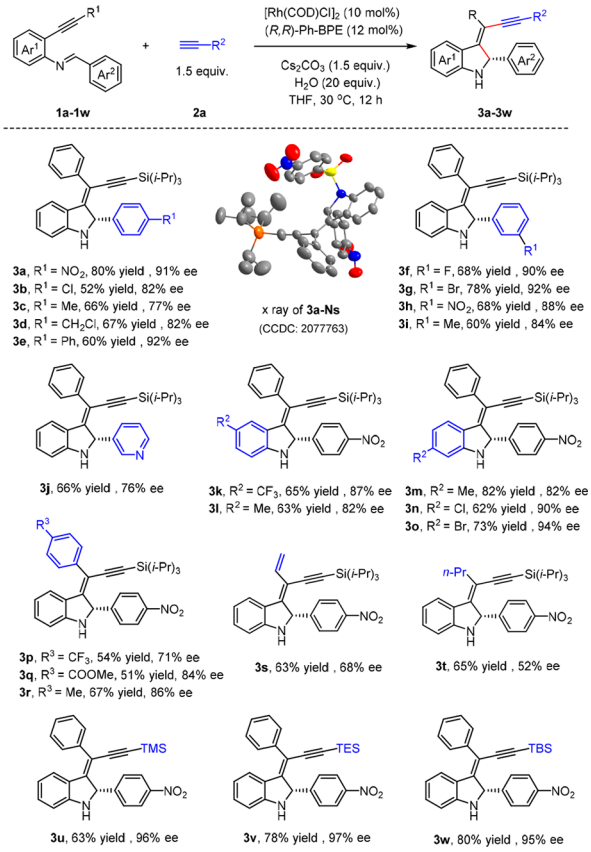
Scheme 2. Substrate Scope of *N*-(*o*-Alkynylaryl)imines[a]

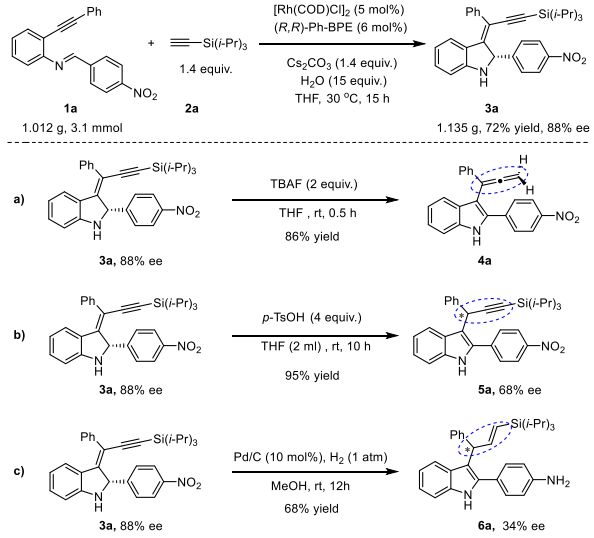


[a]Reaction conditions: **1** (0.10 mmol), **2a** (1.5 equiv), $[Rh(COD)Cl]_2$ (10 mol %), Cs_2CO_3 (1.5 equiv), H_2O (20 equiv), and (*R*,*R*)-Ph-BPE (12 mol %) in THF (2 mL) at 30 °C under Ar for 12 h. The yield refers to isolated yield. The ee value was determined by HPLC.

withdrawing group such as CF_3 at the 4-position of phenylacetylene only led to the product with 54% yield and 71% ee (**3r**), presumably due to the decreased nucleophilic reactivity of the alkenyl rhodium. In addition, the enyne substrate was also suitable for this transition and gave the cyclization product **3s** in 63% yield and 68% ee. Alkyl alkyne derived alkynyl imine substrate had enough reactivity in this transformation, but the stereocontrol was somewhat inefficient (65% yield, 52% ee, **3t**). Next, we studied the alkynylation reagent scope. Various silyl acetylenes such as (trimethylsilyl)-acetylene, (triethylsilyl)acetylene, and (*tert*-butyldimethylsilyl)-acetylene provided the corresponding products with high yields and excellent ee values (63−80% yield, 95−97% ee, **3u**−**3w**). Phenylacetylene was not suitable for this reaction, and the corresponding product was not detected at all. The absolute configuration of the cyclization product **3a** was unequivocally established as (2*S*)-**3a** by X-ray crystallography analysis of its derivative **3a-Ns**.

To demonstrate the synthetic applicability of this method, a gram-scale reaction of **1a** was carried out with only 5.0 mol % catalyst loading, and the enantioenriched 3-methyleneindoline **3a** was isolated with 72% yield and 88% ee (Scheme 3). Under general desilication conditions, the desired terminal-alkyne-contained indoline could not be obtained, and 3-allenylindole **4a** was afforded with 86% yield instead, probably due to the acidity of the proton in the stereocenter and the intense tendency of aromatization.[10b] Taking advantage of the

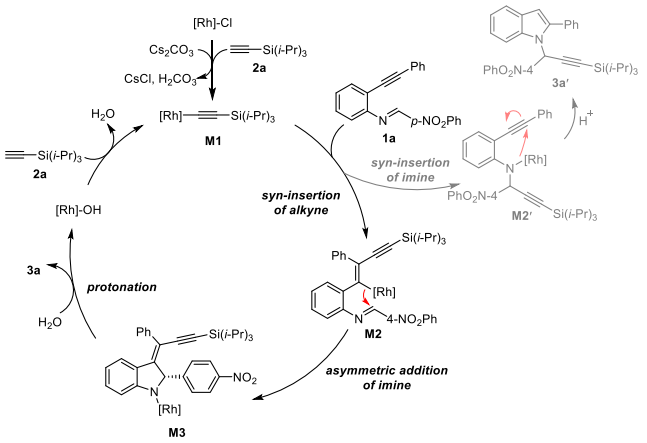
Scheme 3. Gram-Scale Reaction and Synthetic Transformations



aromatization proneness, 3-methyleneindoline **3a** was readily transformed into 3-propargylindole **5a** with diminished ee value (95% yield, 68% ee) in the presence of *p*-TsOH. The unexpected 3-allylindole **6a** could be obtained via selective reduction and isomerization under Pd/C hydrogenation conditions, but unfortunately, the enantioselectivity in the process could not be maintained (68% yield, 34% ee). The isomerization was likely via an allyl-Pd intermediate, which corresponded to the presumption of the acidity of the proton in the stereocenter.

Based on the investigation of the importance of water and cesium carbonate (Table 1, entries 13−16) and literature studies,[11b] a possible catalytic cycle of this protocol was proposed (Scheme 4). First, the catalytic active **Rh(I)**−

Scheme 4. Proposed Catalytic Cycle



acetylide complex **M1** was obtained from Rh precatalyst and **2a** under basic reaction conditions. Subsequently, **M1** reacted with internal alkyne of the substrate via *syn*-insertion to afford vinyl rhodium intermediate **M2**, which could be trapped by the prochiral imine through asymmetric addition to provide the N−Rh(I) complex **M3**. The cesium ion might act as a Lewis acid to coordinate with imine to accelerate the cyclization reaction and take part in the stereocontrol.[13] Finally, the **M3**

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reacted with water to give the indoline product **3a** and the intermediate hydroxy rhodium, which could regenerate the active **Rh(I)**−acetylide complex **M1** via σ-metathesis with terminal alkyne **2a**. Two points need to be noted in the transition: On one hand, applying other chiral ligands such as **L1**−**L4**, the **Rh(I)**-acetylide complex **M1** may reacted with imine first to afford the intermediate **M2′**, which led to the side product **3a′**. On the other hand, the water might play two roles in the reaction: (1) it reacted with N-metalated intermediates to give the indoline products and hydroxy rhodium (2) it reacted as cosolvent to make Cs_2CO_3 dissolved to accelerate the reaction.

In conclusion, we have developed the first Rh-catalyzed asymmetric alkynylative cyclization of *N*-(*o*-alkynylaryl)imines and enabled highly enantioselective synthesis of 3-methylideneindolines. Compared with previous metal-catalyzed annulation reactions of alkynyl imines, this reaction was accelerated by free water and proceeded with an unconventional chemoselectivity. In addition, this tandem process featured 100% atom economy, broad functional group tolerance, and versatile derivation of product. Further mechanism study and investigation of metal-catalyzed asymmetric cyclization of alkynyl imines are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01518.

Experimental procedures; ^{1}H NMR and ^{13}C NMR spectra; HPLC spectra; X-ray crystallographic data (PDF)

Accession Codes

CCDC 2077763 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.

■ AUTHOR INFORMATION

Corresponding Authors

Cheng-Yu He − *Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province, College of Chemistry and Chemical Engineering, China West Normal University, Nanchong 637002, China;* orcid.org/0000-0003-3426-279X; Email: hecy@cwnu.edu.cn

Wen-Dao Chu − *Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province, College of Chemistry and Chemical Engineering, China West Normal University, Nanchong 637002, China;* orcid.org/0000-0003-0058-2461; Email: chuwendaonpo@126.com

Quan-Zhong Liu − *Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province, College of Chemistry and Chemical Engineering, China West Normal University, Nanchong 637002, China*; Email: quanzhongliu@cwnu.edu.cn

Authors

Shi-Yi Yuan − *Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province, College of Chemistry and Chemical Engineering, China West Normal University, Nanchong 637002, China*

Qi-Qi Yan − *Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province, College of Chemistry and Chemical Engineering, China West Normal University, Nanchong 637002, China*

Dan Wang − *Chengdu Institute of Product Quality Inspection Co., Ltd., Chengdu 610000, China*

Ting-Ting Dan − *Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province, College of Chemistry and Chemical Engineering, China West Normal University, Nanchong 637002, China*

Long He − *College of Chemistry and Materials Engineering, Guiyang University, Guiyang 550005, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01518

Notes

The authors declare no competing financial interest.

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