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Enantioselective Construction of Functionalized Tetrahydrocarbazoles Enabled by Asymmetric Relay Catalysis of Gold Complex and Chiral Brønsted Acid

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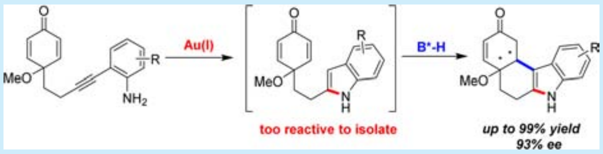
Supporting Information

ABSTRACT: An intramolecular hydroamination/Michael addition cascade is realized using a combination of gold(I) complex and chiral BINOL–phosphoric acid, affording fused-tetrahydrocarbazole scaffolds in excellent yields and high enantioselectivities.



Chiral tetrahydrocarbazoles (THCs) have been recognized as very important structural motifs due to their frequent occurrence in a variety of natural products and pharmacologically active compounds, and many of their synthetic analogues often exhibit potential biological activities (Figure 1).[1] For instance, (−)-alloaristoteline and (+)-aristoteline are two natural alkaloids existing in *Aristotelia chilensis* leaves that are used in Chilean folk medicine to treat pain and inflammation;[1a,d] ambiguine indole alkaloid fischambiguine B displays strong inhibitory activity against *Mycobacterium tuberculosis*;[1c] and alstilobanine A has been reported to possess modest relaxant activity against phenylephrine-induced contractions of thoracic rat aortic rings with endothelium.[1f] The medicinal relevance of THCs has pushed forward the rapid development of synthetic methods to construct such chiral scaffolds.

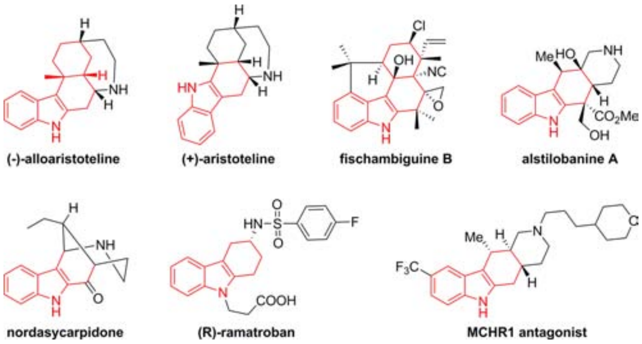
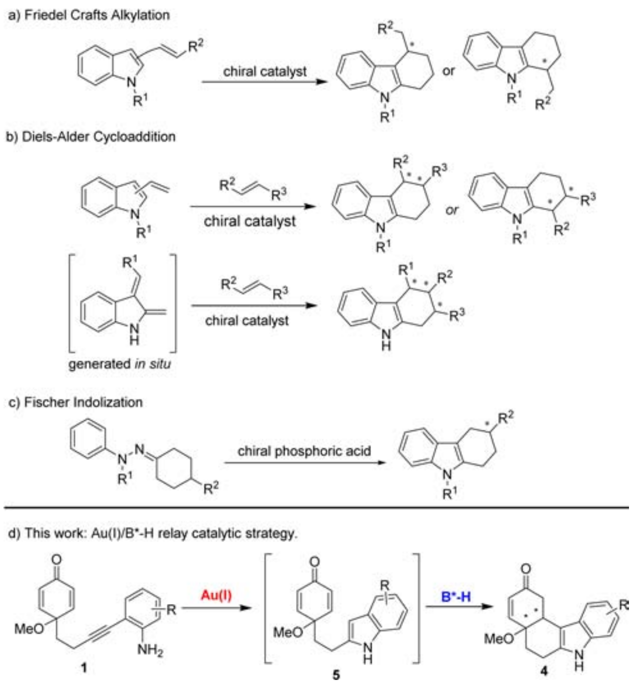


Figure 1. Selected examples of compounds containing tetrahydrocarbazole motifs.

Over the past decades, catalytic asymmetric approaches for the synthesis of optically active THCs have been well developed, rendering it possible to access these important compounds from a variety of readily available starting materials.[2−5] In these endeavors, the catalytic intramolecular Friedel–Crafts-type alkylation of alkenylindoles has proven to be a preeminent strategy for THC synthesis (Scheme 1a).[2] These methods include intramolecular hydroarylations of indole-substituted alkenes, allenes or α,β-unsaturated aldehydes catalyzed by chiral scandium(III),[2b] platinum(II),[2a,d,f] and gold(I)[2c,e,g] complexes and organocatalysts,[2h] respectively. In addition, the catalytic stereoselective Diels–Alder reactions

Scheme 1. Asymmetric Catalytic Approaches to Chiral THCs



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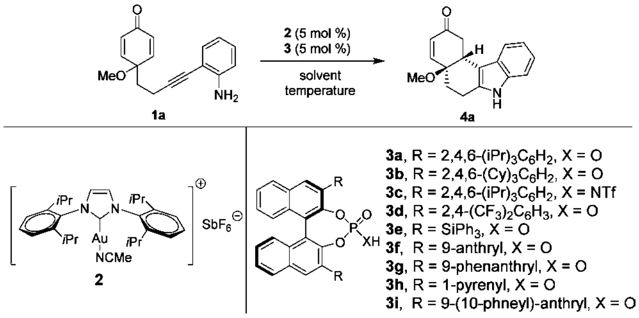
have also provided a number of efficient and straightforward protocols by using 2-vinylindoles,[3b,c,i] 3-vinylindoles,[3a,e,h] or heterocyclic *o*-quinodimethanes generated in situ[3d,f,g] acting as diene substrates (Scheme 1b). Recently, List and co-workers established catalytic asymmetric Fischer indolizations, generating 3-substituted chiral THCs in high yields and excellent levels of enantioselectivities (Scheme 1c).[4] Cascade processes with properly designed indole derivatives as substrates have also provided successful approaches to THCs with high optical purity.[5] Obviously, the known methods to access tetrahydrocarbazole motifs are mostly performed by employing substituted indoles as substrates, which are normally prepared via stepwise procedures. Instead, asymmetric Fischer indolization opened up a unique strategy for constructing chiral THCs, adopting phenylhydrazones as substrates. Therefore, the development of alternative transformations to optically pure THCs from more extensive starting materials is still challenging and highly desirable.

Recently, gold/chiral Brønsted acid[6] relay catalysis has evolved into a general strategy, allowing for the creation of a large number of transformations,[7a−h] and thus been recognized as a robust tool for building up molecular and stereochemical complexity.[7,8] With a proper substrate design, we envisioned that this catalytic system might also contribute to the construction of chiral THCs (Scheme 1d). Substituted 2-ethynylanilines **1** were selected as substrates, which can be easily prepared through Sonogashira coupling. The relay catalytic process consists of a gold-catalyzed indole-formation step and subsequent intramolecular cyclization to give tetracyclic compounds **4** with two adjacent stereocenters in one operation.

The initial investigation of the proposed strategy was performed with 2-ethynylaniline derivative **1a** in the presence of a combined catalyst system consisting of an achiral gold complex **2** (5 mol %) and a chiral phosphoric acid **3a** (5 mol %) in DCE at 25 °C. The transformation proceeded smoothly and afforded polycyclic compound **4a** quantitatively (>99% yield) with moderate enantioselectivity (45% ee, Table 1, entry 1). Later on, various structurally diverse chiral phosphoric acids **3a**−**i** were evaluated to identify the best orgnaocatalyst (entry 1−9). Among them, the phosphoric acid **3f** bearing planar anthryl substituents at 3,3′-positions turned out to be the preeminent catalyst and was able to provide the tetracycle **4a** quantitatively with 74% ee (entry 6). Further decreasing or increasing the size of the plannar substituents was not able to improve the enantioselectivity (entries 7−9). A survey of solvents showed that medium polar solvents (i.e., halogenated hydrocarbons) were beneficial for the stereocontrol and DCE proved to be the optimal one (entry 10−16). With a prolonged reaction time, the reaction could be performed at 0 °C, giving quantitative yield and slightly increased stereoselectivity (entry 17). The enantioselectivity was finally improved to 80% ee in the presence of 5 mol % of IPrAu(MeCN)SbF_6 **2** and 10 mol % of **3f** at −30 °C (entry 18).

Table 1. Optimization of Catalysts and Reaction Conditions[a]



3a, R = 2,4,6-$(iPr)_3C_6H_2$, X = O
3b, R = 2,4,6-$(Cy)_3C_6H_2$, X = O
3c, R = 2,4,6-$(iPr)_3C_6H_2$, X = NTf
3d, R = 2,4-$(CF_3)_2C_6H_3$, X = O
3e, R = $SiPh_3$, X = O
3f, R = 9-anthryl, X = O
3g, R = 9-phenanthryl, X = O
3h, R = 1-pyrenyl, X = O
3i, R = 9-(10-phneyl)-anthryl, X = O

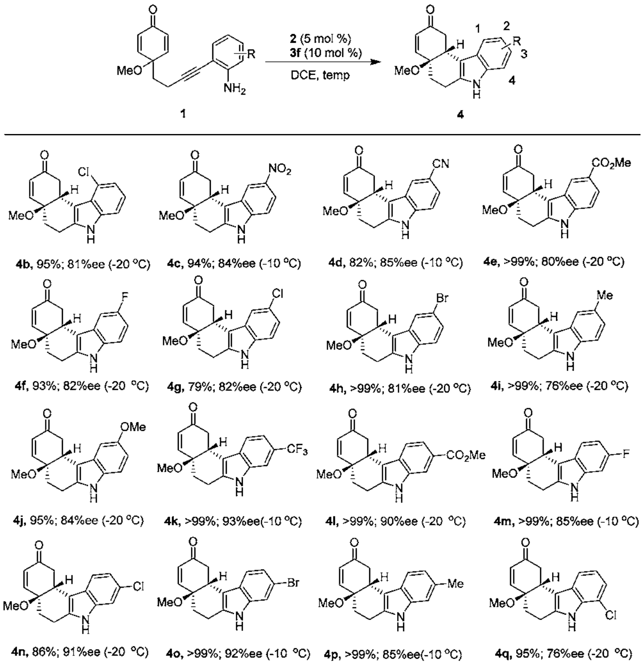
entry	3	solv	temp (°C)	yield[b] (%)	ee[c] (%)
1	**3a**	DCE	25	>99	45
2	**3b**	DCE	25	94	48
3	**3c**	DCE	25	>99	3
4	**3d**	DCE	25	97	46
5	**3e**,	DCE	25	>99	47
6	**3f**	DCE	25	>99	74
7	**3g**	DCE	25	98	57
8	**3h**	DCE	25	77	54
9	**3i**	DCE	25	>99	56
10	**3f**	benzene	25	95	68
11	**3f**	toluene	25	83	65
12	**3f**	MeCN	25	91	68
13	**3f**	DCM	25	83	72
14	**3f**	$CHCl_3$	25	93	66
15	**3f**	dioxane	25	98	61
16	**3f**	$MeNO_2$	25	>99	67
17[d]	**3f**	DCE	0	>99	75
18[d,e]	**3f**	DCE	−30	>99	80

[a] Unless indicated otherwise, all reactions were carried out for 12 h at 0.05 M concentration. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The reaction time was 4 days. [e] 10 mol % of **3** was used.

With the optimized reaction conditions in hand, the generality of the protocol for different substituted substrates was investigated (Table 2). All substrates underwent clean reactions to afford the corresponding products **4b**−**q** in high yields (79 to >99% yield) and with moderate to excellent enantioselectivities (76−93% ee). As most substituted substrates showed lower reactivity than **1a**, an increased temperature was required to allow the reactions to be finished within an acceptable reaction time. Notably, the position of the substituent on the benzene ring exhibited significant effect on the enantioselectivity. For instance, substrates with a substituent at the 3-position gave higher enantioselectivities than those with one at other positions (**4n** vs **4b**, **4g**, **4q; 4l** vs **4e**; **4p** vs **4i** and **4o** vs **4h**). The electron effect of the substituents varied depending on their positions. The electron-withdrawing substituent at the 2-position had a positive effect on the enantioselectivities (**4c**−**j**), while substituents at the 3-position showed an ambiguous influence (**4k**−**p**). The absolute configuration of **4o** was determined by X-ray crystallographic analysis (see the Supporting Information for details).

To better understand the mechanism of this relay catalytic process, the reaction of **1a** in the presence **2** and **3f** in $CDCl_3$ at room temperature was monitored by ^1H NMR spectroscopy. As shown in Figure 2, a broad singlet at 8.06 ppm was observed when the reaction began. As the reaction proceeded forward, the signal of H_a decayed with the concomitant appearance of H_b and H_c from the final product **4a**. This indicates that H_a probably belongs to the key intermediate of this reaction. The chemical shift and splitting pattern of H_a are consistent with N−H from the indole ring of compound **5a**. This confirmed our proposed reaction pathway as shown in Scheme 2. It is noteworthy that intermediate **5a** cannot be isolated due to its high reactivity to transform into the final product. It could undergo a background reaction to form racemic product or a chiral phosphoric acid-catalyzed process leading to optically

Table 2. Substrate Scope[a]



4b, 95%; 81%ee (-20 °C)
4c, 94%; 84%ee (-10 °C)
4d, 82%; 85%ee (-10 °C)
4e, >99%; 80%ee (-20 °C)
4f, 93%; 82%ee (-20 °C)
4g, 79%; 82%ee (-20 °C)
4h, >99%; 81%ee (-20 °C)
4i, >99%; 76%ee (-20 °C)
4j, 95%; 84%ee (-20 °C)
4k, >99%; 93%ee(-10 °C)
4l, >99%; 90%ee (-20 °C)
4m, >99%; 85%ee (-10 °C)
4n, 86%; 91%ee (-20 °C)
4o, >99%; 92%ee (-10 °C)
4p, >99%; 85%ee(-10 °C)
4q, 95%; 76%ee (-20 °C)

[a] All reactions were carried out at 0.05 M concentration until full conversion of **1** (4–7 d).

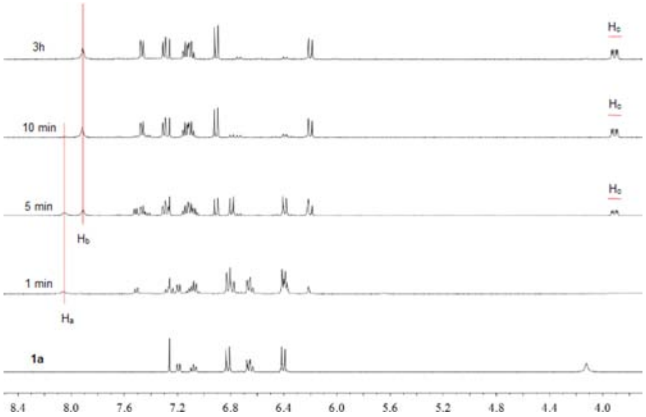
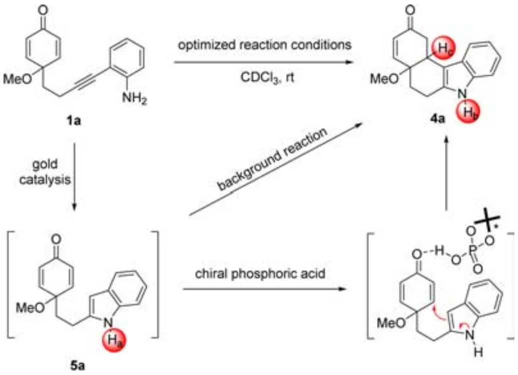


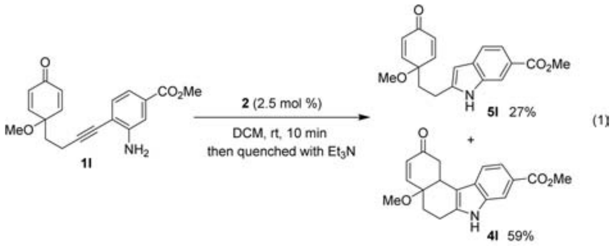
Figure 2. Monitoring of intermediates by ^{1}H NMR spectroscopy.

Scheme 2. Proposed Mechanism for the Tandem Reaction

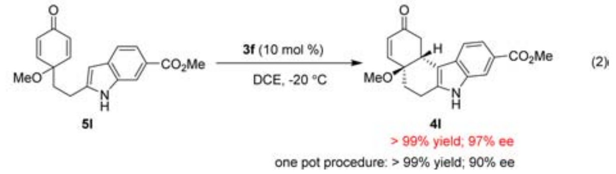


active **4a**. This means conventional asymmetric Friedel–Crafts alkylation from substrate **5a** to construct **4a** is probably infeasible, and on the other hand, it can be easily realized by the relay catalytic strategy described here.

While intermediate **5a** was difficult to isolate, compound **5l**, bearing a more electron-deficient indole motif and thus being less reactive for the intramolecular Michael addition, was successfully isolated (eq 1). Compound **5l** was then applied for the chiral phosphoric acid catalyzed asymmetric Friedel–Crafts reaction. As anticipated, this reaction provided the desired product **4l** with quantitative yield and higher enantioselectivity (97% ee), further confirming the existence of background reaction (eq 2).



(1)



> 99% yield; 97% ee
one pot procedure: > 99% yield; 90% ee

(2)

In summary, we have disclosed an intramolecular hydroamination/Michael addition cascade enabled by gold(I) complex/chiral phosphoric acid relay catalysis leading to chiral tetrahydrocarbazoles bearing two adjacent stereocenters with excellent yields and high enantioselectivities. This strategy provided a novel and efficient alternative to known methods to access highly enantioenriched THCs and holds great potential for applications in the synthesis of polycyclic 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.6b00012.

Complete description of methods and additional results; spectroscopic data for all new compounds; synthesis procedures for substrates (PDF)
X-ray crystal data for **4o** (CIF)

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Notes

The authors declare no competing financial interest.

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