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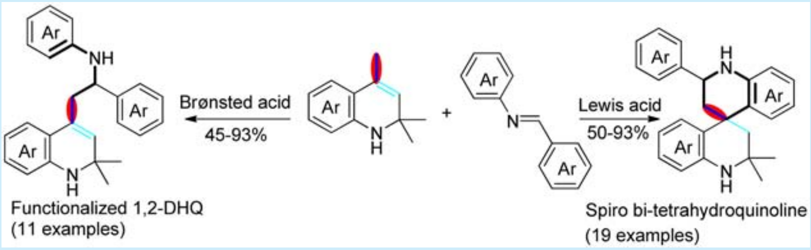
Step-Controlled Povarov-Type Reaction with 1,2-Dihydroquinolines as Precursors of Dienophiles: Direct Synthesis of Spirocyclic Bi-tetrahydroquinolines and Functionalized 1,2-Dihydroquinolines

Xuwen Ren,[†] Guangxun Li,*[,‡] Jin Huang,[‡] Weidong Wang,[†] Yongpo Zhang,[†] Guomin Xing,[†] Chunyan Gao,[†] Gang Zhao,[§] Jinzhong Zhao,*[,†] and Zhuo Tang*[,‡]

[†]College of Art and Sciences, Shanxi Agricultural University Taigu, Shanxi 030800, China
[‡]Natural Product Research Center, Chengdu Institution of Biology, Chinese Academy of Science, Chengdu, Sichuan 610041, China
[§]College of Chemical Engineering, Sichuan University, Chengdu, Sichuan 610041, China

Supporting Information



ABSTRACT: A novel Povarov-type reaction for straightforward synthesis of novel spiro bi-tetrahydroquinolines with readily available 1,2-DHQs (1,2-dihydroquinolines) and aromatic imines was developed. The reaction could be selectively stopped at the first stage under a Brønsted acid catalyst to afford the corresponding functionalized 1,2-DHQs conveniently.

The heterocyclic spiro compounds represent an important structure unit found in many bioactive natural products and synthetic drugs. The unique three-dimensional orientation of the spirocycle is different from the aromatic flatland often encountered in many drug development programs,[1] and as a consequence, this structure has attracted the attention of both medicinal chemists and synthetic chemists for its potential as an important pharmacophore.[2] Among these skeletons, a unique class of spiro piperidine-4,4′-quinoline compounds is well-known in natural products such as lanceomigine[3] or in medicinal chemistry such as for treatment of migraines[4] and schizophrenia[5] (Figure 1). However, to the best of our knowledge, the existing methods for obtaining such compounds are tedious, with long synthetic approaches and low yields.

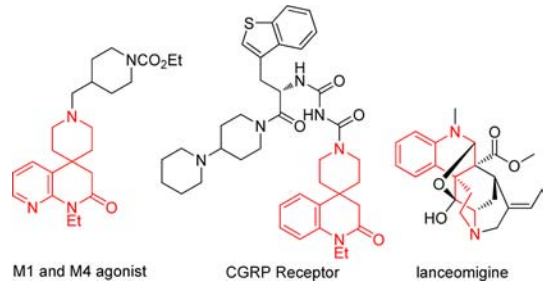
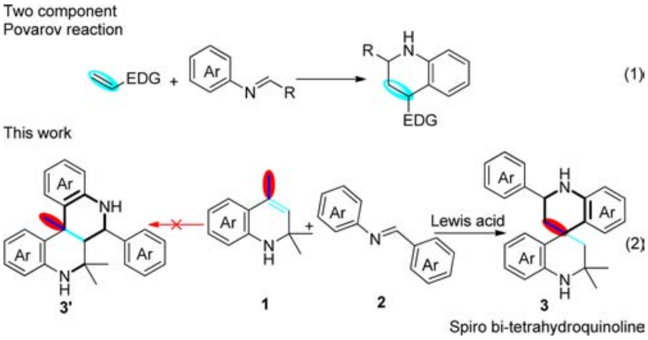


Figure 1. Bioactive spiro-tetrahydroquinolines.

The Povarov reaction is usually promoted by either Brønsted acid or Lewis acid catalysis and can be performed in a multicomponent fashion by the coupling of alkenes, aldehydes, and anilines via the in situ imine formation and subsequent formal [4 + 2]-cycloaddition.[6] The formal [4 + 2]-cycloaddition can be viewed as occurring either through a concerted inverse-electron-demand Diels−Alder reaction mechanism or via a stepwise Mannich-like reaction/intramolecular electrophilic aromatic substitution sequence[7] (Scheme 1, eq 1).

Scheme 1. Variants of the Povarov Reaction



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On one hand, a wide variety of anilines and aldehydes are known to participate in the Povarov reaction. Meanwhile, numerous variants of Povarov reactions focused on the investigation of the use of 2-azadienes such as the ketone-involved Povarov reactions,[8] *N*-arylamines,[9] or *N*-alkylanilines[10] as the precursor of 2-azadienes with different oxidation reagents, and the use of aryl methyl ketones as the precursor of aldehyde under oxidation conditions[11] and oxa-Povarov reaction[12] have been extensively investigated and well-developed in recent years. On the other hand, the use of simple alkenes as dienophiles has met with limited success in the Povarov reaction, which is generally limited to activated, electron-rich alkenes[13] such as cyclic and acyclic enamines,[14] enamides[15] and enol ethers,[16] cyclic conjugated dienes,[17] and activated strained alkenes.[18] Therefore, investigation and development of more Povarov-type reactions with special dienophiles[19] or precursors of dienophiles are important and significant.

Recently, our group reported an efficient way of forming the aza-*o*-xylylene (AOX) by protonation of the double bond of 1,2-DHQ with a catalytic Brønsted acid.[20] The resulting AOX could be efficiently transformed with Hantzsch ester or indoles to the corresponding tetrahydroquinolines (THQs) with high yields and enantioselectivities. Continuing our research toward the postfunctionalization *N*-heterocycles, we envisioned that the electron-rich double bond of 1,2-DHQ could easily react as the traditional Povarov reaction to afford the corresponding *N*-heterocycle **3′** (Scheme 1, eq 2). On the contrary, the resulting product was spiro bi-tetrahydroquinoline **3** with excellent diastereoselectivity (>99:1). The component incorporated in the reaction product was the methyl group rather than the double bond. As part of our continuing efforts for the postfunctionalization of *N*-heterocycles and our interest in the straightforward synthesis of spirocycles, herein we developed a novel Povarov reaction for the fast synthesis of novel spiro bi-tetrahydroquinolines **3** under mild reaction conditions.

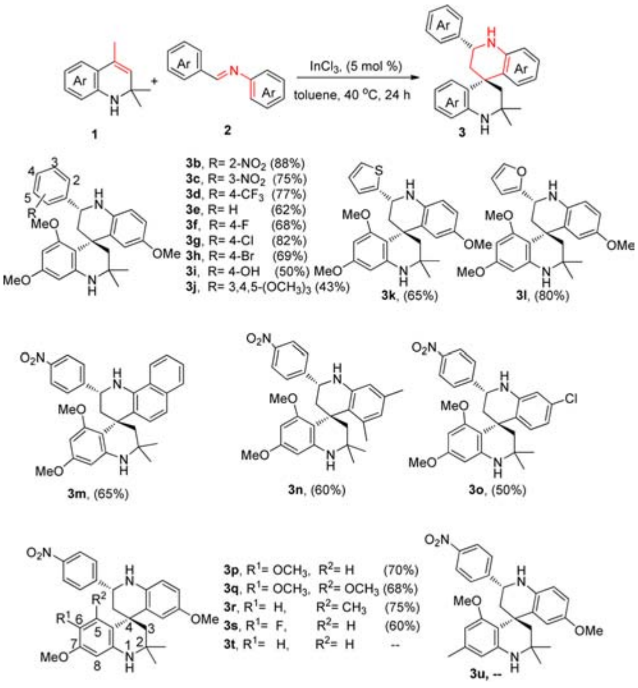
Initially, the reaction between 1,2-DHQ **1a** and aromatic imine **2a** was chosen as a model reaction, and several Lewis acid metal catalysts and solvent were tested (Table 1). Under the Brønsted acid catalyst at low temperature, the reaction stopped at the first stage of the Povarov reaction with the reaction intermediate **4a** exclusively (Table 1, entry 1). After the reaction temperature was increased to 90 °C, the spirocycle **3a** was obtained in 78% yield accompanied by 15% **4a** (Table 1, entry 1). We then turned to screen different Lewis acids such as $MgBr_2$, $AlCl_3$, $InCl_3$, etc. The results revealed that Lewis acid could efficiently catalyze the reaction under mild conditions to afford spirocycle **3a** with high yield (Table 1, entries 3–9). Moreover, $InCl_3$ was more efficient compared with other metal salts. Further screening of the reaction solvent and the reaction temperature revealed that the yield of **3a** could be increased to 93% with toluene as solvent at 40 °C. However, the reaction yield decreased to 82% at high temperature with some unknown decomposition species (Table 1, entry 13). Finally, the catalyst loading could decreased to 5 mol % without sacrificing the reaction yield (Table 1, entry 14).

Table 1. Screening of Reaction Conditions for THQ 3a[a]

entry	cat. (10 mol %)	solvent	temp (°C)	yield[b] (%) 3a	4a
1	TsOH	toluene	25		85
2	TsOH	toluene	90	78	15
3	$MgBr_2$	toluene	25	60	20
4	$AlCl_3$	toluene	25	86	<5
5	$InCl_3$	toluene	25	88	<5
6	$In(OTf)_3$	toluene	25	85	
7	$Cu(OTf)_2$	toluene	25	82	
8	$Yb(OTf)_3$	toluene	25	87	
9	$Sc(OTf)_3$	toluene	25	84	
10	$InCl_3$	CH_2Cl_2	25	85	
11	$InCl_3$	$CHCl_3$	25	87	
12	$InCl_3$	toluene	40	93	
13	$InCl_3$	toluene	60	82	
14[c]	$InCl_3$	toluene	40	93	

[a]Reactions were run with 0.2 mmol of 1,2-DHQ **1a**, 0.2 mmol of imine **2a**, and 2 mL of solvent under nitrogen atmosphere with the corresponding reaction conditions for 18 h. [b]The yield was calculated after purification with silica column. [c]0.01 mmol of $InCl_3$ was used.

Scheme 2. Substrate Scope for Obtaining Spiro Bi-tetrahydroquinole 3



Having identified the optimal reaction conditions ($InCl_3$ as catalyst at 40 °C in toluene), the reaction substrates were screened from the following two parts: the aromatic imines and the 1,2-DHQs (Scheme 2). Therefore, many aromatic imines formed with different aromatic aldehydes and *p*-anisidine were screened under the optimal conditions. Generally, imines formed with electron-deficient aromatic aldehyde could afford the corresponding product with higher yield (**3b–d**). Imines formed with benzyl aldehyde or halogen-substituted benzyl aldehyde gave the corresponding product with moderate yield (**3e–h**). Electron-donating groups such as hydroxy- or methoxy-substituted aromatic imines gave the corresponding product with slightly lower yield (**3i,j**). Interestingly, heterocyclic imines afford the corresponding product smoothly under the reaction condition, (**3k,l**). Meanwhile, the amine part of the imines was also investigated (**3m,n**). Imines formed with electron-rich aromatic amines could react to afford the corresponding product (**3m,n**), while imines formed from electron-deficient aromatic amines could not afford the corresponding product (4-NO_2 or 4-CF_3 benzyl amine, data not shown). Interestingly, imines formed with chlorobenzylamine could react to afford the corresponding product **3o**.

On the other hand, the 1,2-DHQ component was screened as well (**3p-u**). Generally, the substituent on the phenyl ring of the 1,2-DHQ was critical for the reaction product. The 7-methoxy substituent was indispensable for the reaction product. Meanwhile, another substituent at C-5 or C-6 was required as well. Therefore, DHQs meeting the above two requirements were efficiently reacted to afford the corresponding spirocycles (**3p−s**). On the contrary, DHQ without a substituent or DHQ without a 7-methoxy substituent could not afford the corresponding spirocycles **3t,u**. Instead, the Friedel−Crafts alkylation product of the aromatic ring was obtained.

The potential of the reaction was investigated. One gram of the 1,2-DHQ was used under the optimized reaction conditions to afford the corresponding **3g** in 85% yield after column purification and 75% yield after recrystallization. The structure of **3g** was determined by X-ray analysis (Figure 2).

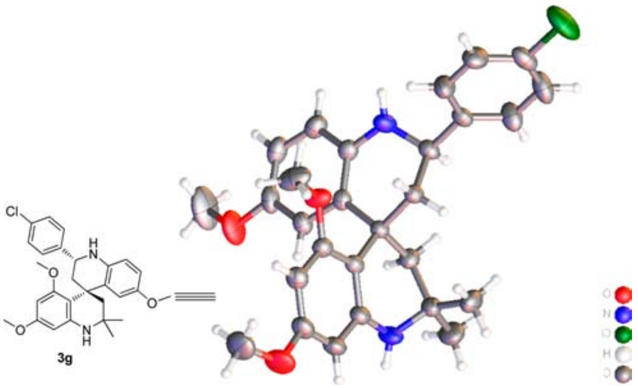


Figure 2. X-ray crystal structure of **3g** (CCDC 1512451).

Based on these results and previous works regarding the Pavorov reaction,[7,12] we tried to explain the high diastereoselectivity of the reactions (Figure 3). According to the transition state of the cyclization step, we found that the exotype cyclization was difficult due to the large steric hindrance. On the contrary, the endotype cyclization proceeded easily.

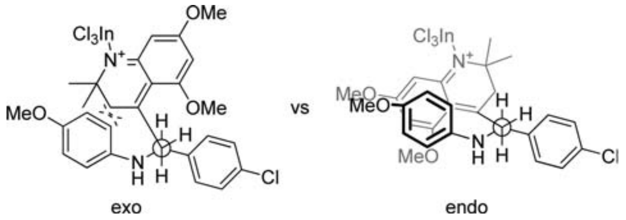
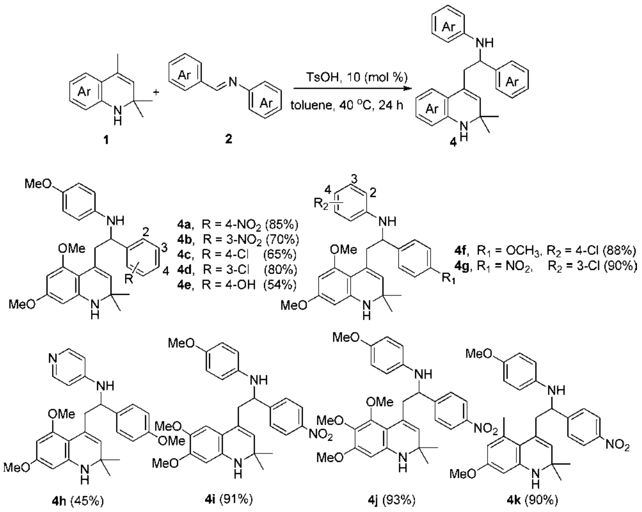


Figure 3. Rationale for the formation of endotype product.

Meanwhile, the reaction intermediate of this special Povarov reaction was interesting, which could be used as an efficient strategy for postfunctionalization of 1,2-DHQs. Therefore, the reaction conditions and reaction substrate scopes were investigated. The optimal reaction conditions (0.1 equiv of TsOH as catalyst at 40 °C in toluene) were ultimately obtained after routine screening of reaction conditions (data not shown). Meanwhile, substrate scopes including the use of different aromatic imines and 1,2-DHQs were investigated under the optimal reaction conditions (Scheme 3). For different aromatic imines, the corresponding 1,2-DHQs **4a−d,f,g** could be obtained with high yield except for imines with hydroxyl groups (**4e**). Meanwhile, imines formed with electron-withdrawing groups afforded the corresponding 1,2-DHQ with slightly higher yield (**4a,b**). Imines formed with different aromatic amines could also react smoothly to afford the corresponding 1,2-DHQ **4f,g**, including imine formed with pyridin-4-amine **4h**.

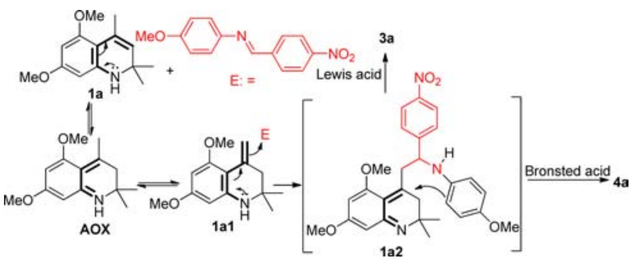
Scheme 3. Substrate Scope for Post-functionalization of 1,2-DHQ



Interestingly, the substituent of 1,2-DHQs was critical in the above reactions. Only substituents meeting the two requirements could afford the corresponding reaction product. We guessed that the Lewis acid could catalyze the formation of AOX easier and cause the in situ formed AOX to be more electron deficient. Therefore, the cyclization would be easier for reactions with Lewis acid.

Based on the above reaction results, we investigated the reaction mechanisms. We found that C−H of the methyl groups could easily deuterated under acid conditions. Meanwhile, the reaction product revealed that 7-methoxy was indispensable, which was required for the formation of AOX based on our previous researches.[20] Therefore, we proposed reasonable reaction mechanisms (Scheme 4). Initially, the

Scheme 4. Proposed Reasonable Reaction Mechanisms



electron-rich double bond of the 1,2-DHQ (the 7-OCH_3 could efficiently enhance the electron density of the double bond) could be easily protonated under acid conditions to afford the AOX intermediate. Then the α,β-unsaturated iminium (AOX) could isomerize to enamine **1a1**, which could be easily deuterated under acid conditions or reacted with imines to afford the corresponding intermediate **1a2**. Finally, the reactive intermediate could isomerized to the functionalized 1,2-DHQ **4a** under Brønsted acid catalyst or reacted through intermolecular Friedel−Crafts reactions under Lewis acid catalyst to afford the spiro bi-tetrahydroquinoline product **3a**.

In summary, we have succeeded in developing an efficient strategy for straightforward synthesis of novel spiro bi-tetrahydroquinolines. To the best of our knowledge, this represents a brand-new Povarov-type reaction incorporating an aliphatic methyl group as a member of a new building ring. Furthermore, this was an unusual example for preparation of spirocycles through Povarov reactions. In addition, the reaction could selectively stop at the first reaction stage under Brønsted acid to afford the functionalized 1,2-DHQs efficiently. On the basis of the reaction products as well as the deuteration experiment, the reaction mechanism is proposed. Further research toward the biological activities of the synthesized new compounds is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03330.

Experimental procedures, NMR data, X-ray crystallographic analysis (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ligx@cib.ac.cn.
*E-mail: zhaojz@sxau.edu.cn.
*E-mail: tangzhuo@cib.ac.cn.

ORCID

Guangxun Li: 0000-0001-6782-2066

Notes

The authors declare no competing financial interest.

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