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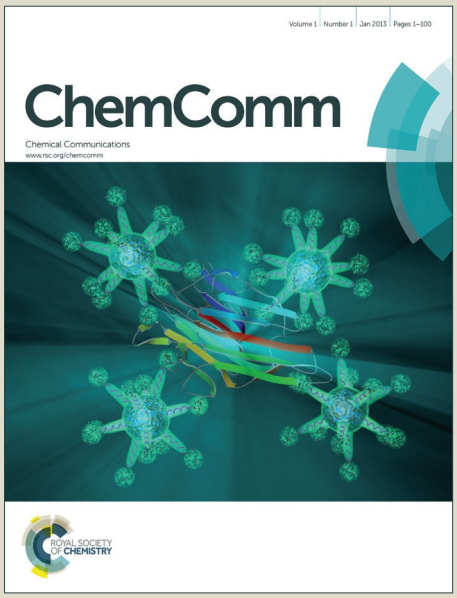

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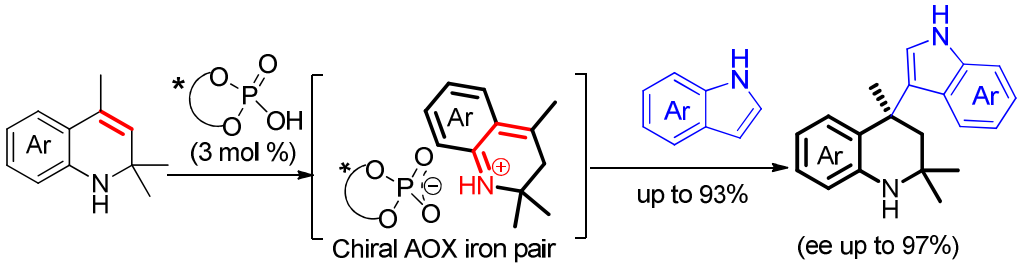

Tetrahydroquinolines (THQs) with all-carbon quaternary stereocenter were effectively obtained via the in situ formation of aza-*ortho*-xylylene (AOX) with easily accessible 1,2- dihydroquinolines as precussors. The reaction was rationalized with chiral phosporic acid to afford chiral THQs with high yield and excellent enantioselectivity.

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Catalytic Enantioselective Synthesis of Tetrahydroquinolines Containing All-carbon Quaternary Stereocenters via Formation of Aza-*ortho*-xylylene with 1,2-Dihydroquinoline as Precursor

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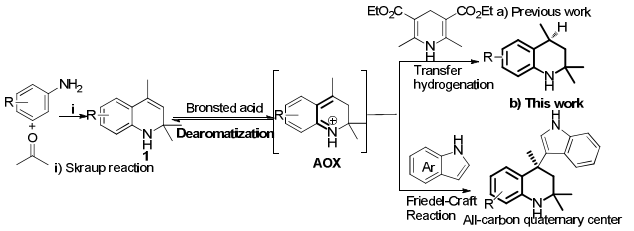
Tetrahydroquinolines (THQs) with an all-carbon quaternary stereocenter were effectively obtained via the in situ formation of aza-*ortho*-xylylene (AOX) with easily accessible 1,2-dihydroquinolines as precussors. The reaction was rationalized with chiral phosporic acid to afford chiral THQs with high yield and excellent enantioselectivity.

Tetrahydroquinolines (**THQs**) belong to a class of nitrogen containing heterocycles, which have attracted attention from medicinal and synthetic chemists because of their abundance in both natural products and drug molecules.[1] Therefore methods for rapid assembly of chiral **THQs** were very demanding despite of the numerous synthetic approaches available.[2] Recently, our group reported an efficient way of forming the aza-*ortho*-xylylene (**AOX**) by dearomatization of 1,2-Dihydroquinolines (**DHQs**) **1** with catalytic Brønsted acid.[3] The resulting intermediate formed in situ could be efficiently transfer hydrogenated with **HEH** to afford **THQs** with high yields and enantioselectivities (Scheme 1a). The advantages of this approach including the highly reactive **AOX** generated through simple way,[4] the easily accessible substrates obtained from simple aromatic amines and ketones, and the highly enantioselectivities of the corresponding chiral **THQs**, prompted us to investigate and develop more reaction types accordingly.

As we know that the preparation of compounds containing all-carbon quaternary stereocenters with catalytic enantioselective reactions are particularly demanding because of their wide distribution in natural products and bioactive substances.[5] However, catalytic enantioselective construction of these centers poses a daunting challenge in spite of the tremendous efforts made in this field.[6] One of the difficulties in constructing all-carbon stereocenter is their congested nature.[7] Inspired by Van Straten's work[8] for constructing all-carbon quaternary center at the C-4 of **DHQs** with $AlCl_3$ as well as our previous work of forming reactive **AOX** with Brønsted acid[3], we challenged the Brønsted acid catalyzed Friedel-Craft reaction with indoles as substrates[9], which could afford **DHQs** containing all-carbon quaternary centers. To our knowledge, accesses to **THQs** containing all-carbon quaternary chiral centers were rare. Herein we report an efficient strategy to form **THQs** with all-carbon quaternary stereocenters based on **DHQs**, in which the double bond was functionalized via the formation of **AOX** and subsequent nucleophilic substitution with indoles (Scheme 1b).



Scheme 1 Ways of the formation and application of **AOX**

Our previous work demonstrated that the electron properties of the **DHQs** played an important role in the formation of **AOX** intermediate. Enhancing the electron density of the alkene by installing electron donating group on the phenyl ring could make the alkene easily protonated with Brønsted acid at mild reaction conditions. Therefore, we initiated this work by screening the **DHQs** accordingly. As a result, several **DHQs** with different substituents on the phenyl ring were prepared and subjected to indoles with 5 mol% TsOH in $CHCl_3$ (Table 1). The results were quite similar with the corresponding transfer hydrogenation. Neither **1a** without substituent (Table 1, entry 1), nor **1b** or **1c** with electron withdrawing groups such as 6-Cl or 6-CF_3 (Table 1, entries 2-3) could react to afford the corresponding **THQs**. The same results were found for **1d** with weak electron

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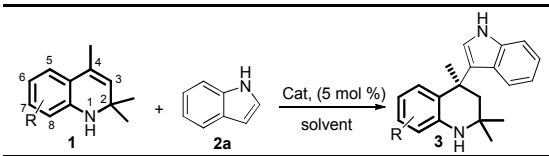
donating group on the phenyl ring (Table 1, entry 4). We therefore further enhanced the electron density of the alkene. Interestingly, **DHQ 1e** with 7-methoxy on the phenyl ring could be efficiently transformed to the corresponding **THQ 3e** (Table 1, entry 5). Nevertheless, **1f** and **1g** with 6-methoxy or 6,8-dimethoxy could not afford the corresponding product (Table 1, entries 6-7). **1h** with 5,7-dimethoxy afforded **THQ 3h** quantitatively (Table 1, entry 8).These results indicated that substitution pattern of electron donating group on the proper position of **DHQs** was crucial for the dearomatization. We then continued to investigate the reaction with different types of catalysts including brønsted acid TFA (Table 1, entry 9), strong Lewis acid $Yb(OTf)_3$ (Table 1, entry 10) and mild Lewis acid $MgBr_2$ (Table 1, entry 11). The results revealed that all of these catalysts could drive the reaction with excellent yield.

Table 1 Screening of appropriate **DHQs**



1 2a 3

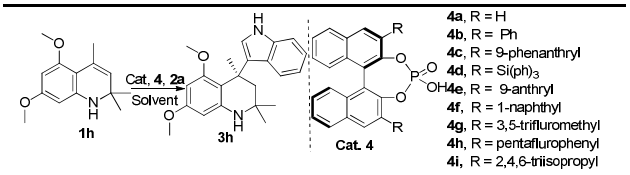
entry[a]	**1**, R	cat.	**3** (%)[b]
1	**1a**, R = H	TsOH	**3a** (-)
2	**1b**, R = 6-Cl	TsOH	**3b** (-)
3	**1c**, R = 6-CF_3	TsOH	**3c** (-)
4	**1d**, R =6-Me	TsOH	**3d** (-)
5	**1e**, R = 7-OCH_3	TsOH	**3e** (95)
6	**1f**, R = 6-OCH_3	TsOH	**3f** (-)
7	**1g**, R = 6,8-di-OCH_3	TsOH	**3g** (-)
8	**1h**, R = 5,7-di-OCH_3	TsOH	3h (98)
9	**1h**, R = 5,7-di-OCH_3	TFA	**3h** (99)
10	**1h**, R = 5,7-di-OCH_3	$Yb(OTf)_3$	**3h** (95)
11	**1h**, R = 5,7-di-OCH_3	$MgBr_2$	**3h** (85)

[a]Reaction conditions: 0.2 mmol **1**, 0.2 mmol **2**, cat. (5 mol %), 2 mL of $CHCl_3$ at 25 ℃, nitrogen atmosphere. [b]Isolated yield

Then we continued to develop an organocatalytic enantioselective synthesis of **THQs** with an all-carbon quaternary center. As we know, using chiral Brønsted acid as catalyst would allow the formation of an ionic pair between **AOX** and an optically active phosphoric anion, which could be trapped by indoles to provide chiral **THQs**[10]. Therefore, we systematically investigated the Friedel-Craft reaction between indole **2a** and **DHQ 1h** in presence of BINOL derived chiral phosphoric acids **4** (Table 2).

We firstly optimized the reaction by screening catalysts. The results revealed that **4c** was better than other catalysts in terms of the enantioselectivities (Table 2, entries 1-9). Then we investigated the reaction solvent and found that chloroform was astonishingly more efficient than other solvents in terms of the reaction yields and enantioselectivities (Table 2, entries 10-13). We guessed that the **AOX** might be formed more easily in chloroform than other solvents, which caused the Friedel-Craft reaction to occur more easily. Next, we examined the reaction temperature and found that conducting the reaction at 0 ℃ could greatly improve the enantioselectivity without sacrificing the yield (Table 2, entry 14). Meanwhile, 4 Å molecular sieves as an additive could improve the reaction enantioselectivity to 88% (Table 2, entry 15). Further decreasing the reaction temperature to -10 ℃ slightly improved enantioselectivity but greatly decreased the reaction yield (Table 2, entry 16). Finally, we examined the catalyst loading of the reaction and found the reaction proceeded smoothly without sacrificing the yield and enantioselectivity with 3 mol % of **4c** (Table 2, entries 17-18). These preliminary studies revealed that the optimal condition was equal equiv. of **1** and **2** with 3 mol % of catalyst **4c** at 0 °C in chloroform for 48 h with 4 Å molecular sieves as additive.

Table 2 Optimizing the reaction conditions



entry[a]	**4** (mol %)	solvent	temp (℃)	ee (%)[b]	yield (%)[c]
1	**4a** (5)	$CHCl_3$	Rt	7	82
2	**4b** (5)	$CHCl_3$	Rt	46	85
3	**4c** (5)	$CHCl_3$	Rt	78	92
4	**4d** (5)	$CHCl_3$	Rt	30	78
5	**4e** (5)	$CHCl_3$	Rt	34	75
6	**4f** (5)	$CHCl_3$	Rt	44	84
7	**4g** (5)	$CHCl_3$	Rt	65	87
8	**4h** (5)	$CHCl_3$	Rt	41	83
9	**4i** (5)	$CHCl_3$	Rt	77	90
10	**4c** (5)	CH_2Cl_2	Rt	-	<5
11	**4c** (5)	Toluene	Rt	-	<5
12	**4c** (5)	THF	Rt	15	62
13	**4c** (5)	Et_2O	Rt	-	<5
14	**4c** (5)	$CHCl_3$	0	83	92
15[d]	**4c** (5)	$CHCl_3$	0	88	92
16[d]	**4c** (5)	$CHCl_3$	-10	89	77
17	**4c** (3)	$CHCl_3$	0	88	90
18	**4c** (1)	$CHCl_3$	0	87	85

[a]General conditions: equal equiv of **1** and **2**. [b]Enantioselectivity was determined by HPLC with chiral OD-H; [c]The yield were determined after purification by flash column; [d]4 Å molecular sieves were added.

Under the obtained optimal reaction condition, we explored the scope of the Brønsted acid catalyzed Friedel-Craft reaction for the formation of various **THQs** with a chiral quaternary carbon center (Table 3). On one hand, indoles **2** with electron donating groups or electron withdrawing groups were rationally used to react with **1h** to get the corresponding **THQs 3i**-**k** with good yields (85-90%) and moderate enantioselectivities (83-88%). On the other hand, **DHQs** with different groups were systematically examined. **THQs** with one methoxy group (**3e**), two methoxy groups (**3l**) and three methoxy groups (**3m**), **THQs** with 7-methoxy and different halogens at C-6 (**3n**-**p**) **THQs** with different 7-alkoxy goups (**3q**-**s**), were obtained under the optimal reaction condition with admirable yields (85-93%) and excellent enantioselectivities (82-97%). Moreover, all these results revealed that bulky alkoxy at C-7 of the **DHQs** was vital for high enantioselectivity. Interestingly, **DHQ** with a methylthio at C-7 afforded the corresponding **THQ** with high yield and enantioselectivity, (**3t**). While **DHQs** with a nitogen containing substituent at C-7 afforded the corresponding **THQs** with

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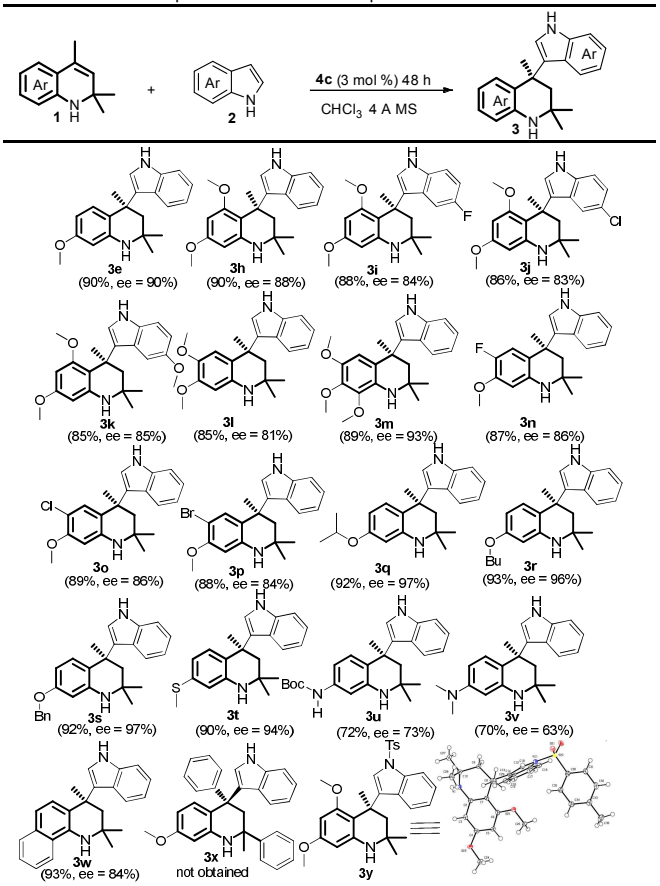
slightly lower ee due to the higher reaction temperature required, (**3u, 3v**). Meanwhile, 7,8-benzo-tetrahydroquinoline **3w** could be achieved with good yield (93%) and moderate ee (84%). However, **3X** which has a phenyl substituted at 4-position, was not obtained due to the slightly large steric hindrance. The absolute configuration of the product was detected by converting **3h** to **3y** and assigned as (*4R*) by X-ray crystallographic analysis (see the Supporting Information).

Table 3 Reaction scope with indoles as nucleophiles.[a,b]



[a] Yields given were isolated yields; ee were analysed with chiral OD-H column; Reaction condition: 0.2 mmol **1**, 0.2 mmol **2**, **4c** (3 mol %), 2 mL of $CHCl_3$ at 0 ℃, nitrogen atmosphere, 100 mg 4 Å molecular sieve as additive. [b] **3u** and **3v** were obtained from the optimized reaction conditions at 30 ℃.

In summary, we succeeded in developing an interesting Friedel-Craft reaction between easily accessible **DHQs** and indoles. Enhancing the electron density of the phenyl ring of **DHQs** could make the alkene group protonated more easily with simple Brønsted acid. The resulted **AOX** intermediate was electrophilically reactive and reacted with indoles to afford **THQs** effectively. Moreover, the method was rationalized with catalytic phosphoric acid to afford **THQs** containing an all-carbon quaternary center with high yields and excellent enantioselectivities. The scopes of the reaction types with this highly reactive **AOX** intermediate, the pharmaceutical activity of the obtained compounds are under investigation in our lab.

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