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Construction of *Spiro*-tetrahydroquinolines via Intramolecular Dearomatization of Quinolines: Free of a Preinstalled Activation Group

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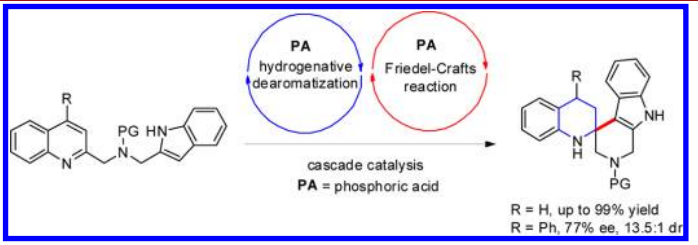
ABSTRACT



A highly efficient synthesis of *spiro*-tetrahydroquinolines (up to 99% yield) has been realized via cascade hydrogenative dearomatization of quinoline and intramolecular *aza*-Friedel–Crafts alkylation reaction.

Dearomatization reactions have shown great potential in the synthesis of complicated targets from relatively simple planar molecules, especially due to their unique efficiency in building spiro quaternary carbon centers.[1] In contrast to the abundant dearomatization protocols of electron-rich aromatic rings, the dearomatization of electron-deficient nitrogen-containing aromatic rings (pyridines, quinolines, isoquinolines, etc.) generally requires activation by *N*-acylation or alkylation. Although this strategy has received broad interest and witnessed full development for constructing spiro nitrogen-containing heterocycles, the removal of the protecting group on nitrogen is needed in a late stage and can be difficult in many cases.[2] Consequently, synthesis of spiro nitrogen-containing heterocycles via dearomatization reactions without preinstallation of activation groups will be highly desirable. As another efficient dearomatization tactic, asymmetric hydrogenation of (hetero)arenes catalyzed by transition-metal complexes or organocatalysts has been successfully explored,[3,7] providing efficient stereoselective construction of various nitrogen-containing skeletons.

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However, a hydrogenation reaction featuring C−H bond formation could not be utilized for constructing spiro compounds with quaternary carbon centers. As part of our ongoing research on dearomatization reactions,[4] we recently envisaged that partial hydrogenation of quinoline followed by cyclization with a tethered nucleophile would provide a straightforward synthesis of *spiro*-tetrahydroquinoline derivatives (Scheme 1). It is noteworthy that *spiro*-tetrahydroquinoline represents an important structural motif in pharmaceuticals and therefore its synthesis has attracted intense attention.[5,6] Here, we report an efficient synthesis of *spiro*-tetrahydroquinolines via cascade hydrogenative dearomatization of quinoline and *aza*-Friedel−Crafts alkylation reaction (indole as the nucleophile).[8]

Scheme 1. Proposed Synthesis of *Spiro*-tetrahydroquinolines from Quinolines

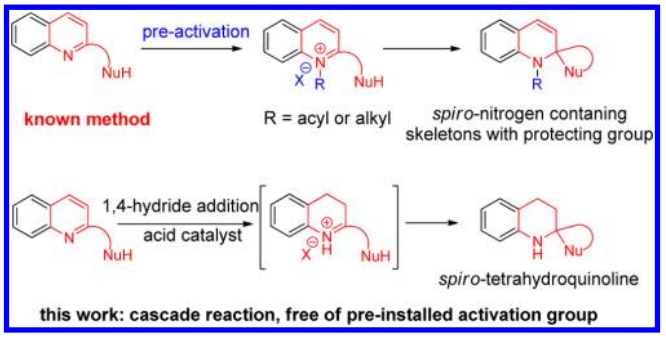
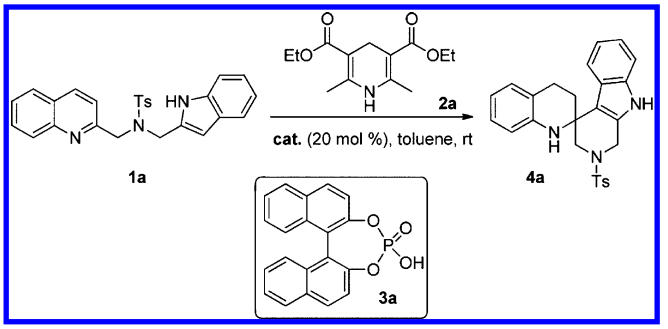


Table 1. Screening of Brønsted Acid Catalysts



entry[a]	cat.	**2a** (equiv)	time (h)	yield (%)[b]
1	**3a**	1	8	70
2	**3a**	1	16	75
3	L-camphorsulfonic acid	1	16	72
4	TFA	1	16	68
5	$TsOH•H_2O$	1	16	63
6	$3,5\text{-}(NO_2)_2C_6H_3COOH$	1	24	53
7	$3\text{-}NO_2C_6H_4COOH$	1	24	<10

[a] Reactions were performed with **1a** (0.1 mmol), Hantzsch ester **2a**, and 20 mol % catalyst in 1 mL of toluene. [b] Isolated yield.

We began our study by choosing compound **1a** as a model substrate, which was subjected to Hantzsch ester **2a** in the presence of a catalytic amount of acids.[9] To our great delight, most of the tested acids could catalyze the transformation smoothly. As shown in Table 1, with 1 equiv of Hantzsch ester **2a** and 20 mol % of racemic phosphoric acid **3a**, the desired product **4a** was obtained in 70% yield in 8 h (entry 1). Prolonging the reaction time could slightly increase the yield of **4a** (entry 2, Table 1). Several acidic catalysts such as L-camphorsulfonic acid, trifluoroacetic acid (TFA), toluenesulfonyl acid (TsOH), and $3,5\text{-}(NO_2)_2C_6H_3COOH$ all could be employed to give the product (53−72% yields, entries 3−6, Table 1). $3\text{-}NO_2C_6H_4COOH$ proved to be inefficient to catalyze this reaction likely due to its relatively weak acidity (entry 7, Table 1).

With 20 mol % of **3a** as the catalyst, various solvents were then screened to further optimize the reaction conditions. The results are summarized in Table 2. Among these tested solvents, CH_2Cl_2 and $CHCl_3$ were the optimal ones (93% yield, entries 3 and 7, Table 2). The reactions in toluene, $ClCH_2CH_2Cl$, CH_3CN, and EtOAc afforded

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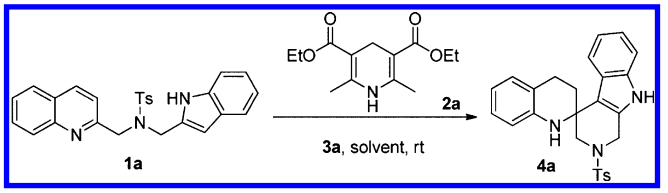
relatively lower yields (entries 1, 4, 6, and 8, Table 2). Et_2O, CCl_4, and *n*-hexane are poor solvents of choice for this reaction (entries 2, 5, and 9, Table 2). Furthermore, the loadings of catalyst **3a** as well as Hantzsch ester **2a** were then examined. With 5 mol % of catalyst **3a** in CH_2Cl_2, the reaction could also proceed smoothly but with a prolonged reaction time (entries 7 and 10, Table 2). Notably, with 5 mol % of **3a**, the reaction could proceed to completion with 1.2 equiv of **2a** (entries 11 and 12, Table 2). To our delight, a 90% yield of **4a** could be obtained even with 1 mol % of **3a** in 48 h (entry 13, Table 2).

Table 2. Screening of Solvents, Loadings of Catalyst, and Hantzsch Ester

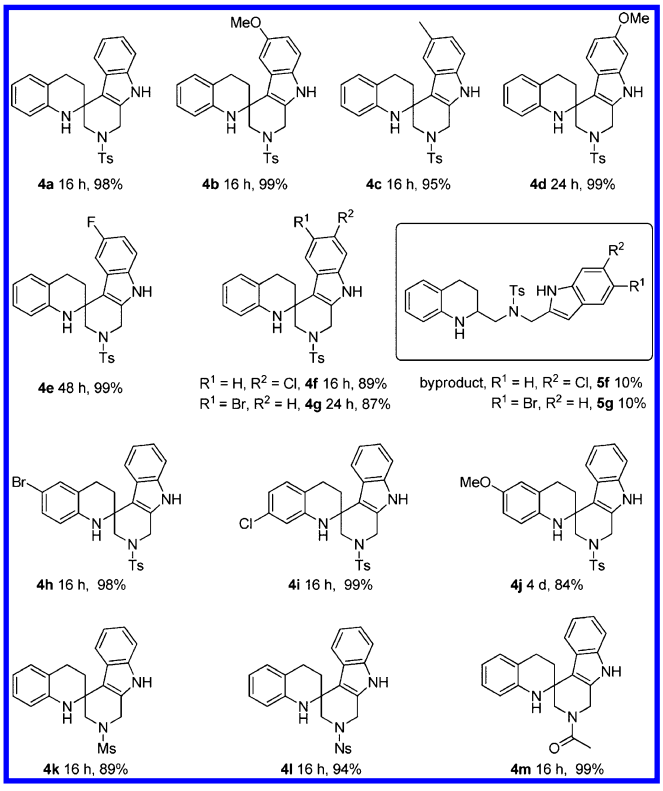


entry[a]	solvent	**3a** (mol %)	**2a** (equiv)	time (h)	yield (%)[b]
1	toluene	20	1	16	75
2	Et_2O	20	1	16	29
3	$CHCl_3$	20	1	16	93
4	$ClCH_2CH_2Cl$	20	1	16	81
5	CCl_4	20	1	16	38
6	CH_3CN	20	1	16	69
7	CH_2Cl_2	20	1	16	93
8	EtOAc	20	1	16	84
9	*n*-hexane	20	1	16	NR
10	CH_2Cl_2	5	1	48	92
11	CH_2Cl_2	5	1.5	16	98
12	CH_2Cl_2	5	1.2	16	98
13[c]	CH_2Cl_2	1	1.2	48	90

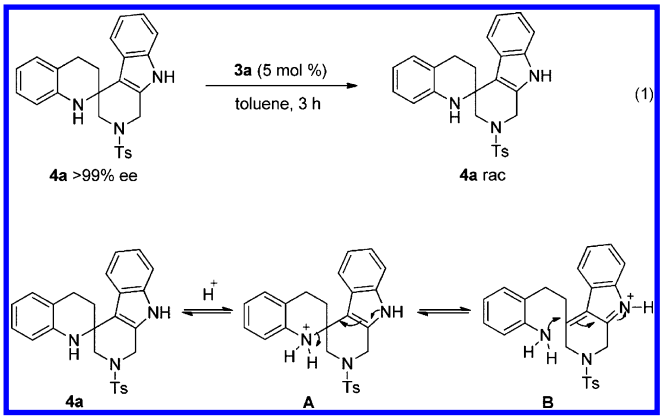
[a] Reactions were performed with **1a** (0.1 mmol), Hantzsch ester **2a**, and catalyst **3a** in 1 mL of solvent. [b] Isolated yield. [c] The reaction was carried out on a 0.3 mmol scale.

Under the optimal reaction conditions (5 mol % of **3a** as catalyst, 1.2 equiv of Hantzsch ester **2a**, CH_2Cl_2, rt), the substrate scope was then explored to test the generality of the reaction. The results are shown in Scheme 2. In general, all the tested substrates were transformed to their corresponding dearomatization products **4** in satisfactory yields (84−99%). Notably, 10% of double hydrogenation byproducts were isolated for two substrates bearing electron-withdrawing groups on the indole core (**4f**, **4g**, Scheme 2). Substrates with electron-withdrawing substituents on the pyridine moiety were converted to the products completely in excellent yields (**4h** and **4i**, Scheme 2). The substrate bearing the 7-OMe group also gave the product in 84% yield (**4j**, Scheme 2). It should be noted that various protecting groups (Ms, Ns, or Ac) of the *N*-linker could be tolerated, and the dearomatization products were all obtained in good to excellent yields (**4k**, **4l**, and **4m**, Scheme 2).

Scheme 2. Substrate Scope for Dearomatization of Quinolines

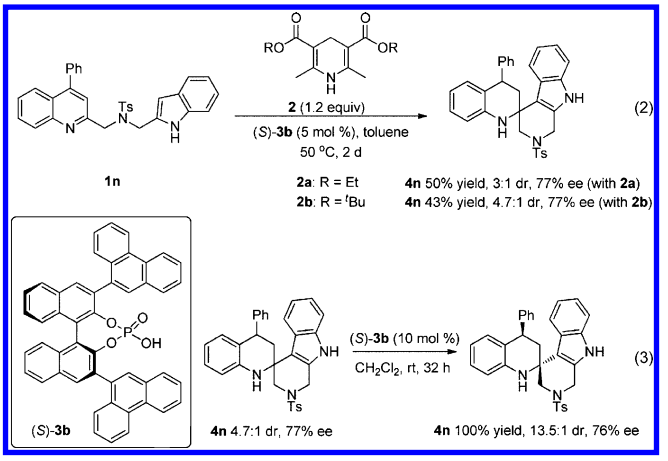


Scheme 3. Epimerization of **4a** under Acidic Conditions



The enantioselective dearomatization reaction of quinolines was then examined. Unfortunately, due to the epimerization of **4a** under acidic conditions, the initial attempt to develop an enantioselective reaction failed (eq 1, Scheme 3).[8] Inspired by the enantioselective hydrogenation of 4-substituted quinolines reported by Rueping and co-workers,[7m] we envisaged that the substrate with the 4-substituent on the quinoline moiety might be suitable for stereoselective control of this dearomatization transformation, given that the generated chiral center during the hydrogenation reaction might induce a diastereoselective

Scheme 4. Stereoselective Synthesis of *Spiro*-tetrahydroquinolines



aza-Friedel–Crafts alkylation reaction. Indeed, the reaction of **1n** led to the formation of product **4n** in moderate levels of yield, diastereoselectivity, and enantioselectivity when chiral phosphoric acid (*S*)-**3b** was used (eq 2, Scheme 4). Utilization of Hantzsch ester **2b** provided better diastereoselectivity for **4n** than **2a** (eq 2, Scheme 4). Interestingly, the diastereoselectivity of **4n** could be significantly enhanced after treatment with 10 mol % of chiral phosphoric acid (*S*)-**3b** without affecting the enantiomeric purity (from 4.7:1 to 13.5:1 dr, eq 3, Scheme 4). Finally, the absolute configuration of **4n** was assigned by X-ray crystallographic analysis of an enantiopure sample (Figure 1).[10]

In conclusion, an efficient synthesis of *spiro*-tetrahydroquinolines has been realized via a cascade hydrogenative dearomatization of quinoline and an *aza*-Friedel–Crafts alkylation reaction. This methodology features readily available starting materials, operational simplicity, excellent yields, and dearomatization of quinolines without preinstallation of an activation group. Further development of highly enantioselective reactions is currently underway in our laboratory.

(10) CCDC 917093 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

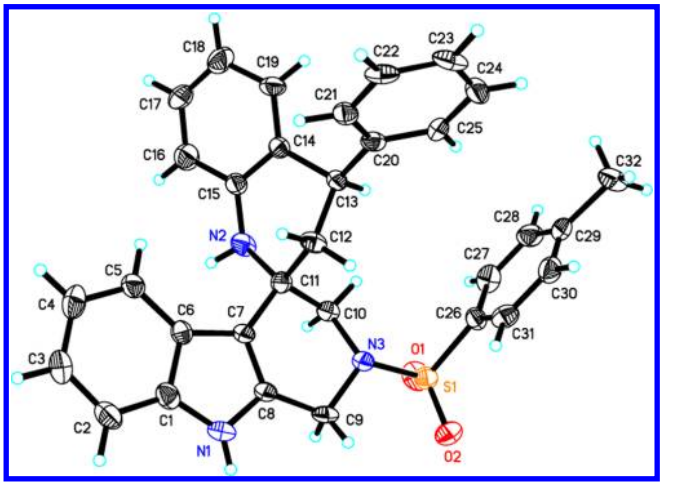


Figure 1. X-ray crystal structure of *Spiro*-tetrahydroquinoline **4n**.

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Supporting Information Available. Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.