

Full Paper

CuCl₂-catalyzed One-pot Formation of Tetrahydroquinolines from *N*-Methyl-*N*-alkylanilines and Vinyl Ethers in the Presence of *t*-Butylhydroperoxide

Xianghua Yang, Chanjuan Xi * and Yanfeng Jiang

Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P.R. China; E-mails: yxh04@mails.tsinghua.edu.cn (X. Yang); jiang@aci.unizh.ch (Y. Jiang)

* Author to whom correspondence should be addressed. E-mail: cjxi@tsinghua.edu.cn

Received: 6 October 2006; in revised form: 12 December 2006 / Accepted: 15 December 2006 / Published: 20 December 2006

Abstract: Tetrahydroquinoline skeletons can be formed by a CuCl₂-catalyzed one-pot reaction of *N*-methyl-*N*-alkylanilines and vinyl ethers in the presence of *t*-butylhydroperoxide.

Keywords: CuCl₂, one-pot reaction, *N*-methyl-*N*-alkylanilines, 1,4-disubstituted tetrahydroquinolines, vinyl ethers.

Introduction

Tetrahydroquinolines are an important structural subunit of natural products and many tetrahydroquinoline derivatives exhibit interesting biological and pharmaceutical activities [1]. Consequently, synthetic methodologies for preparing tetrahydroquinoline derivatives have attracted considerable interest and several methods offering good results have been reported [2-4]. Nonetheless, there are still some features requiring improvement in these methods, e.g. the catalysts used are expensive, the systems require special atmospheres and organic solvents are always needed. Thus, a procedure involving a low-cost catalyst and simple and eco-friendly conditions might be very useful.

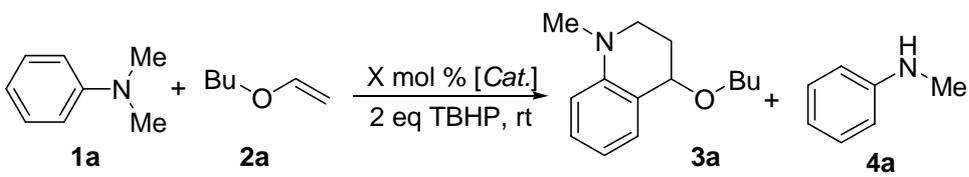
Copper is one of the oldest transition metals used in organic synthesis and copper salts are still broadly employed nowadays [5,6]. Among these copper salts, CuCl₂, as a mild Lewis acid, is

especially favored by chemists due to its inexpensiveness, lack of toxicity and easy-handling. Herein, we wish to report a one-pot synthesis of tetrahydroquinoline derivatives based on a CuCl_2 -catalyzed room temperature reaction of *N*-methyl-*N*-alkylanilines and vinyl ethers in the presence of *t*-butylhydroperoxide (TBHP).

Results and Discussion

Initially, *N,N*-dimethylaniline (**1a**, 1 mmol) was reacted with *n*-butyl vinyl ether (**2a**, 1.0 mmol) in the presence of TBHP (1 mmol) at room temperature. No product was observed even after 2 days. On the other hand, when a catalytic amount of CuCl_2 (5 mol%) was added to the reaction mixture, a smooth reaction occurred and tetrahydroquinoline derivative **3a** was isolated in 40% yield. To optimize the CuCl_2 -based system, different conditions were tested on *N,N*-dimethylaniline (**1a**), and a 1:1.2:2 ratio of **1a/2a/TBHP** was found to work best. Several other catalysts (CuBr , FeCl_2 , CuCl , InCl_3 and SbCl_3) were examined under the optimized conditions (Table 1). CuBr , FeCl_2 , and CuCl were found to be effective in the reaction, but gave much lower yields. It is noteworthy that when CuCl was used as the catalyst, the *N*-demethylation product **4a** was found to be the main product [4c]. As for InCl_3 and SbCl_3 , none of the target product was detected.

Table 1. One-pot synthesis of tetrahydroquinoline catalyzed by Lewis acid



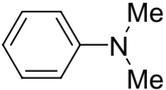
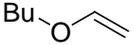
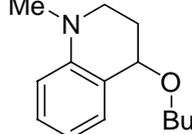
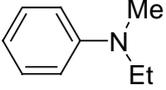
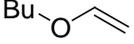
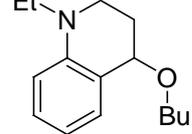
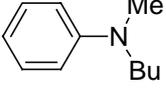
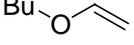
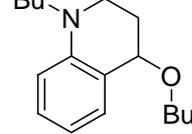
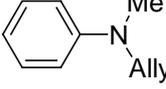
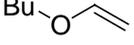
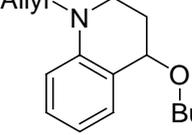
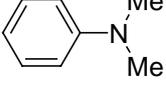
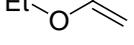
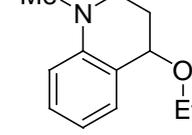
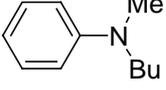
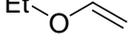
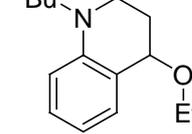
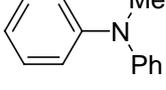
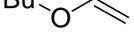
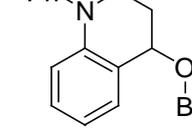
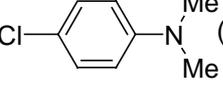
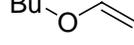
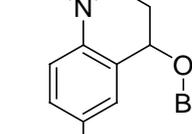
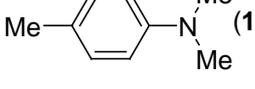
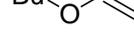
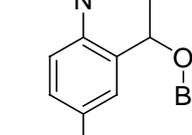
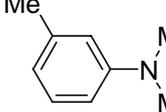
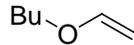
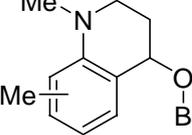
Entry.	Catalyst	X mol %	Yield (%) ^a	
			3a	4a
1	—	0	—	—
2	CuCl_2	5	72	—
3	FeCl_2	5	37	—
4	CuBr	5	21	—
5	CuCl	5	7	46
6	InCl_3	5	—	—
7	SbCl_3	5	—	—

^a Isolated yield

The transformation was found to be general for various aniline derivatives under the optimal conditions. Representative examples are listed in Table 2. In most cases, moderate to good yields of the corresponding tetrahydroquinoline derivatives were obtained. The scope of the reaction could also be extended to substituted *N*-methyl-*N*-alkylanilines **1b-h**. When *para*-chloro-*N,N*-dimethylaniline (**1f**) was used, the desired product **3f** was formed in good yield (Table 2, entry 8). The reaction of *para*-methyl substituted substrate **1g** also afforded the desired product **3g**, however, the yield diminished to 35% (Table 2, entry 9). When *N,N*-3-trimethylbenzenamine (**1h**) was used, a 1:1 mixture of two isomers with the methyl group on either the 5- or 8-positions was observed (entry 10). When ethyl vinyl ether (**2b**) was employed as the olefin and reacted with the *N*-methyl-*N*-alkylanilines, the desired

products were formed in lower yields. Under the optimal condition, when styrene and 1-octene were used as the olefin reacted with the *N*-methyl-*N*-alkylanilines, no target products were observed.

Table 2. Reaction of *N*-methyl-*N*-alkylanilines with vinyl ether catalyzed by CuCl_2

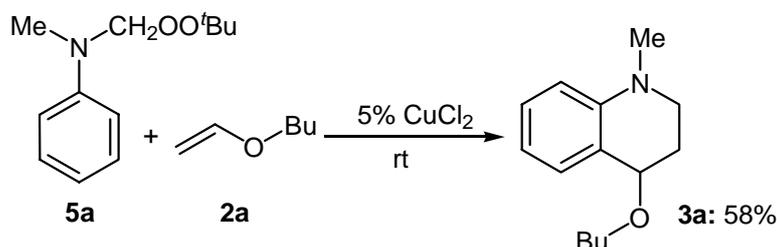
Entry	Aniline	Vinyl ether	Product	Yield(%) ^a
1	 (1a)	 (2a)	 (3a)	72
2	 (1b)	 (2a)	 (3b)	69
3	 (1c)	 (2a)	 (3c)	63
4	 (1d)	 (2a)	 (3d)	45
5	 (1a)	 (2b)	 (3a')	35
6	 (1c)	 (2b)	 (3c')	37
7	 (1e)	 (2a)	 (3e)	32
8	 (1f)	 (2a)	 (3f)	64
9	 (1g)	 (2a)	 (3g)	35
10	 (1h)	 (2a)	 (3h ^b)	42

^aIsolated yield based on the substrate;

^bMixture of the two isomers, the ratio is one to one.

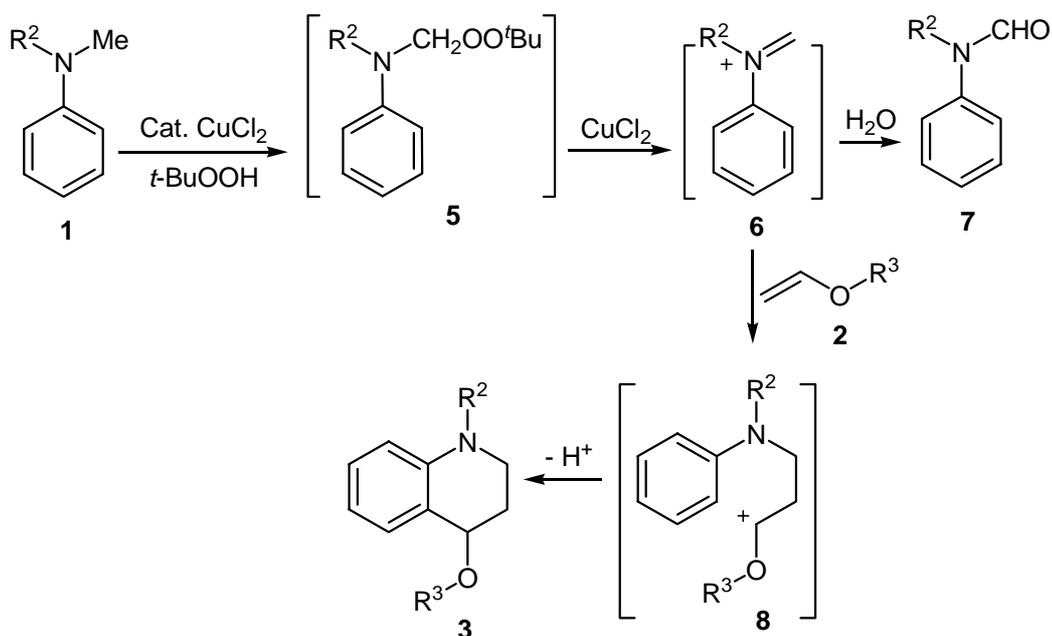
It is known that tertiary *N*-methylanilines can be converted chemoselectively into the corresponding *N*-(*t*-butyl-dioxymethyl)anilines **5** efficiently by the ruthenium-catalyzed oxidation with TBHP [4b-c]. However, such products were not obtained in this work, in which *N*-phenylformamide **7** was obtained after hydrolysis. To clarify whether the final product was formed from *N*-(*t*-butyldioxymethyl)aniline **5**, the compound **5a** was prepared according to literature [4b-c]. The reaction of **5a** with *n*-butyl vinyl ether (**2a**) in the presence of a catalytic amount of CuCl₂ at room temperature was carried out and the tetrahydroquinoline **3a** was obtained in 58 % yield (Scheme 1). This result indicated that CuCl₂ acted as an effective Lewis acid in this reaction. It also explains why no formation of compounds **5** was observed in the presence of CuCl₂.

Scheme 1.



Although the mechanism of reaction presented here is not yet clear, based on the above mentioned results, one possible reaction pathway is shown in Scheme 2. First, *N*-methyl-*N*-alkylaniline **1** reacts with TBHP, catalyzed by CuCl₂, to give compound **5**. The latter transforms into the iminium ion intermediate **6** in the presence of the Lewis acid (CuCl₂), which can form *N*-phenylformamide **7** after quenching by water. Compound **6** then reacts with vinyl ether **2** to give the cationic intermediate **8**. Finally, electrophilic aromatic ring closure affords the 1,4-disubstituted tetrahydroquinoline derivative **3**.

Scheme 2. Proposed mechanism.



Conclusions

In summary, a one-pot reaction for the formation of tetrahydroquinolines based on the reaction of *N*-methyl-*N*-alkylanilines and vinyl ethers in the presence of *t*-butyl hydroperoxide using CuCl₂ as the catalyst was developed. The scope and synthetic applications of this reaction are currently under investigation.

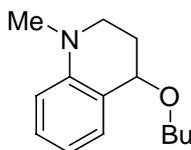
Experimental

General

¹H- and ¹³C-NMR spectra were recorded at 300 and 75 MHz, respectively, using CDCl₃ as solvent on a JEOL JNM-ECA300 spectrometer. ESI-MS were recorded on Bruker Esquire-LC/MSn instrument. Reagents such as *N,N*-dimethylaniline (**1a**), *n*-butyl vinyl ether (**2a**), ethyl vinyl ether (**2b**) and TBHP were purchased; others, like *N*-ethyl-*N*-methylaniline (**1b**), *N*-butyl-*N*-methylaniline (**1c**), *N*-allyl-*N*-methylaniline (**1d**), *N*-methyl-*N*-phenylaniline (**1e**), 4-chloro-*N,N*-dimethylaniline (**1f**), 4,*N,N*-trimethylaniline (**1g**) and 3,*N,N*-trimethylaniline (**1h**) were prepared according to the literature [7].

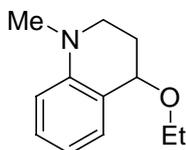
Representative procedure for the CuCl₂-catalyzed one-pot formation of tetrahydroquinolines from N-methyl-N-alkylanilines and vinyl ethers in the presence of t-butyl hydroperoxide: reaction of N,N-dimethylaniline (1a) and n-butyl vinyl ether (2a)

CuCl₂ (14 mg, 0.1 mmol), *N,N*-dimethylaniline (**1a**, 252 μL, 2 mmol), and *n*-butyl vinyl ether (**2a**, 312 μL, 2.4 mmol) were placed together into an open glass vessel and stirred at room temperature. Then, *t*-butyl hydroperoxide (TBHP) (600 μL, 2.0 mmol) was slowly added dropwise. The reaction mixture was stirred at room temperature for 12 h before being quenched with aqueous K₂CO₃. The organic phase was extracted with CH₂Cl₂ (10 mL x 2), the solvent was evaporated under reduced pressure and the residue was isolated by chromatography on a column of neutral Al₂O₃ column (40 mL) using a 1:100 mixture of 1:100 EtOAc/petroleum ether as eluent to give *4-butoxy-1-methyl-1,2,3,4-tetrahydroquinoline* (**3a**) [4d] as a colorless liquid (158 mg, 72 %); ¹H-NMR (CDCl₃): δ = 0.90 (t, *J* = 6.8 Hz, 3H), 1.34-1.44 (m, 2H), 1.52-1.61 (m, 2H), 1.84-1.93 (m, 1H), 2.04-2.12 (m, 1H), 2.89 (s, 3H), 3.04-3.10 (m, 1H), 3.32-3.55 (m, 3H), 4.28 (t, *J* = 3.8 Hz, 1H), 6.59-6.64 (m, 2H), 7.11-7.16 (m, 2H); ¹³C-NMR: δ = 13.9, 19.5, 27.3, 32.2, 38.9, 46.3, 67.5, 73.1, 111.3, 115.6, 121.6, 129.2, 130.3, 146.3; ESI-MS: 242 [M+Na]⁺.

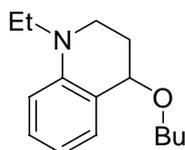


3a

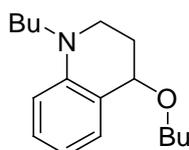
4-Ethoxy-1-methyl-1,2,3,4-tetrahydroquinoline (3a') [3d]. Colorless liquid (35 %); $^1\text{H-NMR}$: $\delta = 1.15$ (t, 3H), 1.83-1.91 (m, 1H), 2.00-2.06 (m, 1H), 2.85 (s, 3H), 3.01-3.05 (m, 1H), 3.34-3.37 (m, 1H), 3.47-3.53 (m, 2H), 4.25 (t, 1H), 6.54-6.56 (m, 2H), 7.04-7.08 (m, 2H); $^{13}\text{C-NMR}$: $\delta = 15.7, 27.5, 39.0, 46.4, 63.1, 73.0, 111.4, 115.6, 121.5, 129.4, 130.5, 146.4$; ESI-MS: 214 $[\text{M}+\text{Na}]^+$.

**3a'**

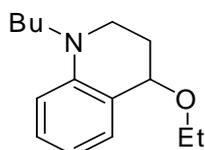
4-Butoxy-1-ethyl-1,2,3,4-tetrahydroquinoline (3b). Colorless liquid (69 %); $^1\text{H-NMR}$: $\delta = 0.89$ (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.20-1.30 (m, 2H), 1.52-1.58 (m, 2H), 1.81-1.89 (m, 1H), 2.07-2.15 (m, 1H), 3.08-3.15 (m, 1H), 3.21-3.36 (m, 1H), 3.38-3.54 (m, 4H), 4.28 (t, $J = 3.4$ Hz, 1H), 6.55-6.65 (m, 2H), 7.10-7.15 (m, 2H); $^{13}\text{C-NMR}$: $\delta = 11.0, 13.9, 19.5, 27.2, 32.2, 43.3, 45.3, 67.4, 73.2, 111.0, 114.8, 121.3, 129.2, 130.8, 144.8$; ESI-MS: 256 $[\text{M}+\text{Na}]^+$.

**3b**

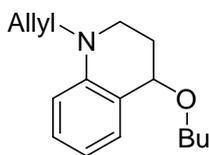
1-Butyl-4-butoxy-1,2,3,4-tetrahydroquinoline (3c). Colorless liquid (78 %); $^1\text{H-NMR}$: $\delta = 0.89$ (t, $J = 7.5$ Hz, 3H), 0.94 (t, $J = 7.2$ Hz, 3H), 1.30-1.42 (m, 4H), 1.54-1.61 (m, 4H), 1.80-1.89 (m, 1H), 2.05-2.11 (m, 1H), 3.10-3.35 (m, 3H), 3.41-3.56 (m, 3H), 4.28 (t, $J = 3.4$ Hz, 1H), 6.54-6.62 (m, 2H), 7.09-7.15 (m, 2H); $^{13}\text{C-NMR}$: $\delta = 14.1, 19.6, 20.5, 27.2, 28.7, 32.3, 44.4, 51.2, 67.5, 73.3, 111.0, 114.7, 121.0, 129.3, 130.8, 145.2, 146.0$; ESI-MS: 284 $[\text{M}+\text{Na}]^+$.

**3c**

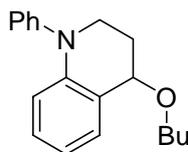
1-Butyl-4-ethoxy-1,2,3,4-tetrahydroquinoline (3c'). Colorless liquid (37 %); $^1\text{H-NMR}$: $\delta = 0.88$ (t, $J = 7.5$ Hz, 3H), 1.14 (t, $J = 7.2$ Hz, 3H), 1.22-1.36 (m, 2H), 1.44-1.56 (m, 2H), 1.74-1.84 (m, 1H), 1.98-2.07 (m, 1H), 3.04-3.52 (m, 6H), 4.22-4.24 (m, 1H), 6.48-6.63 (m, 2H), 7.03-7.16 (m, 2H); $^{13}\text{C-NMR}$: $\delta = 14.1, 15.6, 51.1, 44.3, 38.3, 28.6, 20.5, 62.9, 73.1, 111.0, 112.1, 114.6, 129.2, 129.3, 130.8, 145.1$; ESI-MS: 256 $[\text{M}+\text{Na}]^+$.

**3c'**

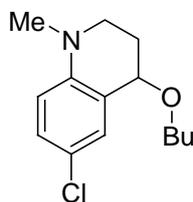
1-Allyl-4-butoxy-1,2,3,4-tetrahydroquinoline (3d). Colorless liquid (45 %); $^1\text{H-NMR}$: δ = 0.94 (t, J = 7.2 Hz, 3H), 1.36-1.48 (m, 2H), 1.56-1.66 (m, 2H), 1.86-1.98 (m, 1H), 2.12-2.18 (m, 1H), 2.95 (s, 1H), 3.12-3.20 (m, 1H), 3.42-3.57 (m, 3H), 3.92 (s, 1H), 4.34 (s, 1H), 5.18-5.24 (m, 2H), 5.82-5.88 (m, 1H), 6.61-6.66 (m, 2H), 7.11-7.19 (m, 2H); $^{13}\text{C-NMR}$: δ = 14.1, 19.6, 27.3, 32.3, 44.2, 53.7, 67.5, 73.3, 111.5, 115.2, 115.9, 121.3, 129.3, 130.6, 133.5, 145.2; ESI-MS: 268 $[\text{M}+\text{Na}]^+$.

**3d**

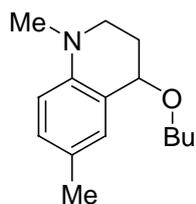
4-Butoxy-1-phenyl-1,2,3,4-tetrahydroquinoline (3e). Colorless liquid (37 %); $^1\text{H-NMR}$: δ = 0.99 (t, J = 7.2 Hz, 3H), 1.36-1.52 (m, 2H), 1.56-1.74 (m, 2H), 2.02-2.14 (m, 1H), 2.21-2.28 (m, 1H), 3.58-3.72 (m, 3H), 3.79-3.90 (m, 1H), 4.46 (s, 1H), 6.76-6.82 (m, 2H), 7.02-7.12 (m, 1H), 7.18-7.24 (m, 1H), 7.30-7.35 (m, 3H), 7.40-7.46 (m, 2H); $^{13}\text{C-NMR}$: δ = 14.0, 19.6, 27.6, 32.3, 46.5, 67.8, 73.0, 115.1, 117.5, 122.9, 124.6, 125.9, 128.5, 129.6, 130.6, 144.4, 147.9.

**3e**

4-Butoxy-6-chloro-1-methyl-1,2,3,4-tetrahydroquinoline (3f). Colorless liquid (74 %); $^1\text{H-NMR}$: δ = 0.93 (t, J = 7.2 Hz, 3H), 1.37-1.45 (m, 2H), 1.57-1.63 (m, 2H), 1.86-1.94 (m, 1H), 2.08-2.13 (m, 1H), 2.90 (s, 3H), 3.09-3.15 (m, 1H), 3.36-3.42 (m, 1H), 3.48-3.58 (m, 2H), 4.26 (t, J = 3.6 Hz, 1H), 6.52-6.54 (m, 1H), 7.08-7.13 (m, 2H); $^{13}\text{C-NMR}$: δ = 14.0, 19.6, 27.2, 32.2, 39.0, 46.4, 67.9, 72.9, 112.5, 120.3, 123.2, 128.9, 129.7, 144.9; ESI-MS: 276 $[\text{M}+\text{Na}]^+$.

**3f**

4-Butoxy-1,6-dimethyl-1,2,3,4-tetrahydroquinoline (3g)[4d]. Colorless liquid (35 %), $^1\text{H-NMR}$: δ = 0.93 (t, J = 7.4 Hz, 3H), 1.34-1.45 (m, 2H), 1.64-1.87 (m, 2H), 1.87-1.96 (m, 1H), 2.08-2.16 (m, 1H), 2.25 (s, 3H), 2.89 (s, 3H), 3.05-3.11 (m, 1H), 3.29-3.38 (m, 1H), 3.49-3.59 (m, 2H), 4.29 (t, J = 3.6 Hz, 1H), 6.56-6.59 (m, 1H), 6.98 (s, 2H); $^{13}\text{C-NMR}$: δ = 14.1, 19.6, 20.4, 27.6, 29.8, 32.3, 39.4, 46.7, 67.8, 73.3, 111.9, 122.0, 125.0, 129.8, 130.9, 144.5; ESI-MS: 256 $[\text{M}+\text{Na}]^+$.

**3g**

N-Methylaniline (**4a**) [4a]. Colorless liquid (46%), $^1\text{H-NMR}$: δ = 2.85 (s, 3H), 3.67 (br, 1H), 6.61-6.65 (m, 2H), 6.70-6.76 (m, 1H), 7.18-7.24 (m, 2H); $^{13}\text{C-NMR}$: δ = 26.6, 30.8, 112.5, 117.3, 129.3, 148.4; ESI-MS: 108 $[\text{M}+\text{H}]^+$.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (20372041) (20572058) and Beijing Department of Education (XK100030514).

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