ChemPubSoc Europe

DOI: 10.1002/chem.201304576

CHEMISTRY
A European Journal
Communication

Organic Synthesis

Ruthenium(II)/Chiral Brønsted Acid Co-Catalyzed Enantioselective Four-Component Reaction/Cascade Aza-Michael Addition for Efficient Construction of 1,3,4-Tetrasubstituted Tetrahydroisoquinolines

Jun Jiang, Xiaochu Ma, Changge Ji, Zhenqiu Guo, Taoda Shi, Shunying Liu,* and Wenhao Hu*[a]

Abstract: An elegant synergistic catalytic system comprising a ruthenium complex with a chiral Brønsted acid was developed for a four-component Mannich/cascade aza-Michael reaction. The ruthenium-associated ammonium ylides successfully trapped with in situ generated imines indicates a stepwise process of proton transfer in the ruthenium-catalyzed carbenoid N–H insertion reaction. The different decomposition abilities of various ruthenium complexes towards diazo compounds were well explained by the calculated thermodynamic data. The transformation features a mild, rapid, and efficient method for the synthesis of enantiomerically pure 1,3,4-tetrasubstituted tetrahydroquinolines bearing a quaternary stereogenic carbon center from simple starting precursors in moderate yields with high diastereo- and enantioselectivity.

The highly efficient construction of chiral polyfunctional molecules has always been one of the most pursued aims in asymmetric synthesis. Asymmetric multicomponent reactions (AMCRs) and cascade reactions provide powerful strategies to construct such molecules in an operationally simple fashion.[1] Combining AMCRs and cascade reactions, in which, the multicomponent reaction forms the precursor with necessary functionalities ready for the subsequent cascade reaction, should present the most efficient approach to construct chiral polyfunctional complex molecules with the maximum synthetic efficiency.[2] In such an attractive approach, the control of reaction selectivity, especially the order control of bond formation and the stereoselectivity of the desired molecules, is a great challenge because many possible chemical transformations may be involved in the reaction systems. The discovery of elegant synergistic catalytic systems may provide an opportunity to conquer this challenge.

Ruthenium complexes are versatile catalysts for chemical transformations.[3] Due to great compatibility and tolerance towards a wide range of organic functionalities including acids and amines,[4] ruthenium complexes should be ideal catalysts of choice in developing synergistic catalytic systems in multicomponent cascade reactions. Nevertheless, only a few catalytic systems combining ruthenium complex and chiral organic small molecules have been reported. MacMillan's group innovatively merged a synergistic system of a ruthenium complex and a chiral imidazolidinone catalyst to accomplish the enantioselective intermolecular α-alkylation of aldehydes under light irradiation, in which the ruthenium complex served as the photoredox catalyst.[5] You and co-workers have reported a sequential catalytic process involving a ruthenium complex and a chiral phosphoric acid for olefin cross-metathesis/intramolecular Friedel–Crafts alkylation to offer polycyclic indoles, in which the two catalysts worked separately but in a one-pot fashion.[6] To the best of our knowledge, no synergistic system of ruthenium complex and chiral Brønsted acid has been reported. Herein, we develop an enantioselective four-component cascade reaction for efficient construction of chiral multisubstituted tetrahydroisoquinolines (THIQs), and a synergistic catalytic system of a ruthenium complex with a chiral phosphoric acid is discovered to efficiently control the reaction selectivity.

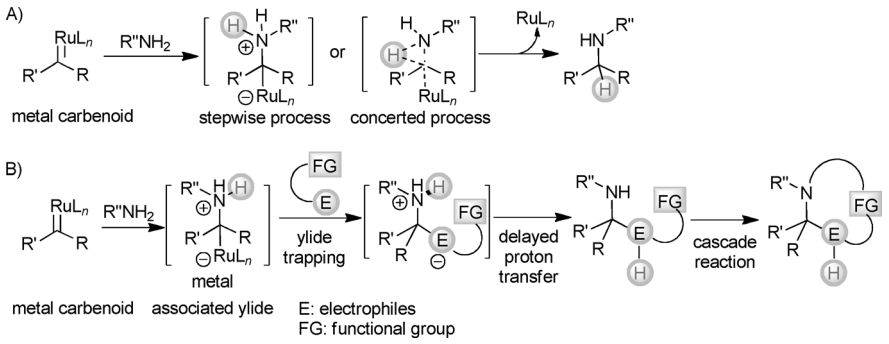
Ruthenium complexes have been reported to be effective catalysts for the decomposition of diazo compounds.[7,8] Recently, Che and collaborators reported that commercially available $[RuCl_2(p\text{-cymene})]_2$ was an efficient catalyst for the carbenoid N–H insertion reaction and the reaction was tolerant towards oxygen and moisture in the atmosphere.[9] As the mechanism of the N–H insertion reaction was still unclear, a stepwise process via ruthenium ylide formation and a subsequential proton transfer was proposed as one possibility (Scheme 1A).

Based on our previous studies in rhodium-catalyzed active ammonium ylide trapping processes,[10] we envision that it is highly possible to trap the proposed ruthenium-associated ammonium ylide with a bifunctional electrophile if the aforementioned stepwise N–H insertion operates (Scheme 1B). The successful trapping process following a cascade reaction will not only provide direct experimental evidence to clarify the reac-

[a] Dr. J. Jiang,[+] X. Ma,[+] Dr. C. Ji, Dr. Z. Guo, T. Shi, Dr. S. Liu, Prof. W. Hu
Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University
Shanghai, 200062 (China)
Fax: (+86) 021-62221237
E-mail: syliu@sist.ecnu.edu.cn
whu@chem.ecnu.edu.cn

[+] These authors contributed equally to this work.

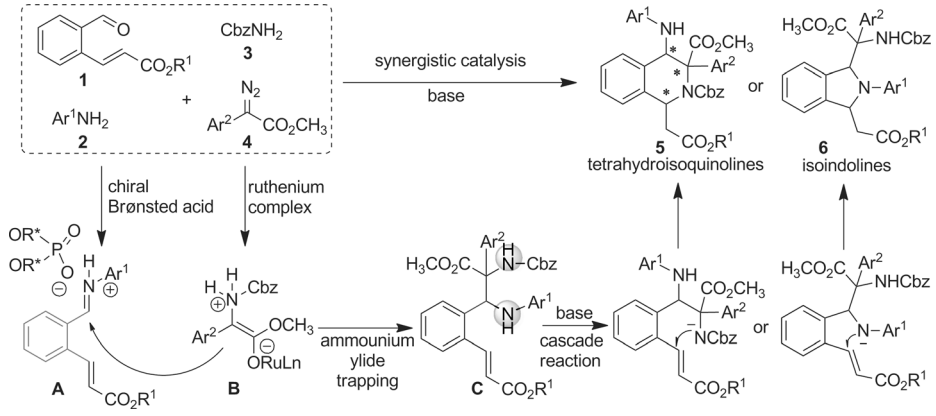
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201304576.



Scheme 1. A) Ruthenium-associated ammonium ylides followed by a proposed stepwise or concerted proton transfer.[9] B) Trapping the ruthenium-associated ammonium ylides by electrophiles to delay proton transfer.

tion pathway for the Ru-catalyzed N–H insertion, but also validate the ruthenium complex as an effective catalyst in the multicomponent reaction for efficient construction of polyfunctional molecules.

The designed four-component cascade reaction of bifunctional substrates **1**, arylamine **2**, benzyl carbamate **3**, and aryl diazoacetate **4** is hypothesized as the following reaction sequence (Scheme 2). Bifunctional electrophile **A** will be generated in situ, and a Brønsted acid promotes the formation of the iminium species. Ruthenium(II) complex catalyzes the decomposition of diazo compound **4** with carbamate **3** to form Ru-associated ammonium ylide **B**. We hope that the trapping of active ammonium ylide **B** by the bifunctional iminium species occurs in a Mannich-type addition to provide a four-component coupling product **C**. A subsequent one-pot cascade process by an intramolecular aza-Michael addition will readily afford 1,3,4-multisubstituted THIQ **5** or isoindoline **6** depending on the reactivity of the two N–H groups. The challenge of the designed process is to control the order of the bond formation and the stereoselectivity of the desired products.



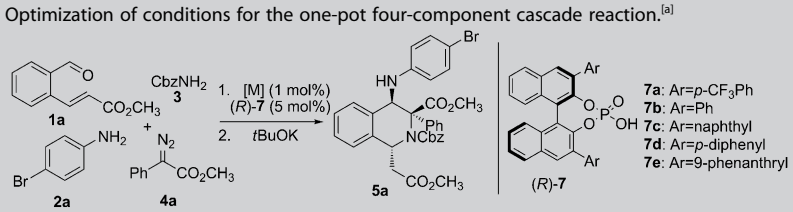
Scheme 2. Schematic of the four-component reaction by synergistic catalysis with a ruthenium complex/chiral Brønsted acid system.

Our initial study began with the reaction of bifunctional substrate **1a**, *p*-bromoaniline **2a**, benzyl carbamate **3**, and methyl phenyldiazoacetate **4a**. We were pleased to find that commercially available $[RuCl_2(p\text{-cymene})]_2$ was a highly compatible catalyst. Decomposition of the diazo compound **4a** went smoothly in the presence of 1 mol% $[RuCl_2(p\text{-cymene})]_2$. Trace amounts of the desired tetrahydroisoquinoline **5a** were exactly detected after treating the reaction mixture with potassium *tert*-butoxide. Significant amounts of N–H insertion product were identified as a side product. The common catalyst, $Rh_2(OAc)_4$, was also used to decompose diazo compound in this reaction system as a control. While in the presence of 1 mol% $Rh_2(OAc)_4$, no diazo decomposition occurred, and only the imine derived from **1a** and **2a** was detected.

To suppress the side reaction and achieve enantioselective control of the desired process, chiral phosphoric acid[11] was employed as a co-catalyst to promote the iminium formation.[12] In the presence of 1 mol% $[RuCl_2(p\text{-cymene})]_2$ and 5 mol% chiral phosphoric acid (*R*)-**7a**, the reaction successfully afforded a Mannich/aza-Michael addition product **5a** in 47% isolated yield with 78:22 diastereomeric ratio (d.r.) and 90:10 enantiomeric ratio (e.r.) of the major diastereomer (Table 1, entry 1). Other ruthenium complexes were then evaluated to catalyze this reaction under otherwise identical reaction conditions. No diazo decomposition occurred when $[RuCl(cod)]_n$ or $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (cod = 1,5-cyclooctadiene; bpy = 2,2′-bipyridine) was used (Table 1, entries 2 and 3). $[RuCl_2(PPh_3)_3]$ only afforded a trace of product **5a** (Table 1, entry 4) because the significant amount of diazo compounds were not decomposed under current conditions.

Other chiral phosphoric acids **7b–e** were then investigated to give comparable yields but much lower d.r. and *ee* values (Table 1, entries 5–8). The reaction conditions were further optimized with various solvents and additives at different temperatures. 1,2-Dichloroethane (DCE) was a better solvent than dichloromethane or toluene, providing **5a** in 51% yield with 85:15 d.r. and 90:10 e.r. (entries 10 vs. 1, 9). Acidic additives were found to have a pronounced effect on the reaction (entries 11–13). (±)-Mandelic acid was identified as the most effective additive when (*R*)-**7a** (5 mol%) was used, evidenced by the enhancement in the distereoselectivity of the reaction from 85:15 to 90:10. The relatively lower temperature was favored to control the reaction selectivity, especially the diastero-

Table 1. Optimization of conditions for the one-pot four-component cascade reaction.[a]



Entry	7	Additive acid (10 mol%)	[M]	Solvent	Yield[b] [%] (major/minor)[c]	e.r.[d]
1	**7a**	–[e]	$[RuCl_2(p\text{-cymene})]_2$	toluene	47 (78:22)	90:10
2	**7a**	–	$[RuCl(cod)]_n$	toluene	n.d.	n.d.
3	**7a**	–	$[Ru(bpy)_3Cl_2]\cdot 6H_2O$	toluene	n.d.	n.d.
4	**7a**	–	$[Ru(PPh_3)_3Cl_2]$	toluene	trace	–
5	**7b**	–	$[RuCl_2(p\text{-cymene})]_2$	toluene	44 (46:54)	46:54
6	**7c**	–	$[RuCl_2(p\text{-cymene})]_2$	toluene	42 (54:46)	54:46
7	**7d**	–	$[RuCl_2(p\text{-cymene})]_2$	toluene	54 (74:26)	74:26
8	**7e**	–	$[RuCl_2(p\text{-cymene})]_2$	toluene	60 (57:43)	57:43
9	**7a**	–	$[RuCl_2(p\text{-cymene})]_2$	CH_2Cl_2	57 (86:14)	78:22
10	**7a**	–	$[RuCl_2(p\text{-cymene})]_2$	DCE	51 (85:15)	94:6
11	**7a**	(±)-10-camphorsulfonic Acid	$[RuCl_2(p\text{-cymene})]_2$	DCE	42 (90:10)	84:16
12	**7a**	(±)-tartaric acid	$RuCl_2(p\text{-cymene})]_2$	DCE	40 (88:12)	90:10
13	**7a**	(±)-mandelic acid	$RuCl_2(p\text{-cymene})]_2$	DCE	57 (90:10)	92:8
14[f]	**7a**	(±)-mandelic acid	$RuCl_2(p\text{-cymene})]_2$	DCE	52 (96:4)	93:7
15[f,g]	**7a**	(±)-mandelic acid	$RuCl_2(p\text{-cymene})]_2$	DCE	66 (96:4)	97:3

[a] Unless otherwise noted, all reactions were carried out at room temperature on a 0.2 mmol scale and **1a**/**2a**/**3**/**4a** = 1.0:1.1:1.2:1.2. 4 Å MS (100 mg) and 1 mol% $[RuCl_2(p\text{-cymene})]_2$ were added, and *t*BuOK (0.22 mmol) was added after the Mannich-type reaction was completed. [b] Isolated yields were obtained after purification by column chromatography. [c] The diastereomeric ratio was detected by ^1H NMR (400 MHz) spectroscopy. [d] Determined by HPLC analysis. [e] No additive acid. [f] Reactions were carried out at −10 °C. [g] The reaction was carried out with 10 mol% of (*R*)-**7a**.

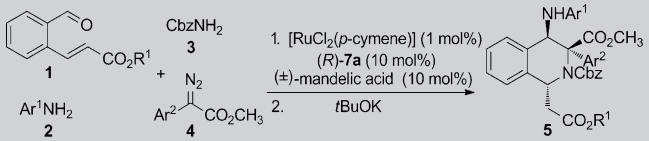
selectivity, as demonstrated by the results at room temperature (90:10 d.r.) and at −10 °C (96:4 d.r., entries 13 vs. 14). The optimal conditions were established as 1 mol% of $[RuCl_2(p\text{-cymene})]$, 10 mol% of phosphoric acid (*R*)-**7a**, and 10 mol% of (±)-mandelic acid in DCE at −10 °C (entry 15).

The general applicability of the protocol was investigated under the optimized reaction conditions, and the results are summarized in Table 2. The process was tolerant to several arylamines **2** (Table 2, entries 1–7). In addition, other bifunctional substrates **1** with different ester groups and additional aryl diazoacetates **4** were feasible substrates in this reaction and gave the corresponding products with satisfactory d.r. and high e.r. values (entries 8–15). The absolute stereochemistry of (1*R*,3*S*,4*R*)-**5a** was established by single-crystal X-ray analysis as a twist-boat conformation (Scheme 3). After deprotonating by base, a *Si*-face attacking to the Michael acceptor will offer a favored product **5a** with twist-boat conformation. A *Re*-face process is unfavored due to the increased steric hindrance.

Removal of the carbobenzyloxy (Cbz) protecting group in the four-component product with Pd/C under a hydrogen atmosphere yielded the corresponding optically active 1,3,4-tetrasubstituted THIQs bearing three chiral stereogenic centers without any loss in enantioselectivity (see the Supporting Information).

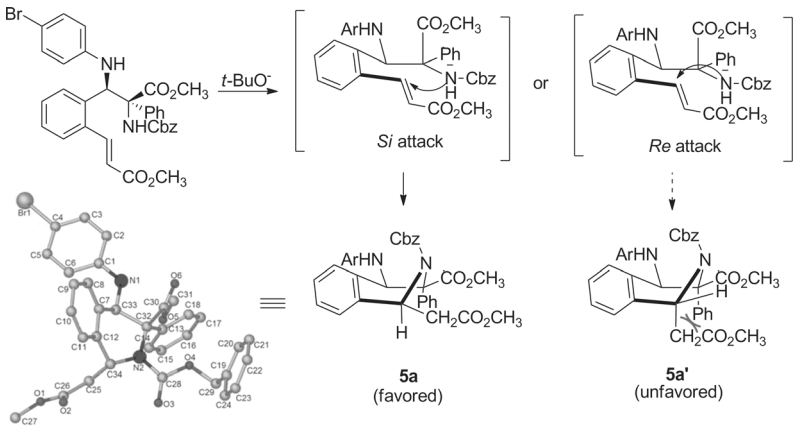
The THIQs ring systems, as an important class of alkaloids, exhibit a vast array of important bioactivities.[13] They are typically present in many complex natural molecules, such as quinocarcin (QNC),[14] ecteinascidin 743,[15] and renieramycin G.[16] Consequently, the merging of potential biological activity with the challenging complexity of molecular architecture makes THIQs attractive molecules for target-directed synthesis. The most frequently used method for the synthesis of THIQs is asymmetric

Table 2. Scope of substrates in the one-pot four-component cascade reaction.[a]



Entry	R^1	Ar^1	Ar^2	Yield[b] [%]	d.r.[c]	e.r.[d]
1	Me	*p*BrPh	Ph	**5a**, 66	96:4	97:3
2	Me	*p*ClPh	Ph	**5b**, 52	87:13	94:6
3	Me	*p*IPh	Ph	**5c**, 48	92:8	94:6
4	Me	*m*MePh	Ph	**5d**, 51	96:4	95:5
5	Me	*p*MePh	Ph	**5e**, 55	86:14	94:6
6	Me	*p*FPh	Ph	**5f**, 57	80:20	97:3
7	Me	*p*EtOPh	Ph	**5g**, 45	76:24	91:9
8	Et	*p*BrPh	Ph	**5h**, 78	86:13	96:4
9	Bn	*p*FPh	Ph	**5i**, 53	95:5	96:4
10	Me	*p*FPh	*p*FPh	**5j**, 67	88:12	94:6
11	Me	*m*MePh	*m*MeOPh	**5k**, 61	85:15	96:4
12	Me	*p*BrPh	*m*MeOPh	**5l**, 53	85:15	95:5
13	Et	*p*FPh	*m*MeOPh	**5m**, 55	92:8	94:6
14	Bn	*p*BrPh	*m*BrPh	**5n**, 72	85:15	96:4
15	Me	*p*BrPh	*m*BrPh	**5o**, 73	86:14	96:4

[a] Unless otherwise noted, all reactions were carried out at −10 °C on a 0.2 mmol scale and **1**/**2**/**3**/**4** = 1.0:1.1:1.2:1.2. 4 Å MS (100 mg), and *t*BuOK (0.22 mmol) was added after the Mannich-type reaction was completed. [b] Isolated yields were obtained after purification by column chromatography. [c] Diastereomeric ratio was detected by ^1H NMR (400 MHz) spectroscopy. [d] Determined by HPLC analysis.



Scheme 3. Proposed processes for the formation of observed stereochemical structures.

hydrogenation of the isoquinoline frameworks.[17] Despite the great advance of this protocol, only 1-alkyl-substituted or 1,3-disubstituted THIQs have been obtained with high enantioselectivity.[17a,b] In addition, due to the easy racemization of 1 or 4-substituted THIQs,[17b,18] the methods for asymmetric synthesis of multisubstituted THIQs, especially 1,3,4-tetrasubstituted THIQs, are considerably rare.[19] Taking advantage of the unique reactivity of the ammonium ylide, the reaction can proceed under mild and neutral conditions allowing rapid construction of structurally constrained chiral 1,3,4-tetrasubstituted THIQs without any racemization of the products.

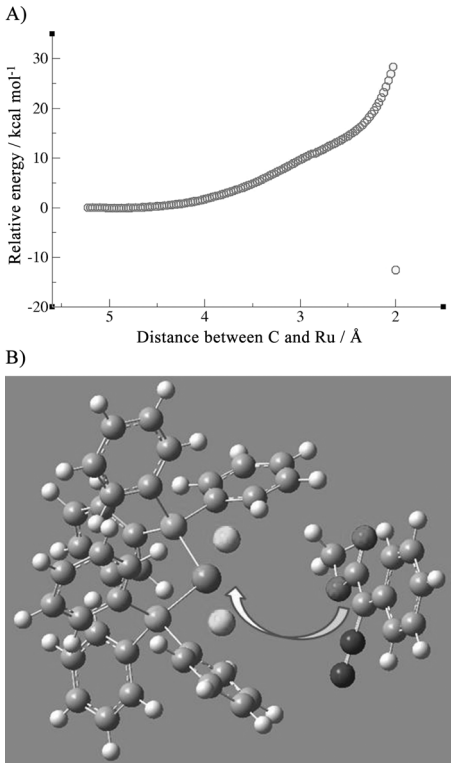


Figure 1. Relaxed potential energy surface along the reaction path for the $[RuCl_2(PPh_3)_3]$-catalyzed reaction.

Carbenoid formation through transition-metal-catalyzed diazo decomposition is a key step in the current process. Here, we tried to explore the catalytic efficiency of Ru complexes in this process through quantum chemical calculations.[20] The computed free energies for transition-metal-catalyzed decomposition of diazo compounds are −9.1, 12.8, and −13.1 kcal mol^{-1} for the catalysis of $[RuCl_2(p\text{-cymene})]$, $[RuCl_2(bpy)_3]\cdot 6H_2O$, and $[RuCl_2(PPh_3)_3]$, respectively, which indicates that $[RuCl_2(p\text{-cymene})]$ and $[RuCl_2(PPh_3)_3]$ can catalyze the decomposition of the diazo compound. $[RuCl_2(bpy)_3]\cdot 6H_2O$ does not work (see the Supporting Information, Table 1S). However, due to the large ligand of $[RuCl_2(PPh_3)_3]$ with the reaction barrier of up to approximately 30 kcal mol^{-1} (Figure 1A), the substrate cannot approach the metal center easily (Figure 1B), which suggests it is very difficult to push the formation of Ru-associated carbenoid forward. These theoretical predictions agree well with our experimental results: $[RuCl_2(p\text{-cymene})]$ efficiently catalyzed the decomposition of the diazo compound to provide the desired tetrahydroisoquinolines, whereas $[RuCl_2(PPh_3)_3]$ only afforded a trace amount of product.

In conclusion, we have developed an elegant synergistic catalytic system comprising a ruthenium complex with chiral Brønsted acid for a four-component Mannich/cascade aza-Michael reaction. The ruthenium-associated ammonium ylides were successful trapped by in situ generated iminiums, which indicates a stepwise process for the ruthenium-catalyzed carbenoid N–H insertion reaction. The calculated thermodynamic data facilitates a better understanding of the decomposition ability of ruthenium complexes towards diazo compounds in this reaction. The transformation features a mild, rapid, and efficient method to synthesize 1,3,4-tetrasubstituted THIQs bearing a quaternary stereogenic carbon center from simple starting precursors in moderate yields with high diastereo- and enantioselectivity. The synergistic catalytic system of ruthenium complexes and chiral Brønsted acids should have a wide application in other ruthenium-catalyzed asymmetric transformations.

Experimental Section

General procedure

A 25 mL flask was charged with bifunctional aldehyde **1** (0.22 mmol), aromatic amine **2** (0.2 mmol), chiral phosphoric acid **7a** (10 mol%), (±)-mandelic acid (10 mol%), and 4 Å MS (0.1 g) in $Cl(CH_2)_2Cl$ (4 mL) and the resulting mixture was stirred at RT for 1 h. $[RuCl_2(p\text{-cymene})]_2$ (1.0 mol%) and benzyl carbamate **3** (2.22 mmol) were then added, and the flask was cooled down to −10 °C. Diazo compound **4** (0.24 mmol) in $Cl(CH_2)_2Cl$ (4 mL) was

added to the reaction mixture over a 1 h time period by a syringe pump. After completion of the addition, potassium *tert*-butoxide (0.24 mmol) was added all at once. After the reaction mixture had been stirred for another 1 h at −10 °C, product **5** from the crude reaction mixture was subjected to ^{1}H NMR spectroscopic analysis for the determination of diastereoselectivity. The reaction mixture was purified by flash chromatography on silica gel (eluent: EtOAc/light petroleum ether 1:10 to 1:5) to give pure **5**

Acknowledgements

We are grateful for financial support from the NSFC (21125209 and 21332003), the MOST of China (2011CB808600), STCSM (12JC1403800), and Fostering Project for National Top Hundred Doctoral Dissertations (PY2011015).

Keywords: Brønsted acid · multicomponent reactions · ruthenium · synergistic catalysis · tetrahydroisoquinolines

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Received: November 22, 2013
Published online on January 16, 2014