Communication

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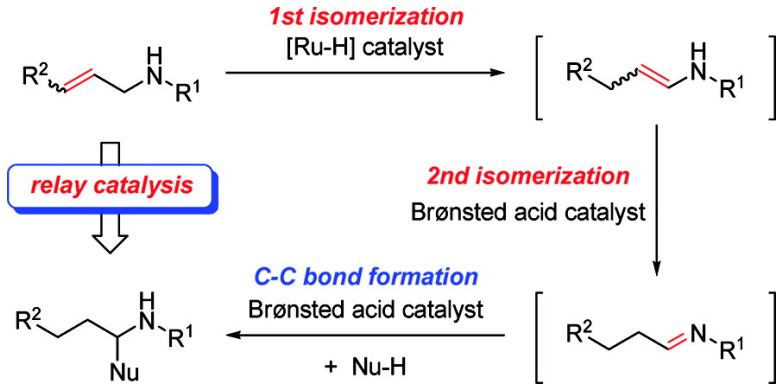

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Relay Catalysis by a Metal-Complex/Brønsted Acid Binary System in a Tandem Isomerization/Carbon−Carbon Bond Forming Sequence

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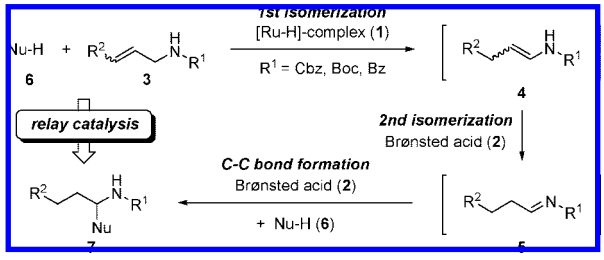
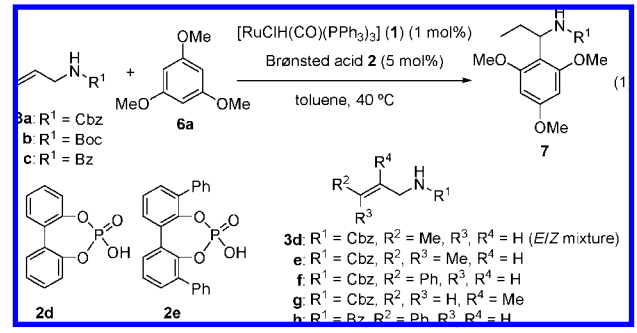
Catalysis by transition metal complexes has been applied to a broad range of organic transformations and occupies a privileged position in synthetic organic chemistry. Much research on catalysis has centered on the use of metal complexes to activate a variety of chemical bonds. In the past decade, however, tremendous progress has been made in catalysis using small organic molecules, namely organocatalysis,[1] in which fundamental organic transformations are efficiently accelerated using a catalytic amount of organic molecules. In recent years, with the idea of taking advantage of both of these catalytic approaches, researchers have combined metal complexes and organic molecules in cooperative catalysis, which has attracted much attention as it could potentially enable unprecedented transformations.[2] Indeed, several excellent approaches have been established using cooperative catalysis.[3,4] In most cases, each reactant is activated by one type of catalyst;[3] for example, a metal complex is used to activate the electrophile while an organic molecule is used to activate the nucleophile. In this communication, we describe an unprecedented relay catalysis[5] for a tandem isomerization/carbon−carbon bond formation sequence using a binary catalytic system consisting of a ruthenium hydride complex (**1**) and a Brønsted acid (**2**) (Scheme 1). The proposed sequential transformation involves a three step relayed catalysis, where (i) isomerization of the allylamide (**3**) to the enamide (**4**) is catalyzed by **1**;[6] (ii) subsequent isomerization of **4** to an imine intermediate (**5**) is relayed by **2**;[7] and (iii) the catalytic sequence is terminated by a carbon−carbon bond forming reaction of **5** with a nucleophilic component (**6**: Nu−H) under the influence of the Brønsted acid catalyst (**2**). The advantage of the present relay catalysis is that the method would enable the generation of reactive imines (**5**) from readily available allylamides (**3**) in a one-pot reaction via tandem isomerization.

Scheme 1. Relay Catalysis by Metal-Complex/Brønsted Acid Binary System for Sequential Transformations



To ascertain the viability of the proposed relay catalysis, we attempted the reaction of trimethoxybenzene (**6a**) with *N*-Cbz protected allylamine (**3a**) under the binary catalytic system to provide the Friedel−Crafts (F−C) product (**7aa**) (eq 1). An initial experiment was performed using 1 mol% of $[RuClH(CO)(PPh_3)_3]$ (**1**)[6c,d] and 5 mol% of TfOH (**2a**) in toluene at 40 °C. To our delight, the corresponding F−C product (**7aa**) was obtained, albeit in low chemical yield (Table 1, entry 1). Screening of Brønsted acids (**2**) identified phosphoric acid (**2d**) as the better catalyst (entries 2−4). Further modification of the phosphoric acid catalyst (**2e**) by the addition of phenyl substituents at the 3,3′-position exhibited a marked effect on the catalytic activity, affording **7aa** in excellent yield (entry 5). Control experiments revealed that both of the catalysts, **1** and **2**, are indispensable in allowing the sequential processes to progress and finally give rise to the F−C product (**7aa**); the reaction did not proceed at all in the absence of **1**, while, under acid-free conditions, isomerization of **3a** to enamide (**4a**) took place but the desired F−C product was not obtained.[8] Further investigation of the protecting group on the allylamine showed that for the *N*-Boc allylamine (**3b**) a substituted phosphoric acid catalyst (**2e**) was suitable (entry 6). Whereas, for the *N*-Bz-protected allylamine (**3c**), stronger acids such as TfOH (**2a**) or Tf_2NH (**2f**) were more effective than the phosphoric acid (**2e**) (entries 7−9).

Table 1. Relay Catalysis for Tandem Isomerization/Friedel−Crafts Sequential Transformation of **3** with **6a** (Eq 1)[a]



entry	2	3	time (h)	7	yield (%)[b]
1	TfOH (**2a**)	**3a**	14	**7aa**: R^1 = Cbz	33
2[c]	TFA (**2b**)	**3a**	24		56
3[c]	CSA (**2c**)	**3a**	24		15
4	**2d**	**3a**	6		74
5	**2e**	**3a**	3		98
6	**2e**	**3b**	5	**7ba**: R^1 = Boc	92
7	**2e**	**3c**	12	**7ca**: R^1 = Bz	89
8	TfOH (**2a**)	**3c**	2		88
9	Tf_2NH (**2f**)	**3c**	2		84

[a] Unless otherwise noted, all reactions were carried out with 0.50 mmol of **3**, 0.75 mmol of **6a** (1.5 equiv), 0.005 mmol of **1** (1 mol%), and 0.025 mmol of **2** (5 mol%) in 1.0 mL of toluene at 40 °C. [b] Isolated yield. [c] At 50 °C.

Table 2 summarizes experiments carried out to probe the scope of the present sequential transformation. Having determined the optimal acid catalyst for different protecting groups on the allylamines (Method A: **2e**/*N*-Cbz or *N*-Boc allylamines, Method B: **2f**/*N*-Bz allylamines), we employed the phosphoric acid catalyst (**2e**) for a series of substituted allylamines (**3**) bearing a *N*-Cbz protecting group (entries 1−4). F−C products were obtained in

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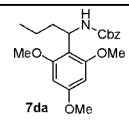
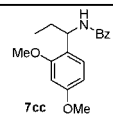
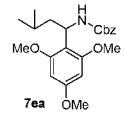
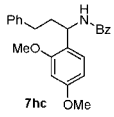
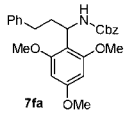
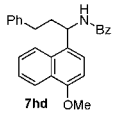
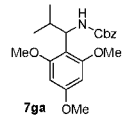
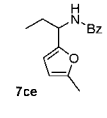
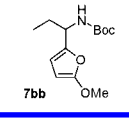
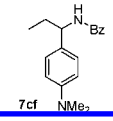
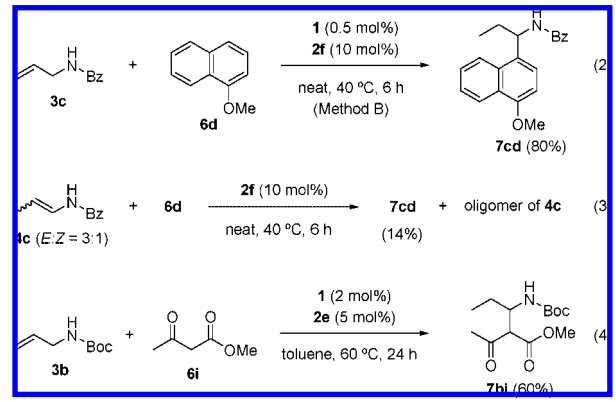
good yields for linear and branched alkyl substituents as well as for an aromatic substituent (entries 1−3). *N*-Cbz methallylamine (**3g**) was also applicable to the present transformation, although the reaction gave a modest chemical yield (entry 4). We next investigated a series of aromatic compounds (**6**). The reaction of 2-methoxyfuran (**6b**) with *N*-Boc allylamine (**3b**) proceeded smoothly using Method A (entry 5). The reaction of 1,3-dimethoxybenzene (**6c**) was conducted by Method B (entries 6,7), that is, using a combination of **2f** and *N*-Bz allylamines, because the F−C product could not be obtained by Method A. Method B is also applicable to other aromatic compounds (entries 8−10), such as 1-methoxynaphthalene (**6d**), 2-methylfuran (**6e**), and *N*,*N*-dimethylaniline (**6f**), affording the corresponding F−C products in good yield.

Table 2. Substrate Scope of Tandem Isomerization/Friedel−Crafts Sequential Transformations[a,b]

entry	7	yield[c] conditions	entry	7	yield[c] conditions
1[d]	 **7da**	80% Method A 110 °C, 8 h	6	 **7cc**	79% Method B 40 °C, 2 h
2[d]	 **7ea**	85% Method A 110 °C, 8 h	7	 **7hc**	69% Method B 130 °C, 36 h
3	 **7fa**	91% Method A 110 °C, 8 h	8[d]	 **7hd**	82%[g] Method B 110 °C, 36 h
4[d]	 **7ga**	55% Method A 110 °C, 36 h	9[e]	 **7ce**	88% Method B 40 °C, 2 h
5	 **7bb**	69% Method A 40 °C, 12 h	10[f]	 **7cf**	77% Method B 80 °C, 16 h

[a] Method A: The reactions were carried out with 0.50 mmol of **3**, 0.75 mmol of **6**, 0.005 mmol of **1** (1 mol%), and 0.025 mmol of **2e** (5 mol%) in 1.0 mL of toluene. [b] Method B: The reactions were carried out with 0.50 mmol of **3**, 5.0 mmol of **6**, 0.005 mmol of **1** (1 mol%), and 0.050 mmol of Tf_2NH (**2f**, 10 mol%) under solvent-free conditions. [c] Isolated yield. [d] 2 mol% of **1**. [e] 3.0 equiv of **6e** in 1 mL of toluene. [f] 1.5 equiv of **6f** in 1 mL of toluene. [g] 4-Addition product/2-addition product = 94:6.

The distinct advantage of the present relay catalysis is highlighted in comparison with a control experiment using enamide (**4**) (eq 2 vs 3). The reaction of **6d** with enamide (**4c**) in the presence of **2f** gave an oligomer of the enamide (**4c**) as the major product, and the F−C product (**7cd**) was obtained in low yield (eq 3). This result clearly shows that enamide (**4c**) on its own functions as a nucleophilic component and reacts predominantly with the intermediary imine (**5c**) delivered from isomerization of **4c**. In contrast, the present sequential transformation provided the desired F−C product (**7cd**) in good yield (eq 2). It is considered that the concentration of **4c** is maintained at low levels under the relay catalysis, and hence the oligomerization of **4c** was effectively suppressed. The present relay catalysis is also applicable to the reaction of a 1,3-dicarbonyl compound (**6i**) as a nucleophilic component. The corresponding Mannich product (**7bi**) was obtained in an acceptable yield using 2 mol% of **1** and 5 mol% of **2e** (eq 4).



In conclusion, we have successfully demonstrated a one-pot tandem isomerization/C−C bond forming sequence using a ruthenium complex/Brønsted acid binary catalytic system. The present relay catalysis enables the use of readily available allylamides to generate imines for further successive transformations. In future studies we will continue to develop related catalytic sequences, including an enantioselective version of the methodology described herein.

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Supporting Information Available: Representative experimental procedure including details of control experiments and spectroscopic data for the reaction products (**7**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) 1:1 *E*/*Z* mixture of *N*-Cbz protected enecarbamate (**4a**) was obtained.

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