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COMMUNICATION

Ru-catalyzed β-selective and enantioselective addition of amines to styrenes initiated by direct arene-exchange†

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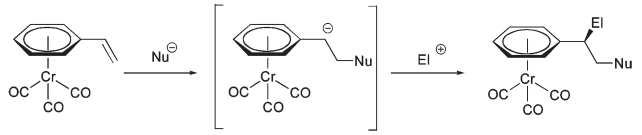
A catalytic β-selective addition of amines to styrenes proceeded in the presence of cationic Ru complexes combined with diphosphine ligands. In the reaction of α-methylstyrene, an enantioselective addition was achieved by using xylylBINAP.

η^6-Arene metal complexes have a number of distinguishing features, which free arenes do not show and the stabilization of the negative charge on the benzylic position is one of them.[1] Actually, η^6-arene chromium tricarbonyl ((arene)$Cr(CO)_3$) complexes are widely used in organic synthesis. For example, (styrene)$Cr(CO)_3$ complexes undergo nucleophilic attack at exclusively the β-position of the complexed styrenes. The generated anion reacts with electrophiles (El^+) in a highly stereoselective manner, because the metal moiety of the complexes effectively shields one of the π-faces of benzene (Scheme 1).[2] The synthesis of (styrene)$Cr(CO)_3$ complexes and the demetallation of (transformed-styrene)$Cr(CO)_3$ complexes are so facile that this method can be used for the synthesis of various substituted arenes.

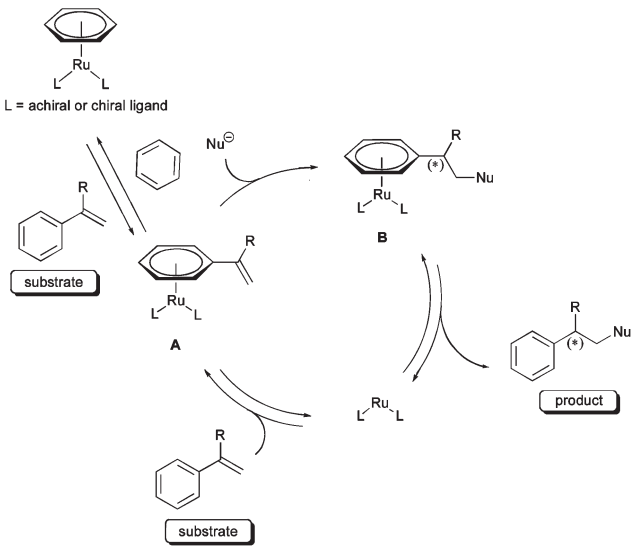
Recently we developed an exclusively β-selective nucleophilic addition of various heteronucleophiles to (styrene)$Cr(CO)_3$ complexes. Alcohols, amines, and thiols could be used as nucleophile, and the functionalized substituted arenes could be readily obtained by exposure to sunlight in air.[3] This transformation is useful, but the major drawback is the use of a stoichiometric amount of transition metal, and the development of a catalytic version of this reaction is a challenging topic, because of the stability of η^6-arene metal complexes. Actually, as far as we know, there is only an example, which realized catalytic β-selective nucleophilic addition to styrenes *via* η^6-arene metal complexes, however the reaction required thermally sensitive ruthenium complex (Ru(cod)(2-methylallyl)$_2$) and strong acid (trifluoromethanesulfonic acid) for the preparation of η^6-arene Ru complexes.[4]

On the other hand, we have previously developed the catalytic S_NAr reaction of nonactivated arenes with amines using [Ru(benzene)Cl_2]$_2$, AgOTf, and P(*p*-FC_6H_4)$_3$.[5] This reaction proceeded *via* η^6-fluoroarene ruthenium complexes, which were generated *in situ* by direct arene-exchange of the benzene coordinated to ruthenium with fluoroarenes. We then hypothesized that the desired catalytic β-selective nucleophilic addition to styrenes could proceed using our catalysis. Moreover, in the reaction of α-substituted styrenes, the use of chiral ligands could achieve enantioselective and β-selective nucleophilic addition *via* η^6-arene ruthenium complexes (Scheme 2).

In this report, we demonstrate the ruthenium-catalyzed β-selective nucleophilic addition of amines to styrenes *via*



Scheme 1 Regioselective addition of nucleophiles and electrophiles to (styrene)$Cr(CO)_3$ complexes.



Scheme 2 Proposed mechanism of catalytic (enantioselective) nucleophilic addition to α-substituted styrenes *via* η^6-arene ruthenium complexes.

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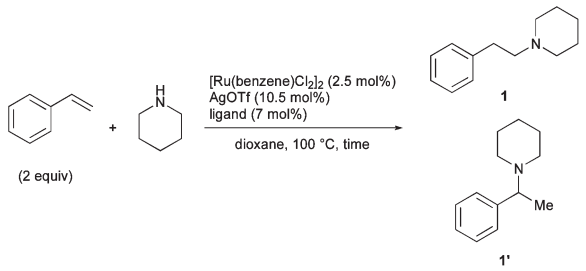
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob25457c

Table 1 Optimization of reaction conditions



Entry	Ligand	Time (h)	Yield of **1** (%)	Yield of **1′** (%)
1	2P(p-FC_6H_4)$_3$	24	24	5
2	2PPh_3	24	22	10
3	2P(p-$OMeC_6H_4$)$_3$	24	50	20
4	DPPF	24	48	27
5	DPPPent	24	40	0
6	DPPPent	72	78	0

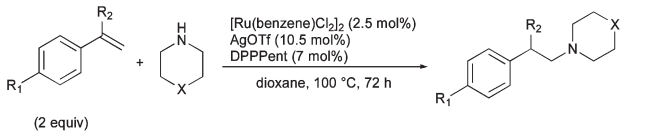
DPPF: 1,1′-bis(diphenylphosphino)ferrocene, DPPPent: 1,5-bis (diphenylphosphino)pentane.

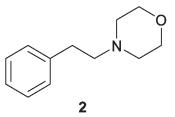
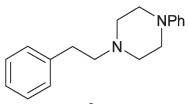
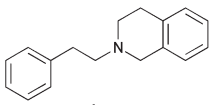
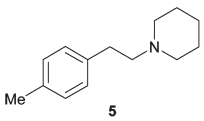
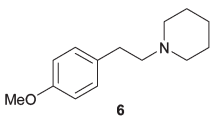
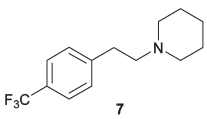
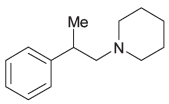
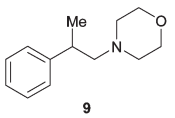
η^6-arene metal complexes. We further describe the first catalytic enantioselective nucleophilic addition of amines to styrenes, in which η^6-arene metal complexes are used as chiral templates.

First we screened phosphine ligands for the β-selective nucleophilic addition using styrene and piperidine as model substrates in dioxane at 100 °C for 24 h (Table 1). When P(p-FC_6H_4)$_3$ was examined, which was the most efficient ligand for the catalytic S_NAr reaction,[5] the desired catalytic reaction proceeded and β-adduct **1** was obtained in 24% yield, while α-adduct **1′** was also obtained as a by-product (entry 1). Then other monodentate phosphine ligands were examined. Using PPh_3, undesired α-adduct **1′** was also obtained along with β-adduct **1** (entry 2). In the case of the electron-donating ligand P(p-$OMeC_6H_4$)$_3$, the conversion ratio increased, and the yield of desired product **1** was significantly improved to 50%, but α-adduct **1′** was also obtained in 20% yield (entry 3). Next, we explored the bidentate phosphine ligands: ferrocenyl ligand DPPF gave almost the same result as P(p-$OMeC_6H_4$)$_3$ (entry 4). When DPPPent was used, only β-adduct **1** was obtained in 40% yield without the formation of α-adduct **1′** (entry 5). As a result of the prolonged reaction time from 24 h to 72 h, the conversion ratio was improved significantly, and the corresponding product **1** was obtained in 78% yield as a sole product (entry 6).

Under the optimal reaction conditions (entry 6 in Table 1), the substrate scope was examined (Table 2). When the reaction of morpholine with styrene was tested, the corresponding product **2** was obtained in comparable yield as with piperidine (entry 1). The reaction of *N*-phenylpiperazine also proceeded to give the desired product **3** in moderate yield (entry 2). On the other hand, tetrahydroisoquinoline gave the corresponding product **4** in good yield (entry 3). *p*-Methylstyrene, bearing electron-donating group, also underwent the addition to give the corresponding product **5** in 67% yield (entry 4), however the reaction of a styrene possessing more the electron-donating methoxy group did not proceed at all, probably because the methoxy substituted-styrene is too electron-rich to undergo the nucleophilic addition

Table 2 β-Selective nucleophilic addition of amines to styrenes

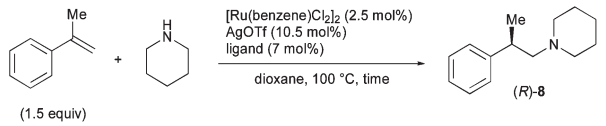


Entry	Product	Yield (%)
1	 **2**	73
2	 **3**	43
3	 **4**	75
4	 **5**	67
5	 **6**	N.D.
6	 **7**	15
7	 **8**	50
8	 **9**	52

(entry 5). When a styrene with an electron-deficient CF_3 group was examined, the reaction proceeded, albeit in low yield (entry 6). It is probably difficult for *p*-trifluoromethylstyrene to undergo arene-exchange with benzene of the Ru complex. Then, we examined α-substituted styrene and found that α-methylstyrene was a suitable substrate, which reacted with piperidine and morpholine giving the corresponding products **8** and **9**, containing an asymmetric carbon atom, in moderate yields (entries 7 and 8).

To develop an enantioselective reaction, we further screened chiral phosphine ligands in the nucleophilic addition of piperidine to α-methylstyrene (Table 3). When (*S*,*S*)-CHIRAPHOS was tested, the desired reaction did not efficiently proceed (entry 1). On the other hand, the desired catalytic reaction proceeded when (*S*)-Et-FerroTANE was used, and the yield was increased significantly (entry 2). Besides, (*S*)-BINAP gave a

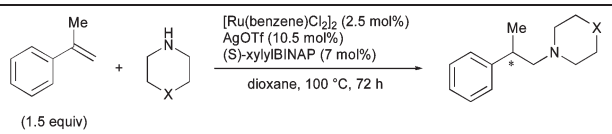
Table 3 Screening of chiral ligands

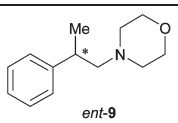
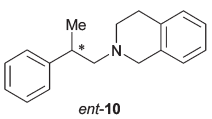
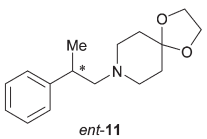


Entry	Ligand	Time (h)	Yield (%)	Ee (%)
1	(*S*,*S*)-CHIRAPHOS	24	4	6
2	(*S*,*S*)-Et-FerroTANE	24	26	39
3	(*S*)-BINAP	24	27	42
4	(*S*)-tolBINAP	24	25	45
5	(*S*)-xylylBINAP	24	27	76
6	(*S*)-xylylBINAP	72	52	76

(*S*,*S*)-CHIRAPHOS: (−)-(2*S*,3*S*)-bis(diphenylphosphino)butane, (*S*,*S*)-Et-FerroTANE: (−)-1,1′-bis((2*S*,4*S*)-2,4-diethylphosphotano)ferrocene.

Table 4 Enantioselective β-selective nucleophilic addition of amines to α-methylstyrene

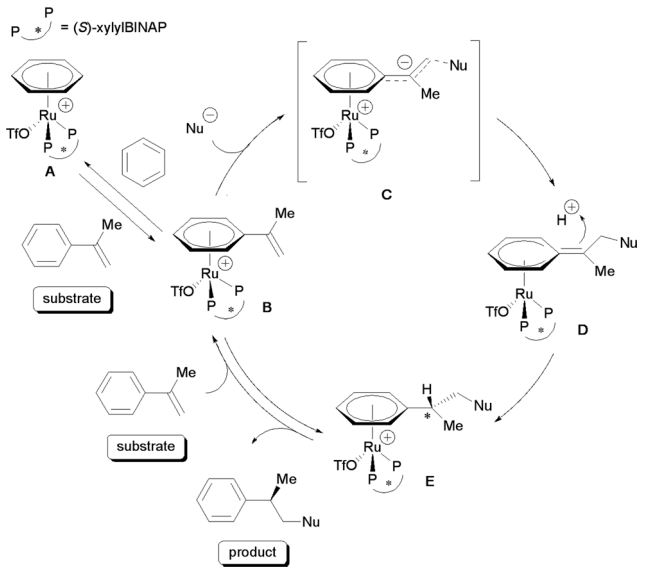


Entry	Product	Yield (%)	Ee (%)
1	 *ent*-**9**	44	61
2	 *ent*-**10**	25	64
3	 *ent*-**11**	20	75

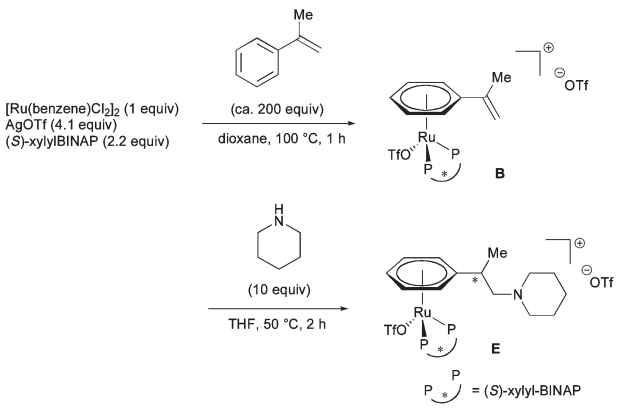
similar result to (*S*)-Et-FerroTANE (entry 3). Then, we screened BINAP derivatives: (*S*)-tolBINAP did not improve the yield nor enantioselectivity of the β-adduct, while (*S*)-xylylBINAP achieved good enantioselectivity (76% ee) (entries 4 and 5). When the reaction time was prolonged, the yield was improved to 52% without loss of enantioselectivity (entry 6).[6,7]

Under the optimal conditions (Table 3, entry 6), the nucleophilic addition of a few amines was examined (Table 4). When morpholine was examined, the desired nucleophilic addition proceeded to give the corresponding product *ent*-**9** in 44% yield with 61% ee (entry 1). In the case of tetrahydroisoquinoline, the yield of *ent*-**10** was low, but the enantioselectivity was good (entry 2). 4-Piperidone ethylene ketal also gave the corresponding product *ent*-**11** with high enantioselectivity, albeit in low yield (entry 3).

Next, we considered the proposed mechanism of the present reaction; first, complex **A** is transformed into complex **B** by



Scheme 3 Proposed reaction mechanism.



Scheme 4 Characterization of η^6-arene Ru complexes **B** and **E**.

arene-exchange from benzene to α-methylstyrene. Second, complex **B** undergoes nucleophilic attack. At the step of the formation of **D** *via* transition state **C**, the enantioselection is induced. The protonation to **D** proceeds from the other side of the ruthenium, and complex **E** is obtained. Finally, complex **E** dissociates the product along with association with the starting material (Scheme 3).

We tried to ascertain the formation of the proposed intermediates by ESI-MS analysis (Scheme 4). To a mixture of [Ru(benzene)Cl_2]$_2$, AgOTf, and (*S*)-xylylBINAP in dioxane, an excess amount of α-methylstyrene was added, and the mixture was heated at 100 °C for 1 h. Then the excess amount of α-methylstyrene was removed *in vacuo*, and the resulting crude products were analyzed. As a result, the desired complex **B** was successfully detected ($[M]^+$) (see ESI†). Next, to the crude products including complex **B**, 10 equiv. of piperidine was added in THF at 50 °C for 2 h, and the resulting mixture was analyzed and the desired complex **E** was also detected ($[M - TfOH]^+$) (see ESI†).

In conclusion, we demonstrated the β-selective catalytic nucleophilic addition of amines to styrenes *via* η^6-arene

ruthenium complexes. Furthermore, an asymmetric version of the reaction was also realized using an α-substituted styrene in the presence of a chiral ruthenium catalyst. The enantioselective nucleophilic addition is the first example of η^6-arene ruthenium complexes as chiral templates.

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Notes and references

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6 Only two examples of enantioselective β-selective addition of amines to styrenes have been reported by using chiral Pd catalysts, but the amines were limited to aniline derivatives: (*a*) M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2000, **122**, 9546; (*b*) A. Hu, M. Ogasawara, T. Sakamoto, A. Okada, K. Nakajima, T. Takahashi and W. Lin, *Adv. Synth. Catal.*, 2006, **348**, 2051.

7 The absolute configuration of compound **8** was determined to be *R* from by the comparison of the sign of optical rotation (*R*)-**8**, which was prepared from (*R*)-2-phenylpropan-1-amine.

