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Ruthenium-Catalyzed Intermolecular Coupling Reactions of Arylamines with Ethylene and 1,3-Dienes: Mechanistic Insight on Hydroamination vs *ortho*-C–H Bond Activation

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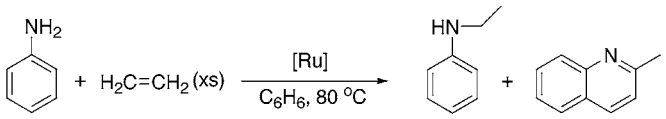
ABSTRACT



The cationic ruthenium complex $[(PCy_3)_2(CO)(Cl)Ru{=}CHCH{=}C(CH_3)_2]^+BF_4^-$ was found to be an effective catalyst for the coupling reaction of aniline and ethylene to form a ~1:1 ratio of *N*-ethylaniline and 2-methylquinoline products. The analogous reaction with 1,3-dienes resulted in the preferential formation of Markovnikov addition products. The normal isotope effect of $k_{NH}/k_{ND} = 2.2$ (aniline and aniline-d_7 at 80 °C) and the Hammett $\rho = -0.43$ (correlation of para-substituted *p*-X-$C_6H_4NH_2$) suggest an N–H bond activation rate-limiting step for the catalytic reaction.

Transition metal-catalyzed hydroamination of alkenes and alkynes is a highly effective method for forming new C−N bonds.[1] Though early transition and lanthanide metal catalysts have been successfully utilized for hydroamination reactions,[2] late transition metal catalysts have been shown to be particularly promising for the functionalized substrates. Since Milstein's pioneering example of Ir-catalyzed hydroamination reaction of norbornene,[3] a number of late transition metal catalysts have been developed for the hydroamination reactions. Most notably, Hartwig recently developed highly effective chiral Pd−phosphine catalysts for the asymmetric version of hydroamination of aryl-substituted alkenes and dienes.[4] Ozawa and co-workers developed highly active cationic Pd−allyl catalysts for the hydroamination of 1,3-dienes.[5] Furthermore, several groups recently achieved *anti*-Markovnikov hydroamination reactions of α-olefins[6] and intramolecular hydroamination of unactivated alkenes[7] by using late metal catalysts. One of the remaining challenges for the hydroamination reaction is to develop practical catalytic systems that can lead to an extension of a relatively

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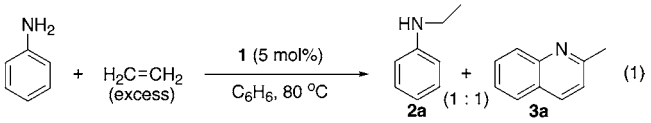
narrow reaction scope and are applicable to organic synthesis. We recently developed a new catalytic method for forming synthetically useful cyclic imines from the C−H bond activation reaction of cyclic amines and alkenes.[8] In an effort to extend the scope of the catalytic reaction, we have begun to explore the catalytic activity of ruthenium complexes for the hydroamination of alkenes and dienes.

We previously found that the cationic ruthenium−alkylidene complex $[(PCy_3)_2(CO)(Cl)Ru{=}CH{-}CH{=}C(CH_3)_2]^+BF_4^-$ (**1**) is an effective catalyst for hydrovinylation and silylation reactions.[9] Initially, we explored the catalytic activity of **1** for the hydroamination of alkenes. For example, the treatment of aniline (60 mg, 0.65 mmol) with ethylene (7 mmol) in the presence of **1** (5 mol %) in benzene at 80 °C gave a ∼1:1 mixture of *N*-ethylaniline (**2a**) and 2-methylquinoline (**3a**) in 71% combined yield (eq 1). The organic products **2a** and **3a** were isolated by column chromatography, and their structures were completely established by spectroscopic methods.



The survey of ruthenium catalysts showed that the cationic ruthenium complexes, **1** and that formed in situ from $(PCy_3)_2(CO)(Cl)RuH$ (**4**)/$HBF_4{\cdot}OEt_2$,[9a] were found to be equally effective for the hydroamination of aniline and ethylene (Table 1). The addition of excess acid marginally influenced

Table 1. Coupling Reaction of Aniline and Ethylene[a]

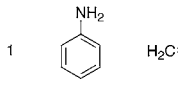
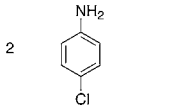
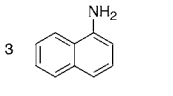
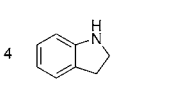
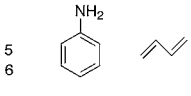
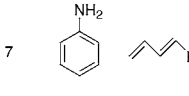
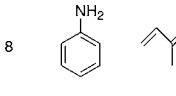
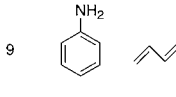
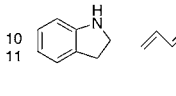
entry	catalyst	additive (mol %)	**2a** (% yield)[b]	**3a** (% yield)[b]
1	**1**		34	37
2	**4**		<1	0
3	**4**	$HBF_4{\cdot}OEt_2$ (10)	38	40
4	**4**	$HBF_4{\cdot}OEt_2$ (20)	40	28
5	**4**	CF_3SO_3H (10)	1	4
6	**4**	NH_4Cl (10)	<1	0
7	$(PPh_3)_3RuHCl$		0	0
8	$(PPh_3)_3RuHCl$	$HBF_4{\cdot}OEt_2$ (10)	0	1
9	$[(PCy_3)_2(CH_3CN)_2(CO)RuH]BF_4$		0	1
10	$Ru_3(CO)_{12}$	NH_4PF_6 (15)	<1	0
11	$RuCl_3{\cdot}3H_2O$	$HBF_4{\cdot}OEt_2$ (10)	<1	0
12	$[Ru(cod)Cl_2]_x$	$HBF_4{\cdot}OEt_2$ (10)	<1	<1

[a] Reaction conditions: aniline (0.3 mmol), ethylene (6 mmol), Ru catalyst (5 mol %), benzene (2 mL), 80 °C, 48 h. [b] Determined by GC.

the product ratio of **2a** and **3a** for the reactions catalyzed by **4**/$HBF_4{\cdot}OEt_2$ (entries 3, 4). A salient feature of **1** is that the catalyst does not require any acids or other additives to effect the catalytic reaction. The formation of 2-methylquinoline products has been previously reported in metal-catalyzed amination reactions.[10] The catalytic synthesis of quinoline derivatives is of considerable interest in part due to their biological and pharmacological importance.[11]

The scope of the reaction was surveyed by using the catalyst **1** (Table 2). Both primary arylamines and secondary

Table 2. Hydroamination of Ethylene and 1,3-Dienes[a]

entry	amine	alkene	product (s)	temp (°C)	t (h)	yield (%)[b]
1		$H_2C{=}CH_2$	**2a** (48:52) **3a**	80	48	71
2			**2b** (46:54) **3b**	80	48	88
3			**2c** (40:60) **3c**	80	48	85
4			**2d** (65:35) **4d**	80	36	81
5			**5e** (70:30) **6e**	45	36	92
6				20	36	97[c]
7			**5f** (>95:5) **6f**	100	36	50
8			**5g** (90:10) **6g**	90	36	68
9			**5h**	90	36	35
10			**5i** (73:27) **6i**	45	24	95
11				20	36	97[c]

[a] Reaction conditions: amine (0.65 mmol), alkene (6−7 mmol), **1** (5 mol %), benzene (2−5 mL). [b] Isolated yield. [c] **4** (5 mol %)/$HBF_4{\cdot}OEt_2$ (10 mol %) was used as the catalyst.

benzocyclic amines were found to be suitable substrates for the hydroamination reaction. A mixture of the hydroamination and the quinoline products **2** and **3** was formed for aryl-substituted amines (entries 1−3), while the reaction of indoline with ethylene gave a mixture of **2d** and the dehydrogenation product **4d** (entry 4). Only ethylene was found to give the coupling products among selected alkenes; no activity was observed with alkyl-substitued alkenes and styrene.

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The hydroamination reaction of butadiene proceeded at a considerably lower temperature to form the Markovnikov addition product **5e** predominantly over the anti-Markovnikov addition product **6e** (entries 5 and 6). High regioselectivity for the Markovnikov addition products was observed for substituted 1,3-dienes, albeit with moderate yields (entries 7−9). No *ortho*-C−H bond activation product was observed for these dienes.

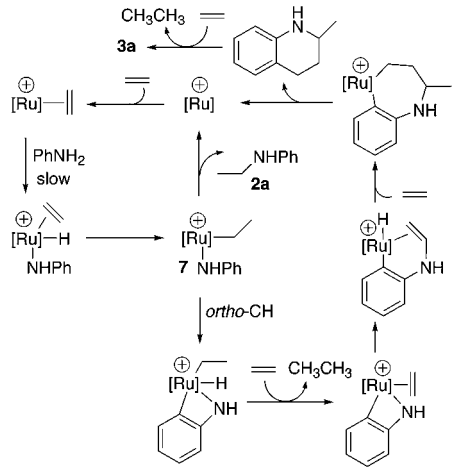
To discern the factors influencing the formation of hydroamination vs C−H bond activation products, the following mechanistic studies were performed by using aniline and ethylene. (1) The empirical reaction rate was found to be first-order with respect to both [aniline] and [**1**] and was independent of [ethylene] for a wide range of concentrations (3.2−13.5 mM) (Supporting Information). The rate constant $k_{obs} = 3.4 \times 10^{-2}$ h^{-1} was obtained under pseudo-first-order reaction conditions at [aniline] = 0.65 mM and [**1**] = 32 μM.

(2) A normal deuterium isotope effect was observed for the reaction of $C_6H_5NH_2$ and $C_6D_5ND_2$. The pseudo-first-order plots of the catalytic reaction from both aniline and aniline-d_7 at 80 °C led to $k_{obs} = 2.9 \times 10^{-2}$ h^{-1} and $k_{obs} = 1.3 \times 10^{-2}$ h^{-1}, respectively, which translated to $k_{NH}/k_{ND} = 2.2 \pm 0.1$ at 80 °C (Figure S1, Supporting Information). A similar normal deuterium isotope effect has been observed on the distribution of both products, **2a** vs **2a**-*d* and **3a** vs **3a**-*d*. In contrast, a negligible isotope effect of k_{CH}/k_{CD} was observed from $C_6H_5NH_2$ and $C_6D_5NH_2$ with ethylene at 80 °C. These results indicate that the N−H bond activation is the rate-limiting step of the catalytic reaction and the subsequent *ortho*-C−H bond and alkene insertion steps are relatively facile.

(3) The reaction rate was found to be moderately accelerated by an electron-releasing group of aniline. A Hammett value ρ of −0.43 was obtained from the correlation of para-substituted *p*-X-$C_6H_4NH_2$ (X = OMe, CH_3, H, CF_3) with σ_p^+ (Figure S6, Supporting Information). A better correlation with σ_p^+ compared to σ_p suggests the importance of resonance stabilization in the cationic transition state.[12]

A possible mechanistic scheme of the catalytic reaction is shown in Scheme 1. Both the observation of the normal isotope effect of $k_{NH}/k_{ND} = 2.2$ and the Hammett value $\rho = -0.43$ support a mechanism with the N−H bond activation as the rate-limiting step, in which the N−H bond activation step is promoted by an electron-releasing group. The subsequent alkene insertion and the reductive elimination via an alkyl-amido species **7** would give the product **2**. The zero-order dependence on [ethylene] suggests that the alkene insertion step is rapid and reversible. The formation of 2-methylquinoline product **3** can be rationalized by invoking a competitive *ortho*-arene C−H bond activation from **7**. The subsequent ethylene insertion, β-H elimination, reinsertion, and reductive elimination steps would lead to the 2-methyl tetrahydroquinoline product, which further undergoes ruthenium-promoted dehydrogenation to form the quinoline product **3**.[13] The apparent lack of the formation of quinoline products for 1,3-dienes can be readily explained by the preferential formation of a sterically demanding secondary allyl intermediate species from 2,1-insertion of a diene, which would prohibit the *ortho*-C−H bond activation.[14]

Scheme 1



In summary, the cationic ruthenium complex **1** was found to be an effective catalyst for the hydroamination of ethylene and 1,3-dienes. The formation of a nearly equal ratio of products **2** and **3** is explained by an initial N−H bond activation rate-limiting step followed by energetically compatible reductive elimination vs *ortho*-C−H bond activation pathways. Further research is warranted for a detailed understanding on the factors influencing the *ortho*-C−H bond activation of arylamines.

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Supporting Information Available: Experimental procedures and spectroscopic data of organic products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Treatment of tetrahydroquinoline with ethylene and **1** (5 mol %) gave the quinoline product **3a**. A similar result was also reported in ref 10a.

(14) Observed Hammett and the kinetic isotope effect data are also consistent with a mechanism involving reversible nucleophilic addition of aniline to a cationic (π-alkene)Ru species followed by rate-limiting proton transfer, though this mechanism cannot readily explain the formation of quinoline products.[4,5] A "domino" mechanism of sequential addition of alkenes via an imine intermediate has been proposed for the formation of quinoline products.[10b]