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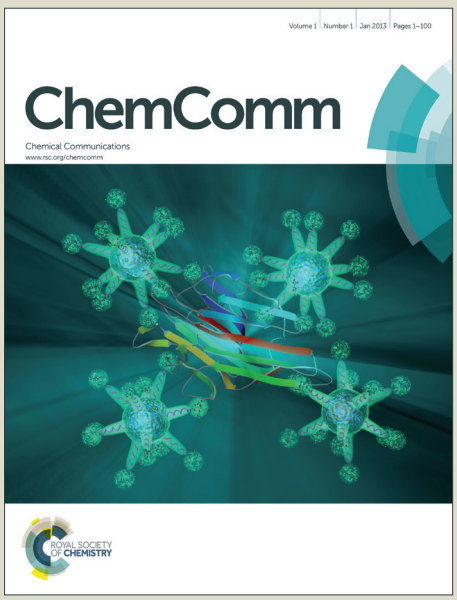

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A Formal *anti*-Markovnikov Hydroamination of Allylic Alcohols via Tandem Oxidation/1,4-Conjugate Addition/1,2-Reduction with Ru Catalyst

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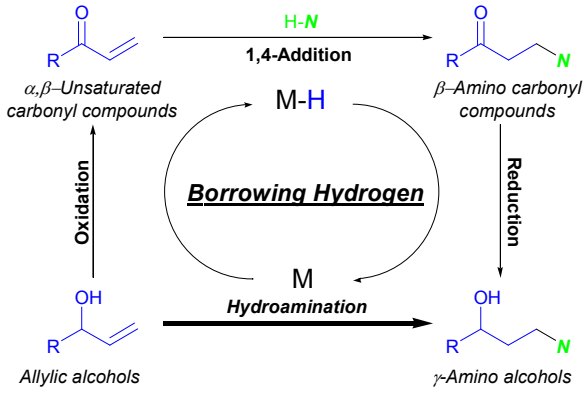
A formal anti-Markovnikov hydroamination of allylic alcohols with Ru catalyst via tandem oxidation/1,4-conjugate addition/1,2-reduction was developed. Thus, the reaction of allylic alcohols with amines was performed in the presence of the catalyst generated from $RuClH(CO)(PPh_3)_3$ and 2,6-bis(*n*-butyliminomethyl)pyridine in situ to afford the corresponding γ-amino alcohols efficiently.

Various reactions have been developed on the basis of the reactivity of transition metal complexes. In particular, the catalytic hydroamination of olefins is a very important reaction for a synthetic and modifying method of amines, as the transformation is very environmentally benign.[1] Various intra- and intermolecular hydroaminations catalyzed by transition metal complexes have been reported to date.[2-7] Among them, *anti*-Markovnikov hydroamination of terminal alkenes is still difficult.[8] Although the Ru and Rh-catalyzed *anti*-Markovnikov hydroamination reported by Hartwig et al. are known,[9] the applicable scope of substrates has been limited to vinyl arenes. Very recently, an efficient method for the *anti*-Markovnikov hydroamination uses a stoichiometric amount of organozirconium compounds[10] and a two-step catalytic process through the Pd-catalyzed *anti*-Markovnikov Wacker reaction and Ru-catalyzed reductive amination[11] have been reported. Nicewicz et al. reported a metal-free *anti*-Markovnikov hydroamination catalyzed by the organic photoredox system.[12] However, *anti*-Markovnikov hydroamination of the terminal carbon-carbon double bond in allylic alcohols, which are readily prepared by the reaction of vinyl-metal compounds with aldehydes and frequently used in organic synthesis, has not been reported so far.

We paid our attention on "borrowing hydrogen" methodology[13] to develop the formal *anti*-Markovnikov hydroamination of allylic alcohols. Our hypothetical reaction pathway is as follows: the oxidation of allylic alcohols occurs through the *β*-hydride elimination of metal-alkoxide species generated *in situ* to give the corresponding *α,β*-unsaturated carbonyl compounds. Subsequent 1,4-conjugated addition of amines onto the intermediates affords the *β*-amino carbonyl compounds, which are finally hydrogenated with the metal-hydride species before mentioned to provide the *γ*-amino alcohols (Scheme 1). Using this method makes it possible to introduce amino groups into the terminal carbon of C=C bond of the allylic alcohols.

The use of allylic alcohols in the modification of nucleophiles through the "borrowing hydrogen" processes are rare. Concerning the amine nucleophiles, *N*-allylation of amines using allylic alcohols as an alkylating reagent proceeds with the PNN-Ru pincer complexes catalyst have only reorted.[14] Although the reactions of allylic alcohols with carbon nucleophiles via the 1,4-addition as shown in Scheme 2 have been independently reported by Williams et al. (Al-catalyst)[15] and Quintard et al. (Fe-catalyst),[16] the formal hydroamination of allylic alcohols with amine nucleophiles has not been reported so far. This rarity of allylic alcohols in "borrowing hydrogen" reactions is presumably due to the difficulty in controlling various side reactions of *in situ* generated *α,β*-unsaturated carbonyl compounds such as isomerizations,[17] reduction of C-C and/or C-O double bonds,[18] and formation of allylic amines mediated[14] by the intra- and intermolecular hydride transfers and in combination with 1,2-addition of amines to temporarily generated carbonyl species (Scheme 2). We report here a novel and an efficient formal *anti*-Markovnikov hydroamination of allylic alcohols through the tandem oxidation/1,4-conjugate addition/1,2-reduction catalyzed by a $RuClH(CO)(PPh_3)_3$/2,6-bis(*n*-butyliminomethyl)pyridine catalytic system, where the expected side reactions described above are extremely suppressed.



Scheme 1 Our hypothetic reaction mechanism.

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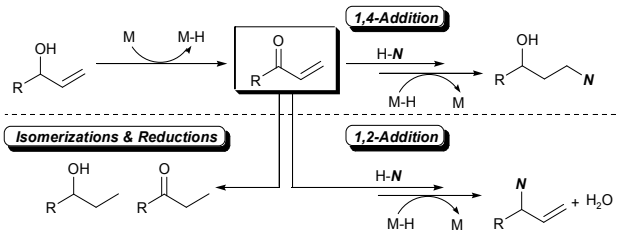
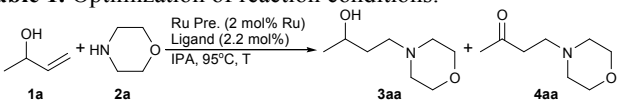


Scheme 2 Predicted reactions of allylic alcohols and amines in the presence of transition metal complexes.

As our first attempt, we examined the reaction of 3-buten-2-ol (**1a**) and morpholine (**2a**) in the presence of various Ru catalysts (Table 1). Various combinations of Ru precursors and ligands (such as phosphine, amine, and both of them) and various reaction conditions were tested (*see Supporting Information*). However, the desired hydroamination product **3aa** was not obtained (Entries 1-4). In many cases, the amino ketone **4aa**, which was the precursor of **3aa**, was detected by ^{1}H NMR spectra of the crude products accompanied by the formation of the expected 2-butanol and 2-butanone (Entries 1, 2, 4). Formation of these compounds suggested that hydrogen was still wasted by undesired intra- and intermolecular hydride transfer. To avoid the undesired reactions, the Ru complexes bearing diphosphine and diamine ligands, which have been reported to selectively 1,2-reduct α,β-unsaturated carbonyl compounds,[19] were examined. However, the desired product **3aa** was not obtained (Entries 5, 6). To continuously investigate the control of the undesired hydride transfer, we next focused on the ligands with C=O or C=N bond in the molecules, which

Table 1. Optimization of reaction conditions.[a]



Entry	Ru pre.	Ligand	T (h)	Yield (%) **3aa**/**4aa**[b]
1[c]	$RuCl_2(p\text{-cymene})_2$	dppf	5	0/trace
2[c]	$RuCl_2(p\text{-cymene})_2$	dppbe.[d]	5	0/73
3[c]	$RuCl_2(p\text{-cymene})_2$	en[e]	5	0/0
4[c]	$RuCl_2(p\text{-cymene})_2$	**L1**	5	0/15
5	$RuCl_2$(dppf)(en)	-	22	0/2
6	$RuCl_2$(dppbe.)(en)	-	22	0/4
7	$RuCl_2(p\text{-cymene})_2$	**L2**	22	0/4
8	$RuCl_2(p\text{-cymene})_2$	**L3**	22	0/5
9	$RuCl_2(p\text{-cymene})_2$	**L4**	22	0/5
10	$RuClH(CO)(PPh_3)_3$	**L4**	22	trace/7
11[f]	$RuClH(CO)(PPh_3)_3$	**L4**	22	26/0
12[f]	$RuClH(CO)(PPh_3)_3$	**L5**	22	0/12
13[f]	$RuClH(CO)(PPh_3)_3$	**L6**	22	trace/0
14[g]	$RuClH(CO)(PPh_3)_3$	**L4**	22	>99/0
15[g]	$RuCl_2(PPh_3)_3$	**L4**	22	72
16[g]	$[Ru(CO)_3Cl_2]_2$	**L4**	22	0

[a]Reaction conditions: Ru pre. (2 mol% Ru), Ligand (2.2 mol%), **1a** (2.2 mmol), **2a** (2.0 mmol), and IPA (0.5 mL), at 95°C. [b]Determined by ^{1}H NMR. [c]**1a** (6.0 mmol) was used. [d]1,2-Bis(diphenylphosphino)b-enzene. [e]Ethylenediamine. [f]KOBu^t (5 mol%) was added. [g]**1a** (2.6 mmol) was used. KOBu^t (3 mol%) was added, at 70°C.

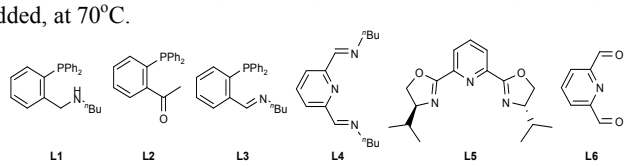
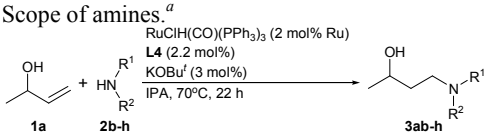


Fig. 1 Structure of ligands (**L1-L6**)

could tentatively participate in the redox reaction by hydride transfers on the metal center (Entries 7-10). With great pleasure, the trace amount of the desired hydroamination product **3aa** was obtained when $RuClH(CO)(PPh_3)_3$ with impressive ability for hydride transfer reaction[20] and 2,6-bis(*n*-butyliminomethyl)pyridine (**L4**) were used as a catalyst (Entry 10). Then, the addition of KOBu^t (5 mol %) gave **3aa** in 26% yield (Entry 11). Under the reaction conditions, using the ligand **L5** and **L6**, which are similar N-N-N ligand and precursor of **L4** respectively, were tested but gave no product or only the trace amounts (Entry 12, 13). Further optimizing the reaction conditions revealed that the reaction of **1a** (2.6 mmol) with **2a** (2.0 mmol) was conducted in the presence of $RuClH(CO)(PPh_3)_3$ (2 mol%), 2,6-bis(*n*-butyliminomethyl)pyridine (**L4**) (2.2 mol%), and KOBu^t (3 mol%) as the base in IPA (0.5 mL) at 70°C for 22 h to provide **3aa** in >99%

Table 2. Scope of amines.[a]



Entry	Amine	Product	Yield (%)[b]
1	**2b**	**3ab**	86
2	**2c**	**3ac**	>99
3	**2d**	**3ad**	90
4	**2e**	**3ae**	75
5	**2f**	**3af**	86
6	**2g**	**3ag**	74
7	**2h**	**3ah**	44

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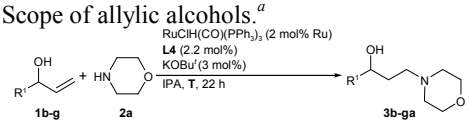
[a]Reaction conditions: $RuClH(CO)(PPh_3)_3$ (0.04 mmol), **L4** (0.044 mmol), $KOBu^t$ (0.06 mmol), **1a** (2.6 mmol), amine (2 mmol), and IPA (0.5 mL), at 70°C, for 22 h. [b]Determined by ^1H NMR.

yield (Entry 14).[21] Note that we observed the good control the generations of the undesired saturated alcohol (2-butanol) and ketone (2-butanone), and could not detect allylic amine formed via 1,2-addition by ^1H NMR analysis. Although $RuCl_2(PPh_3)_3$ and $[Ru(CO)_3Cl_2]_2$ were tested under the reaction conditions as entry 14 (Entry 15, 16), these two ruthenium precursors showed lower catalytic efficiency than $RuClH(CO)(PPh_3)_3$.

Next, we investigated the applicable scope of the substrates for our present hydroamination (Table 2). The use of cyclic amines including indoline **2f** gave the corresponding hydroamination products in good yields (Entries 1-6). The oxorane group, which is used as the protecting group for the carbonyl compounds, is tolerated. On the other hand, using primary amine **2h** slightly reduced the reaction efficiency, presumably due to the primary amines having lower nucleophilicity than the secondary cyclic amines. In this case, no amino diol, which is afforded by the further hydroamination of the hydroamination product **3ah**, was detected.

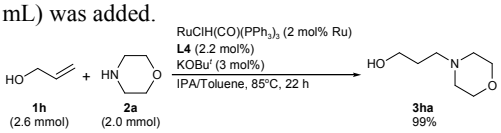
The scope of allylic alcohols on our present hydroamination is summarized in Table 3. Although using allylic alcohols bearing phenyl, benzyl, phenethyl, and phenoxy groups required more various and higher temperatures than those of the reaction with 3-buten-2-ol (**1a**) and the addition of toluene as a co-solvent, the corresponding hydroamination products were obtained in high yields (Entries 1-9). These results indicated that functional groups on α-carbon of allylic

Table 3. Scope of allylic alcohols.[a]



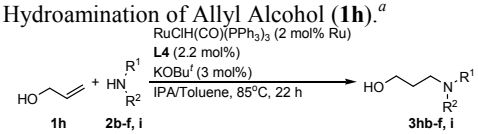
Entry	R^1	T (°C)	Product	Yield (%)[b]
1	**1b**	70	**3ba**	>99
2	**1c**	70	**3ca**	90
3[c]	**1d**	90	**3da**	0
4[c]		100		91
5	**1e**	80	**3ea**	trace
6[c]		80		>99
7[c]	**1f**	80	**3fa**	52
8[c]		65		70
9[c]	**1g**	90	**3ga**	92

[a]Reaction conditions: $RuClH(CO)(PPh_3)_3$ (0.04 mmol), **L4** (0.044 mmol), $KOBu^t$ (0.06 mmol), allylic alcohols (2.6 mmol), **2a** (2.0 mmol), and IPA (0.5 mL), for 22h. [b]Determined by ^1H NMR. [c]Toluene (0.5 mL) was added.



Scheme 3. Hydroamination of allyl alcohol (**1h**).

Table 4. Hydroamination of Allyl Alcohol (**1h**).[a]



Entry	Amine	Product	Yield (%)[b]
1	**2b**	**3hb**	94
2[c]	**2c**	**3hc**	98
3	**2d**	**3hd**	95
4	**2e**	**3he**	80
5	**2f**	**3hf**	92
6	**2i**	**3hi**	87

[a]Reaction conditions: $RuClH(CO)(PPh_3)_3$ (0.04 mmol), **L4** (0.044 mmol), $KOBu^t$ (0.06 mmol), **1h** (2.6 mmol), amine (2 mmol), IPA (0.5 mL), and Toluene (0.5 mL), at 85°C, for 22 h. [b]Determined by ^1H NMR. [c]at 90°C.

alcohols strongly affected the hydroamination.

Furthermore, the reaction with allyl alcohol (**1h**) was investigated. In this case, the reaction intermediate produced by the hydride transfer was α,β-unsaturated aldehyde, which is generally more reactive than ketones. Therefore, it is considered that the allylic amines could be formed competitively. However, the reaction proceeded highly chemospecifically. Thus, the reaction was performed in the presence of $RuClH(CO)(PPh_3)_3$ (2 mol%), **L4** (2.2 mol%), and $KOBu^t$ (3 mol%), and the reaction of **1h** (2.6 mmol) and **2a** (2.0 mmol) in IPA (0.5 mL) and Toluene (0.5 mL) at 85°C for 22 h provided the desired hydroamination product **3ha** in 99% yield (Scheme 3).

Table 4 shows the applicable scope of amines for hydroamination of allyl alcohol (**1h**) (Table 4). Various amines (such as piperidine, piperadine, isoquinoline, and indoline) were applicable to afford the desired hydroamination products in 80-94% yield. It is noteworthy that by-products via 1,2-addition were not detected in all cases.

To confirm the present hydroamination proceeds via our proposed reaction pathway, we conducted a control experiment with allylic ether substrate **1c'**. When the reaction of **1c'** with **2a** was performed

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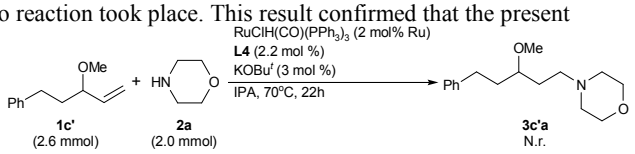
under the same reaction conditions of **1c** with **2a** (Entry 2, Table 3), no reaction took place. This result confirmed that the present



Scheme 4. Reaction of **1c'** and **2a**.

hydroamination proceeds through the formation of α,β-unsaturated carbonyl compounds as expected.

In summary, we successfully developed a formal *anti*-Markovnikov hydroamination of allylic alcohols via tandem oxidation/1,4-conjugate addition/1,2-reduction. The present hydroamination was catalyzed by the $RuClH(CO)(PPh_3)_3$/2,6-bis(*n*-butyliminomethyl)pyridine catalytic system to give the corresponding γ-amino alcohols in a good-to-excellent yield. The identification of the catalytically active species formed by the mixing of $RuClH(CO)(PPh_3)_3$ and 2,6-bis(*n*-butyliminomethyl)pyridine, elucidation of the detailed reaction mechanism, and further expansion of the applicable scope of the substrates including asymmetric synthesis are now in progress.

Notes and references

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† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/c000000x/

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21 In our hydroamination, the addition effect of $KOBu^t$ was crucial. The hydroamination scarcely progressed with either no $KOBu^t$ or an excess amount of $KOBu^t$ (see S*upporting Information*).

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Textual Abstract
A formal Ru-catalyzed *anti*-Markovnikov hydroamination of allylic alcohols via tandem oxidation/1,4-conjugate addition/1,2-reduction was developed.