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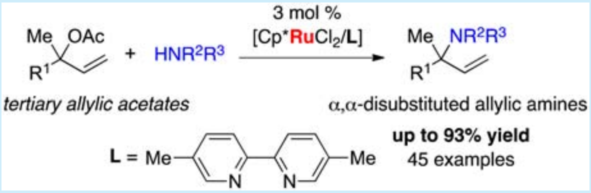
Regioselective Construction of α,α-Disubstituted Allylic Amines by the Ruthenium-Catalyzed Allylic Amination of Tertiary Allylic Acetates

Shota Mizuno, Shou Terasaki, Toru Shinozawa, and Motoi Kawatsura*

Department of Chemistry, College of Humanities & Sciences, Nihon University, Sakurajosui, Setagaya-ku, Tokyo 156-8550, Japan

Supporting Information

ABSTRACT: The ruthenium-catalyzed regioselective allylic amination of tertiary allylic acetates with several types of amines has been accomplished. The reaction was effectively catalyzed by Cp*RuCl$_2$/5,5′-dimethyl-2,2′-bipyridine or its related ruthenium catalyst systems, and α,α-disubstituted allylic amines were formed as a single regioisomer in moderate to high yields.



The transition-metal-catalyzed allylic amination of allylic compounds is one of the most useful reactions to construct allylic amines, and several transition-metal catalysts have been employed for such reactions.[1] However, the reactions of tertiary allylic compounds with amines, which provide α,α-disubstituted allylic amines, are still difficult reaction processes compared to the reaction of secondary or primary allylic compounds. To the best of our knowledge, there are only a limited number of examples of the regioselective allylic amination of tertiary allylic compounds; some palladium,[2] iridium,[3] iron,[4] and rhodium[5] catalysts are known as effective catalysts to realize such reactions. On the other hand, ruthenium is also known to catalyze the allylic amination reaction of allylic compounds with amines,[6−11] but there is still no example of the reaction of tertiary allylic compounds. Based on this background, during the course of our research on the several types of ruthenium-catalyzed allylic substitutions,[10,12] we examined the reaction of tertiary allylic acetates, which are easy to prepare, with several amines and succeeded in obtaining α,α-disubstituted allylic amines.

We first examined the reaction of tertiary allylic acetate **1a** with morpholine (**2a**) using several ruthenium catalysts (RuCl$_3$, [RuCl$_2$(*p*-cymene)]$_2$, Ru$_3$(CO)$_{12}$, Cp*RuCl$_2$, etc.)[13] and solvents and then confirmed that the reaction by Cp*RuCl$_2$ (3 mol %) in CH$_3$CN provided the intended α,α-disubstituted allylic amines (**3aa**) in 75% NMR yield as a single regioisomer (Table 1, entries 1−3). We next examined the reaction in the presence of 2,2′-bpy (2,2′-bipyridine, **L1**) as a ligand at 60 °C and succeeded in increasing the yield of **3aa** to 86% (entries 4−8). These results suggest that the Ru(II) species, which was formed from Ru(III) precatalyst in the presence of 2,2′-bpy and CH$_3$CN, played an active catalyst for the desired allylic amination reactions.[8a,14] To attain a higher yield of **3aa**, we then attempted the reaction with other ligands (**L2−7**) (entries 9−14) and revealed that the highest yield (97% NMR yield, 91% isolated yield) was obtained when 5,5′-dimethyl-2,2′-bipyridine (**L5**) was used instead of **L1** (entry 12).

With the standard reaction conditions (Table 1, entry 12) in hand, we investigated the reaction of **1a** with several aliphatic amines **2b−p**. As shown in Table 2, most of the reactions smoothly proceeded, and we succeeded in obtaining the desired α,α-disubstituted allylic amines in good to high yields without forming a regioisomer. For example, cyclic aliphatic amines **2b−j** provided the intended products in the range of 79−90% yield (entries 1−9). We further examined the reaction with acyclic aliphatic secondary amines (**2k−n**) (entries 10−13). Unfortunately, the reactions with diethylamine (**2k**) or *N*-methylcyclohexylamine (**2n**) resulted in a low yield even at 40 °C (entries 10 and 13) because the formation of 2-phenyl-1,3-butadiene due to the undesirable elimination reaction of **1a**,[15] but *N*-methylbenzylamine (**2l**) and *N*-methylbutylamine (**2m**) gave the corresponding allylic amines in good yields (entries 11 and 12). We also examined and confirmed that the reactions with aliphatic primary amines, such as **2o** and **2p**, afforded the desired α,α-disubstituted allylic amines **3ao** and **3ap** in 93% and 82% yields, respectively (entries 14 and 15).

We next examined the reaction of **1a** with aniline (**2q**), but again our optimized reaction conditions provided the diene, which was formed from **1a** as the major product and did not give any trace amount of the intended product **3aq** (Table 3, entry 1). Based on this initial observation, we reinvestigated the suitable catalyst conditions for the reaction with an aromatic amine **2q**. To our delight, although the exact role is not clear,[10] we found that the addition of a tertiary amine is effective to allow the intended regioselective allylic amination reaction to occur. For example, when NEt$_3$ (2 equiv) was added to the reaction system, the desired reaction proceeded, and allylic amine **3aq** was formed in 71% yield (entry 2). We further examined the reaction by other tertiary amines and then confirmed that the highest yield (84%) was attained by adding EtN^{i}Pr$_2$ (entries 3−5).[16] We also examined the reaction with

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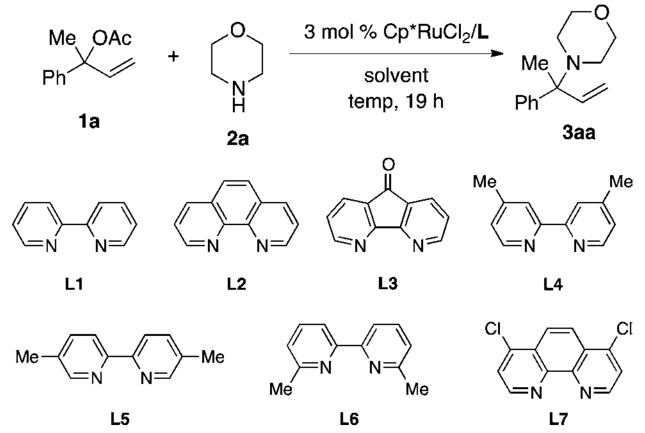
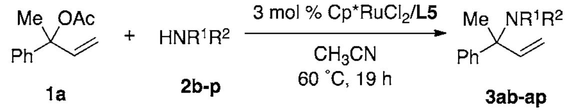
Table 1. Ruthenium-Catalyzed Allylic Amination of **1a** with Morpholine (**2a**)[a]

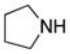
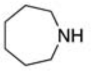
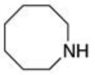
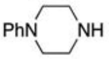
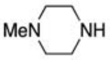
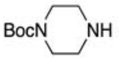
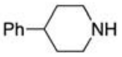
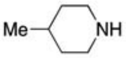


entry	L	solvent	temp (°C)	yield[b] (%)
1		THF	40	6
2		toluene	40	8
3		CH_3CN	40	75
4	**L1**	THF	60	14
5	**L1**	toluene	60	12
6	**L1**	CH_3CN	40	81
7	**L1**	CH_3CN	60	86
8	**L1**	CH_3CN	80	77
9	**L2**	CH_3CN	60	74
10	**L3**	CH_3CN	60	87
11	**L4**	CH_3CN	60	95
12	**L5**	CH_3CN	60	97 (91)[c]
13	**L6**	CH_3CN	60	57
14	**L7**	CH_3CN	60	82

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), Cp^*RuCl_2 (0.009 mmol), and **L** (0.009 mmol) in solvent (1.0 mL) at the indicated temperature for 19 h. [b] Yields are determined by ^1H NMR of crude materials using an internal standard (phenanthrene). [c] Isolated yield is shown in parentheses.

Table 2. Ruthenium-Catalyzed Allylic Amination of **1a** with Aliphatic Amines[a]



entry	**2**	yield[b] of **3** (%)
1	 **2b**	84 (**3ab**)
2	 **2c**	80 (**3ac**)
3	 **2d**	80 (**3ad**)
4	 **2e**	79 (**3ae**)
5	 **2f**	90 (**3af**)
6	 **2g**	90 (**3ag**)
7	 **2h**	87 (**3ah**)
8	 **2i**	86 (**3ai**)
9	 **2j**	83 (**3aj**)
10[c]	Et NH Et **2k**	58 (**3ak**)
11	Bn NH Me **2l**	80 (**3al**)
12	^{n}Bu NH Me **2m**	76 (**3am**)
13[c]	Cy NH Me **2n**	<5 (**3an**)
14	$BnNH_2$ **2o**	93 (**3ao**)
15	$^nBuNH_2$ **2p**	82 (**3ap**)

[a] Reaction conditions: **1a** (0.3 mmol), **2b–p** (0.6 mmol), Cp^*RuCl_2 (0.009 mmol), and **L5** (0.009 mmol) in CH_3CN (1.0 mL) at 60 °C for 19 h. [b] Isolated yields after chromatography are shown. [c] Reaction was conducted at 40 °C.

other aniline analogues, such as 4-methoxyaniline (**2r**), 4-trifluoromethylaniline (**2s**), or 1-naphthylamine (**2t**), in the presence of EtN^iPr_2. As we expected, the reaction with **2r** afforded a good result, but the reactions with **2s** and **2t** resulted in moderate yields because a diene was formed as a byproduct (entries 7 and 8). Unfortunately, the present ruthenium catalyst system was not effective for the reaction with *N*-methylaniline (**2u**), and the reaction did not produce any allylic amines (entry 10).

We further demonstrated the reaction of several tertiary allylic acetates **1b–g** with several amines, such as the cyclic secondary aliphatic amine **2a**, acyclic secondary aliphatic amine **2m**, aliphatic primary amine **2o**, or primary aromatic amines **2q**, and the results are summarized in Scheme 1. For the reactions with morpholine (**2a**), we observed a decreased yield for the reactions of **1c–e**, which possessed the *p*-methoxy group, *p*-methyl group, or *o*-methyl group on the phenyl group due to the formation of dienes. However, the reactions of **1b** and **1f** provided the desired products **3ba** and **3fa** in 90% and 83% yields, respectively. These results indicate that the steric hindrance at the *ortho* position of the aryl group inhibits the desired allylic amination reaction, and electron-donating groups on the phenyl group also decreased the yields of allylic amines due to the formation of dienes. Unfortunately, the reaction of **1g**, which has an alkyl group instead of an aryl group, with **2a** using the optimized ruthenium catalysts exhibited a low conversion (<10%) of **1g**, but when the ligand was changed from **L5** to 4,7-dichloro-1,10-phenanthroline (**L7**), we succeeded in obtaining the intended allylic amine **3ga** in 88% yield.

The reactions of **1b–g** with *N*-methylbutylamine (**2m**) were also examined, and they confirmed that the reaction of **1c–e** again resulted in a low yield, but **1b** and **1f** afforded the *α*,*α*-disubstituted allylic amines **3bm** and **3fm** in good yield, respectively. Furthermore, although the yield was moderate, we could obtain **3gm** in 40% yield when **L7** was used. The reactions of **1b–g** with benzylamine (**2o**) also gave a similar result, and we obtained the corresponding products in the range of 32–80% isolated yields. We further investigated the reactions of **1b–g** with aniline (**2q**) and succeeded in obtaining

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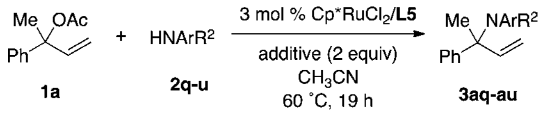
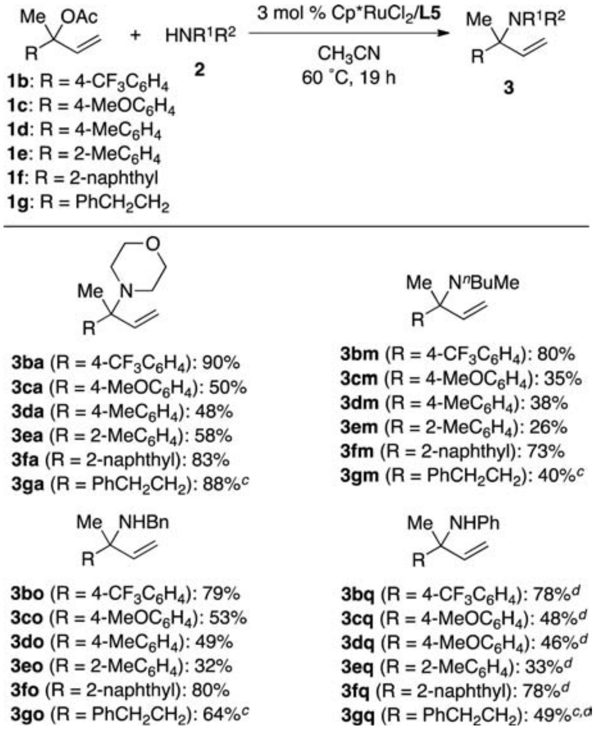
Table 3. Reaction of 1a with Anilines 2q−u[a]



entry	2	additive	yield[b] (%)
1	$PhNH_2$ (**2q**)		0
2	$PhNH_2$ (**2q**)	Et_3N	71 (**3aq**)
3	$PhNH_2$ (**2q**)	EtN^iPr_2	84 (**3aq**)
4	$PhNH_2$ (**2q**)	DABCO	63 (**3aq**)
5	$PhNH_2$ (**2q**)	DBU	43 (**3aq**)
6	$4\text{-}MeOC_6H_4NH_2$ (**2r**)	EtN^iPr_2	70 (**3ar**)
7	$4\text{-}CF_3C_6H_4NH_2$ (**2s**)	EtN^iPr_2	49 (**3as**)
8	1-naphthylamine (**2t**)	EtN^iPr_2	44 (**3at**)
9[c]	1-naphthylamine (**2t**)	EtN^iPr_2	66 (**3at**)
10	PhNHMe (**2u**)	EtN^iPr_2	0

[a] Reaction conditions: **1a** (0.3 mmol), **2q−u** (0.6 mmol), additive (0.6 mmol), Cp^*RuCl_2 (0.009 mmol), and **L5** (0.009 mmol) in CH_3CN (1.0 mL) at 60 °C for 19 h. [b] Isolated yields after chromatography are shown. [c] Reaction was conducted at 40 °C.

Scheme 1. Ruthenium-Catalyzed Allylic Amination of Several Allylic Acetates 1b−g with Amines 2a,m,o,q[a,b]



[a] Reaction conditions: **1b−g** (0.3 mmol), **2** (0.6 mmol), Cp^*RuCl_2 (0.009 mmol), and **L5** (0.009 mmol) in CH_3CN (1.0 mL) at 60 °C for 19 h. [b] Isolated yields after chromatography are shown. [c] **L7** was used instead of **L5**. [d] Reaction was conducted in the presence of EtN^iPr_2 (0.6 mmol).

the intended *α*,*α*-disubstituted allylic amines in acceptable yields other than the reaction of **1e**. These results clarified that the present ruthenium catalyst systems effectively works for the combination of several types of tertiary allylic acetates and amines.

In conclusion, we examined the ruthenium-catalyzed regioselective allylic amination of tertiary allylic acetates with several types of amines. Our two types of ruthenium catalyst systems effectively catalyzed the intended regioselective allylic amination with several types of aliphatic amines and primary aromatic amines and succeeded in obtaining the desired *α*,*α*-disubstituted allylic amines in moderate to high yields. Further investigation of the ruthenium-catalyzed regio- and enantioselective allylic substitutions of tertiary allylic acetates with several types of nucleophiles, which include amides, is currently underway by our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03672.

> Experimental procedures and spectral data for the products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kawatsur@chs.nihon-u.ac.jp.

ORCID

Motoi Kawatsura: 0000-0002-8341-6866

Notes

The authors declare no competing financial interest.

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(13) All reactions with $RuCl_3$, $[Ru(Cl_2(p\text{-cymene}))_2$, or $Ru_3(CO)_{12}$ resulted in no reaction.

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(16) We also examined the reaction with inorganic bases, such as K_2CO_3, Cs_2CO_3, NaHMDS, or LiHMDS, instead of organic bases, but none of the reactions provided any intended products.

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