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Synthesis of α-Tertiary Amines by the Ruthenium-catalyzed Regioselective Allylic Amination of Tertiary Allylic Esters

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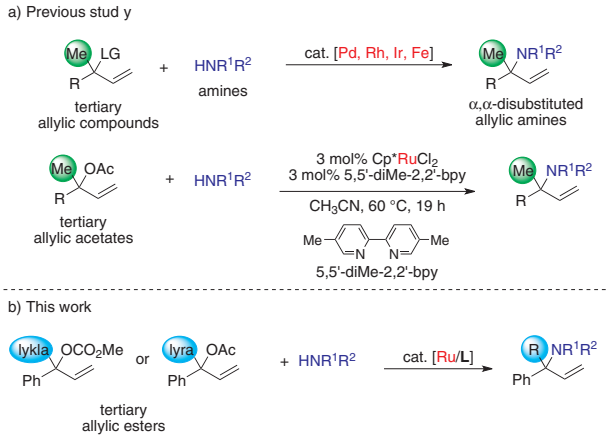
We demonstrated a ruthenium-catalyzed regioselective allylic amination of tertiary allylic esters with various amines using [Cp*Ru(CH_3CN)$_3$][PF_6]/5,5′-dimethyl-2,2′-bipyridine (5,5′-diMe-2,2′-bpy) and related ruthenium catalytic systems, and successfully obtained a diverse range of α-tertiary amines as single regioisomers. The present ruthenium catalytic system was effective for reactions with various types of amines.

Keywords: Ruthenium | Amination | α-Tertiary amines

Transition-metal-catalyzed allylic amination of allylic compounds is one of the most useful reactions to synthesize allylic amines,[1] and several types of reactions in this category have been reported. However, the reactions of tertiary allylic compounds with amines, which provide α,α-disubstituted allylic amines, are more difficult as compared to the reactions of primary or secondary allylic compounds. Pd,[2] Rh,[3] Ir,[4] and Fe[5] catalysts are known to be effective for the allylic amination of tertiary allylic compounds, and we have previously reported a ruthenium-catalyzed reaction[6] (Scheme 1a). Although the intended reactions of tertiary allylic compounds were carried out in those studies, there was a limitation in that at least one substituent on the allylic compound had to be a methyl group.[7] On the other hand, α-tertiary amines are useful organic components in the fields of pharmaceutical chemistry and materials science.[8] However, allylic amination of tertiary allylic compounds bearing an ethyl group or a methoxymethyl group generally does not proceed, or produces linear products.[2i] Therefore, it is important to establish a method that provides access to α-tertiary amines possessing other alkyl or aryl groups instead of a methyl group, by the transition-metal-catalyzed reaction of tertiary allylic compounds. Against this background, we attempted the ruthenium-catalyzed regioselective allylic amination of tertiary allylic esters and succeeded in obtaining α-tertiary amines (Scheme 1b).

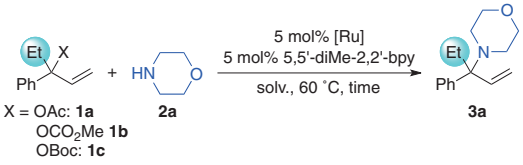
We first carried out the reaction of tertiary allylic acetate **1a** to contain ethyl and phenyl groups with morpholine (**2a**) in the presence of Cp*$RuCl_2$ (5 mol %)/5,5′-diMe-2,2′-bpy (5 mol %) in acetonitrile at 60 °C for 19 h, which were effective conditions for the reaction of a methyl group-bearing tertiary allylic acetate with an amine (Table 1, Entry 1).[6] However, the reaction resulted in low conversion (<5%) to α-tertiary amine **3a**. Based on this initial result, we anticipated that it is necessary to use other ruthenium precatalysts for the intended reaction.

Accordingly, we performed the reaction of **1a** with **2a** using a ruthenium precatalyst such as $RuCl_3$, [$RuCl_2$(*p*-cymene)]$_2$, or $Ru_3(CO)_{12}$, but these attempts were unsuccessful.[9,10] On the other hand, we confirmed that the Cp*-ligated ruthenium precatalyst with 5,5′-diMe-2,2′-bpy afforded the intended aminated product **3a**, although the yield was low (Entries 2–4). To enhance the



Scheme 1. Synthesis of α,α–disubstituted allylic amines by allylic amination.

Table 1. Optimization of ruthenium-catalyzed allylic amination of tertiary allylic esters[a]

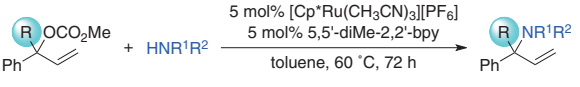


entry	sub	[Ru]	solv.	time (h)	yield[b] (%)
1	**1a**	Cp*$RuCl_2$	CH_3CN	19	3[c]
2	**1a**	Cp*Ru(allyl)Cl_2	CH_3CN	19	15
3	**1a**	Cp*Ru(cod)Cl	CH_3CN	19	14
4	**1a**	[Cp*Ru(CH_3CN)$_3$][PF_6]	CH_3CN	19	20
5	**1a**	[Cp*Ru(CH_3CN)$_3$][PF_6]	DMF	19	12
6	**1a**	[Cp*Ru(CH_3CN)$_3$][PF_6]	THF	19	<2[c]
7	**1a**	[Cp*Ru(CH_3CN)$_3$][PF_6]	DCE	19	16
8	**1a**	[Cp*Ru(CH_3CN)$_3$][PF_6]	toluene	19	41
9	**1a**	[Cp*Ru(CH_3CN)$_3$][PF_6]	xylene	19	38
10	**1a**	[Cp*Ru(CH_3CN)$_3$][PF_6]	toluene	48	44
11	**1a**	[Cp*Ru(CH_3CN)$_3$][PF_6]	toluene	72	48
12	**1b**	[Cp*Ru(CH_3CN)$_3$][PF_6]	toluene	72	66
13	**1c**	[Cp*Ru(CH_3CN)$_3$][PF_6]	toluene	72	50

[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), 5 mol % of [Ru], and 5 mol % of 5,5′-diMe-2,2′-bpy in solvent (1.0 mL). [b]Isolated yield. [c]Determined by ^{1}H NMR of crude materials.

formation of **3a**, we next attempted the reaction with [Cp*Ru(CH_3CN)$_3$][PF_6]/5,5′-diMe-2,2′-bpy in several solvents

Table 2. Ruthenium-catalyzed allylic amination of tertiary allylic carbonates with amines[a]

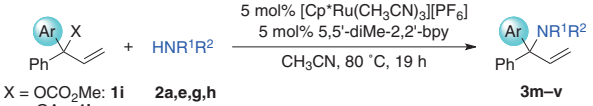


1b–h 2a–g 3a–l

entry	R	HNR^1R^2	product	yield[b] (%)
1	Et (**1b**)	morpholine (**2a**)	**3a**	66
2	Et (**1b**)	piperidine (**2b**)	**3b**	41
3	Et (**1b**)	pyrrolidine (**2c**)	**3c**	35
4	Et (**1b**)	HNBnMe (**2d**)	**3d**	43
5	Et (**1b**)	H_2NBn (**2e**)	**3e**	58
6	Et (**1b**)	H_2NiPr (**2f**)	**3f**	43
7	Et (**1b**)	H_2NPh (**2g**)	**3g**	55
8	nBu (**1d**)	morpholine (**2a**)	**3h**	54
9	iPr (**1e**)	morpholine (**2a**)	**3i**	<2[c]
10	$MeOCH_2$ (**1f**)	morpholine (**2a**)	**3j**	32
11	Bn(**1g**)	morpholine (**2a**)	**3k**	38
12	CF_3 (**1h**)	morpholine (**2a**)	**3l**	<2[c]

[a]Reaction conditions: **1b–h** (0.3 mmol), **2a–g** (0.6 mmol), 5 mol % of $[Cp^*Ru(CH_3CN)_3][PF_6]$, and 5 mol % of 5,5′-diMe-2,2′-bpy in toluene (1.0 mL) at 60 °C for 72 h. [b]Isolated yield. [c]Determined by ^1H NMR of crude materials.

Table 3. Ruthenium-catalyzed allylic amination of α,α-diaryl allylic acetates with amines[a]



X = OCO_2Me: **1i**
OAc: **1j–p**

2a,e,g,h **3m–v**

entry	Ar	HNR^1R^2	product	yield[b] (%)
1[c]	Ph (**1i**)	morpholine (**2a**)	**3m**	62
2[c]	Ph (**1j**)	morpholine (**2a**)	**3m**	69
3	Ph (**1j**)	morpholine (**2a**)	**3m**	79
4	Ph (**1j**)	$HNEt_2$ (**2h**)	**3n**	69
5	Ph (**1j**)	H_2NBn (**2e**)	**3o**	84
6	Ph (**1j**)	H_2NPh (**2g**)	**3p**	51
7	2-naphthyl (**1k**)	H_2NBn (**2e**)	**3q**	76
8	2-MeC_6H_4 (**1l**)	H_2NBn (**2e**)	**3r**	59
9	4-MeC_6H_4 (**1m**)	H_2NBn (**2e**)	**3s**	75
10	4-ClC_6H_4 (**1n**)	H_2NBn (**2e**)	**3t**	83
11	4-$CF_3C_6H_4$ (**1o**)	H_2NBn (**2e**)	**3u**	46
12	4-PhC_6H_4 (**1p**)	H_2NBn (**2e**)	**3v**	61

[a]Reaction conditions: **1i–p** (0.3 mmol), **2a**, **2e**, **2g**, and, **2h** (0.6 mmol), 5 mol % of $[Cp^*Ru(CH_3CN)_3][PF_6]$, and 5 mol % of 5,5′-diMe-2,2′-bpy in toluene (1.0 mL) at 80 °C for 19 h. [b]Isolated yield. [c]Toluene was used instead of CH_3CN.

such as DMF, THF, DCE, toluene, and xylene (Entries 5–9); **3a** was obtained in 41% yield (88% conversion of **1a**) when toluene was used (Entry 8). We also observed 100% conversion of **1a** when the reaction time was increased to 72 h, but the yield of **3a** increased only slightly (48% yield) (Entries 10 and 11). We further examined the reaction by changing the leaving group of the tertiary allylic compounds from acetate to methyl or *tert*-butyl carbonate (**1b** and **1c**, respectively) and obtained **3a** in 66% yield as a single regioisomer when using **1b** (Entries 12 and 13). Then, we established the optimal conditions as follows: reaction of **1b** with **2a** using $[Cp^*Ru(CH_3CN)_3][PF_6]$/5,5′-diMe-2,2′-bpy in toluene at 60 °C for 72 h. Furthermore, we confirmed that 1,3-diene was formed as a byproduct from **1b** in 32% yield.

With the standard conditions (Table 1, Entry 12) in hand, we next investigated the reaction of allylic carbonates **1b–h** with several amines **2a–g** (Table 2). The reactions with cyclic aliphatic amines **2b** and **2c** provided the desired amination products **3b** and **3c** in moderate yields, while the reactions with acyclic aliphatic secondary amines **2d** gave the desired α,α-disubstituted allylic amine in 43% yield (Entries 2–4). The reactions of **1b** with aliphatic and aromatic primary amines, such as benzylamine (**2e**), isopropylamine (**2f**), and aniline (**2g**), afforded the desired allylic amines **3e**, **3f**, and **3g** in 58%, 43%, and 55% yields, respectively (Entries 5–7). We next carried out the reaction of other alkyl group-substituted allylic carbonates **1d–h** with **2a** (Entries 8–12). The reaction of *n*-butyl group substituted allylic carbonate **1d** also proceeded to furnish allylic amine **3h** (Entry 8). Unfortunately, **1e**, which had an *iso*-propyl group, did not give the desired aminated product **3i** but produced only a 1,3-diene (Entry 9).[11] This was probably because **1e** underwent elimination more rapidly than amination due to the increased steric hindrance as compared to that observed with the ethyl group.[12] Accordingly, the reactions of substrates including a methylene carbon at the α-position with morpholine were also attempted: **1f** and **1g** afforded the α,α-disubstituted allylic amines in 32% and 38% yields, respectively (Entries 10 and 11). On the other hand, allylic carbonate **1h** with strong electron-withdrawing groups not gave **3l** (Entry 12).[13]

We next carried out the reaction of allylic carbonate **1i** bearing two aryl groups; since the reaction proceeded smoothly in the presence of the $[Cp^*Ru(CH_3CN)_3][PF_6]$/5,5′-diMe-2,2′-bpy catalyst, we changed the reaction time from 72 h to 19 h (Table 3, Entry 1). Screening of the reaction conditions revealed that the use of allylic acetate **1j**, with acetonitrile instead of toluene, led to an increase in the yield (Entries 2 and 3). Having established the optimal reaction conditions, we next investigated the scope of the allylic amination of **1j** with other amines (Entries 4–6). The reaction with aliphatic secondary or primary amines such as **2h** and **2e** produced the desired products **3n** and **3o** in 69% and 84% yields, respectively (Entries 4 and 5). On the other hand, aniline (**2g**) reacted with **1j** to give the desired product **3p** in only moderate yield (Entry 6). Furthermore, the reactions of other aromatic group-substituted carbonates with benzylamine (**2e**) proceeded to afford the corresponding products in good yields (Entries 7–12). The reactions of **1k** bearing a 2-naphthyl group and **1l** bearing methyl groups at the *ortho*-position of the aromatic rings proceeded to give the desired aminated products in 76% and 59% yields, respectively (Entries 7 and 8). Both electron-donating (**1m**) and electron-withdrawing (**1n–p**) substituents at the *para*-position of the phenyl rings were well tolerated, and the corresponding amination products were obtained in 46%–83% yields (Entries 9–12).

The details of the mechanism underlying the ruthenium-catalyzed amination are still not clear. However, the active catalyst is proposed to be a $Cp^*Ru(2,2'\text{-bipyridine})(CH_3CN)$[14,15] complex on the basis of the ruthenium catalyst system

([Cp*Ru(CH_3CN)$_3$][PF_6]/2,2′-bipyridine) and the known coordination chemistry of ruthenium.[16] Generally, π-allylruthenium, σ-allylruthenium, and σ-enylruthenium[17] complexes are possible reaction intermediates in ruthenium-catalyzed allylic amination. Further investigations into the mechanistic details as well as the reaction of ruthenium complexes and other types of substrates will be the subject of a future study.

In conclusion, we have demonstrated that the ruthenium-catalyzed allylic amination of allylic esters provides a variety of α-tertiary allylic amines. Although the detailed reaction mechanism is still unclear, we have proposed the possible intermediates of the ruthenium catalysts that would be involved in the formation of allyl or enylruthenium complexes. Investigation of the ruthenium-catalyzed enantioselective allylic amination of tertiary allylic esters with nitrogen nucleophiles and detailed mechanistic studies are underway in our laboratory.

Supporting Information is available on https://doi.org/10.1246/cl.200107.

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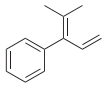

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