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Ruthenium-catalyzed linear selective allylic aminations of monosubstituted allyl acetates

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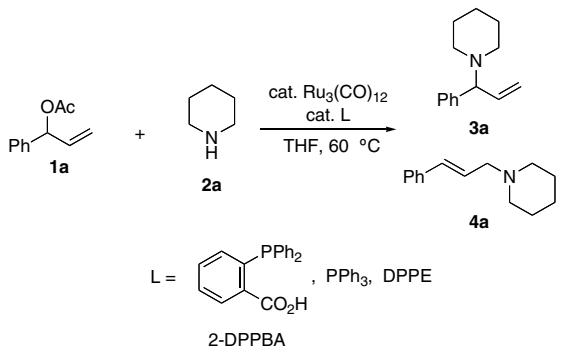
ABSTRACT

The ruthenium-catalyzed highly linear selective allylic amination of monosubstituted allylic acetates with secondary amines was developed. The regioselectivity was controlled by the $Ru_3(CO)_{12}$/2-DPPBA catalyst, and a linear-type aminated product was obtained as a single regioisomer.

The transition metal-catalyzed allylic amination of allyl substrates is one of the most useful carbon–nitrogen bond forming reactions, of which there are several examples known to date.[1–3] However, control of the regiochemistry during the reaction of monosubstituted allyl substrates, which forms both linear and branched isomers, is still a challenging process. Generally, palladium catalysts produces linear-type product as a major regioisomer, but ruthenium catalysts prefer to form branch-type product. To the best of our knowledge, three research groups independently reported the ruthenium-catalyzed allylic amination of monosubstituted allyl substrates.[4–7] According to their reports, the regioselectivity is highly dependent on the reaction conditions, such as the ruthenium complexes, solvent or allyl substrates. It has been recognized; however, that ruthenium catalysts generally form a branch-type product in preference to a linear-type product. There are only a few exceptional linear selective results, and these can be explained by the ruthenium-catalyzed isomerization of branched allylic amines into their linear isomers.[4–6] On the other hand, we recently reported the first example of the ruthenium-catalyzed highly linear selective allylic alkylation of mono-substituted allyl acetate with malonate anions.[8] During the course of this study, we found that the $Ru_3(CO)_{12}$/2-DPPBA [2-(diphenylphosphino)benzoic acid] catalyst system also produces the linear selective allylic amination of monosubstituted allyl acetate with several amines.

According to our previous result of the allylic alkylation with the malonate anion, we applied the ruthenium catalyst, which was generated from $Ru_3(CO)_{12}$ and 2-DPPBA, to the allylic amination reaction of 1-phenyl-2-propenyl acetate (**1a**) with piperidine (**2a**) (Scheme 1). Unfortunately, the desired amination reaction did not occur at 60 °C in THF (Table 1, entry 2). To realize the intended ruthenium-catalyzed allylic amination of **1a**, we added several bases to the reactions, which confirmed that the DBU is the most suitable base to initiate the desired amination reaction (entries 3–6). Typically, the reaction was carried out as follows: 3.3 mol % of $Ru_3(CO)_{12}$, 10 mol % 2-DPPBA, allyl acetate **1a**, and DBU (2.0 equiv) in THF were allowed to react with piperidine (**2a**) at 60 °C for 12 h. The reaction smoothly proceeded under these conditions, and the linear-type allylic amine **4a** was obtained



Scheme 1.

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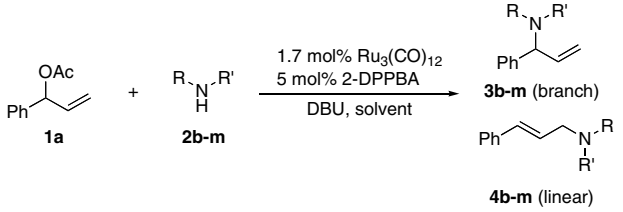
Table 1
Ruthenium-catalyzed allylic amination of **1a** with **2a**[a]

Entry	L	Base	Yield[b] (%)	**3a**:**4a**[c,d]
1	—	—	0	—
2	2-DPPBA	—	0	—
3	2-DPPBA	Et_3N	0	—
4	2-DPPBA	DABCO	0	—
5	2-DPPBA	K_2CO_3	37	2:>98
6	2-DPPBA	DBU	95	2:>98
7[e]	2-DPPBA	DBU	48	2:>98
8	PPh_3	DBU	0	—
9	DPPE	DBU	76	5:95

[a] Reaction conditions: **1a** (0.33 mmol), **2a** (0.50 mmol), $Ru_3(CO)_{12}$ (3.3 mol %), **L** (10 mol % for 2-DPPBA and DPPE, 20 mol % for PPh_3), base (0.66 mmol), THF (0.7 mL), 60 °C, 12 h.
[b] Isolated yield after purification by column chromatography.
[c] The ratio was determined by 400 MHz ^{1}H NMR analysis of crude materials.
[d] The ratio of *E*/*Z* isomers of **4a** was determined to be 95:5 by 400 MHz ^{1}H NMR analysis of crude materials.
[e] The reaction was stopped for 0.5 h, and the conversion of **1a** was determined to be 61%.

as a single regioisomer. We also confirmed that the use of 2-DPPBA is important for attaining this highly linear selective allylic amination in high yield (95%). For example, the reaction using PPh_3 resulted in no reaction (entry 7). Another phosphine ligand, DPPE, catalyzed the amination reaction, but the yield was lower (76%) and a detectable amount of the branch-type product was also formed (entry 8). As we mentioned above, it is well known that many palladium catalysts perform the linear selective allylic amination. However, some palladium catalysts form detectable amount of branch-type product.[9] On the other hand, the $Ru_3(CO)_{12}$/2-DPPBA catalyst exhibited the perfect linear selectivity and gave **4a** as a single regioisomer.

Based on the initial results, we examined the allylic amination of **1a** with several amines (Scheme 2). The reaction with morpholine (**2b**) gave the same result as that with **2a** (Table 2, entry 1), but the reaction with diethylamine (**2c**) did not occur at 60 °C in THF (entry 2). We then reinvestigated the reaction conditions, and found that the desired linear selective reaction proceeded at 100 °C in dioxane (entry 3). The reaction with other secondary alkyl amines **2d–g** also gave linear-type allylic amines as the major regioisomer (entries 4–7). However, this catalytic reaction is very sensitive to the steric factor of the amines, and the reaction with **2h** and **2i** did not form any aminated products (entries 8 and 9). The reaction with *N*-methylaniline (**2k**) and 4-methoxy-*N*-methylaniline (**2l**) also gave a linear-type product selectively, but the reactions were slightly slow (entries 11 and 12). Unfortunately, only a trace amount of the aminated product was formed in the reaction with the primary amines **2m** (entry 13).[10,11] Furthermore, we demonstrated the $Ru_3(CO)_{12}$/2-DPPBA-catalyzed allylic amination of cinnamyl acetate (**1b**), which is a regioisomer of **1a**, with several amines (Scheme 3). As we expected, the acetate **1b** exhibited a similar reactivity with the same linear selectivity as obtained for the reaction of **1a**. For example, the reaction of **1b** with secondary alkyl amines **2a–g** proceeded with excellent regioselectivity in

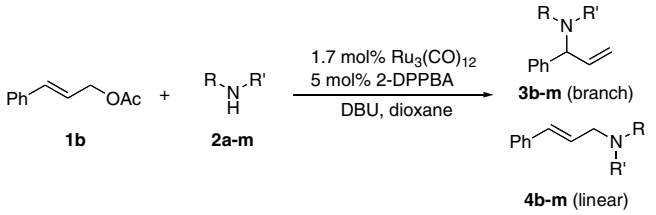


Scheme 2.

Table 2
$Ru_3(CO)_{12}$/2-DPPBA catalyzed allylic amination of **1a** with amines **2b–m**[a]

Entry	Amine **2**	Solvent	Temp. (°C)	Yield[b] (%)	**3**:**4**[c,d]
1	Morpholine (**2b**)	THF	60	85	2:>98
2	Et_2NH (**2c**)	THF	60	0	—
3	Et_2NH (**2c**)	Dioxane	100	73	2:>98
4	Bu_2NH (**2d**)	Dioxane	100	72	2:>98
5	Heptamethyleneimine (**2e**)	Dioxane	100	79	2:>98
6	BuNHMe (**2f**)	Dioxane	100	90	2:>98
7	CyNHMe (**2g**)	Dioxane	100	75	2:>98
8	iPr_2NH (**2h**)	Dioxane	100	0	—
9	Cy_2NH (**2i**)	Dioxane	100	0	—
10	MeNHTs (**2j**)	Dioxane	100	70	2:>98[e]
11	PhNHMe (**2k**)	Dioxane	100	37	2:>98
12	*p*-AnNHMe (**2l**)	Dioxane	100	50	2:>98
13	$BuNH_2$ (**2m**)	Dioxane	100	<5	ND

[a] Reaction conditions: **1a** (1.0 mmol), **2b–m** (2.0 mmol), $Ru_3(CO)_{12}$ (1.7 mol %), 2-DPPBA (5 mol %), DBU (2.0 mmol) solvent (0.2 mL), 12 h.
[b] Isolated yield after purification by column chromatography.
[c] The ratio of **3**/**4** was determined by 400 MHz ^{1}H NMR analysis of crude materials.
[d] The ratio of *E*/*Z* isomers of **4** was determined to be >95:5 by 400 MHz ^{1}H NMR analysis of crude materials unless otherwise noted.
[e] The ratio of *E*/*Z* isomers of **4j** was determined to be 60:40 by 400 MHz ^{1}H NMR analysis of crude materials.



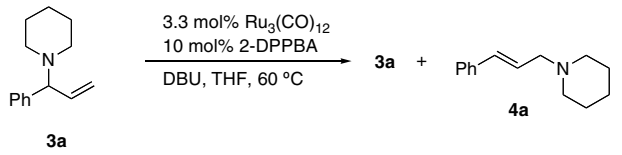
Scheme 3.

moderate to good yield (Table 3, entries 1–7), but the reaction with sterically hindered amines **2h** and **2j** did not produce any aminated products (entries 8 and 9). Again, the reaction with **2j–l** gave linear-type products as a single regioisomer (entries 10–12), but that with a primary amine did not form desired aminated product (entry 13).[10,11] These results suggest that both the reaction of

Table 3
$Ru_3(CO)_{12}$/2-DPPBA catalyzed allylic amination of **1b** with amines **3a–m**[a]

Entry	Amine **2**	Temp. (°C)	Yield[b] (%)	**3**:**4**[c,d]
1	Piperidine (**2a**)	60	95	2:>98
2	Morpholine (**2b**)	60	90	2:>98
3	Et_2NH (**2c**)	100	68	2:>98
4	Bu_2NH (**2d**)	100	87	2:>98
5	Heptamethyleneimine (**2e**)	100	84	2:>98
6	BuNHMe (**2f**)	100	74	2:>98
7	CyNHMe (**2g**)	100	84	2:>98
8	iPr_2NH (**2h**)	100	0	—
9	Cy_2NH (**2i**)	100	0	—
10	MeNHTs (**2j**)	100	62	2:>98[e]
11	PhNHMe (**2k**)	100	37	2:>98
12	*p*-AnNHMe (**2l**)	100	67	2:>98
13	$BuNH_2$ (**2m**)	100	<5	ND

[a] Reaction conditions: **1b** (1.0 mmol), **2a–m** (2.0 mmol), $Ru_3(CO)_{12}$ (1.7 mol %), 2-DPPBA (5 mol %), DBU (2.0 mmol) dioxane (0.2 mL), 12 h.
[b] Isolated yield after purification by column chromatography.
[c] The ratio of **3**/**4** was determined by 400 MHz ^{1}H NMR analysis of crude materials.
[d] The ratio of *E*/*Z* isomers of **4** was determined to be >95:5 by 400 MHz ^{1}H NMR analysis of crude materials unless otherwise noted.
[e] The ratio of *E*/*Z* isomers of **4j** was determined to be 60:40 by 400 MHz ^{1}H NMR analysis of crude materials.

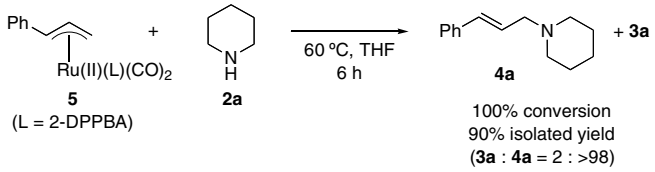


Scheme 4.

Table 4
Ruthenium-catalyzed isomerization of **3a** to **4a**[a]

Entry	Time (h)	**3a**:**4a**[b]
1	12	97:3
2	24	83:17
3	53	58:42
4	89	51:49

[a] Reaction conditions: **3a** (1.0 mmol), DBU (2.0 mmol), THF (0.2 mL).
[b] The ratio was determined by 400 MHz ^{1}H NMR analysis of crude materials.



Scheme 5.

monosubstituted allyl acetates **1a** and **1b** proceeds through the same π-allylruthenium intermediate.[12]

We next studied the reaction pathway of this linear selective allylic amination by the $Ru_3(CO)_{12}$/2-DPPBA catalyst. As mentioned, the ruthenium-catalyzed isomerization of branched allylic amines into their linear isomers is a known process in π-allylruthenium chemistry.[4–6] Based on this previous observation, we examined the isomerization of the branch-type allylic amine **3a** into the linear-type allylic amine **4a** using the $Ru_3(CO)_{12}$/2-DPPBA catalyst. Allylic amine **3a** was treated with $Ru_3(CO)_{12}$ (3.3 mol %), 2-DPPBA (10 mol %) and DBU (2.0 equiv) in THF at 60 °C. The ratio of **3a** and **4a** was measured by the ^{1}H NMR spectrum of the crude materials. As shown in Scheme 4 and Table 4, a trace amount of the linear-type allylic amine **4a** was produced in 12 h (entry 1), and the amount of **4a** slowly increased (entries 2 and 3). However, the ratio of **3a** to **4a** was 51:49 after 89 h, and the reaction had almost stopped (entry 4). This result revealed that our ruthenium catalyst systems also catalyze the isomerization reaction from **3a** to **4a**, but it was slow.

We earlier reported the linear selective nucleophilic attack by malonate anion on the π-allylruthenium intermediate **5**,[8a] which was generated from either the regioisomeric allyl acetates **1a** or **1b** using the $Ru_3(CO)_{12}$/2-DPPBA catalyst. Based on this previous study, we anticipated that nitrogen nucleophiles also selectively attack the sterically less hindered π-allyl terminus and directly produce the linear-type aminated product. To prove this hypothesis, we next examined the stoichiometric reaction of π-allylruthenium complex **5** with **2a** (Scheme 5). The complex **5** was treated with **2a** at 60 °C for 6 h, and we then confirmed by the ^{1}H NMR spectrum the 100% conversion (90% isolated yield after silica gel column chromatography) and almost perfect linear selectivity (>98%).[13,14] This result is in good agreement with the catalytic reactions, and also supports the fact that the $Ru_3(CO)_{12}$/2-DPPBA catalyst selectively forms linear-type allylic amines.

In conclusion, we demonstrated the $Ru_3(CO)_{12}$/2-DPPBA-catalyzed linear selective allylic amination of monosubstituted allylic acetates with secondary amines. The regioselectivity was highly controlled by the $Ru_3(CO)_{12}$/2-DPPBA catalyst, and a linear-type aminated product was obtained.

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13. We also examined the same reaction for 1 h, then confirmed the 70% conversion of the ruthenium complex **5** and the ratio of **3a**/**4a** to be 2/>98 by ^{1}H NMR analysis of crude materials.
14. The reaction of ruthenium complex **5** with primary amine **2m** resulted in no reaction, and recovered the complex **5**.