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Ruthenium-Catalyzed Regio- and Enantioselective Allylic Amination of Racemic 1-Arylallyl Esters

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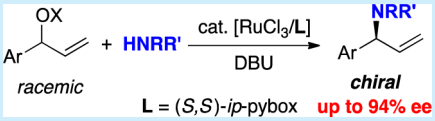
Supporting Information

ABSTRACT: The regio- and enantioselective allylic amination of racemic monosubstituted allylic esters, such as 1-arylallyl acetates, with cyclic secondary amines has been accomplished. The $RuCl_3$/(*S*,*S*)-*ip*-pybox catalyst system has effectively catalyzed the reaction to afford the enantiomerically enriched branch-type allylic amines with perfect regioselectivity and high enantioselectivity.



The transition-metal-catalyzed allylic amination of allylic substrates[1] is one of the most useful reactions to construct allylic amines, and its asymmetric reaction[2] is also a powerful method to prepare enantiomerically enriched allylic amines. For such a transition-metal-catalyzed asymmetric allylic amination, several types of allylic substrates can be used, including symmetrical 1,3-disubstituted allylic substrates, but the reaction of the unsymmetrical monosubstituted substrates is a more challenging system because the reaction requires controlling both the regioselectivity and enantioselectivity. To the best of our knowledge, only palladium[3] and iridium[4−10] are known as effective catalysts for such an intermolecular asymmetric allylic amination of monosubstituted allylic substrates. The first example of the palladium-catalyzed reaction was reported by Hayashi and Ito in 1990.[3a] More recently, Hartwig's group investigated the highly enantioselective allylic amination of monosubstituted allylic esters and alcohols by an iridium catalyst.[4]

However, still it is a challenging topic to discover an alternative transition metal catalyst, which allows the asymmetric allylic amination of racemic monosubstituted allylic compounds. Although there are several studies on the ruthenium-catalyzed asymmetric allylic substitution[11−17] after Onitsuka and Takahashi's report in 2001,[12a] there are still no reports about the intermolecular asymmetric allylic amination of racemic monosubstituted allylic substrates. During the course of our study on the ruthenium-catalyzed regioselective allylic substitution,[18] we succeeded in the intermolecular enantioselective allylic amination of racemic monosubstituted allylic esters with cyclic secondary amines.

We first examined the allylic amination of the racemic 1-phenyl-2-propenyl acetate (**1a**) with morpholine (**2a**) by several chiral ruthenium catalysts, which were generated in situ from the ruthenium precatalyst and (*S*,*S*)-*ip*-pybox (**L**). As shown in Table 1, when the reactions were conducted without an additive, the desired branch-type product **3aa** was obtained in low yield or as a mixture of linear-type products **4aa** (entries 1−4). However, the addition of DBU (2 equiv to **1a**) to the reaction using $RuCl_2$(cod) or $RuCl_3$ effectively increased the branch selectivity (entries 6 and 8), and we observed a moderate enantioselectivity (54% ee) for the reaction using the $RuCl_3$ precatalyst with **L**. The higher enantioselectivity was attained by reducing the amount of DBU from 2 to 1 equiv at 40 °C (entries 9 and 10), and the highest enantioselectivity (85% ee) was obtained when the amount of **L** was increased from 5 to 10 mol % (2 equiv to Ru) (entry 11). We also examined other additives, such as DABCO, Et_3N, DMAP, or Cs_2CO_3, and confirmed that the DBU is a crucial additive for the perfect branch selectivity and high enantioselectivity (entries 12−15).

With these optimized reaction conditions in hand, we investigated the ruthenium catalyzed intermolecular asymmetric allylic amination of several racemic 1-arylallyl acetates **1a−j** with six-membered aliphatic amines, such as **2a−f** (Table 2). Most of the reactions proceeded smoothly, and we succeeded in obtaining the desired product in high yield with a high enantiomeric excess. Especially, the reaction of **1a** with phenylpiperazine (**2d**) gave the highest enantioselectivity (94% ee) (Table 2, entry 3). The reactions of **1b−d**, which have an electron-withdrawing group at the *para*-position on the phenyl group, also afforded good results (entries 6−11). On the other hand, we confirmed that the reaction of **1e**, which has a methoxy group at the *para*-position on the phenyl group, gave **3ea** in 60% yield with 12% ee (entry 12), but increasing the amount of ligand from 10 to 20 mol % significantly increased the enantiomeric excess up to 85% ee (entry 13). Furthermore, we examined the reaction of allyl acetates **1f−i** and succeeded in obtaining the intended enantiomercially enriched products with both acceptable yields and enantiomeric excess (entries 14−21). Unfortunately, the reactions of the 1-naphthyl group substituted allyl acetate **1j** gave the desired products in low yield with low ee (entries 22 and 23).

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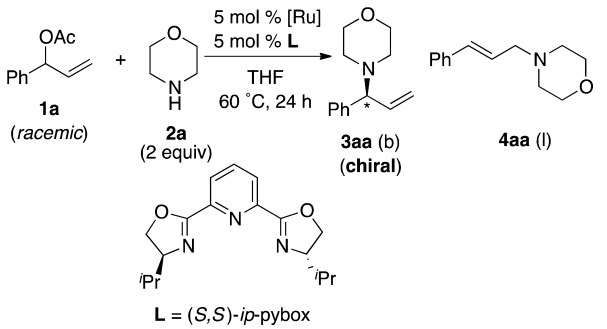
Table 1. Ru Catalysts for the Alkylation of 1a with 2a



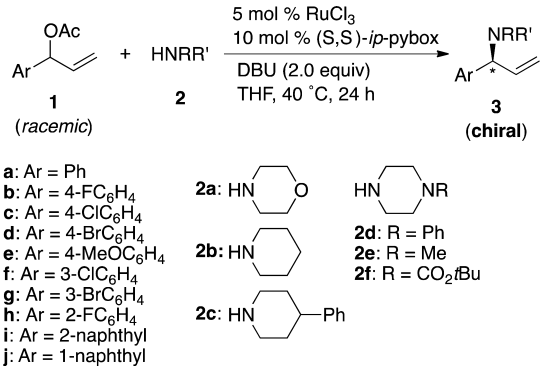
entry	[Ru]	additive (2 equiv)	yield[a] (%) 3aa	yield[a] (%) 4aa	ee (%) of 3aa
1	[Ru-1][b]	–	<2	<2	nd
2	$RuCl_2$(cod)	–	47	39	0
3	$Ru_3(CO)_{12}$	–	7	73	nd
4	$RuCl_3$	–	6	40	0
5	[Ru-1][b]	DBU	37	<2	31
6	$RuCl_2$(cod)	DBU	78	4	16
7	$Ru_3(CO)_{12}$	DBU	<2	<2	–
8	$RuCl_3$	DBU	71	<2	54
9	$RuCl_3$	DBU[c]	75	<2	65
10[d]	$RuCl_3$	DBU[c]	80	<2	81
11[d,e]	$RuCl_3$	DBU[c]	90 (85)[f]	<2	85
12[d,e]	$RuCl_3$	DABCO	17	<2	0
13[d,e]	$RuCl_3$	Et_3N	18	<2	0
14[d,e]	$RuCl_3$	DMAP	<2	<2	nd
15[d,e]	$RuCl_3$	Cs_2CO_3	23	<2	12

[a]The yields were determined by ^{1}H NMR of crude materials using an internal standard (trioxane). [b][Ru-1] = $[RuCl_2(p\text{-cymene})]_2$. [c]1 equiv of DBU was used. [d]Reactions were conducted at 40 °C. [e]10 mol % of **L** was used. [f]Isolated yield in parentheses.

Although we succeeded in realizing that reactions of **1a–i** with six-membered aliphatic amines provided enantioenriched allylic amines in both good yields and high ee values, we also realized that the reaction with pyrrolidine (**2g**) gave a poor result (Table 3, entry 1). To improve these poor results, we reinvestigated the catalyst conditions for the reaction with **2f**. During the reaction of **1a** with **2g**, we observed the formation of the deacetylated allylic alcohol from **1a**; therefore we changed the leaving group of the allyl substrate from acetate to methyl carbonate **1a′** or *tert*-butyl carbonate **1a″**. Changing of the leaving group improved the reaction results, and **1a″** produced the desired aminated product **3af** in good yields (entries 3–5); the best result (82% yield with 80% ee) was attained when the reaction was conducted using 20 mol % of the pybox ligand (4 equiv to Ru) at 60 °C (entry 5). All the other reactions of **1e″**, **1f″**, or **1g″** with **2f** also gave enantiomerically enriched allylic amines with good enantioselectivities (81–84% ee) (entries 6–8).

We further examined the reaction of **1a** with other amines, such as azepane (**2h**) or acyclic amine **2i** (Table 4), but again our optimized conditions gave allylic amines in low yields and low enantiomeric excesses (entries 1 and 4). However, we succeeded in determining the suitable reaction conditions for the reaction with **2h** or **2i**, and acceptable results (93% yield with 82% ee for **2h**, and 92% yield with 82% ee for **2i**) were obtained by increasing the amount of amines and DBU to 3 equiv and changing the solvents from THF to acetone (entries 3 and 5). We also demonstrated the reaction of other allylic

Table 2. Ruthenium-Catalyzed Enantioselective Allylic Amination of Racemic 1-Arylallyl Acetates with Amines[a]



entry	1	2	yield[b] (%) of 3	% ee of 3
1	**1a**	**2b**	91 (**3ab**)	80
2	**1a**	**2c**	84 (**3ac**)	86
3	**1a**	**2d**	90 (**3ad**)	94
4	**1a**	**2e**	90 (**3ae**)	88
5	**1a**	**2f**	93 (**3af**)	86
6	**1b**	**2a**	88 (**3ba**)	86
7	**1b**	**2c**	87 (**3bc**)	90
8	**1b**	**2d**	87 (**3bd**)	93
9	**1c**	**2c**	83 (**3cc**)	90
10	**1c**	**2d**	88 (**3cd**)	94
11	**1d**	**2d**	81 (**3dd**)	94
12	**1e**	**2d**	60 (**3ed**)	12
13[c]	**1e**	**2d**	87 (**3ed**)	85
14	**1f**	**2b**	77 (**3fb**)	90
15	**1f**	**2d**	74 (**3fd**)	87
16	**1g**	**2b**	67 (**3gb**)	90
17	**1g**	**2d**	64 (**3gd**)	90
18	**1h**	**2d**	71 (**3hd**)	86
19	**1h**	**2e**	88 (**3he**)	86
20	**1i**	**2a**	78 (**3ia**)	81
21	**1i**	**2d**	90 (**3id**)	86
22	**1j**	**2a**	35 (**3ja**)	24
23	**1j**	**2d**	22 (**3jd**)	4

[a]Reaction conditions: **1a–j** (1.0 mmol), **2a–f** (2.0 mmol), DBU (2.0 mmol), 5 mol % of $RuCl_3$, and 10 mol % of (*S,S*)-*ip*-pybox in THF at 40 °C for 24 h. [b]Isolated yield. [c]20 mol % of **L** was used.

acetates (**1b–d** and **1i**) with **2i** and could obtain enantiomerically enriched allylic amines with good enantiomeric excesses (entries 6–9). The details of the reaction mechanism of the $RuCl_3$/(*S,S*)-*ip*-pybox catalyzed enantioselective reaction, including the key intermediate, active ruthenium species, or the role of DBU, have not yet been clarified, but we believe that the reaction proceeds through (*S,S*)-*ip*-pybox ligated π-allyl and/or σ-allylruthenium complexes, and epimerization had occurred in those ruthenium intermediates to afford the enantiomerically enriched allylic amines.

In conclusion, we demonstrated the $RuCl_3$/(*S,S*)-*ip*-pybox catalyzed allylic amination of racemic 1-arylallyl esters with amines (mainly aliphatic secondary amines)[19] and succeeded in obtaining enantiomerically enriched allylic amines with a high enantioselectivity with perfect regioselectivity. Further studies, such as the reaction of other allylic esters,[20] reaction with aromatic amines, or study of the mechanistic details, are currently in progress in our group.

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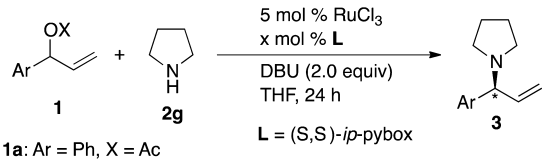
Table 3. Reaction with Pyrrolidine (2g)[a]

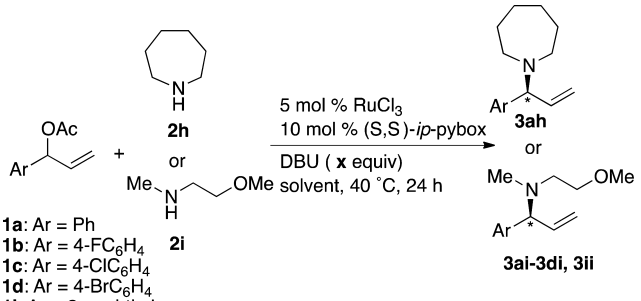


1a: Ar = Ph, X = Ac
1a': Ar = Ph, X = CO_2Me
1a": Ar = Ph, X = $CO_2{}^tBu$
1e": Ar = 3-FC_6H_4, X = $CO_2{}^tBu$
1f": Ar = 3-ClC_6H_4, X = $CO_2{}^tBu$
1g": Ar = 2-naphthyl, X = $CO_2{}^tBu$

entry	1	L (mol %)	temp (°C)	yield[b] (%) of 3	ee (%) of 3
1	**1a**	10	40	50 (**3ag**)	80
2	**1a'**	10	40	29 (**3ag**)	44
3	**1a"**	10	40	72 (**3ag**)	65
4	**1a"**	10	60	80 (**3ag**)	76
5	**1a"**	20	60	82 (**3ag**)	80
6	**1e"**	20	60	62 (**3eg**)	83
7	**1f"**	20	60	61 (**3fg**)	81
8	**1g"**	20	60	90 (**3gg**)	84

[a]Reaction conditions: **1** (1.0 mmol), **2g** (2.0 mmol), DBU (2.0 mmol), 5 mol % of $RuCl_3$, and 10 or 20 mol % of (*S,S*)-*ip*-pybox in THF for 24 h. [b]Isolated yield.

Table 4. Enantioselective Allylic Amination with 2h and 2i[a]



1a: Ar = Ph
1b: Ar = 4-FC_6H_4
1c: Ar = 4-ClC_6H_4
1d: Ar = 4-BrC_6H_4
1i: Ar = 2-naphthyl

entry	1	2 (equiv)	DBU (*x* equiv)	solvent	yield[b] (%) of 3	ee (%) of 3
1	**1a**	**2h** (2)	2	THF	29 (**3ah**)	44
2	**1a**	**2h** (3)	3	THF	88 (**3ah**)	70
3	**1a**	**2h** (3)	3	acetone	93 (**3ah**)	82
4	**1a**	**2i** (2)	2	THF	20 (**3ai**)	50
5	**1a**	**2i** (3)	3	acetone	92 (**3ai**)	82
6	**1b**	**2i** (3)	3	acetone	77 (**3bi**)	77
7	**1c**	**2i** (3)	3	acetone	82 (**3ci**)	81
8	**1d**	**2i** (3)	3	acetone	51 (**3di**)	81
9	**1i**	**2i** (3)	3	acetone	73 (**3ii**)	80

[a]Reaction conditions: **1** (1.0 mmol), **2h–i** (2.0 or 3.0 mmol), DBU (2.0 or 3.0 mmol), 5 mol % of $RuCl_3$, and 10 mol % of (*S,S*)-*ip*-pybox in THF or acetone at 40 °C for 24h. [b]Isolated yield.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) Reactions of cinnamyl acetate or cinnamyl chloride with morpholine resulted in no reaction under our optimized conditions.
(20) Reactions with aniline, MeNHTs, or $(Boc)_2NH$ resulted in no reaction under our optimized conditions.

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