Regio- and Enantioselective Pd-Catalyzed Allylic Amination of Monosubstituted Allylic Substrates with BocNHOMe

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Abstract: A new type of N-nucleophile has been developed in Pd-catalyzed asymmetric allylic amination with monosubstituted allyl substrates, affording corresponding branched allyl amines in high regio- and enantioselectivities. Either OMe or Boc group in products can be removed easily to provide primary amine derivatives with the optical purity unchanged.

Key words: palladium, allylic amination, catalysis, regioselectivity, enantioselectivity

Palladium-catalyzed asymmetric allylic substitution reaction has become a very powerful tool for asymmetric construction of carbon–carbon and carbon–heteroatom bonds and has found widespread applications in organic synthesis.[1] Recent advancements allowed various 'hard' carbanions used in this reaction with exquisite selectivity.[2,3] In sharp contrast, the development using nitrogen nucleophiles falls far behind. Especially, regio- and enantiocontrol in Pd-catalyzed allylic amination with monosubstituted allyl substrates constitutes a long-standing challenge, as it preferentially affords linear product. The reversibility of nucleophilic attack or branched-to-linear isomerization in allylic amination contribute to the formation of linear product.[4] Although four kinds of N-nucleophiles, including unprotected aziridine, hydrazine, hydroxylamine, and benzylamine, have been used in this reaction with regiocontrol so far,[5] enantiocontrol was achieved only in the case of using benzylamine as nucleophile.[5a,b] However, the use of benzylamine may limit later elaboration because there are two benzylic groups in products enabling selective cleavage to be difficult when aryl-substituted allyl substrates were employed. Apparently, the exploitation of new type of N-nucleophile in Pd-catalyzed asymmetric allylic substitution reaction with regio- and enantiocontrol remains to be highly desirable to make the reaction practicable in organic synthesis.

We have developed a series of SIOCPhox ligands (Figure 1) and used them successfully in the Pd-catalyzed asymmetric allylic substitution reactions of monoallyl substrates and 'hard' carbanions, high regio- and enantioselectivities being realized.[3] In this communication, we report a Pd-catalyzed allylic amination reaction of monosubstituted allyl substrates using BocNHOMe as a new and practical nucleophile with excellent regio- and enantioselectivities, moreover, either Boc or MeO group was removed selectively from the products.[6]

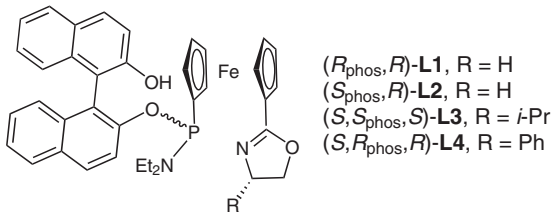

Figure 1 Ferrocene-based ligands SIOCPhox

We commenced our study using phthalimide as the nucleophile in the amination reaction of allyl ester **1a**, because phthalimide is a general source of primary amine, and the resulting product would be facial for later elaboration. However, the reaction did not proceed at all in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/(*R*,*R*)-SIOCPhox (**L1**, entry 1, Table 1). Same results were given when $(Boc)_2NH$, $BocNH_2$, and $BocNHNMe_2$ were used (entries 2–4, Table 1). We surmised that these results may be attributed to the low nucleophilicity of the nucleophiles. It was reported that incorporation of methoxy group would enhance nucleophilicity at the nitrogen center via the α-effect without increasing the pK_a value.[7] Thus, BocNHOMe (**2a**) was subjected to the amination reaction with allyl phosphate **1a**. Allylamines **3a** and **4a** with a ratio of 95:5 were obtained, **3a** being isolated in 77% yield, the ee of **3a** being 98% (entry 5, Table 1).

Subsequently, allyl substrates **1** with different leaving groups were examined. It was found that excellent regio- and enantioselectivities were achieved in all cases (entries 6–8, Table 1) while the carbonates **1c** and **1d** were proved to be superior in terms of the yield (entries 7 and 8 vs. entries 5 and 6, Table 1). When branched acetate **1e** was used as substrate, similar stereoselectivities were obtained as that using linear acetate **1b**, suggesting that memory effect[8] is not involved in this amination reaction (entries 5 vs. 9, Table 1). Less time was needed when K_3PO_4 was the base compared to that using K_2CO_3 as the base while the regio- and enantioselectivities of the reaction were maintained (entries10 vs. 8, Table 1). The screen of com-

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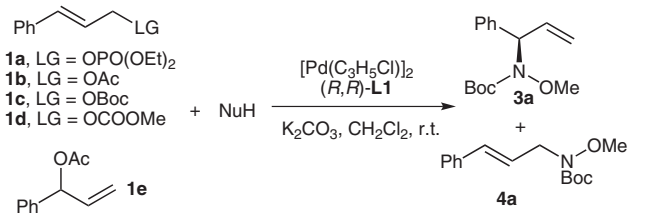
Table 1 Regio- and Enantioselective Pd-Catalyzed Allylic Amination[a]



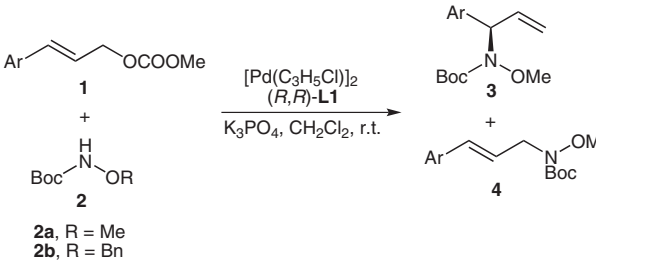
Entry	1	NuH	Time (h)	3a/4a[b]	Yield of 3a (%)[c]	ee (%)[d]
1	**1a**	phthalimide	30	–	n.r.[e]	–
2	**1a**	$(Boc)_2NH$	30	–	n.r.[e]	–
3	**1a**	$BocNH_2$	30	–	n.r.[e]	–
4	**1a**	$BocNNMe_2$	30	–	n.r.[e]	–
5	**1a**	BocNHOMe (**2a**)	30	95:5	77	98
6	**1b**	BocNHOMe (**2a**)	30	96:4	78	99
7	**1c**	BocNHOMe (**2a**)	30	95:5	91	99
8	**1d**	BocNHOMe (**2a**)	30	96:4	90	99
9	**1e**	BocNHOMe (**2a**)	48	95:5	89	96
10[f]	**1d**	BocNHOMe (**2a**)	22	95:5	93	98

[a] Molar ratio of **1**/NuH/K_2CO_3/$[Pd(C_3H_5)Cl]_2$/**L1** = 100:150:150:2.5:5.
[b] Determined by ^1H NMR.
[c] Isolated yield.
[d] Determined by chiral GC.
[e] n.r. = no reaction.
[f] K_3PO_4 used as base.

mon solvents, including THF, Et_2O, CH_2Cl_2, and toluene, showed that CH_2Cl_2 was the optimal choice. As we found before,[3] the different combination of chiral elements as well as the substituent on oxazoline ring of the SIOCPhox ligands have a great impact on the selectivities of the reaction, and the best results were afforded when (*R*,*R*)-SIOCPhox (**L1**) was the ligand (Figure 1 and see Supporting Information).

The substrate scope was investigated under the optimized conditions, and the results are shown in Table 2. A wide range of allyl methyl carbonates **1** were viable substrates in the reaction with BocNHOMe (**2a**), affording allyl amines **3** in 66–93% yields with the ratio of 89–97:11–3 for **3/4** and the ee value of over 94% ee for **3** except for one example (vide infra). Excellent regio- and enantioselectivities (the ratio of 93–97:7–3 for **3/4** and 96–98% ee for **3**) were obtained for the allyl methyl carbonates **1** bearing either electron-withdrawing or electron-donating groups at the *para* position of the phenyl ring (entries 2–6, Table 2). The incorporation of a substituent at a *meta* position led to the same enantioselectivity albeit the regioselectivity was a little bit lower (entries 7–9, Table 2). The amination was also applicable to the naphthyl-substituted carbonate **1** with excellent regio- and enantioselectivities (entry 12, Table 2). Carbonate **1** with an *ortho*-methoxyphenyl ring provided the corresponding allylamine **3k** in high regio- and enantioselectivities (entry 11, Table 2). However, much lower regioselectivity and yield were obtained for carbonate **1** with an *ortho*-chlorophenyl ring, for unclear reasons (entry 10, Table 2). The reaction using BocNHOBn (**2b**) as the nucleophile also gave high regio- and enantioselectivities and high yield (entry 13, Table 2).

Table 2 Substrate Scope for Pd-Catalyzed Allylic Amination of *tert*-Butyl-Carbamates **2** and Methyl Carbonates **1**[a]



Entry	Ar	2	3/4[b]	Yield of 3[12] (%)[c]	ee (%)[d]
1	Ph	**2a**	95:5	**3a** 93	98
2	4-FC_6H_4	**2a**	97:3	**3b** 91	98[g]
3	4-ClC_6H_4	**2a**	96:4	**3c** 87	98
4	4-BrC_6H_4	**2a**	93:7	**3d** 89	98
5	4-MeC_6H_4	**2a**	96:4	**3e** 92	97[g]
6	4-$MeOC_6H_4$	**2a**	97:3	**3f** 85	96
7	3-ClC_6H_4	**2a**	89:11	**3g** 85	98[g]
8	3-BrC_6H_4	**2a**	90:10	**3h** 83	99[g]
9	3-$MeOC_6H_4$	**2a**	92:8	**3i** 87	97[g]
10[e]	2-ClC_6H_4	**2a**	65:35	**3j** 44	88
11	2-$MeOC_6H_4$	**2a**	94:6	**3k** 66	97
12[f]	1-naphthyl	**2a**	95:5	**3l** 94	99
13[e]	Ph	**2b**	90:10	**3m** 82	94

[a] Molar ratio of **1/2**/K_3PO_4/$[Pd(C_3H_5)Cl]_2$/**L1** = 100:150:150:2.5:5.
[b] Determined by ^1H NMR.
[c] Isolated yield.
[d] Determined by chiral GC or HPLC.
[e] $OPO(OEt_2)$ was used as leaving group.
[f] **L4** was used as ligand.
[g] The ee was determined after removal of Boc group of the products **3**.

The absolute configuration of the product **3a** was determined to be *R* by comparing the optical rotation of the *N*-Boc derivative **6a** with that reported by Kibayashi.[9] Either protective group on nitrogen of the allylamine **3a** can be removed selectively without the loss of optical purity. Cleavage of Boc–N bond using the conventional reagent, 3 M HCl–EtOAc solution, afforded *N*-OMe amine **5a** quantitatively. The chiral *N*-OMe amines are found in nat-

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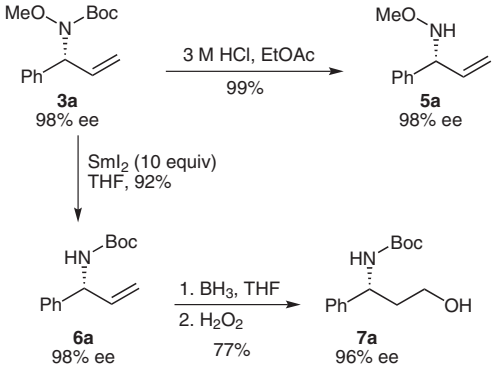
ural products such as agelastatin A.[10] Removal of OMe group was realized by using SmI_2, generating *N*-Boc allyl amine **6a** in 92% yield, which was easily converted into the chiral 1,3-amino alcohol **7a** in 77% yield by routine operations of hydroboration and oxidation (Scheme 1). The analogues of the chiral allyl amine **6a** and 1,3-amino alcohol **7a** have been reported to serve as key building blocks in the synthesis of bioactive natural products and pharmaceutically important compounds such as (+)-CP-99,994, (+)-CP-122,721, (–)-cytoxazone, (*S*)-dapoxetin, and (–)-lasubine.[9,11]



Scheme 1 Selective deprotection of the allyl amine **3a**

In conclusion, a new type of N-nucleophile has been developed in Pd-catalyzed asymmetric allylic amination with monosubstituted allyl substrates, affording corresponding branched allyl amines in high regio- and enantioselectivities. Either OMe or Boc group in products can be removed easily to provide primary amine derivatives with the optical purity unchanged. Both Boc-protected allyl amines and their hydroboration–oxidation products are useful in organic synthesis. Further investigations on their uses as well as the applications of the protocol in organic synthesis are in progress.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **General Procedure for the Allylic Amination**
To a flame-dried Schlenk tube were added $[Pd(C_3H_5)Cl]_2$ (1.8 mg, 0.005 mmol), ligand (*R*,*R*)-**L1** (6.4 mg, 0.010 mmol), and CH_2Cl_2 (2.0 mL) under Ar at r.t. The solution was allowed to stir for 5 min before ester **1** (0.2 mmol), MeONHBoc (44 mg, 0.3 mmol), and K_3PO_4 (63 mg, 0.3 mmol) were added. The reaction was allowed to stir at r.t. and monitored by TLC until the disappearance of the ester **1**. The reaction mixture was passed through a short plug of kieselgur eluted with CH_2Cl_2. The solvent was removed under reduced pressure. The crude residue [after ^1H NMR analysis to check the regioisomeric ratio (**3/4**)] was purified by flash chromatography (FC) with EtOAc–PE as the eluent (generally, the two regioisomers could be separated by FC) to afford the compound **3**.

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