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Catalytic Asymmetric Synthesis of Vicinal Diamine Derivatives through Enantioselective *N*-Allylation Using Chiral π-Allyl Pd-Catalyst

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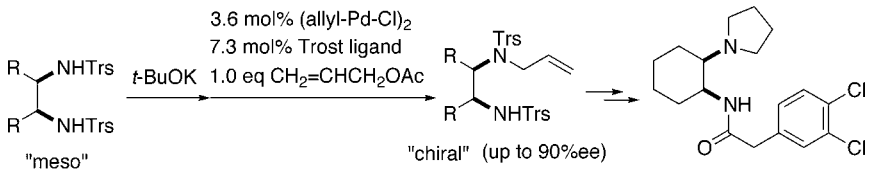
ABSTRACT



***N*-Monoallylation of *meso*-vicinal diamine bistrisylamides using a chiral π-allyl-Pd catalyst proceeded in an enantioselective manner (up to 90% ee) to give desymmetrization products in good yields. The product was converted to the known σ-receptor agonist in short steps. In addition, the present catalytic asymmetric *N*-allylation was applied to kinetic resolution of *racemic*-diamide.**

Vicinal diamines and their derivatives have received much attention in the field of medicinal and synthetic chemistry. Various optically active synthetic vicinal diamine derivatives have been used as medicinal agents[1,2] and chiral ligands (or chiral auxiliaries) for asymmetric reactions.[2] These nonracemic diamines have been mainly prepared through a multistep sequence from a chiral pool precursor, optical resolution using a chiral reagent or an enzyme,[3] or asymmetric reaction using a stoichiometric chiral reagent or a chiral auxiliary.[2] Recently, enantioselective syntheses of these diamines through nonenzymatic catalytic asymmetric reactions have been reported by several groups.[4] On the other hand, although chiral cyclic *syn*-vicinal diamine derivatives such as unsymmetrical *cis*-1,2-diaminocycloalkanes are well-known as potent medicinal agents,[2,5] catalytic asymmetric synthesis of these compounds has been uncommon up to date. Thus, there still remain some problems in the synthesis of vicinal diamines using catalytic asymmetric methods.

In this paper, we report a new method for the preparation of optically active vicinal diamines through enantioselective *N*-monoallylation of *meso*-diamine derivatives with a chiral π-allyl-Pd catalyst. Furthermore, conversion of the product to a σ-receptor agonist and an application of the technique to kinetic resolution of a *racemic*-diamine derivative are also described.

We are interested in catalytic asymmetric desymmetrization of *meso*-diamine derivatives because this reaction should provide a new synthetic method for optically active unsymmetrical *cis*-vicinal diamine derivatives. In contrast to cata-

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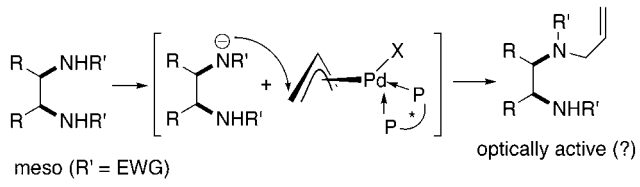
lytic asymmetric desymmetrization of *meso*-diol,[6] there is no report to the best of our knowledge on that of *meso*-diamine derivatives. The enantiocontrol in the reaction with diamine substrates may be difficult because of high nucleophilic reactivity of the amino group and the strong ability to chelate with transition metals which may result in dissociation of the chiral ligand from the catalyst center and deactivation of the catalyst. We expected that catalytic asymmetric desymmetrization of *meso*-substrate having two less reactive amide groups may be achieved through enantioselective *N*-monoallylation using a chiral π-allyl-Pd catalyst (Scheme 1).[7]

Scheme 1

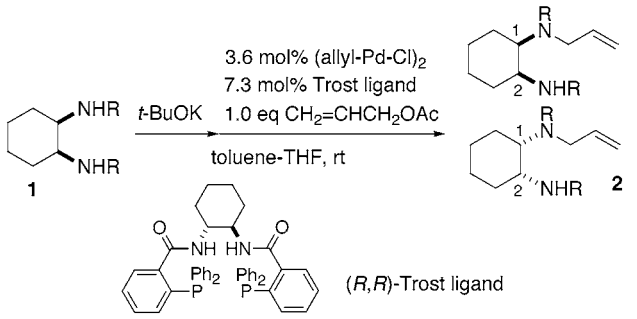


Initially, in the presence of a chiral phosphine−palladium catalyst (chiral phosphine 0.073 equiv, allylpalladium chloride dimer 0.036 equiv) and allyl acetate (1 equiv), *N*-monoallylation of sodium amide prepared from *meso*-cyclohexane-1,2-diamine bistosylamide **1a** and NaH was examined in THF at room temperature. Although a survey of various representative chiral phosphine ligands was performed [BINAP, DTBM-SEGPHOS, BPPFA, CHIRAPHOS, DIOP, Me-DUPHOS, NORPHOS, P,N-LIGAND, PHANEPHOS, BCPM], good enantioselectivity could not be obtained (less than 25% ee). The best result was observed in the reaction with the (*R*,*R*)-Trost ligand;[8] in this case, monoallyl product **2a** of 46% ee was obtained in 65% yield. Subsequently, change of the base (*t*-BuOK, $CsCO_3$), allylic reagent (cinnamyl acetate, prenyl acetate), and solvent (toluene, CH_2Cl_2) was also investigated. However, in all cases, no appreciable increase in the enantioselectivity was observed, while the reaction using *t*-BuOK as a base in toluene−THF led to a slight increase in the enantioselectivity (68%, 52% ee, Table 1 entry 1).

For improvement of the enantioselectivity, the substituent effect on the nitrogen atom was examined under the optimized conditions (Table 1). Since the *N*-monoallylation of carboxamide derivative such as **1b** did not proceed (entry 2), the reaction with several sulfonamides **1c**−**e** was conducted (entries 3−5). It was found that the reaction of bissulfonamide **1e** having a bulky trisyl (2,4,6-triisopropylbenzenesulfonyl) substituent proceeds with good enantioselectivity (81% ee) to give the *N*-monoallylated product **2e** in 69% yield (entry 5). Interestingly, in the reaction of trisylamide **1e**, the opposite enantioselectivity from those of tosylamide **1a** and 2-nitrobenzenesulfonamide **1d** was observed.[9]

When the reaction of **1e** was conducted at lower temperature (−15−0 °C), the ee of allylated product **2e** increased to 90% (70% yield, Scheme 2). The present method was also applied to asymmetric desymmetrization of other vicinal diamine bis-trisylamides **1f** and **1g** (Scheme 2). Although a

Table 1. Catalytic Asymmetric Desymmetrization of *meso*-Cyclohexane-1,2-diamine Derivatives[a]

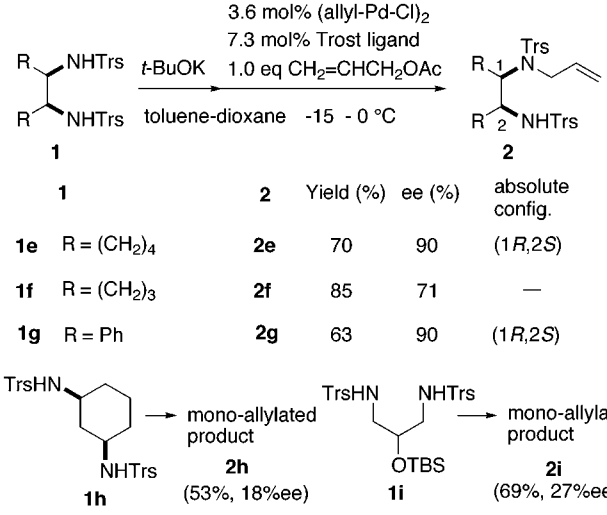


entry	1	2	yield[b] (%)	ee[c] (%)	absolute config[d]
1	**1a**, R = Ts	**2a**	68	52	(1*S*,2*R*)
2	**1b**, R = COPh	**2b**	0		
3	**1c**, R = 2-$CF_3C_6H_4SO_2$	**2c**	69	55	*e*
4	**1d**, R = 2-$NC_2C_6H_4SO_2$	**2d**	74	70	(1*S*,2*R*)
5	**1e**, R = Trs	**2e**	69	81	(1*R*,2*S*)

[Trs = 2,4,6-(*i*-Pr)$_3$$C_6H_2SO_2$]

[a] Desymmetrization reaction: **1** (0.3 mmol), *t*-BuOK (0.3 mmol), Pd (0.011 mmol), Trost ligand (0.022 mmol), allyl acetate (0.3 mmol) in toluene−dioxane (1.5−1.5 mL) at r. [b] Isolated yield. [c] The ee was determined by HPLC analysis using a chiral column (**2a**,**c**,**d**: CHIRALPACK AD, **2e**: CHIRALCEL OD-H). [d] The absolute configuration of the major enantiomer is shown. [e] The absolute configuration of the major enantiomer was not determined.

Scheme 2



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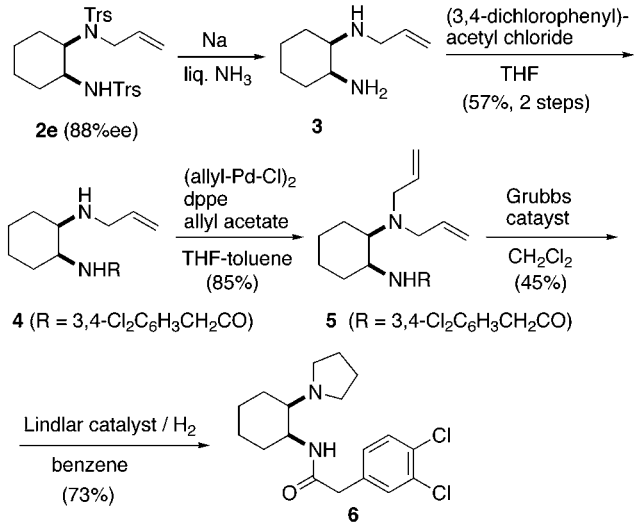
decrease in the enantioselectivity was observed, the reaction with bistrisylamide of cyclopentane-1,2-diamine **1f** also proceeded enantioselectively (71% ee) to give the *N*-monoallylated product **2f** in a good yield (85%). In the reaction of 1,2-diphenylethylenediamine derivative **1g**, similar to the case of **1e**, the product **2g** was obtained with high enantioselectivity (90% ee, 63% yield). In the reactions of **1e**−**g**, a very small amount of bisallylated trisylamide was observed as a side product (less than 3% yield).

Unfortunately, under the same conditions, *N*-monoallylation of 1,3-bistrisylamide derivatives **1h**,**i** proceeded with poor enantioselectivity (18% ee and 27% ee) to give the products **2h**,**i** (53% and 69% yield, Scheme 2).

As an application of the present reaction, we next attempted conversion of the desymmetrization product to a known medicinal agent (Scheme 3). Two trisyl groups of

Scheme 3

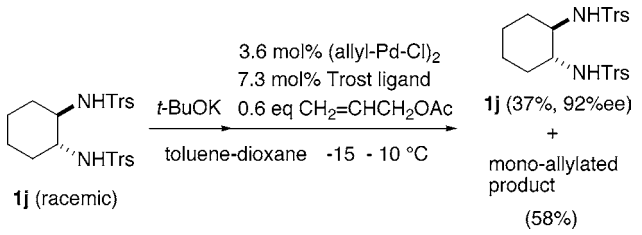


2e were removed by Birch reduction,[10] and the obtained diamine **3** was subsequently converted to (3,4-dichlorophenyl)acetamide **4**. Acylation of **3** with the phenylacetyl chloride at rt proceeded regioselectively at the primary amino group without the formation of the regioisomer and bisacyl derivative. The *N*-allylation of **4**, followed by the ring-closing metathesis using the Grubbs catalyst and the hydrogenation using the Lindlar catalyst, gave pyrrolidinylcyclohexylamide **6** which is known as a selective σ-receptor agonist.[5,11]

On the basis of this conversion, the absolute configuration of the major enantiomer of **2e** (90% ee) which was obtained by the use of the (*R*,*R*)-Trost ligand, was confirmed to be (1*R*,2*S*). In addition, the major enantiomer of desymmetrization product **2g** having high optical purity (90% ee) was determined as (1*R*,2*S*)-isomer by comparing with the authentic sample derived from commercially available (1*S*,2*R*)-2-amino-1,2-diphenylethanol (see the Supporting Information).[12]

The present *N*-monoallylation using chiral π-allyl-Pd complex was also applied to kinetic resolution of racemic vicinal diamine derivative (Scheme 4). Under the above conditions, *N*-monoallylation of *racemic-trans*-cyclohexane-1,2-

Scheme 4



diamine bistrisylamide **1j** with 0.6 equiv of allyl acetate gave *N*-monoallylated product in 58% yield together with recovery of **1j** (37%). The ee of recovered **1j** was estimated to be 92%, which indicates an *s* value = 15.8. Moreover, the major enantiomer of **1j** (92% ee) was confirmed as the (1*R*,2*R*)-isomer by comparison with the authentic sample prepared through bistrisylation of (1*R*,2*R*)-1,2-diaminocyclohexane (commercially available).[13]

In conclusion, we have succeeded in the development of new synthetic methodology for optically active vicinal diamine derivatives through enantioselective *N*-monoallylation with a chiral π-allyl-Pd catalyst. The present reaction is the first example of asymmetric desymmetrization of *meso*-diamine derivatives through catalytic asymmetric reaction, which provides a new promising method for synthesis of chiral vicinal diamines. In addition, in the reaction of a nitrogen nucleophile with a chiral π-allyl-Pd complex, although asymmetric induction at the allylic reagent site is well-known,[7,14] that at the nitrogen nucleophile site has not thus far been reported except for the synthesis of atropisomeric anilides recently reported by us and Curran group.[15] Thus, the present reaction should provide a new prototype in the field of chiral π-allyl-Pd chemistry.

Supporting Information Available: Experimental procedures and characterization data for compounds **1a**−**j**, **2a**,**c**−**i**, and **4**−**6** and a reaction scheme for the determination of the absolute configuration of **2a**,**d**,**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The reverse of the enantioselectivity in the reaction of **1e** was confirmed by converting **2e** to **2a** (see the Supporting Information). The absolute configuration of the major enantiomer of the product **2d** was also determined by conversion to **2a** (see the Supporting Information), while that of **2c** was not determined.

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