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Sequential asymmetric homoallenylation of primary amines with a palladium catalyst

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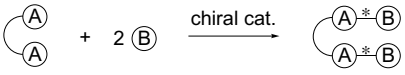
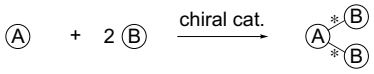
ABSTRACT

Optically active bis(homoallenyl)amines bearing two chiral axes with the same sense of axial chirality were prepared by a one-pot, palladium-catalyzed sequential homoallenylation of primary amines with 2,3-allenyl phosphates.

Sequential asymmetric induction has attracted much attention toward the ultimate goal of developing one-pot sequential synthetic reactions.[1] One-pot asymmetric reactions of molecules bearing multiple and remote functionalities (Eq. 1) have been studied extensively for sequential asymmetric inductions in many types of organic reactions including oxidation of sulfides,[2] epoxidation of trienes,[3] phosphination of dibromides,[4] hydrogenation of diketones,[5] alkylation of dialdehydes with diethyl zinc,[6] and cyanation–aldol reactions.[7] In contrast, asymmetric inductions performed via successive enantiomeric differentiations on the same reaction point (Eq. 2) are not as frequently reported despite their potential importance in various fields of organic synthesis such as catalytic allylation[8] and 1,4-conjugate additions.[9] The difficulties in this mode of asymmetric induction are probably due to the fatal conflict of enantiomeric differentiation which commonly arises from the inevitable generation of the adjacent diastereoface by the first asymmetric induction.

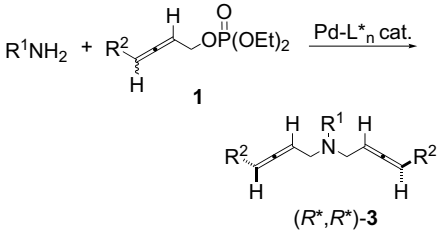


(1)



(2)

During the course of our systematic studies on catalytic coupling reactions via π-allyl palladium intermediates,[10] we found that catalytic homoallenylation of primary amines[11a] is a rare and suitable platform for the above sequential asymmetric induction (Eq. 2). This is due to the specific axial chirality of α-methylene-π-allyl intermediates,[11,12] which would prevent the above conflict of facial differentiation. In this Letter, we describe a practical method for one-pot asymmetric bishomoallenylation of primary amines with 2,3-allenyl phosphates in the presence of palladium complex catalysts (Eq. 3). Since bishomoallenylamino compounds have been used as starting materials in a variety of carbocyclizations such as [2+2] cycloadditions[13] and stannylative cyclizations,[14,15] the reaction provides a facile and convenient method for synthesizing a wide variety of optically active nitrogen-containing carbon skeletons.



(3)

The sequential asymmetric homoallenylation was examined using the reaction of diethyl 5,5-dimethyl-2,3-hexadienyl phosphate (**1a**) with benzylamine in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.025 equiv) and (*R*)-SEGPHOS [(*R*)-**4**][16] (0.05 equiv) in THF at 20 °C (Scheme 1). ^1H NMR analysis of the time-dependent change

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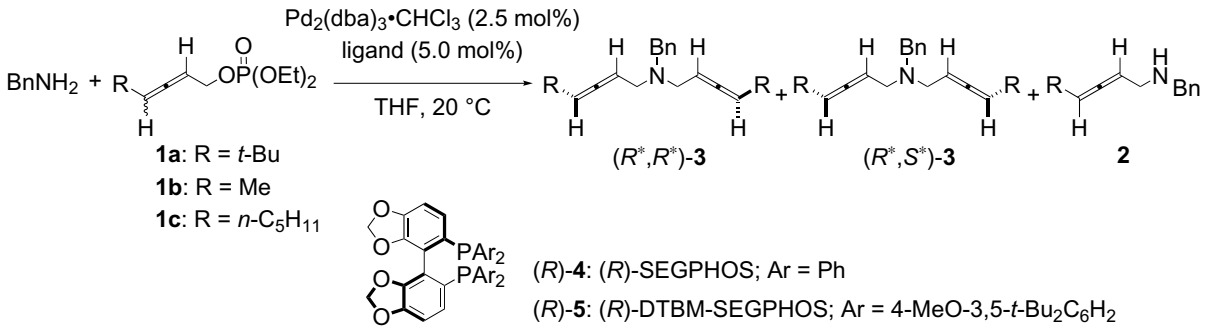
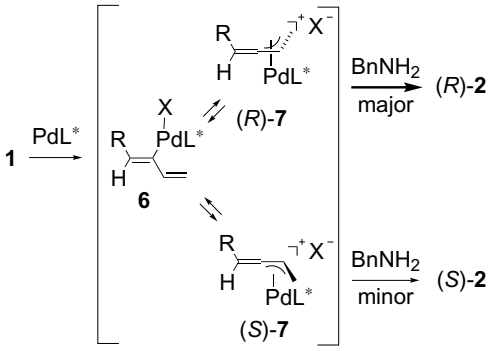


Scheme 1. Palladium-catalyzed homoallenylation of benzylamine.

in product distribution showed that the process occurs via the initial formation of *N*-benzyl-5,5-dimethyl-2,3-hexadienylamine (**2a**), which undergoes subsequent catalytic homoallenylation to afford the chiral (R^*,R^*) form of *N*,*N*-bis(5,5-dimethyl-2,3-hexadienyl)benzylamine (**3a**) along with achiral (R^*,S^*)-**3a** with a diastereoselectivity of 81/19. HPLC analysis using a chiral stationary phase column showed that moderately high enantioselectivity was observed for the product (R^*,R^*)-**3a** (88% ee). Compounds **2a** and **3a** exhibited (−) specific rotations,[17] from which their absolute configurations were assigned to be (*R*) and (*R*,*R*), respectively, from the established molecular structure of (*R*)-(−)- and (*S*)-(+)-*N*-benzyl-*N*-methyl-2,3-pentadienylamine.[18]

Sequential asymmetric homoallenylations of primary amines can be performed with 2,3-allenyl phosphates. Representative results for the reactions with benzylamine are shown in Table 1. Moderate to high enantio- and diastereoselectivities were observed in the reactions with 2,3-allenyl phosphates **1a–c** bearing substituents at C4 position, when (*R*)-SEGPHOS [(*R*)-**4**] or (*R*)-DTBM-SEGPHOS [(*R*)-**5**] was used as the chiral ligand (entries 1, 3, and 5). Other chiral ligands such as BINAP showed moderate enantioselectivity. The use of the (*S*)-ligands afforded (*S*,*S*)-products with nearly identical diastereo- and enantioselectivities (entries 2 and 4).

The present asymmetric induction can be rationalized by the mechanism shown in Scheme 2,[11] where oxidative addition of the chiral palladium species to the 2,3-allenyl phosphate **1** gives σ-1,3-alkadienylpalladium **6**[11b] and the equilibrated chiral isomers of the α-methylene-π-allylpalladium intermediates (*R*)- and (*S*)-**7**. The enantiomer differentiating reaction of primary amines with **7** affords optically active monohomoallenylamine (*R*)- or (*S*)-**2**, which in turn acts as a nucleophile in this asymmetric reaction

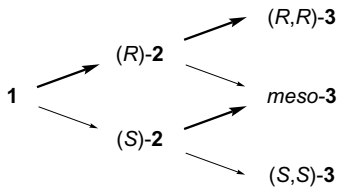


Scheme 2. Asymmetric induction of chiral axes by palladium-catalyzed homoallenylation of benzylamine.

to afford the (*R*,*R*)- or (*S*,*S*)-form of the bishomoallenylamines **3** with high enantioselectivity.

Similar treatment of **1a** with benzylamine (0.7 equiv) in the presence of achiral catalyst, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.025 equiv) and dppp (0.05 equiv), afforded a mixture of (R^*,R^*)- and (R^*,S^*)-**3a** in a 50:50 ratio (total yield 71%). This result indicates that nucleophilic attack of (*R*)-**2a** to α-methylene-π-allylpalladium intermediate (*R*)-**7** proceeds at the same rate as that of (*S*)-**2**. Thus, we can be fairly certain that the system is substantially protected from the common diastereomeric conflict, which is encountered in sequential aldol and Michael reactions. This can be ascribed to the molecular structure of the homoallenylamines, whose asymmetric carbon (C4) is located in a sufficiently remote position from the reactive nitrogen atom.

As shown in Scheme 3, a minor product, *meso*-**3**, is formed both by the major reaction with the minor intermediate, (*S*)-**2**, and the minor reaction with the major intermediate, (*R*)-**2**. Thus, it is noteworthy that the present sequential process can substantially achieve high enantioselectivity of the product, since most of the minor intermediate is transformed into the removable meso compound in the second step.[19] Principally, 95% ee of (*R*,*R*)-**3** can be obtained by enantioselectivities of 86:14 both in the first and in



Scheme 3. Statistical enantiomeric amplification by sequential homoallenylation.

Table 1
Palladium-catalyzed sequential asymmetric homoallenylation of benzylamine[a]

Entry	Phosphate	Ligand	Product	Yield[b] (%)	(R^*,R^*)/(R^*,S^*)[c]	ee of (R^*,R^*)-**3**[d] (%)
1	**1a**	(*R*)-**4**	**3a**	75	81:19	88 (*R*,*R*)
2	**1a**	(*S*)-**4**	**3a**	78	82:18	87 (*S*,*S*)
3	**1a**	(*R*)-**5**	**3a**	52	85:15	95 (*R*,*R*)
4	**1b**	(*S*)-**4**	**3b**	68	73:27[e]	75 (*S*,*S*)
5	**1c**	(*R*)-**4**	**3c**	72	73:27	75 (*R*,*R*)

[a] All reactions were conducted in THF (0.075 M) at room temperature for 20–24 h. The ratio of **1**/benzylamine/$Pd_2(dba)_3{\cdot}CHCl_3$/ligand was 100/70/2.5/5.0.
[b] Isolated yield based on phosphate **1**.
[c] (R^*,R^*)/(R^*,S^*) was determined by HPLC analysis with a chiral stationary phase column using calibration curves.
[d] Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column, and the absolute configurations of the major enantiomer are shown in parentheses.
[e] Determined by GLC analysis using a chiral stationary phase column.

the second homoallenylation steps. Further studies are currently underway.

Acknowledgments

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17. A typical procedure is exemplified by the preparation of **3a**. A solution of 2,3-allenyl phosphate **1a** (0.30 mmol), benzylamine (0.21 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (7.50×10^{-3} mmol), and (*R*)-DTBM-SEGPHOS [(*R*)-**5**, 1.50×10^{-2} mmol] in THF (4 mL) was stirred at 20 °C for 20 h. After the usual work-up, bishomoallenylamine **3a** was isolated by a simple column chromatographic separation through silica gel (25 mg, 52%). HPLC analysis using Chiralpak® OD (hexane–*i*-PrOH = 99:1) showed the diastereomeric ratio of **3a** to be (R^*,R^*)/(R^*,S^*) = 85:15 and enantiomeric excess of (R^*R^*)-**3a** to be 95% ee (*R*,*R*). (*R*,*R*)-**3a**: $[\alpha]_D$ −81.88 (*c* 0.149, $CHCl_3$); IR (neat) 3029, 2866, 1960 (C=C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.08 [s, 18H, $(CH_3)_3C$], 3.11–3.21 (m, 4H, $NCH_2CH{=}C{=}CH$), 3.61–3.72 (m, 2H, $PhCH_2N$), 5.12–5.16 (m, 2H, *t*-$BuCH{=}C{=}CHCH_2N$), 5.21 (ddt, *J* = 2.5, 6.5, 7.5 Hz, 2H, *t*-$BuCH{=}C{=}CHCH_2N$), 7.21–7.26 (m, 2H, Ar*H*), 7.28–7.37 (m, 3H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.2, 31.8, 52.9, 57.0, 89.7, 103, 126.8, 128.1, 129.1, 202.4; HRMS calcd for $C_{23}H_{33}N^+$: 323.2613, found 323.2609. Monohomoallenylamine **2a** was isolated from the similar reaction of **1a** with an equimolar amount of benzylamine using (*R*)-SEGPHOS [(*R*)-**4**] as a ligand. (*R*)-**2a**: $[\alpha]_D$ −54.0 (*c* 0.183, $CHCl_3$); IR (neat) 3320, 3028, 2960, 1960 (C=C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.04 [s, 9H, $(CH_3)_3C$], 3.28 (dd, 2H, *J* = 3.0, 6.3 Hz, $NCH_2CH{=}C{=}C$), 3.82 (d, 1H, *J* = 14 Hz, PhC*H*HN), 3.87 (d, 1H, *J* = 14 Hz, PhCH*H*N), 5.22 (dt, 1H, *J* = 6.3, 3.0 Hz, *t*-$BuCH{=}CH{=}CH$), 5.29 (dt, 1H, *J* = 6.3, 6.3 Hz, $NCH_2CH{=}C{=}CH$), 7.24–7.36 (m, 5H, ArH).
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