Highly Diastereoselective Conjugate Addition of Aryllithium to Chiral β-Nitrostyrene Derivative: An Application to the Asymmetric Synthesis of 4-Aryl-1,2,3,4-tetrahydroisoquinoline

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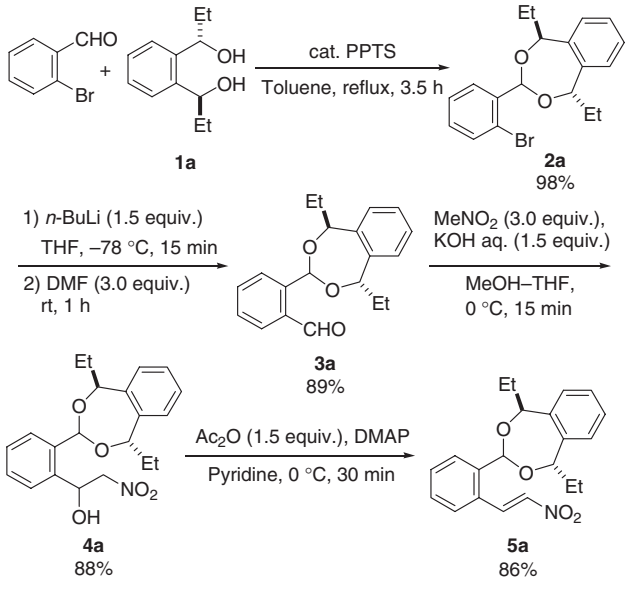
Highly diastereoselective conjugate addition of aryllithium to β-nitrostyrene derivative, having chiral acetal moiety derived from (*S*,*S*)-1,2-bis(1-hydroxypropyl)benzene, was achieved. The adduct was transformed to 4-aryl-1,2,3,4-tetrahydroisoquinoline in high enantiomeric excess (ee).

Chiral acetals prepared from chiral diols are useful compounds in asymmetric reactions as chiral synthetic equivalents of carbonyl compounds[1a,1b,2] as well as chiral protecting group of carbonyl compounds having the reactive prochiral center in the vicinity.[1b,1c,3] C_2-Symmetrical chiral diols are of attension among various chiral diols as they can avoid the formation of diastereoisomers.[1] Previously, we reported a convenient method for the preparation of C_2-symmetrical chiral 1,4-diol, 1,2-bis-(1-hydroxyalkyl)benzene,[4] and an application of the chiral diol to highly diastereoselective photochemical cyclization of an indolylfulgide derivative.[5] The result prompted us to examine asymmetric reactions employing acetals derived from chiral 1,2-bis(1-hydroxypropyl)benzene **1a**. Here, we wish to report effectiveness of chiral acetal moiety derived from (*S*,*S*)-1,2-bis(1-hydroxypropyl)benzene **1a** in diastereoselective 1,4-addition of aryllithium to β-nitrostyrene derivative **5a**, and transformation of the adduct to chiral 4-aryl-1,2,3,4-tetrahydroisoquinoline framework which is involved in naturally occurring alkaloids[6] and several useful biologically active compounds.[7]

In the first place, β-nitrostyrene derivative **5a** was prepared in five steps from *o*-bromobenzaldehyde by the conventional methods as shown in Scheme 1. β-Nitrostyrene derivatives **5b**–**5d** were also prepared from *o*-bromobenzaldehyde and C_2-symmetrical chiral diols, (*S*,*S*)-hydrobenzoine **1b**, (2*S*,4*S*)-2,4-pentanediol **1c**, or (2*S*,3*S*)-2,3-dimethoxybutane-1,4-diol **1d**, in the similar manner, respectively.



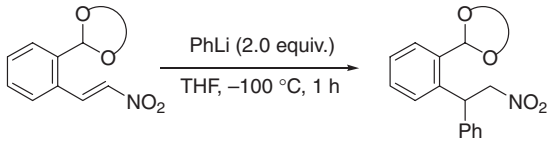
Scheme 1. Preparation of β-nitrostyrene **5a**.

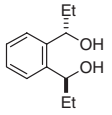
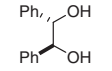
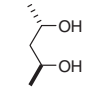
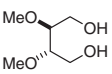
Then, the reaction of **5a** and phenyllithium (1.5 equiv.) was carried out in THF at −78 °C for 30 min to give the desired adduct **6a** in 76% as a mixture of diastereomers. The ratio of the diastereomers was estimated to be 96.5:3.5 [93% diastereomeric excess (de)] by 270 MHz ^{1}H NMR. The de was improved to 95% when the reaction was carried out at −100 °C (83%). When the reaction was carried out using **5b**–**5d**, the de's were 33, 5, and 65%, respectively. Thus, the effectiveness of (*S*,*S*)-1,2-bis(1-hydroxypropyl)benzene **1a** was realized. The results are summarized in Table 1.

As the high selectivity was achieved by the conjugate addition of phenyllithium to **5a**, conjugate addition of various aryllithiums, generated in situ from the corresponding arylbromides and butyllithium, was conducted in THF at −100 °C. The products were obtained in good yields with high de's in every case as shown in Table 2.

Although the biological activity of 4-aryl-1,2,3,4-tetrahydroisoquinoline depends on the stereochemistry at the C-4

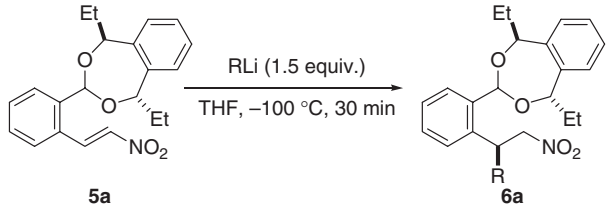
Table 1. 1,4-Addition of phenyllithium to β-nitrostyrenes having chiral acetal with C_2 axis of symmetry



5	C_2-Symmetrical diol		Yield/%	de/%
a		**1a**	83[a]	95[b] (*S*)
b		**1b**	78	33[c] (*R*)
c		**1c**	45	5[c] (*S*)
d		**1d**	81	65[b] (*R*)

[a]Reaction was carried out using 1.5 equiv. of PhLi for 30 min. [b]Determined by ^{1}H NMR. [c]Determined after conversion to **8**.

Table 2. 1,4-Addition of various aryllithiums to β-nitrostyrene **5a**



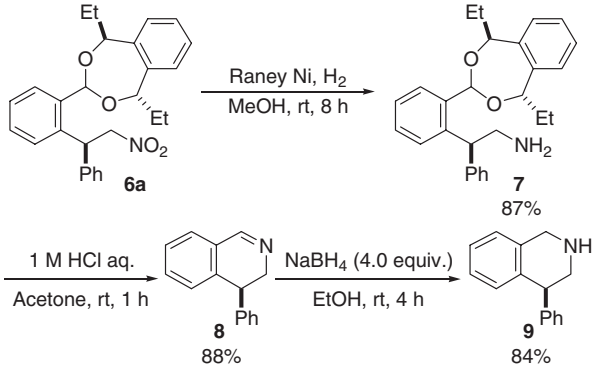
5a **6a**

Entry	R	Yield/%	de[a]/%
1	Ph	83	95
2	*o*-MeC_6H_4	67	92
3	*m*-MeC_6H_4	75	96
4	*p*-MeC_6H_4	79	96
5	*p*-ClC_6H_4	91	98
6	*p*-$MeSC_6H_4$	82	96
7	*p*-$MeOC_6H_4$	85	93
8	3,4-MethylenedioxyC_6H_3	90	95
9	1-Naphthyl	84	96

[a]Determined by ^{1}H NMR.

position of the isoquinoline ring,[7a,7c] only a limited number of methods have been reported so far on the enantioselective synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinoline.[8] Thus, we examined a transformation of the adduct **6a** to chiral 4-phenyl-1,2,3,4-tetrahydroisoquinoline **9**. At first, the nitro group in **6a** was reduced to amino group in 87% by hydrogenation in the presence of Raney Ni (MeOH, rt, 8 h). Then, the acetal moiety of the resulting amine **7** was hydrolyzed (1 M aqueous HCl–acetone, rt, 1 h) to aldehyde and 4-phenyl-3,4-dihydroisoquinoline **8** was obtained in 88% by the spontaneous intramolecular cyclization. The enantiomeric excess (ee) of the resulting **8** was 94% by HPLC analysis which indicated that the stereochemistry at C-4 was maintained during the transformations. The chiral auxiliary, (*S*,*S*)-1,2-bis(1-hydroxypropyl)benzene **1a**, was recovered quantitatively by usual work up without the loss of ee. Then, **8** was reduced to (*S*)-(−)-4-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (84%, $[\alpha]_D^{26}$ −11.8 (*c* 1.01, MeOH)), (lit.;[7c] $[\alpha]_D^{20}$ −11.1 (*c* 0.85, MeOH)) by $NaBH_4$ (EtOH, rt, 4 h) (Scheme 2).

We assume the stereochemical course of the reaction of **5a** and aryllithium as follows; in the most stable conformation of **5a** obtained by conformational search carried out by the MM3 force field with stochastic search algorithm,[9] *re* face of the nitrostyrene moiety is blocked by one of the ethyl substituents in the



Scheme 2. Asymmetric synthesis of 4-phenyl-1,2,3,4-tetrahydroisoquinoline **9**.

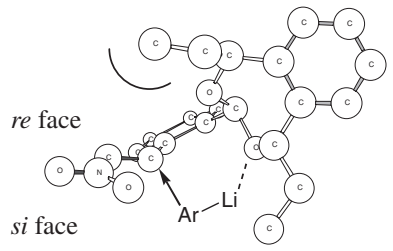


Figure 1. The most stable conformation of **5a**. The hydrogen atoms are omitted for clarity.

acetal moiety. Aryllithium approaches **5a** from *si* face with the aid of the coordination by one of oxgen atoms of the acetal and adds to the double bond to afford **6a** with high stereoselectivity (Figure 1).

It should be noted that the conjugate addition of aryllithium to β-nitrostyrene derivative having the chiral acetal moiety, derived from (*S*,*S*)-1,2-bis(1-hydroxypropyl)benzene **1a**, proceeded with high diastereoselectivity, and 4-aryl-1,2,3,4-tetrahydroisoquinoline was obtained conveniently in high ee. Other applications of (*S*,*S*)-1,2-bis(1-hydroxypropyl)benzene **1a** in asymmetric reaction is now in progress.

Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 80th birthday.

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