Enantioselective Synthesis of α-Benzylalanine Using *trans*-3,4-Dihydro-3,4-diaryldibenzo[*c*,*g*]phenanthrene-3,4-diols

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Abstract: Asymmetric benzylation of a benzophenone Schiff's base of alanine ethyl ester was successfully conducted using *trans*-3,4-dihydro-3,4-diaryldibenzo[*c*,*g*]phenanthrene-3,4-diol as a chiral source.

Key words: amino acids, asymmetric synthesis, biaryls, diols, phase-transfer catalysis

α,α-Disubstituted amino acids have attracted considerable attention because of their potential as enzyme inhibitors, pharmaceuticals, and tools of biochemical research.[1] Various stereocontrolled syntheses of optically active α,α-disubstituted amino acids have been reported.[2] Among them, enantioselective alkylation of enolates of amino acid using phase-transfer catalysts has been an area of focus in recent years. In 1989, O'Donnell reported the first enantioselective synthesis of α-amino acid derivatives using phase-transfer catalyst[3] and the same group reported the synthesis of α,α-disubstituted α-amino acids in 1992[4] using cinchona-derived quaternary ammonium catalysts and the Schiff's base of alanine. In addition to cinchona-derived ammonium catalysts,[5] several artificial quaternary ammonium catalysts have been developed recently for the synthesis of α,α-disubstituted amino acids.[6]

Chiral alkoxides derived from chiral diol or amino alcohol have also been found to catalyze C-alkylation of Schiff's bases of alanine under phase-transfer conditions. For the chiral diol/amino alcohol, enantiomerically pure TADDOL, NOBIN,[7] and BINOLAM[8] are used (Figure 1).

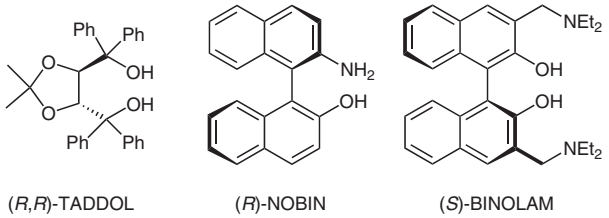
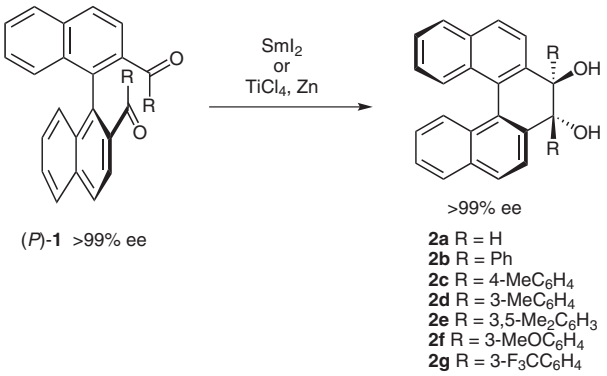


Figure 1

We previously reported the synthesis of new optically active C_2-symmetric *trans*-diols by intramolecular pinacol cyclization of 2,2′-biaryldicarbonyl compounds.[9] In this reaction, where the starting biphenyl is configurationally stable, the axial chirality of the dicarbonyl compounds is stereospecifically transmitted onto two stereogenic centers of the product. By this method, various enantiomerically pure 3,4-dihydrodibenzo[*c*,*g*]phenanthrene-3,4-diols **2** were synthesized (Equation 1).



Equation 1

The X-ray crystal structure of **2** shows the two substituents R placed at axial positions suggesting that the complex of **2** with an appropriate metal constitutes an effective asymmetric environment. That is, imagine the complex of *trans*-diol **2**, metal M, and substrate A–B where A is the reaction point and both A and B coordinate to metal M as shown in Figure 2. Reactant Y approaches from the top face of the complex because the bottom face is shielded by substituent R.[10]

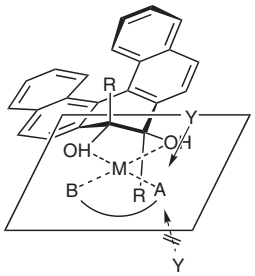


Figure 2

Based on the hypothesis, we examined the several reactions and found that the *trans*-diol **2** could be used as a chiral source in the enantioselective C-alkylation reaction of the Schiff's base of alanine ester for the synthesis of

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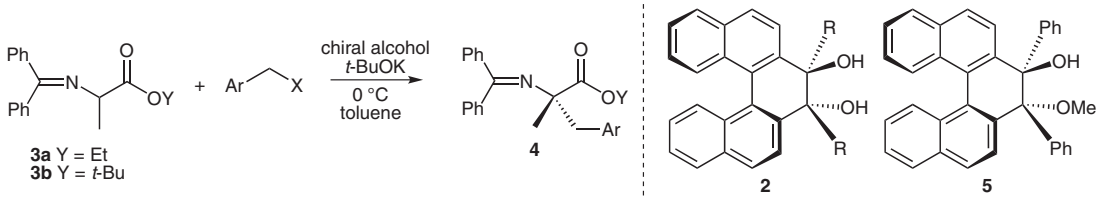
α-benzyl-α-methyl α-amino acids. In this communication, we describe the outcome of the investigation.

We began examining the alkylation of Schiff's base **3**[11] with benzyl halide in toluene in the presence of a chiral diol and potassium *tert*-butoxide as a base (Table 1).[12] Entries 1–16 list the results using benzyl bromide. First, we examined benzylation of Schiff's base of alanine ethyl ester **3a**. When simple diol **2a** was used as a chiral source, the starting Schiff's base **3a** was consumed within 15 minutes and the desired alkylated product **4a** was obtained in 81% yield with an enantiomeric excess of 3% (entry 1). When diol **2b**, with phenyl groups as substituents R, was used as a chiral source, **4a** was obtained with an ee of 31% (entry 2). The reaction of **4a** became slower and the enan-

Table 1 Enantioselective Benzylation of Schiff's Base **3** Using Benzyl Halides[a]



Entry	3	Ar	X	Chiral alcohol	R	Time	4	Yield (%)[b]	ee (%)[c,d]
1	**3a**	Ph	Br	**2a**	H	15 min	**4a**	81	3
2	**3a**	Ph	Br	**2b**	Ph	5 min	**4a**	75	31
3[e]	**3a**	Ph	Br	**2b**	Ph	1.5 h	**4a**	60	0
4	**3b**	Ph	Br	**2b**	Ph	40 min	**4a**	94	4
5	**3a**	Ph	Br	**2b**	Ph	1 h[f]	**4a**	66	58
6	**3a**	Ph	Br	**2b**	Ph	2 h[f]	**4a**	58	65
7	**3a**	Ph	Br	**2b**	Ph	3 h[f]	**4a**	62	67
8	**3a**	Ph	Br	**2b**	Ph	4.5 h[f]	**4a**	50	65
9	**3a**	Ph	Br	**2b**	Ph	6 h[f]	**4a**	59	65
10	**3a**	Ph	Br	**2c**	4-MeC_6H_4	1 h[f]	**4a**	71	26
11	**3a**	Ph	Br	**2d**	3-MeC_6H_4	1 h[f]	**4a**	65	70
12	**3a**	Ph	Br	**2d**	3-MeC_6H_4	3 h[f]	**4a**	61	74
13	**3a**	Ph	Br	**2e**	3,5-$Me_2C_6H_3$	1 h[f]	**4a**	68	60
14	**3a**	Ph	Br	**2f**	3-$MeOC_6H_4$	3 h[f]	**4a**	70	15
15	**3a**	Ph	Br	**2g**	3-$F_3CC_6H_4$	1 h[f]	**4a**	70	37
16	**3a**	Ph	Br	**5**	–	1 h[f]	**4a**	39	0
17	**3a**	Ph	Cl	**2d**	3-MeC_6H_4	3 h[f]	**4a**	65	87
18	**3a**	Ph	Cl	**2b**	Ph	3 h[f]	**4a**	64	84
19	**3a**	2-MeC_6H_4	Cl	**2d**	3-MeC_6H_4	3 h[f]	**4b**	55	69[g]
20	**3a**	3-MeC_6H_4	Cl	**2d**	3-MeC_6H_4	3 h[f]	**4c**	63	90[g]
21	**3a**	4-MeC_6H_4	Cl	**2d**	3-MeC_6H_4	3 h[f]	**4d**	65	90[g]

[a] Reaction was conducted with **3**, $ArCH_2X$ (1.5 equiv), and *t*-BuOK (3 mol) in the presence of chiral alcohol **2** or **5** (10 mol%) in toluene (0.15 M). The reaction mixture was a suspension because *t*-BuOK was insoluble in toluene.
[b] Isolated yield.
[c] The enantiomeric excess (ee) of **4** was determined by HPLC analysis using a chiral column (DAICEL CHIRALCEL AD-H, hexane–*i*-PrOH = 99:1).
[d] The absolute configurations of all optically active products **4a** were *S*. For information on how the absolute configuration was determined, see ref. 13.
[e] *t*-BuONa was used instead of *t*-BuOK.
[f] $ArCH_2X$ was added slowly for the given time, after which the reaction was quenched.
[g] Absolute stereochemistry was undetermined.

tioselectivity was not observed when sodium *tert*-butoxide was used instead of potassium *tert*-butoxide (entry 3). Reaction of *tert*-butyl ester **3b** was slower compared to ethyl ester **3a** and gave **4a** in high yield but low ee (entry 4).

Next benzyl bromide was added slowly in order to react with the enolate of the Schiff's base **3a** which was constructed in the asymmetric environment adequately, since the reaction using potassium *tert*-butoxide, diol **2b** and Schiff's base **3a** proceeded very rapidly (within 5 min, entry 2). For an addition time of one hour, product **4a** was obtained with an ee of 58% (entry 5). For a longer addition time of three hours, **4a** was obtained with an ee of 67% (entry 7). Further prolongation of the addition time did not improve the ee (entries 8 and 9).

In a preliminary study of the effect of substituent R in diol **2** in giving product **4a**, we found bulkier phenyl groups to be more effective than hydrogen in increasing the value of ee (entry 1 vs. entry 2). Therefore, we examined diol **2** with various substituted phenyl groups as substituents R for alkylation of **3a** with benzyl bromide under slow addition conditions. Diol **2c** with *para*-tolyl groups gave **4a** with a low ee (entry 10). Diol **2d** with *meta*-tolyl groups gave **4a** with ee = 74% (entry 12). Diol **2e** with *meta*-dimethylphenyl groups was unremarkable (entry 13) and diols **2f** and **2g** with *meta*-methoxyphenyl and *meta*-trifluorophenyl groups, respectively, were ineffective (entries 14 and 15) in increasing the ee. For mono-ol **5**, prepared from diol **2b** (Ag_2O, MeI, DMF, 82%), enantioselectivity was not observed, suggesting that the diol part in **2** is important for the induction of enantioselectivity.

Next, we changed the alkylating reagent from benzyl bromide to benzyl chloride. Diol **2d** gave **4a** with an ee of 87% (entry 17). Diol **2b** with phenyl groups gave **4a** with an ee of 84% (entry 18). Various tolymethyl chlorides were also used in this reaction (entries 19–21); *meta*- and *para*-methylbenzyl chloride gave α,α-disubstituted amino acids **4** with an ee of 90% (entries 20 and 21).

For all entries that gave optically active **4a**, the absolute configurations was *S*.[13]

The observed good enantioselectivity may be attributable to selective formation of the rigid enolate fixed by square planer K^+ as shown in Figure 3.[14] The *Re*-face of the enolate of **3a** is shielded by the aryl group in *trans*-diol **2**. Therefore electrophilic attack of benzyl halide occurs on the *Si*-face of the enolate to give (*S*)-**4a**. The lack of enantioselectivity with mono-ol **5** can be attributed to the difficulty of forming a rigid enolate in an asymmetric environment.

In conclusion, we have used *trans*-3,4-dihydro-3,4-diaryldibenzo[*c*,*g*]phenanthrene-3,4-diol as the chiral source for enantioselective benzylation of a Schiff's base of alanine. In this reaction, use of benzyl chloride and its slow addition were essential for high enantioselectivity of the product.

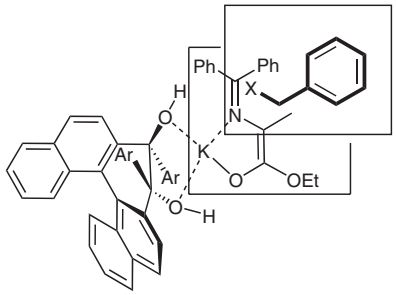


Figure 3

Acknowledgment

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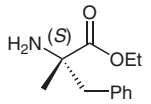

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Figure 4

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