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First Application of Optically Active *trans*-1,2-Bis(2- aminophenyl) cyclopentane for Asymmetric Reaction: Enantioselective *N*-Acetylation of Secondary Alkyl Amines

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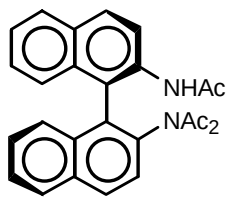
Abstract: First application of optically active *trans*-1,2-Bis(2-aminophenyl)cyclopentane **2** for asymmetric reaction, enantioselective *N*-acetylation of secondary alkyl amines, is described. This acetylation with tetraacetylated **3** which was prepared from **2**, gave the *N*-acetylamines with up to 21% ee.

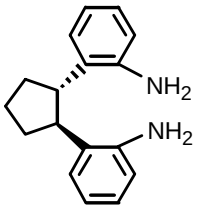
Keywords: Chiral, enantioselective *N*-acetylation.

Optically active amines are essential constituents or building blocks for the synthesis of many medicines. Efficient resolution of racemic amines through enzymatic or nonenzymatic methods plays an important role in the production of chiral amines[1]. The kinetic resolution of amines through nonenzymatic acetylation catalysts has been the focus of our interest. For this purpose, we have developed the first enantioselective *N*-acetylation reagent **1** (**Figure 1**), which was derived from 1,1'-binaphthyl-2,2'-diamine, to resolve various amines[2]. This reagent has been proved to provide a moderate level of activity and selectivity which led us to develop other new reagents with higher enantioselectivity.

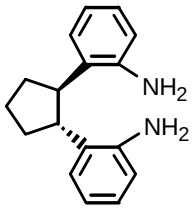
Figure 1



1



(*S,S*)-(-)-**2**



(*R,R*)-(+)-**2**

Scheme 1

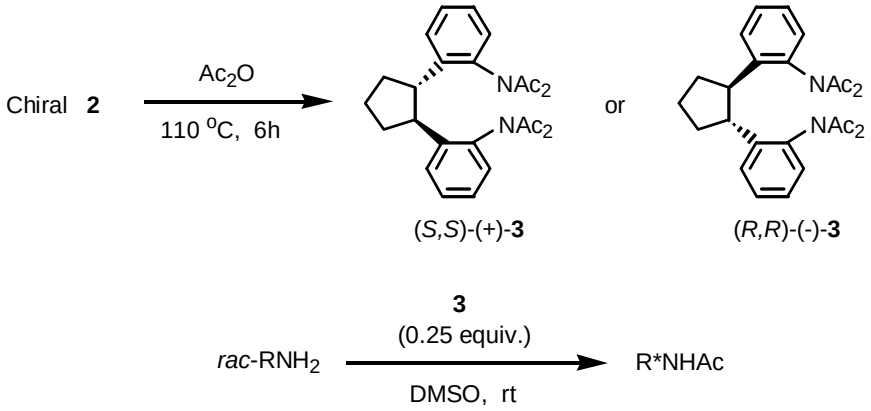
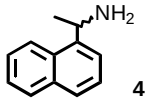
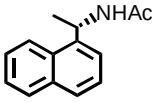
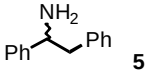
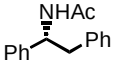
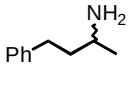
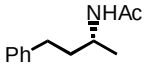
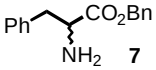
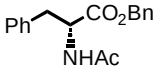
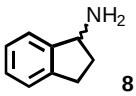
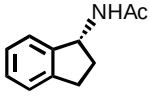


Table 1 Enantioselective *N*-acetylation of Various Amines with **3** (0.25 eq.) at room temperature in DMSO [a]

Entry[b]	Starting Amines	Time (h)	Products	Chemical[c] yields (%)	E.e. (%) [d]
1	 **4**	24		15	21
2	 **5**	36		20	15
3	 **6**	12		21	7
4	 **7**	48[e]		15	14
5	 **8**	6		25	8

[a] The reaction was run until **3** disappeared. [b] (*S,S*)-(+)-**3** was used for entries 2, 3, 4, 5 while (*R,R*)-(–)-**3** was used for entry 1. [c] Isolated yields. [d] The ee values of *N*-acetylamines were determined by HPLC analysis using chiral phase columns (For **4, 5**: Chiralcel OD; For **6, 7, 8**: Chiralcel OJ). The absolute configurations of *N*-acetylamines were determined by comparison with the commercially available acetylated amines of known configurations. [e] rt, 24 h; then 45 °C, 24 h.

Quite recently, we reported[3] the synthesis and resolution of a novel chiral BINOL-like C_2-symmetric bisaniline **2**. It contains two aromatic rings, which attach to the cyclopentane ring as a *trans* arrangement acting as a chiral shielding wall that can restrict the conformational flexibility of the molecule. This novel structural framework is expected to enhance the chiral induction that makes its further application worthwhile. In this paper, we would like to report the first application of optically active bisaniline **2** for asymmetric reaction, enantioselective *N*-acetylation of secondary alkyl amines[4].

Chiral bisaniline **2** were readily tetraacetylated to afford the corresponding chiral **3** by treatment with Ac_2O under 110°C for 6h in the yield of 62-75%[5]. Then, chiral **3** was used as an enantioselective *N*-acetylation reagent to react with a variety of racemic secondary alkyl amines (**Scheme 1**). At first, we used the optimal reaction conditions for the enantioselective *N*-acetylation of **1**[2], thus, the reaction was carried out in DMSO under room temperature with the use of 0.25 equivalent of chiral **3**. The chemical yields and enantiomeric excesses of the resultant *N*-acetylated amines are listed in **Table 1**. The ee values were up to 21%, which values greatly changed depending on the structures of the starting amines[6].

In summary, we have shown the first application of optically active bisaniline **2** for asymmetric reaction, enantioselective *N*-acetylation of secondary alkyl amines. Despite the disappointing results in terms of reactivity and selectivity of the reagent **3**, the optimal reaction conditions of *N*-acetylation are currently being explored in our lab and experimental results will be reported in due course.

Acknowledgments

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References and Notes

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2. K. Kondo, T. Kurosaki, Y. Murakami *Synlett* **1998**, 725.
3. J. S. Yang, K. Kondo, Y. Murakami *Coll. Czech. Chem. Comm.* **2000**, *65*, 549.
4. Quite recently, Fu has reported an effective planar-chiral reagent for enantioselective *N*-acetylation: Y. Ie, G. C. Fu *Chem. Commun.* **2000**, 119.
5. Spectral data for (*R,R*)-(–)-**3**: mp 110-112 °C (colorless prisms, Et_2O / *n*-hexane). $[\alpha]_D^{22}$: –103.4 (*c* 0.75, $CHCl_3$). IR (Nujol): 1705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.64 (6H, s), 1.67-1.80 (2H, m), 1.89-1.97 (2H, m), 2.19-2.29 (2H, m), 2.36 (6H, s), 3.12-3.20 (2H, m), 6.90 (2H, d, *J* = 7.8 Hz), 7.21 (2H, td, *J* = 2.0, 7.1 Hz), 7.37-7.44 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3, 26.4, 27.0, 36.8, 48.4, 127.2, 127.4, 128.8, 129.4, 137.6, 142.4, 172.7, 172.8. EI-MS *m/z*: 420 (M^+), 378, 336, 293, 43. Anal. Calcd for

$C_{25}H_{28}N_2O_4$: C 71.41%; H 6.71%; N 6.66%. Found: C 71.29%; H 6.48%; N 6.61%. Data for (*S*,*S*)-(+)-**3**: mp 111-113 °C (colorless prisms, Et_2O / *n*-hexane). $[\alpha]_D^{23}$: 102.7 (*c* 0.78, $CHCl_3$). Anal. Calcd for $C_{25}H_{28}N_2O_4$: C 71.41%; H 6.71%; N 6.66%. Found: C 71.41%; H 6.73%; N 6.81%.

6. The recovery yields and ee values of the unreacted starting amines were as follows: **4** (69%, 3% ee); **5** (71%, 4% ee); **6** (72%, 3% ee); **7** (68%, 7% ee); **8** (64%, 1% ee).

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