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Axially Chiral Binaphthyl Surrogates with an Inner N−H−N Hydrogen Bond

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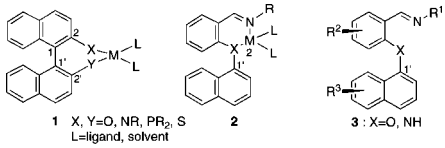
Chiral binaphthyls have been extensively used in asymmetric synthesis. In particular, metal complexes of 2,2′-disubstituted-1,1′-binaphthyls (**1**) have been shown to be extremely effective catalysts for a variety of asymmetric transformations.[1−3] While the catalytically active metal center (M) in **1** is located far from the chiral axis (C(1)−C(1′)) by three bonds, it is quite effective for asymmetric induction in many cases. The ultimate structure to minimize the distance between the catalytically active metal center and the chiral axis is shown as **2**, where the central metal is directly connected to the chiral C(1′)−X axis. Rational precursors for **2** are shown as **3**. A crucial question about **3** is whether enantiomers of **3** with axial chirality can exist without rapid racemization at ambient temperature. We describe here the design and synthesis of axially chiral binaphthyl surrogates such as **3** (X = NH) with half-lives of racemization of up to 2 years at ambient temperature.



We chose compounds **4** and **5** as candidates for **3**, and molecular modeling was performed by DFT calculations (Figure 1). The calculated most stable structure of biaryl ether **4** is shown as **A**.[4] While an s-*cis* conformer around the C(4)−C(10) bond is suitable for **3**, the most stable structure (**A**) of **4** adopts an s-*trans* conformation. Accordingly, biaryl ether **4** does not seem to be feasible as a candidate for **3**. On the other hand, the calculated most stable structure (**B**) of biaryl amine **5** adopts an s-*cis* conformation around the C(4)−C(10) bond and consists of a pseudobinaphthyl skeleton with an inner N−H−N H-bond (Figure 1, **B**). A six-membered ring consisting of N(1)−C(9)−C(10)−C(4)−N(3)−H is coplanar with the adjacent phenyl ring. The dihedral angle between the pseudo-naphthalene ring with an inner N−H−N H-bond, and the naphthalene ring was 148° (**B**, side view), which indicates that **5** is feasible as an axially chiral binaphthyl surrogate.

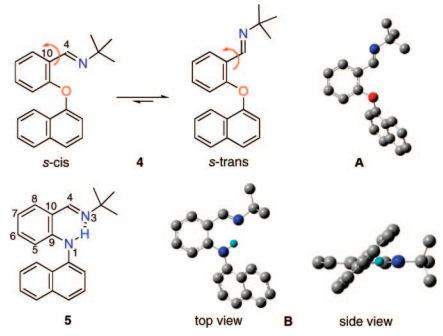
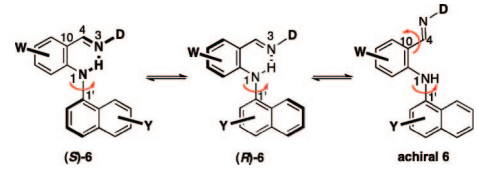


Figure 1. B3LYP/6-31G(d,p) optimized geometries of **4** and **5**.

According to the results of molecular modeling, we chose biaryl amines as candidates for **3**, and focused on the creation of axially chiral biaryl amines such as **5** with long half-life of racemization at ambient temperature.[5,6]

We planned the synthesis of binaphthyl surrogates **6** with an inner N−H−N H-bond. One of the critical preconditions for **6** to maintain stable axial chirality is the formation of an extremely strong H-bond, since the non-H-bonded form of **6** must adopt an s-*trans* conformation around the C(4)−C(10) bond, and it should be achiral due to rapid bond rotation around the C(1′)−N(1) axis. To generate a stronger H-bond, donor substituents **D** on N(3) and electron-withdrawing substituents **W** on the upper pseudonaphthalene ring are assumed to be preferable. Sterically demanding substituents **Y** on the lower naphthalene ring are expected to be effective in increasing the rotational barrier around the C(1′)−N(1) axis. According to this hypothesis, several compounds, **7**−**14**, were prepared via Buchwald cross coupling reactions[7] between substituted 1-aminonaphthalenes and substituted phenyl bromides (see Supporting Information).



The ^{1}H NMR spectrum of **7** at 20 °C showed two diastereotopic isopropyl methyl peaks, indicating restricted bond rotation along the C(1′)−N(1) axis. The rotational barrier of the N(1)−C(1′) bond was determined to be 19.3 kcal/mol (92 °C) by variable-temperature NMR measurements in d_8-toluene (400 MHz NMR, $\Delta\nu_{AB}$ = 9.9 Hz, T_{coales} = 365 K, Table 1, entry 1).[8] The half-life of racemization of **7** at 20 °C was roughly estimated to be 10 s based on the assumption that $\Delta S^{\ddagger}$ of the restricted bond rotation is nearly zero.[9] Enantiomers of **8** with electron-withdrawing substituents (NO_2) could be separated at ambient temperature by HPLC with a chiral stationary phase. Time-dependent racemization of the separated enantiomer was monitored by HPLC analysis at 22 °C and found to proceed with a half-life of 2.3 h. Based on the rate of racemization, the rotational barrier of the N(1)−C(1′) bond of **8** was determined to be 23.2 kcal/mol (entry 2). Similarly, enantiomers of **9**−**14** were separated by HPLC with chiral stationary phases. Their rotational barriers and half-lives of racemization were determined and shown in entries 3−8 in Table 1. **11**−**14** with 6,8-dinitro and 2′,8′-dimethyl groups have rotational barriers larger than 27 kcal/mol, which corresponds to the longer half-lives of racemization of 3 months at 20 °C (entries 5−8). The ^{1}H NMR chemical shifts of N−H of **11**−**14** are in the range δ 13.01−13.33 ppm, which indicates the extremely strong H-bonding. This observation is consistent with the hypothesis that extremely strong H-bonding is critical for stable axial chirality. Substituent effects at N(3) were

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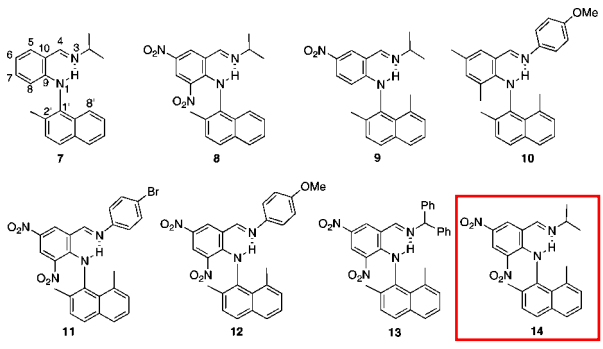
investigated with **11**−**14** (entries 5−8). Among these compounds, the half-life of racemization increased with an increase in the donating ability of the substituents. The contribution of the electron-withdrawing group (NO_2) to the stability of axial chirality is obvious when the half-life of racemization of **12** with 6,8-dinitro substituents (4.3 months) is compared with that of **10** with 6,8-dimethyl substituents (2.4 days) (entry 4 vs 6).[10] The effect of sterically demanding substituents on the naphthalene ring is also obvious when the half-life of racemization of **8** (2.3 h) is compared with that of **14** (24 months), which has an additional 8′-methyl substituent (entry 2 vs 8). Among these compounds, **14** with an electron-donating isopropyl group at N(3), electron-withdrawing nitro groups at C(6) and C(8), and sterically demanding methyl groups at C(2′) and C(8′) has the largest rotational barrier (28.2 kcal/mol) and the longest half-life of racemization (24 months at 20 °C) (entry 8). A single crystal of **13** was subjected to X-ray analysis, and the structure is shown in Figure 2. A ring consisting of nine atoms of N(1)−C(9)−C(8)−C(7)−C(6)−C(5)−C(10)−C(4)−N(3) is almost completely planar (Figure 2a and b), which suggests the formation of a pseudonaphthalene ring involving the N−H−N H-bond. The dihedral angle between the pseudonaphthalene ring and the naphthalene ring is 128° (Figure 2b). The CD spectra of **13** shown in Figure 2c clearly indicates the enantiomeric relationship. All of the experimental evidence indicates the formation of axially chiral binaphthyl surrogates with an inner N−H−N H-bond. These compounds have surprisingly stable axial chirality along the C(1′)−N(1) axis due to strong H-bonding as well as steric effects caused by nearby substituents.

Table 1. Behavior towards Racemization of Chiral Binaphthyl Surrogates with an Inner N−H−N H-Bond

entry	compd	$\Delta G^{\ddagger}$ (kcal/mol)[a]	$t_{1/2}$ racemization (20 °C)[b]	δ_{NH}(ppm)[c]
1	**7**	19.3(92°C)[d]	10 s	11.07
2	**8**	23.2(22°C)[e]	2.3 h[g]	13.47
3	**9**	23.6(22°C)[e]	5.0 h[g]	12.02
4	**10**	24.9(22°C)[e]	2.4 days[g]	11.44
5	**11**	27.0(80 °C)[f]	3.0 months	13.01
6	**12**	27.2(80 °C)[f]	4.3 months	13.33
7	**13**	27.4(80 °C)[f]	6.0 months	13.24
8	**14**	28.2(80 °C)[f]	24 months	13.30

[a] Rotational barrier of the chiral axis. [b] Half-life of racemization at 20 °C roughly estimated on the assumption that $\Delta S^{\ddagger}$ of the restricted C−N bond rotation is nearly zero unless otherwise indicated. [c] ^{1}H NMR (400 MHz) chemical shift (ppm) of N−H measured in $CDCl_3$ at 21 °C. [d] Determined by VNMR. [e] Determined by time-dependent racemization of an isolated enantiomer at 22 °C by HPLC analysis. [f] Determined by time-dependent racemization of an isolated enantiomer at 80 °C (benzene reflux) by HPLC analysis. [g] Half-life or racemization at 22 °C determined by time-dependent racemization of an isolated enantiomer by HPLC analysis.



In conclusion, we have developed novel chiral binaphthyl surrogates with an inner N−H−N H-bond that possess stable axial chirality at ambient temperature. Since the proton in the N−H−N H-bond is located in a highly asymmeyric microenvironment, these binaphthyl surrogates are expected to be a new class of chiral proton sources. The metal complexes of the chiral binaphthyl surrogates may contribute to the development of a new generation of asymmetric organometallic catalysts. Investigations are currently underway in our laboratory.

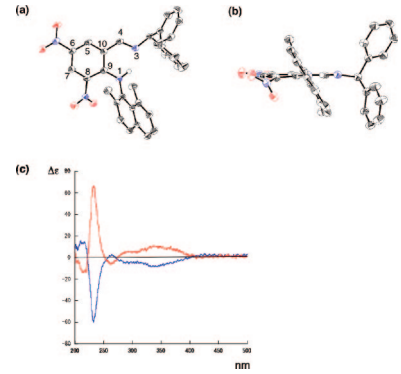


Figure 2. Properties of binaphthyl surrogate **13**. (a) Top view and (b) side view of X-ray structure of **13**. Hydrogens except N−H were omitted for clarity. (c) CD spectra of the separated enantiomers of **13**.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge at http://pubs.acs.org.This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Mei, L.; Xuan, L. X. *Asian J. Chem.* **2006**, *18*, 2089–2106.
(2) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857–897.
(3) Kocovsky, P.; Vyskocil, S.; Smrcina, M. *Chem. Rev.* **2003**, *103*, 3213–3245.
(4) Conformationally stable atropisomers of biaryl ethers have been reported, see: (a) Fuji, K.; Oka, T.; Kawabata, T.; Kinoshita, T *Tetrahedron Lett.* **1998**, *39*, 1373–1376. (b) Betson, M. S.; Clayden, J.; Worrall, C. P.; Peace, S *Angew. Chem., Int. Ed.* **2006**, *45*, 5803–5807. (c) Clayden, J.; Worrall, C. P.; Moran, W. J.; Helliwell, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3234–3237.
(5) For an example of conformational studies of alkyl aryl amines, see : Casarini, D.; Lunazzi, L.; Placucci, G. *J. Org. Chem.* **1987**, *52*, 4721–4726.
(6) For asymmetric synthesis of atropisomeric aromatic amine derivatives, see: (a) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131–3132. (b) Hughes, A. D.; Simpkins, N. S. *Synlett* **1998**, 967–968. (c) Ates, A.; Curran, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 5130–5131. (d) Clayden, J.; Mitjans, D.; Youssef, L. H. *J. Am. Chem. Soc.* **2002**, *124*, 5266–5267. (e) Kitagawa, O.; Yoshikawa, M.; Tanabe, H; Morita, T.; Takahashi, M; Dobashi, Y; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923–12931. (f) Brandes, S.; Bella, M.; Kjarsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1147–1151. (g) Leusse, S. B.; Counceller, C. M.; Wilt, J. C.; Perkins, B. R.; Johnston, J. N. *Org. Lett.* **2008**, *10*, 2445–2447.
(7) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.
(8) Racemization barriers of **7** were solvent-dependent: $\Delta G^{\ddagger}$ = 19.3 (in d_8-toluene), 18.9 (in $(CDCl_2)_2$), 18.0 (in CD_3CN), 17.9 (in d_6-ethanol), and 17.8 (in d_7-DMF) kcal/mol.
(9) $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for racemization of **13** in toluene are experimentally determined to be 24.5 kcal/mol and−8.3 eu, respectively, based on the racemization barriers at various temperatures.
(10) The larger rotational barrier of **12** compared to that of **10** does not seem to be due to steric effects because the steric bulkiness of a nitro group (*A*-value = ∼1.2) is estimated to be similar or even smaller than that of a methyl group (*A*-value = ∼1.7).

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