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Synthesis of Axially Chiral Amino Acid and Amino Alcohols via Additive−Ligand-Free Pd-Catalyzed Domino Coupling Reaction and Subsequent Transformations of the Product Amidoaza[5]helicene

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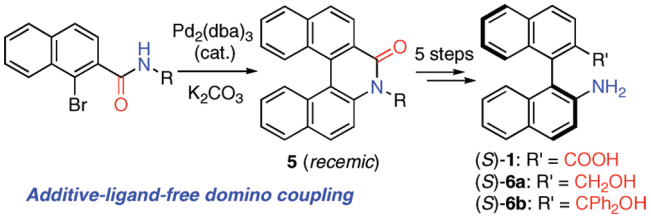

Novel optically active axially chiral amino acid and amino alcohols have been synthesized efficiently via lactam ring-opening, with the aid of an optically active alcohol, amidoaza[5]helicene **5**, which has been readily prepared by an additive-ligand-free Pd catalyzed domino coupling reaction in a single step. The stereostructures of these chiral molecules have also been clarified.

Axially chiral biaryls, such as BINOL and BINAP are well-known as reliable chiral inducers in asymmetric synthesis as well as key components of asymmetric molecular recognition in host−guest chemistry. The discovery of novel axially chiral biaryl groups and the development of efficient synthetic methods to prepare them are increasing in importance with the increasing prevalence of chirality in pharmaceuticals and organic materials.[1]

Unnatural amino acids are chiral molecules that have attracted attention as promising organocatalysts[2] and ligands[3] for asymmetric synthesis as well as chiral building blocks for peptidomimetics.[4] Although unnatural amino acids possessing central chirality have been well developed,[5] the synthesis and application of axially chiral amino acids have not yet been fully exploited.[6] C_2-Symmetric 2,2′-diamino analogue **2**[7] and 2,2′-dicarboxylic acid analogue **3**[8] have been widely employed as chiral inducers in a variety of asymmetric syntheses. However, the corresponding non-C_2-symmetric binaphthyl amino acid **1**, one of the simplest axially chiral amino acids possessing amino and carboxylic acid groups at the C-2 and C-2′ positions, has not been reported to date (Figure 1).

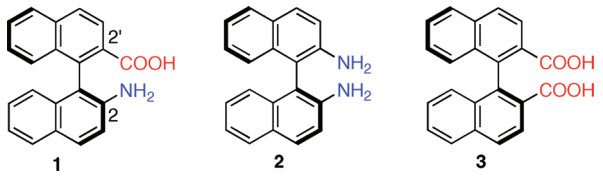

FIGURE 1. Axially chiral binaphthyls.

Non-C_2-symmetric axially chiral biaryl compounds have been most commonly prepared by using transition-metal catalyzed cross-coupling reactions between aryl halides or triflates and aryl metal species. Although cross-coupling

(1) For reviews on axially chiral biaryls, see: (a) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427. (b) Baudoin, O. *Eur. J. Org. Chem.* **2005**, 4223–4229.

(2) For reviews on amino acids as organocatalysts, see: (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–557. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591. (c) List, B. *Chem. Commun.* **2006**, 819–824.

(3) For a review on amino acids as ligands, see: Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450–1460.

(4) For reviews on amino acids as building blocks for peptidomimetics, see: (a) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366–1375. (b) Horne, W. S.; Gellman, S. H. *Acc. Chem. Res.* **2008**, *41*, 1399–1408.

(5) For reviews on central chiral unnatural amino acids, see: (a) Perdih, A.; Dolenc, S. *Curr. Org. Chem.* **2007**, *11*, 801–832. (b) de Graaf, A. J.; Kooijman, M.; Hennink, W. E.; Mastrobattista, E. *Bioconjugate Chem.* **2009**, *20*, 1281–1295.

(6) For examples of axially chiral amino acid, see: (a) Ridvan, L.; Abdallah, N.; Holakovsky, R.; Tichy, M.; Zvada, J. *Tetrahedron: Asymmetry* **1996**, *7*, 231–236. (b) Mazaleyrat, J.-P.; Gaucher, A.; Wakselman, M.; Tchertanov, L.; Guilhem, J. *Tetrahedron Lett.* **1996**, *37*, 2971–2974. (c) Tichy, M.; Holanová, J.; Závada, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3497–3504. (d) Ridvan, L.; Budesinsky, M.; Tichy, M.; Malon, P.; Závada, J.; Podlaha, J.; Císarová, I. *Tetrahedron* **1999**, *55*, 12331–12348. (e) Formaggio, F.; Crisma, M.; Toniolo, C.; Tchertanov, L.; Guilhem, J.; Mazaleyrat, J.-P.; Gaucher, A.; Wakselman, M. *Tetrahedron* **2000**, *56*, 8721–8734. (f) Formaggio, F.; Peggion, C.; Crisma, M.; Toniolo, C.; Tchertanov, L.; Guilhem, J.; Mazaleyrat, J.-P.; Goubard, Y.; Gaucher, A.; Wakselman, M. *Helv. Chem. Acta* **2001**, *84*, 481–501. (g) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055–3057. (h) Kano, T.; Tokuda, O.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 7423–7426. (i) Kano, T.; Tokuda, O.; Takai, J.; Maruoka, K. *Chem. Asian. J.* **2006**, *1*−*2*, 210–215. (j) Wright, K.; Lohier, J.-F.; Wakselman, M.; Mazaleyrat, J.-P.; Formaggio, F.; Peggion, C.; Zotti, M. D.; Toniolo, C. *Tetrahedron* **2008**, *64*, 2307–2320. (k) Dutot, L.; Wright, K.; Gaucher, A.; Wakselman, M.; Mazaleyrat, J.-P.; Zotti, M. D.; Peggion, C.; Formaggio, F.; Toniolo, C. *J. Am. Chem. Soc.* **2008**, *130*, 5986–5992.

(7) For examples, see: (a) Huang, H.; Okuno, T.; Tsuda, K.; Yoshimura, M.; Kitamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 8716–8717. (b) Kano, T.; Tanaka, Y.; Maruoka, K. *Org. Lett.* **2006**, *8*, 2687–2689. (c) Sakakura, A.; Suzuki, K.; Nakano, K.; Ishihara, K. *Org. Lett.* **2006**, *8*, 2229–2232. (d) Sakakura, A.; Suzuki, K.; Ishihara, K. *Adv. Synth. Catal.* **2006**, *348*, 2457–2465. (e) Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* **2007**, *63*, 8658–8664. (f) Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *J. Org. Chem.* **2008**, *73*, 7387–7389. (g) Rabalakos, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 13524–13525. (h) Alamsetti, S. K.; Mannam, S.; Mutupandi, P.; Sekar, G. *Chem.—Eur. J.* **2009**, *15*, 1086–1090.

(8) For examples, see: (a) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054–10055. (b) Hashimoto, T.; Hirose, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 7556–7557.

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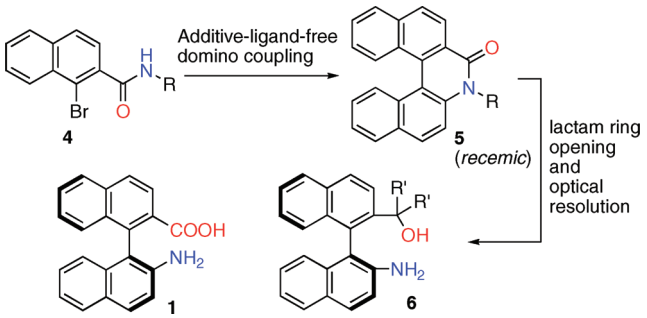
SCHEME 1. Synthetic Plan



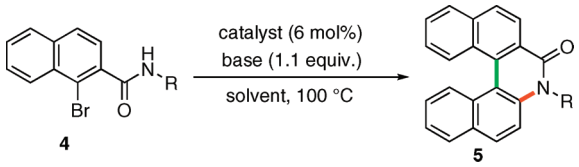
reactions represent a promising strategy for the synthesis of axially chiral compounds, they require the separate preparation of each coupling partner. This requirement sometimes complicates the preparation of non-C_2-symmetric biaryl groups compared with the preparation of C_2-symmetric compounds because the latter can be prepared by using a homocoupling reaction from a single starting material.

One drawback to the use of transition-metal-catalyzed coupling reactions is the requirement for expensive ligands under many reaction conditions. Therefore, ligand-free coupling reactions have recently been investigated for ecological and economic benefits.[9] Ligand-free conditions that facilitate the large scale synthesis of axially chiral biaryl compounds, however, have scarcely been investigated.[10]

We have previously developed the Pd-catalyzed domino homocoupling reaction of *o*-bromoarylamide derivatives to yield phenanthridinone derivatives in the presence of phosphine ligands.[11] During the course of our investigation of the domino coupling reactions, we found that the coupling reaction of *o*-bromonaphthamide derivative **4** proceeded smoothly under an additive−ligand-free conditions to afford coupling product **5** (Scheme 1). The homocoupling of a single starting material **4** afforded a non-C_2-symmetric binaphthyl compound possessing amide nitrogen and carbonyl substituents on the distinct naphthyl moieties of **5**. Because compound **5** contains an amide group within a fused pentacyclic-ring system, it represents a novel variant of a azahelicene derivative that could be named amidoaza[5]helicene.

We envisioned that the amidoaza[5]helicene **5** would be a valuable intermediate to form novel axially chiral amino acid **1**, amino alcohol **6**, and related chiral molecules via lactam ring-opening and optical resolution (Scheme 1). Herein, we report the syntheses of optically active amino acid **1** and amino alcohol **6**, which were accessed from compound **5**.

TABLE 1. Domino Coupling under Additive−Ligand-Free Conditions



entry	4	R[b]	cat.[c]	base	solvent	time (h)	5	yield (%)
1	**4a**	PMB	$Pd(OAc)_2$	Cs_2CO_3	dioxane	32	**5a**	78
2	**4a**	PMB	$Pd(OAc)_2$	Cs_2CO_3	toluene	24	**5a**	46
3	**4a**	PMB	$Pd(OAc)_2$	Cs_2CO_3	DMF	18	**5a**	60
4	**4a**	PMB	$Pd_2(dba)_3$	Cs_2CO_3	DMF	12	**5a**	78
5	**4a**	PMB	$Pd_2(dba)_3$	Na_2CO_3	DMF	12	**5a**	74
6	**4a**	PMB	$Pd_2(dba)_3$	K_2CO_3	DMF	12	**5a**	100
7[a]	**4a**	PMB	$Pd_2(dba)_3$	K_2CO_3	DMF	30	**5a**	96
8	**4b**	Bn	$Pd_2(dba)_3$	K_2CO_3	DMF	16	**5b**	98
9	**4c**	*n*-Bu	$Pd_2(dba)_3$	K_2CO_3	DMF	10	**5c**	91
10	**4d**	PMP	$Pd_2(dba)_3$	K_2CO_3	DMF	48	**5d**	51
11	**4e**	H	$Pd_2(dba)_3$	K_2CO_3	DMF	12	**5e**	38
12	**4f**	Boc	$Pd_2(dba)_3$	K_2CO_3	DMF	12	**5f**	

[a]The reaction was conducted with 0.5 mol % of $Pd_2(dba)_3$. [b]PMB = *p*-methoxybenzyl, PMP = *p*-methoxyphenyl. [c]dba = dibenzylideneacetone.

We initially investigated the additive-ligand-free domino coupling conditions of *o*-bromonaphthamide derivatives **4** to generate amidoaza[5]helicene **5** (Table 1). Upon treatment of *N*-PMB (*p*-methoxybenzyl)bromonaphthamide **4a** with $Pd(OAc)_2$ (6 mol %) in the presence of Cs_2CO_3, the domino coupling reaction proceeded smoothly to afford **5a** in good yield (Table 1, entry 1). This reaction included successive C−C (green colored) and C−N bond (red colored) formations concomitant with a deamidation event.[12] Further optimization of the reaction conditions, including changing the Pd reagents, base, and solvent, was performed. Use of toluene or DMF as the solvent was found to diminish the yield of **5a** (Table 1, entries 2 and 3). On the other hand, the yield was improved in the presence of $Pd_2(dba)_3$ and K_2CO_3 in DMF to afford **5a** in quantitative yield (Table 1, entry 6). Furthermore, the coupling reaction proceeded in the presence of 0.5 mol % of Pd catalyst to afford **5a** in high yield (Table 1, entry 7). These conditions were readily applicable to a scale-up synthesis that afforded **5a** in gram quantities (see the Experimental Section). The additive−ligand-free domino coupling reaction was applicable not only to *N*-alkyl-substituted derivatives (entries 8 and 9) but also to an *N*-aryl (PMP: *p*-methoxyphenyl)-substituted substrate (entry 10). Primary amide **4e**[13] was also applicable as a substrate for the reaction (entry 11). However, the coupling reaction of *N*-Boc-protected substrate **4f** under the optimized conditions did not occur (entry 12). To the best of our knowledge, this reaction represents the first example of an additive-ligand-free Pd-catalyzed domino coupling reaction to yield helicene-type molecules in a single step.

X-ray crystallographic analysis of PMP-protected derivative **5d** clearly showed the helically twisted structure of the

(9) For examples, see: (a) Dyker, G. *J. Org. Chem.* **1993**, *58*, 6426–6428. (b) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987–4990. (c) Dyker, G. *Angew. Chem., Int. Ed.* **2004**, *33*, 103–105. (d) Felpin, F.-X. *J. Org. Chem.* **2005**, *70*, 8575–8578. (e) Liu, L.; Zhang, Y.; Xin, B. *J. Org. Chem.* **2006**, *71*, 3994–3997. (f) Deng, C.-L.; Guo, S.-M.; Xie, Y.-X.; Li, J.-H. *Eur. J. Org. Chem.* **2007**, 1457–1462. (g) Maegawa, T.; Kitamura, Y.; Sako, S.; Udzu, T.; Sakurai, A.; Tanaka, A.; Kobayashi, Y.; Endo, K.; Bora, U.; Kurita, T.; Kozaki, A.; Monguchi, Y.; Sajiki, H. *Chem.—Eur. J.* **2007**, *13*, 5937–5943. (h) Kitamura, Y.; Sako, S.; Udzu, T.; Tsutsui, A.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Chem. Commun.* **2007**, 5069–5071. (i) Felpin, F.-X.; Lory, C.; Sow, H.; Acherar, S. *Tetrahedron* **2007**, *63*, 3010–3016. (j) Liu, C.; Shen, D.-M.; Chen, Q.-Y. *J. Org. Chem.* **2007**, *72*, 2732–2736. (k) Gauthier, D.; Beckendorf, S.; Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *J. Org. Chem.* **2009**, *74*, 3536–3539. (l) Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980–2983.

(10) Ullmann coupling reactions are a few examples of a ligand-free method to afford axially chiral biaryls, although an equivalent amount of Cu reagent was required. See: (a) Degnan, A. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1999**, *121*, 2762–2769. (b) Kelly, T. R.; Xie, R. L. *J. Org. Chem.* **1998**, *63*, 8045–8048. (c) Seki, M.; Yamada, S.; Kuroda, T.; Imashiro, R.; Shimizu, T. *Synthesis* **2000**, 1677–1680.

(11) Furuta, T.; Kitamura, Y.; Hashimoto, A.; Fujii, S.; Tanaka, K.; Kan, T. *Org. Lett.* **2007**, *9*, 183–186.

(12) For a possible reaction mechanism, see ref 11. Also see: Ferraccioli, R.; Carenzi, D.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2006**, *128*, 722–723.

(13) Müller, P.; Boléa, C. *Helv. Chem. Acta* **2001**, *84*, 1093–1111.

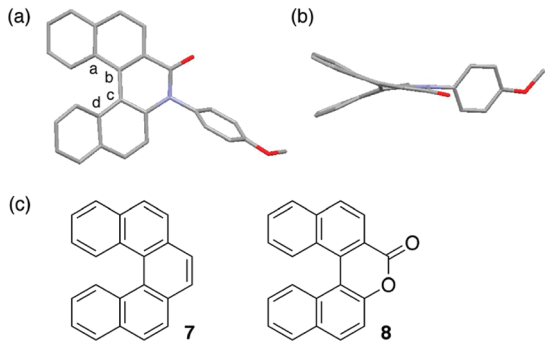
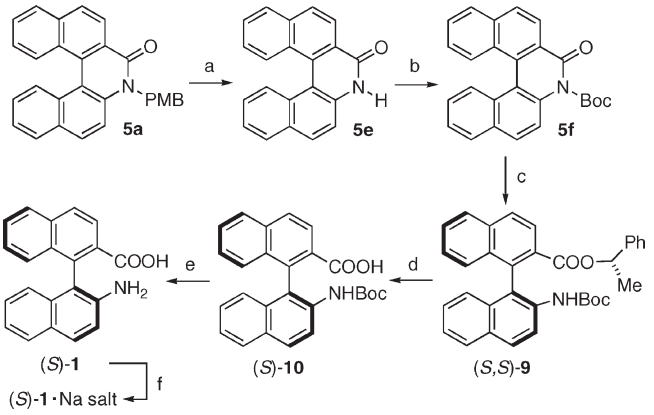


FIGURE 2. Stereostructure of **5d**: (a) side view; (b) top view. (c) [5]Helicene-related compounds.

pentacyclic-ring sysem, in which the dihedral angle of a,b−c, d was 31° (Figure 2a,b). HPLC analysis of **5a** on a chiral stationary phase exhibited two peaks corresponding to the enantiomers. The racemization barrier of **5a** was estimated to be 24.6 kcal/mol by following the decrease of optical purity of the isolated enantiomer of **5a** by HPLC analysis.[14] This racemization barrier was found to be higher than that of carbo[5]helicene **7** (23.5 kcal/mol)[15] and binaphthyl lactone **8** (21.8 kcal/mol) (Figure 2c).[16]

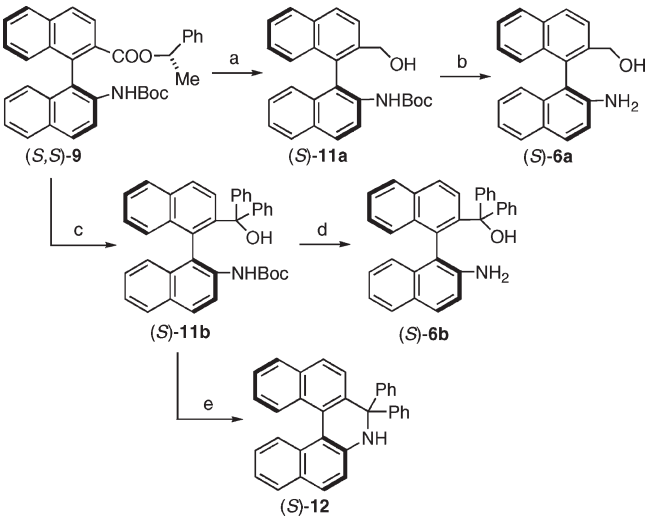
SCHEME 2. Transformation to Axially Chiral Amino Acid[a]



[a]Reagent and conditions: (a) TFA (100%); (b) *n*-BuLi, THF, −78 to 0 °C; Boc_2O, 0 °C (78%); (c) NaH, (*S*)-phenylethanol, THF, −78 °C to rt, (100%); recrystallizaion from hexane−EtOH ((*S,S*)-**9**, 40%, 99% de); (d) $Pd(OH)_2$, MeOH, rt (95%); (e) 10% TFA, CH_2Cl_2 (76%); (f) NaOH.

Next, we focused on the conversion of **5a** to axially chiral amino acid **1** (Scheme 2). The PMB group of **5a** was removed under acidic conditions to yield **5e**. Subsequent introduction of a Boc group was achieved by treatment of **5e** with *n*-BuLi and Boc_2O to afford **5f**. The imide moiety of **5f** was directly cleaved by the in situ generated sodium alkoxide of (*S*)-phenylethanol to afford *N*-Boc ester **9**. The diastereomers of **9** were easily separated by recrystallization to afford optically active (*S,S*)-**9**, in which the absolute configuration of the axial chirality was unambiguously determined by X-ray crystallographic analysis.[17]

SCHEME 3. Transformation to Axially Chiral Amino Alcohols and Secondary Amine[a]



[a]Reagent and conditions: (a) $LiBH_4$, THF, 0 °C to rt, (54%); (b) 10% TFA, CH_2Cl_2 (83%); (c) PhLi (3 equiv), THF, −78 °C to rt (82%); (d) *t*-BuONa, THF, 60 °C (61%); (e) AcOH (10%), EtOAc, H_2O (90%).

The ester moiety was removed to generate *N*-Boc amino acid (*S*)-**10** in 99% ee. The Boc group of (*S*)-**10** was readily deprotected with TFA to give novel axially chiral amino acid (*S*)-**1**. Compound **1** was found to be relatively unstable and spontaneously cyclized to the lactam ring, generating amidoaza[5]helicene **5e** within a few days. The instability of (*S*)-**1** might explain why the synthesis of this amino acid has not been reported to date, even though this compound possesses a simple structure and a promising binaphthyl framework. Gratifyingly, the sodium salt of (*S*)-**1** was stable could be stored under ambient temperature.

Amino alcohols **6** were also prepared from (*S,S*)-**9** (Scheme 3). Upon treatment of (*S,S*)-**9** with $LiBH_4$, selective reduction of the ester group proceeded to give *N*-Boc amino alcohol (*S*)-**11a**. Subsequent deprotection of the Boc group under acidic conditions afforded (*S*)-**6a** in good yield. Furthermore, amino alcohol (*S*)-**6b** that included a diphenylcarbinol moiety was also readily synthesized.

Addition of 3 equiv of PhLi to (*S,S*)-**9** yielded (*S*)-**11b**, which was then transformed to amino alcohol (*S*)-**6b** by removal of the Boc group under basic conditions. X-ray analysis of the racemic form of **11b** showed that both the Boc-protected amine group and hydroxy group were located around the chiral axis (Figure 3), suggesting that free amino

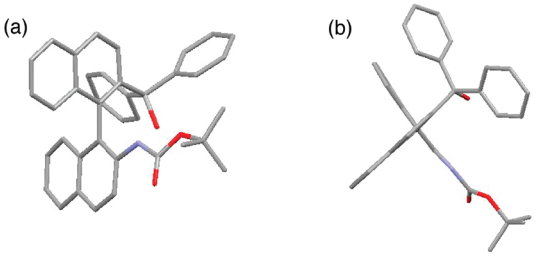


FIGURE 3. Stereostructure of racemic **11b**: (a) side view; (b) top view.

(14) See the Supporting Information.
(15) For the racemization barrier of **7**, see: Goedicke, C.; Stegemeyer, H. *Tetrahedron Lett*. **1970**, 937–940.
(16) For the racemization barrier of **8**, see: Bringmann, G.; Haubes, M.; Breuning, M.; Göbel, L.; Ochse, M.; Schöner, B.; Schupp, O. *J. Org. Chem*. **2000**, *65*, 722–728.
(17) See the Supporting Information.

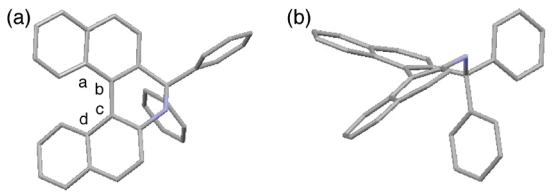


FIGURE 4. Stereostructure of racemic **12**: (a) side view; (b) top view.

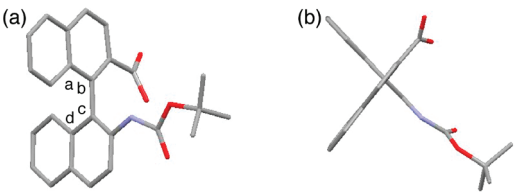
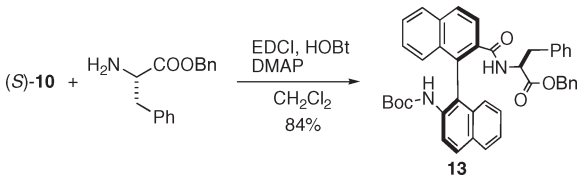


FIGURE 5. Stereostructure of racemic **10**: (a) side view; (b) top view.

alcohols **6a** and **6b** may be useful as chiral ligands and catalysts.

Interestingly, treatment of (*S*)-**11b** with acetic acid afforded chiral secondary amine (*S*)-**12** (Scheme 3). The stereostructure and optical behavior of axially chiral **12** were investigated (Figure 4). The side view of the X-ray structure of racemic **12** exhibited a twisted π-system having a wider dihedral angle (a,b−c,d: 45°) than that of amidoaza[5]helicene **5d** (Figure 4b vs Figure 2b). The chirality of the binaphtyl moiety was transferred to the orientation of the *gem*-diphenyl moiety. The stereostructure indicated that the two phenyl groups were located in the pseudoaxial and equatorial positions. These conformational properties might be responsible for the higher racemization barrier of (*S*)-**12** (26.2 kcal/mol)[18] than that of **5a**. These results provide evidence that **12** has the potential to be useful as a chiral amine catalyst.

SCHEME 4. Synthesis of Dipeptide



As a preliminary application of the utility of axially chiral amino acids, *N*-Boc amino acid (*S*)-**10** was tested as a chiral building block. Condensation of (*S*)-**10** with L-phenylalanine benzyl ester afforded *N*-Boc dipeptide **13** in good yield (Scheme 4).

Taking the crystal structure of racemic **10** (dihedral angle of a,b−c,d: 93°) into account (Figure 5), (*S*)-**10** would be useful as a chiral building block in peptidomimetic applications.[4] The inclusion of (*S*)-**10** in novel peptides could enforce unique turn structures because the moieties at C2 and C2′ are located in a perpendicular geometry around the chiral axis.

In summary, we have developed a practical synthesis of optically active binaphthyl amino acid and amino alcohols through an additive-ligand-free Pd catalyzed domino coupling to racemic amidoaza[5]helicenes **5**, followed by lactam ring-opening with an optically active alcohol and subsequent separation of diastereomeric mixture of **9**. These novel binaphthyl molecules have unique structural features that have the potential to be useful as chiral ligands and catalysts as well as chiral building blocks. Applications of these molecules in catalytic asymmetric reactions are currently under investigation in our laboratory.

(18) For the determination of the racemization barrier of **12**, see the Supporting Information.

Experimental Section

Typical Procedure for an Additive−Ligand-Free Domino Coupling (Table 1, Entry 7). The mixture of **4a** (16 g, 43 mmol), $Pd_2(dba)_3$ (198 mg, 0.22 mmol, 0.5 mol %), and K_2CO_3 (6.6 g, 48 mmol) in DMF (80 mL) was stirred for 30 h at 100 °C under Ar atmosphere. After the reaction mixture was cooled to rt, H_2O was added, and the mixture was extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 5:1) to afford **5a** (8.6 g, 96%) as light yellow needles.

Light yellow needles (*n*-hexane−AcOEt): mp 229 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 5.57 (br d, J = 13.8 Hz, 1H), 5.82 (br s, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.20−7.35 (m, 4H), 7.39−7.44 (m, 1H), 7.56−7.64 (m, 2H), 7.81−7.94 (m, 3H), 7.96−8.09 (m, 3H), 8.60 (d, J = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.3, 55.2, 113.5, 114.2, 115.4, 123.7, 124.8, 124.9, 125.3, 125.7, 127.7, 127.8, 128.0, 128.1, 128.5, 128.7, 129.1, 129.2, 129.5, 130.4, 132.8, 135.4, 136.5, 158.7, 162.2; IR (KBr) 1690, 2956, 3057, 3446 cm^{-1}; MS (FAB) m/z 416 $(M + H)^+$, 438 $(M + Na)^+$; HRMS (FAB) m/z calcd for $C_{29}H_{22}NO_2$ $(M + H)^+$ 416.1650, found 416.1649.

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Supporting Information Available: Experimental methods, characterization data for all new compounds, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.