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# Synthesis of 2,6-dimethyl-9-aryl-9-phosphabicyclo[3.3.1]nonanes: their application to asymmetric synthesis of chiral tetrahydroquinolines and relatives

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Dedicated to the memory of the Late Professor Yoshihiko Ito

**Abstract**—Synthesis of 2,6-dimethyl-9-aryl-9-phosphabicyclo[3.3.1]nonanes from 1,5-cyclooctadiene and their application to asymmetric cyclization leading to chiral tetrahydroquinolines and relatives through palladium-catalyzed allylic alkylation are described.


## 1. Introduction

Chiral phosphines have proved to play a crucial role as chiral ligands for transition-metal catalyzed asymmetric synthesis and their combinations with transition metals have been shown to be especially useful and versatile catalysts for a variety of enantioselective reactions, for example, asymmetric hydrogenation, asymmetric allylic alkylation, asymmetric hydrosilylation, asymmetric intramolecular Heck reaction, and so on.[1] Several years ago, we have developed a new class of monodentate ligands, (1*R*,2*S*,5*R*,6*S*)-2,6-dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane and its enantiomer ((*R*)- and (*S*)-9-PBNs, **1**),[2] as shown in Figure 1 and these phosphines in combination with palladium are efficient catalysts for the formation of carbon–carbon, carbon–nitrogen, and carbon–oxygen bonds, and asymmetric cyclization through asymmetric allylic alkylation reaction.[3,4] In the course of our studies on development of chiral auxiliaries with the 2,6-dimethyl-9-phosphabicyclo[3.3.1]nonane skeleton, we have been interested in replacement of the *P*-substituent on the 9-PBN for improving their enantiodiscriminating ability. In this article, we describe here the full detail of preparation of 9-PBNs and new monodentate phosphines, 2,6-dimethyl-9-(1-naphthyl)-9-phosphabicyclo[3.3.1]nonanes ((*S*)-and (*R*)-9-NapBNs, **2**)[5] and their application to asymmetric cyclization leading to chiral tetrahydroquinolines and relatives through palladium-catalyzed allylic alkylation. Although we have already examined this approach using a racemic substrate,[3c,d] there is, to date, no enantioselective approach through palladium-catalyzed allylic alkylation leading to the tetrahydroquinolines. Chiral tetrahydroquinolines are synthetically important targets as a result of their presence in natural products, pharmaceuticals, and other bioactive molecules. For example, martinelline and martinellic acid, novel bradykinin antagonists, are natural products with a unique pyrrolo[3,2-*c*]quinoline ring.[6,7] Their important properties and usefulness have prompted efforts for their efficient synthesis.[8]

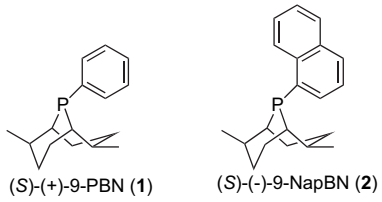


**Figure 1**.

## 2. Results and discussion

### 2.1. Design and synthesis of monodentate phosphines, 2,6-dimethyl-9-aryl-9-phosphabicyclo[3.3.1]nonanes

In designing a monodentate phosphine bearing an inherent lack of chelating ability, we envisaged that restriction of

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free rotation around the bond between the metal and the phosphine in the catalyst might be a key element and enhance the enantiodiscriminating ability. Thus, we used the 1,3-diaxial interaction on the six-membered ring for this purpose as shown in Figure 2. For an easy preparation and prevention of flipping at the six-membered ring, the new skeleton, 2,6-dimethyl-9-aryl-9-phosphabicyclo[3.3.1]-nonane, for the monodentate phosphines was designed, which would be efficiently constructed from 1,5-dimethyl-1,5-cyclooctadiene through hydroboration.

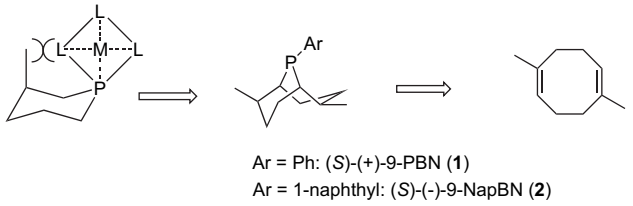



**Figure 2**.

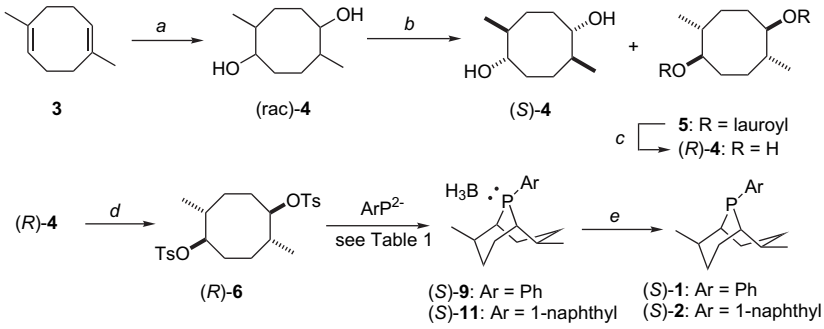
The preparation of optically active **1** was carried out from commercially available 1,5-dimethyl-1,5-cyclooctadiene (**3**) through enzymatic resolution as shown in Scheme 1. Hydroboration of **3** with sodium borohydride and boron trifluoride etherate gave (*rac*)-diol **4** in moderate yield.[9] Subsequent resolution[10] of **4** with lipase My was performed in the presence of an excess amount of lauric acid in heptane at 50 °C. The reaction was quite sluggish even at 50 °C but was found to afford efficiently (*S*)-diol **4** and (*R*)-dilauroyl ester **5** with high optical purities. Further purification of the (*S*)-diol **4** was achieved by recrystallization and its optical purity was confirmed to be 100% ee after conversion to the diMTPA ester by the NMR analysis. The (*R*)-diester **5** was hydrolyzed with potassium carbonate in methanol to provide after recrystallization the enantiomerically pure (*R*)-**4**. The absolute stereochemistry of each diol was confirmed by both the results of the lipase My-catalyzed esterification and the modified Mosher method.[11] Tosylation of (*S*)-**4** gave the labile ditosylate **6**. The double substitution reaction of the freshly prepared **6** was first problematic as shown in Table 1. The yield of the product was dependent on the counter cation used. The dilithium phenylphosphide generated from phenylphosphine (**7**) and *n*-butyl lithium caused complete decomposition of the substrate. Fortunately, the dipotassium phenylphosphide in situ generated from phenylphosphine (**7**) and potassium/sodium alloy

**Table 1**. Double substitution reaction of **6**

| Entry | Phosphide anion | Yield (%) of (*S*)-**9** |
|---|---|---|
| 1 | $PhPH_2$ (**7**), *n*-BuLi, THF, 0 °C; then $BH_3\cdot THF$ | 0 (dec) |
| 2 | $PhPH_2$, K–Na alloy, $PhCH_3$/dioxane, 23 °C; then $BH_3\cdot THF$ | 0–60 |
| 3 | $PhPH_2\cdot BH_3$ (**8**), KO$^t$Bu, $BnEt_3NCl$, $PhCH_3$, −10 °C, 1 h; 23 °C, 14 h | 62 |
| 4 | 1-NaphthylP$H_2\cdot BH_3$ (**10**), KO$^t$Bu, $BnEt_3NCl$, $PhCH_3$, 23 °C, 18 h | 52[a] |

[a] Yield of (*S*)-**11**.

(75/25 weight ratio), however, proceeded after treatment with the borane/tetrahydrofuran complex for purification to furnish the desired (1*R*,2*S*,5*R*,6*S*)-2,6-dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane borane complex ((*R*)-9-PBN$\cdot BH_3$, **9**) as air-stable crystals. After several trials, the above double substitution reaction, however, was found to bear the problem of reproducibility. In our efforts to overcome this problem, we were pleased to find a new reliable method using the phosphine borane–quaternary ammonium salt base rather than the phosphide dianion. The phosphine borane complex **8** was prepared by mixing **7** with borane/THF complex solution in toluene and directly used for the next reaction. The double substitution reaction of (*R*)-ditosylate **6** (1 equiv) with $PhPH_2\cdot BH_3$ (**8**, 1.1 equiv) was carried out in the presence of potassium *tert*-butoxide (3 equiv) and benzyltriethylammonium chloride (0.2 equiv) in toluene at 23 °C for 14 h to afford (*S*)-9-PBN$\cdot BH_3$ (**9**) in 62% yield as nice crystallines. The required free phosphine (*S*)-**1** is quantitatively regenerated by the reaction of phosphine borane **9** with 1,4-diazabicyclo[2.2.2]octane (DABCO, 1 equiv)[12] and can be conveniently used as its hexane solution. The stereochemical integrity of the final phosphine **1** and lack of racemization through the substitution reaction were unequivocally confirmed using chiral HPLC analysis. The antipodal (*R*)-9-PBN (**1**) was similarly prepared from the (*R*)-diol. In addition, the absolute configuration of thus obtained (*R*)-**9** was unambiguously determined by the X-ray crystallography of its borane complex,[2] which supports the above results of the enzymatic resolution and the modified Mosher method. The synthesis of (*S*)-9-NapBN (**2**) was also performed by using the above method. The required 1-naphthylphosphine was prepared according to the known method.[13] The phosphine borane **10** was prepared by mixing 1-naphthylphosphine with borane/dimethylsulfide complex in toluene and directly used for the next substitution reaction.



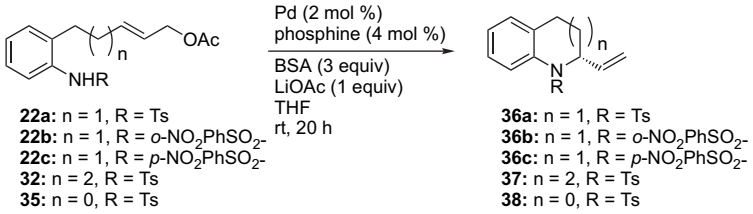

**Scheme 1**. Preparation of 6-dimethyl-9-aryl-9-phosphabicyclo[3.3.1]nonane. Reagents and conditions: (a) $NaBH_4$, $BF_3\cdot OEt_2$, THF; then NaOH, $H_2O_2$; (b) lipase My, lauric acid, heptane; (c) $K_2CO_3$, MeOH; (d) *p*-TsCl, pyridine; (e) DABCO, THF.

The double substitution reaction of (*R*)-ditosylate **6** (1.07 equiv) with the 1-naphthylphosphine borane complex **10** (1 equiv) was carried out in the presence of potassium *tert*-butoxide (3 equiv) and benzyltriethylammonium chloride (0.18 equiv) in toluene at 23 °C for 18 h to afford (*S*)-9-NapBN·$BH_3$ (**11**) in 52% yield as nice crystallines. The free phosphine (*S*)-**2** was obtained by treatment of **11** with DABCO in refluxing tetrahydrofuran for 2 h in 83% yield as crystallines.

## 2.2. Asymmetric cyclization through allylic substitution reaction

To explore the potential of 9-PBN and new 9-NapBN, we selected asymmetric cyclization[14] of *o*-substituted aniline sulfonamides **22a–c** leading to chiral tetrahydroquinolines **36a–c** as an initial test reaction. The results are summarized in Table 2. The substrates **22a–c** were easily prepared from commercially available *o*-iodoaniline (**12**) in 10 steps as shown in Scheme 2. Thus, Sonogashira coupling reaction of **12** with the propargyl alcohol derivative gave the three-carbon homologated **13**, which was subjected to a four-step standard manipulation, hydrogenation of **13**, *N*-protection with di-*tert*-butyl dicarbonate, removal of the tetrahydropyranyl group, and oxidation of the resulting alcohol **16**, to afford cyclized hemiaminal **17** in good yield. Wittig olefination of **17** proceeded selectively to produce α,β-unsaturated ester **18**, which was converted into substrate **22a** by a four-step sequence, reduction of **18**, acetylation of the resulting alcohol **19**, deprotection of *tert*-butoxycarbonyl group, and tosylation of the amino function. The other substrates **22b** and **22c** were obtained by the use of *o*- and *p*-nitrobenzenesulfonyl chloride, respectively. The cyclization reaction was carried out by using the previously developed conditions,[2] bis(dibenzylideneacetone)palladium ($Pd(dba)_2$, 2 mol %) or allyl palladium chloride dimer ($[(\eta^3\text{-}C_3H_5)PdCl]_2$, 5 mol %) and our phosphine in the presence of bis(trimethylsilyl)acetamide (BSA, 3 equiv) and lithium acetate (1 equiv) in tetrahydrofuran at 23 °C for 20 h (Table 2). The initial experiment using the *N*-tosyl substrate **22a** and (*S*)-9-PBN (**1**) was found to afford tetrahydroquinoline **36a** in 68% yield with 72% ee. The enantiomeric excess was determined by HPLC analysis. With this encouraging result in hand, we examined the bulkiness of the N-protecting group and the acidity of the sulfonamide (entries 2 and 3), which proved no or little effects. The effect of the ligand was next investigated by using (*S*)-NapBN (**2**) and in the case of the *N*-tosyl substrate **22a** the corresponding product was obtained in 48% yield with 92% ee but the reaction was incomplete with recovery of the substrate (28% yield). In order to overcome the low conversion, 5 mol % $Pd(dba)_2$ and 10 mol % phosphine were applied but the yield was still moderate (entry 5). The reaction using the *N*-*p*-nitrobenzenesulfonamide substrate **22c** with hope of improving the chemical yield proceeded with 94% ee but the reaction was still incomplete (entry 6). Use of allyl palladium chloride dimer somewhat improved the chemical yield and the enantioselectivity (entry 7). On the contrary, asymmetric allylic substitution reactions using the typical ligands, (*R*)-BINAP (**39**) and Trost's ligand **40**, under the similar condition to that in entry 7

**Table 2**. Asymmetric cyclization to the tetrahydroquinoline derivatives

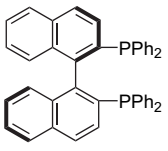



**22a:** n = 1, R = Ts
**22b:** n = 1, R = *o*-$NO_2PhSO_2$-
**22c:** n = 1, R = *p*-$NO_2PhSO_2$-
**32:** n = 2, R = Ts
**35:** n = 0, R = Ts

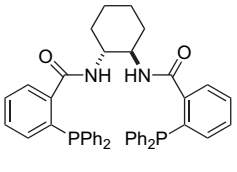
**36a:** n = 1, R = Ts
**36b:** n = 1, R = *o*-$NO_2PhSO_2$-
**36c:** n = 1, R = *p*-$NO_2PhSO_2$-
**37:** n = 2, R = Ts
**38:** n = 0, R = Ts

| Entry | Substrate | Pd | Phosphine | Yield[a] (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | **22a** | $Pd(dba)_2$ | (*S*)-9-PBN | 68 (26) | *72* (*R*) |
| 2 | **22b** | $Pd(dba)_2$ | (*S*)-9-PBN | 51 (26) | *56* (*R*) |
| 3 | **22c** | $Pd(dba)_2$ | (*S*)-9-PBN | 86 (8) | *65* (*R*) |
| 4 | **22a** | $Pd(dba)_2$ | (*S*)-9-NapBN | 48 (28) | *92* (*R*) |
| 5[b] | **22a** | $Pd(dba)_2$ | (*S*)-9-NapBN | 55 (16) | *92* (*R*) |
| 6 | **22c** | $Pd(dba)_2$ | (*S*)-9-NapBN | 28 (30) | *94* (*R*) |
| 7[c] | **22a** | $[(\eta^3\text{-}C_3H_5)PdCl]_2$ | (*R*)-9-NapBN | 61 (14) | *94* (*S*) |
| 8[d] | **22a** | $[(\eta^3\text{-}C_3H_5)PdCl]_2$ | (*R*)-BINAP **39** | 60 (14) | *0* |
| 9[d] | **22a** | $[(\eta^3\text{-}C_3H_5)PdCl]_2$ | Trost's ligand **40** | 48 (35) | *17* |
| 10[c] | **32** | $[(\eta^3\text{-}C_3H_5)PdCl]_2$ | (*R*)-9-NapBN | 29 | *55* |
| 11[c] | **35** | $[(\eta^3\text{-}C_3H_5)PdCl]_2$ | (*S*)-9-NapBN | Trace | *62* |

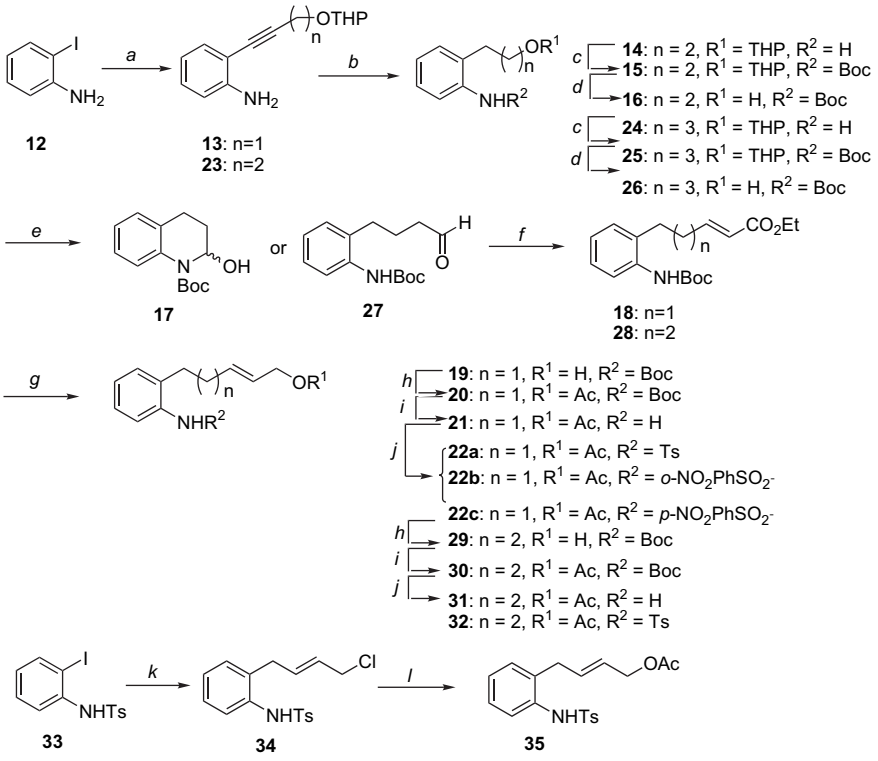
[a] Isolated Yield. The value in parentheses is the recovery yield of the starting material.
[b] $Pd(dba)_2$ of 5 mol % was used.
[c] $[(allyl)PdCl]_2$ of 5 mol % and (*R*)-9-NapBN of 20 mol % were used.
[d] The reaction was carried out by using 5 mol % $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and 10 mol % ligand for 36 h.




(*R*)-BINAP **39**




Trost ligand **40**




**Scheme 2**. Preparation of the substrates for asymmetric cyclization. Reagents and conditions: (a) tetrahydro-2-(2-propynyloxy)-2*H*-pyran, $(Ph_3P)_2PdCl_2$, CuI, $Et_2NH$ for **13**; tetrahydro-2-(but-3-ynyloxy)-2*H*-pyran, $(Ph_3P)_2PdCl_2$, CuI, $Et_2NH$ for **23**; (b) $H_2$, 5% Pd/C, MeOH; (c) $Boc_2O$, $Et_3N$, THF; (d) PPTS, EtOH; (e) Swern oxidation; (f) $Ph_3P{=}CHCO_2Et$, $PhCH_3$; (g) DIBAL, $PhCH_3$; (h) $Ac_2O$, pyridine; (i) $CF_3CO_2H$; (j) *p*-TsCl and pyridine for **22a** and **32**; *o*-NsCl and pyridine for **22b**; *p*-NsCl and pyridine for **22c**; (k) *n*-BuLi, 1,4-dichloro-2-butene; (l) KOAc, DMSO.

showed much lower enantioselectivities (entries 8 and 9), which revealed the excellent features of our phosphines, 9-PBN and 9-NapBN. Other substrates leading to the benzoazepine **37** and indoline **38** were next investigated in this asymmetric cyclization. The required substrate **32** for **37** was also prepared by using the similar method to that for **22a**. The substrate **35** for **38** was prepared by direct coupling of 1,4-dichloro-2-butene and the aryl lithium generated by halogen/lithium exchange reaction from *N*-(*o*-iodophenyl)-*p*-toluenesulfonamide (**33**) (Scheme 2). As depicted in Scheme 3, the absolute configuration of the tetrahydroquinoline **36a** was established after conversion to the known tetrahydroquinolineacetic acid derivative **41**. Thus, **36a** with 24% ee ($[\alpha]_D^{26}$ −7.88 (*c* 1.21, $CHCl_3$)) was hydroborated with borane dimethylsulfide complex and the resulting alcohol was oxidized to the carboxylic acid with Jones' reagent, which was esterified with iodomethane and potassium hydrogen carbonate in dimethylformamide and N-deprotected with magnesium in methanol to furnish **41** with 21% ee ($[\alpha]_D^{25}$ −22.6 (*c* 0.415, $CHCl_3$)). The comparison with the literature value[15] has unambiguously established that the tetrahydroquinoline **36a** has the *R* configuration at the C2 position.

Although the reaction mechanism of the asymmetric induction with a high level of enantioselectivity through intramolecular allylic alkylation is not clear at present, we speculate that the reaction proceeds via the allyl/palladium complex avoiding the steric interaction with the methyl and the *P*-naphthyl substituents at the (*S*)-phosphine ligand to afford the (*R*)-product as shown in Figure 3.

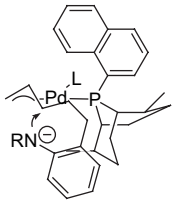
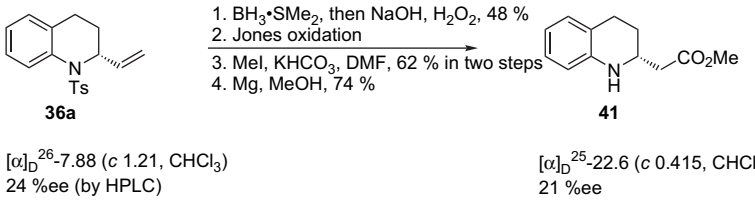



**Figure 3**.




**Scheme 3**.

## 3. Conclusion

We have succeeded in the development of a new class of chiral monodentate phosphines, 2,6-dimethyl-9-aryl-9-phosphabicyclo[3.3.1]nonanes (9-PBNs and 9-NapBNs). Their application to asymmetric cyclization through intramolecular palladium-catalyzed allylic alkylation demonstrates a potential of these phosphines.

## 4. Experimental

### 4.1. General

Melting points were measured with a SIBATA NEL-270 melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO P-1020 polarimeter with a sodium lamp (589 nm). Infrared spectra were recorded on a SHIMADZU FTIR-8100 JASCO FT/IR-230 spectrometer. NMR spectra were recorded on JEOL JNM-GSX-400A and JNM-ECP-400 spectrometers with tetramethylsilane as an internal standard, unless otherwise indicated. Mass spectra were measured on a JMX-AX-500 spectrometer. Column chromatography was performed with silica gel BW-820MH or BW-200 (Fuji Davison Co.). HPLC analyses were carried out on the chiral column indicated in each experiment. All commercially available reagents were used as received.

### 4.2. Synthesis of 2,6-dimethyl-9-aryl-9-phosphabicyclo-[3.3.1]nonanes

**4.2.1. 2,6-Dimethyl-1,5-cyclooctanediol (4).** To a stirred mixture of $NaBH_4$ (5.08 g, 0.13 mol) and 1,5-dimethyl-1,5-cyclooctadiene (**3**) (23.2 g, 0.17 mol) in THF (110 ml) cooled to 0 °C was added dropwise boron trifluoride etherate (25.5 g, 0.18 mol) over 1 h. After stirring the mixture at room temperature for 1 h and at reflux for 1 h, the reaction mixture was cooled to room temperature and quenched by dropwise addition of ethanol (10.6 ml, 0.18 mol). Aqueous NaOH (3 M, 60 ml) and 30% aqueous $H_2O_2$ (36 ml, 0.36 mol) were added dropwise, maintaining the internal temperature below 45 °C. The mixture was stirred at 40–50 °C for 1 h, cooled to room temperature, saturated with $K_2CO_3$, and extracted with ethyl acetate (200 ml×2). The combined organic layers were washed with saturated brine (100 ml×2), dried over $MgSO_4$, and concentrated in vacuo. The residue was crystallized from ethyl acetate/*n*-hexane and the resulting crude diol **4** was recrystallized from 1,2-dichloroethane to give pure diol **4** (16.02 g, 55%) as colorless needles: mp 109.5–111 °C; IR (KBr): 3322, 2953, 1040, 1011 $cm^{-1}$; $^1H$ NMR ($CDCl_3$/DMSO-$d_6$, 60 MHz): $\delta$ 0.98 (d, $J$=6 Hz, 6H), 1.17–2.07 (m, 10H), 2.96–3.41 (m, 2H), 3.58 (d, $J$=5 Hz, 2H).

**4.2.2. Resolution of 2,6-dimethyl-1,5-cyclooctanediol (4).** A mixture of the (*rac*)-diol **4** (50 g, 0.29 mol), lauric acid (116 g, 0.6 mol), and lipase My (14.8 g) in heptane (290 ml) was stirred at 50 °C for 8 days. The reaction mixture was cooled to room temperature, then the enzyme and the unreacted (*S*)-diol **4** were filtered off. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (*n*-hexane to *n*-hexane/ethyl acetate= 9/1) to give a mixture of (*R*)-1,5-bis(lauroyloxy)-2,6-dimethylcyclooctane (**5**) and lauric acid. The mixture was recrystallized from 90% aqueous MeOH to give (*R*)-**5** (66.5 g, 43%) as colorless fine crystals. The mixture of the enzyme and the unreacted (*S*)-diol **4** was washed with hot benzene/THF (1/1) (230 ml×2) and the filtrate was concentrated in vacuo. The resulting crude (*S*)-diol **4** was recrystallized from dichloroethane to give (*S*)-diol **4** (19.7 g, 40%) as colorless needles. Compound (*S*)-**4**: mp 138 °C; $[\alpha]_D^{20}$ +12.84 (*c* 1.05, MeOH); IR (KBr): 3324, 2953, 1040, 1011 $cm^{-1}$; $^1H$ NMR ($CDCl_3$/DMSO-$d_6$, 60 MHz): $\delta$ 0.96 (d, $J$=6 Hz, 6H), 1.14–2.07 (m, 10H), 2.87–3.38 (m, 2H), 4.04 (d, $J$=5 Hz, 2H); Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.49; H, 11.79. Compound (*R*)-**5**: mp 46–47 °C (MeOH); $[\alpha]_D^{20}$ −31.01 (*c* 1.01, $CHCl_3$); IR (KBr): 2915, 1728, 1175 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz): $\delta$ 0.87 (t, $J$=7 Hz, 6H), 0.93 (d, $J$=7 Hz, 6H), 1.05–2.02 (m, 46H), 2.10–2.44 (m, 4H), 4.41–4.82 (br, 2H). Anal. Calcd for $C_{34}H_{64}O_4$: C, 76.06; H, 12.02. Found: C, 76.14; H, 12.11.

A mixture of (*R*)-**5** (30.39 g, 57 mmol) and $K_2CO_3$ (20 g, 145 mmol) in MeOH (500 ml) was stirred at room temperature for 44 h. The reaction mixture was concentrated in vacuo and the resulting white solids were washed thoroughly with ether. The filtrate was concentrated in vacuo and the resulting crude (*R*)-diol **4** was washed with *n*-hexane and recrystallized from dichloroethane to give pure (*R*)-diol **4** (6.76 g, 69%) as colorless needles: mp 138–139 °C; $[\alpha]_D^{20}$ −12.75 (*c* 1.04, MeOH); IR (KBr): 3320 (–OH), 2953, 1040, 1011 $cm^{-1}$; $^1H$ NMR ($CDCl_3$/DMSO-$d_6$, 60 MHz): $\delta$ 0.98 (d, $J$=6 Hz, 6H,), 1.16–2.01 (m, 10H), 2.89–3.41 (m, 2H), 3.86 (d, $J$=5 Hz, 2H). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.54; H, 11.51.

**4.2.3. Determination of optical purities of the diols 4.** The (*S*)- and (*R*)-diols **4** were converted to the corresponding (*S*)-MTPA esters and their optical purities were determined by comparison of their $^1H$ NMR spectra.

**4.2.3.1. (*S*)-MTPA ester of the (*S*)-diol 4.** To a solution of the above (*S*)-diol **4** (7 mg, 0.041 mmol) and DMAP (50 mg, 0.41 mmol) in ether (1 ml) was added a 0.14 M solution of MTPACl (prepared by the reaction of MTPA with thionyl chloride) in $CH_2Cl_2$ (1 ml). The mixture was stirred at room temperature for 0.5 h. After dilution with ether (50 ml), the mixture was washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and saturated brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified on a silica gel plate (E. Merck Art. 5715) to give 20 mg (78%) of the (*S*)-MTPA ester as a colorless viscous oil; IR: 1744, 1272, 1169, 1123, 1022, 995, 720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 0.80 (d, $J$=6.6 Hz, 6H,), 1.40–1.48 (m, 2H), 1.75–1.98 (m, 8H), 3.552 (d, $J$= 1.1 Hz, 6H, O–$CH_3$), 4.78–4.83 (m, 2H), 7.37–7.41 (m, 6H), 7.52–7.55 (m, 4H). The $^1H$ NMR spectrum showed the absence of the corresponding isomer derived from the (*R*)-diol.

**4.2.3.2. (*S*)-MTPA ester of the (*R*)-diol 4.** Prepared from the above (*R*)-diol **4** (7 mg, 0.041 mmol) as described above; IR: 1744, 1271, 1171, 1123, 1022, 994, 720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 0.91 (d, $J$=6.8 Hz, 6H), 1.33–1.42 (m, 2H), 1.65–1.97 (m, 8H), 3.527 (d, $J$=1.1 Hz, 6H, O–$CH_3$), 4.79–4.84 (m, 2H), 7.37–7.42 (m, 6H), 7.51–7.53 (m, 4H). The $^1H$ NMR spectrum showed the absence of the corresponding isomer derived from the (*S*)-diol.

**4.2.4. (1*R*,2*R*,5*R*,6*R*)-1,5-Bis(*p*-toluenesulfonyloxy)-2,6-dimethylcyclooctane (6).** A mixture of the (*R*)-diol **4** (3.46 g, 20 mmol) and *p*-toluenesulfonyl chloride (15.3 g, 80 mmol) in pyridine (20 ml) was stirred at 0 °C for 21 h, then $H_2O$ (10 ml) was added and the mixture was stirred at 5 °C for 1 h. The mixture was diluted with $CH_2Cl_2$/ether (1/2, 200 ml) and the organic layer was washed with 1 M $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was triturated with *n*-hexane/$Et_2O$ and the resulting white solid was filtered, washed with *n*-hexane, and dried in vacuo (room temperature, 1 h) to give (*R*)-**6** (9.05 g, 94%) as unstable colorless solids. The analytical sample was recrystallized from $CH_2Cl_2$/ether/*n*-hexane to give pure (*R*)-**6** as colorless flaky crystals: mp 91–92 °C (decomp.); $[\alpha]_D^{18}$ −40.11 (*c* 1.83, $CHCl_3$); IR (KBr): 1362, 1171, 899, 668, 552 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 0.79 (d, *J*=6.9 Hz, 6H), 1.21–1.29 (m, 2H), 1.67–1.91 (m, 8H), 2.43 (s, 6H), 4.26–4.33 (m, 2H), 7.33 (d, *J*=8.6 Hz, 4H), 7.77 (d, *J*=8.3 Hz, 4H). Anal. Calcd for $C_{24}H_{32}O_6S_2$: C, 59.97; H, 6.71. Found: C, 59.89; H, 6.80. The ditosylate is labile under room temperature and decomposes by long standing under reduced pressure. The ditosylate should be briefly dried in vacuo and stored in refrigerator.

**4.2.5. (1*S*,2*S*,5*S*,6*S*)-1,5-Bis(*p*-toluenesulfonyloxy)-2,6-dimethylcyclooctane (6).** Compound (*S*)-**6** (9.105 g, 95%) was prepared from the (*S*)-diol **4** (3.45 g, 20 mmol) as described above: mp 92–94 °C (decomp.); $[\alpha]_D^{20}$ +40.02 (*c* 1.84, $CHCl_3$); IR (KBr): 1362, 1171, 897, 668, 552 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 0.79 (d, *J*=6.9 Hz, 6H), 1.21–1.29 (m, 2H), 1.67–1.91 (m, 8H), 2.44 (s, 6H), 4.23–4.30 (m, 2H), 7.33 (d, *J*=8.6 Hz, 4H), 7.77 (d, *J*=8.3 Hz, 4H). Anal. Calcd for $C_{24}H_{32}O_6S_2$: C, 59.97; H, 6.71. Found: C, 59.81; H, 6.91.

**4.2.6. (1*S*,2*R*,5*S*,6*R*)-2,6-Dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane borane complex (9, (*S*)-9-PBN·$BH_3$).** Potassium (938 mg, 24 mmol) and sodium (235 mg, 10.2 mmol) were melted together in a Schlenk tube at 180 °C under reduced pressure, cooled to room temperature, and charged with argon gas. Then, dioxane (40 ml) followed by a 3 M solution of phenylphosphine (**7**) in toluene (4 ml) was added to the resulting suspension. The mixture was stirred at room temperature for 10 h and at 95–100 °C for 2 h, then cooled to room temperature. A solution of ditosylate (*R*)-**6** (5.77 g, 12 mmol) in toluene (40 ml) was added dropwise and stirred at room temperature for 2.5 h. The mixture was filtered through a cotton plug under an argon atmosphere and concentrated in vacuo to give crude phosphine (*S*)-**7**. The crude phosphine (*S*)-**7** was treated with a 1 M solution of $BH_3$/THF in THF (12 ml). The mixture was stirred at room temperature for 0.5 h and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/$CH_2Cl_2$=3/2) to give the (*S*)-9-PBN-borane complex **9** (1.37 g, 44%, air stable) as white solids, then recrystallization from $CH_2Cl_2$/ether/*n*-hexane gave colorless prisms: mp 165–169 °C; $[\alpha]_D^{21}$ −2.56 (*c* 1.26, $CH_2Cl_2$); IR (KBr): 2953, 2359 (B–H), 2334 (B–H), 1067, 704 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 0.81–0.99 (m, 1H), 0.95 (d, *J*=7.3 Hz, 3H), 1.50 (d, *J*=7.3 Hz, 3H), 1.55–2.77 (m, 10H), 7.43–7.60 (m, 5H). Anal. Calcd for $C_{16}H_{26}BP$: C, 73.87; H, 10.07. Found: C, 73.72; H, 9.95.

**4.2.7. (1*R*,2*S*,5*R*,6*S*)-2,6-Dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane borane complex (9, (*R*)-9-PBN·$BH_3$).** To a stirred suspension of ditosylate (*S*)-**6** (2.41 g, 5 mmol), benzyltriethylammonium chloride (228 mg, 1 mmol), and potassium *tert*-butoxide (1.69 g, 15 mmol) in toluene (40 ml) at −20 °C was added a solution of phenylphosphine borane complex **8** (prepared by mixing phenylphosphine (2.5 M in toluene solution, 2.2 ml, 5.5 mmol) with a 1 M solution of $BH_3$/THF (6 ml, 6 mmol) at 0 °C for 30 min). The reaction mixture was stirred at −10 °C for 1 h and at room temperature for 18 h. Then the mixture was diluted with ether and filtered through a Celite pad. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (*n*-hexane/$CH_2Cl_2$=3/2) to give the (*R*)-9-PBN-borane complex **9** (811 mg, 62.4%, air stable) as colorless crystals. Recrystallization from $CH_2Cl_2$/ether/*n*-hexane gave colorless prisms: mp 166–170 °C; $[\alpha]_D^{21}$ +2.48 (*c* 1.26, $CH_2Cl_2$); IR (KBr): 2953, 2359 (B–H), 2334 (BH), 1067, 704 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 0.73–0.86 (m, 1H), 0.88 (d, *J*=7.3 Hz, 3H), 1.43 (d, *J*=7.3 Hz, 3H), 1.49–2.68 (m, 11H), 7.37–7.53 (m, 5H). Anal. Calcd for $C_{16}H_{26}BP$: C, 73.87; H, 10.07. Found: C, 73.90; H, 10.02.

**4.2.8. (1*R*,2*S*,5*R*,6*S*)-2,6-Dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane (1, (*R*)-9-PBN).** The (*R*)-9-PBN·$BH_3$ (**9**, 260 mg, 1 mmol) and DABCO (112 mg, 1 mmol) were dissolved in dry THF (2 ml) under an argon atmosphere. The reaction mixture was refluxed for 2 h and the solvent was evaporated. The residue was treated with dry hexane (10 ml) and filtered through a cotton plug to give 0.1 M (*R*)-9-PBN solution in *n*-hexane. (*R*)-9-PBN **1**: $[\alpha]_D^{29}$ −30.7 (*c* 1, *n*-hexane); $^1H$ NMR ($CDCl_3$): $\delta$ 0.86–0.95 (m, 1H), 0.88 (d, *J*=7.1 Hz, 3H), 1.27 (m, 1H), 1.30 (d, *J*=7.3 Hz, 3H), 1.48 (m, 1H), 1.6–2.38 (m, 8H), 2.49 (d, *J*=10 Hz, 1H), 7.13 (m, 1H), 7.24 (m, 2H), 7.38 (m, 2H).

**4.2.9. (1*S*,2*R*,5*S*,6*R*)-2,6-Dimethyl-9-(1-naphthyl)-9-phosphabicyclo[3.3.1]nonane borane complex (11, (*S*)-9-NapBN·$BH_3$).** To a stirred suspension of the ditosylate (*R*)-**6** (7.69 g, 16 mmol), benzyltriethylammonium chloride (729 mg, 3.2 mmol), and potassium *tert*-butoxide (5.05 g, 45 mmol) in toluene (105 ml) at 5 °C was added a solution of 1-naphthylphosphine borane **10** (prepared by mixing 1-naphthylphosphine (1 M in toluene solution, 15 ml, 15 mmol) with $BH_3$·$SMe_2$ (1.65 ml, 16.5 mmol) at 23 °C for 2 h). The reaction mixture was stirred at 5 °C for 1 h and at 23 °C for 18 h. Then the mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (*n*-hexane/$CH_2Cl_2$=3/2) to give the (*S*)-9-NapBN borane complex **11** (2.42 g, 52%, air stable): $^1H$ NMR ($CDCl_3$): $\delta$ 0.49 (d, *J*=7.02 Hz, 3H), 0.7–1.4 (m, 3H), 1.49 (d, *J*=7.32 Hz, 3H), 1.55–1.9 (m, 5H), 2.0–2.2 (m, 2H), 2.25–2.45 (m, 2H), 2.65 (br s, 1H), 2.75–2.9 (m, 2H), 7.45–7.57 (m, 3H), 7.6–7.7 (m, 1H), 7.8–7.95 (m, 2H), 8.1–8.35 (m, 1H). Anal. Calcd for $C_{20}H_{28}BP$: C, 77.43; H, 9.10. Found: C, 77.51; H, 9.14.

**4.2.10. (1*S*,2*R*,5*S*,6*R*)-2,6-Dimethyl-9-(1-naphthyl)-9-phosphabicyclo[3.3.1]nonane (2, (*S*)-9-NapBN).** The (*S*)-9-NapBN·$BH_3$ (**11**, 621 mg, 2 mmol) and DABCO (246 mg, 2.2 mmol) were dissolved in dry THF (5 ml) under

an argon atmosphere. The reaction mixture was refluxed for 2 h and the solvent was evaporated. The residue was recrystallized from methanol to give (*S*)-9-NapBN **2** (494 mg, 83%): mp 127–129 °C; $[\alpha]_D^{21}$ −248.8 (*c* 0.9, *n*-hexane); IR (KBr): 3047, 2952, 2857, 1560, 1502, 1444, 1371, 796, 773 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 0.47 (d, *J*=6.71 Hz, 3H), 1.0–1.08 (m, 1H), 1.32–1.37 (m, 2H), 1.55–1.61 (m, 2H), 1.68–1.83 (m, 2H), 2.07–2.15 (m, 1H), 2.19–2.3 (m, 1H), 2.3–2.37 (m, 1H), 2.52–2.54 (m, 1H), 2.65 (br s, 2H), 7.36 (m, 1H), 7.5 (m, 2H), 7.2 (m, 1H), 7.71 (d, *J*=8.24 Hz, 1H), 7.82 (d, *J*=7.63 Hz, 1H), 8.27 (d, *J*=7.94 Hz, 1H). Anal. Calcd for $C_{20}H_{25}P$: C, 81.05; H, 8.50. Found: C, 81.20; H, 8.53.

### 4.3. Preparation of the substrates for asymmetric cyclization

**4.3.1. 2-[3-(Tetrahydropyran-2-yloxy)prop-1-ynyl]phenylamine (13).** To a stirred solution of 2-iodoaniline (**12**, 1.02 g, 4.57 mmol) in $Et_2NH$ (9 ml) were added $(Ph_3P)_2PdCl_2$ (16 mg, 0.023 mmol), CuI (8.7 mg, 0.046 mmol), and tetrahydro-2-(2-propynyloxy)-2*H*-pyran (640 mg, 4.57 mmol) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature. After 5 h, the volatile was removed in vacuo. The residue was diluted with ethyl acetate and washed with water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=6/1) to give **13** (981 mg, 93%) as a yellow oil; IR: 3467, 3361, 2222, 1618 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.54–1.88 (m, 6H) 3.56–3.59 (m, 1H) 3.86–3.92 (m, 1H) 4.54 (d, *J*=3.9 Hz, 2H), 4.91 (t, *J*=3.5 Hz, 1H), 6.63–6.68 (m, 2H), 7.11 (dt, *J*=7.8, 1.6 Hz, 1H), 7.28 (dd, *J*=7.7, 1.6 Hz, 1H). LRMS (FAB, NBA) *m/z*: 232 ($[M+H]^+$).

**4.3.2. 2-[3-(Tetrahydropyran-2-yloxy)propyl]phenylamine (14).** To a stirred solution of **13** (592 mg, 2.56 mmol) in methanol (13 ml) was added 5% Pd on carbon (60 mg) under a nitrogen atmosphere. The reaction mixture was stirred under a hydrogen atmosphere at room temperature. After 19 h, the reaction mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=6/1) to give **14** (562 mg, 93%) as a yellow oil; IR: 3460, 3367, 1624 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.55–1.94 (m, 8H), 2.62 (dt, *J*=7.6, 2.1 Hz, 2H), 3.42 (m, 2H), 3.78–3.92 (m, 2H), 4.60 (m, 1H), 6.65–6.73 (m, 2H). LRMS (FAB, NBA) *m/z*: 236 ($[M+H]^+$).

**4.3.3. 1-*tert*-Butoxycarbonylamino-2-[3-(tetrahydropyran-2-yloxy)propyl]benzene (15).** To a stirred solution of **14** (18.5 g, 0.079 mol) in THF (100 ml) were added $Boc_2O$ (25.7 g, 0.12 mol) in THF (50 ml) and $Et_3N$ (11.9 g, 0.12 mol) and the reaction mixture was stirred at room temperature. After 24 h, the reaction mixture was diluted with ethyl acetate and washed with 1 M $KHSO_4$, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=6/1) to give **15** (25 g, 93%) as a colorless oil; IR: 3336, 1730, 1539 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.40 (s, 9H), 1.55–1.81 (m, 6H), 1.85–1.92 (m, 2H), 2.65–2.78 (m, 2H), 3.34–3.39 (m, 1H), 3.49–3.52 (m, 1H), 3.69 (q, *J*=5.4 Hz, 1H), 3.86–3.96 (m, 1H), 4.61 (m, 1H), 7.01–7.21 (m, 3H), 7.10 (br s, 1H), 7.74 (d, *J*=8.1 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 19.7, 25.2, 26.7, 28.2, 30.0, 30.5, 62.5, 64.8, 79.8, 98.5, 22.6, 123.9, 126.4, 127.2, 128.1, 129.4, 131.6, 136.3, 153.5. HRMS (FAB, NBA) calcd for $C_{19}H_{29}NO_4$: 335.2097 ($M^+$); found: 335.2085.

**4.3.4. 1-*tert*-Butoxycarbonylamino-2-(3-hydroxypropyl)-benzene (16).** To a stirred solution of **15** (67.7 mg, 0.202 mmol) in ethanol (2 ml) was added PPTS (5.03 mg, 0.020 mmol) and the reaction mixture was stirred at 55 °C. After 16 h, the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=2/1) to give **16** (48.7 mg, 96%) as colorless crystals: mp 48–53 °C (ethyl acetate/*n*-hexane); IR (KBr): 3311, 1697, 1523 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.51 (s, 9H) 1.81–1.88 (m, 2H), 2.10 (br s, 1H), 2.71 (t, *J*=7.2 Hz, 2H), 3.59 (m, 2H), 7.01–7.21 (m, 3H), 7.26 (br s, 1H), 7.71 (d, *J*=6.7 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 26.5, 29.3, 32.3, 60.7, 80.1, 122.5, 124.1, 126.7, 129.5, 131.8, 136.3, 153.8. HRMS (FAB, NBA) calcd for $C_{14}H_{21}NO_3$: 251.1521 ($M^+$); found: 251.1517. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.04; H, 8.48; N, 5.52.

**4.3.5. 1-*tert*-Butoxycarbonyl-1,2,3,4-tetrahydroquinoline-2-o1 (17).** A solution of oxalyl chloride (481 mg, 3.79 mmol) in $CH_2Cl_2$ (10 ml) was cooled at −78 °C. A solution of DMSO (462 mg, 5.92 mmol) in $CH_2Cl_2$ (5 ml) was added dropwise at −78 °C under a nitrogen atmosphere and the reaction mixture was stirred at −78 °C for 25 min. A solution of **16** (359 mg, 1.44 mmol) in $CH_2Cl_2$ (6 ml) was added dropwise. The mixture was stirred for an additional 35 min at −78 °C, warmed to −40 °C, and kept at −40 °C for 2 h. Then, $Et_3N$ (2.10 g, 0.79 mmol) was added slowly. The reaction mixture was warmed to 0 °C and stirred for 10 min at 0 °C. After addition of saturated aqueous $NH_4Cl$, the mixture was extracted with ethyl acetate and washed with brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=3/1) to give **17** (224.5 mg, 63%) as yellow crystals: mp 55–63 °C (ether/*n*-hexane); IR (KBr): 3448, 2976, 1678 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.55 (s, 9H), 1.74–1.83 (m, 1H), 2.20–2.28 (m, 1H), 2.51–2.58 (m, 1H), 2.63–2.70 (m, 1H), 3.93 (br s, 1H), 5.79 (dt, *J*=6.6, 3.1 Hz, 1H), 6.97–7.18 (m, 3H), 7.51 (d, *J*=8.1 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 24.6, 28.4, 31.0, 76.7, 81.3, 82.1, 123.5, 123.8, 125.6, 126.2, 27.2, 132.0, 136.3, 154.6. HRMS (FAB, NBA) calcd for $C_{14}H_{19}NO_3$: 249.1365 ($M^+$); found: 249.1367. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.56; H, 7.72; N, 5.63.

**4.3.6. Ethyl 5-(2-*tert*-butoxycarbonylamino)phenyl-2-pentenoate (18).** To a stirred solution of **17** (192 mg, 0.774 mmol) in toluene (4 ml) was added (carbethoxymethylene)triphenylphosphorane (323 mg, 0.929 mmol) under a nitrogen atmosphere and the reaction mixture was stirred at 100 °C. After 12 h, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column

chromatography (*n*-hexane/ethyl acetate=8/1) to give **18** (201 mg, 82%) as colorless crystals: mp 45–47 °C (ether/*n*-hexane); IR (KBr): 3346, 2979, 1714, 1653 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.29 (t, $J$=7.1 Hz, 3H), 1.52 (s, 9H), 2.48–2.54 (m, 2H), 2.70–2.74 (m, 2H), 4.20 (q, $J$=7.1 Hz, 2H), 5.85–5.90 (m, 1H), 6.19 (br s, 1H), 6.98–7.24 (m, 4H), 7.69 (d, $J$=7.8 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 14.2, 28.3, 29.8, 32.0, 60.3, 80.5, 122.2, 123.1: 124.7, 127.2, 9.1, 131.5, 135.6, 147.5, 153.4, 166.4. HRMS (FAB, NBA) calcd for $C_{18}H_{25}NO_4$: 320.1862 ([M+H]$^+$); found: 320.1853. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.82; H, 7.97; N, 4.42.

**4.3.7. 1-*tert*-Butoxycarbonylamino-2-(5-hydroxy-3-pentenyl)benzene (19).** To a stirred solution of **18** (148 mg, 0.464 mmol) in toluene (2 ml) at −78 °C was added 1.5 M DIBAL in toluene (1.1 ml, 1.65 mmol) under a nitrogen atmosphere and the reaction mixture was stirred at −78 °C. After 2 h, the reaction mixture was quenched with $Na_2SO_4\cdot 10H_2O$, filtered through a Celite pad, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=2/1) to give **19** (98 mg, 77%) as colorless crystals: mp 54–56 °C (ethyl acetate/*n*-hexane); IR (KBr): 3336, 2979, 1697 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.52 (s, 9H), 1.64 (br s, 1H), 2.36 (q, $J$=7.2 Hz, 2H), 2.66 (t, $J$=7.6 Hz, 2H), 4.06 (br s, 1H), 5.60–5.76 (m, 2H), 6.30 (br s, 1H), 7.04–7.22 (m, 3H), 7.69 (d, $J$=8.0 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 26.5, 27.7, 28.4, 28.9, 32.3, 60.4, 60.7, 60.9, 80.1, 122.4, 124.0, 126.7, 129.5, 131.7, 136.3, 153.8. HRMS (FAB, NBA) calcd for $C_{16}H_{23}NO_3$: 278.1756 ([M+H]$^+$); found: 278.1760. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.19; H, 8.37; N, 4.96.

**4.3.8. 1-*tert*-Butoxycarbonylamino-2-(5-acetoxy-3-pentenyl)benzene (20).** To a stirred solution of **19** (76.4 mg, 0.277 mmol) in pyridine (1.5 ml) was added acetic anhydride (42.4 mg, 0.415 mmol) and the reaction mixture was stirred at room temperature. After 12 h, the reaction mixture was cooled to 0 °C and treated with saturated aqueous $NaHCO_3$ (0.2 ml) for 30 min. The whole was extracted with ethyl acetate. The organic phase was washed with 1 M hydrochloric acid and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=6/1) to give **20** (85 mg, 96%) as a colorless oil; IR: 3356, 2978, 1734 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.52 (s, 9H), 2.06 (s, 3H), 2.36 (q, $J$=7.4 Hz, 2H), 2.66 (t, $J$=7.8 Hz, 2H), 4.52 (d, $J$=6.4 Hz, 2H), 5.58–5.65 (m, 1H), 5.79–5.86 (m, 1H), 6.27 (br s, 1H), 7.03–7.22 (m, 3H), 7.71 (d, $J$=7.6 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.9, 28.3, 30.6, 32.2, 64.9, 0.4, 122.7, 124.3, 125.0, 126.9, 129.2, 131.8, 134.7, 135.6, 153.4, 170.8. HRMS (FAB, NBA) calcd for $C_{18}H_{25}NO_4$: 320.1862 ([M+H]$^+$); found: 320.1872.

**4.3.9. 2-(5-Acetoxy-3-pentenyl)aniline (21).** To a stirred solution of **20** (387.1 mg, 1.22 mmol) at 0 °C was added trifluoroacetic acid (2 ml) and the reaction mixture was stirred at 0 °C. After 2 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic phase was washed with saturated aqueous $NaHCO_3$, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=3/1) to give **21** (192 mg, 100%) as a brown oil; IR: 3456, 3377, 3022, 1734 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.06 (s, 3H), 2.36–2.41 (m, 2H), 2.56–2.60 (m, 2H), 3.59 (br s, 2H), 4.52 (d, $J$=6.6 Hz, 2H), 5.60–5.67 (m, 1H), 5.82–5.89 (m, 1H), 6.67–6.75 (m, 2H), 7.02–7.06 (m, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.9, 30.5, 31.2, 64.9, 115.5, 118.6, 124.5, 125.4, 127.0, 129.3, 135.2, 144.0, 170.7. LRMS (FAB, NBA) *m/z*: 220 ([M+H]$^+$). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.10; H, 7.99; N, 6.26.

**4.3.10. 1-Toluenesulfonylamino-2-(5-acetoxy-3-pentenyl)benzene (22a).** To a stirred solution of **21** (94.1 mg, 0.431 mmol) in pyridine (2 ml) at 0 °C was added toluenesulfonyl chloride (98.7 mg, 0.518 mmol) and the reaction mixture was stirred at room temperature. After 3 h, the reaction mixture was treated with water (0.2 ml) for 30 min, diluted with ethyl acetate, and washed with 1 M hydrochloric acid, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=2/1) to give **22** (159 mg, 99%) as colorless crystals: mp 75–80 °C (ethyl acetate/*n*-hexane); IR (KBr): 3275, 2935, 1736 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.07 (s, 3H), 2.13–2.19 (m, 2H), 2.40 (s, 3H), 2.49–2.53 (m, 2H), 4.47 (d, $J$=6.4 Hz, 2H), 5.43–5.50 (m, 1H), 5.65–5.72 (m, 1H), 6.44 (br s, 1H), 7.10–7.24 (m, 6H), 7.62 (d, $J$=8.0 Hz, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.9, 21.4, 28.3, 30.0, 32.5, 41.4, 64.8, 124.9, 125.2, 126.5, 126.9, 127.2, 129.5, 129.8, 133.9, 134.5, 135.8, 136.7, 143.6, 170.9. HRMS (FAB, NBA) calcd for $C_{20}H_{23}NO_4S$: 374.1426 ([M+H]$^+$); found: 374.1407. Anal. Calcd for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.15; H, 6.38; N, 3.69.

**4.3.11. 1-(*N*-2-Nitrobenzenesulfonyl)amino-2-(5-acetoxy-3-pentenyl)benzene (22b).** To a stirred solution of **21** (36.4 mg, 0.167 mmol) in pyridine (1 ml) at 0 °C was added 2-nitrobenzenesulfonyl chloride (55.5 mg, 0.250 mmol) and the reaction mixture was stirred for 18 h at 23 °C. The reaction mixture was diluted with ethyl acetate and washed with 1 M hydrochloric acid, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=2/1) to give **22b** (70 mg, 99%) as a yellow oil; IR: 3307, 1735, 1542 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.07 (s, 3H), 2.71–2.67 (m, 2H), 4.48 (dd, 2H, $J$=6.3, 0.9 Hz), 5.46–5.53 (m, 1H), 5.69–5.76 (m, 1H), 7.23–7.10 (m, 4H), 7.61 (dt, 1H, $J$=7.7, 1.2 Hz), 7.73 (dt, 1H, $J$=7.7, 1.5 Hz), 7.79 (dd, 1H, $J$=7.8, 1.3 Hz), 7.89 (dd, 1H, $J$=8.0, 1.2 Hz); $^{13}C$ NMR ($CDCl_3$): $\delta$ 13.1, 19.6, 21.3, 23.3, 27.3, 30.7, 39.1, 39.3, 39.5, 39.7, 39.9, 46.5, 47.5, 59.7, 60.9, 124.4, 124.8, 125.8, 127.4, 127.9, 131.1, 131.7, 134.2, 168.4. HRMS (FAB, NBA) calcd for $C_{19}H_{20}N_2O_6S$: 405.1114 ([M+H]$^+$); found: 405.1089.

**4.3.12. 1-(*N*-4-Nitrobenzenesulfonyl)amino-2-(5-acetoxy-3-pentenyl)benzene (22c).** Compound **22c** was prepared from **21** using 4-nitrobenzenesulfonyl chloride as described in Section 4.3.11.

The crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1). Compound **22c**: a yellow oil; IR: 3273, 3105, 2937, 1736, 1531 $cm^{-1}$; $^1H$ NMR

($CDCl_3$): $\delta$ 2.08 (s, 3H), 2.24–2.19 (m, 2H), 2.60–2.56 (m, 2H), 4.48 (d, 2H, $J$=6.1 Hz), 5.45–5.38 (m, 1H), 5.72–5.65 (m, 1H), 6.75 (br s, 1H), 7.00–7.24 (m, 4H), 7.93 (d, 2H, $J$=8.7 Hz), 8.31 (d, 2H, $J$=8.7 Hz); $^{13}$C NMR $CDCl_3$): $\delta$ 13.1, 19.6, 21.3, 23.3, 27.3, 30.7, 46.5, 47.5, 59.7, 60.9, 124.4, 124.9, 125.8, 127.5, 128.0, 131.1, 131.7, 134.2, 168.4. HRMS (FAB, NBA) calcd for $C_{19}H_{20}N_2O_6S$: 405.1114 ([M+H]$^+$); found: 405.1121.

**4.3.13. 2-[4-(Tetrahydropyran-2-yloxy)but-1-ynyl]phenylamine (23).** Compound **23** (5.34 g, 68%) was prepared from **12** (7.0 g, 32 mmol) using *O*-tetrahydropyranylbutyn-4-ol as described in Section 4.3.1. Compound **23**: yellow oil; IR: 3456, 3368, 2944, 1616 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.48–1.92 (m, 7H), 2.77 (t, $J$=13.6 Hz, 2H), 3.44–3.58 (m, 1H), 3.63–3.71 (m, 1H), 3.88–3.98 (m, 2H), 4.16–4.31 (br, 2H), 4.69 (t, $J$=6.8 Hz, 1H), 6.66 (m, 2H), 7.08 (dt, $J$=1.6, 7.4 Hz, 1H), 7.23 (dd, $J$=1.6, 9.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 19.3, 21.0, 25.2, 30.4, 62.1, 65.7, 65.9, 78.0, 92.9, 98.6, 108.2, 113.9, 117.4, 128.8, 131.7, 147.8. HRMS (FAB, NBA) calcd for $C_{15}H_{19}NO_2$: 245.1416 (M$^+$); found: 245.1410.

**4.3.14. 2-[4-(Tetrahydropyran-2-yloxy)butyl]phenylamine (24).** Compound **24** (5.09 g, 94%) was prepared from **23** (5.34 g, 21.8 mmol) as described in Section 4.3.2. Compound **24**: yellow oil; IR: 3447, 3369, 2939, 2864, 1624 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.46–1.88 (m, 10H), 2.52 (t, $J$=8.4 Hz, 2H), 3.33–3.55 (m, 2H), 3.55–3.75 (m, 2H), 3.75–3.94 (m, 2H), 4.57 (t, $J$=4.0 Hz, 1H), 6.66 (d, $J$=8.0 Hz, 1H), 6.71 (t, $J$=8.4 Hz, 1H), 7.02 (t, $J$=8.8 Hz, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 19.7, 25.4, 25.5, 29.4, 30.7, 30.9, 62.4, 67.2, 98.9, 115.5, 118.6, 126.5, 126.9, 129.5, 144.1. HRMS (FAB, NBA) calcd for $C_{15}H_{23}NO_2$: 249.1729 (M$^+$); found: 249.1724.

**4.3.15. 1-*tert*-Butoxycarbonylamino-2-[4-(tetrahydropyran-2-yloxy)butyl]benzene (25).** Compound **25** (6.42 g, 90%) was prepared from **24** (5.09 g, 20.4 mmol) as described in Section 4.3.3. Compound **25**: pale yellow oil; IR: 2940, 2867, 1790, 1730, 1455 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.39 (s, 9H), 1.47–1.85 (m, 12H), 2.57 (m, 2H), 3.32–3.57 (m, 2H), 3.68–3.97 (m, 2H), 4.57 (q, $J$=5.0 Hz, 1H), 6.98–7.35 (m, 4H); $^{13}$C NMR ($CDCl_3$): $\delta$ 18.3, 19.5, 19.6, 25.3, 26.3, 26.4, 27.3, 27.8, 28.3, 29.3, 29.7, 30.6, 30.7, 30.9, 62.2, 62.4, 67.2, 67.3, 67.6, 80.3, 98.9, 124.0, 126.3, 126.6, 127.8, 129.2, 129.3, 135.6, 137.8, 139.2, 151.6, 153.3. HRMS (EI) calcd for $C_{20}H_{31}NO_4$: 349.2253 (M$^+$); found: 349.2262.

**4.3.16. 1-*tert*-Butoxycarbonylamino-2-(4-hydroxybutyl)-benzene (26).** Compound **26** (2.89 g, 59%) was prepared from **25** (6.42 g, 18.4 mmol) as described in Section 4.3.4. Compound **26**: pale yellow oil; IR: 3427, 1695, 1523 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.52 (s, 9H), 1.57–1.73 (m, 4H), 2.61 (t, $J$=7.4 Hz, 2H), 3.71 (q, $J$=7.6 Hz, 2H), 6.99–7.26 (m, 4H); $^{13}$C NMR ($CDCl_3$): $\delta$ 25.7, 26.0, 27.8, 28.3, 30.6, 30.8, 31.6, 32.5, 62.5, 80.3, 82.5, 122.3, 124.1, 126.4, 126.7, 127.9, 128.4, 129.2, 129.3, 135.7, 137.8, 139.2, 151.8, 153.5. HRMS (FAB, NBA) calcd for $C_{15}H_{23}NO_3$: 265.1678 (M$^+$); found: 265.1674.

**4.3.17. 4-(2-*tert*-Butoxycarbonylamino)phenyl-butanal (27).** Compound **27** (1.86 g, 65%) was prepared from **23** (2.89 g, 10.9 mmol) as described in Section 4.3.5. Compound **27**: yellow oil; IR: 3387, 2979, 1637 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.40 (s, 9H), 1.62–2.83 (m, 6H), 7.03–7.25 (m, 4H), 9.77 (s, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 21.9, 22.0, 27.8, 27.9, 28.2, 28.3, 30.1, 30.5, 43.0, 43.4, 82.6, 126.9, 127.1, 128.0, 128.6, 129.3, 129.4, 138.2, 151.7. HRMS (EI) calcd for $C_{15}H_{21}NO_3$: 263.1521 (M$^+$); found: 263.1516.

**4.3.18. Ethyl 6-(2-*tert*-butoxycarbonylamino)phenyl-2-hexenoate (28).** Compound **28** (2.11 g, 89%) was prepared from **27** (1.86 g, 7.1 mmol) as described in Section 4.3.6. Compound **28**: pale yellow oil; IR: 3354, 2979, 2932, 1722 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.23–1.32 (m, 3H), 1.39 (s, 9H), 1.71–1.83 (m, 2H), 2.18–2.32 (m, 2H), 2.49–2.64 (m, 2H), 4.16–4.24 (m, 2H), 5.77–5.91 (m, 1H), 6.22 (s, 1H), 6.88–7.37 (m, 4H), 7.72 (d, $J$=8.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 14.2, 27.8, 27.8, 28.3, 29.0, 30.4, 30.5, 30.8, 31.6, 31.9, 60.1, 80.4, 82.5, 121.6, 121.9, 122.7, 124.3, 126.6, 126.8, 126.9, 127.9, 128.4, 128.5, 129.1, 129.3, 131.9, 135.6, 137.9, 138.6, 148.2, 148.4, 149.3, 151.6, 153.3, 166.5. HRMS (FAB, NBA) calcd for $C_{19}H_{27}NO_4$: 333.1940 (M$^+$); found: 333.1941.

**4.3.19. 1-*tert*-Butoxycarbonylamino-2-(6-hydroxy-4-hexenyl)benzene (29).** Compound **29** (1.84 g, quant.) was prepared from **28** (2.11 g, 6.33 mmol) as described in Section 4.3.7. Compound **29**: pale yellow oil; IR: 3385, 2987, 2931, 2086, 1653 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.52 (s, 9H), 1.71 (quin, $J$=7.6 Hz, 2H), 2.07–2.16 (m, 2H), 2.58 (t, $J$=7.8 Hz, 2H), 4.07–4.18 (m, 2H), 5.65–5.77 (m, 2H), 6.63 (s, 1H), 7.04 (dt, $J$=1.2, 7.2 Hz, 1H), 7.14 (dd, $J$=1.6, 7.6 Hz, 1H), 7.19 (dt, $J$=2.0, 7.6 Hz, 1H), 7.71 (d, $J$=4.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 26.7, 28.3, 29.0, 29.3, 30.2, 30.6, 31.4, 58.5, 63.6, 80.6, 122.5, 124.2, 126.7, 129.3, 129.4, 130.2, 132.1, 132.3, 135.6, 153.5. HRMS (FAB, NBA) calcd for $C_{17}H_{25}NO_3$: 292.1913 ([M+H]$^+$); found: 292.1904.

**4.3.20. 1-*tert*-Butoxycarbonylamino-2-(6-acetoxy-4-hexenyl)benzene (30).** Compound **30** (1.52 g, 87%) was prepared from **29** (1.52 g, 5.23 mmol) as described in Section 4.3.8. Compound **30**: pale yellow oil; IR: 3387, 2082, 1645 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.52 (s, 9H), 1.65–1.75 (m, 2H), 2.05–2.23 (m, 5H), 2.56 (t, $J$=8.0 Hz, 2H), 4.53 (d, $J$=7.2 Hz, 2H), 5.56–5.67 (m, 1H), 5.75–5.84 (m, 1H) 6.27 (s, 1H) 7.04 (t, $J$=7.2 Hz, 1H), 7.13 (dd, $J$=1.6, 8.0 Hz, 1H), 7.19 (dt, $J$=1.6, 7.2 Hz, 1H), 7.73 (d, $J$=7.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 21.0, 27.1, 28.3, 28.7, 29.2, 30.5, 31.7, 60.3, 65.1, 80.4, 122.4, 124.1, 124.3, 126.8, 129.3, 134.4, 135.6, 153.3, 170.8. HRMS (FAB, NBA) calcd for $C_{19}H_{28}NO_4$: 334.2018 ([M+H]$^+$); found: 334.2012.

**4.3.21. 2-(6-Acetoxy-4-hexenyl)aniline (31).** Compound **31** (1.52 g, 87%) was prepared from **30** (1.52 g, 5.23 mmol) as described in Section 4.3.9. Compound **31**: yellow oil; IR: 3387, 2933, 2859, 2068, 1731, 1629 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 1.73 (m, 2H), 2.05–2.24 (m, 5H), 2.49 (t, $J$=8.0 Hz, 2H), 4.52 (d, $J$=6.4 Hz, 2H), 5.55–5.66 (m, 1H), 5.75–5.88 (m, 1H), 6.67 (dd, $J$=0.8, 8.0 Hz, 1H), 6.73 (t, $J$=6.8 Hz, 1H), 6.99–7.06 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 20.8, 27.6, 30.3, 31.8, 53.3, 65.0, 115.4, 118.5, 124.3, 126.0, 126.8, 129.3, 135.6, 143.9, 170.6. HRMS (FAB, NBA) calcd for $C_{14}H_{19}NO_2$: 233.1416 (M$^+$); found: 233.1418.

**4.3.22. 1-Toluenesulfonylamino-2-(6-acetoxy-4-hexenyl)-benzene (32).** Compound **31** (117 mg, 47%) was prepared from **28** (115 mg, 0.66 mmol) as described in Section 4.3.10. Compound **32**: pale yellow oil; IR: 3447, 2080, 1731, 1637 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.47 (quin, $J$=8.0 Hz, 2H), 1.99 (q, $J$=7.2 Hz, 2H), 2.08 (s, 3H), 2.34 (t, $J$=7.6 Hz, 2H), 2.39 (s, 3H), 4.53 (dd, $J$=1.2, 6.4 Hz, 2H), 5.50–5.61 (m, 1H), 5.64–6.76 (m, 1H), 6.35 (s, 1H), 7.07–7.31 (m, 6H), 7.61 (d, $J$=8.0 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 21.0, 21.5, 28.9, 29.9, 31.6, 65.1, 124.6, 124.6, 124.7, 126.3, 126.9, 127.2, 128.0, 129.4, 129.5, 129.7, 129.7, 133.9, 135.3, 135.5, 136.7, 143.7, 170.9. HRMS (FAB, NBA) calcd for $C_{21}H_{26}NO_4S$: 388.1583 ($[M+H]^+$); found: 388.1590.

**4.3.23. 1-Toluenesulfonylamino-2-(4-chloro-2-butenyl)-benzene (34).** To a stirred solution of *N*-(2-iodophenyl) toluenesulfonamide (**33**, 1.12 g, 3 mmol) in THF (15 ml) at −78 °C under an argon atmosphere was added dropwise a 1.6 M solution of *n*-butyl lithium in hexane (4 ml, 6.4 mmol) and the reaction mixture was stirred at same temperature for 1 h. Then 1,4-dichloro-2-butene (0.75 g, 6 mmol) was added at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h and quenched with saturated aqueous $NaHCO_3$. The whole was extracted with ethyl acetate. The organic layer was washed with 10% aqueous citric acid, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (chloroform) to give **34** (473 mg, 47%) as a yellow oil; IR: 3065, 2923 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.43 (s, 3H), 3.91 (d, $J$=6.0 Hz, 2H), 4.18 (d, $J$=6.4 Hz, 2H), 5.61–5.78 (m, 2H), 7.00–7.06 (m, 2H), 7.22–7.34 (m, 4H), 7.48 (d, $J$=8.4 Hz, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 21.5, 43.8, 52.1, 127.7, 127.9, 128.8, 129.0, 129.4, 130.0, 135.4, 139.1, 143.5. HRMS (FAB, NBA) calcd for $C_{17}H_{24}ClNO_2S$: 336.0825 ($[M+H]^+$); found: 336.0816.

**4.3.24. 1-Toluenesulfonylamino-2-(4-acetoxy-2-butenyl)-benzene (35).** To a stirred solution of **34** (473 mg, 1.41 mmol) in DMSO (7 ml) at room temperature was added potassium acetate (166 mg, 1.69 mmol) and the reaction mixture was stirred for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate=4/1) to give **35** (424 mg, 83%) as yellow solids: mp 94–95 °C; IR (KBr): 3461, 3046, 2917 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.00 (s, 3H), 2.43 (s, 3H), 4.18 (dd, $J$=0.8, 6.0 Hz, 2H), 4.41 (dd, $J$=1.2, 6.0 Hz, 2H), 5.56–5.74 (m, 2H), 7.00–7.05 (m, 2H), 7.22–7.32 (m, 2H), 7.48 (d, $J$=8.4 Hz, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.8, 21.6, 52.3, 63.8, 127.7, 127.9, 128.2, 128.3, 128.9, 129.1, 129.4, 129.5, 135.5, 139.1, 143.5, 170.5. HRMS (FAB, NBA) calcd for $C_{19}H_{21}NO_4S$: 360.1270 ($[M+H]^+$); found: 360.1268. Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.35; H, 5.80; N, 3.90.

### 4.4. Synthesis of chiral tetrahydroquinolines and relatives

**4.4.1. (*rac*)-*N*-Tosyl-2-allyl-1,2,3,4-tetrahydroquinoline ((*rac*)-36a).** A mixture of $Pd(dba)_2$ (2.3 mg, 0.00403 mmol) and triphenylphosphine (2.1 mg, 0.00806 mmol) in THF (1 ml) was stirred for 30 min at −15 °C under an argon atmosphere. The sulfonamide **22a** (29.7 mg, 0.0806 mmol) in THF (2 ml) was added to the solution at −15 °C. The clear solution was degassed by three freeze–thaw cycles and stirred for 30 min at −15 °C. The reaction mixture was heated to reflux for 3 h, and allowed to cool to room temperature, quenched with saturated aqueous $NH_4Cl$, extracted with ethyl acetate, and washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=10/1) to give **36a** (18.9 mg, 76%) as a yellow oil; IR: 3066, 3021, 2927, 1652 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.55–1.63 (m, 1H), 1.77–1.85 (m, 1H), 1.97–2.04 (m, 1H), 2.38 (s, 3H), 2.43–2.50 (m, 1H), 4.89–4.92 (m, 1H), 5.11 (dd, $J$=10.5, 1.2 Hz, 1H), 5.28 (dd, $J$=17.1, 1.2 Hz, 1H), 5.74–5.82 (m, 1H), 6.96–7.23 (m, 5H), 7.44 (d, $J$=8.3 Hz, 2H), 7.78 (d, $J$=8.3 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 21.5, 24.3, 27.4, 57.2, 77.4, 116.0, 125.2, 126.3, 126.7, 127.1, 128.3, 129.0, 129.5, 132.1, 135.5, 136.5, 137.0, 143.4. HRMS (FAB, NBA) calcd for $C_{18}H_{19}NO_2S$: 313.1137 (M+); found: 313.1132.

**4.4.2. *N*-Tosyl-2-allyl-1,2,3,4-tetrahydroquinoline (36a) using (*S*)-9-PBN.** To a stirred solution of $Pd(dba)_2$ (0.9 mg, 0.00149 mmol) and lithium acetate (4.9 mg, 0.0744 mmol) in THF (1 ml) was added 0.1 M (*S*)-9-PBN (0.0298 ml, 0.00298 mmol) in heptane at −15 °C under an argon atmosphere. The mixture was degassed by three freeze–thaw cycles and stirred for 30 min at −15 °C. The sulfonamide **22a** (27.7 mg, 0.0744 mmol) in THF (2 ml) and *N*,*O*-bis(trimethylsilyl)acetamide (0.0552 ml, 0.223 mmol) were added to the solution at −15 °C. The clear solution was stirred for 30 min at −15 °C, warmed to room temperature, and stirred for 20 h. The reaction mixture was quenched with saturated aqueous $NH_4Cl$, extracted with ethyl acetate, and washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=10/1–2/1) to give **36a** (15.9 mg, 68%, 72% ee) as a yellow oil. The HPLC analysis of **36a** was carried out using the Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH=99/1, flow rate: 0.5 ml/min, UV 254 nm). (*S*)-Isomer: 27.8 min and (*R*)-isomer: 30.3 min (major).

**4.4.3. *N*-(2-Nitrobenzenesulfonyl)-2-allyl-1,2,3,4-tetrahydroquinoline (36b).** The reaction of **22b** was carried out as described in Section 4.4.2. Yield: 51% and 56% ee. Compound **36b**: yellow crystals: mp 92–94 °C; IR (KBr): 3088, 2940, 1548, 1375 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.66–1.74 (m, 1H), 2.23–2.15 (m, 1H), 2.33–2.26 (m, 1H), 2.52–2.58 (m, 1H), 5.05–5.14 (m, 2H), 5.27–5.32 (m, 1H), 5.74–5.82 (m, 1H), 7.02–7.24 (m, 3H), 7.45–7.71 (m, 5H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 24.7, 28.6, 57.7, 78.7, 116.3, 123.8, 125.8, 125.9, 126.9, 128.5, 31.0, 131.1, 132.2, 133.1, 133.6, 134.8, 136.8. HRMS (FAB, NBA) calcd for $C_{17}H_{16}N_2O_4S$: 344.0831 ($M^+$); found: 344.0835. Anal. Calcd for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13. Found: C, 59.07; H, 4.67; N, 8.27. The HPLC analysis of **36b** was carried out using the Daicel Chiralpak AD column (*n*-hexane/*i*-PrOH=2/1 (0.1% $Et_2NH$), flow rate: 0.5 ml/min, UV 254). (*S*)-Isomer: 11.2 min and (*R*)-isomer: 12.5 min.

**4.4.4. *N*-(4-Nitrobenzenesulfonyl)-2-allyl-1,2,3,4-tetrahydroquinoline (36c).** The reaction of **22c** was carried out as

described in Section 4.4.2. Yield: 86% and 65% ee. **36c**: yellow crystals: mp 65–72 °C; IR (KBr): 3098, 2954, 1606, 1528 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.68–1.57 (m, 1H), 1.97–1.81 (m, 2H), 2.53–2.46 (m, 1H), 4.93–4.91 (m, 1H), 5.16 (d, $J$=13.7 Hz, 1H), 5.30 (d, $J$=16.1 Hz, 1H), 5.84–5.76 (m, 1H), 6.99–7.28 (m, 3H), 7.77 (d, $J$=8.2 Hz, 1H), 7.72 (d, $J$=9.0 Hz, 2H), 8.23 (d, $J$=9.0 Hz, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 24.5, 28.0, 30.0, 116.5, 124.1, 126.1, 126.3, 127.1, 28.3, 128.6, 132.4, 134.7, 136.4, 145.0, 150.0. HRMS (FDA, NBA) calcd for $C_{17}H_{16}N_2O_4S$: 344.0831 ($M^+$); found: 344.0825. Anal. Calcd for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13. Found: C, 59.31; H, 4.79; N, 7.90. The HPLC analysis of **36c** was carried out using the Daicel Chiralcel OD-H (*n*-hexane/*i*-PrOH=9/1, flow rate: 0.5 ml/min, UV 254 nm). (*S*)-Isomer: 26.0 min and (*R*)-isomer: 38.8 min.

**4.4.5. *N*-Tosyl-2-allyl-1,2,3,4-tetrahydroquinoline (36a) using (*R*)-9-NapBN.** To a stirred solution of $[(allyl)PdCl]_2$ (1.3 mg, 0.0035 mmol) and lithium acetate (9.2 mg, 0.14 mmol) in THF (0.5 ml) at 23 °C under an argon atmosphere was added 0.2 M (*R*)-9-NapBN (0.070 ml, 0.014 mmol) in toluene. *N*,*O*-Bis(trimethylsilyl)acetamide (85 mg, 0.42 mmol) and a 1 M solution of the sulfonamide **22a** in toluene (140 µl, 0.14 mmol) were added to the solution at 23 °C. The reaction mixture was stirred for 18 h. The reaction mixture was quenched with saturated aqueous $NH_4Cl$, extracted with ethyl acetate, and washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=7/1) give **36a** (27 mg, 61%, 94% ee) as a yellow oil: $[\alpha]_D^{20}$ −91.2 (*c* 0.62, $CHCl_3$).

**4.4.6. 1-(Toluene-4-sulfonyl)-2-vinyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine (37).** The reaction of **32** was carried out as described in Section 4.4.5. Yield: 29% and 55% ee. Compound **37**: pale yellow oil; IR: 3411, 2940 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.43–1.75 (m, 3H), 1.89–2.03 (m, 1H), 2.40–2.47 (m, 5H), 5.02 (d, $J$=10.4 Hz, 2H), 5.17 (d, $J$=18 Hz, 2H), 5.49–5.64 (m, 1H), 7.06–7.30 (m, 6H), 7.62 (d, $J$=8.0 Hz, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.8, 21.4, 32.5, 58.9, 116.3, 125.3, 126.6, 127.5, 128.3, 128.9, 129.3, 129.7, 130.4, 131.3, 136.6, 138.8, 141.7, 143.0, 143.2. HRMS (FAB, NBA) calcd for $C_{19}H_{21}NO_2S$: 327.1293 ($M^+$); found: 327.1294. The HPLC analysis of **37** was carried out using the Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH=99/1, flow rate: 0.5 ml/min, UV 254 nm). $t_R$: 24.825 and 27.375 min (major).

**4.4.7. 1-(Toluene-4-sulfonyl)-2-vinyl-2,3-dihydro-1*H*-indole (38).** The reaction of **35** was carried out by using (*S*)-NapBN as described in Section 4.4.5. Yield: 1.2% and 61.5% ee. Compound **38**: yellow oil; IR: 3065, 2919, 1596, 1492, 1349, 1165 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.37 (s, 3H), 3.54–3.61 (m, 1H), 3.74 (q, $J$=9.6 Hz, 1H), 4.17 (t, 1H) 5.01–5.11 (m, 1H), 5.47–5.59 (m, 1H), 7.00 (d, $J$=4.8 Hz, 2H), 7.12–7.25 (m, 3H), 7.62–7.70 (m, 3H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 21.5, 44.8, 55.6, 115.1, 117.1, 123.9, 125.1, 127.3, 128.3, 129.6, 133.8, 133.9, 137.3, 141.7, 144.1. HRMS (EI) calcd for $C_{17}H_{17}NO_2S$: 299.0980 ($M^+$); found: 299.0982. The HPLC analysis of **38** was carried out using the Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH=99/1, flow rate: 0.5 ml/min, UV 254 nm). $t_R$: 25.508 (major) and 28.117 min.

## 4.5. Determination of the absolute configuration for 36a

**4.5.1. 2-[1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinolin-2-yl]ethanol.** To a stirred solution of (−)-**36a** ($[\alpha]_D^{26}$ −7.88 (*c* 1.21, $CHCl_3$), 24% ee, 104 mg, 0.33 mmol) in THF (2 ml) was added borane dimethylsulfide complex (0.032 ml, 0.33 mmol) and the reaction mixture was stirred at 23 °C for 2 h. The reaction mixture was allowed to cool to 0 °C, diluted with water, and treated with 3 M NaOH (1 ml) and 30% hydrogen peroxide (1 ml). After stirring the mixture for 2 h, the mixture was extracted with ethyl acetate and the extract was washed with water and brine. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate=1/2) to give the alcohol (53 mg, 48%) as a colorless oil: $[\alpha]_D^{20}$ −112 (*c* 1.50, $CHCl_3$); IR: 3532, 3406, 2928, 1598, 1487 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.31–1.38 (m, 1H), 1.47–1.53 (m, 1H), 1.61–1.70 (m, 1H), 1.82–1.89 (m, 1H), 2.38 (s, 3H), 2.41–2.43 (m, 1H), 272–2.98 (m, 1H), 3.06–3.68 (m, 1H), 3.92–3.99 (m, 1H), 4.45–4.51 (m, 1H), 6.99 (d, $J$=8.3 Hz, 1H), 7.14 (dt, $J$=1.2, 8.3 Hz, 1H), 7.18 (d, $J$=8.3 Hz, 2H), 7.22–7.73 (m, 2H), 7.39 (d, $J$=6.3 Hz, 2H), 7.77 (dd, $J$=1.0, 8.3 Hz, 1H).

**4.5.2. [1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinolin-2-yl]acetic acid methyl ester.** To a stirred solution of the above alcohol (22 mg, 0.067 mmol) in acetone (1 ml) was added Jones' reagent (4 equiv) at −15 °C and the reaction mixture was stirred at −15 °C for 30 min. The reaction mixture was quenched with 2-propanol and extracted with $CHCl_3$. The extract was washed with water and brine. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give the carboxylic acid, which was used for the next esterification without any purification. The residue was dissolved in DMF (0.5 ml) and treated with $KHCO_3$ (13 mg, 0.13 mmol) and iodomethane (0.006 ml) and the reaction mixture was stirred at 23 °C for 18 h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate=4/1) to give the methyl ester (15 mg, 62% in two steps) as a colorless oil: $[\alpha]_D^{13}$ −13.2 (*c* 0.755, $CHCl_3$); $^1H$ NMR ($CDCl_3$): $\delta$ 1.37–1.42 (m, 1H), 1.64–1.75 (m, 1H), 1.95–2.25 (m, 1H), 2.30–2.35 (m, 1H), 2.37 (s, 3H), 2.45–2.52 (m, 1H), 2.83–2.87 (m, 1H), 3.67 (s, 3H), 4.60–4.65 (m, 1H), 6.96 (d, $J$=7.6 Hz, 1H), 7.12–7.15 (m, 1H), 7.16 (d, $J$=8.3 Hz, 2H), 7.22–7.24 (m, 1H), 7.36 (d, $J$=8.3 Hz, 2H), 7.70 (d, $J$=8.3 Hz, 1H).

**4.5.3. (1,2,3,4-Tetrahydroquinolin-2-yl)acetic acid methyl ester (41).** To a stirred solution of the above methyl ester (15.4 mg, 0.043 mmol) in methanol (1 ml) at 23 °C was added magnesium turning (42 mg, 1.7 mmol) and the reaction mixture was stirred at 23 °C for 5 h. The reaction mixture was diluted with ethyl acetate and extracted with chloroform. The extract was washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate=2/1) to give **41** (6.5 mg, 74%) as a colorless oil: $[\alpha]_D^{25}$ −22.6 (*c* 0.415, $CHCl_3$); IR: 3394, 2924, 2849, 1732, 1607, 1488 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.67–1.76 (m, 1H), 1.92–1.99 (m, 1H), 2.52 (d, $J$=6.8 Hz, 2H), 2.69–2.75 (m, 1H), 2.80–2.88 (m,

1H), 3.72 (s, 3H), 4.50 (br s, 1H), 6.50 (d, $J$=8.1 Hz, 1H), 6.62 (t, $J$=7.3 Hz, 1H), 6.94–6.99 (m, 2H). The absolute configuration of the above (−)-**41** was determined to be *R* by comparison to the known (*S*)-**41**[15] ($[\alpha]_D^{20}$ +104.7 (*c* 1, $CHCl_3$)). Accordingly, (−)-**36a** was confirmed to bear (*R*)-configuration.

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