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An Efficient Synthesis of 2- and 2,6-Substituted Piperidines Using Pd^{II}-Catalyzed 1,3-Chirality Transfer Reaction

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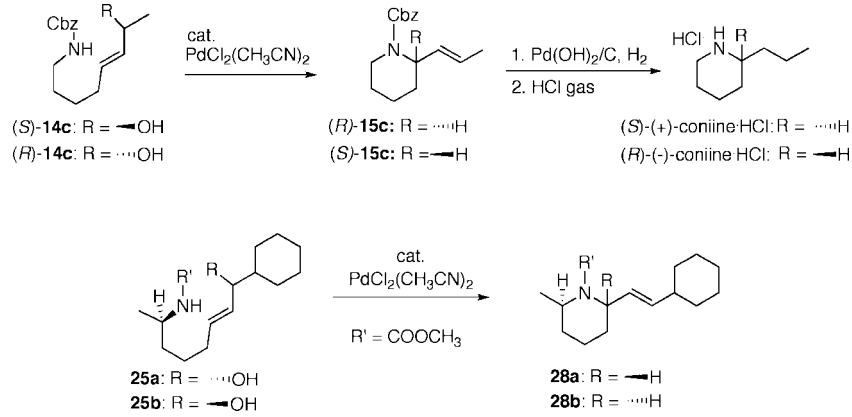

An efficient and general method for 2- and 2,6-substituted piperidine syntheses using Pd^{II}-catalyzed 1,3-chirality transfer reaction has been developed. The various *N*-protected ζ-amino allylic alcohols cyclize in the presence of $PdCl_2(CH_3CN)_2$ to give substituted piperidines with high stereoselectivities. The syntheses of (*S*)-(+)- and (*R*)-(−)-coniine were achieved in 3 steps from the optically pure allylic alcohols (*S*)-**14c** and (*R*)-**14c**, respectively. Although the rates of reactions were significantly accelerated in CH_2Cl_2, THF gave the highest stereoselectivity. $PdCl_2(CH_3CN)_2$ was found to be the best catalyst for this transformation. A plausible reaction pathway involving the formation of the Pd π-complex directed by the chiral secondary allylic alcohol followed by *syn*-azapalladation, and subsequent *syn*-elimination of PdCl(OH) is proposed.

1. Introduction

Piperidine alkaloids and their analogues comprise a large family of pharmacologically important compounds.[1] Particularly, piperidines bearing the alkyl substituent group at the 2- and/or 2,6-position on the ring can be found as a core structure in many naturally occurring alkaloids that possess a large spectrum of interesting biological activities. They serve as attractive scaffolding for medicinal agents to bind to biological targets. Among them, (*S*)-(+)- and (*R*)-(−)-coniine (**1a**) and (**1b**),[2] (−)-lobeline (**2**),[3] alkaloid 241D (**3**),[4] and (−)-cassine (**4**)[5] are some of the representative examples having simple substituted piperidine rings, which are known to be inhibitors of the neuromuscular, ganglionic, central neuronal nicotinic acetylcholine receptors and HIV-protease. Because of the known dependence between the biological activity of a molecule and its absolute configuration, stereoselective synthesis of various substituted piperidines have evoked immense interest from a both synthetic and

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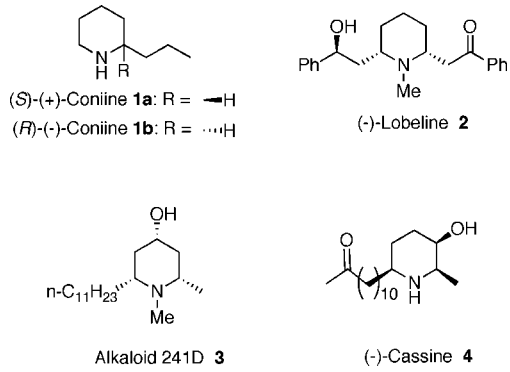


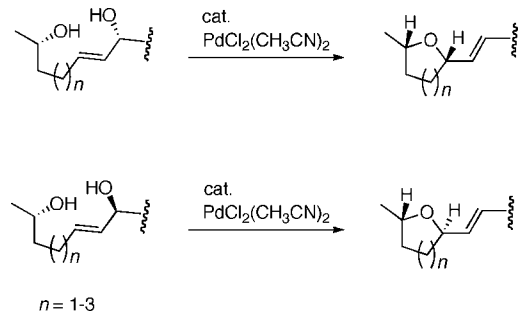
FIGURE 1. Structures of some naturally occurring piperidine alkaloids.

biological standpoint. Although there are many synthetic methods of piperidines reported in literature,[1,6−10] including Mannich-type reaction,[6] Michael addition,[7] ring-closing metathesis,[8] iminium ion cyclization,[9] aza Diels−Alder reaction[10] etc. a more efficient, convenient, and highly stereoselective synthetic method is desired.

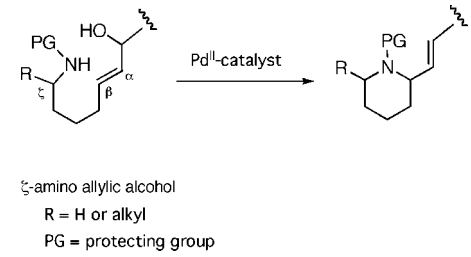
Pd^{II}-catalyzed C−N bond formation reactions have been documented well in literature,[11] and they proceed under milder conditions with high functional group tolerance and high stereoselectivities.[12] Both *syn*- and *anti*-azapalladation were discussed with their stereochemistry; however, the exact mechanistic course of this reaction remains unknown. Several reports have demonstrated the *anti*-azapalladation process,[13] whereas some recent studies show that the nitrogen nucleophiles bearing electron-withdrawing groups such as sulfonamides and carbamates undergo oxidative coupling with alkenes through *syn*-azapalladation.[14] Most recently, Stahl and co-workers illustrated that, although *syn*-azapalladation is more favored in such type of a reaction, *anti*-azapalladation could occur as well.[15] This depends upon the substrate, the catalyst, and reaction conditions.

Recently we have reported the Pd^{II}-catalyzed stereospecific synthesis of 5-, 6-, and 7-membered oxaheterocycles by 1,3-chirality transfer reaction using chiral allylic alcohols (Scheme 1).[16] In this reaction, the stereochemistry at the newly formed chiral center is produced by *syn*-oxypalladation and *syn*-elimination processes. The advantages of this method are; (i) No oxidant such as $CuCl_2$ is required, because the Pd^{II}-catalyst is regenerated during the reaction. This is how it differs from other oxidative cyclizations to an alkene[17] by Wacker-type reactions. (ii) The reaction proceeds smoothly at 0 °C with excellent selectivities. Since only a few examples of piperidine synthesis using Pd^{II}-catalyzed cyclization of ζ-amino allylic alcohols were reported in literature,[18] there is not much known about the reaction mechanism. Because of our continuous interest in this area, we decided to apply this methodology to the synthesis of chiral 2- and 2,6-disubstituted piperidines (Scheme 2). To establish this as a general method, we synthesized various *N*-protected ζ-amino allylic alcohols and examined the cyclization reaction using different Pd^{II}-catalysts and solvents. Herein, we report the full account of our study in the synthesis of chiral piperidines and discuss the mechanistic details of this reaction.

SCHEME 1. Pd^{II}-catalyzed Cyclizations of Oxygen Nucleophile to Chiral Allylic Alcohols



SCHEME 2. Pd^{II}-catalyzed Cyclizations of Nitrogen Nucleophile to Chiral Allylic Alcohols



2. Results and Discussion

2.1. Synthesis of Various *N*-Protected ζ-Amino Allylic Alcohols. As is mentioned above, the protecting group on amino functionality is expected to be important in the Pd-catalyzed cyclization for piperidine synthesis. We planned the synthesis of precursors **14a−f** possessing six protecting groups on the nitrogen atom via their common intermediate **12**. The synthesis is shown in Schemes 3 and 4.

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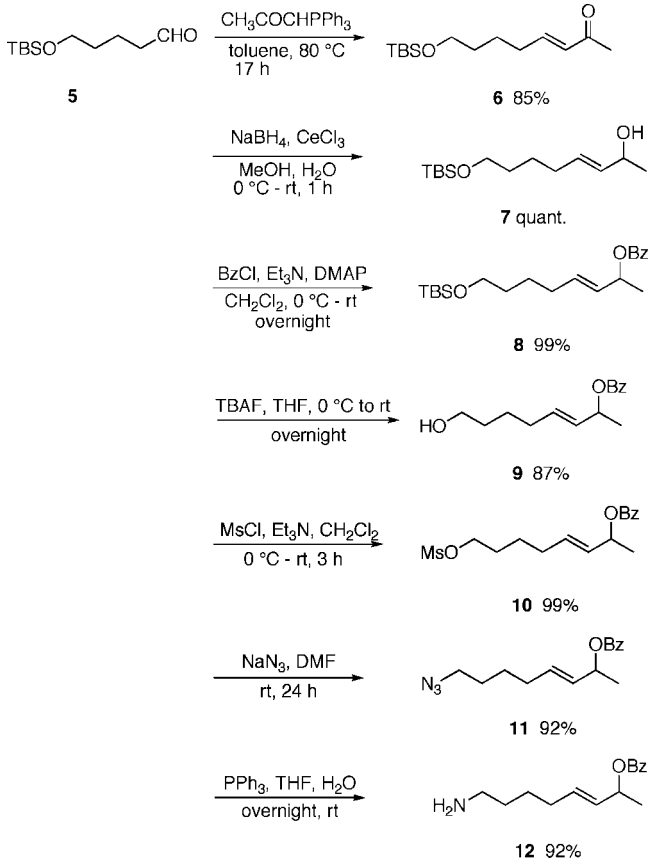
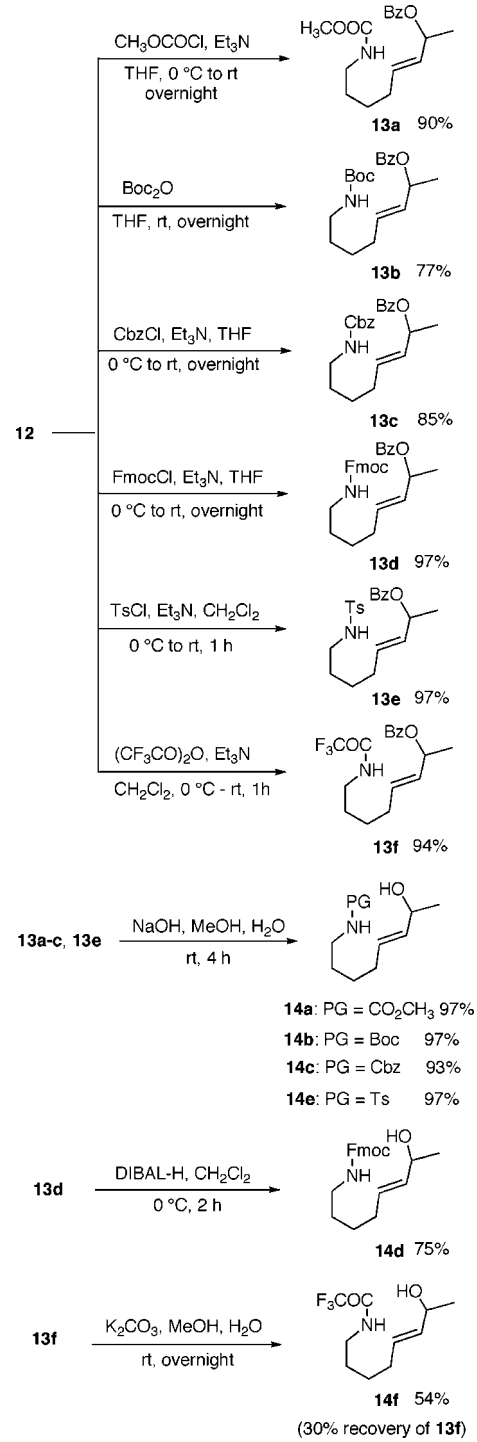
SCHEME 3. Preparation of 12



Compound **12** was synthesized from δ-silyloxypentanal **5**[19] in seven steps. Wittig olefination of **5** gave the α,β-unsaturated ketone **6**[20] in 85% yield. Reduction of ketone by sodium borohydride in the presence of $CeCl_3$ and protection of the resultant allylic alcohol **7** with benzoyl chloride gave benzoate **8** in quantitative yield in two steps. Desilylation of **8** with TBAF followed by mesylation with methanesulfonyl chloride gave **10** in 87 and 99% yields, respectively. Treatment of **10** with sodium azide in DMF afforded azide **11** in 92% yield, which on subsequent reduction with triphenylphosphine in the presence of H_2O gave **12** in 92% yield.

The nitrogen atom of **12** was then protected with methyl carbonate, Boc, Cbz, Fmoc, Ts, and trifluoroacetyl groups. Using the standard procedures,[21] **13a**−**f** were obtained in good yields as shown in Scheme 4. Basic hydrolysis of benzoates **13a**−**c** and **13e** gave cyclization precursors **14a**−**c** and **14e** in 93−97% yields. In the case of **13d**, deprotection of Fmoc group took place faster than hydrolysis of the benzoate. Therefore, deprotection of benzoate by DIBAL-H was carried out to provide **14d** in 75% yield. Methanolysis of **13f** afforded **14f** in 54% yield along with 30% recovery of starting material. Elongation of reaction time for this reaction resulted in hydrolysis of trifluoroacetamide.

SCHEME 4. Preparation of Precursors 14a−f for Cyclizations



2.1.1. Cyclization of 14a−f Using Pd^{II}-Catalysts in Different Solvents. With precursors **14a**−**f** in hand, the cyclization reaction was investigated. First, we chose the four most efficient Pd^{II}-catalysts—$PdCl_2(CH_3CN)_2$, $PdCl_2(PhCN)_2$, $Pd(OAc)_2$, and $Pd(OCOCF_3)_2$—from the exhaustive screening in the study of oxy-palladation for tetrahydropyran synthesis. Then, we selected some common solvents such as CH_2Cl_2, THF, toluene, and acetonitrile. Primary screenings were performed in a multiple reaction kit using dry solvents under an argon atmosphere. Among the four catalysts, $PdCl_2(CH_3CN)_2$ and $PdCl_2(PhCN)_2$ were found to be the best catalysts to give

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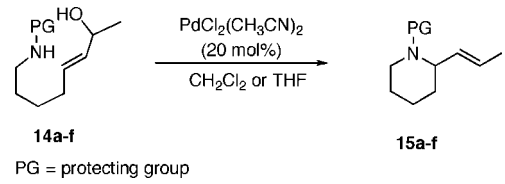
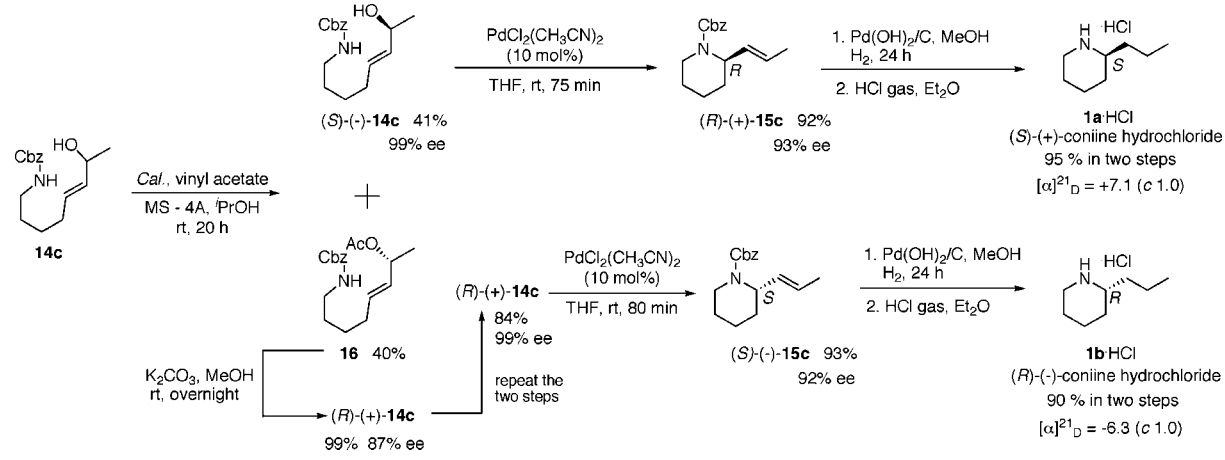
TABLE 1. Pd^{II}-Catalysed Cyclization of Substrates 14a−f



		CH_2Cl_2			THF			
entry	substrate (PG)	time (min)	temp (°C)	yield (%)	time (min)	temp (°C)	yield (%)	product
1	**14a** ($COOCH_3$)	15	0	89	30	rt	82	**15a**, see ref 22
2	**14b** (Boc)	5	0	93	60	0	91	**15b**, see ref 23
3	**14c** (Cbz)	10	0	95	45	rt	95[a]	**15c**
4	**14d** (Fmoc)	30	0	85	90	rt	92	**15d**
5	**14e** (Ts)	5	0	83	30	rt	91	**15e**
6	**14f** ($COCF_3$)	30	rt	-[b,c]	120	rt	-[b,c]	**15f**

[a] The results with the use of 1, 5, and 10 mol % of catalyst, see coniine synthesis in the main text. [b] No cyclization was observed. [c] Complex mixtures were obtained at 40 °C.

SCHEME 5. Pd^{II}-Catalyzed Synthesis of (*S*)-(+)- and (*R*)-(−)-Coniine



cyclized product **15** in CH_2Cl_2 or THF in excellent yields. The reaction with $PdCl_2(CH_3CN)_2$ was quite slower in toluene at 0 °C because of the reduced solubility of the catalyst. Note that $Pd(OCOCF_3)_2$ was also effective in THF to complete the reactions, generally in 20 min at room temperature for **14b** and in 5 min at room temperature for **14e**, whereas reactions with $Pd(OAc)_2$ required heating at 40 °C for a longer period of time. Among the solvents used, CH_2Cl_2 was found to be the best in reaction at 0 °C. THF and toluene are the next choice of solvents in which the transformation is clean but slower than that in CH_2Cl_2 at room temperature. Reactions in CH_3CN were even slower, and in most cases, a majority of the starting materials were recovered. The coordination of CH_3CN on the catalyst might decrease the reaction rate, which can retard the formation of π-complex or the attack of nucleophile in the azapalladation reaction. This could be the reason why the rate of reaction in THF was also slower and far slower in CH_3CN.

Table 1 lists selected results. The reactions in THF required higher temperature and longer period of time than those in CH_2Cl_2. Nucleophilicity of nitrogen and stereic factor are important for the rate of reactions. The results indicate *N*-carbamoyl and *N*-sulfonyl groups can be used for cyclization (entries 1−5), although the *N*-trifluoroacetyl group is unsuitable for this purpose in both solvents (entry 6).

2.1.2. Enantioselective Synthesis of (*S*)-(+)- and (*R*)-(−)-Coniine. In view of these findings, we now focus on the stereochemical outcome of this reaction and the related reaction mechanism. For this purpose, we choose the synthesis of (*S*)-(+)- and (*R*)-(−)-coniine[2] using (*S*)-(−)-**14c** and (*R*)-(+)-**14c** as the chiral starting materials. Although Hirai et al. reported the synthesis of (*R*)-coniine from (*S*)-(−)-**14c** using $PdCl_2(CH_3CN)_2$ catalyst,[24] the structure in their report indicated the (*R*)-configuration but the (+)-sign was shown. As per our prediction, the stereospecific attack of the nucleophile based on the stereochemistry of oxaheterocycles[16] should take place from syn with respect to the chiral alcohol to afford (*S*)-(+)-coniine from (*S*)-(−)-**14c**, contrary to the results that appeared in their report. Therefore, re-examinations were carried out. Our results are depicted in Scheme 5.

Lipase (Candida Antarctica lipase; Novozyme 435) catalyzed kinetic acetylation of racemic **14c** gave (*R*)-acetate **16** in 40% yield along with an (*S*)-**14c** in 41% yield with >99% ee. Although methanolysis of **16** gave (*R*)-**14c** in 99% yield with 87% ee, the enzymatic acetylation and methanolysis of the resulted acetate were repeated to raise its ee value up to 99%. Treatment of enantiomerically pure (*S*)-(−)-**14c** with 10 mol % of $PdCl_2(CH_3CN)_2$ in THF at room temperature for 75 min afforded (*R*)-(+)-**15c**[25] in 92% yield with 93% ee. This result was reproducible when the reaction of (*R*)-(+)-**14c** in THF at room temperature for 80 min gave (*S*)-(−)-**15c** in 93% yield with 92% ee. When this reaction was carried out in CH_2Cl_2 at

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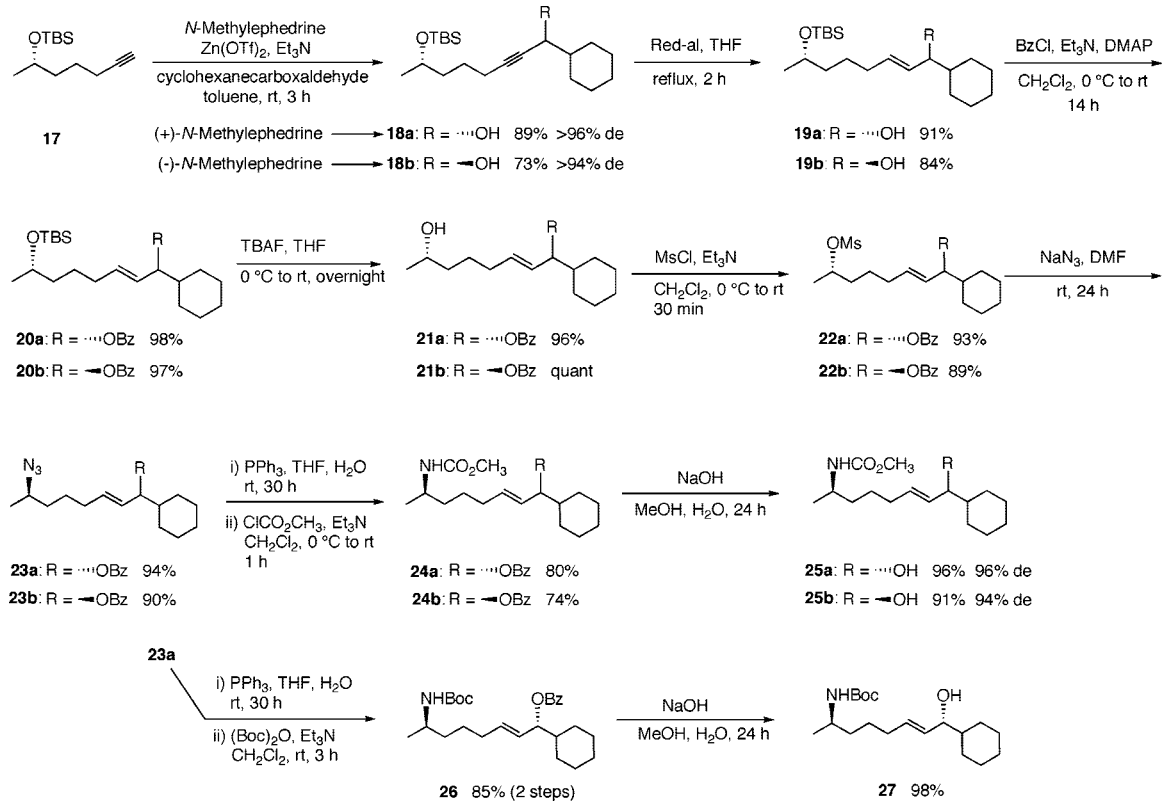
SCHEME 6. Preparation of 25a, 25b, and 27



0 °C for 30 min, (*S*)-(−)-**15c** was obtained with 91% ee. On the other hand, catalysts can be reducible to 5 mol %. The reaction took for 2 h in THF at rt leading to the cyclized product in 89% yield. However, when 1 mol % of $PdCl_2(CH_3CN)_2$ was used, the reaction stopped after 3.5 h and the cyclized product was obtained in 58% yield along with the recovery of starting material in 39% yield. Having successfully effected the key chirality transfer step, we then deprotected the Cbz group and reduced the double bond of (*R*)-(+)-**15c** all in one step using Pearlman's catalyst under a H_2 atmosphere. This gave (*S*)-(+)-coniine **1a**, which was then treated with HCl gas in ether to give (*S*)-(+)-coniine hydrochloride in two steps with 95% yield. (*R*)-(−)-Coniine **1b** hydrochloride was obtained in 90% yield from (*S*)-(−)-**15c** using the same two steps. The absolute configurations of **1a** and **1b** indicated in Scheme 5 were determined by specific degrees, which were consistent with the data of (+)- and (−)-coniine reported in literature.[2] Therefore, the stereochemical outcome in the piperidine synthesis is similar to that in the tetrahydropyran synthesis. Thus, in both the reactions, the formation of the product was directed by the chiral secondary allylic hydroxy group. However, it should be noted that the diastereoselectivity was nearly 92−3% de (96:4 to 97:3 ratio), which meant an occurrence of 3−4% of antiazapalladation. In comparison, the synthesis of the tetrahydropyran ring was exclusively stereospecific by syn-oxypalladation.[16]

2.2. Stereocontrolled Synthesis of 2,6-Disubstituted Piperidine.

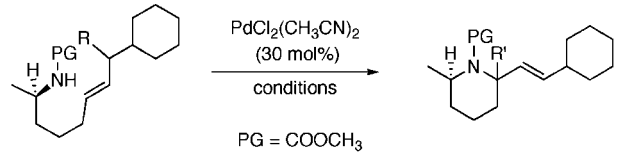
2.2.1. Synthesis of Precursors of Cyclization Bearing Two Chiral Centers. Knowing the importance of solvent, catalyst, and protecting group for this cyclization reaction, the chemistry was developed for the synthesis of optically active 2,6-disustituted piperidines. The preparation of precursors **25a**, **25b**, and **27** are shown in Scheme 6.

The key chiral alcohols were generated by Carreira's asymmetric alkynylation.[26] Alkynylation of cyclohexanecarboxaldehyde with (*S*)-6-sililoxy-1-heptyne **17**[27] in the presence of $Zn(OTf)_2$ and (+)-*N*-methylephedrine produced (*R*)-propargyl alcohol **18a** in 89% yield with 96% de.[16b] Similarly, when (−)-*N*-methylephedrine was used instead of (+)-*N*-methylephedrine, the diastereomer **18b** was obtained in 73% yield with 94% de. A partial reduction of **18a** and **18b** with Red-al followed by benzoylation of the generated allylic alcohols **19a** and **19b** gave benzoates **20a** in 89% yield and **20b** in 81% yield in two steps, respectively. The *O*-TBS group of **20** was transformed to a $NHCOOCH_3$ group in 6 steps. Desilylation of **20a** and **20b** with TBAF and the resultant alcohols **21a** and **21b** were treated with methanesulfonyl chloride in the presence of triethylamine to afford **22a** and **22b** both in 89% yield in two steps, respectively. The SN2 displacement of the mesylate with NaN_3 gave azides **23a** in 94% yield and **23b** in 90% yield. The reduction of azido group in **23a** was effected by PPh_3 in THF/H_2O, and the produced amine was protected in situ with methyl chlorocarbonate in the presence of triethylamine, giving **24a** in 80% yield. A similar reaction with **23b** afforded **24b** in 74% yield. Hydrolysis of benzoate by NaOH in aq. methanol gave **25a** in 96% yield with 96% ee and also gave **25b** in 91% yield with 94% ee, respectively. After the reduction of **23a**, in situ protection of the amine with Boc anhydride gave **26** in 85% yield in 2 steps, and the subsequent hydrolysis of benzoate provided **27** in 98% yield.

2.2.2. Diastereoselective Synthesis of Cis and Trans 2,6-Disubstituted Piperidine Derivatives. Next, we examined the cyclization reaction on **25a** and **25b**. The results are listed

(24) Hirai, Y.; Nagatsu, M. *Chem. Lett.* **1994**, *23*, 21–22.
(25) Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 15878–15892.

TABLE 2. Synthesis of Cis and Trans 2,6-Disubstituted Piperidine Derivatives 28



25a: R = ····OH
25b: R = —OH
28a: R' = —H (*trans*)
28b: R' = ····H (*cis*)

entry	substrate[a]	solvent	time (h)[b]	product	yield (%)	de (%)[c]
1	**25a**	THF	6.5	**28a**	81	88
2	**25a**	CH_2Cl_2	0.5	**28a**	79	49
3	**25a**	$ClCH_2CH_2Cl$	0.75	**28a**	75	69
4	**25a**	toluene	15	**28a**	83	82
5	**25a**	CH_3CN	6	**28a**	68	44
6	**25b**	THF	3.5	**28b**	85	86
7	**25b**	CH_2Cl_2	11[d]	**28b**	82	19

[a] Compounds **25a** with 96% de and **25b** with 94% de were used. [b] Reactions were conducted at room temperature except stated otherwise. [c] The de values were calculated based on ^{1}H NMR spectra. [d] The reaction was conducted at 0 °C.

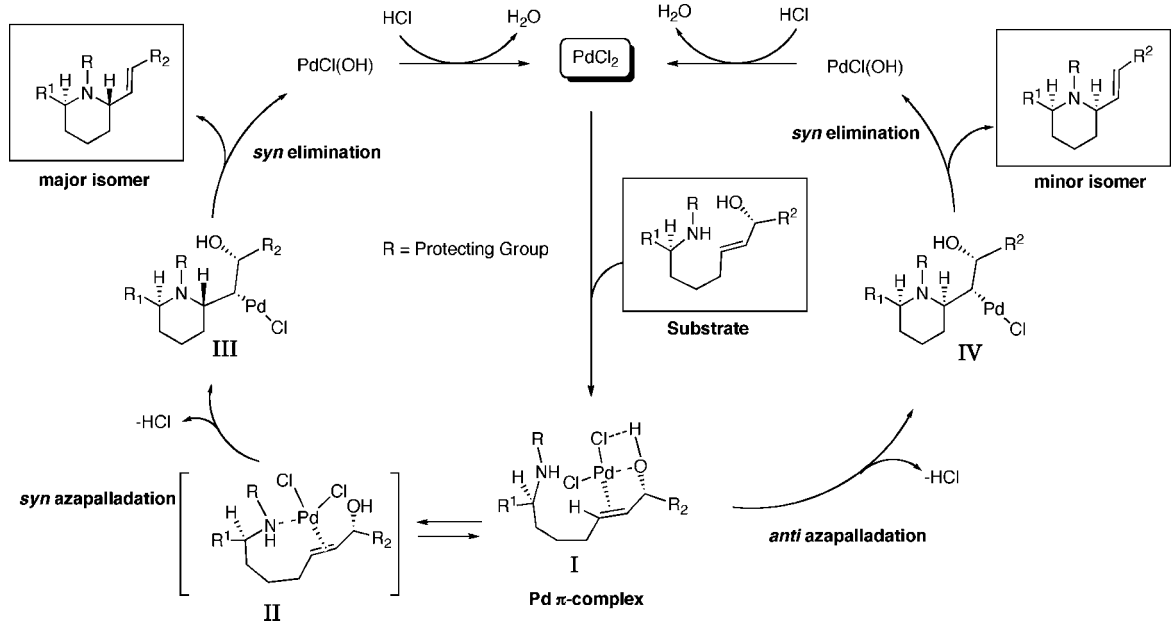


FIGURE 2. Plausible mechanistic and stereochemical pathway for piperidine synthesis by 1,3-chirality transfer process.

in Table 2. First, cyclization of **25a** with 96% de was conducted under the same conditions described for the synthesis of coniine.

However, the reaction was slow and did not go to the completion even after 24 h. When Pd^{II}-catalyst was increased to 30 mol%, the cyclization of **25a** occurred faster at room temperature to give **28a** in 81% yield with 88% de (entry 1). The reactions of **25a** were faster in halogenated solvents, CH_2Cl_2 or dichloroethane, and were completed in 30 and 45 min at room temperature to give **28a** in 79 and 75% yields, respectively (entries 2 and 3). However, surprisingly, the diastereoselectivity decreased to 49% de and 69% de. The higher selectivity with 82% de obtained in toluene (entry 4) was similar to that in THF (entry 1). The reaction in CH_3CN was not clean, resulting in a poor yield with less selectivity (entry 5). Similarly, the reaction of diastereomer **25b** with 94% de in THF was completed in 3.5 h to give cis piperidine **28b** in 85% yield with 86% de, whereas that in CH_2Cl_2 was completed in 11 h at 0 °C to give **28b** in 82% yield with only 19% de. It is interesting that the formation of cis 2,6-substituted piperidine is faster than that of trans piperidine in both solvents. Overall, the use of THF was proved to be the best for the synthesis of 2,6-disubstituted piperidines. Using **27** bearing Boc group instead of methoxycarbonyl group on the nitrogen atom resulted in no reaction. The stereochemistry of **28a** and **28b** was confirmed by NOE experiments.

2.2.3. Mechanism of the Cyclization. A proposed reaction mechanism for the Pd^{II}-catalyzed stereoselective ring formation of piperidine by 1,3-chirality transfer is outlined in Figure 2. Coordination of the Pd^{II}-catalyst to both the chiral allylic alcohol and the double bond forms the palladium π-complex I, from syn to the chiral secondary allylic alcohol.[28]

In the next step, a ligand exchange occurs to give complex II, which is in an equilibrium with I. The step is important for the chiral induction in which the nitrogen nucleophile attacks

(26) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.
(27) Drian, C. L.; Greene, A. E. *J. Am. Chem. Soc.* **1982**, *104*, 5473–5483.
(28) The possibility of anti-coordination of Pd with respect to the chiral hydroxy group is not considered here. The argument of this possibility was discussed well in the case of oxy-palladation reaction in the previous article. See ref 16c.

the alkenyl carbon from the same side of Pd π-complex. Syn-azapalladation gives σ-Pd intermediate III by elimination of a HCl molecule, which on subsequent syn-elimination of Pd-Cl(OH) delivers the major isomer (trans) in this case. Depending on the substrate and reaction conditions, the reaction may proceed partially through the antiazapalladation pathway from the palladium π-complex I to give the complex IV, which on syn-elimination of PdCl(OH) gives the minor isomer (cis) in this case. The catalyst is regenerated by the reaction of PdCl(OH) with HCl during the reaction sequence. The low selectivity obtained in solvents like CH_2Cl_2 can be justified based on the stability of complex II. If complex II is less stable than complex I, the antiattack of nucleophile leading to IV (i.e., from the opposite side of the Pd π-complex) may take place, which will give the minor product. When compared, the corresponding complex II of the 2-substituted piperidine (i.e., $R_1 = H$) is more stable than the complex II of 2,6-disubstituded piperidine (i.e., $R_1 = CH_3$), because in the latter case it is under more steric demand. Because of this reason, the better selectivity was obtained in monosubstituted piperidine (Scheme 5) than that in the 2,6-disubstituted piperidine (Table 2).

3. Conclusions

In conclusion, we have described a Pd^{II}-catalyzed intramolecular cyclization of *N*-protected ζ-amino allylic alcohols and the stereospecific synthesis of 2-substituted and 2,6-disubstituted piperidines. The concise syntheses of (*S*)-(+)- and (*R*)-(−)-coniine were achieved using this method. The reaction gives a syn SN2′ product majorly through syn-coordination of the Pd^{II}-catalyst to the allylic alcohol followed by syn-azapalladation and syn-elimination of PdCl(OH), leading to the product. Although the syn-azapalladation is found to be more favored, the formation of a minor isomer suggests that the anti-azapalladation is also plausible and it depends upon the substrate and solvent. The reaction and its rate suffer in a steric environment with an *N*-protecting group and an alkyl group. For the formation of 2,6-disubstituted piperidine, the reaction rate was slower than that of 2-substituted piperidine due to the steric hindrance. The reaction in dichloromethane was generally faster as compared to other solvents, although THF indicated higher stereoselectivity in the case of 2,6-disubstituted piperidine. This method will allow efficient and flexible synthesis of chiral 2- or 2,6-substituted piperidines.

4. Experimental Section

(*E*)-8-(*tert*-Butyldimethylsilyloxy)oct-3-en-2-one (6). 1-(Triphenylphosphoranylidene)-2-propanone (17 g, 53.37 mmol) was added to a solution of aldehyde **5** (10.5 g, 48.52 mmol) in toluene (240 mL), and the reaction mixture was stirred at 80 °C for 15 h. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 10% EtOAc in hexane gave **6** (10.62 g, 85%): colorless oil; $R_f = 0.28$ (10% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (dt, 1H, $J = 16.0$, 6.8 Hz), 6.05 (dt, 1H, $J = 16.0$, 1.5 Hz), 3.60 (m, 2H), 2.22 (s, 3H), 2.17−2.25 (m, 2H), 1.40−1.59 (m, 4H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 148.2, 131.3, 62.6, 32.2, 32.1, 26.8, 25.9, 24.4, 18.3, −5.4; IR (film, cm^{-1}) 2930, 2854, 1677, 1253, 1100; MS (CI) *m*/*z* 257 (M + H$^+$); HRMS calcd for $C_{14}H_{29}O_2Si$ (M + H$^+$) 257.1937; Found: *m*/*z* 257.1931.

(*E*)-8-(*tert*-Butyldimethylsilyloxy)oct-3-en-2-ol (7). $NaBH_4$ (2.31 g, 61.1 mmol) was added in small portions to a stirred solution of **6** (10.45 g, 40.75 mmol) and $CeCl_3 \cdot 7H_2O$ (15.18 g, 40.75 mmol) in methanol (300 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction was recooled to 0 °C, quenched with water, acidified with 1N HCl to its pH between 5−6 and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 25% EtOAc in hexane gave **7** (10.52 g, quant): colorless oil; $R_f = 0.25$ (10% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (dt, 1H, $J = 15.4$, 6.8 Hz), 5.50 (dd, 1H, $J = 15.4$, 6.4 Hz), 4.25 (dq, 1H, $J = 6.4$, 6.2 Hz), 3.60 (t, 2H, $J = 6.3$ Hz), 2.02 (dt, 2H, $J = 7.2$, 6.8 Hz), 1.70 (br, 1H), 1.35−1.56 (m, 4H), 1.24 (d, 3H, $J = 6.4$ Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.3, 130.8, 68.9, 63.0, 32.3, 31.8, 25.9, 25.4, 23.4, 18.3, −5.3; IR (film, cm^{-1}) 3349, 2930, 2857, 1472, 1254, 1102. MS (FAB) *m*/*z* 281 (M + Na$^+$); HRMS calcd for $C_{14}H_{30}O_2SiNa$ (M + Na$^+$) 281.1913; Found: *m*/*z* 281.1918.

(*E*)-2-Benzoyloxy-8-(*tert*-butyldimethylsilyloxy)oct-3-ene (8). Benzoyl chloride (9.65 mL, 83.03 mmol) was added at 0 °C to a stirred solution of **7** (10.72 g, 41.5 mmol), Et_3N (28.9 mL, 207.6 mmol) and DMAP (0.507 g, 4.15 mmol) in CH_2Cl_2 (250 mL). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with H_2O, and the organic layer was separated. The aqueous layer was extracted (CH_2Cl_2), and the combined organic extract was dried over $MgSO_4$. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 10% EtOAc in hexane gave **8** (14.96 g, 99%): colorless oil; $R_f = 0.75$ (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 2H, $J = 7.1$ Hz), 7.54 (t, 1H, $J = 7.1$ Hz), 7.42 (t, 2H, $J = 7.1$ Hz), 5.73−5.85 (m, 1H), 5.48−5.70 (m, 2H), 3.60 (t, 2H, $J = 6.2$ Hz), 2.07 (dt, 2H, $J = 7.2$, 7.0 Hz) 1.40−1.57 (m, 4H), 1.42 (d, 3H, $J = 6.0$ Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 133.2, 132.7, 130.9, 129.7, 129.5, 128.2, 71.7, 63.0, 32.3, 31.9, 26.0, 25.2, 20.5, 18.3, −5.3; IR (film, cm^{-1}) 2930, 2857, 1729, 1451, 1271, 1108; MS (CI) *m*/*z* 363 (M + H$^+$); HRMS calcd for $C_{21}H_{35}O_3Si$ (M + H$^+$) 363.2355; Found: *m*/*z* 363.2359.

(*E*)-2-Benzoyloxy-8-hydroxyoct-3-ene (9). TBAF (1.0 M in THF, 45.4 mL, 45.4 mmol) was added to a stirred solution of **8** (14.94 g, 41.24 mmol) in THF (196 mL) at room temperature. The reaction mixture was stirred overnight. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with 50% EtOAc in hexane to give **9** (8.86 g, 87%): colorless oil; $R_f = 0.25$ (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, 2H, $J = 7.7$, 1.5 Hz), 7.54 (tt, 1H, $J = 7.3$, 1.1 Hz), 7.42 (t, 2H, $J = 7.7$ Hz), 5.78 (dt, 1H, $J = 14.3$, 6.6 Hz), 5.51−5.62 (m, 2H), 3.63 (t, 2H, $J = 6.3$ Hz), 2.08 (dt, 2H, $J = 7.1$, 6.6 Hz), 1.44−1.62 (m, 5H), 1.42 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 132.9, 132.7, 130.8, 129.8, 129.5, 128.2, 71.7, 62.7, 32.1, 31.8, 25.0, 20.5; IR (film, cm^{-1}) 3374, 2933, 2861, 1716, 1451, 1273, 1111; MS (CI) *m*/*z* 249 (M + H$^+$); HRMS calcd for $C_{15}H_{21}O_3$ (M + H$^+$) 249.1491; Found: *m*/*z* 249.1493.

(*E*)-2-Benzoyloxy-8-(methanesulfonyloxy)oct-3-ene (10). MsCl (5.5 mL, 71.2 mmol) was added to a stirred solution of **9** (8.44 g, 35.61 mmol) and Et_3N (24.8 mL, 178.1 mmol) in CH_2Cl_2 (200 mL) at 0 °C. The reaction mixture was stirred for 30 min at room temperature. The reaction was then quenched with H_2O, and the organic layer was separated. The aqueous layer was extracted (CH_2Cl_2), and the combined organic layer was dried over $MgSO_4$. Filtration and evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 30% EtOAc in hexane gave **10** (11.52 g, 99%): colorless oil; $R_f = 0.25$ (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 2H, $J = 7.2$ Hz), 7.55 (t, 1H, $J = 7.3$ Hz), 7.43 (t, 2H, $J = 7.3$ Hz), 5.75 (dt, 1H, $J = 14.5$, 6.7 Hz), 5.52−5.63 (m, 2H), 4.22 (t, 2H, $J = 6.4$ Hz), 2.99 (s, 3H), 2.00 (dt, 2H, $J = 7.2$, 6.7 Hz), 1.70−1.80 (m, 2H), 1.47−1.57 (m, 2H), 1.42 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 132.8, 132.1, 130.7, 130.5, 129.5, 128.3, 71.5, 69.8, 37.4, 31.4, 28.5, 24.7, 20.5; IR (film, cm^{-1})

2938, 1714, 1451, 1274, 1112; MS (FAB) *m/z* 349 ($M + Na^+$); HRMS calcd for $C_{16}H_{22}O_5SNa$ ($M + Na^+$) 349.1086; Found: *m/z* 349.1091.

(*E*)-8-Azido-2-benzoyloxy-oct-3-ene (11). A mixture of **10** (11.5 g, 35.23 mmol) and sodium azide (6.87 g, 105.7 mmol) in dry DMF (120 mL) was stirred at room temperature for 24 h. After a removal of DMF under vaccum, water was added and the mixture was extracted with EtOAc. The extract was dried over $MgSO_4$. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 10% EtOAc in hexane gave **11** (8.83 g, 92%): colorless oil; $R_f = 0.77$ (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, 2H, $J = 7.3$, 1.5 Hz), 7.55 (tt, 1H, $J = 7.3$, 1.5 Hz), 7.43 (dt, 2H, $J = 7.3$, 1.5 Hz), 5.77 (dt, 1H, $J = 14.5$, 6.8 Hz), 5.52−5.64 (m, 2H), 3.26 (t, 2H, $J = 6.7$ Hz), 2.08 (dt, 2H, $J = 7.2$, 6.8 Hz), 1.56−1.63 (m, 2H), 1.44−1.52 (m, 2H), 1.43 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 132.7, 132.4, 130.8, 130.2, 129.5, 128.3, 71.5, 51.3, 31.6, 28.3, 26.0, 20.5; IR (film, cm^{-1}) 2935, 1716, 1451, 1271, 1110; MS (CI) *m/z* 274 ($M + H^+$); HRMS calcd for $C_{15}H_{20}N_3O_2$ ($M + H^+$) 274.1555; Found: *m/z* 274.1554.

(*E*)-8-Amino-2-benzoyloxy-oct-3-ene (12). A mixture of **11** (4 g, 12.8 mmol) and triphenylphosphine (7.68 g, 25.61 mmol) in H_2O (6 mL) and THF (120 mL) was stirred at room temperature for 24 h. Evaporation of solvents and purification of the residue by column chromatography on silica gel eluted with 20% MeOH in chloroform gave **12** (3.34 g, 92%): colorless oil; $R_f = 0.33$ (10% MeOH in chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, 2H, $J = 7.1$, 1.3 Hz), 7.54 (tt, 1H, $J = 7.3$, 1.3 Hz), 7.42 (dt, 2H, $J = 7.1$, 1.3 Hz), 5.78 (dt, 1H, $J = 14.5$, 6.6 Hz), 5.30−5.63 (m, 2H), 2.69 (t, 2H, $J = 6.6$ Hz), 2.06 (dt, 2H, $J = 6.8$, 6.6 Hz), 1.88 (br s, 2H), 1.42 (d, 3H, $J = 6.0$ Hz), 1.40−1.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 133.0, 132.7, 130.8, 129.8, 129.5, 128.2, 71.7, 41.8, 32.8, 31.9, 26.2, 20.5; IR (film, cm^{-1}) 3370, 2979, 1715, 1451, 1272, 1111; MS (EI) *m/z* 247 (M^+); HRMS calcd for $C_{15}H_{21}NO_2$ (M^+) 247.1572; Found: *m/z* 247.1577.

General Procedure for Pd^{II}-Catalyzed Cyclization. A mixture of precursor **14a**−**f** (0.1 mmol) and $PdCl_2(CH_3CN)_2$ (10 or 20 mol %) was stirred in dry solvent (2.5 mL) at 0 °C to room temperature. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 10% EtOAc in hexane gave the corresponding **15a**−**f**. The chemical yields and their characteristic data are indicated in Table 1 and in the Supporting Information.

Lipase Catalyzed Kinetic Acetylation of Racemic 14c. MS 4 Å (1.78 g), Novozyme 435 (0.45 g), and vinyl acetate (3.04 mL, 44.55 mmol) were added to a solution of **14c** (1.5 g, 8.91 mmol) in diisopropyl ether (175 mL) at room temperature. The mixture was stirred for 20 h and filtered through a celite pad. The filtrate was condensed, and the residue was purified by column chromatography on silica with 15% EtOAc in hexane as an eluent to give (*S*)-**14c** (621 mg, 41%) with 99% ee and with 25% EtOAc in hexane as an eluent to give **16** (811 mg, 40%) with 87% ee. Compound (*S*)-**14c**: amorphous solid, mp 28−29 °C; $[\alpha]_D^{23}$ −2.9 (*c* 0.51, $CHCl_3$); other spectroscopic data were all matched with those in racemic **14c** described above. The enantiomeric purities were determined by chiral HPLC, the details for which are described in the Supporting Information.

Preparation of (*R*)-14c. A solution of **16** (811 mg, 2.54 mmol) with 87% ee in methanol (20 mL) and aq. K_2CO_3 (702 mg, 5.08 mmol) in H_2O (1 mL) was stirred overnight at room temperature. After removal of solvent under vaccum, water was added to the residue and the mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and purified by column chromatography on silica gel eluted with 50−60% EtOAc in hexane to give (*R*)-**14c** (695 mg, 99%) with 87% ee. This was subjected to the above lipase catalyzed kinetic acetylation to give **16** in 84% yield with 99% ee: colorless oil; $[\alpha]_D^{20}$ +38.0 (*c* 0.2, $CHCl_3$): $R_f = 0.65$ (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.36 (m, 5H), 5.65 (dt, 1H, $J = 15.2$, 6.6 Hz), 5.45 (dd, 1H, $J = 15.2$, 6.7 Hz), 5.29 (dq, 1H, $J = 6.7$, 6.4 Hz), 5.09 (s, 2H), 4.85 (br, 1H), 3.18 (q, 2H, $J = 6.4$), 2.02 (s, 3H), 1.98−2.07 (m, 2H), 1.39−1.49 (m, 4H), 1.28 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 156.3, 136.5, 132.5, 129.9, 128.4, 128.0 (2C), 71.0, 66.5, 40.8, 31.6, 29.3, 25.9, 21.3, 20.3; IR (film, cm^{-1}) 3346, 2934, 1730, 1532, 1243, 1136; MS (FAB) *m/z* 342 ($M + Na^+$); HRMS calcd for $C_{18}H_{25}NO_4Na$ ($M + Na^+$) 342.1681; Found: *m/z* 342.1676. This optically pure (*R*)-acetate was hydrolyzed again to give pure (*R*)-**14c** in 98% yield with 99% ee.; $[\alpha]_D^{24}$ +1.7 (*c* 0.53, $CHCl_3$).

Preparation of (*R*)-15c and (*S*)-15c. The reaction was performed by the general procedure for Pd^{II}-catalyzed cyclization. Compound (*R*)-**15c**[25] was obtained from (*S*)-**14c** in 92% yield with 93% ee; colorless oil; $[\alpha]_D^{22}$ +37.3 (*c* 0.72, $CHCl_3$). $R_f = 0.74$ (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25−7.35 (m, 5H), 5.41−5.58 (m, 2H), 5.13 (q, 2H, J =12.3 Hz), 4.82 (br s, 1H), 4.01 (d, 1H, $J = 12.8$ Hz), 2.91 (dt, 1H, $J = 12.8$, 2.7 Hz), 1.68 (dd, 3H, $J = 4.6$, 1.5 Hz), 1.37−1.69 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 137.0, 129.0, 128.3, 127.7, 127.6, 126.8, 66.8, 52.1, 39.9, 29.3, 25.5, 19.3, 17.7; IR (film, cm^{-1}) 2936, 2857, 1697, 1497, 1255, 1171; MS (EI) *m/z* 259 (M^+); HRMS calcd for $C_{16}H_{21}NO_2$ (M^+) 259.1572; Found: *m/z* 259.1578. Compound (*S*)-**15c** was obtained from (*R*)-**14c** in 93% yield with 92% ee; colorless oil, $[\alpha]_D^{22}$ −38.2 (*c* 0.62, $CHCl_3$). These enantiomeric purities were determined by chiral HPLC, the details for which are described in the Supporting Information.

Synthesis of Coniines 1a and 1b Hydrochlorides. A mixture of (*R*)-**15c** (96 mg, 0.3 mmol) and $Pd(OH)_2$/C (8 mg) in methanol (10 mL) was stirred under H_2 atmosphere at room temperature for 24 h. The reaction mixture was then filtered through a ceilite bed. Then, HCl gas was bubbled into the obtained filtrate. Evaporation of the solvent gave the corresponding coniine hydrochloride, (*S*)-(+)-Coniine **1a** hydrochloride, in 95% yield in two steps. White solid; $[\alpha]_D^{21}$ +7.1 (*c* 1.00, EtOH); colorless crystals, mp 214−216 °C (methanol), lit.[2d] mp 213−215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (br s, 1H), 9.18 (br s, 1H), 3.44 (d, 1H, $J = 10.5$ Hz), 2.93 (br s, 1H), 2.83 (br s, 1H), 1.62−1.96 (m, 7H), 1.37−1.52 (m, 3H), 0.94 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.2, 44.8, 35.3, 28.2, 22.4, 22.2, 18.6, 13.7; MS (EI) *m/z* 127 (M^+); HRMS calcd for $C_8H_{17}N$ (M^+) 127.1361; Found: *m/z* 127.1357. (*R*)-(−)-Coniine **1b** hydrochloride. HCl was obtained from (*S*)-**15c** in 90% yield in two steps. White solid; $[\alpha]_D^{21}$ −6.3 (*c* 1.00, EtOH); colorless crystals, mp 218−220 °C (methanol); MS (EI) *m/z* 127 (M^+); HRMS calcd for $C_8H_{17}N$ (M^+) 127.1361; Found: *m/z* 127.1353.

(1*S*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-1-cyclohexyloct-2-yn-1-ol (18b). Et_3N (0.257 mL, 1.8 mmol) was added in one portion to a stirred suspension of $Zn(OTf)_2$ (618 mg, 1.65 mmol, predried overnight at 125 °C under vacuum) and (−)-*N*-methylephedrine (332 mg, 1.8 mmol) in dry toluene (4.9 mL). After the white slurry was stirred at room temperature for 3 h, alkyne **17** (350 mg, 1.5 mmol) was added. The mixture was stirred for 30 min and then treated with freshly distilled cyclohexanecarboxaldehyde (173 mg, 1.5mmol). After the mixture was stirred for 3 h at room temperature, a saturated NH_4Cl solution was added to the mixture, and the aqueous layer was extracted (EtOAc). After filtration and evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with 5% of EtOAc in hexane to give product **18b** (382 mg, 73%): colorless oil; $[\alpha]_D^{23}$ +11.6 (*c* 1.08, $CHCl_3$) (>94% de, based on chiral HPLC); $R_f = 0.32$ (10% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4,13 (br, 1H), 3.81 (qt, 1H, $J = 6.0$, 5.5 Hz), 2.19−2.24 (m, 2H), 1.43−1.85 (m, 10H), 1.13 (d, 3H, $J = 6.0$ Hz), 1.02−1.26 (m, 5H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.2, 80.3, 68.2, 67.4, 44.4, 38.8, 28.6, 28.1, 26.4, 25.9, 25.9, 25.0, 23.8, 23.7, 18.8, 18.1, −4.4, −4.7; IR (film, cm^{-1}) 3367, 2927, 1450, 1374, 1254, 1186, 1136, 1023, 892, 835, 774; MS (FAB) *m/z* 361 ($M + Na^+$). HRMS calcd for $C_{20}H_{38}O_2SiNa$ ($M + Na^+$): 361.2539; Found: *m/z* 361.2544. The enantiomeric purities were determined by chiral HPLC, the details for which are described in the Supporting Information.

(*E*,1*S*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-1-cyclohexyloct-2-en-1-ol (19b). Red-al (70% in toluene solution, 1.27 mL, 4.37 mmol) was added to a solution of **18b** (370 mg, 1.09 mmol) in THF (39 mL). The mixture was refluxed for 2 h, quenched with a saturated NH_4Cl and was extracted with EtOAc. The extract was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel eluted with 5% of EtOAc in hexane gave **19b** (311 mg, 84%): colorless oil $[\alpha]_D^{23}$ +8.90 (*c* 1.10, $CHCl_3$); $R_f = 0.32$ (10% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 (dt, 1H, $J = 15.4$, 6.6 Hz), 5.45 (dd, 1H, $J = 15.4$, 7.3 Hz), 3.78 (m, 2H), 2.03 (m, 2H), 1.63−1.87 (m, 5H), 1.31−1.51 (m, 6H), 1.11 (d, 3H, $J = 6.0$ Hz), 0.95−1.24 (m, 5H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.8, 131.6, 77.7, 68.4, 43.7, 39.2, 32.2, 28.8, 28.7, 26.5, 26.1, 26.0, 25.9, 25.4, 23.8, 18.1, −4.4, −4.7; IR (film, cm^{-1}) 3366, 2927, 2855, 1450, 1374, 1254, 1135, 1005, 891, 835, 774; MS (FAB) *m*/*z* 363 (M + Na^+). HRMS calcd for $C_{20}H_{40}O_2SiNa$ (M + Na^+): 363.2696; Found: *m*/*z* 363.2689.

Benzoylation of 19. Et_3N (1.08 mL, 7.79 mmol), DMAP (9.5 mg, 0.078 mmol), and benzoyl chloride (0.271 mL, 2.34 mmol) were succesively added to a stirred solution of **19a**[16b] (265 mg, 0.78 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 h and was quenched with water. The mixture was extracted with CH_2Cl_2, and the extract was dried over $MgSO_4$. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 3% EtOAc in hexane gave **20a** (337 mg; 98%): colorless oil; $[\alpha]_D^{23}$ −3.53 (*c* 0.65, $CHCl_3$); R_f = 0.5 (5% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, 2H, $J = 7.8$, 1.5 Hz), 7.54 (tt, 1H, $J = 7.3$, 1.5 Hz), 7.43 (dt, 2H, J = 7.8, 7.3 Hz), 5.76 (dt, 1H, $J = 15.2$, 6.4 Hz), 5.49 (dd, 1H, $J = 15.2$, 7.7 Hz), 5.26 (dd, 1H, $J = 7.2$, 6.9 Hz), 3.77 (m, 1H), 2.05 (m, 2H), 1.65−1.85 (m, 5H), 1.04−1.53 (m, 10H), 1.09 (d, 3H, $J = 6.0$ Hz), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 135.1, 132.6, 130.9, 129.5, 128.3, 126.8, 79.5, 68.4, 42.0, 39.1, 32.2, 28.8, 28.7, 26.4, 26.0, 25.9, 25.8, 25.2, 23.8, 18.1, −4.4, −4.7; IR (film, cm^{-1}) 2928, 2855, 1719, 1270, 1109; MS (FAB) *m*/*z* 467 (M + Na^+). HRMS calcd for $C_{27}H_{44}O_3SiNa$ (M + Na^+): 467.2958; Found: *m*/*z* 467.2963. The diastereoisomer **20b** was obtained from **19b** in 97% yield: colorless oil; $[\alpha]_D^{23}$ +11.00 (*c* 1.29, $CHCl_3$); R_f = 0.5 (5% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, 2H, $J = 7.7$, 1.5 Hz), 7.54 (m, 1H), 7.43 (t, 2H, $J = 7.7$ Hz), 5.76 (dt, 1H, $J = 15.2$, 6.8 Hz), 5.49 (dd, 1H, $J = 15.2$, 7.7 Hz), 5.27 (dd, 1H, $J = 7.2$, 7.0 Hz), 3.75 (m, 1H), 2.04 (m, 2H), 1.60−1.81 (m, 5H), 1.31−1.51 (m, 5H), 1.04−1.26 (m, 5H), 1.11 (d, 3H, $J = 6.0$ Hz), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 135.1, 132.7, 132.6, 129.4, 129.5, 128.3, 128.2, 126.9, 79.5, 68.4, 42.0, 39.1, 32.2, 28.7, 28.6, 26.4, 26.0, 25.9, 25.8, 25.2, 23.8, 18.1, −4.4, −4.8; IR (film, cm^{-1}) 2928, 2855, 1720, 1272, 1109; MS (FAB) *m*/*z* 467 (M + Na^+). HRMS calcd for $C_{27}H_{44}O_3SiNa$ (M + Na^+): 467.2958; Found: *m*/*z* 467.2965.

Deprotection of TBDMS Ether of 20. A mixture of **20a** (322 mg, 0.72 mmol) and TBAF (1.0 M in THF, 5.73 mL, 5.79 mmol) in THF (8 mL) was stirred at room temperature overnight. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with ether to give **21a** (230 mg, 96%): colorless oil; $[\alpha]_D^{24}$ −9.07 (*c* 0.65, $CHCl_3$); R_f = 0.33 (40% Et_2O in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 2H, $J = 7.0$ Hz), 7.53 (t, 1H, $J = 7.3$ Hz), 7.43 (t, 2H, $J = 7.0$ Hz), 5.75 (dt, 1H, $J = 15.4$, 6.8 Hz), 5.49 (dd, 1H, $J = 15.4$, 7.5 Hz), 5.24 (dd, 1H, $J = 7.3$, 7.0 Hz), 3.77 (m, 1H), 2.07 (m, 2H), 1.64−1.84 (m, 6H), 1.16 (d, 3H, $J = 6.2$ Hz), 0.86−1.52 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 134.8, 132.6, 130.8, 129.5, 128.2, 127.0, 79.5, 67.8, 41.8, 38.7, 32.2, 28.7, 28.6, 26.3, 25.8, 25.9, 25.1, 23.4; IR (film, cm^{-1}) 3387, 2927, 2854, 1716, 1272, 1112; MS (FAB) *m*/*z* 331 (M + H^+). HRMS calcd for $C_{21}H_{31}O_3$ (M + H^+): 331.2273; Found: *m*/*z* 331.2265. The diastereoisomer **21b** was obtained from **20b** in quantitative yield: colorless oil; $[\alpha]_D^{22}$ +13.2 (*c* 1.05, $CHCl_3$); R_f = 0.33 (40% Et_2O in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 2H, $J = 7.0$ Hz), 7.54 (t, 1H, J = 7.3 Hz), 7.42 (t, 2H, $J = 7.0$ Hz), 5.75 (dt, 1H, $J = 15.4$, 6.8 Hz), 5.49 (dd, 1H, $J = 15.4$, 7.5 Hz), 5.24 (dd, 1H, $J = 7.3$, 7.0 Hz), 3.78 (m, 1H), 2.07 (m, 2H), 1.49−1.85 (m, 6H), 1.16 (d, 3H, J = 6.2 Hz), 0.86−1.46 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 134.8, 132.6, 130.8, 129.5, 128.2, 127.0, 79.5, 67.8, 41.9, 38.7, 32.2, 28.7, 28.6, 26.4, 25.9, 25.8, 25.0, 23.4; IR (film, cm^{-1}) 3385, 2928, 2854, 1718, 1271, 1111; MS (FAB) *m*/*z* 331 (M + H^+). HRMS calcd for $C_{21}H_{31}O_3$ (M + H^+): 331.2273; Found: *m*/*z* 331.2266.

Mesylation of Alcohol 21. MsCl (0.34 mL, 4.4 mmol) was added to a stirred solution of **21a** (940 mg, 2.93 mmol) and Et_3N (1.22 mL, 8.8 mmol) in CH_2Cl_2 (69 mL) at 0 °C. The mixture was stirred for 30 min at room temperature and then poured into water and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 10% EtOAc in hexane gave **22a** (1.08 g; 93%): colorless oil; $[\alpha]_D^{23}$ −8.26 (*c* 0.52, $CHCl_3$); R_f = 0.41 (40% Et_2O in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, 2H, $J = 7.2$, 1.5 Hz), 7.54 (tt, 1H, $J = 7.5$, 1.5 Hz), 7.43 (dt, 2H, $J = 7.5$, 7.2 Hz), 5.72 (dt, 1H, $J = 15.4$, 6.8 Hz), 5.50 (dd, 1H, $J = 15.4$, 7.3 Hz), 5.24 (dd, 1H, $J = 7.2$, 7.0 Hz), 4.78 (tq, 1H, $J = 6.4$, 5.8 Hz), 2.96 (s, 3H) 2.09 (m, 2H,), 1.42−1.85 (m, 10H), 1.39 (d, 3H, $J = 6.4$ Hz), 1.03−1.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 133.9, 132.7, 130.8, 129.5, 128.3, 127.7, 79.9, 79.3, 41.8, 38.6, 35.9, 31.7, 28.8, 28.6, 26.3, 25.9, 25.8, 24.3, 21.1; IR (film, cm^{-1}) 2930, 2854, 1714, 1272, 1112; MS (FAB) *m*/*z* 409 (M + H^+). HRMS calcd for $C_{22}H_{33}O_5S$ (M + H^+): 409.2048; Found: *m*/*z* 409.2040. Diastereoisomer **22b** was obtained from **21b** in 89% yield: colorless oil; $[\alpha]_D^{22}$ +14.7 (*c* 1.03, $CHCl_3$); R_f = 0.41 (40% Et_2O in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, 2H, $J = 7.1$, 1.5 Hz), 7.54 (tt, 1H, $J = 7.5$, 1.5 Hz), 7.43 (dt, 2H, $J = 7.5$, 7.1 Hz), 5.72 (dt, 1H, $J = 15.4$, 6.6 Hz), 5.51 (dd, 1H, $J = 15.4$, 7.5 Hz), 5.24 (dd, 1H, $J = 7.2$, 7.0 Hz), 4.78 (tq, 1H, $J = 6.2$, 5.5 Hz), 2.96 (s, 3H) 2.09 (m, 2H,), 1.37−1.85 (m, 10H), 1.39 (d, 3H, $J = 6.2$ Hz), 1.03−1.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 134.0, 132.7, 130.8, 129.5, 128.3, 127.7, 79.9, 79.3, 41.8, 38.6, 35.9, 31.7, 28.8, 28.6, 26.3, 25.9, 25.8, 24.3, 21.1; IR (film, cm^{-1}) 2929, 2854, 1714, 1272, 1112; MS (FAB) *m*/*z* 431 (M + Na^+). HRMS calcd for $C_{22}H_{33}O_5SNa$ (M + Na^+): 431.1868; Found: *m*/*z* 431.1861.

Substitution of Methanesulfonate with Azide. A mixture of **22a** (1.036 g, 2.53 mmol) and sodium azide (989 mg, 15.22 mmol) was stirred in dry DMF (25 mL) at room temperature for 24 h. After removal of DMF under vaccum, water was added and the mixture was extracted with EtOAc. The extract was dried on $MgSO_4$ and condensed. The residue was purified by column chromatography on silica gel eluted with 5% ether in hexane to give **23a** (847 mg; 94%): colorless oil; $[\alpha]_D^{23}$ −35.2 (*c* 1.14, $CHCl_3$); R_f = 0.66 (10% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, 2H, J = 7.0, 1.5 Hz), 7.55 (tt, 1H, $J = 7.3$, 1.5 Hz), 7.44 (dt, 2H, J = 7.3, 7.0 Hz), 5.74 (dt, 1H, $J = 15.2$, 6.8 Hz), 5.50 (dd, 1H, J = 15.2, 7.5 Hz), 5.26 (dd, 1H, $J = 7.3$, 7.0 Hz), 3.42 (m, 1H), 2.08 (m, 2H,), 1.40−1.85 (m, 10H), 1.23 (d, 3H, $J = 6.6$ Hz), 1.04−1.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 134.3, 132.7, 130.8, 129.5, 128.3, 127.4, 79.4, 57.7, 41.9, 35.5, 31.9, 28.8, 28.6, 26.4, 25.9, 25.8, 25.3, 19.4; IR (film, cm^{-1}) 2928, 2854, 1716, 1270, 1111; MS (FAB) *m*/*z* 378(M + Na^+). HRMS calcd for $C_{21}H_{29}N_3O_2Na$ (M + Na^+): 378.2157; Found: *m*/*z* 378.2163. Diastereomer **23b** was obtained from **22b** in 90% yield: colorless oil; $[\alpha]_D^{24}$ −7.8 (*c* 1.00, $CHCl_3$); R_f = 0.66 (10% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, 2H, $J = 7.0$, 1.5 Hz), 7.55 (tt, 1H, $J = 7.3$, 1.5 Hz), 7.44 (dt, 2H, $J = 7.3$, 7.0 Hz), 5.75 (dt, 1H, $J = 15.4$, 6.6 Hz), 5.50 (ddt, 1H, $J = 15.4$, 7.5, 1.2 Hz), 5.26 (dd, 1H, $J = 7.2$, 7.0 Hz), 3.42 (m, 1H), 2.08 (m, 2H,), 1.38−1.86 (m, 10H), 1.23 (d, 3H, $J = 6.6$ Hz), 1.04−1.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 134.3, 132.7, 130.8, 129.5, 128.3, 127.4, 79.4, 57.7, 41.9, 35.5, 31.9, 28.8, 28.6, 26.4, 25.9, 25.8, 25.3, 19.4; IR (film, cm^{-1}) 2929, 2854, 1717, 1270, 1111; MS (FAB) *m*/*z* 378 (M + Na^+). HRMS calcd for $C_{21}H_{29}N_3O_2Na$ (M + Na^+): 378.2157; Found: *m*/*z* 378.2164.

Preparation of 24a and 24b. Triphenylphosphine (885 mg, 3.37 mmol) and H_2O (0.45 mL) were added to a stirred solution of **23a** (300 mg, 0.84 mmol) in THF (22 mL), and the reaction was stirred for 30 h at room temperature. Solvent was removed and the residue was dried under high vaccum. The residue was then dissolved in CH_2Cl_2 (10 mL), and methyl chloroformate (0.13 mL, 1.68 mmol) and Et_3N (0.45 mL, 3.37 mmol) were added at 0 °C. After the addition, it was allowed to warm to room temperature and was stirred for an additional 1 h. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 5% EtOAc in hexane gave **24a** (244 mg; 80%): colorless oil; $[\alpha]_D^{24}$ −8.78 (*c* 1.07, $CHCl_3$); R_f = 0.37 (25% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 2H, *J* = 7.0 Hz), 7.53 (t, 1H, *J* = 7.3 Hz), 7.42 (t, 2H, *J* = 7.7 Hz), 5.72 (dt, 1H, *J* = 15.4, 6.6 Hz), 5.48 (dd, 1H, *J* = 15.4, 7.7 Hz), 5.24 (dd, 1H, *J* = 7.2, 7.0 Hz), 4.45 (br, 1H), 3.64 (br, 1H), 3.62 (br s, 3H), 2.03 (m, 2H,), 1.64−1.84 (m, 6H), 1.40 (m, 4H), 1.16−1.25 (m, 5H), 1.10 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 156.4, 134.5, 132.7, 130.9, 129.5, 128.3, 127.3, 79.5, 51.8, 46.9, 41.9, 36.5, 32.0, 28.8, 28.6, 26.4, 26.0, 25.9, 25.3, 21.3; IR (film, cm^{-1}) 3339, 2929, 2854, 1714, 1530, 1271, 1111; MS (FAB) *m*/*z* 388 (M + H^+). HRMS calcd for $C_{23}H_{34}NO_4$ (M + H^+): 388.2488; Found: *m*/*z* 388.2483. Diastereisomer **24b** was obtained from **23b** in 74% yield: colorless oil; $[\alpha]_D^{23}$ +18.5 (*c* 0.53, $CHCl_3$); R_f = 0.37 (25% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 2H, *J* = 7.0 Hz), 7.54 (t, 1H, *J* = 7.5 Hz), 7.43 (t, 2H, *J* = 7.7 Hz), 5.72 (dt, 1H, *J* = 15.4, 6.6 Hz), 5.48 (dd, 1H, *J* = 15.4, 7.7 Hz), 5.23 (dd, 1H, *J* = 7.2, 7.0 Hz), 4.48 (br, 1H), 3.66 (br, 1H), 3.64 (br s, 3H), 2.05 (m, 2H,), 1.64−1.85 (m, 6H), 1.16−1.39 (m, 8H), 1.09 (d, 3H, *J* = 6.6 Hz) 1.03−1.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 156.4, 134.7, 132.7, 130.8, 129.5, 128.2, 127.2, 79.5, 51.8, 46.8, 41.8, 36.4, 32.0, 28.7, 28.6, 26.4, 25.9, 25.8, 25.2, 21.3; IR (film, cm^{-1}) 3341, 2928, 2854, 1714, 1530, 1271, 1111; MS (FAB) *m*/*z* 388 (M + H^+). HRMS calcd for $C_{23}H_{34}NO_4$ (M + H^+): 388.2488; Found: *m*/*z* 388.2479.

Preparation of 26. Triphenylphosphine (295 mg, 1.12 mmol) and H_2O (0.15 mL) were added to a stirred solution of **23a** (100 mg, 0.28 mmol) in THF (7.5 mL), and the reaction was stirred for 30 h at room temperature. Solvents were evaporated and the residue was dried under high vaccum. The residue was then dissolved in CH_2Cl_2 (4.5 mL), and Boc anhydride (119 mg, 0.54 mmol) and Et_3N (0.15 mL, 1.1 mmol) were added at room temperature, and the mixture was stirred for 3 h. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 5% EtOAc in hexane gave **26** (103 mg; 85%): colorless oil; $[\alpha]_D^{24}$ −10.37 (*c* 1.32, $CHCl_3$); R_f = 0.45 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 2H, *J* = 7.1 Hz), 7.53 (t, 1H, *J* = 7.3 Hz), 7.42 (t, 2H, *J* = 7.1 Hz), 5.73 (dt, 1H, *J* = 15.4, 6.7 Hz), 5.47 (dd, 1H, *J* = 15.4, 7.7 Hz), 5.25 (dd, 1H, *J* = 7.1, 7.0 Hz), 4.27 (br, 1H), 3.61 (br, 1H), 2.03 (m, 2H,), 1.62−1.85 (m, 6H), 1.42 (s, 9H), 1.15−1.50 (m, 9H), 1.07 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 155.3, 134.7, 132.6, 130.8, 129.5, 128.2, 127.1, 79.4, 46.2, 41.8, 36.7, 32.0, 28.7, 28.6, 28.3, 27.3, 26.3, 25.9, 25.8, 25.3, 21.3; IR (film, cm^{-1}) 3371, 2929, 2854, 1714, 1517, 1271, 1113; MS (FAB) *m*/*z* 430 (M + H^+). HRMS calcd for $C_{26}H_{40}NO_4$ (M + H^+): 430.2957; Found: *m*/*z* 430.2952.

Hydrolysis of Benzoates 24a, 24b, and 26. A solution of benzoate (0.4 mmol) in methanol (15 mL) and aq NaOH (3.2 M solution, 1.5 mL, 4.8 mmol) was stirred for 24 h at room temperature. Solvent was removed under vaccum, water was added to the residue, and the mixture was extracted with EtOAc. The organic extract was dried on $MgSO_4$. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 40% EtOAc in hexane gave the corresponding alcohol **25a**, **25b**, and **27**.

Compound 25a. was obtained from **24a** in 96% yield; colorless oil $[\alpha]_D^{25}$ −2.19 (*c* 1.05, $CHCl_3$); R_f = 0.16 (25% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (dt, 1H, *J* = 15.4, 6.2 Hz), 5.46 (dd, 1H, *J* = 15.4, 7.1 Hz), 4.45(br, 1H), 3.75 (t, 1H, *J* = 6.8 Hz), 3.67 (br, 1H), 3.64 (br s, 3H), 2.05 (m, 2H,), 1.63−1.85 (m, 7H), 1.34−1.46 (m, 5H), 1.16−1.32 (m, 4H), 1.12 (d, 3H, *J* = 6.6 Hz),; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 132.2, 132.1, 77.5, 51.8, 46.7, 43.6, 36.4, 31.8, 28.8, 28.7, 26.5, 26.1, 26.0, 25.3, 21.1; IR (film, cm^{-1}) 3325, 2924, 1698, 1537, 1256, 1085; MS (FAB) *m*/*z* 306 (M + Na^+). HRMS calcd for $C_{16}H_{29}NO_3Na$ (M + Na^+): 306.2045; Found: *m*/*z* 306.2041.

Compound 25b. was obtained from **24b** in 91% yield; colorless oil $[\alpha]_D^{26}$ +8.2 (*c* 1.26, $CHCl_3$); R_f = 0.16 (25% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (dt, 1H, *J* = 15.2, 6.2 Hz), 5.46 (dd, 1H, *J* = 15.2, 7.0 Hz), 4.48 (br, 1H), 3.75 (t, 1H, *J* = 6.8 Hz), 3.68 (br, 1H), 3.64 (br s, 3H), 2.04 (m, 2H,), 1.54−1.86 (m, 6H), 1.12 (d, 3H, *J* = 6.6 Hz), 1.12−1.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 132.2, 132.0, 77.5, 51.8, 46.9, 43.6, 36.6, 32.0, 28.8, 28.6, 26.5, 26.1, 26.0, 25.4, 21.2; IR (film, cm^{-1}) 3324, 2924, 1698, 1537, 1256, 1085; MS (FAB) *m*/*z* 306(M + Na^+). HRMS calcd for $C_{16}H_{29}NO_3Na$ (M + Na^+): 306.2045; Found: *m*/*z* 306.2054.

Compound 27. was obtained from 26 in 98% yield; colorless oil $[\alpha]_D^{23}$ −3.78 (*c* 0.95, $CHCl_3$); R_f = 0.18 (25% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (dt, 1H, *J* = 15.2, 6.2 Hz), 5.44 (dd, 1H, *J* = 15.2, 7.1 Hz), 4.33 (br, 1H), 3.73 (t, 1H, *J* = 6.8 Hz), 3.62 (br, 1H), 2.02 (m, 2H,), 1.62−1.85 (m, 6H), 1.41 (s, 9H), 1.29−1.47 (m, 6H), 1.07 (d, 3H, *J* = 6.6 Hz), 0.87−1.22 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 132.3, 132.0, 78.9, 77.5, 46.0, 43.6, 36.6, 31.9, 28.7, 28.7, 28.3, 26.5, 26.1, 26.0, 25.4, 21.1; IR (film, cm^{-1}) 3343, 2926, 1693, 1527, 1248, 1078; MS (FAB) *m*/*z* 326 (M + H^+). HRMS calcd for $C_{19}H_{36}NO_3$ (M + H^+): 326.2695; Found: *m*/*z* 326.2702.

Pd(II)-Catalyzed Cyclization. A mixture of **25** (20 mg, 0.064 mmol) and $PdCl_2(CH_3CN)_2$ (5.6 mg, 0.021 mmol) was stirred in THF (1.6 mL) at room temperature for 6.5 h. After removal of the solvent, the residue was purified by column chromatography on silica gel eluted with 5% EtOAc in hexane to give **28**. Compound **28a** was obtained from **25a** in 81% yield: colorless oil; $[\alpha]_D^{25}$ −31.11 (*c* 1.26, $CHCl_3$); R_f = 0.77 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (m, 2H), 4.41(m, 1H), 4.03 (m, 1H), 3.67 (s, 3H), 1.87−1.97(m, 2H), 1.40−1.80 (m, 10H), 1.23 (d, 3H, *J* = 6.8 Hz), 0.99−1.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 135.8, 128.8, 52.6, 52.0, 47.5, 40.3, 32.9, 32.8, 29.7, 26.5, 26.2, 26.0, 25.7, 20.6, 13.8.; IR (film, cm^{-1}) 2924, 2852, 1698, 1445, 1360; MS (EI+) *m*/*z* 265(M^+). HRMS calcd for $C_{16}H_{27}NO_2$ (M^+): 265.2042; Found: *m*/*z* 265.2037. Compound **28b** was obtained from **25b** in 85% yield: colorless oil; $[\alpha]_D^{24}$ +17.4 (*c* 0.78, $CHCl_3$); R_f = 0.77 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (m, 2H), 4.70(m, 1H), 4.35 (m, 1H), 3.69 (s, 3H), 1.49−1.76 (m, 9H), 1.14 (d, 3H, *J* = 6.9 Hz), 0.99−1.35 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 136.4, 128.9, 52.3, 50.9, 46.4, 40.5, 32.8, 32.7, 30.2, 29.7, 28.2, 26.2, 26.0, 20.5, 14.2; IR (film, cm^{-1}) 2924, 2852, 1698, 1443, 1360; MS (FAB) *m*/*z* 266 (M+H^+). HRMS calcd for $C_{16}H_{28}NO_2$ (M+H^+): 266.2120; Found: *m*/*z* 266.2113.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds and synthetic procedures and physical and characterization data for **13a**−**f**, **14a**−**f**, **15a**−**b**, and **15d**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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