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Homoallylamines

Zirconocenes vs. Alanes: a Crucial Choice of the Allyl Source for Highly Diastereoselective Allylzincation of Nonracemic Chiral Imines

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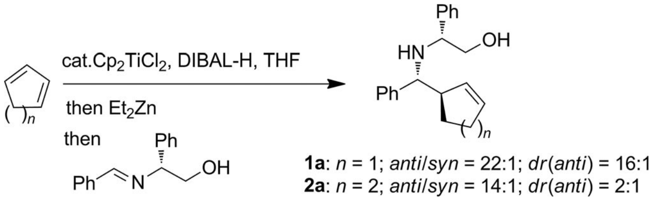
Abstract: An efficient in-situ generation of allylzinc compounds from allylzirconocenes applied to the allylmetallation of phenylglycinol-derived imines is described. The key advantage of the method lies in the concomitant formation of a zirconocene during the Zr–Zn transmetallation step, which appears to be beneficial for the stereoselectivity of the reaction. In the specific case of coupling of imines with racemic chiral allylzinc compounds, this method provides highly diastereoselective access to valuable enantiomerically enriched amines with high synthetic potential.

Introduction

Synthetic transformations involving the kinetic dynamic resolution of an organometallic reagent constitute a powerful and challenging approach for the preparation of enantiomerically enriched molecules.[1] Among efficient asymmetric C–C bond-forming reactions, the allylmetallation of nonracemic imines[2] is of particular interest, due to the high synthetic potential of the resulting homoallylic amines.[3] However, examples of allylmetallation of nonracemic imines implying the kinetic dynamic resolution of a chiral organometallic reagent are rare. In 2008, Reddy's group reported an efficient and highly diastereoselective addition of racemic allylzinc compounds onto *tert*-butanesulfinylimines.[4]

Recently, we described the generation of cyclopent-2-en-1-ylzinc reagents by a titanium-catalyzed hydroalumination of cyclopentadiene/transmetallation sequence.[5] Applied to the allylation of phenylglycinol-derived imines, this mode of generation of the allylzinc compound gave moderate to good stereoselectivities. In contrast, when the same sequence was applied to the homologous cyclohexadiene, a severe drop in diastereoselectivity among the *anti* isomers was observed (Scheme 1).

In 2010, Lin and co-workers demonstrated the dramatic effect of solvents and additives on the stereoselectivity in the cinnamylzincation of imines.[6] The authors suggested that, depending on the reaction conditions, the mechanism could evolve from a Traxler–Zimmermann-like motif to an antiperiplanar organization of the two partners, resulting in a reversal of the stereofacial selectivity.



1a: *n* = 1; *anti*/*syn* = 22:1; *dr*(*anti*) = 16:1
2a: *n* = 2; *anti*/*syn* = 14:1; *dr*(*anti*) = 2:1

Scheme 1. Addition of cyclopent- and cyclohex-2-en-1-ylzinc, generated from alanes onto phenylglycinol-derived imines.

In reconsidering our hydroalumination/transmetallation-to-zinc approach, a question remained about the influence of the aluminum species, co-product of the transmetallation step, upon the stereochemical outcome of the allylzincation of imines.[5] We envisioned that the alternative use of allylzirconocenes, which are inert towards imines, as allylzinc sources,[7] may constitute an approach amenable to producing a less active Lewis acid as the co-product (Figure 1).

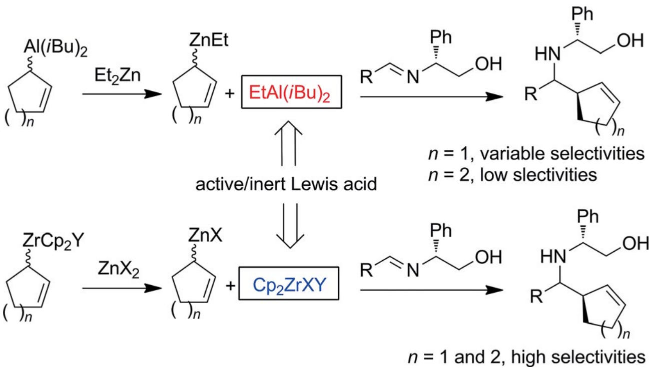


Figure 1. Allylalanes vs. allylzirconocenes as allylzinc precursors. Influence of the metallic species co-generated during the transmetallation upon the diastereoselectivity of the chiral imine allylation.

In this paper, we disclose the generation of cyclopent- and cyclohex-2-en-1-ylzinc from the corresponding zirconocenes, as

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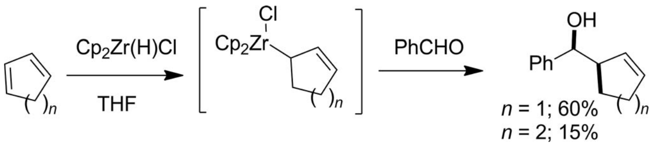
applied to the diastereoselective synthesis of optically enriched homoallylic amines.

Results and Discussion

The hydroboration of 1,3-cyclohexadiene being known for providing allylborane,[8] this study began by first investigating the feasibility of achieving a regioselective hydrozirconation of conjugated cyclic dienes. This reaction would constitute a new approach to generating allylzirconocenes. Thus, the Schwartz reagent was added to a solution of cyclopentadiene or 1,3-cyclohexadiene in THF at room temperature. Under these conditions, the hydride was consumed within 30 min leading to a deep red solution, which was allowed to react with benzaldehyde at the same temperature for 1 h prior to hydrolysis. Whereas the cyclopentadiene-derived alcohol was obtained in good yield, the reaction with 1,3-cyclohexadiene as the substrate gave a disappointing result (Scheme 2). These disparities of outcome may originate from a regioselectivity difference for the two dienes.



Scheme 2. Hydrozirconation of conjugated cyclic dienes.

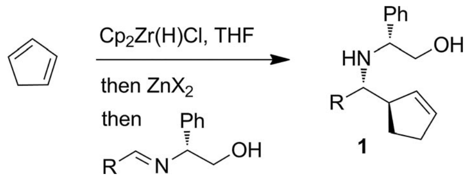
With the hydrozirconations of cyclopentadiene as encouragement, the generation of the analogous allylzinc compound was next examined by testing zinc-based additives as Zr → Zn transmetallation promotors.

In a typical experiment, the zinc derivative was added to a solution of allyzirconocene, generated by hydrozirconation. The resulting mixture was stirred at room temperature for 2 h, then cooled to –60 °C, prior to imine addition. Under these conditions, the use of $ZnCl_2$ was unproductive. In contrast, $Zn(OTf)_2$ seemed to act as an effective transmetallating agent. Ultimately, Et_2Zn appeared as the additive of choice, providing the model homoallylic amine **1a** with an excellent stereoselectivity (Table 1).

To extend the scope of the reaction, nonracemic imines were tested, affording diversely substituted homoallylic amines (Table 1). The stereoselectivity was good in most cases, allowing for efficient access to enantiomerically enriched homoallylic amines bearing an aryl (Table 1, Entries 3–5), a heteroaryl (Table 1, Entries 6–8), a vinyl (Table 1, Entry 9), or an alkyl group (Table 1, Entries 10–12) in moderate to good yields.

Relative to the results obtained using the parent hydroalumination/Al → Zn transmetallation sequence (Table 1, Column 4)[5] (aluminum route), a significant increase of the diastereoselectivity was observed using the present strategy (zirconium route). It would be interesting to validate this tendency with the homologous six-membered zirconocene. Unfortunately, the attractive hydrozirconation method was not an efficient means of generating the corresponding allylzirconocene (Scheme 2).

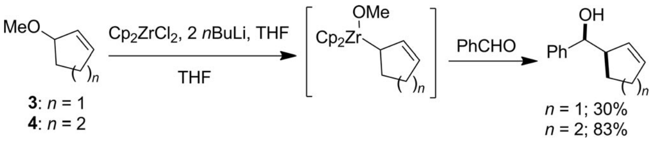
Table 1. Cyclopentenylation of phenylglycinol-derived imines.



Entry	ZnX_2	R	*dr(anti)*[a] Zr (Al[b])	Yield (%)[c]
1	$ZnCl_2$	Ph	n.d.	**1a** (10)[d,e]
2	$Zn(OTf)_2$	Ph	4:1	**1a** (75)[f,g]
3	Et_2Zn	Ph	20:1 (16:1)	**1a** (80)
4	Et_2Zn	4-$MeOC_6H_4$	20:1 (14.5:1)	**1b** (70)
5	Et_2Zn	4-$MeO_2CC_6H_4$	20:1 (7.3:1)	**1c** (57)
6	Et_2Zn	2-furyl	14:1	**1d** (74)
7	Et_2Zn	3-furyl	20:1 (11:1)	**1e** (61)
8	Et_2Zn	3-pyridyl	20:1 (12:1)	**1f** (38)
9	Et_2Zn	(*E*)-CH=CHPh	20:1 (4.4:1)	**1g** (67)
10	Et_2Zn	*i*Pr	20:1 (16:1)	**1h** (68)
11	Et_2Zn	*n*Bu	4:1	**1i** (67)[h]
12	Et_2Zn	$(CH_2)_4OBn$	4.6:1	**1j** (71)[h]

[a] Determined by ^1H NMR analysis of the crude reaction mixture. [b] Results previously obtained using the allylalanes (ref.[5]). [c] Isolated yield. [d] NMR yield. [e] The configuration of **1b** was established by X-ray analysis,[5] the configuration of the others compounds was assigned by analogy. [f] Obtained as a 1.3:1 *anti/syn* mixture of isomers. [g] Isolated yield of combined *syn* and *anti* isomers. [h] Isolated yield of combined *anti* isomers.

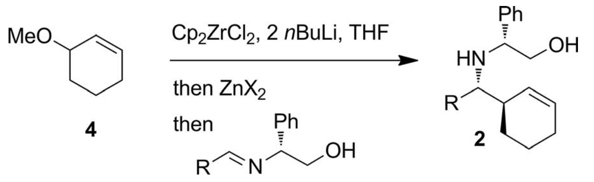
Nevertheless, allylzirconocenes can be alternatively obtained from allylic ethers according to the Taguchi and Hanzawa protocol.[7d,9] Typically, this approach involves Cp_2Zr-butene, the so-called Negishi reagent, generated in situ from Cp_2ZrCl_2 and 2 equiv. of *n*BuLi. The reaction is initiated by ligand exchange between the allylic ether and the Negishi reagent. The resulting zirconacyclopropane then undergoes a β-alkoxy elimination to give the allylzirconocene. Thus, methyl ethers **3** and **4**,[10] were submitted to the Taguchi and Hanzawa protocol, and the reactions were quenched with benzaldehyde. In contrast to the hydrozirconation procedure, better results were obtained with the six-membered ether **4** (Scheme 3) indicating that such a strategy is not well suited for smaller than six-membered cyclic compounds. A similar trend, with respect to ring size, was previously observed in the titanium series.[11] In this case, the formation of the six-membered carbocyclic allyltitanium compound was unsatisfactory, whereas seven-, eight-, and nine-membered complexes were readily prepared.



Scheme 3. Conversion of cyclic allyl ethers into zirconocenes.

The procedure was next evaluated with respect to the Zr → Zn transmetallation step by testing Et_2Zn and $Zn(OTf)_2$ as additives (Table 2). In both cases, a high level of stereoselectivity was observed. However, a much better yield was obtained using $Zn(OTf)_2$ as the transmetallating agent (Table 2, Entries 1 and 2).

Table 2. Cyclohexenylation of phenylglycinol-derived imines.



Entry	ZnX_2	R	dr(anti)[a]	Yield (%)[b]
1	Et_2Zn	Ph	20:1	**2a** (26)[c]
2	$Zn(OTf)_2$	Ph	20:1	**2a** (89)[c]
3	$Zn(OTf)_2$	4-$MeOC_6H_4$	20:1	**2b** (63)[c]
4	$Zn(OTf)_2$	4-$MeO_2CC_6H_4$	20:1	**2c** (84)[c]
5	$Zn(OTf)_2$	2-furyl	12:1	**2d** (94)[c]
6	$Zn(OTf)_2$	3-pyridyl	20:1	**2e** (73)[c]
7	$Zn(OTf)_2$	(*E*)-CH=CHPh	20:1	**2f** (77)[c]
8	$Zn(OTf)_2$	(*E*)-CCH_3=CHPh	20:1	**2g** (83)[c]
9	$Zn(OTf)_2$	*i*Pr	20:1	**2h** (79)[c]
10	$Zn(OTf)_2$	*n*Bu	16:1	**2i** (63)[c]
11	$Zn(OTf)_2$	CH_2OBn	18:1	**2j** (70)[c]
12	$Zn(OTf)_2$	$(CH_2)_4OBn$	14:1	**2k** (38)[c]

[a] Determined by ^1H NMR analysis of the crude reaction mixture. [b] Isolated yield. [c] The configuration of the major isomer was assigned by analogy to compounds of type **1**.

To complete the study, the sequence was next applied to several imines (Table 2). Pleasantly, generally high diastereoselectivities were observed providing homoallylic amines bearing an aryl (Table 2, Entries 2–4), a heteroaryl (Table 2, Entries 5 and 6), a vinyl (Table 2, Entries 7 and 8), or an alkyl substituent (Table 2, Entries 9–12). Finally, and in contrast with the aluminum method, a protected alcohol-containing chain can now be incorporated during such reactions (Table 2, Entries 11 and 12).

By comparing the results obtained using the zirconium route (Tables 1 and 2) with those generated using the allylaluminum route,[5] it appears that the transmetallation co-product plays an important role in asymmetric induction (zirconium vs. aluminum) in the case of cyclopent-2-en-1-ylzinc, and plays an even larger role for the cyclohex-2-en-1-ylzinc scenario (Scheme 1). Whereas zirconium species seem to be inert, the presence of aluminum species, which may act as disruptive Lewis acids, results in a competitive mechanistic pattern, thereby altering the reaction stereoselectivity. It seems likely that allylzincation of phenylglyinol-derived imines might proceed through a Traxler–Zimmerman-type transition state **I** in the presence of a zirconocene (Figure 2). In contrast, a competitive synclinal or antiperiplanar[6] approach of organozinc species **II** may also operate in the presence of aluminum species (Figure 2).

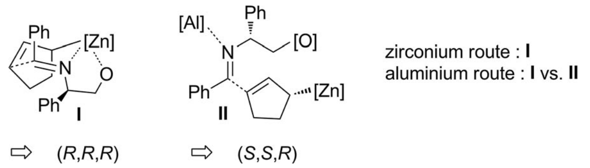
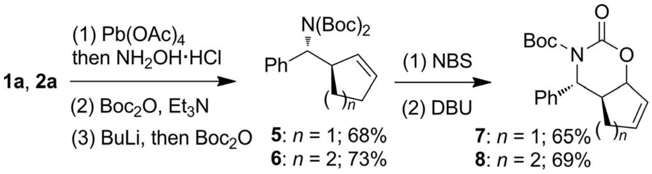


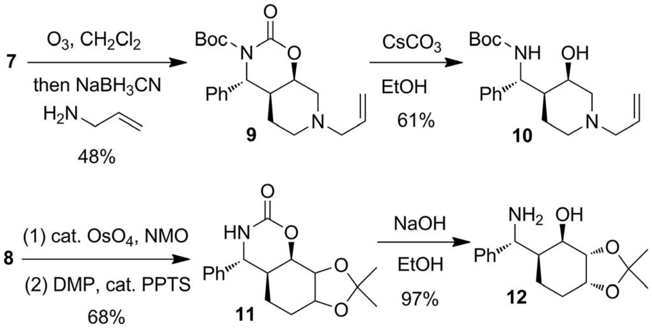
Figure 2. Possible transition states for the allylzincation of phenylglycinol-derived imines.

With a protocol for the two series of homoallylic amines in hand, we next decided to illustrate the synthetic potential of the method by stereoselectively functionalizing the cyclic skeleton by side-chain-assisted bromination. At first, the chiral auxiliary residue was removed by $Pb(OAc)_4$-mediated oxidative cleavage to afford the corresponding primary amines.[2a,5,12] Two consecutive condensations with Boc_2O provided the required bromination-inducing group.[13] Completely diastereoselective bromination[14] of **5** and **6** followed by dehydrobromination[15] afforded cyclopentenes **7** and **8** as platforms for potential further transformations (Scheme 4).



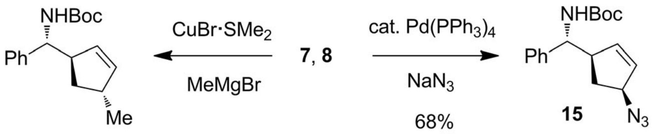
Scheme 4. Preparation of bicyclic carbamates **7** and **8**.

Among possible applications, access to 4-substituted 3-hydroxypiperidines could be readily envisioned. This framework has been targeted as the scaffold characteristic of a number of 5-HT4 receptor ligands,[16] and has served as an intermediate for preparing fluoride analogues, which also exhibit pharmacological activities such as T-type calcium channel inhibitors.[17] For instance, **10** was prepared from **7** by ozonolysis followed by a double reductive amination using allylamine and $NaBH_3CN$;[18] hydrolysis of the cyclic carbamate[19] afforded hydroxypiperidine **10** (Scheme 5). In parallel, the totally diastereoselective dihydroxylation of **8** could be achieved using OsO_4/NMO.[20] Subsequent diol protection and carbamate cleavage[21] provided tetrasubstituted cyclohexane **12** (Scheme 5).



Scheme 5. Synthetic applications of carbamates **7** and **8**.

Finally, stereoselective transition-metal-mediated allylic substitutions with opposite stereoselections were also performed (Scheme 6). First, a methyl group could be introduced in a *trans* fashion with respect to the leaving group when submitting **7** and **8** to $CuBr·SMe_2$/MeMgBr.[22] Finally, the Pd^0-catalyzed allylic addition to **7** afforded *syn* product **15** by using NaN_3 as the nucleophile.[23]



13: *n* = 1; 74%
14: *n* = 2; 89%

Scheme 6. Cu- and Pd-mediated allylic transformations of **7** and **8**.

Conclusions

Diastereoselective access to enantiomerically enriched homoallylic amines involving cycloalk-2-en-1-ylzinc compounds, generated from zirconocene, is reported. This approach was shown to be superior, in terms of stereoselectivity, to the parent method involving the allylaluminum analogues. Indeed, the presence of the zirconocene, co-generated during the transmetallation step, appears to be beneficial for the stereoselectivity of the reaction. The production of aluminum species from allylalanes may result in competitive mechanistic patterns, thus altering the stereoselectivity of the reaction. This method appears to be general and is envisioned to enable facile access to valuable nonracemic building blocks.

Experimental Section

General Methods: All experiments were carried out under air. Flash column chromatography was performed on silica gel (40–63 µm). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-250 instrument. High-resolution mass spectra were recorded with a Micromass Q-TOF micro MS spectrometer. All reagents were used as received from commercial sources without further purification. The Schwartz reagent, $Cp_2Zr(H)Cl$, was prepared according to an established procedure.[24]

General Procedure for the Synthesis of Homoallylic Amines 1. Compound 1a: To a solution of freshly distilled cyclopentadiene in THF (0.2 mL), was added $Cp_2Zr(H)Cl$ (257.5 mg, 1 mmol) in one portion. The reaction mixture was stirred until complete dissolution (ca. 30–45 min). The deep red solution was cooled to 0 °C, and a solution of Et_2Zn (1 M in hexanes, 1 mL) was slowly added. The solution was stirred at room temperature for 2 h, then cooled to –60 °C. A solution of imine (90 mg, 0.4 mmol) in THF (0.5 mL) was added; the stirring was continued at –60 °C for 1 h, then the mixture was slowly warmed to room temperature over 2 h. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (2 mL), and the resulting biphasic mixture was vigorously stirred for 1 h. The aqueous layer was extracted with Et_2O (2 × 2 mL). The organic phases were combined, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of petroleum ether (PE)/AcOEt to give **1a** (94 mg, 80 %) as a white solid.

(*R*)-2-({(*R*)-[(*R*)-Cyclopent-2-en-1-yl](phenyl)methyl}amino)-2-phenylethanol (1a):[5] M.p. 93 °C. $[\alpha]_D$ = +19.6 (*c* = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 10 H), 5.99–5.95 (m, 1 H), 5.93–5.89 (m, 1 H), 3.84 (dd, *J* = 10.2, 4.5 Hz, 1 H), 3.77 (t, *J* = 4.7 Hz, 1 H), 3.66 (d, *J* = 7.5 Hz, 1 H), 3.60 (dd, *J* = 10.3, 4.9 Hz, 1 H), 3.17–3.06 (m, 1 H), 2.55 (br. s, 2 H), 2.42–2.24 (m, 2 H), 1.92–1.78 (m, 1 H), 1.71–1.58 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 142.9, 141.9, 133.0, 128.4, 128.2, 127.3, 127.1, 126.9, 65.1, 64.4, 61.0, 52.6, 32.0, 27.3 ppm. HRMS-ESI: calcd. for $C_{20}H_{24}NO$ $[M + H]^+$ 294.1858, found 294.1853.

(*R*)-2-({(*R*)-[(*R*)-Cyclopent-2-en-1-yl](4-methoxyphenyl)-methyl}amino)-2-phenylethanol (1b):[5] White solid (70 %). M.p. 68 °C. $[\alpha]_D$ = +17.3 (*c* = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.25–7.14 (m, 5 H), 7.05 (d, *J* = 8.6 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 5.89 (dq, *J* = 5.7, 1.9 Hz, 1 H), 5.82 (dq, *J* = 5.7, 2.0 Hz, 1 H), 3.77–3.72 (m, 4 H), 3.68 (t, *J* = 4.6 Hz, 1 H), 3.54–3.47 (m, 2 H), 3.06–2.95 (m, 1 H), 2.64–1.96 (br. m, 4 H), 1.83–1.69 (m, 1 H), 1.60–1.47 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 158.4, 142.0, 135.1, 132.8, 131.8, 128.35, 128.25, 127.3, 127.2, 127.1, 113.6, 113.5, 64.4, 64.3, 60.8, 55.1, 52.6, 31.9, 27.2 ppm. HRMS-ESI:calcd. for $C_{21}H_{25}NO_2Na$ $[M + Na]^+$ 346.1783, found 346.1789.

Methyl 4-((*R*)-[(*R*)-Cyclopent-2-en-1-yl]{[(*R*)-2-hydroxy-1-phenylethyl]amino}methyl)benzoate (1c):[5] White solid (57 %). M.p. 59 °C. $[\alpha]_D$ = +37 (*c* = 0.4, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.3 Hz, 2 H), 7.22–7.11 (m, 7 H), 5.87–5.82 (m, 2 H), 3.89 (s, 3 H), 3.75 (dd, *J* = 10.1, 4.4 Hz, 1 H), 3.69–3.64 (m, 2 H), 3.55 (dd, *J* = 10.0, 5.3 Hz, 1 H), 3.08–3.03 (m, 1 H), 2.68 (br. s, 1 H), 1.85–1.71 (m, 1 H), 1.62–1.49 (m, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 166.9, 148.4, 141.5, 133.3, 131.1, 129.4, 128.7, 128.4, 127.4, 127.1, 65.2, 65.0, 61.8, 52.5, 52.0, 32.0, 27.0 ppm. HRMS-ESI: calcd. for $C_{22}H_{26}NO_3$ $[M + H]^+$ 352.1913, found 352.1911.

(*R*)-2-{(*R*)-[(*R*)-Cyclopent-2-enyl](furan-2-yl)methylamino}-2-phenylethanol (1d): Yellow oil (74 %). $[\alpha]_D$ = +64.8 (*c* = 1.4, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.29–7.15 (m, 6 H), 6.18 (d, *J* = 2.9 Hz, 1 H), 5.99 (d, *J* = 2.9 Hz, 1 H), 5.90–5.79 (m, 2 H), 3.75–3.66 (m, 2 H), 3.51 (dd, *J* = 12.1, 7.3 Hz, 1 H), 3.62 (d, *J* = 7.3 Hz, 1 H), 3.10–2.97 (m, 1 H), 2.37–2.15 (m, 4 H), 1.97–1.74 (m, 1 H), 1.62–1.48 (m, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 156.0, 151.6, 141.3, 132.9, 131.6, 128.3, 127.2, 127.0, 109.7, 106.8, 65.0, 61.7, 58.9, 50.5, 32.0, 26.9 ppm. HRMS-ESI: calcd. for $C_{18}H_{21}NO_2Na$ $[M + Na]^+$ 306.1470, found 306.1460.

(*R*)-2-({(*R*)-[(*R*)-Cyclopent-2-en-1-yl](furan-3-yl)methyl}amino)-2-phenylethanol (1e):[5] Yellow oil (61 %). $[\alpha]_D$ = +41.4 (*c* = 0.45, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.30–7.18 (m, 7 H), 6.17 (s, 1 H), 5.84–5.81 (m, 2 H), 3.80 (dd, *J* = 6.1, 4.6 Hz, 1 H), 3.71 (dd, *J* = 10.7, 4.6 Hz, 1 H), 3.56 (d, *J* = 7.2 Hz, 1 H), 3.51 (dd, *J* = 10.7, 6.2 Hz, 1 H), 3.11–2.96 (m, 1 H), 2.36 (br. s, 2 H), 2.26 (m, 2 H), 1.96–1.82 (m, 1 H), 1.69–1.55 (m, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 142.8, 141.6, 139.5, 132.7, 131.6, 128.4, 128.3, 127.3, 127.1, 109.0, 65.1, 61.3, 56.0, 51.2, 31.9, 26.5 ppm. HRMS-ESI: calcd. for $C_{18}H_{22}NO$ $[M + H]^+$ 284.1651, found 284.1642.

(*R*)-2-({(*R*)-[(*R*)-Cyclopent-2-en-1-yl](pyridin-3-yl)methyl}amino)-2-phenylethanol (1f):[5] Yellow oil (38 %). $[\alpha]_D$ = +54.8 (*c* = 0.25, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.40–8.34 (m, 2 H), 7.43 (dt, *J* = 7.8, 1.7 Hz, 1 H), 7.20–7.07 (m, 7 H), 5.85 (m, 2 H), 3.77–3.70 (m, 2 H), 3.63–3.57 (m, 2 H), 3.12–3.03 (m, 1 H), 2.34 (br. s, 2 H), 2.23 (td, *J* = 7.0, 1.8 Hz, 2 H), 1.87–1.72 (m, 1 H), 1.61–1.47 (m, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 149.4, 148.1, 141.3, 138.7, 134.8, 133.6, 131.0, 128.4, 127.4, 127.3, 123.0, 65.6, 63.4, 62.7, 52.4, 32.0, 26.9 ppm. HRMS-ESI: calcd. for $C_{19}H_{23}N_2O$ $[M + H]^+$ 295.1810, found 295.1804.

(*R*)-2-({(*S,E*)-1-[(*R*)-Cyclopent-2-en-1-yl]-3-phenylallyl}amino)-2-phenylethanol (1g):[5] Yellow oil (68 %). $[\alpha]_D$ = +92.5 (*c* = 0.2, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.32–7.17 (m, 10 H), 6.36 (d, *J* = 15.9 Hz, 1 H), 5.91–5.76 (m, 3 H), 3.87 (dd, *J* = 6.7, 4.7 Hz, 1 H), 3.72 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.52 (dd, *J* = 10.5, 6.7 Hz, 1 H), 3.23 (dd, *J* = 7.8, 6.6 Hz, 1 H), 3.01–2.90 (m, 1 H), 2.54 (br. s, 2 H), 2.37–2.24 (m, 2 H), 2.04–1.89 (m, 1 H),1.81–1.67 (m, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 142.1, 137.0, 132.9, 131.7, 131.3, 130.8, 128.5, 128.4, 127.3, 127.2 (2 C), 126.2, 65.4, 63.0, 61.3, 50.6, 32.2, 26.0 ppm. HRMS-ESI: calcd. for $C_{22}H_{26}NO$ [M + H]$^+$ 320.2014, found 320.2014.

(*R*)-2-({(*S*)-1-[(*R*)-Cyclopent-2-en-1-yl]-2-methylpropyl}amino)-2-phenylethanol (1h):[5] Colorless oil (68 %). $[\alpha]_D$ = +18.8 (*c* = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34–7.22 (m, 5 H), 5.88 (dq, *J* = 5.7, 1.9 Hz, 1 H), 5.82 (dq, *J* = 5.7, 2.1 Hz, 1 H), 3.83 (dd, *J* = 8.1, 4.7 Hz, 1 H), 3.66 (dd, *J* = 10.5, 4.7 Hz, 1 H), 3.53 (dd, *J* = 10.5, 8.2 Hz, 1 H), 2.96–2.86 (m, 1 H), 2.47–2.21 (m, 3 H), 2.00 (dtd, *J* = 13.0, 8.7, 4.3 Hz, 1 H), 1.77–1.64 (m, 1 H), 1.63–1.48 (m, 1 H), 0.82 (d, *J* = 6.9 Hz, 3 H), 0.68 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 141.9, 133.0, 131.8, 128.3, 127.5, 127.4, 66.4, 64.4, 63.6, 48.7, 31.9, 31.0, 28.5, 19.7, 17.7 ppm. HRMS-ESI: calcd. for $C_{17}H_{26}NO$ [M + H]$^+$ 260.2014, found 260.2006.

(*R*)-2-({(*S*)-1-[(*R*)-Cyclopent-2-en-1-yl]pentyl}amino)-2-phenylethanol (1i): Pale yellow oil (67 %). Isolated as a 4:1 mixture of diastereoisomers. Major isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.40–7.21 (m, 5 H), 5.81–5.77 (m, 1 H), 5.62–5.57 (m, 1 H), 3.88 (dd, *J* = 8.6, 4.6 Hz, 1 H), 3.66 (dd, *J* = 10.6, 4.5 Hz, 1 H), 3.47 (dd, *J* = 10.5, 8.6 Hz, 1 H), 3.06–2.94 (m, 1 H), 2.50 (dt, *J* = 9.4, 4.6 Hz, 1 H), 2.36–2.29 (m, 2 H), 1.93 (dtd, *J* = 14.3, 8.5, 6.1 Hz, 1 H), 1.67 (ddt, *J* = 13.3, 8.5, 6.5 Hz, 1 H), 1.32–0.99 (m, 7 H), 0.78 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 141.7, 132.2, 131.8, 128.5, 127.4, 127.2, 66.5, 62.0, 57.8, 48.8, 32.3, 31.4, 28.2, 24.9, 22.7, 13.9 ppm. HRMS-ESI: calcd. for $C_{18}H_{28}NO$ [M + Na]$^+$ 274.2171, found 274.2179.

(*R*)-2-({(*S*)-2-(Benzyloxy)-1-[(*R*)-cyclopent-2-en-1-yl]pentyl}amino)-2-phenylethanol (1j): Colorless oil (71 %). $[\alpha]_D$ = +32.2 (*c* = 0.2, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.44–7.14 (m, 10 H), 5.78 (dq, *J* = 5.5, 2.2 Hz, 1 H), 5.60–5.54 (m, 1 H), 4.45 (s, 2 H), 3.87 (dd, *J* = 8.6, 4.5 Hz, 1 H), 3.65 (dd, *J* = 10.5, 4.5 Hz, 1 H), 3.48 (dd, *J* = 10.5, 8.8 Hz, 1 H), 3.35 (t, *J* = 6.0 Hz, 2 H), 3.07–2.95 (m, 1 H), 2.54–2.48 (m, 1 H), 2.40–2.23 (m, 3 H), 2.00–1.86 (m, 1 H), 1.72–1.58 (m, 1 H),1.48–1.10 (m, 7 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 141.5, 138.6, 132.02, 131.99, 128.5, 128.3, 127.57, 127.52, 127.47, 127.2, 72.8, 70.1, 66.5, 62.1, 57.9, 48.7, 32.3, 31.5, 29.7, 24.9, 22.7 ppm. HRMS-ESI: calcd. for $C_{25}H_{34}NO_2$ [M + H]$^+$ 380.2590, found 380.2579.

General Procedure for the Synthesis of Homoallylic Amines 2. Compound 2a: To a solution of **4** (112 mg, 1 mmol) and Cp_2ZrCl_2 (322 mg, 1.02 mmol) in THF (8 mL) was added dropwise a solution of *n*BuLi (2.5 M in hexanes, 0.8 mL, 2 mmol) at 0 °C. The resulting solution was stirred at room temperature for 3 h, then $Zn(OTf)_2$ (363 mg, 1 mmol) was added in one portion. The mixture was stirred at room temperature for 1 h then cooled to –40 °C. A solution of imine (90 mg, 0.4 mmol) in THF (0.5 mL) was added, and the mixture was stirred at –40 °C for 1 h, then slowly warmed to room temperature over 2 h. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added, and the heterogeneous mixture was vigorously stirred for 30 min. The aqueous layer was extracted with Et_2O (2 × 5 mL), the organic phases were combined, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of PE/AcOEt to give the homoallylic amine **2a** (103 mg, 89 %) as a pale yellow solid.

(*R*)-2-({(*R*)-[(*R*)-Cyclohex-2-en-1-yl](phenyl)methyl}amino)-2-phenylethanol (2a): M.p. 79 °C. $[\alpha]_D$ = +5.3 (*c* = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.28–7.06 (m, 10 H), 5.99 (d, *J* = 10.4 Hz, 1 H), 5.79 (d, *J* = 9.7 Hz, 1 H), 3.77 (dd, *J* = 10.3, 4.5 Hz, 1 H), 3.68 (t, *J* = 4.8 Hz, 1 H), 3.57–3.51 (m, 2 H), 2.46–2.40 (m, 1 H), 2.01–1.89 (m, 2 H), 1.71–1.60 (m, 1 H), 1.50–1.36 (m, 2 H), 1.27–1.15 (m, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 142.7, 141.9, 129.0, 128.5, 128.4, 128.2, 127.2, 126.9, 65.3, 64.6, 61.2, 41.8, 26.6, 25.3, 21.5 ppm. HRMS-ESI: calcd. for $C_{20}H_{26}NO$ [M + H]$^+$ 308.2014, found 308.2008.

(*R*)-2-({(*R*)-[(*R*)-Cyclohex-2-en-1-yl](4-methoxyphenyl)methyl}amino)-2-phenylethanol (2b): Pale yellow oil (63 %). $[\alpha]_D$ = +1 (*c* = 0.8, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.30–7.12 (m, 5 H), 7.03 (d, *J* = 8.6 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 5.98 (dq, *J* = 10.2, 2.1 Hz, 1 H), 5.78 (dq, *J* = 9.6, 3.1 Hz, 1 H), 3.80–3.74 (m, 4 H), 3.68 (t, *J* = 7.9 Hz, 1 H), 3.54 (dd, *J* = 10.3, 5.1 Hz, 1 H), 3.48 (d, *J* = 8.0 Hz, 1 H), 2.47–2.28 (br. m, 3 H), 2.00–1.90 (m, 2 H), 1.70–1.59 (m, 1 H), 1.52–1.38 (m, 2 H), 1.26–1.16 (m, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 158.5, 141.8, 134.7, 128.9, 128.7, 128.3, 127.3, 127.2, 113.5, 64.6, 64.5, 61.1, 55.2, 41.7, 26.5, 25.3, 21.4 ppm. HRMS-ESI: calcd. for $C_{22}H_{28}NO_2$ [M + H]$^+$ 338.2120, found 338.2122.

Methyl 4-((*R*)-[(*R*)-Cyclohex-2-en-1-yl]{[(*R*)-2-hydroxy-1-phenylethyl]amino}methyl)benzoate (2c): White solid (84 %). M.p. 108 °C. $[\alpha]_D$ = +5.1 (*c* = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.28–7.07 (m, 8 H), 7.90 (d, *J* = 7.9 Hz, 2 H), 5.92 (d, *J* = 10.2 Hz, 1 H), 5.84–5.76 (m, 1 H), 3.89 (s, 3 H), 3.76 (dd, *J* = 10.1, 4.1 Hz, 1 H), 3.67 (dd, *J* = 5.3, 4.2 Hz, 1 H), 3.63–3.55 (m, 2 H), 2.49–2.33 (m, 2 H), 2.00–1.90 (m, 2 H), 1.71–1.36 (m, 5 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.4, 25.2, 26.4, 41.7, 52.0, 62.0, 65.0, 65.4, 127.2, 127.4, 127.8, 127.9, 128.3, 128.4, 128.7, 129.4, 129.4, 141.4, 148.4, 166.9 ppm. HRMS-ESI: calcd. for $C_{23}H_{28}NO_3$ [M + H]$^+$ 366.2069, found 366.2060.

(*R*)-2-({(*R*)-[(*R*)-Cyclohex-2-en-1-yl](furan-2-yl)methyl}amino)-2-phenylethanol (2d): Yellow oil (94 %). $[\alpha]_D$ = +21.8 (*c* = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.27–7.15 (m, 6 H), 6.18 (t, *J* = 2.4 Hz, 1 H), 5.98 (d, *J* = 3.1 Hz, 1 H), 5.91 (d, *J* = 10.4 Hz, 1 H), 5.78 (dq, *J* = 10.1, 1.8 Hz, 1 H), 3.75–3.67 (m, 2 H), 3.58–3.50 (m, 2 H), 2.54–2.44 (m, 1 H), 2.32 (br. s, 2 H), 2.02–1.92 (m, 2 H), 1.74–1.63 (m, 1 H), 1.58–1.40 (m, 2 H), 1.35–1.20 (m, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 155.4, 141.6, 141.2, 129.0, 128.4, 128.3, 127.2, 127.0, 109.6, 107.2, 65.1, 61.9, 59.2, 39.9, 26.1, 25.2, 21.4 ppm. HRMS-ESI: calcd. for $C_{19}H_{24}NO_2$ [M + H]$^+$ 298.1807, found 298.1798.

(*R*)-2-({(*R*)-[(*R*)-Cyclohex-2-en-1-yl](pyridin-3-yl)methyl}amino)-2-phenylethanol (2e): White solid (73 %). M.p. 99 °C. $[\alpha]_D$ = +10.5 (*c* = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.41–8.34 (m, 2 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 7.22–7.08 (m, 6 H), 5.90 (d, *J* = 10.6 Hz, 1 H), 5.85–5.77 (m, 1 H), 3.78–3.71 (m, 2 H), 3.65–3.56 (m, 2 H), 2.66 (br. s, 2 H), 2.53–2.42 (m, 1 H), 2.01–1.90 (m, 2 H), 1.72–1.60 (m, 1 H), 1.55–1.41 (m, 2 H), 1.26–1.11 (m, 2 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 149.3, 148.1, 140.9, 138.2, 134.9, 129.8, 128.4, 127.4, 127.3, 123.0, 65.6, 63.6, 63.0, 41.5, 26.2, 25.2, 21.3 ppm. HRMS-ESI: calcd. for $C_{20}H_{25}N_2O$ [M + H]$^+$ 309.1967, found 309.1953.

(*R*)-2-({(*S*,*E*)-1-[(*R*)-Cyclohex-2-en-1-yl]-3-phenylallyl}amino)-2-phenylethanol (2f): Pale yellow oil (77 %). $[\alpha]_D$ = +39.5 (*c* = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.33–7.11 (m, 10 H), 6.36 (d, *J* = 15.9 Hz, 1 H), 5.92 (dd, *J* = 15.9, 8.1 Hz, 1 H), 5.66–5.84 (m, 2 H), 3.87 (dd, *J* = 6.8, 4.6 Hz, 1 H), 3.73 (dd, *J* = 10.7, 4.6 Hz, 1 H), 3.54 (dd, *J* = 10.6, 6.9 Hz, 1 H), 3.20 (t, *J* = 7.2 Hz, 1 H), 2.36 (br. s, 1 H), 2.03–1.95 (m, 2 H), 1.83–1.72 (m, 1 H), 1.58–1.35 (m, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 141.9, 137.0, 131.4, 130.9, 129.0, 128.5, 128.4, 127.3, 127.23, 127.18, 126.2, 65.6, 63.0, 62.3, 39.8, 25.35, 25.30, 21.6 ppm. HRMS-ESI: calcd. for $C_{24}H_{30}NO$ [M + H]$^+$ 348.2327, found 348.2312.

(*R*)-2-({(*R*,*E*)-1-[(*R*)-Cyclohex-2-en-1-yl]-2-methyl-3-phenylallyl}amino)-2-phenylethanol (2g): Pale yellow solid (83 %). M.p. 70 °C. $[\alpha]_D$ = –49.8 (*c* = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.42–7.04 (m, 10 H), 6.29 (s, 1 H), 6.10 (d, *J* = 9.2 Hz, 1 H), 5.81 (d, *J* = 9.9 Hz, 1 H), 3.82–3.67 (m, 2 H), 3.57 (dd, *J* = 11.5, 7.7 Hz, 1 H), 2.99 (d, *J* = 9.5 Hz, 1 H), 2.19–1.96 (m, 3 H), 1.77–1.66 (m, 1 H), 1.62–1.24 (m, 8 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 142.3, 137.8, 137.5, 128.85, 128.81, 128.6, 128.4, 128.3, 127.9, 127.3, 127.2, 126.1, 71.0, 64.9, 63.9, 38.1, 26.6, 25.3, 21.2, 12.6 ppm. HRMS-ESI: calcd. for $C_{24}H_{30}NO$ [M + H]$^+$ 348.2327, found 348.2336.

(*R*)-2-({(*S*)-1-[(*R*)-Cyclohex-2-en-1-yl]-2-methylpropyl}amino)-2-phenylethanol (2h): Colorless oil (79 %). $[\alpha]_D$ = +38 (*c* = 0.9, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36–7.263 (m, 5 H), 5.80–5.63 (m, 2 H), 3.85 (dd, *J* = 8.5, 4.7 Hz, 1 H), 3.66 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.54 (dd, *J* = 10.6, 8.5 Hz, 1 H), 2.45–2.35 (m, 1 H), 2.22 (t, *J* = 4.6 Hz, 1 H), 2.05–1.98 (m, 2 H), 1.82–1.65 (m, 3 H), 1.57–1.45 (m, 2 H), 0.80 (d, *J* = 6.7 Hz, 3 H), 0.74 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 141.4, 130.1, 128.3, 127.9, 127.5, 127.4, 66.6, 65.8, 63.3, 38.0, 30.5, 27.1, 25.3, 22.4, 20.5, 18.7 ppm. HRMS-ESI: calcd. for $C_{18}H_{28}NO$ [M + H]$^+$ 274.2171, found 274.2176.

(*R*)-2-({(S)-1-[(*R*)-Cyclohex-2-en-1-yl]pentyl}amino)-2-phenylethanol (2i): Pale yellow oil (63 %). $[\alpha]_D$ = –54.6 (*c* = 0.6, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.42–7.22 (m, 5 H), 5.79–5.69 (m, 1 H), 5.36 (d, *J* = 9.9 Hz, 1 H), 3.89 (dd, *J* = 8.9, 4.5 Hz, 1 H), 3.68 (dd, *J* = 10.7, 4.5 Hz, 1 H), 3.56 (dd, *J* = 10.5, 9.1 Hz, 1 H), 2.90 (br. s, 2 H), 2.54–2.36 (m, 2 H), 2.02–1.94 (m, 2 H), 1.84–1.74 (m, 2 H), 1.63–0.99 (m, 10 H), 0.79 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 140.6, 129.5, 128.7, 128.5, 127.6, 127.3, 66.5, 62.0, 58.3, 37.4, 60.6, 28.7, 25.5, 23.6, 22.6, 22.2, 13.9 ppm. HRMS-ESI: calcd. for $C_{19}H_{30}NO$ [M + H]$^+$ 288.2327, found 288.2321.

(*R*)-2-({(*R*)-2-(Benzyloxy)-1-[(*R*)-cyclohex-2-en-1-yl]}ethyl)amino-2-phenylethanol (2j): Colorless yellow oil (70 %). $[\alpha]_D$ = –16 (*c* = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.40–7.19 (m, 10 H), 5.73 (dq, *J* = 9.8, 3.2 Hz, 1 H), 5.52 (d, *J* = 10.4 Hz, 1 H), 4.32 (s, 2 H), 3.86 (dd, *J* = 9.2, 4.5 Hz, 1 H), 3.64 (dd, *J* = 10.6, 4.5 Hz, 1 H), 2.75 (q, *J* = 5.2 Hz, 1 H), 2.75 (q, *J* = 5.2 Hz, 1 H), 2.60 (br. s, 1 H), 2.52–2.40 (m, 1 H), 2.04–1.92 (m, 2 H), 1.89–1.26 (m, 5 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 141.1, 138.3, 128.9, 128.6, 128.5, 128.2, 127.45, 127.40, 127.3, 127.2, 72.8, 70.5, 66.8, 61.9, 58.3, 36.4, 25.3, 24.4, 22.2 ppm. HRMS-ESI: calcd. for $C_{23}H_{30}NO_2$ [M + H]$^+$ 352.2277, found 352.2284.

(*R*)-2-({(*S*)-5-(Benzyloxy)-1-[(*R*)-cyclohex-2-en-1-yl]pentyl}-amino)-2-phenylethanol (2k): Yellow oil (38 %). $[\alpha]_D$ = –28.3 (*c* = 0.6, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 10 H), 5.77–5.67 (m, 1 H), 5.34 (d, *J* = 12.0 Hz, 1 H), 4.46 (s, 2 H), 3.85 (dd, *J* = 8.8, 4.4 Hz, 1 H), 3.49 (dd, *J* = 10.4, 9.0 Hz, 1 H), 3.65 (dd, *J* = 10.5, 4.5 Hz, 1 H), 3.36 (t, *J* = 6.2 Hz, 2 H), 2.50–2.26 (m, 4 H), 2.03–1.94 (m, 2 H), 1.84–1.74 (m, 2 H), 1.60–1.16 (m, 8 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 141.2, 138.6, 129.7, 128.5, 128.3, 127.50, 127.45, 127.40, 127.3, 72.8, 70.1, 61.7, 58.0, 37.3, 30.8, 29.6, 25.5, 23.4, 23.2, 22.2 ppm. HRMS-ESI: calcd. for $C_{26}H_{36}NO_2$ [M + H]$^+$ 394.2746, found 394.2733.

General Procedure for Bis-Boc Protection of 1a and 2a. Compound 5: To a solution of **1a** (0.79 g, 2.7 mmol) in a 1:1 mixture of MeOH/CH_2Cl_2 (28 mL) at 0 °C was added $Pb(OAc)_4$ (1.5 g, 3.37 mmol) in one portion. The solution was stirred for 1 h; then $NH_2OH{\cdot}HCl$ (1.9 g, 27 mmol) was added at 0 °C. The stirring was continued at room temperature for 1 h. The solvents were removed under reduced pressure. CH_2Cl_2 (40 mL) was added, and the solid was filtered off. The filtrate was washed with an aqueous solution of NaOH (10 %, 3 × 10 mL), dried with $MgSO_4$ and filtered. Et_3N (0.42 mL, 3 mmol) and Boc_2O (0.59 g, 2.7 mmol) were added to the filtrate, and the resulting mixture was stirred for 4 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a 5:1 mixture of PE/Et_2O to give the mono-Boc-protected amine (646 mg, 87 %). To a solution of the above mono-Boc-protected amine (646 mg, 2.36 mmol) in THF (10 mL) was added a solution of *n*BuLi (2.5 M in hexanes, 0.94 mL, 2.36 mmol) at –78 °C. The solution was stirred for 30 min, then a solution of Boc_2O (510 mg, 2.36 mmol) in THF (2 mL) was added. The solution was stirred at room temperature for 12 h, then water (5 mL) was added. The aqueous layer was extracted with Et_2O (2 × 5 mL), the organic phases were combined, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with a 5:1 mixture of PE/Et_2O to give **5** (690 mg, 78 %) as a colorless oil.

{(*R*)-[(*R*)-Cyclopent-2-en-1-yl](di-*tert*-butoxycarbonylamino)-methyl}benzene (5): $[\alpha]_D$ = +70 (*c* = 2, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$)(250 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 6.9 Hz, 2 H), 7.36–7.18 (m, 3 H), 5.86 (dm, *J* = 5.5 Hz, 1 H), 5.76 (dm, *J* = 5.5 Hz, 1 H), 5.03 (d, *J* = 10.9 Hz, 1 H), 3.93–3.81 (m, 1 H), 2.50–2.28 (m, 2 H), 2.15–2.01 (m, 1 H), 1.48–1.38 (m, 1 H), 1.38 (s, 18 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 139.9, 132.6, 131.8, 128.3, 127.9, 127.0, 82.0, 63.8, 46.6, 32.1, 29.1, 27.8 ppm; note: 1 C resonance was not discernible. HRMS-ESI: calcd. for $C_{22}H_{31}NO_4Na$ [M + Na]$^+$ 396.2151, found 396.2150.

{(*R*)-[(*R*)-Cyclohex-2-en-1-yl](di-*tert*-butoxycarbonylamino)-methyl}benzene (6): Colorless oil (73 %). $[\alpha]_D$ = +73.7 (*c* = 2, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.0 Hz, 2 H), 7.28–7.10 (m, 3 H), 5.76 (d, *J* = 10.3 Hz, 1 H), 5.66 (d, *J* = 10.3 Hz, 1 H), 4.95 (d, *J* = 11.2 Hz, 1 H), 3.33–3.21 (m, 1 H), 1.97–1.89 (m, 2 H), 1.69–1.47 (m, 3 H), 1.32 (s, 18 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 153.2, 139.2, 129.2, 128.7, 127.9, 127.5, 127.2, 81.9, 63.7, 34.7, 27.8, 27.3, 27.1, 25.2, 20.2 ppm. HRMS-ESI: calcd. for $C_{23}H_{33}NO_4Na$ [M + Na]$^+$ 410.2307, found 410.2314.

General Procedure for the Oxobromination of 5 and 6. Compound 5′: A solution of **5** (690 mg, 1.85 mmol) and NBS (507 mg, 2.77 mmol) in CH_2Cl_2 (10 mL) was stirred under reflux for 36 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel eluting with a 5:1 mixture of PE/Et_2O to give **5′** (81 %) as a white solid.

***tert*-Butyl (4*R*,4a*S*,7*R*,7a*R*)-7-Bromo-2-oxo-4-phenylhexahydro-cyclopenta[*e*][1,3]oxazine-3(2*H*)-carboxylate (5′):** M.p. 108 °C. $[\alpha]_D$ = –15.2 (*c* = 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.46–7.18 (m, 5 H), 5.40 (d, *J* = 2.3 Hz, 1 H), 4.70 (d, *J* = 4.8 Hz, 1 H), 4.37 (d, *J* = 5.1 Hz, 1 H), 3.19–3.12 (m, 1 H), 2.64–2.36 (m, 2 H), 2.26–2.17 (m, 1 H), 1.74 (m, 1 H), 1.87–1.78 (m, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 151.5, 140.0, 129.1, 127.9, 125.0, 85.4, 84.3, 59.7, 52.2, 40.6, 33.5, 27.7, 26.2 ppm. HRMS-ESI: calcd. for $C_{18}H_{22}BrNO_4Na$ [M + Na]$^+$ 418.0630, found 418.0641.

***tert*-Butyl (4*R*,4a*S*,8*R*,8a*R*)-8-Bromo-2-oxo-4-phenylhexahydro-2*H*-benzo[*e*][1,3]oxazine-3(4*H*)-carboxylate (6′):** White solid (73 %). M.p. 149 °C. $[\alpha]_D$ = –32.5 (*c* = 2, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.46–7.29 (m, 3 H), 7.21 (d, *J* = 7.4 Hz, 2 H), 5.12 (s, 1 H), 4.44 (br. s, 1 H), 4.40 (br. s, 1 H), 2.61–2.51 (m, 1 H), 2.17 (ddd, *J* = 15.8, 9.9, 3.4 Hz, 1 H), 1.96–1.55 (m, 5 H), 1.29 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 150.7, 148.0, 140.2, 128.7, 127.7, 124.8, 83.7, 73.6, 63.0, 47.8, 34.7, 27.4, 27.2, 24.9, 18.8 ppm. HRMS-ESI: calcd. for $C_{19}H_{24}BrNO_4Na$ [M + Na]$^+$ 432.0786, found 432.0778.

General Procedure for the Dehydrobromination. Compound 7: To a solution of the above product (300 mg, 0.75 mmol) in THF (1.5 mL), was added DBU (0.33 mL, 2.25 mmol). The resulting solution was stirred under reflux for 12 h, then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a 5:1 mixture of PE/Et_2O to give **7** (192 mg, 81 %) as a colorless oil.

***tert*-Butyl (4*R*,4a*S*,7a*S*)-2-Oxo-4-phenyl-4,4a,5,7a-tetrahydro-cyclopenta[*e*][1,3]oxazine-3(2*H*)-carboxylate (7):** $[\alpha]_D$ = +98 (*c* = 2, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.23–7.13 (m, 5 H), 5.45 (s, 1 H), 5.78 (s, 1 H), 6.07 (d, *J* = 4.9 Hz, 1 H), 5.22 (d, *J* = 8.2 Hz, 1

H), 3.26 (q, *J* = 7.5 Hz, 1 H), 2.75 (dd, *J* = 17.5, 8.5 Hz, 1 H), 2.47–2.32 (m, 1 H), 1.42 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 152.8, 150.2, 139.3, 138.0, 129.8, 128.9, 127.7, 125.8, 84.7, 83.8, 59.1, 40.0, 37.6, 27.9 ppm. HRMS-ESI: calcd. for $C_{18}H_{21}NO_4Na$ $[M + Na]^+$ 338.1368, found 338.1376.

***tert*-Butyl (4*R*,4a*S*,8a*S*)-2-Oxo-4-phenyl-4,4a,5,6-tetrahydro-2*H*-benzo[*e*][1,3]oxazine-3(8a*H*)-carboxylate (8):** White solid (95 %). M.p. 136 °C. $[\alpha]_D$ = +2.6 (*c* = 1.3, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.46–7.20 (m, 5 H), 6.06–5.97 (m, 1 H), 5.84–5.76 (m, 1 H), 5.18 (d, *J* = 2.6 Hz, 1 H), 4.60 (d, *J* = 4.4 Hz, 1 H), 2.40–2.09 (m, 3 H), 1.91–1.77 (m, 2 H), 1.34 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 151.4, 148.4, 140.8, 133.6, 128.7, 127.6, 125.0, 123.3, 83.5, 69.8, 62.3, 38.1, 27.4, 24.8, 22.1 ppm. HRMS-ESI: calcd. for $C_{19}H_{23}NO_4Na$ $[M + Na]^+$ 352.1525, found 352.1524.

***tert*-Butyl (4*R*,4a*S*,8a*R*)-7-Allyl-2-oxo-4-phenylhexahydro-2*H*-pyrido[4,3-*e*][1,3]oxazine-3(4*H*)-carboxylate (9):** O_3 was bubbled through a solution of **7** (200 mg, 0.64 mmol) in CH_2Cl_2 (10 mL) until a blue color persisted. The solution was stirred for 15 min, degassed with a flow of N_2 prior to Me_2S addition (0.2 mL). The solution was slowly warmed to room temperature, then allylamine (75 µL, 1 mmol), $NaBH_3CN$ (169 mg, 2.5 mmol), and AcOH (one drop) were added. The resulting mixture was stirred at room temperature for 36 h. Water (10 mL) was added. The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with AcOEt to give **9** as a colorless oil (104 mg, 48 %). $[\alpha]_D$ = –16.8 (*c* = 0.5, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 3 H), 7.23 (d, *J* = 7.9 Hz, 2 H), 5.84 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1 H), 5.21–5.11 (m, 3 H), 4.35 (br. s, 1 H), 3.17 (d, *J* = 12.5 Hz, 1 H), 3.04–2.97 (m, 3 H), 2.10–1.86 (m, 4 H), 1.81–1.77 (m, 1 H), 1.30 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 151.4, 148.9, 141.1, 134.7, 128.9, 127.8, 125.1, 118.0, 83.7, 70.8, 62.2, 60.9, 55.6, 51.4, 38.3, 27.5, 25.6 ppm. HRMS-ESI: calcd. for $C_{21}H_{29}N_2O_4$ $[M + H]^+$ 373.2127, found 373.2138.

***tert*-Butyl {(*R*)-[(3*R*,4*S*)-1-Allyl-3-hydroxypiperidin-4-yl]-(phenyl)methyl}carbamate (10):** To a solution of **9** (71 mg, 0.19 mmol) in MeOH (2 mL) was added $CsCO_3$ (10 mg, 0.05 mmol), and the mixture was stirred at room temperature for 48 h. The reaction was quenched with a saturated solution of NH_4Cl (1 mL), and the aqueous layer was extracted with CH_2Cl_2 (4 × 2 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with Et_2O to give **10** (40 mg, 61 %) as a white solid. M.p. 121 °C. $[\alpha]_D$ = +48.7 (*c* = 0.6, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.38–7.23 (m, 5 H), 6.10 (d, *J* = 8.5 Hz, 1 H), 5.84 (ddt, *J* = 16.8, 10.3, 6.0 Hz, 1 H), 5.21–5.10 (m, 2 H), 4.71 (t, *J* = 7.3 Hz, 1 H), 3.74 (br. s, 1 H), 3.55–3.44 (m, 1 H), 3.05–2.91 (m, 4 H), 2.02–1.85 (m, 3 H), 1.68–1.55 (m, 1 H), 1.42 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 156.1, 141.8, 134.7, 128.5, 127.0, 126.5, 118.1, 79.3, 65.1, 61.1, 59.6, 57.4, 53.0, 28.4, 24.4 ppm. HRMS-ESI: calcd. for $C_{20}H_{31}N_2O_3$$[M + H]^+$ 347.2335, found 347.2330.

***tert*-Butyl (4*R*,4a*S*,7*R*,8*R*,8a*R*)-7,8-Dihydroxy-2-oxo-4-phenyl-hexahydro-2*H*-benzo[*e*][1,3]oxazine-3(4*H*)-carboxylate:** To a solution of **8** (150 mg, 0.46 mmol) in a 10:1 mixture of acetone/H_2O (9 mL) were added a solution of OsO_4 (4 % in H_2O, 0.25 mL) and *N*-methylmorpholine *N*-oxide (107 mg, 0.91 mmol). The mixture was stirred for 6 h, then sodium sulfite (100 mg) was added, and stirring was continued for 1 h. The mixture was filtered and the solvent evaporated. The residue was purified by flash column chromatography on silica gel eluting with a mixture of PE and AcOEt (50:50 → 0:100) to give the corresponding diol (161 mg, 97 %) as a single isomer. White solid, m.p. 114 °C. $[\alpha]_D$ = –19.7 (*c* = 0.7, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.43–7.25 (m, 3 H), 7.17 (d, *J* = 7.4 Hz, 2 H), 5.07 (s, 1 H), 4.46 (br. s, 1 H), 4.00 (br. s, 1 H), 3.91–3.83 (m, 1 H), 3.59 (br. s, 2 H), 2.24 (d, *J* = 10.2 Hz, 1 H), 1.97–1.54 (m, 4 H), 1.23 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 150.9, 149.4, 140.8, 128.8, 127.8, 125.0, 84.1, 74.8, 68.3, 67.1, 62.8, 34.7, 27.3, 26.2, 23.9 ppm. HRMS-ESI: calcd. for $C_{19}H_{25}NO_6Na$ $[M + Na]^+$ 386.1580, found 386.1585.

(4*R*,4a*S*,7*R*,8*R*,8a*R*)-7,8-Dihydroxy-7,8-isopropylidene-4-phenyl-octahydro-2*H*-benzo[*e*][1,3]oxazin-2-one (11): A mixture of the above diol (152 mg, 0.42 mmol), DMP (1 mL, 8.4 mmol) and APTS (8 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) was stirred for 12 h, then the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of PE/AcOEt (50:50 → 10:90) to give **11** (90 mg, 71 %) as a white solid. M.p. 220 °C. $[\alpha]_D$ = –59 (*c* = 0.9, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.45–7.22 (m, 5 H), 6.67 (br. s, 1 H), 4.48–4.39 (m, 2 H), 4.32 (q, *J* = 5.8 Hz, 1 H), 4.19 (dd, *J* = 5.6, 3.0 Hz, 1 H), 2.20–2.11 (m, 1 H), 2.03–1.57 (m, 4 H), 1.40 (s, 3 H), 1.30 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 153.5, 141.3, 128.8, 127.9, 125.7, 108.7, 74.0, 72.9, 72.2, 58.3, 34.7, 27.7, 25.53, 25.49, 21.2 ppm. HRMS-ESI: calcd. for $C_{17}H_{21}NO_4Na$ $[M + H]^+$ 326.1368, found 326.1373.

(3a*S*,4*R*,5*S*,7a*R*)-5-[(*R*)-Amino(phenyl)methyl]-2,2-dimethylhexa-hydrobenzo[*d*][1,3]dioxol-4-ol (12): To a solution of **11** (83 mg, 0.27 mmol) in EtOH (5 mL) was added an aqueous solution of NaOH (10 %, 5 mL), and the resulting mixture was heated to reflux for 12 h. EtOH was removed under reduced pressure, and the residue was extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined, dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give pure **12** (76 mg, 94 %) as a white solid. M.p. 118 °C. $[\alpha]_D$ = +1.6 (*c* = 0.7, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.44–7.21 (m, 5 H), 4.37–4.28 (m, 1 H), 4.21 (d, *J* = 5.8 Hz, 1 H), 4.09–4.05 (m, 2 H), 1.99–1.89 (m, 2 H), 1.65–1.50 (m, 3 H), 1.45 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.5, 26.0, 27.2, 28.2, 41.8, 58.2, 69.3, 73.0, 77.6, 107.8, 126.0, 127.3, 128.6, 143.4 ppm. HRMS-ESI: calcd. for $C_{16}H_{23}NO_3Na$ $[M + Na]^+$ 300.1576, found 300.1583.

General Procedure for the Copper-Mediated Allylic Methylation. Compound 13: To a suspension of $CuBr\cdot Me_2S$ (131 mg, 0.64 mmol) in THF (1.5 mL) was added a solution of MeMgBr (3 M in THF, 0.21 mL, 0.63 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, then a solution of **7** (100 mg, 0.32 mmol) was added dropwise. The mixture was stirred at room temperature for 5 h, then a solution of NaOH (1 M, 1.5 mL) was added, and the stirring was continued overnight. The aqueous layer was extracted with Et_2O (3 × 2 mL). The organic phases were combined, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with a mixture of PE/Et_2O (4:1) to give **13** (67 mg, 74 %) as a white solid.

***tert*-Butyl {(*R*)-[(1*R*,4*R*)-4-Methylcyclopent-2-en-1-yl](phenyl)-methyl}carbamate (13):** M.p. 92 °C. $[\alpha]_D$ = +100 (*c* = 0.5, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.40–7.11 (m, 5 H), 5.82 (dt, *J* = 5.7, 2.0 Hz, 1 H), 5.49–5.44 (m, 1 H), 4.93 (br. d, *J* = 7.5 Hz, 1 H), 4.68 (br. s, 1 H), 3.20 (br. s, 1 H), 2.85–2.75 (m, 1 H), 1.93 (ddd, *J* = 13.0, 8.3, 4.5 Hz, 1 H), 1.52 (ddd, *J* = 13.8, 9.0, 5.5 Hz, 1 H), 1.42 (s, 9 H), 0.98 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 155.6, 142.6, 140.7, 128.2, 126.7, 126.2, 79.3, 57.7, 51.6, 39.7, 28.3, 21.2 ppm. HRMS-ESI: calcd. for $C_{18}H_{25}NO_2Na$ $[M + Na]^+$ 310.1783, found 310.1777.

***tert*-Butyl {(*R*)-[(1*R*,4*R*)-4-Methylcyclohex-2-en-1-yl](phenyl)-methyl}carbamate (14):** White solid (89 %). M.p. 150 °C. $[\alpha]_D$ = +118 (*c* = 0.2, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.39–7.12 (m, 5 H), 5.66 (d, J = 10.2 Hz, 1 H), 5.45 (d, J = 9.7 Hz, 1 H), 4.91 (d, J = 6.9 Hz, 1 H), 4.61 (br. s, 1 H), 2.57–2.44 (m, 1 H), 2.23–2.09 (m, 1 H), 1.91–1.56 (m, 2 H), 1.43 (s, 9 H), 1.36–1.08 (m, 2 H), 0.94 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 137.6, 128.3, 126.8, 126.3, 124.7, 41.8, 31.2, 30.7, 28.4, 27.3, 21.6 ppm; note: 2 C resonances were not discernible. HRMS-ESI: calcd. for $C_{19}H_{27}NO_2Na$ [M + Na]$^+$ 324.1939, found 324.1945.

***tert*-Butyl {(*R*)-[(1*R*,4*S*)-4-Azidocyclopent-2-en-1-yl](phenyl)-methyl}carbamate (15):** To a solution **7** (146 mg, 0.46 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.024 mmol) in a 2:1 mixture of degassed THF/H_2O (4.5 mL) was added a solution of NaN_3 (65 mg, 1 mmol) in H_2O (0.5 mL). The resulting mixture was stirred at room temperature under argon for 10 h. The reaction mixture was diluted with Et_2O (5 mL), the aqueous layer was extracted with Et_2O (5 mL), the organic phases were combined, washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with a mixture of PE/Et_2O (4:1) to give **15** (99 mg, 68 %) as a pale yellow solid. M.p. 109 °C. $[\alpha]_D$ = +6.5 (c = 0.5, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.46–7.11 (m, 5 H), 5.91–5.80 (m, 2 H), 4.97 (d, J = 8.6 Hz, 1 H), 4.78–4.67 (m, 1 H), 4.43 (br. dd, J = 6.5, 5.2 Hz, 1 H), 3.14 (br. s, 1 H), 2.40 (dt, J = 14.8, 8.4 Hz, 1 H), 1.63 (dt, J = 13.6, 4.8 Hz, 1 H), 1.48–1.11 (m, 10 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 155.5, 135.0, 132.1, 128.5, 127.2, 126.2, 79.6, 66.4, 56.9, 51.0, 33.4, 28.3 ppm; note: 1 C resonance was not discernible. HRMS-ESI: calcd. for $C_{17}H_{22}N_4O_2Na$ [M + Na]$^+$ 337.1640, found 337.1631.

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