Stereoselective Synthesis of Quaternary Benzylic Carbons Using C_2 Symmetric Imidazolines and Tetrahydrofuran as Electrophile

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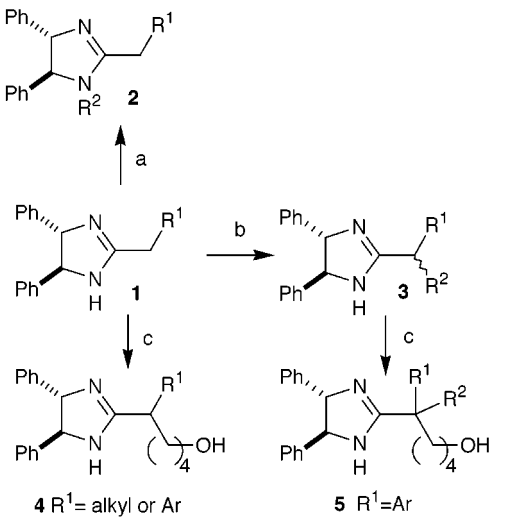
Alkylative ring opening of tetrahydrofuran in the presence of 9-BBN triflate is studied. Dianions derived from C_2 symmetric imidazolines induce excellent to modest acyclic diastereoselectivity to form quaternary benzylic centers, using the 9-BBN triflate/THF system or methyl iodide as electrophiles. The direction of the stereoinduction is consistent in both cases. Absolute configuration for the newly created stereogenic center was established by chemical correlation. Low-temperature NMR studies of the dilithiated intermediates **42** and **43** suggest the presence of *N*- and *C*-metalated compounds, where the metal-bearing benzylic carbon is sp^3 hybridized.

Introduction

Despite advances in asymmetric synthesis, the stereoselective preparation of quaternary carbon centers[1] in benzylic position remains challenging. Of particular difficulty is the preparation of fully *C*-substituted carbons by intermolecular reactions. This is a consequence of supplementary shielding caused by the presence of both a chiral inductor and an aromatic ring in an inherently crowded position, thus hindering efficient carbon−carbon bond formation. From a handful of methodology available, probably the most thoroughly investigated reactions are the S_N2-type substitution reactions using Meyers' bicyclic lactams[2] and chiral oxazolines.[3] These chiral systems, which offer excellent stereocontrols, have ultimately proved their usefulness in the synthesis of natural products.[2c,d,3a] Spartein-mediated enantioselective lithiation followed by alkylation[4] was also reported; however, this methodology seems to be limited to simple molecules where polar functionalities do not interfere with the delicate balance of the complexation pattern. Noteworthy, in all of the aforementioned cases, the stereodifferentiation occurs on *cyclic* intermediates.

Preparatively useful diastereoselectivities have been obtained in Michael-type additions using chiral metalloenolethers[5] or -enamines.[6] Finally, the newest class to date of the stereoselective preparation of quaternary benzylic centers via intermolecular reaction implies the powerful tandem [4 + 2]/[3 + 2] cycloadditions strategy,[7] reported by the Denmark group.

Scheme 1



[a]Reaction conditions. (a) BuLi (1.1 eq), THF, -78°C, then R^2X; (b) BuLi (2.2 eq), THF, -25 to 0°C, then R^2X; (c) BuLi (2.2 eq),THF, -25°C, then 9-BBN OTf (1.5 eq), -78°C.

During the course of a study concerning the reactivity of imidazoline **1**, we observed some years ago[8] that, after deprotonation in THF, the resulting nucleophilic species gave rise to *N*- or *C*-alkylated imidazoline derivatives of general formulas **2** or **3** in the presence of alkyl halides depending on the stoiechiometry of either *n*- or *sec*-butyllithium used as the base[9] (Scheme 1).

It was also observed that imidazoline[10] dianion led to an alkylative ring opening of THF with the electrophilic

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(1) For review concerning asymmetric creation of quaternary carbon centers, see: (a) Corey, E. J. Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388. (b) Wang, R.; Yang, X.-W. *Huaxue* **1996**, *54*, 169. (c) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

(2) (a) Meyers, A. I.; Brengel, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1. (b) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 4565. (c) Elworthy, T. L.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 6089. (d) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. See also: (e) Schwarz, J. B.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 1619 and references there in.

(3) (a) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297. (b) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.

(4) (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2283. (b) Hoppe, I.; Marsch, M.; Harms, K.; Boche, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2158.

(5) Taber, D. F.; Mack, J. F.; Rheingold, A. L.; Geib, S. J. *J. Org. Chem.* **1989**, *54*, 3831.

(6) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459.

(7) (a) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. (b) Denmark, S. E.; Middleton, D. S. *J. Org. Chem.* **1998**, *63*, 1604.

(8) Dalko, P. I.; Langlois, Y. *Tetrahedron Lett.* **1992**, *33*, 5213.

(9) An unsuccessful attempt to generate the 2-methylimidazoline dianion has been previously reported: Jones, R. C. F.; Schofield, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 375. The difference of reactivity between the two series of imidazolines is probably due to the greater solubility in THF of 4,5-diphenylimidazoline mono- and dianions.

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assistance of 9-BBN triflate, affording stereoselectively functionalized imidazolines **4** and **5** bearing a tertiary or a quaternary stereogenic center on the side chain (Scheme 1).[8]

This unusual and efficient alkylation reaction prompted us to embark on a systematic study to uncover some features. In the present paper we describe further scopes in preparing fully substituted benzylic centers and, also, a stereochemical correlation. This led us to secure the absolute configurations for quaternary stereogenic centers in imidazolines of type **5** and to propose a model for the dianionic intermediate alkylation. Additionally, stereoselective alkylation with methyl iodide demonstrated the generality of these reactions and gave further insight into the reaction mechanism.

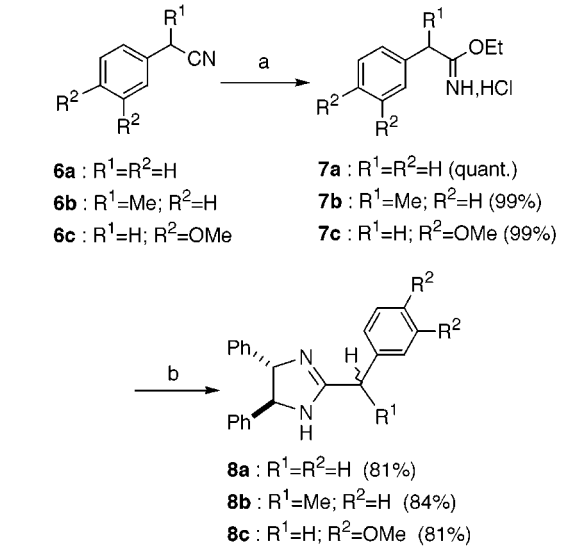
Results and Discussion

Preparation of Imidazolines. Imidazolines **8a**−**c** were prepared by classical condensation of the corresponding iminoether hydrochloride[11] **7a**−**c** with racemic or optically active *threo*-1,2-diamino-1,2-diphenylethane. According to this procedure, commercially available arylacetonitriles **6a**−**c** were transformed into the corresponding iminoether hydrochlorides **7a**−**c** under Pinner's conditions[11] and then condensed with the diamine. This iminoether route was shown to be more efficient than direct condensation of the corresponding carboxylic esters with diamine in the presence of trimethylaluminum under Hudkins' conditions.[12] Likewise, the requisite indan iminoether **10b** was obtained from the corresponding nitrile derivative **10a**, prepared from indanone **9** and *p*-tolylsulfonylmethyl isocyanide[13] (TOSMIC), and converted in good overall yield into the imidazoline **11** (Scheme 2).

Imidazolines **14** and **15** were in turn obtained by regioselective side chain alkylation of imidazoline dianions. Deprotonation of imidazolines **8a** or **8c** with 2 equiv of *n*-butyllithium at −25 °C followed by addition of 1.1 molar equiv of electrophiles **12a** or **13** at 0−5 °C afforded the *C*-alkylated products **14** and **15**, respectively, in good yields, as a chromatographically unseparable mixture of the two diastereomers. With the bis electrophile, 1-bromo-2-chloroethane **12b**, the bicyclic imidazoline **16** was obtained directly. Formation of this compound constituted indirect proof for the existence of a dianionic intermediate (Scheme 3).

Benzylic centers were shown to be prone to epimerization.[14] Deuterium incorporation experiments run in CD_3OD showed that proton−deuterium exchange occurs rapidly in these positions at room temperature. Under neutral conditions, compound **8b** incorporated deuterium with $t_{1/2} = 9$ h and the *N*-alkylated **18** somewhat faster with $t_{1/2} = 6.5$ h (Scheme 4). This observation was in contrast with results obtained using **20** where no measurable incorporation of deuterium was observed into an alkyl-substituted center, even after 30 days.

Scheme 2



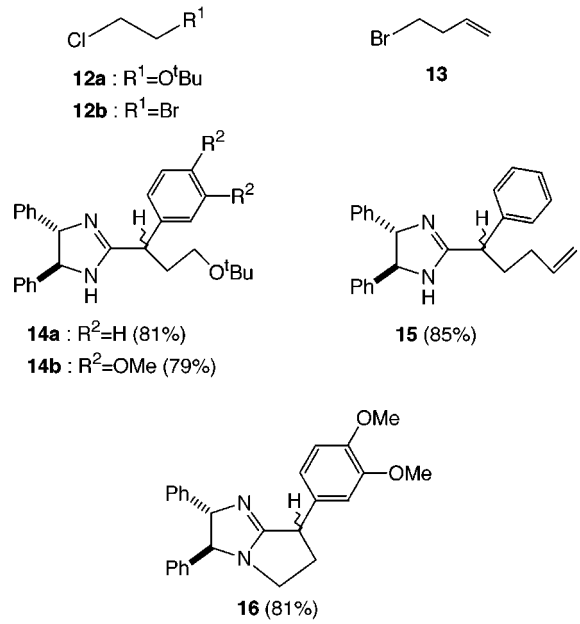
6a : R^1=R^2=H
6b : R^1=Me; R^2=H
6c : R^1=H; R^2=OMe

7a : R^1=R^2=H (quant.)
7b : R^1=Me; R^2=H (99%)
7c : R^1=H; R^2=OMe (99%)

8a : R^1=R^2=H (81%)
8b : R^1=Me; R^2=H (84%)
8c : R^1=H; R^2=OMe (81%)

[a]Reaction conditions. (a) HCl, EtOH; (b) *threo*-1,2-diphenyl-1,2-ethylenediamine, CH_2Cl_2, Et_3N; (c) KO^{t}Bu (1 eq.), TOSMIC (2 eq.), 48 h, r.t.

Scheme 3



12a : R^1=O^{t}Bu
12b : R^1=Br

13

14a : R^2=H (81%)
14b : R^2=OMe (79%)

15 (85%)

16 (81%)

[a]Reaction conditions. BuLi (2.2 eq.), THF, -25°C to 0°C, 25 min., then RX (1.1 eq.), 0-5°C, 16h.

(10) For recent applications of chiral imidazolines in asymmetric synthesis, see: (a) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1997**, *38*, 1647. (b) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1707.

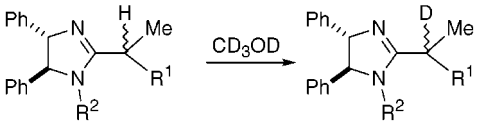
(11) (a) Dunn, P. J. Amides and *N*-Substituted Amides. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds-in-chief; Elsevier: Cambridge, U.K., 1995. (b) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567. (c) Delaby, R.; Reynaud, P.; Lilly, F. *Bull. Soc. Chim. Fr.* **1961**, 2067. (d) Pridgen, L. N.; Killmer, L. B.; Webb, R. L. *J. Org. Chem.* **1982**, *47*, 1985. (e) Dox, A. V. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 5.

(12) Hudkins, R. L. *Heterocycles* **1995**, *41*, 1045.

(13) Crombie, L.; Tuchinda, P.; Powell, M. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1477.

(14) The observed batch dependent variation in the diastereomeric ratio of **8b**, **11**, and **12**−**18** is probably due to the facile epimerization of the stereogenic benzylic center under the isolation conditions.

Scheme 4



compd.	R^1	R^2	product	R^2	$t_{1/2}$
8b	Ph	H	**17**	D	9 h
18	Ph	Me	**19**	Me	6.5 h
20	H	H	**21**	D	>> 30 days

Scheme 5

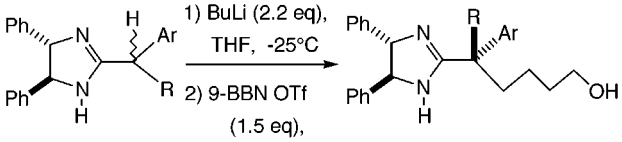


Table 1

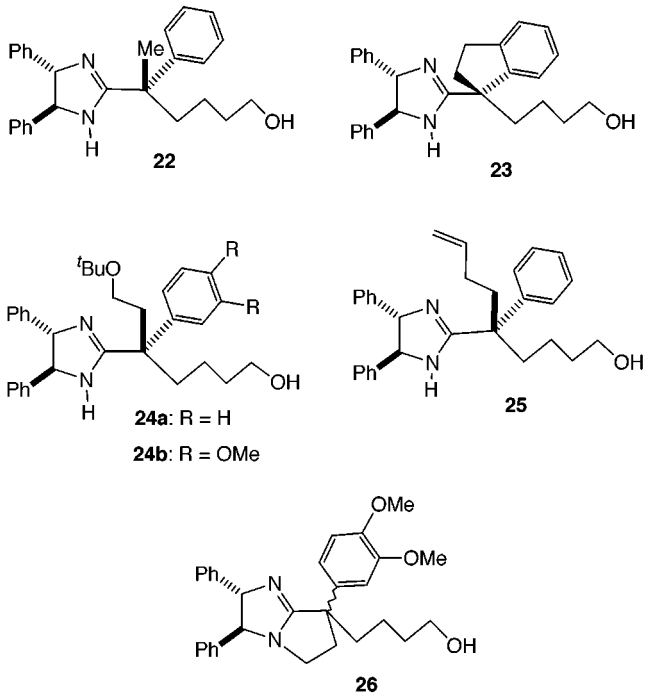
Entry	Starting material	Temp. (°C)	Product	Yield (%)	Selectivity (de %)
1	**8b**	-100	**22**	86	81
2	**8b**	20	**22**	39	71
3	**11**	-100	**23**	77	73
4	**14a**	-100	**24a**	81	77
5	**14b**	-100	**24b**	82	72
6	**14b**	-78	**24b**	79	72
7	**15**	-100	**25**	84	88
8	**16**	-100	**26**	88	14

9-BBN Triflate Mediated Alkylation of Imidazolines. Deprotonation of imidazolines **8b**, **14** and **15** with 2 molar equiv of *sec*-butyllithium or *n*-butyllithium in THF was performed at −25 °C (Scheme 5). After 25 min at this temperature, the dark red reaction mixture was cooled to −100 °C and a *freshly opened*[15] hexane solution of 9-BBN triflate was added dropwise. The mixture was stirred for an additional 3 min and quenched with water before warming to room temperature. After the usual workup procedure, the crude products were often contaminated with boron impurities which were difficult to remove by chromatography. To facilitate purification, the crude reaction mixture was treated with an excess of hydrogen peroxide prior to extraction. Yields and stereoselectivities of these alkylations are indicated in the table.

In all cases a very fast alkylation occurred even at rather low temperature (−100 °C). Alkylations at the benzylic position were observed with a variety of functionalized imidazolines (Scheme 6). Yields and diastereoselectivities were generally good, with two exceptions. (i) Low conversion, probably due to the unstability of the dianion above 0 °C was observed when the reaction was run at room temperature (entry 2). (ii) *N*-Substituted bicyclic imidazoline **16** gave only modest diastereoselectivity (entry 8). This lack of stereoselectivity suggests differences between the structures of the mono- and dimetalated intermediates.

(15) Yields and conversion of starting materials are decreased when old batches of 9-BBN triflate solutions were used.

Scheme 6

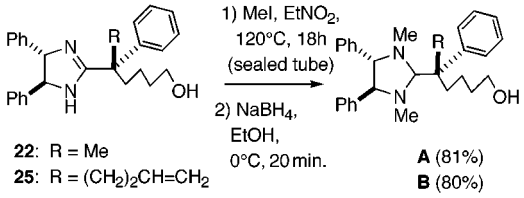


Although low temperature promoted higher diastereoselectivities, still preparatively useful de was obtained at room temperature (entry 2). A somewhat lower yield, but essentially identical de was observed when the reaction was run at −78 °C instead of −100 °C (entries 5 and 6).

The effect of the electron density of the reaction center on the diastereoselectivity of the alkylation was monitored by selecting substituted aryl compounds on the lateral chain. Methoxy substituents, which increases the electron density on the aromatic ring and thus destabilizes the carbanion in the benzylic position, afforded slightly lower stereoselectivity than the unsubstituted counterpart (entries 4 and 5).

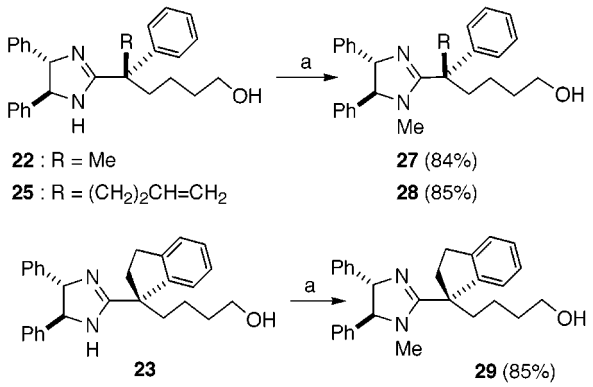
Measurement of the Diastereoselectivity. Due to the lack of general methodology to measure accurately the diastereoselectivity of the reaction, ways of overcoming the difficulties were devised case by case.[16] Diastereoselectivity was deduced directly from ^{1}H NMR spectra

(16) Interestingly, only poor ^{1}H NMR signal splitting was observed in the diastereomeric mixture of **A** and **B** which were prepared using alkylation/reduction sequence, from **22** and **25**, respectively.



This unanticipated difficulty was indeed surprising because such types of chiral imidazolidine derivatives, which are the condensation products of aldehydes and chiral diphenylethylenediamines are extensively used in the NMR technique to measure the diastereopurity of the parent substituted aldehydes. See: (a) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P.; Feneau-Dupont, J.; Declercq, J. P. *Synthesis* **1995**, 1038. (b) Mangeney, P.; Alexakis, A.; Normant, J.-F. *Tetrahedron Lett.* **1988**, *29*, 2677.

Scheme 7



[a]Reaction conditions. (a) MeI, BaO, $MeNO_2$, 80°C, 4h (sealed tube).

with imidazolines **22**, **24** and **26**. In imidazoline **22** two singlets were observed for the methyl group on the side chain. For imidazolines **24a** and **24b** the *O t*-Bu group gave two singlets. Bicyclic imidazoline **26** was characterized by the apparent split of several signals.

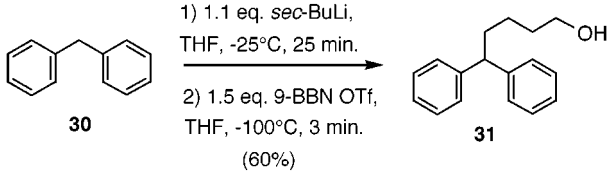
When no well-separated, primary NMR signals were available, as was the case with compounds **23** and **25**, diastereoselectivities were measured after chemical transformations. To correlate the thus obtained result, compound **22** was transformed in a parallel experiment likewise. Methylation in the presence of an excess of methyl iodide under pressure afforded selectively the *N*-methylimidazolines **27**, **28** and **29** (Scheme 7). The diastereoselectivity was deduced in these compounds by integration of split signals of one of the benzylic hydrogens at C4−H or C5−H in the imidazoline ring.

Reactivity and Stereoselectivity Related Studies. To uncover some additional features of the 9-BBN triflate mediated alkylative fragmentation reaction, the roles of the imidazoline moiety, of Lewis acid, and of the concentration/aggregation stage dependence were examined.

Alkylative cleavage of cyclic ethers in the presence of Lewis acid is abundantly illustrated in the literature.[8,17−19] Much less is known however about the factors which allow fragmentation/alkylation tandem with C−C bond formation.[8,18] To check the feasibility of the 9-BBN triflate mediated alkylation in the absence of the imidazoline moiety, in a model reaction, lithiated diphenylmethane was treated under standard conditions with 9-BBN triflate, and the alkylated product **31** was obtained[18e] in 60% yield (Scheme 8).

The question of the Lewis acidity on the reactivity was addressed by selecting stronger and weaker boron Lewis acids respectively for the reaction. Surprisingly, by choosing compound **8b** and a considerably stronger Lewis acid such as $BF_3{\cdot}Et_2O$, the reaction afforded only trace amounts of alkylated product **22** under standard conditions (−100 °C, 3 min). Other boron Lewis acids, such

Scheme 8



as Et_3B, which cleaved efficiently cyclic etheral bonds[19] in the presence of $NaBH_4$, afforded under the aforementioned conditions (−100 °C, 3 min) a low conversion of **8b** to an inextricable mixture of *N*- and *C*-ethylated products. No formation of the desired alcohol **22** was observed.

The roles of aggregates in enolate alkylation have been frequently addressed.[2b,23,45b] In particular, aggregate formation was evoked to explain the irregular diastereoselectivities of benzyllithium compounds containing lithium amide or lithium alkoxide functionalities.[20] Usually, aggregate formation is sensitive on concentration changes. However, in our hands, the model reaction **8b** → **22**, varying the concentration over 1 order of magnitude ($c = 0.05-0.5$ M[21]) produced no significant changes in product ratio.[22]

To increase stereoselectivity, the effect of additives were examined. It is well documented that in alkylation reaction of some mono- or dilithiated compounds the addition of an excess of lithium salts may influence the selectivity by changing the aggregation stage of the reacting organolithium.[23] Although an excess (6 equiv) of LiBr inhibits the 9-BBN triflate mediated alkylation reaction,[24] the addition of 2 molar equiv of anhydrous $CeCl_3$ to the dilithiated **8b** at 0 °C (10 min) followed by addition of 9-BBN triflate at −100 °C afforded product **22**, albeit with low selectivity (de = 47%) and yield (28%).[25] These results show that both the reactivity and the stereoselectivity of this particular 9-BBN triflate/THF alkylation system are highly sensitive to the reaction conditions. In all experiences, additives which may interact with the lithiated species or with the boron triflate reagent resulted in loss of efficiency in the alkylation reaction.

Other C_2 symmetric chiral imidazolines were also tested. Imidazoline **32** derived from chiral 1,2-cyclohexyldiamine[26] afforded high stereoinduction under routinely used conditions (Scheme 9). It is interesting to compare the two auxiliary systems. In both cases (i.e. using

(17) For some recent examples of cleavage of the tetrahydrofuran derivatives using metal complexes, see: (a) Boise, C.; Berthet, J. C.; Lance, M.; Nierlich, M.; Ephritikhine, M. *J. Chem. Soc., Chem. Commun.* **1996**, 2129. (b) Avens, L. R.; Barnhart, D. M.; Burns, C. J.; McKee, S. D. *Inorg. Chem.* **1996**, *35*, 537. (c) You, Y.; Zhang, Y.; Ling, R. *Synth. Commun.* **1993**, *23*, 1973. (d) Ramòn, D. J.; Yus, M. *Tetrahedron* **1992**, *48*, 3585. (e) Mudryk, B. B.; Cohen, T. *J. Am. Chem. Soc.* **1991**, *94*, 1866.

(18) (a) Harrowen, D. C.; Dainty, R. F. *Tetrahedron Lett.* **1997**, *38*, 7123. (b) Saito, S.; Ito, M.; Maruoka, K.; Yamamoyo, H. *Synlett* **1997**, 357. (c) Imai, T.; Muramoto, T.; Tsuji, T. *Chem. Lett.* **1995**, 355. (d) Lohray, B. B.; Enders, D. *Synthesis* **1993**, 1092. (e) Maercker, A.; Passlack, M. *Chem. Ber.* **1983**, *116*, 710.

(19) Brown, H. C.; Krishnamurthy, S.; Coleman, R. A. *J. Am. Chem. Soc.* **1972**, *94*, 1750.

(20) Münck-Lichtenfeld, C.; Ahlbrecht, H. *Tetrahedron* **1996**, *52*, 10025.

(21) Higher concentration resulted in lower conversion, probably because of the spark solubility of the dianion under the given conditions.

(22) Moreover, identical stereoselectivity was obtained in reactions run with either racemic or enantioenriched imidazoline **8b**. This fact suggests that bimolecular chiral base complex formation between the *n*-BuLi and the chiral imidazoline is unlikely.

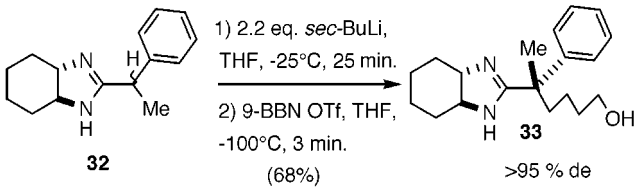
(23) (a) Seebach, D.; Beck, A.; Studer, A. in *Modern Synthetic Methods*; Leumann, C., Ed.; VHCA (Basel) and VCH (Weinheim); 1995; Vol. 7, B, pp 1−178. (b) Myers, A. G.; Gleason, J. L.; Yoon T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (c) Loupy, A.; Haudrechy, A. *Effets de milieu en synthèse organique*; Masson: Paris, 1996.

(24) In a parallel experiment LiBr salt additive did not influence the reactivity of conventional electrophiles such as methyl iodide with dimetalated imidazoline **8b** and afforded alkylated product (vide infra).

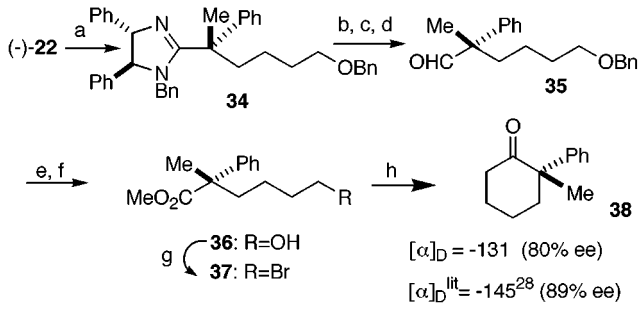
(25) A considerable amount (51%) of unreacted starting material was also recovered in this reaction.

(26) For review of 1,2-diaminocycohexane related asymmetric synthesis, see: Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161.

Scheme 9



Scheme 10

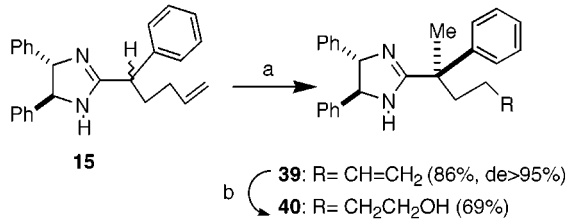


[a]Reaction conditions. (a) NaH, BnBr (2.3 eq.), THF, TBAI (cat.), 20°C, 12h, 87%; (b) MeI (5 eq.), $EtNO_2$, BaO, (0.25 eq), 120°C, 4h, sealed tube; (c) $NaBH_4$, EtOH, 0°C, 20 min; (d) HCl (1 M), MeOH, 0°C, 30 min, 81% overall ; (e) $Ca(OCl)_2$ (6 eq.), MeOH, 0°C, 34h; (f) $Pd(OH)_2$ (20%w/w), H_2, EtOAc, 20°C, 1.5h, 65%, two steps combined; (g) PPh_3 (3.5 eq.), CBr_4 (3.3 eq.), Et_2O, 20°C, 18h, 87%; (h) CH_2I_2 (5eq.), Sm (5.5 eq.), THF, HMPA, 61%.

cyclohexyl- and diphenyl-substituted imidazolines) the reaction supports the formation of a highly organized lithium-chelated entities in the transition state. The main difference is probably in the rigidity of the cyclohexyl system. A similar effect was noticed in the alkylation reaction of related diazaphosphorinanes.[27]

Determination of the Configuration of the Newly Formed Stereocenter. The absolute configuration of the newly created stereogenic center was established by a chemical correlation starting from (−)-**22** and transforming it to the known cyclohexanone derivative[28] **38** (Scheme 10). According to this sequence, **34** was subjected to an *N*-alkylation in a sealed tube using methyl iodide in nitroethane. The resulting stable imidazolinium salt was treated directly with sodium borohydride[29] to afford the corresponding imidazolidine intermediate bearing a sensitive aminal function. The aldehyde was deprotected by acidic hydrolysis and compound **35** was secured as a key intermediate in the sequence.[30] This simple and high-yielding sequence presents an alternative methodology to break down the otherwise inert imidazoline nucleus[31] and transforms it to a chemically more flexible substrate. Oxidation of the aldehyde with $Ca(OCl)_2$ in methanol afforded the corresponding carboxylic acid methyl ester. Under these oxidative conditions, partial debenzylation was observed which was completed by catalytic hydrogenation over palladium under atmospheric pressure, leading to compound **36**. To set up the appropriate functions for the cyclization reaction, the primary alcohol was transformed to bromide, using a standard procedure. The bromo ester **37** underwent a cyclization reaction in the presence of samarium diiodide under Molander's condition[32] and afforded the known ketone[28] **38** (Scheme 10). This sequence allowed the unambiguous attribution of the stereochemistry of the newly formed stereocenter. In accord with these results, alkylation occurred from the *si* side of (−)-**8b** using (*S*,*S*)-diphenylimidazoline chiral auxiliary. The rationalization of this acyclic stereoselectivity, however, did not appear to be straightforward and required further studies (vide infra).

Scheme 11



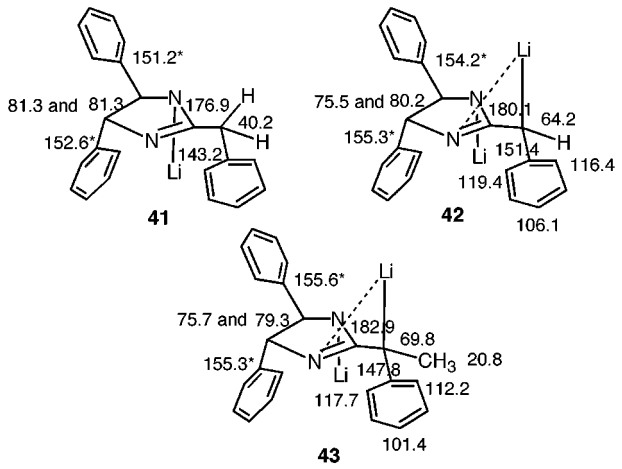
[a]Reaction conditions. (a) BuLi (2.2eq), THF, -25°C, MeI (1.1eq); (b) BH_3Me_2S, THF, then H_2O_2, NaOH.

Alkylation of Imidazolines Using Methyl Iodide as Electrophile. We recently showed[33] that lithiated intermediates of chiral imidazolines might be alkylated with a high degree of stereocontrol using alkyl halides as electrophiles. To rationalize the stereochemistry of both methodologies, i.e., in alkylations using the 9-BBN OTf/THF system or MeI, respectively, a stereocorrelation between the two types of alkylation methods was undertaken (Scheme 11). Accordingly, imidazoline **15** was deprotonated with 2.2 equiv of *n*-butyllithium and alkylated subsequently with methyl iodide to afford imidazoline **39**. The diastereoselectivity of this alkylation with de > 95% is noteworthy. Hydroboration−oxidation of **39** gave rise to imidazoline **40**, a diastereomer of imidazoline **22** (Scheme 10). Therefore this experiment showed an identical stereochemical course in both the 9-BBN triflate mediated alkylation reaction and in alkylations using a fast reacting and/or noncomplexing alkyl halide, such as MeI.

Structure Elucidation of the Metalated Imidazoline Intermediates by Low-Temperature NMR Experiments. The high level of the acyclic 1,4-stereoinduction in the alkylation reaction of lithiated imidazolines was intriguing. In particular, this result was surprising considering the apparent lack of any chelating elements in the molecule which would have been at the right distance from the lithium and could rigidify efficiently the structure and/or shield one of the stereotopic faces of the C_2 symmetric chiral inductor. In this context, it is interesting to compare the imidazoline system with that of the structurally similar oxazolines. In the latter case, a chelating side chain seems to be necessary to obtain good stereocontrol.[34] Although both steric and stereoelectronic effects were thoroughly studied and evoked as stereocontrolling elements in the alkylation

(27) Kranz, M.; Denmark, S. E.; Swiss, K. A.; Wilson, S. R. *J. Org. Chem.* **1986**, *51*, 8551.
(28) Paquette, L. A.; Gilday, J. P.; Maynard, G. D. *J. Org. Chem.* **1989**, *54*, 5044.
(29) For the reduction of benzimidazolium salts, see: El'tsov, A. V. *Zh. Org. Khim.* **1965**, *1*, 1112.
(30) The enantiopurity of intermediate **35** was ascertained by reducing the aldehyde to alcohol using $NaBH_4$ in ethanol and transforming it to the corresponding (*R*)-MTPA ester derivative.
(31) Classical acidic hydrolysis of **22** afforded an inextricable complex mixture.
(32) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1996**, *118*, 4095.
(33) Dalko, P. I.; Langlois, Y. *J. Chem. Soc., Chem. Commun.* **1998**, 331.

Scheme 12



[a] *Key*: the mark* means non attributed, interchangable chemical shift values.

step in related systems,[2a,b,3,35] it seemed to be difficult for us to isolate such effects and identify them as stereodeterminant factors in the present case.

To gain insight into the structure of the metalated imidazoline intermediate in solution, a low-temperature ^{13}C NMR study[36,37] of compounds **8a** and **8b** was undertaken. Results are summarized in Scheme 12.

A ^{13}C NMR spectrum of the monolithiated intermediate **41** at −69 °C shows a single set of well-resolved signals[38] which were consistent with the expected *N*-lithiated product (δ C_α = 40.2 ppm, t, $^1J_{C-H}$ = 125 Hz). Although the benzylic carbons of the imidazoline nucleus afforded magnetically identical signals (δ $C_{4,5}$ = 81.3 ppm, d, $^1J_{C-H}$ = 125 Hz), the appearance of three anisotropic quaternary aryl carbons showed the breakdown of the C_2 symmetry of the imidazoline nucleus in **41** at this temperature since a disymmetric structure emerged. Dimetalation, using the standard procedure, afforded a single, unsymmetrical product[39] whose ^{13}C NMR signals at −69 °C were consistent with those of the *N* and C_α bis-lithiated compound **42**. Benzyl-lithiated compounds are considered as intermediates between true ion pair and covalently linked species, which was demonstrated by a series of elegant experiments by Fraenkel.[37c] In **42**, the lithiated carbon (δ C_α = 64.2 ppm, d) was shown to have some sp^3 character ($^1J_{C-H}$ = 157 Hz),[40,41] thus being stereogenic. The same conclusion can be drawn by analyzing the chemical shifts of the benzylic stereogenic center of the dimetalated derivative relative to the monolithiated starting material. As Peoples and Grutzner showed[42] earlier, the downfield shift difference of the metalated center with regard to the starting material is proportional with the hybridization.[43] In **42** the downfield shift difference of the metalated carbon with regard to **41** (ΔC_α = 24.0 ppm) lies between the canonical ΔC_α = 33.9 ppm and ΔC_α = 10.1 ppm, measured for the planar and pyramidal carbometalated centers, respectively. This result is consistent with a pyramidal benzylic carbon with some degrees of delocalization into the benzene ring, which is clearly shown in the significant upfield shifts of the related *ortho* and *para* carbons of the aromatic side chain of **42**. It is interesting to point out that the two *ortho* carbons of this benzylic side chain were found to be magnetically nonequivalent at this temperature which indicated restrained conformational freedom of the lateral appendage. Noteworthy, both benzylic carbons of the imidazoline nucleus (δ $C_{4\ and\ 5}$ = 75.7 ppm, d, and 79.3 ppm, d) were slightly more planar ($^1J_{C-H}$ = 137 Hz and $^1J_{C-H}$ = 136 Hz, respectively) than the classical sp^3 character would predict (i.e. 125 Hz), which may be attributed to steric congestion on both faces.

Dilithiation of α-methylated imidazoline **8b** using standard procedures resulted in quantitatively similar results[44] (Scheme 12). Accordingly, subsequent *mono*- and *di*-lithiation resulted in the characteristic downfield shifts of the side chain benzylic carbon (δ C_α = 64.2 ppm). As depicted in **43**, the ^{13}C NMR signals at −69 °C were in agreement with those of the *N* and C_α bis-lithiated compound, with some degree of pyramidalization of the metalated carbon center.

In agreement with these results, dilithiation of C_2 symmetric imidazolines gave *N*- and *C*-metalated[4,45] products. The structures **42** and **43** account for the characteristic features of this structure. In these intermediates the benzylic carbon is pyramidalized, thus stereogenic. The formation of such a chiral organolithium compound may be the consequence of either kinetic or thermodynamic factors. In the latter case the conformation of the carbometalated benzylic center would be determined by an optimal spatial and polar arrangement between the aryl group of the lateral chain,

(34) Stereoselective alkylation in tandem nucleophilic addition−substitution reaction without side arm cooperativity was earlier reported. (a) Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292. (b) Meyers, A. I.; Shipman, M. *J. Org. Chem.* **1991**, *56*, 7098.

(35) See also: (a) Tomioka, K.; Cho, Y.-S.; Sato, F.; Koga, K. *J. Org. Chem.* **1988**, *53*, 4094. (b) Hon, Y.-S.; Chang, Y.-C.; Gong, M. L. *Heterocycles* **1990**, *31*, 191. (c) Micouin, L.; Jullian, V.; Quirion, J. C.; Husson, H. P. *Tetrahedron: Asymmetry* **1996**, *7*, 2839.

(36) Lithiation was performed with commercially available (Fluka) *n*-BuLi (10 N) in THF-d_8, using the standard procedure.

(37) For use of ^{13}C NMR in investigating the structure of metalation products, see: (a) Fraenkel, G.; Qiu, F. *J. Am. Chem. Soc.* **1997**, *119*, 3571. (b) Reich, H. J.; Holladay, J. E. *J. Am. Chem. Soc.* **1995**, *117*, 8470. (c) Fraenkel G.; Martin, K. V. *J. Am. Chem. Soc.* **1995**, *117*, 10336. (d) Croisat, D.; Seyden-Penne, J.; Strzalko T.; Wartski, L. *J. Org. Chem.* **1992**, *57*, 6435. (e) Strzalko T.; Seyden-Penne, J.; Wartski, L. *J. Am. Chem. Soc.* **1998**, *63*, 3287.

(38) ^{13}C NMR (THF-d_8, −69 °C, 100 MHz): 40.2, 81.3, 126.1−130.8, 143.2, 151.2, 152.6, 176.9.

(39) ^{13}C NMR (THF-d_8, −69 °C, 100 MHz): 64.2, 75.5, 80.2, 106.1, 116.4, 119.4, 126.1−130.8, 151.4, 154.2, 155.3, 180.1.

(40) $^1J_{C-H}$ couplings are diagnostic and were used routinely to provide structural information. In particular, these couplings have been shown to be directly proportional to the fraction of s-character in the given C−H bonds, and this has been taken advantage of investigate the hybridization of molecules.

(41) See: (a) Abraham, J. R.; Fisher J.; Loftus, P. *Introduction to NMR Spectroscopy*; Wiley: Chichester, 1988; pp 51−53. (b) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*, 3rd ed.; VCH: New York, 1987; pp 134−140.

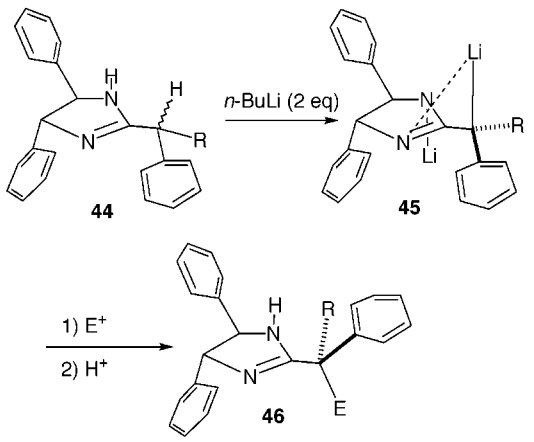
(42) (a) Peoples, P. R.; Grutzner, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 4709. (b) For recent examples of using the same principles for analyzing hybridization of metalated benzylic carbons, see: Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561.

(43) It was shown that the formation of the planar (7-phenylnorbornyl)potassium caused a 33.9 ppm downfield shift while the pyramidal (7-phenylnorbornyl)lithium made merely a 10.1 ppm downfield shift compared to the 7-phenylnorbornane starting material.

(44) ^{13}C NMR (THF-d_8, −69 °C, 62.5 MHz): 20.8, 69.8, 75.7, 79.3, 101.4, 112.2, 117.7, 125.7−131.7; 147.8, 155.3, 155.6, 182.9.

(45) Recent reviews on stereoselective carbometalation and alkylation: (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. (b) Seebach, D.; Sting A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708. (c) Stereoselective Synthesis. In *Houben-Weyl-Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21a, pp 762−881. (d) Hoppe, D.; Hinze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479 and ref 4.

Scheme 13



the functionalized heterocycle, and the (coordinated and/or solvated) metal. It seems to us reasonable to speculate that the stereoselectivity of the alkylation reaction is controlled by the conformation of the carbolithiated center (Scheme 13). Following earlier observations,[4,42b,45,46] the alkylation reaction proceeds with inversion of configuration at the benzylic position with regard to the lithium, using noncomplexing/fast reacting electrophiles[42b,46a,47] such as methyl iodide, as depicted in Scheme 13.

Conclusion

Further scope of the alkylative ring opening of THF in the presence of 9-BBN triflate with imidazoline dianion has been studied. Stereoselective formation of acyclic, quaternary benzylic centers were observed using C_2 symmetric imidazolines as chiral inductors, in an efficient, fast reaction (−100 °C, 3 min, de = 71 → 95%). Stereoselectivity decreases by adding supplementary polar or bulky functions in the molecule which may interact with the complexation pattern of the organometallic intermediate. The alkylation reaction of the dimetalated intermediate, using methyl iodide, afforded product with excellent stereocontrol, and with an identical stereochemical course as the 9-BBN triflate/THF system. The configuration of the newly formed stereocenter was established by chemical correlation. This sequence offers also an alternative methodology to transform the imidazoline nucleus to a chemically more flexible substrate.

Light was shed on the structure of the dimetalated intermediate. Preliminary, low-temperature NMR studies suggest the presence of a *C*-metalated contact ion pair compound, whose formation may be the stereodeterminant step of the alkylation reaction.

Although some key elements of this reaction have been highlighted, the true nature of the reaction is not fully understood, especially concerning the reactivity of the 9-BBN triflate/THF system. One hypothesis is the existence of a single-electron-transfer pathway[48] between the lithiated molecule and the 9-BBN triflate complexed THF derivative. Such a mechanism, which may imply reaction between open shell intermediates, would explain the fast rate, diminished sensitivity toward steric hindrance, and the diminished stereoselectivity, compared to alkylation of the same system using methyl iodide. These concerns as well as other synthetic applications of this efficient reaction are actively studied in our laboratory.

Experimental Section

General. Commercial reagents were used without additional purification. All reactions were carried out under Ar employing dried solvents, following standard procedures. TLC analyses were carried out on glass-backed silica gel 60 F_{254} plates. Compounds were visualized with UV light and by spraying with Dragendorff or acidic $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$/$Ce(SO_4)_2$ solution and heated. Melting points were uncorrected. ^{1}H NMR spectra were recorded at 200, 250, and 400 MHz at room temperature, employing $CDCl_3$ as solvent. Chemical shifts are reported in part per million (ppm) relative to TMS. ^{13}C NMR spectra were performed at 50, 62.5, or 100 MHz. Unless mentioned otherwise, low-resolution mass spectra were recorded using the FAB technique. Relative intensities, compared to the base fragment in percent, are noted in parentheses.

Indan-1-carbonitrile 10a.[13] Into a mixture of freshly distilled *tert*-butyl alcohol (420 mL) and potassium (16.25 g, 417.0 mmol) was added a solution of indan-1-one (5.51 g, 41.7 mmol) in dimethoxyethane (400 mL) slowly at 0 °C under continuous stirring. The temperature was allowed to rise to 20 °C, and *p*-tolylsulfonylmethyl isocyanide (TOSMIC) (16.32 g, 83.6 mmol) was added in small portions during 2 h. The red-brown solution was stirred for 48 h and then cooled to 0 °C. Saturated aqueous sodium chloride (100 mL) was then added with vigorous stirring. The mixture was poured into saturated aqueous sodium chloride (800 mL) and extracted with ether (4 × 250 mL). The pooled organic phases were dried on sodium sulfate, filtered, and evaporated. Chromatography on neutral alumina (activity 1) with hexane and ether as eluant afforded the carbonitrile derivative **10a** (5.07 g, 85%) as colorless oil whose ^{1}H NMR spectral data are identical to those described in the literature.[13] ^{1}H NMR (250 MHz): δ 2.32 (2H, m), 2.95 (2H, m), 4.05 (1H, t, J = 8.1 Hz), 7.25 (4H, m).

General Procedure for the Preparation of Iminoethers 7a−c and 10b. A solution of the benzylnitrile derivative (50 mmol) in ethanol (55 mmol) was saturated with dry HCl (gas) at 0−5 °C until an excess of HCl was detected at the exit bubbler. The mixture was left at 0−5 °C overnight, and the iminoether was crystallized out. The remaining solvent was evaporated at reduced pressure affording the crystalline iminoether as the hydrochloride salt. The crude salt is usually pure as shown by ^{1}H NMR, and could be used in the next reaction step without further purification. The crystalline salt was moisture sensitive, but stable on storage at 0−5 °C under argon. If partial decomposition occurs due to improper storage, an analytically pure sample could be reobtained by trituration of the mixture with dry ether.

Ethyl 2-phenylacetoimidate hydrochloride salt (7a) was obtained from phenylacetonitrile as white crystals (quantitative): mp 94−96 °C (lit.[11b] mp 94 °C); IR (KBr, cm^{-1}) 2874 (b), 1653; ^{1}H NMR (250 MHz) δ 1.29 (3H, t, J = 7.1 Hz), 3.92 (2H, s), 4.49 (2H, q, J = 7.1 Hz), 7.25 (5H, m); ^{13}C NMR δ 13.3, 39.0, 70.7, 128.1, 128.6, 129.3, 131.1, 177.0; MS *m*/*z* 164 (100); HRMS (electron spray ionization technique) *m*/*z* 164.1079 ($C_{10}H_{14}NO$ requires 164.1075).

Ethyl 2-methyl-2-phenylacetoimidate hydrochloride salt (7b) was obtained from α-methylphenylacetonitrile as white crystals (99%): mp 104−107 °C (lit.[11c] mp 106 °C); IR (KBr, cm^{-1}) 2763, 1638; ^{1}H NMR (250 Hz) δ 1.24 (3H, t, J = 7.0 Hz), 1.41 (3H, d, J = 7.3 Hz), 4.32 (2H, q, J = 7.1 Hz), 4.46 (1H, q; J = 7.3 Hz), 7.25 (5H, m); ^{13}C NMR δ 13.2, 16.7,

(46) (a) Thayumanavan, S.; Basu A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 8209. (b) Hammerschmidt, F.; Hanninger, A.; Völlenkle H. *Chem. Eur. J.* **1997**, *3*, 728. (c) Pippel, D. J.; Curtis, M. D.; Du, H.; Beak, P. *J. Org. Chem.* **1998**, *63*, 2.

(47) (a) Norsikian, S.; Marek, I.; Poisson, J.-F.; Normant, J. F., Marek, I. *J. Org. Chem.* **1997**, *62*, 4892. (b) Klein, S.; Marek, I.; Poisson, J.-F.; Normant, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 8853. (c) Mück-Lichtenfeld, C.; Ahlbrecht, H. *Tetrahedron* **1996**, *52*, 10025.

(48) Dalko, P. I. *Tetrahedron* **1995**, *51*, 7579.

30.9, 43.1, 70.7, 126.5, 128.2, 128.9, 136.8, 179.7; MS *m*/*z* 178 (100); HRMS (electron spray ionization technique) *m*/*z* 178.1234 ($C_{11}H_{16}NO$ requires 178.1232).

Ethyl 2-(3,4-dimethoxyphenyl)acetoimidate hydrochloride salt (7c) was obtained from homoveratronitrile as white crystals (99%): mp 114−116 °C (lit.[11d] mp 115−117 °C); IR (KBr, cm^{-1}) 2865, 1653; ^1H NMR (250 MHz) δ 1.21 (3H, t, J = 7.1 Hz), 3.62 (3H, s), 3.68 (3H, s), 3.75 (2H, s), 4.41 (2H, q, J = 6.9 Hz), 6.82 (1H, dd, J = 8.2 Hz, J = 1.6 Hz), 6.90 (1H, dd, J = 8.2 Hz, J = 1.6 Hz), 7.05 (1H, s); ^{13}C NMR δ 13.6, 38.9, 55.9, 56.2, 71.0, 111.4, 112.8, 121.8, 123.5, 149.0, 149.3, 177.4; MS *m*/*z* 224 (100); HRMS (electron spray ionization technique) *m*/*z* 224.1280 ($C_{12}H_{18}NO_3$ requires 224.1287).

Ethyl indan-1-carboximidate hydrochloride salt (10b) was obtained from hydrindanenitrile as white crystals (95%): mp 87−89 °C; IR (KBr, cm^{-1}) 2797, 1634; ^1H NMR (200 MHz) δ 1.38 (3H, t, J = 7.0 Hz), 2.42 (2H, m), 3.05 (2H, q, J = 9.2 Hz), 3.11 (2H, q, J = 8.6 Hz), 4.60 (2H, dd, J = 8.4 Hz, J = 7.2 Hz), 4.73 (1H, dd, J = 8.1 Hz, J = 5.8 Hz), 7.30 (4H, m); ^{13}C NMR δ 13.5, 29.4, 32.0, 48.7, 71.0, 124.7 125.0, 127.1, 128.7, 138.3, 144.3, 180.3; MS *m*/*z* 190 (100); HRMS (electron spray ionization technique) *m*/*z* 190.1229 ($C_{12}H_{16}NO$ requires 190.1232).

General Procedure To Prepare Imidazolines from Iminoethers Using *threo*-1,2-Diamino-1,2-diphenylethane or *trans*-1,2-Diaminocyclohexane. Into a solution of *threo*-1,2-diamino-1,2-diphenylethane (6.71 g, 31.66 mmol) or alternatively of *trans*-1,2-diaminocyclohexane (3.62 g, 31.66 mmol) and iminoether hydrochloride salt (**7** or **10**) (31.66 mmol) in dichloromethane (80 mL), triethylamine (10 mL) was added and the mixture was left for 5 h under continuous stirring. The slurry was poured on water and then separated in a separatory funnel. The aqueous layer was extracted with dichloromethane. The unified organic phases were dried over Na_2SO_4, filtered, and evaporated in a vacuum. The crude products were recrystallized from diethyl ether.

(4*R,5*R**)-2-Benzyl-4,5-dihydro-4,5-diphenyl-1*H*-imidazole (8a)** was obtained from **7a** as white crystals (81%): R_f 0.49 (dichloromethane saturated with ammonia/pentane 1:2); mp 141−142 °C; IR (KBr, cm^{-1}) 3059, 3024, 2930, 1595; ^1H NMR (200 MHz) (major isomer) δ 3.70 (2H, d, J = 6.0 Hz), 3.90 (1H, bs), 4.71 (2H, s), 7.14−7.42 (15H, m); ^{13}C NMR (major isomer) δ 36.3, 74.8, 126.4, 127.4, 128.6, 128.9, 143.3, 165.1; HRMS *m*/*z* 312.1632 ($C_{22}H_{20}N_2$ requires 312.1626).

[2(1′*RS*),4*R,5*R**]-4,5-Dihydro-4,5-diphenyl-2-(1′-phenylethyl)-1*H*-imidazole (8b)** was obtained from **7b** as white crystals (84%, mixture of two diastereoisomer): R_f 0.48 (dichloromethane saturated with ammonia/pentane 1:2); mp 162−163 °C; IR (KBr, cm^{-1}) 3061, 3026, 2930, 1596; ^1H NMR (250 MHz) δ 1.61 and 1.65 (3H, 2d, J = 7.2 Hz); 3.80 and 3.86 (1H, 2q, J = 7.2 Hz), 4.62 (2H, d, J = 7.6 Hz), 7.08−7.40 (15H, m); ^{13}C NMR δ 19.1, 19.4, 40.6, 74.9, 126.5, 126.6, 127.5, 128.7, 129.0, 129.1; MS *m*/*z* 327 (100); HRMS, *m*/*z* 326.1778 ($C_{23}H_{22}N_2$, requires 326.1783).

[2(1′*RS*),4*S*,5*S*]-4,5-Dihydro-4,5-diphenyl-2-(1′-phenylethyl)-1*H*-imidazole ((−)-8b) was obtained from (1*S*,2*S*)-1,2-diamino-1,2-diphenylethane and **7b** as white crystals (84%, approximately 9:10 mixture of two diastereoisomers): mp 142−146 °C; $[\alpha]_D$ = −159 (c = 2.33, methanol).

(4*R,5*R**)-4,5-Dihydro-2-(2,3-dimethoxybenzyl)-4,5-diphenyl-1*H*-imidazole (8c)** was obtained from **7c** as a white solid (81%): R_f 0.41 (dichloromethane saturated with ammonia/pentane 1:2); mp 151−153 °C; IR (KBr, cm^{-1}) 3175, 1611; ^1H NMR (200 MHz) δ 3.66 (2H, s), 3.85 (6H, 2s), 4.68 (2H, s), 6.75−7.30 (13H, m); ^{13}C NMR δ 35.9, 55.9, 74.8, 111.3, 111.7, 126.4, 127.4, 128.6, 143.4, 165.3; MS *m*/*z* 372 (100), 267 (43), 151 (45); HRMS, *m*/*z* 372.1833 ($C_{24}H_{24}N_2O_2$ requires 372.1838).

[2(1′*RS*),4*R,5*R**]-4,5-Dihydro-2-(1′,2′-dihydroindan-1′-yl)-4,5-diphenyl-1*H*-imidazole (11)** was obtained from **10** as white solid (80%, mixture of two diastereoisomers): R_f 0.53 (dichloromethane saturated with ammonia/pentane 1:2); mp 186−187 °C; IR (KBr, cm^{-1}) 3027, 2924, 1599; ^1H NMR (200 MHz) δ 2.49 (1H, q, J = 8.1 Hz), 2.61 (1H, q, J = 8.0 Hz), 3.09 (2H, m), 4.30 (1H, t, J = 7.9 Hz), 7.18−7.35 (14H, m); ^{13}C NMR δ 31.2, 32.0, 45.9, 124.3, 124.7, 126.3, 126.7, 127.1, 127.6, 128.2, 128.5, 142.3, 143.6, 144.4, 168.4; MS *m*/*z* 339 (100); HRMS, *m*/*z* 338.1783 ($C_{24}H_{22}N_2$, requires 338.1783).

[4*R,5*R**]-4,5-Dihydro-4,5-diphenyl-2-ethyl-1*H*-imidazole (20)** was obtained from iminoether[8] as white crystals (87%): R_f 0.36 (dichloromethane saturated with ammonia/pentane 1:2); mp 132 °C; IR (KBr, cm^{-1}) 3026, 1607, 1489; ^1H NMR (200 MHz) δ 1.27 (3H, t, J = 8.6 Hz), 2.38 (2H, q, J = 8.6 Hz), 4.17 (2H, s), 5.12 (1H, bs), 7.08−7.48 (10H, m); ^{13}C NMR δ 11.2, 22.7, 74.7, 125.9, 127.3, 128.6, 143.7, 167.6; MS *m*/*z* 251 (100), 196 (31); HRMS, *m*/*z* 251.153 ($C_{17}H_{19}N_2$, requires 251.158).

[2(1′*RS*),3a*R,7a*R**]-3a,4,5,6,7,7a-hexahydro-2-(1′-phenylethyl)-1*H*-benzimidazole (32)** was obtained from **7b** as a viscous oil (87%): R_f 0.36 (dichloromethane saturated with ammonia/pentane 1:2); IR (KBr, cm^{-1}) 3026, 2931, 1597; ^1H NMR (250 MHz) (mixture of two diastereoisomers) δ 1.21 (2H, m), 1.39 (2H, m), 1.50 (3H, apparent t, J = 7.4 Hz), 1.71 (2H, m), 2.10 (2H, m), 2.87 (2H, m), 3.57 (0.5H, q, J = 7.4 Hz), 3.70 (0.5H, q, J = 7.5 Hz), 7.15−7.40 (5H, m); ^{13}C NMR δ 18.8, 19.3, 24.8, 30.6, 40.9, 69.2, 127.0, 127.2, 128.7, 128.9, 141.7, 142.6, 170.9; MS *m*/*z* 229 (100); HRMS (HCl salt), *m*/*z* 229.1713 ($C_{15}H_{21}N_2$, requires 229.1705).

***tert*-Butoxychloroethane[49] (12a).** Amberlyst H-15 (1.25 g) was added to a solution of of 2-chloroethanol (5.00 g, 62.1 mmol) in 25 mL of heptane at room temperature. With gentle stirring isobutene was bubbled into this reaction mixture at a such rate that almost no excess isobutene was detected at the exit bubbler. After 4 h at room temperature the acid catalyst was filtered off, and the solvents were evaporated. The residue was distilled over a few milligrams of K_2CO_3 (bp 28−29 °C (18 mmHg)) to obtain 7.71 g (91%) of protected alcohol as colorless liquid: ^1H NMR (250 MHz) δ 1.11 (9H, s), 3.44 (4H, apparent dd, J = 6.8 Hz, J = 3.9 Hz); ^{13}C NMR δ 27.5, 43.7, 62.4, 73.6.

General Methodology To Prepare imidazolines 15−17 by Alkylation Reaction. In a degassed solution of imidazoline **8** or **11** (4.57 mmol) in THF (15 mL), *sec*-butyllithium (10.05 mmol, 4.02 mL, 2.5 M in hexane) was added at −25 °C and under an Ar atmosphere. After 25 min the neat alkyl halide (5.04 mmol) was slowly added to the dark red solution via syringe. The mixture was allowed to reach 0−5 °C and kept at this temperature for 16 h more, quenched with some drops of saturated ammonium chloride, and extracted twice with water. The pooled aqueous phases were reextracted with dichloromethane; then the unified organic phases were dried over Na_2SO_4 and concentrated in a vacuum. The crude mixture was recrystallized from diethyl ether or, eventually, chromatographed on a short column of silica gel using gradient eluants (dichloromethane/dicloromethane−methanol 20:1) to obtain the desired product.

[2(1′*RS*),4*R,5*R**]-2-(3′-*tert*-Butoxy-1′-phenylpropyl)-4,5-dihydro-4,5-diphenyl-1*H*-imidazole (14a)** was obtained from **8a** and **12a** as white solid (81%, mixture of two diastereoisomers): R_f 0.54 (dichloromethane saturated with ammonia/pentane 1:2); mp 189−190 °C (acetone); IR (KBr, cm^{-1}) 3063, 2971, 1593; ^1H NMR (250 MHz) (major isomer) δ 1.09 (9H, s), 2.12 (1H, m), 2.43 (1H, m), 3.22 (1H, m), 3.40 (1H, apparent t, J = 5.6 Hz), 3.89 (1H, apparent t, J = 7.5 Hz), 4.60 (2H, bs), 7.05−7.40 (15H, m); ^{13}C NMR (major isomer) δ 27.7, 34.2, 42.8, 58.9, 72.8, 110.1, 126.5, 126.7, 127.4, 127.8, 128.2, 128.6, 128.8, 143.6, 168.0; MS *m*/*z* 413 (100), 355 (6); HRMS, *m*/*z* 412.2526 ($C_{28}H_{32}N_2O$, requires 412.2515).

[2(1′*RS*),4*R,5*R**]-2-[3′-*tert*-Butoxy-1′-(2,3-dimethoxyphenyl)propyl]-4,5-dihydro-4,5-diphenyl-1*H*-imidazole (14b)** was obtained from **8c** and **12a** as a white solid (79%, mixture of two diastereoisomers): R_f 0.48 (dichloromethane saturated with ammonia/pentane 1:2); mp 177−179 °C (acetone); IR (KBr, cm^{-1}) 3371, 2934, 1593; ^1H NMR (400 MHz) δ 1.12 (9H, s), 2.05 (1H, m), 2.35 (1H, m), 3.20 (1H, m), 3.34 (1H, m), 3.71 (6H, s), 4.55 (2H, bs), 6.7−7.25 (13H, m); ^{13}C

(49) This methodology was originally described by Alexakis, A.; Gardett, M.; Colin, S. *Tetrahedron Lett.* **1988**, *29*, 2951.

NMR δ 27.7, 34.2, 34.4, 42.2, 55.9, 58.8, 58.9, 69.8, 80.1, 110.1, 110.9, 111.2, 126.3, 127.3, 128.6, 133.4, 143.9, 144.4, 148.2, 168.2; MS, *m/z* 473 (100), 315 (21); HRMS, *m/z* 472.2725 ($C_{30}H_{36}N_2O_3$, requires 472.2726).

[2(1′*RS*),4*R,5*R**]-4,5-Dihydro-4,5-diphenyl-2-(1′-phenylpent-4-en-1-yl)-1*H*-imidazole (15)** was obtained from **8a** and 4-bromobutene **13** as white crystals (85%, mixture of two diastereoisomers): mp 175−176 °C (ether); R_f 0.60 (dichloromethane saturated with ammonia/pentane 1:2); IR (KBr, cm^{-1}) 3028, 2920, 1599; ^{1}H NMR (250 MHz) δ 2.03 (3H, m), 2.32 (1H, 2q, *J* = 6.3 Hz), 3.61 (1H, 2t, *J* = 7.8 and 6.4 Hz), 4.60 (2H, d, *J* = 7.7 Hz), 4.98 (2H, m), 5.78 (1H, m,), 7.05−7.45 (15H, m); ^{13}C NMR δ 31.6, 31.8, 32.4, 45.6, 74.5, 115.4, 125.7−129.0, 138.0, 143.5, 168.1; MS (FAB technique), *m/z* (relative intensity) 339 ($[M - C_2H_4]^{+\bullet}$, 100%); HRMS, *m/z* 366.2096(M^+) ($C_{26}H_{26}N_2$, requires 366.2096).

(7*RS*,2*R,3*R**)-7-(2,3-Dimethoxyphenyl)-2,3-diphenyl-2,3,4,5,6,7-hexahydro-pyrrolo[1,2-*a*]imidazole (16)** was obtained from **8c** and chlorobromoethane **12b** as a pale yellow amorphous solid (81%, mixture of two diastereoisomers): R_f 0.70 (dichloromethane saturated with ammonia/pentane 1:2); mp 87−96 °C; IR (KBr, cm^{-1}) 3361, 2937, 1628; ^{1}H NMR (250 MHz) δ 2.45 (1H, m), 2.87 (2H, m), 3.10 (1H, m), 3.22 (1H, t, *J* = 7.1 Hz), 3.85 and 3.89 (3H, 2s), 3.95 and 3.99 (3H, 2s), 4.29 and 4.40 (1H, 2d, *J* = 9.7 Hz, *J* = 7.1 Hz), 5.22 and 5.31 (1H, 2d, *J* = 9, 4 Hz, *J* = 7.8 Hz), 6.85−7.40 (13H, m); ^{13}C NMR δ 35.7, 35.9; 40.7, 41.3, 42.9, 44.9, 55.9, 73.9, 75.8, 85.5, 85.9, 111.0, 111.3, 111.6, 119.6, 119.9, 126.6, 126.8, 127.1, 127.2, 127.7, 127.8, 128.2, 128.3, 128.6, 128.8, 133.2, 139.8, 140.3, 142.4, 147.9, 149.0, 175.5; MS (FAB technique) *m/z* 398 (80), 91 (100%); HRMS, *m/z* 398.1992 ($C_{26}H_{26}N_2O_2$, requires 398.1994).

General Procedure for the Alkylation of Aryl-Substituted Imidazolines with THF. Into a degassed solution of imidazoline (2.5 mmol) in THF (7.5 mL) was added *sec*-butyllithium (2.4 mL, 2.5 M solution in hexane) at −25 °C and under an Ar atmosphere. After 25 min the mixture was cooled to −100 °C, and 9-BBN triflate (7.5 mL, 0.5 M solution in hexane) was slowly added via syringe. The progress of the reaction could be monitored simply by following the change in the color of the mixture which turned from dark red to orange. The mixture was quenched after 3 min with some drops of water and allowed to reach room temperature. Then H_2O_2 (1.0 mL, 35%, 10.3 mmol) and NaOH (2.5N, 3.0 mL, 7.5 mmol) were added, and the mixture was stirred for 1 h at room temperature. The solution was extracted twice with water, and then the aqueous layer was extracted three times with dichloromethane. The unified organic phases were dried over Na_2SO_4, concentrated in a vacuum, and chromatographied on preparative TLC using a mixture of dichloromethane saturated with ammonia and hexane (1:1) as eluents.

[5*S*-5(4′*S*,5′*S*)]-5-(4′,5′-Dihydro-4′,5′-diphenyl-1*H*-imidazol-2′-yl)-5-phenylhexan-1-ol (22) was obtained from (−)-**8b** as a colorless viscous oil (86%, 9.8:1 mixture of two diastereoisomers): R_f 0.31 (dichloromethane saturated with ammonia); $[\alpha]_D = -130$ (*c* = 1.05, MeOH); IR (KBr, cm^{-1}) 3248 (b), 3060, 3028, 2931, 1600; ^{1}H NMR (400 MHz) (major diastereomer) δ 1.45 (4H, m), 1.62 (3H, s), 1.96 (1H, m), 2.20 (1H, td, *J* = 10.8 Hz *J* = 2.1 Hz), 3.52 (2H, td, *J* = 7.1 Hz, *J* = 7.1 Hz), 4.66 (2H, bs), 7.02−7.48 (15H, m); ^{13}C NMR δ 21.1, 24.5, 32.7, 39.0, 44.9, 61.9, 74.7 (broad), 126.4, 126.6, 127.1, 127.6, 128.7, 169.1; MS *m/z* 399 (13), 167 (36), 150 (100); HRMS, *m/z* 398.2367 ($C_{27}H_{30}N_2O$, requires 398.2358).

[1*RS*,1(4′*R,5′*R**)]-1-(4′,5′-Dihydro-4′,5′-diphenyl-1*H*-imidazol-2′-yl)-1-(4-hydroxybutyl)indan (23)** was obtained from **11** as a colorless viscous oil (77%, 6.5:1 mixture of two diastereoisomers): R_f 0.30 (dichloromethane saturated with ammonia); IR (KBr, cm^{-1}) 3274 (b), 3028, 2929, 1594; ^{1}H NMR 250 MHz) (major isomer) δ 1.48, (4H, m), 2.15 (2H, m), 2.49 (1H, m), 2.65 (1H, apparent td, *J* = 15.8 Hz, *J* = 8.8 Hz), 3.02 (2H, m), 3.50 (2H, apparent t, *J* = 5.6 Hz), 4.60 (2H, s), 6.95−7.30 (14H, m); ^{13}C NMR (major isomer) δ 21.3, 31.0, 32.0, 36.6, 37.7, 53.9, 61.6, 74.5 (broad), 124.3, 125.3, 126.3, 126.7; 127.6, 127.8; 128.7, 143.5, 170.7; MS *m/z* 411 (97), 337 (83), 106 (100); HRMS, *m/z* 410.2357 ($C_{28}H_{30}N_2O$ requires 410.2358).

[5*RS*,5(4′*R,5′*R**)]-7-*tert*-Butoxy-5-(4′,5′-dihydro-4′,5′-diphenyl-1*H*-imidazol-2′-yl)-5-phenylheptan-1-ol (24a)** was obtained from **14a** as colorless amorphous solid (81%, 7.8:1 mixture of two diastereoisomers): R_f 0.41 (dichloromethane saturated with ammonia); IR (neat, cm^{-1}) 3368 (b), 2969, 1600; ^{1}H NMR (250 MHz) (major isomer) δ 1.05 (9H, s), 1.45 (2H, tt, *J* = 6.0 Hz, *J* = 5.9 Hz), 1.60 (2H, q, *J* = 6.3 Hz), 2.28 (2H, m), 2.48 (2H, m), 3.41 (2H, t, *J* = 6.5 Hz), 3.61 (2H, td, *J* = 6.0 Hz, *J* = 3.0 Hz), 4.78 (2H, s), 7.18−7.50 (15H, m); ^{13}C NMR (major isomer) δ 20.5, 27.6, 32.4, 35.9, 36.2, 47.4, 58.3, 62.2, 126.3, 126.4, 126.7, 126.9, 127.x, 127.9, 128.7, 129.0, 143.6, 170.6; MS *m/z* 485 (100), 412 (12), 384 (15); HRMS, *m/z* 484.3077 ($C_{32}N_{40}N_2O_2$ requires 484.3090).

[5*RS*,5(4′*R,5′*R**)]-7-*tert*-Butoxy-5-(4′,5′-dihydro-4′,5′-diphenyl-1*H*-imidazol-2′-yl)-5-(3,4-dimethoxyphenyl)heptan-1-ol (24b)** was obtained from **14b** as a colorless viscous oil (77%, 6.3:1 mixture of two diastereoisomers): R_f 0.31 (dichloromethane saturated with ammonia); IR (KBr, cm^{-1}) 3392 (b), 2931, 1602; ^{1}H NMR (400 MHz) (major isomer) δ 1.00 (9H, s), 1.41 (2H, m), 1.51 (4H, m), 1.28 (2H, m), 2.28 (1H, dt, *J* = 12.8 Hz, *J* = 3.0 Hz), 2.40 (1H, dt, *J* = 13.1 Hz, *J* = 2.8 Hz), 3.38 (1H, tt, *J* = 7.8 Hz, *J* = 2.8 Hz), 3.52 (2H, m), 3.69 (1H, tt, *J* = 8.3 Hz *J* = 2.1 Hz), 3.73 (6H, s), 4.93 (2H, s), 6.82−7.35 (13H, m); ^{13}C NMR (major isomer) δ 20.4, 27.5, 32.6, 35.7, 36.0, 46.8, 55.9, 58.2, 62.2, 73.1 (broad), 110.3, 110.8, 118.8, 126.5, 127.4, 128.6, 136.1, 143.6, 170.7; MS *m/z* 544 (8), 488 (27), 472 (48), 385 (100); HRMS, *m/z* 544.3318 ($C_{34}N_{44}N_2O_4$ requires 544.3301).

[5*RS*,5(4′*R,5′*R**)]-5-(4′,5′-Dihydro-4′,5′-diphenyl-1*H*-imidazol-2′-yl)-5-phenylnon-8-en-1-ol (25)** was obtained from **15** as a colorless viscous oil (84%, 15:1 mixture of two diastereoisomers): R_f 0.32 (dichloromethane, saturated with ammonia); IR (KBr, cm^{-1}) 3222 (b), 2941, 1594; ^{1}H NMR (250 MHz) (major isomer) δ 1.31 (1H, td, *J* = 14.0 Hz Hz, *J* = 6.9 Hz), 1.45 (1H, td, *J* = 14.5 Hz, *J* = 6.3 Hz), 1.88 (1H, apparent q, *J* = 7.6 Hz), 1.95 (1H, apparent q, *J* = 7.2 Hz), 2.11 (4H, apparent q, *J* = 8.1 Hz), 3.45 (2H, apparent t, *J* = 6.2 Hz), 4.61 (2H, bs), 4.91 (2H, m), 5.72 (1H, m), 7.10−7.45 (15H, m); ^{13}C NMR (major isomer) δ 20.4, 28.3, 32.8, 34.5, 47.9, 62.1, 114.6, 126.2, 16.6, 126.8, 127.0, 127.1, 127.2, 127.4, 127.5, 127.6, 128.2, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 138.4, 143.2, 143.5, 170.8; MS *m/z* (relative intensity) 439 (100), 282 (42), 161 (99); HRMS, *m/z* 438.2660 ($C_{30}H_{34}N_2O$ requires 438.2671).

[5*R,5(3a′*R**,7a′*R**)]-5-(3a′,4′,5′,6′,7′,7a′-hexahydro-1*H*-benzimidazol-2′-yl)-5-phenylhexan-1-ol (33)** was obtained from **32** as a colorless viscous oil (68%): R_f 0.30 (dichloromethane, saturated with ammonia); IR (KBr, cm^{-1}) 2942, 1594; ^{1}H NMR (250 MHz) δ 1.22 (2H, m), 1.40 (1H, m), 1.51 (3H, s), 1.71 (2H, m), 1.90 (1H, m), 2.10 (1H, m), 2.68 (2H, m), 3.6 (2H, m), 5.30 (1H, bs), 7.20−7.35 (5H, m); ^{13}C NMR δ 20.5, 23.1, 25.0, 30.7, 31.2, 38.3, 45.2, 60.7, 125.9, 126.9, 127.4, 128.7, 129.2, 145.2, 174.1; MS *m/z* (relative intensity) 301 (100); HRMS (HCl salt), *m/z* 301.2287 ($C_{19}H_{29}N_2O$ requires 301.2287).

(7*RS*,2′*R,3′*R**)-[7-(2,3-Dimethoxyphenyl)-2′,3′-diphenyl-2′,3′,4′,5′,6′,7′-hexahydropyrrolo[1′,2′-*a*]imidazol-7′-yl]-4-butan-1-ol (26).** Into a degassed solution of **18** (0.995 mg, 2.5 mmol) in THF (7.5 mL) was added *sec*-butyllithium (1.2 mL, 2.5 M solution in hexane) at −78 °C and under Ar. After 15 min of incubation, 9-BBN triflate (7.5 mL, 0.5 M solution in hexane) was slowly introduced via syringe, and shortly (3 min) some drops of water were added. A mixture of H_2O_2 (1.0 mL, 35%, 10.3 mmol) and NaOH (2.5N, 3.0 mL, 7.5 mmol) was added to the reaction at room temperature, and the solution was stirred for 2 h more. The solution was washed twice with water; then the aqueous layer was extracted with dichloromethane. The unified organic phases were dried over Na_2SO_4, concentrated in a vacuum, and chromatographed on preparative TLC using 1:1 dichloromethane−hexane as eluant saturated with ammonia. The alcohol **26** (1.032 g, 88%) was isolated as a colorless viscous oil (3:4 mixture of two diastereoisomers): R_f 0.41 (dichloromethane saturated with ammonia); IR (neat, cm^{-1}) 3389 (b), 2937, 1624; ^{1}H NMR δ 1.45 (2H, m), 2.00 (2H, m), 2.70 (4H, m), 3.50 (2H, s), 3.90 (6H, 2s), 4.28 and 4.30 (1H, 2d, *J* = 7.8 Hz, *J* = 6.9 Hz), 5.15 and 5.32

(1H, 2d, $J = 7.8$ Hz, $J = 6.9$ Hz), 6.71−7.49 (13H, m); ^{13}C NMR δ 20.1, 21.3, 32.5, 32.7, 39.3, 39.6, 40.0, 40.5, 41.6, 43.5, 47.6, 55.8, 61.2, 61.4, 73.0, 75.2, 85.1, 85.3, 110.2, 110.6, 110.8, 111.1, 118.5, 126.5, 126.7, 126.9, 127.1, 127.6, 127.9, 128.3, 128.5, 128.8, 140.0, 148.7, 169.9, 170.8; MS *m*/*z* 470 (27), 453 (20), 398 (100); HRMS, *m*/*z* 470.2569 ($C_{30}H_{34}N_2O_3$, requires 470.2569).

General Procedure for Selective *N*-Methylation of Imidazolines. In a sealed tube, under an argon atmosphere, a mixture of imidazoline (**24**, **25**, **27**, respectively) (0.40 mmol) in 2.0 mL of dry nitromethane, methyl iodide (125 μL, 2.0 mmol), and finely powdered anhydrous BaO (80 mg, 0.514 mmol) was heated under continuous stirring at 80 °C for 4 h. Filtered on a glass fritter, the solid was washed with a small portion of ether and then evaporated. Chromatography on a preparative TLC plate (SiO_2, dichloromethane, saturated with ammonia) afforded the products.

[2(1′*RS*),4*R,5*R**]-4,5-Dihydro-4,5-diphenyl-1-methyl-2-(1′-phenylethyl)-1*H*-imidazole (18)** was obtained from **8b**, as a colorless viscous oil (84%): R_f 0.60 (dichloromethane, saturated with ammonia/pentane 1:2); IR (film, cm^{-1}) 2936, 1590, 1575; ^{1}H NMR (200 MHz) δ 1.68 and 1.70 (3H, 2d, $J =$ 7.6 Hz), 2.40 and 2.51 (3H, 2s), 3.82 and 3.82 (1H, 2q, $J = 6.9$ Hz), 4.10 and 4.18 (1H, 2d, $J = 10.3$ Hz), 4.85 and 4.88 (1H, 2d, $J = 10.1$ Hz), 7.21−7.65 (15H, m); ^{13}C NMR δ 21.2, 21.9, 31.8, 32.2, 39.1, 39.3, 125.5, 126.4, 126.5, 126.9, 127.1, 127.4, 127.5, 127.7, 127.8, 128.1, 128.4, 128.8, 141.3, 143.8, 168.3, 168.7; MS *m*/*z* 341 (100), 313 (16); HRMS (HCl salt), *m*/*z* 341.2027 ($C_{24}H_{25}N_2$ requires 341.2018).

[5*RS*,5(4′*R,5′*R**)]-5-(4′,5′-Dihydro-4′,5′-diphenyl-1′-methylimidazol-2′-yl)-5-phenylhexan-1-ol (27)** was obtained from **22** as a colorless viscous oil (84%): R_f 0.38 (dichloromethane, saturated with ammonia); IR (film, cm^{-1}) 3390 (b), 2936, 1590, 1576; ^{1}H NMR (250 MHz) (major isomer) δ 1.50 (4H, m), 1.19 (3H, s), 2.08 (2H, apparent dd, $J = 7.6$ Hz, $J = 6.6$ Hz), 2.11 (3H, s), 3.50 (2H, apparent t, $J = 5.6$ Hz), 4.61 (2H, bs), 4.18 (1H, d, $J = 9.7$ Hz), 4.38 (1H, bs), 4.81 (1H, d, $J = 9.7$ Hz), 7.10−7.45 (15H, m); ^{13}C NMR (major isomer) δ 21.3, 25.4, 32.1, 31.8, 33.4, 39.6, 45.3, 61.6, 75.3, 78.3; 125.7, 126.0, 127.0, 127.1, 127.2, 127.4, 127.5, 127.6, 128.6, 128.9, 129.2, 140.6, 143.2, 144.5, 170.6; MS *m*/*z* 413 (100), 399 (9), 340 (8); HRMS, *m*/*z* 412.2499 ($C_{28}H_{32}N_2O$ requires 412.2515).

[5*RS*,5(4′*R,5′*R**)]-5-(4′,5′-Dihydro-4′,5′-diphenyl-1′-methylimidazol-2′-yl)-5-phenylnon-8-en-1-ol (28)** was obtained from **25**, as colorless viscous oil (85%): R_f 0.38 (dichloromethane, saturated with ammonia); IR (neat, cm^{-1}) 2930, 1575; ^{1}H NMR (250 MHz) δ (major isomer) 1.38 (2H, m), 1.58 (2H, apparent dq, $J = 17.2$ Hz, $J = 6.5$ Hz), 1.95 (2H, m), 2.05 (3H, s), 2.22 (4H, m), 3.60 (2H, apparent td, $J = 4.8$ Hz, $J =$ 1.8 Hz), 4.11 (1H, d, $J = 10.7$ Hz), 4.95 (3H, m), 5.78 (1H, m), 7.05−7.40 (15H, m); ^{13}C NMR δ (major isomer) 20.9, 28.9, 32.4, 33.4, 35.3, 35.7, 48.5, 62.3, 76.1, 78.7, 114.9, 126.4, 126.8, 127.0, 127.5, 128.1, 128.7, 129.0, 138.5, 140.8, 143.4, 169.5; MS *m*/*z* 453 (100); HRMS, *m*/*z* 452.2847 ($C_{31}H_{36}N_2O$ requires 452.2828).

[1*RS*,1(4′*R,5′*R**)]-1-(4′,5′-Dihydro-4′,5′-diphenyl-1′-methylimidazol-2′-yl)-1-(4-hydroxybutyl)indan (29)** was obtained from **23**, as a colorless amorphous solid (85%): R_f 0.38 (dichloromethane, saturated with ammonia); IR (neat, cm^{-1}) 2932, 1591, 1575; ^{1}H NMR (250 MHz) δ (major isomer) 1.45 (2H, m), 1.70 (2H, m), 2.08 (3H, s), 2.28 (3H, m), 2.52 (1H, q, $J = 9.7$ Hz), 3.08 (1H, q, $J = 8.1$ Hz), 3.12 (1H, $J = 8.5$ Hz), 3.60 (2H, m), 4.12 (1H, d, $J = 8.9$ Hz), 4.90 (1H, d, $J =$ 8.9 Hz), 7.10−7.40 (14H, m); ^{13}C NMR δ (major isomer) 21.6, 30.2, 30.6, 33.4, 36.1, 36.9, 53.9, 61.0, 73.9, 124.0, 124.8, 125.3, 126.6, 126.9, 127.3, 127.7, 128.4, 128.9, 129.2, 140.3, 142.8, 143.2, 144.7, 169.7; MS *m*/*z* 425 (100); HRMS, *m*/*z* 424.2513 ($C_{29}H_{32}N_2O$ requires 424.2515).

[5*S*,5(4′*S*,5′*S*)]-5-(1′-Benzyl-4′,5′-dihydro-4′,5′-diphenyl-imidazol-2′-yl)-5-phenylhexan-1-ol Benzyl Ether (34). Imidazoline **22** (1.10 g, 2.73 mmol) in 10 mL of dry THF was added at room temperature to a slurry of NaH (0.84 g, 50%, 17.5 mmol, washed prealably twice with 2.0 mL of pentane) in 10 mL of dry THF, and the solution was stirred under an Ar atmosphere for 2 h. Freshly distilled benzyl bromide (neat) (1.07 g, 6.26 mmol) and a catalytic amount of tetrabutylammonium iodide (as solid) were introduced, and the stirring was maintained for 7 h more. The mixture was cooled to 0−5 °C in a ice bath, quenched with a small amount of methanol, and washed with water; then the aqueous layer was extracted twice with dichloromethane. The unified organic layers were dried over anhydrous Na_2SO_4 and the solvents evaporated in a vacuum. The crude product was purified on a short column of silica gel using gradient eluants (dichloromethane−dichloromethane/methanol 20:1) to afford 1.37 g of product (87%) as a colorless viscous oil: R_f 0.67 (dichloromethane, saturated with ammonia/hexane, 1:1); $[\alpha]_D = -134$ ($c = 2.70$, MeOH); IR (neat, cm^{-1}) 3390 (b), 2942, 1666, 1590, 1575; ^{1}H NMR (400 MHz) (major isomer) δ 1.60 (4H, m), 1.72 (3H, s), 2.18 (1H, m), 2.35 (1H, td, $J = 12.4$ Hz, $J = 3.3$ Hz), 3.32 (1H, d, $J =$ 18.0 Hz), 3.39 (2H, m), 4.05 (1H, d, $J = 18.2$ Hz), 4.15 (1H, d, $J = 6.7$ Hz), 4.42 (2H, s), 5.04 (1H, d, $J = 6.7$ Hz), 6.45−7.48 (25 H, m); ^{13}C NMR δ 21.0, 24.8, 30.2, 40.7, 44.0, 70.3, 72.8, 75.8, 126.4, 126.8, 127.1, 127.2, 127.5, 127.7, 128.2, 128.4, 128.7, 128.8, 129.1, 130.1; MS *m*/*z* 579 (100), 416 (10); HRMS, *m*/*z* 578.3302 ($C_{41}H_{42}N_2O$, requires 578.3297).

(*S*)-6-Benzyloxy-2-methyl-2-phenylhexanal (35). In a 25 mL sealed tube, equipped with a stirrbar, under an argon atmosphere, imidazoline **34** (1.08 g, 1.869 mmol) in 8.0 mL of dry nitroethane, methyl iodide (250 μL, 4.016 mmol), and finely powdered BaO (0.08 g, 0.513 mmol) were heated under continuous stirring at 120 °C for 4 h. After filtration, the solid was washed with a small amount of dry ethanol. The crude mixture was evaporated to dryness in a vacuum, and the residue was redissolved in 10 mL of dry ethanol. Sodium borohydride (230 mg, 6.080 mmol) was added portionwise to the cooled mixture at 0−5 °C, in 5 min, and the mixture was stirred at this temperature for 20 min and at room temperature for an additional 10 min (TLC:hexanes−ethyl acetate 4:1, $R_f = 0.58$).

At 0−5 °C the mixture was acidified slowly with HCl (aq) (1 N, 10 mL) and then allowed to stir for 30 min at this temperature. Extracted three times with an equivolume mixture of hexanes−ether solution, and the unified organic phases were dried over Na_2SO_4, filtered, and evaporated in a vacuum, affording 448 mg (81%) of aldehyde **35**. An analytically pure sample was obtained by preparative TLC using a 4:1 hexanes−ethyl acetate eluant mixture: R_f 0.52 (hexanes−ethyl acetate 4:1); $[\alpha]_D = +7.9$ ($c = 1.82$, cyclohexane); IR (neat, cm^{-1}) 3421 (b), 2938, 1652; ^{1}H NMR (400 MHz) δ 1.20 (2H, m), 1.43 (3H, s), 1.58 (2H, m), 1.80 (1H, td, $J = 4.6$ Hz and $J =$ 12.1 Hz), 1.92 (1H, td, $J = 4.8$ Hz; $J = 13.6$ Hz), 3.38 (2H, t, $J = 6.4$ Hz), 4.42 (2H, s), 7.15−7.7.33 (10H, m); ^{13}C NMR δ 18.8, 20.8, 30.2, 35.7, 54.0, 70.0, 72.9, 127.1, 127.5, 127.7, 128.4, 128.8, 140.0, 202.5; MS *m*/*z* 314 (100), 297 (77); HRMS, *m*/*z* 296.1779 ($C_{20}H_{24}O_2$, requires 296.1776).

Methyl (*S*)-6-Hydroxy-2-methyl-2-phenylhexanoate (36). Under an argon atmosphere, into a cooled solution (0−5 °C) of aldehyde **35** (520 mg, 1.757 mmol) and 2.6 mL of dry methanol, $Ca(OCl)_2$ (4 × 330 mg, 4 × 2.307 mmol) and acetic acid (4 × 100 μL) were added simultaneously, four times in 5 h intervals. Each time, after the addition, the cooling bath was removed and the reaction was allowed to reach room temperature by vigorous stirring. After the consumption of all starting material (TLC, eluant: hexanes−ethyl acetate 4:1), the mixture was diluted with water and extracted three times with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness.

The crude mixture was diluted with ethyl acetate (10 mL), $Pd(OH)_2$ (20%; 100 mg) and Na_2CO_3 (100 mg) were added, and the mixture was hydrogenated under atmospheric pressure and at room temperature for 1 h 30 min. The slurry was filtered over a cake of Celite, the cake was washed with a small amount (2 mL) of ethyl acetate, and the organic phase was evaporated under reduced pressure. The hydroxy ester was purified on preparative TLC using a 2:1 hexanes−ethyl acetate solvent mixture and yielded 270 mg (65%) of alcohol as a colorless viscous oil: R_f 0.12 (hexanes−ethyl acetate 4:1); $[\alpha]_D = +15.7$ ($c = 0.97$, cyclohexane); IR (neat, cm^{-1}) 3395 (b), 2944, 1729; ^{1}H NMR (400 MHz) δ 1.20 (2H, m), 1.50 (3H, s), 1.51 (1H, m), 1.70 (1H, m), 1.88 (1H, dt $J = 6.8$ Hz, $J = 13.0$ Hz), 1.98 (1H, dt, $J = 6.7$ Hz; $J = 13.1$ Hz), 3.55 (2H, t, $J = 7.0$

Hz), 3.59 (3H, s); 7.18−7.32 (5H, m); ^{13}C NMR δ 21.1, 22.7, 33.0, 39.1, 50.3, 52.2, 62.5, 125.9, 126.7, 127.9, 128.5, 143.8, 176.9; MS *m*/*z* 254 (100), 237 (89); HRMS, *m*/*z* 236.1388 ($C_{14}H_{20}O_3$, requires 236.1388).

Methyl (*S*)-6-bromo-2-methyl-2-phenylhexanoate (37). Under argon, CBr_4 (330 mg, 0.988 mmol) and PPh_3 (270 mg, 1.027 mmol) were successively added to a solution of alcohol **36** (70 mg, 0.297 mmol) dissolved in 2.0 mL of ether. The mixture was stirred at room temperature for 18 h. After this period of time, the reaction mixture was diluted in pentane and filtered through a pad of Celite to remove the most of the phosphorous salts. The crude product was purified by flash chromatography using a pentane/pentane−ethyl acetate 9:1 solvent gradient: yield 76.9 mg (87%), colorless viscous oil; R_f 0.57 (pentane−ethyl acetate 9:1); $[\alpha]_D = +18.4$ (*c* = 1.60, cyclohexane); ^{1}H NMR (400 MHz) δ 1.25 (2H, m), 1.48 (3H, s), 1.51 (1H, m), 1.80 (2H, td, *J* = 1.6 Hz, *J* = 6.8 Hz), 1.85 (1H, dt *J* = 5.8 Hz, *J* = 3.4 Hz), 1.97 (1H, dt, *J* = 6.6 Hz, *J* = 2.6 Hz), 3.30 (2H, t, *J* = 6.8 Hz), 3.59 (3H, s), 7.15−7.28 (5H, m); ^{13}C NMR δ 22.6, 23.4, 33.0, 33.4, 38.4, 50.2, 52.2, 62.5, 125.9, 126.8, 128.5, 143.6, 176.6; MS *m*/*z* 316 (100), 299 (22); HRMS, *m*/*z* 298.0543 ($C_{14}H_{19}BrO_2$ requires 298.0543).

(*S*)-2-Methyl-2-phenylcyclohexanone (38). Under an inert atmosphere and at room temperature, diiodomethane (160 mg, 0.567 mmol) was added to a vigorously stirred suspension of Sm (138 mg, 0.926 mmol) in 2 mL of dry THF. The resultant blue-green reaction mixture was stirred for 2.5 h at room temperature, and then HMPA (460 μL) was added and the solution was stirred for an additional 15 min at this temperature. The deep purple solution was cooled to 0 °C, and then a solution of bromoester **37** (32 mg, 0.107 mmol) in dry THF (2.0 mL) was added via syringe pump under 2 h. After the introduction was complete, the mixture was stirred for an additional 30 min at room temperature. Within that time the characteristic deep purple color disappeared, and a brown precipitate was formed in a transparent solution. The reaction was quenched with a saturated $NaHCO_3$ (aq) solution. After extraction, the crude product was purified on preparative TLC using a 9:1 pentane−ethyl acetate solvent mixture and afforded 12.3 mg of product (61%) as a colorless oil: R_f 0.59 (pentane−ethyl acetate 9:1); $[\alpha]_D = -131$ (*c* = 0.41, cyclohexane); IR (neat, cm^{-1}) 3430 (b), 2935, 1706, 1625; ^{1}H NMR (400 MHz) δ 1.20 (3H, s), 1.65 (4H, m), 1.89 (1H, m), 2.25 (2H, m), 2.61 (1H, dt, *J* = 7.0 Hz, *J* = 1.8 Hz), 7.15−7.28 (5H, m); ^{13}C NMR δ 21.3, 28.6, 38.3, 40.0, 54.5, 126.2, 126.7, 129.1, 143.4, 214.2; MS *m*/*z* 376 (64), 206 (100), 189 (48); HRMS, *m*/*z* 188.1203 ($C_{13}H_{16}O$ requires 188.1203).

[5*SR*,5(4′*R,5′*R**)]-5-(4′,5′-Dihydro-4′,5′-diphenyl-1*H*-imidazol-2′-yl)-5-phenylhex-1-ene (39).** In a degassed solution of imidazoline **15** (1.673 g, 4.57 mmol) in THF (15 mL) *sec*-butyllithium (4.02 mL 2.5 M solution in hexanes) was added at −25 °C and under an Ar atmosphere. After 25 min the reaction mixture was cooled to −78 °C, and after 15 min of incubation at this temperature, methyl iodide (5.04 mmol) was slowly introduced (neat) via a syringe. The mixture was stirred at this temperature for 6 h more and then quenched with a few drops of saturated ammonium chloride. Dichloromethane (10 mL) was added at this point to the mixture, the solution was extracted twice with water, and then the aqueous layer was extracted twice with dichloromethane. The unified organic phases were dried over Na_2SO_4, concentrated in a vacuum, and subjected to chromatography on a short column of silica gel using a dicloromethane−pentane (1:1) (saturated with ammonia) solvent mixture, to give compound **39**: R_f 0.47 (dichloromethane saturated with ammonia/pentane 1:2); IR (KBr, cm^{-1}) 2923, 2853, 1591; ^{1}H NMR (200 MHz) δ 1.69 (3H, s), 1.80 (1H, m), 1.99 (1H, m), 2.15 (1H, dd, *J* = 11.9 Hz, *J* = 4.6 Hz), 2.21 (1H, dd, *J* = 11.9 Hz, *J* = 4.6 Hz), 4.55 (2H, bs); 4.83 (1H, d, *J* = 10.3 Hz), 4.90 (1H, dd, *J* = 17.1 Hz, *J* = 1.3 Hz), 5.76 (1H, m), 7.21 (15H, m); ^{13}C NMR δ 24.6, 29.4, 39.3, 45.0, 115.0, 127.1, 127.5, 127.9, 129.1, 129.2, 139.2, 144.1; MS *m*/*z* 381 (100); HRMS, *m*/*z* 380.2252 ($C_{27}H_{28}N_2$, requires 380.2252).

[5*SR*,5(4′*R,5′*R**)]-5-(4′,5′-Dihydro-4′,5′-diphenyl-1′*H*-imidazol-2′-yl)-5-phenyl-hexan-1-ol (40).** Into a stirred solution of olefin **39** (15 mg, 39.5 mmol) in dry THF (100 μL) BH_3−Me_2S (2 M in THF, 200 μL), the complex was added at room temperature, and the solution was stirred for 5 h under an argon atmosphere. Hydrogen peroxide (300 μL, 35%) and an aqueous solution of NaOH (1.0 mL, 2.5 N) were slowly introduced at 0−5 °C, stirred for an additional 1 h at room temperature, and then extracted three times with dichloromethane. The unified organic layers were dried over Na_2SO_4, filtered, evaporated and purified on TLC to give 10.8 mg (69%) of alcohol as a colorless viscous oil: R_f 0.40 (dichloromethane saturated with ammonia); IR (KBr, cm^{-1}) 3250 (b), 3028, 2930, 1599; ^{1}H NMR (250 MHz) δ 1.43 (2H, m), 1.65 (3H, s), 1.98 (1H, m), 2.11 (1H, t, *J* = 9.1 Hz), 3.58 (2H, m), 4.62 (2H, bs), 7.05−7.45 (15H, m); ^{13}C NMR (62.5 MHz) δ 21.0, 24.0, 31.9, 39.1, 61.8, 125.9, 126.4,126.9, 127.1, 127.6, 127.8, 128.1, 128.3, 128.5, 128.8; MS *m*/*z* 399 (100), 326 (12); HRMS, *m*/*z* 398.2348 ($C_{27}H_{30}N_2O$, requires 398.2358).

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds not accompanied by elemental analyses (66 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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