DESIGN AND SYNTHESIS OF CHIRAL *N*-HETEROCYCLIC CARBENES WITH APPLICATIONS TO ASYMMETRIC SYNTHESES AND SYNTHESIS OF DIBENZAZEPINONES BY PALLADIUM–CATALYZED INTRAMOLECULAR ARYLATION OF *O*-(2'-BROMOPHENYL)ANILIDE ENOLATES

by

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DESIGN AND SYNTHESIS OF CHIRAL *N*-HETEROCYCLIC CARBENES WITH APPLICATIONS TO ASYMMETRIC SYNTHESES AND SYNTHESIS OF DIBENZAZEPINONES BY PALLADIUM–CATALYZED INTRAMOLECULAR ARYLATION OF *O*-(2'-BROMOPHENYL)ANILIDE ENOLATES

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Chiral *N*-heterocyclic carbene (NHC) ligands were prepared and examined in three asymmetric syntheses (oxindole synthesis, pyrrolidine synthesis and cyanosilylation of aldehydes). The ligand generated from (4*R*,5*R*)-1,3-bis(*ortho*-cyclohexylphenyl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate provided the best asymmetric oxindole synthesis: yields of oxindoles up to 99% with enantioselectivities (ee) up to 80% were achieved in 3 h; catalyst loadings as low as 1 mol % could be used; the imidazolinium salt can be made efficiently in only two steps. A mechanism for this asymmetric oxindole synthesis was proposed. The rotation barrier of the N-aryl bond in the oxidative addition products was found crucial for the enantioselectivity.

A new approach for the convenient synthesis of dibenzazepinones is reported. The key step is the formation of the seven-membered ring through palladium-catalyzed intramolecular arylation of an anilide enolate. The reactions were completed in 10 min at 100 ℃ with moderate to excellent yields. Aminodibenzazepinone, the core structure in γ-secretase inhibitor LY411575, can be prepared in five steps from 2-bromophenylboronic acid and 2-iodoaniline in 60% overall yield. The synthesis reported here compares favorably with presently available approaches to this interesting ring system.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

PREFACE

I'm honored to express my deepest gratitude to Prof. Craig Wilcox for giving me the wonderful opportunity to pursue exciting research under his supervision. He has offered me valuable ideas, suggestions and criticisms with his profound knowledge in science and rich research experience. His patience and kindness are greatly appreciated. Besides, he always puts high priority on my dissertation writing and was willing to discuss with me at anytime he was available.

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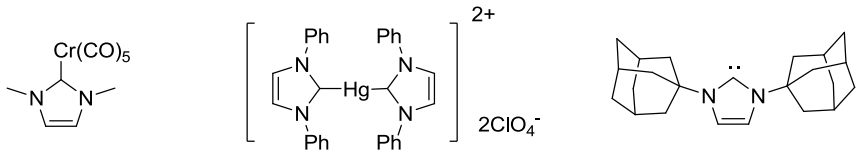
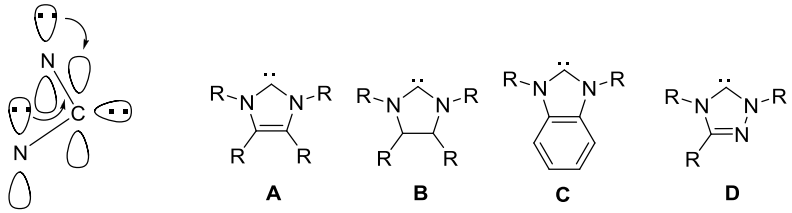
1.0 DESIGN AND SYNTHESIS OF CHIRAL *N*-HETEROCYCLIC CARBENES WITH APPLICATIONS TO ASYMMETRIC SYNTHESES

N-Heterocyclic carbenes (NHCs) were introduced as ligands in 1968 when carbene complexes **1**[1] and **2**[2] were prepared. But the chemistry of NHCs and their application in catalysis did not rapidly develop until the first free carbene ligand **3** was isolated.[3]



1 **2** **3**

N-Heterocyclic carbenes, including imidazolylidenes **A**, imidazolinylidenes **B**, benzimidazolylidenes **C** and triazolinylidines **D**, share a common substructure (Figure 1). Two nitrogens are connected by the sp^2 carbene carbon and donate electron density into the empty p-orbital of the carbene carbon. The electronegativity of nitrogen also helps stabilize the *N*-heterocyclic carbene.



A **B** **C** **D**

Figure 1. Structures of *N*-heterocyclic carbenes

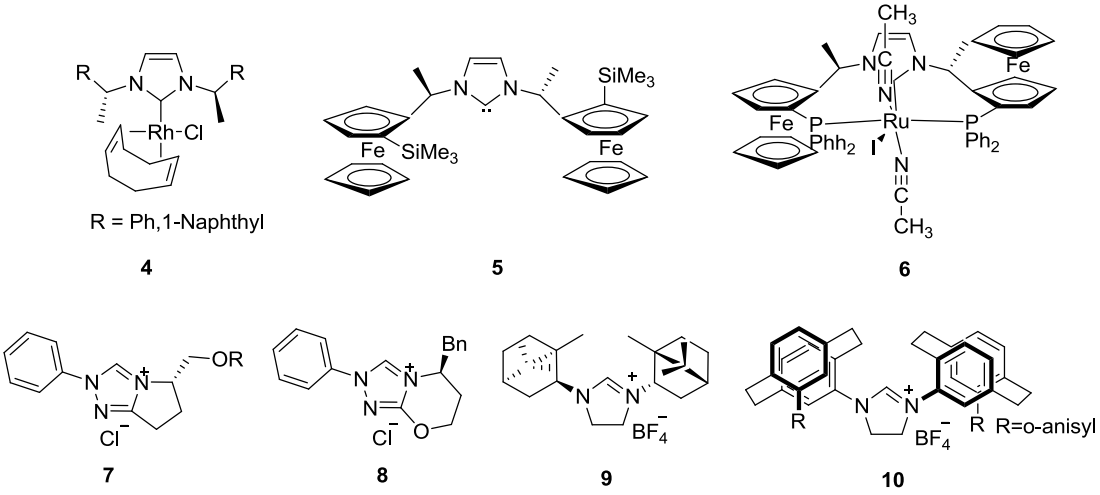
This unique structure makes *N*-heterocyclic carbenes good ligands. They are similar to trialkylphosphines and alkylphosphinates,[4] but they are better σ donors and poor π acceptors.[5] Free carbene ligands can displace several types of ligands such as halides, alkenes, carbonyls, arenes, phosphines, ethers and amines.[6] Numerous molecular structures based on the crystallographic data show that the metal-carbene bonds are rather long (>210 pm). In Fischer- and Schrock-type complexes, these distances are below 200 pm because of backbonding.[6] Thus, metal-carbene bonds are extremely strong, making these kinds of complexes superior to those of trialkylphosphines and alkylphosphinates. NHCs are easy to make, have versatile structures and better air and thermal stability, and due to their high affinity to the metals, do not require excess ligand for complete complexation of the metal.

Most *N*-heterocyclic carbenes are made from the corresponding azolium salts via deprotonation. Strong bases such as NaO*t*-Bu are usually used. Triethylamine can also deprotonate the azolium salts. The deprotonation may be driven by the precipitation of halide salts, the formation of complexes or the decomposition of carbenes.[7]

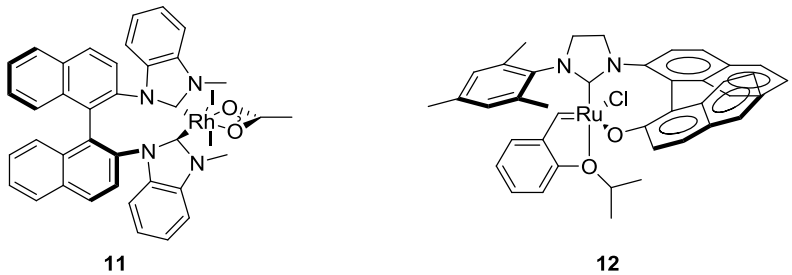
A number of *N*-heterocyclic carbenes have been applied in many reactions as either ligands of catalysts or catalysts and show promising activity compared to trialkylphosphines and alkylphosphinates.[6] Based on this fact, the application of chiral NHC ligands in asymmetric syntheses started in 1995 and the first efficient chiral NHC ligand was published in 2001.[8] Although NHC ligands are very similar to phosphines, they may not create an "edge-to-face" arrangement of their aryl substitutes which are very common in many chiral diphosphines.[8] Based on the structure, they can be categorized as follows:[8]

1. Carbenes with chiral *N*-substituents and chiral centers most often on the C atoms adjacent to the N atoms. The main drawback of these carbenes could be a fast rotation of the

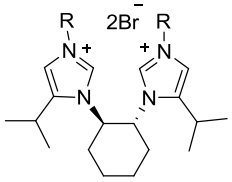
C-N bond[8] (complex **4**[9] and carbene **5**[10]), making the chiral environment less defined. The trimethylsilyl group in **5** is replaced with a diphenylphosphinyl group (complex **6**[11]) which could coordinate to the metal, and the rotation of the C-N bond is fixed by this coordination. This rotation is also blocked in triazolium salts **7** and **8** which feature a bicyclic structure.[12] Another important contribution to this kind of NHC (with controlled rotation of the C-N bond) is imidazolinium salts **9**[13] and **10**,[14] in which the steric bulk of the chiral *N*-substituents is greatly increased.



2. Carbenes incorporating 1,1'-binaphthyl units. The 1,1'-binaphthyl unit is commonly employed as a component in asymmetric catalysts (BINAP and BINOL). The rotation of the inter-ring C-C bond is blocked, making stable atropoisomers possible. Based on the structures of (*S*)-BINAP and (*S*)-BINOL, complexes **11**[15] and **12**[16] have been reported.



3. Carbenes joined by *trans*-cyclohexane. Both carbenes are connected by a *trans*-cyclohexane in imidazolium salt **13**,[17] and a carbene opposes an imine in imidazolium salt **14**.[18] When they coordinate to a metal simultaneously, a chiral environment is developed.



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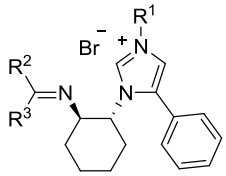
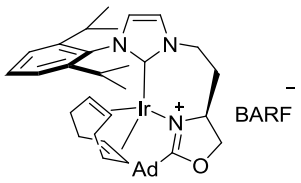


14

4. Carbenes incorporating oxazoline units. Due to its rigidity, quasi-planarity and facile accessibility by condensation of an amino-alcohol with a carboxyl acid derivative,[19,20] the oxazoline ring has been widely used in the ligand design for asymmetric catalysts. As shown in complexes **15**[21,22] and **16**,[23] the nitrogen atom on the oxazoline coordinates to the metal, and the stereodirecting substituent is delivered to the metal center.



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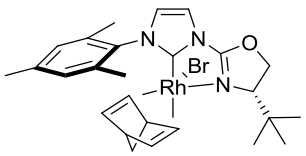


16

5. Carbenes with chiral elements within the backbone of the NHC. Other positions on the carbene may also be modified to introduce chirality. The 4 and 5 positions of the imidazolinylidene are sp^3-hybridized carbon atoms. It is possible to introduce a chiral carbon by appropriate substitutions (*t*-butyl, phenyl groups and *trans*-cyclohexane moiety (Figure 2)). In taking this approach, chiral information is expected to be transferred to the metal center by the means of a second order response from the R^1 substituent.

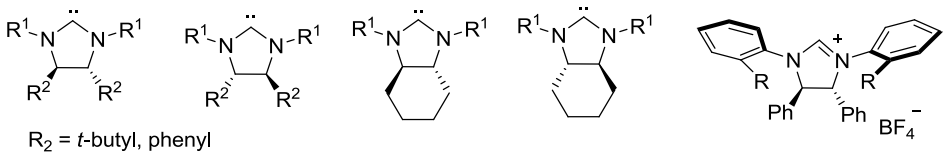
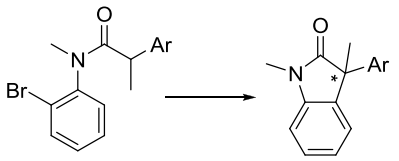


Figure 2. *N*-Heterocyclic carbenes with different back bone chirality

1,3-Bis(*ortho*-substitutedphenyl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborates (Figure 2) were introduced as the precursors of chiral NHCs in a ruthenium-catalyzed olefin metathesis reaction.[24] The crystal data of the NHC metal complexes show that these NHC ligands are approximately *C2*-symmetric with the *ortho*-substituents *anti* to the phenyl groups on the imidazole ring, and the stereochemistry of the phenyl groups on the imidazole ring is effectively transferred to the metal center.[25] The rotation of the N-Ar bond in these NHCs is hindered which results in strong conformational preferences both in the solution and the solid state.[26] The family of these NHCs has been explored in many asymmetric syntheses and gives moderate to excellent results.[27]

The oxindole is a very important substructure in many biologically active natural products and pharmaceutically active candidates.[28] In 2001, three NHC ligands were employed in the palladium-catalyzed α-methyl-α-aryl oxindole synthesis (eq 1) which cannot be achieved by the intramolecular Heck reactions, and their outcomes were superior to those of 19 other chiral phosphine ligands.[13] After that, many NHC ligands were tried in this reaction.[29] Before we started our new ligand exploration in 2005, the best results of the oxindole reaction in the literature were 69% ee, 91% yield with 1 mol % of the catalyst at 25 ℃ for 26 h (Ar = 1-naphthyl)[13] and 67% ee, 14% yield with 20 mol % of the catalyst at 100 ℃ for 12 h (Ar = phenyl).[29c] We believed there was an opportunity to improve the reactivity and enantioselectivity of the oxindole reaction and tried to develop a new NHC ligand.

A good chiral ligand should be C_2 symmetrical in order to reduce the number of diastereomeric intermediates and transition states which play a role in the catalytic cycle.[30] The region around the metal center should have a fixed chiral environment, but the environment cannot be too restrictive or the desired transition states may be impossible to form. There is a balance to be sought between reactivity and selectivity. Moreover, the ligand should be easy to make and recycle, and have air and thermal stability. Here we report our efforts toward the synthesis of new NHCs and their application in the asymmetric syntheses.



A Ar = 1-naphthyl
B Ar = phenyl
C Ar = 4-isobutyl phenyl

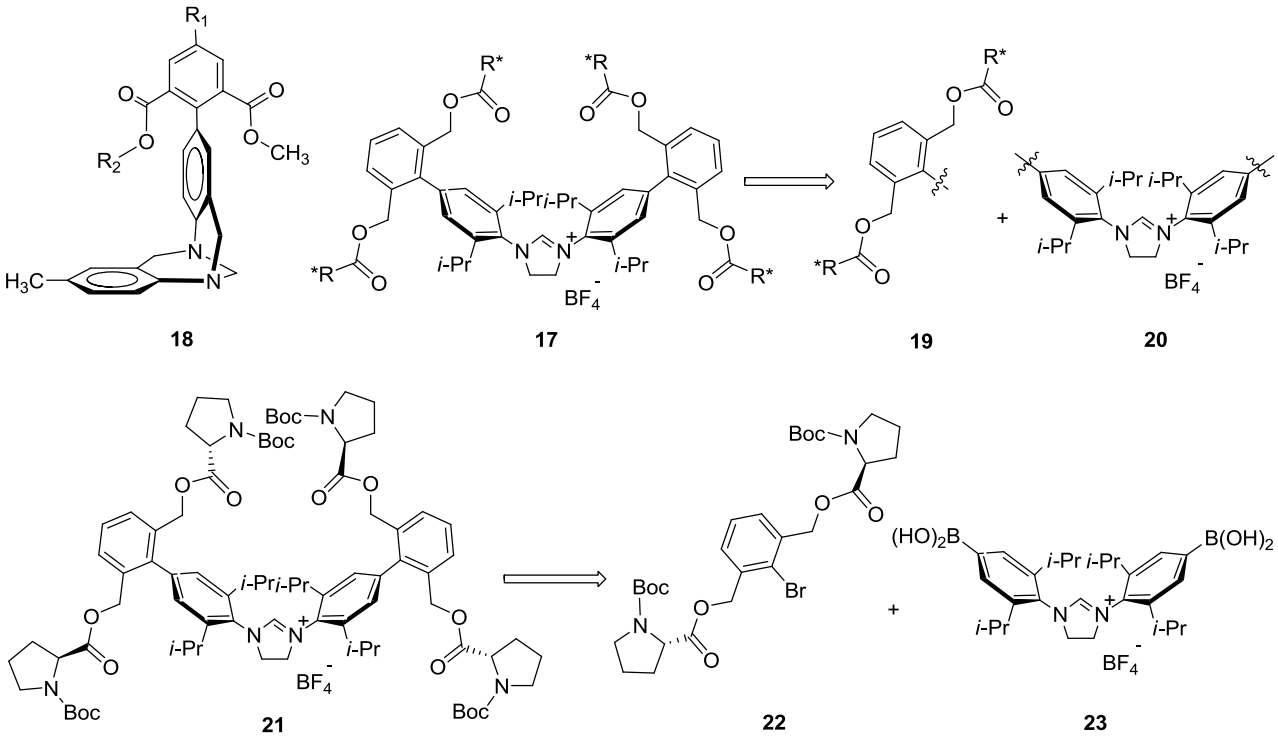
(**1**)

1.1 EXPLORATION OF IMIDAZOLINIUM SALTS WITH THE 'ARM' AND 'CORE' STRUCTURES

In our first investigation, deriving an idea from our torsion balance model **18** (Scheme 1), we sought to prepare analogs of imidazolinium salt **17**. The target can be divided into two principal parts with **19** as an 'arm' structure and **20** as a 'core' structure. The isopropyl groups lock the phenyl ring in a position vertical to the NHC ring. The external 'arm' phenyl rings are vertical to the internal phenyl rings and, on average, coplanar with the heterocycle. The idea we wanted to explore was to bring the chiral group close to the metal center by directing it from a remote position. We perceived that the chiral R substituent can be changed by esterification of the benzyl alcohol in order to provide different chiral environments at the metal center. Amino acids seemed to be a good choice for this modification. To test this idea, imidazolinium salt **21**

(an analog of **17** in which Boc-*L*-proline is the R* substituent) was first explored, and its synthesis would call for the Suzuki coupling of bromoarene **22** and boronic acid **23**.

Scheme 1. Imidazolinium salts **17** and **21**

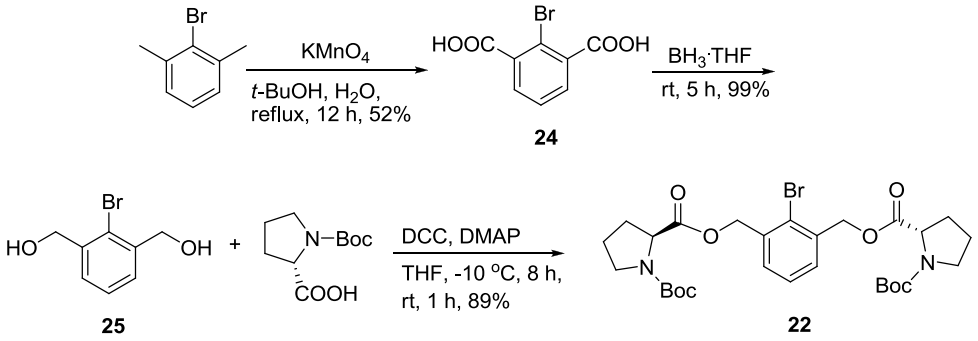


Synthesis of bromoarene 22. As shown in Scheme 2, the oxidation of 2,6-dimethylbromobenzene with $KMnO_4$ provided diacid **24** in 52% yield[31] which was reduced to diol **25** quantitatively with BH_3.[32] The esterification of **25** with Boc-*L*-proline under standard DCC/DMAP conditions afforded **22** in 89% yield.[33]

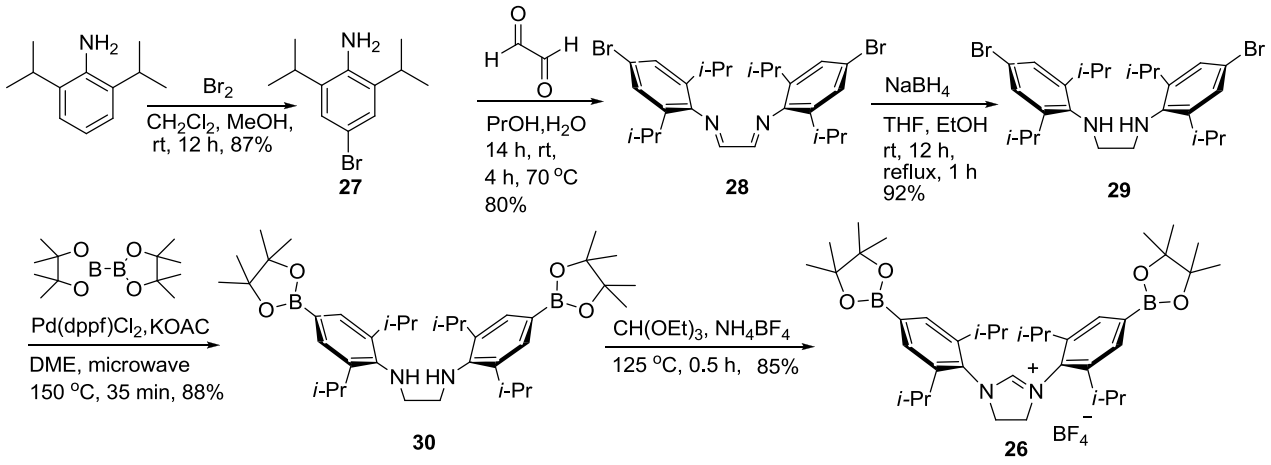
Synthesis of imidazolinium salt 26 (an alternative to boronic acid 23). As shown in Scheme 3, the bromination of 2,6-diisopropylaniline with Br_2 gave bromoaniline **27** in 87% yield.[34] The treatment of **27** with oxalaldehyde provided diimine **28** in 80% yield.[35] Further reduction of **28** with $NaBH_4$ afforded diamine **29** in 92% yield.[36] Our synthetic plan called for the lithiation-borylation reaction, but neither **28** nor **29** gave a product through this pathway.

Finally, borylated diamine **30** was obtained in 88% yield by the Miyaura borylation of **29** with bis(pinacolato)diboron in a microwave reactor.[37] The treatment of **30** with $CH(OEt)_3$ and NH_4BF_4 gave **26**, the desired core unit, in 85% yield.[13]

Scheme 2. Synthesis of bromoarene **22**



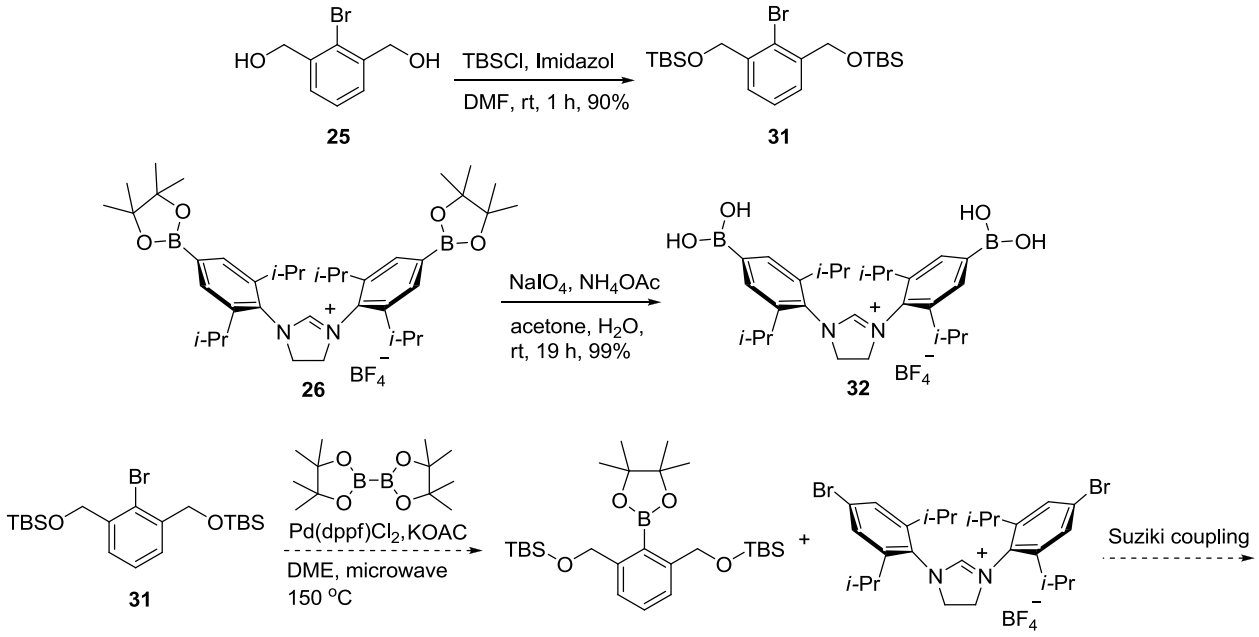
Scheme 3. Synthesis of imidazolinium salt **26**



Efforts for assembling 'core' 26 and 'arms'. The core unit **26**, could function as a versatile precursor to a variety of new NHC ligands. For this to succeed, the core must be susceptible to Suzuki coupling. We attempted coupling of the core **26** and the arm **22** by the Suzuki reaction methods. However, the reaction was unsuccessful – possibly because of the bulky and base labile components (ester) on **22**. The Suzuki reaction of **26** and diol **25** also failed most likely due to the hydroxyl groups. Accordingly, the hydroxyl groups on **25** were

protected with TBSCl to give TBS ether **31** in 90% yield (Scheme 4).[38] However, the Suzuki coupling of **26** and **31** was also unsuccessful. Different palladium catalysts ($Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd(dppf)Cl_2$, Pd/C, $Pd_2(dba)_3$ with P(*n*-Bu)$_3$ and $Pd(OAc)_2$ with PCy_3) and different bases (K_2CO_3, Na_2CO_3, K_3PO_4, $NaHCO_3$ and KF) in different solvents (DME, benzene, DMF, EtOH, MeOH, CH_2Cl_2, dioxane and H_2O) at 80 ℃ to 140 ℃ in an oil bath or a microwave reactor were tried but failed in the Suzuki coupling of **26** and **31**.

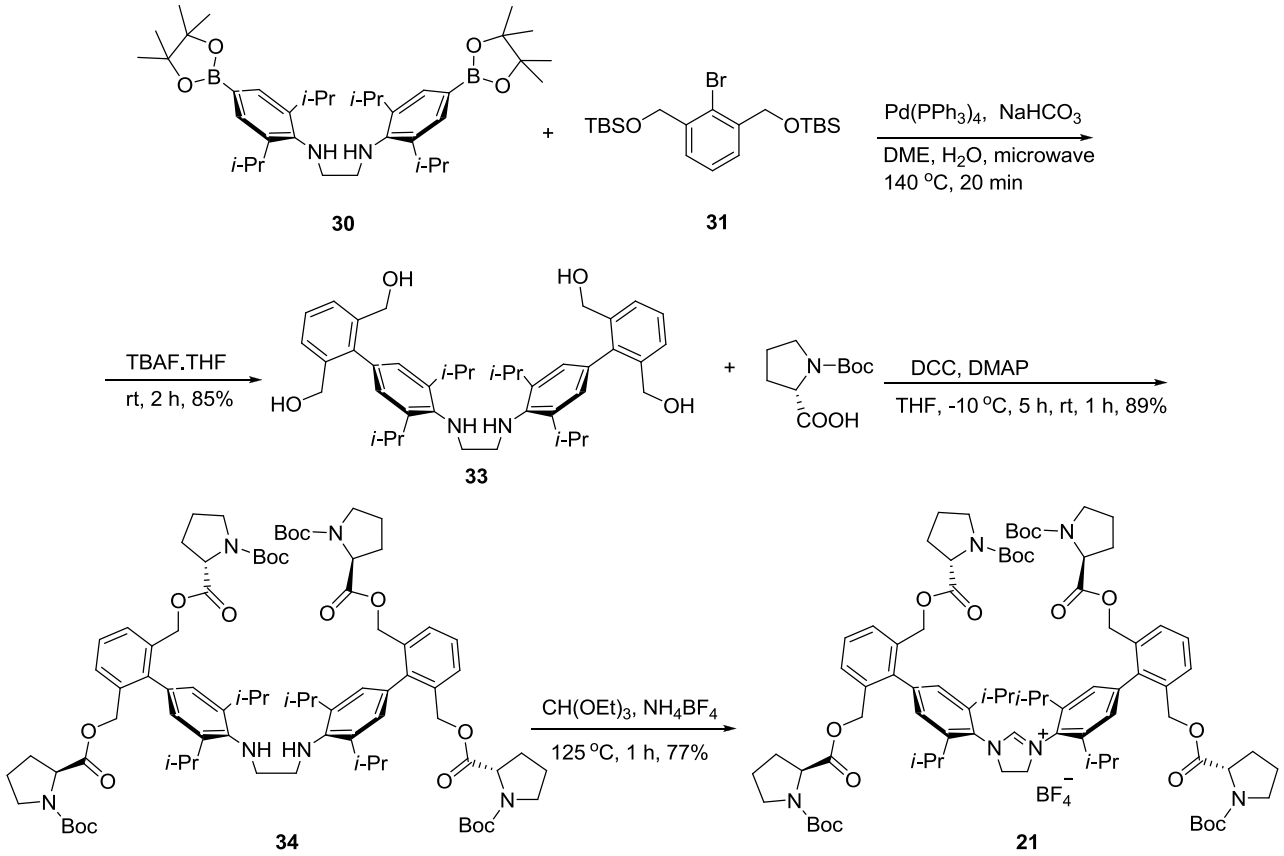
Scheme 4. Efforts for the Suzuki coupling of the 'arm' and the 'core'



2,6-Dimethylbromobenzene, a simple substrate, was also difficult to couple with the core **26**. Therefore, the problem is probably due to **26**. Diboronate **26** was then transformed to diboronic acid **32** in 99% yield with $NaIO_4$ and NH_4OAc (Scheme 4).[39] However, the Suzuki coupling of **32** and **31** was also unsuccessful. We also tried reversing the position of the boronic acid and the aryl bromide (Scheme 4). Unfortunately, the Miyaura borylation of **31** failed.

Synthesis of imidazolinium salt 21 involving the Suzuki coupling of diamine 30 and bromoarene 31 (Scheme 5). Despite extensive effort, no satisfactory method for the Suzuki reaction of the core **26** was found. Therefore we attempted to couple the arm and diamine **30**, expecting that the imidazolinium salt could be formed after the coupling. In the event, diamine **30** was coupled with **31** successfully in a microwave reactor.[40] Following deprotection of the coupling product by TBAF gave tetraol **33** in 85% yield over these two steps.[41] We found that the coupling could not be achieved directly from diol **25** and **30** under these conditions in the microwave reactor. The esterification of **33** with Boc-*L*-proline afforded tetraester **34** in 89% yield which was cyclized to imidazolinium salt **21** with $CH(OEt)_3$ and NH_4BF_4 in 77% yield.

Scheme 5. Synthesis of imidazolinium salt **21**

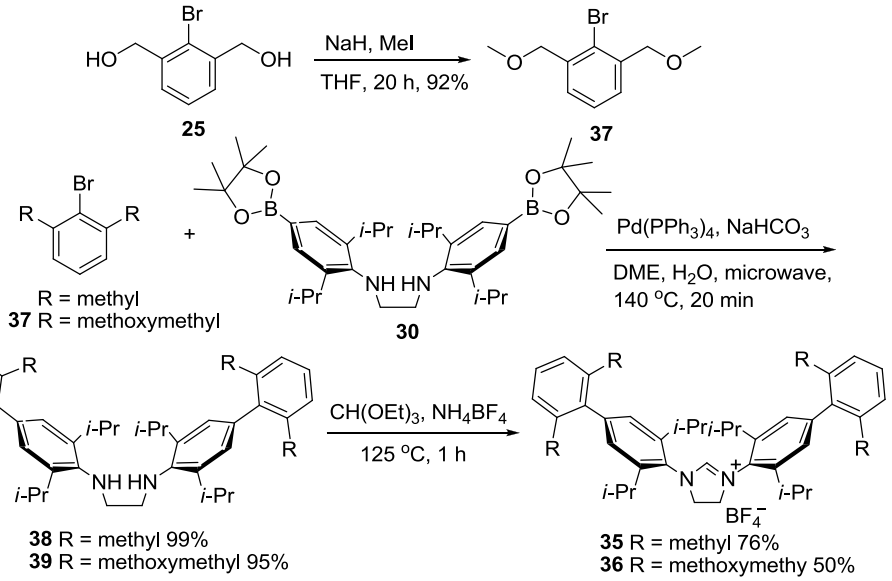


Testing imidazolinium salt 21 in the asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl). With **21** in hand, we turned to evaluate this ligand in the asymmetric oxindole reaction. Unfortunately, the oxindole reaction did not occur until the temperature was raised to 80 ℃ and the product that did form was racemic. Tests showed that this reaction could take place without **21** at 80 ℃.

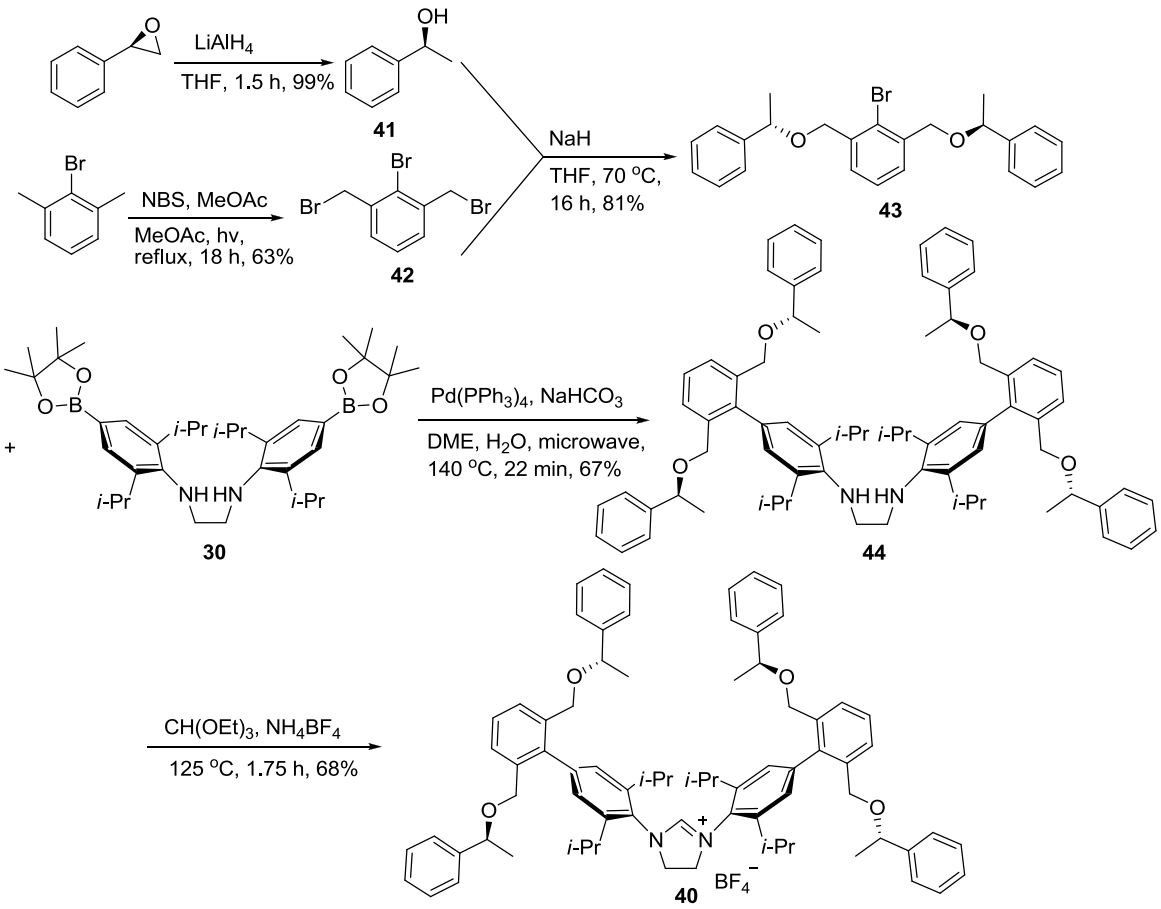
Exploration of imidazolinium salts 35 and 36. Imidazolinium salt **21** is not an effective ligand possibly because of a bulky group leading to steric hindrance and the base labile component. To test this hypothesis, imidazolinium salts **35** (methyl) and **36** (methoxymethyl) were prepared (Scheme 6). The methylation of diol **25** with MeI provided diether **37** in 92% yield.[42] The Suzuki coupling of 2,6-dimethylbromobenzene and **30** gave diamine **38** in 99% yield which was cyclized with $CH(OEt)_3$ and NH_4BF_4 to afford imidazolinium salt **35** in 76% yield. The same reaction sequence with bromodiether **37** gave diamine **39** in 95% yield and imidazolinium salt **36** in 50% yield. The asymmetric oxindole reaction (eq 1, Ar = 1-naphthyl) proceeded smoothly at room temperature with imidazolinium salts **35** or **36**. This established that the remote chiral unit in **21** was interfering with the reaction.

Exploration of imidazolinium salt 40. Based on the structure of achiral imidazolinium salt **36**, imidazolinium salt **40** with chiral benzyl ether groups was designed and prepared (Scheme 7). (*R*)-2-Phenyloxirane was reduced to benzyl alcohol **41** quantitatively with $LiAlH_4$.[43] The bromination of 2,6-dimethylbromobenzene with NBS under illumination gave benzylbromide **42** in 63% yield.[44] The treatment of **42** with **41** and NaH afforded diether **43** in 81% yield.[45] The Suzuki coupling of **43** and diamine **30** in a microwave reactor gave diamine **44** in 67% yield. Finally, cyclization of **44** with $CH(OEt)_3$ and NH_4BF_4 provided imidazolinium salt **40** in 68% yield.

Scheme 6. Synthesis of imidazolinium salts **35** and **36**



Scheme 7. Synthesis of imidazolinium salt **40**



Imidazolinium salt **40** was then tested in the asymmetric oxindole reaction (eq 1, Ar = 1-naphthyl, Table 1). The best results achieved were 12% ee with 97% yield when 10 mol % of **40**, $Pd(dba)_2$ and 1.5 equiv of NaO*t*-Bu were used in dioxane at 25 ℃ for 20 h (entry 3). Although the reactivity is good, the ee is poor. The low ee may be due to the relatively large distance between the chiral groups and the metal center.

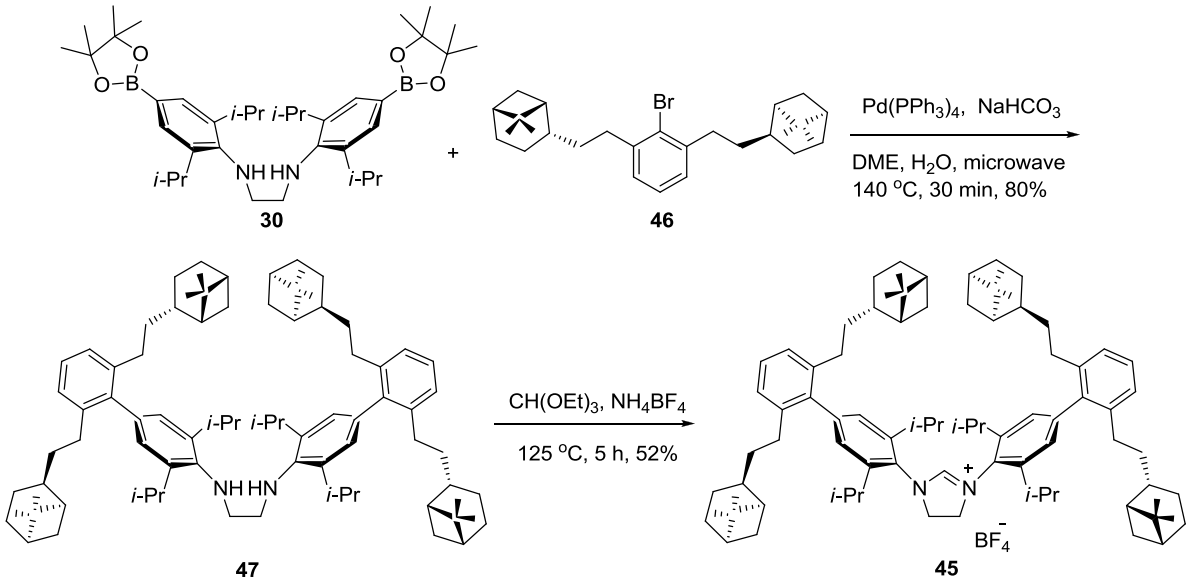
Table 1. Asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) with **40**[a]

Entry	Pd	Solvent	T (℃)	Time (h)	Yield[b] (%)	Ee[c] (%)
1	$Pd_2(dba)_3$	DME	50	14	42	4
2	$Pd(dba)_2$	DME	25	20	35	2
3	$Pd(dba)_2$	dioxane	25	20	97	12

[a]Reaction run with 10 mol % of **40**, $Pd(dba)_2$ and 1.5 equiv of NaO*t*-Bu. [b]The yield of oxindole **A** was calculated from isolated product after chromatography. [c]The ee was determined by chiral OD-H HPLC.

Synthesis of imidazolinium salt 45. Prior investigations in our laboratory by Dr. Jae Kon Kim had resulted in the synthesis of a related chiral NHC, imidazolinium salt **45** (Scheme 8). We sought to compare our synthetic methods with his process. The Suzuki coupling of bromobenzene **46** (from Dr. Kim) and **30** provided diamine **47** in 80% yield. The cyclization of **47** with $CH(OEt)_3$ and NH_4BF_4 provided imidazolinium salt **45** in 52% yield. The steps in this new pathway are fewer than those in Dr Kim's and of overall higher yield.

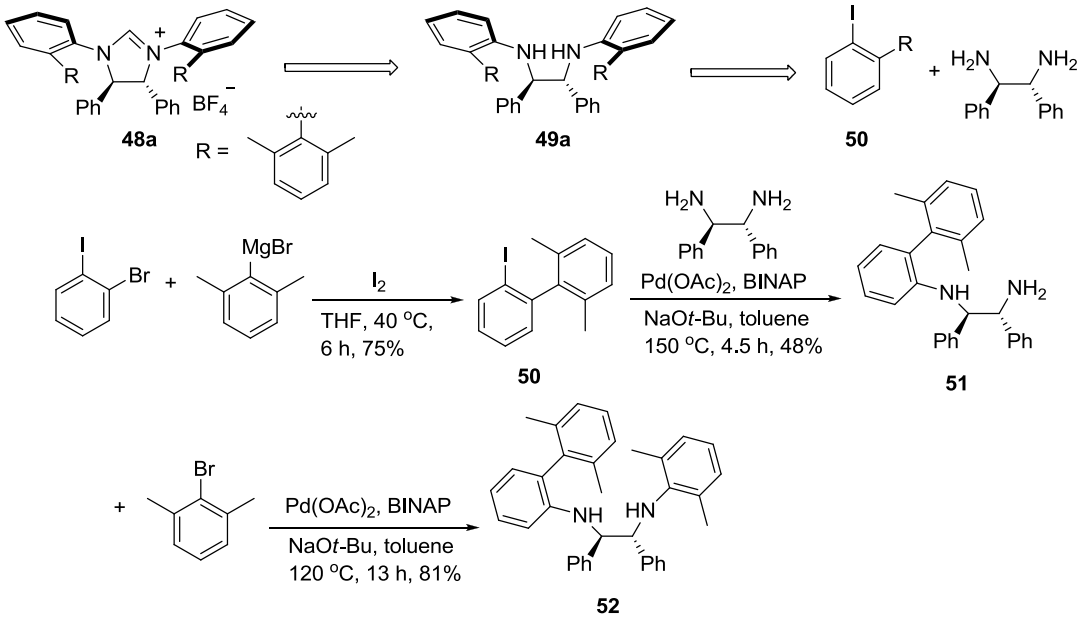
Scheme 8. Synthesis of imidazolinium salt **45**



1.2 EXPLORATION OF (4*R*,5*R*)-1,3-BISARYL-4,5-DIPHENYL-4,5-DIHYDRO-1*H*-IMIDAZOL-3-IUM TETRAFLUOROBORATES

The NHC ligands we made above may be useful for other reactions but are not good in the asymmetric oxindole synthesis. We surmised that the structures of these failed NHC ligands were too crowded, and the chiral controlling groups were too far from the reaction center. Accordingly, (4*R*,5*R*)-1,3-bisaryl-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborates were designed and imidazolinium salt **48a** (R = 2,6-dimethylphenyl) was first targeted (Scheme 9). In this design, the 2,6-dimethylphenyl group is moved from the *para* position (imidazolinium salt **35**) to the *ortho* position of the N-benzene ring. A key idea here is that the phenyl groups in the backbone of the NHC would control the conformation of the dimethylphenyl group opposite to them. The chirality is then transferred from the backbone of the NHC to the reaction center.

Scheme 9. Synthesis of imidazolinium salt **48a**

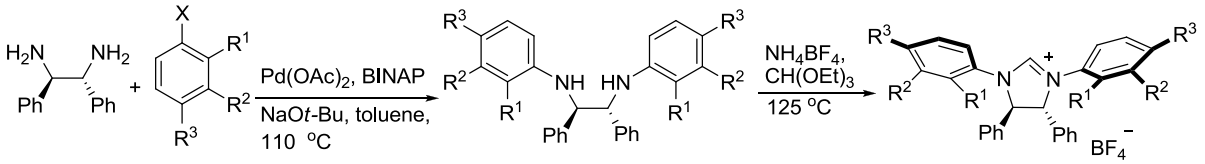


Synthesis of imidazolinium salt 48a. As shown in Scheme 9, imidazolinium salt **48a** would undoubtedly come from the cyclization of diamine **49a**, which would call for the Hartwig-Buchwald coupling of iodoarene **50** and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine. The Hart coupling of 2-bromo-iodobenzene and 2,6-dimethylphenylmagnesium bromide with I_2 provided **50** in 75% yield.[46] Unfortunately, the Hartwig-Buchwald coupling of **50** and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine only afforded monocoupled product **51** in 48% yield.[47] Further Hartwig-Buchwald coupling of **51** and **50** was fruitless. However, the Hartwig-Buchwald coupling of **51** and 2,6-dimethylbromobenzene furnished diamine **52** in 81% yield. Therefore the failure of the dicoupling is most likely due to the steric bulk of **50**. We envisioned that the dimethyl group on **50** could be eliminated and prepared imidazolinium salt **48b** (R = phenyl).[27d]

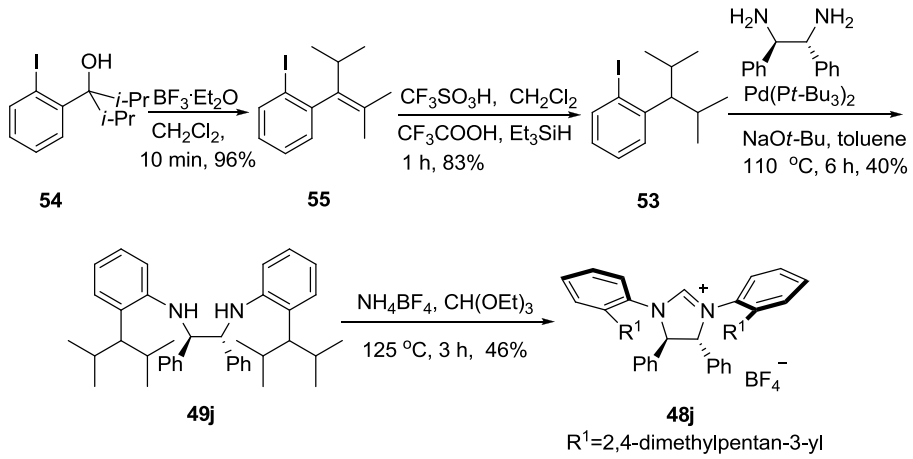
Synthesis of imidazolinium salt 48b–48j. Because of the similarities of (4*R*,5*R*)-1,3-bisaryl-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborates **48b–48j**, their syntheses are described together in Scheme 10. The Buchwald–Hartwig coupling of (1*R*,2*R*)-1,2-

diphenylethane-1,2-diamine and bromo- or iodo-arenes provided diamines **49b–49i** in 23–96% yield. Further cyclization of **49b–49i** with $CH(OEt)_3$ and NH_4BF_4 afforded imidazolinium salts **48b–48i** in 41–84% yield.

Scheme 10. Synthesis of imidazolinium salts **48b–48j**



X	R^1	R^2	R^3	yield		yield	
I	phenyl	H	H	**49b**	34%	**48b**	41%
Br	benzyl	H	H	**49c**	91%	**48c**	84%
Br	cyclohexyl	H	H	**49d**	92%	**48d**	72%
Br	H	H	H	**49e**	84%	**48e**	41%
Br	methyl	H	H	**49f**	95%	**48f**	84%
Br	isopropyl	H	H	**49g**	96%	**48g**	42%
Br	methyl	phenyl	H	**49h**	93%	**48h**	79%
Br	methoxyl	methoxyl	methoxyl	**49i**	23%	**48i**	69%



54 **55** **53** **49j** **48j**

R^1=2,4-dimethylpentan-3-yl

By contrast, the synthesis of imidazolinium salt **48j** with *ortho*-2,4-dimethylpentan-3-yl-phenyl group was a challenge. The synthesis of the required iodobenzene derivative **53** by direct reduction of tertiary benzyl alcohol **54** with TFA and $NaBH_4$[48] or TFA and Et_3SiH[49] was not successful. Styrene **55** was achieved as the byproduct. Furthermore, the hydrogenation of **55** failed with conventional heterogeneous (Pd/C 10% or Pt/C 5%, PtO_2 in EtOH, EtOAc or AcOH with H_2 (1 atm, 35psi or 50 psi) at room temperature or 70 °C) and homogeneous catalysts (Wilkinson's catalyst in THF and *t*-BuOH with 50 psi H_2 at room temperature). Fortunately,

with the addition of $BF_3 \cdot Et_2O$, TFA and Et_3SiH directly reduced **54** to **53**. Efforts were made to optimize the reaction. Without TFA, the reduction of **54** to **53** did not occur. When **55** was treated under the same reaction conditions as **54** ($BF_3 \cdot Et_2O$, TFA and Et_3SiH), **53** was also achieved (detected from the crude ^1H NMR spectrum). The treatment of **54** with $BF_3 \cdot Et_2O$ afforded **55** in 96% yield. Without $BF_3 \cdot Et_2O$, the reduction of **55** to **53** did not occur. We reasoned that BF_3 increased the acidity of TFA which could protonate the double bond, and the resulting cation was reduced by Et_3SiH and TFA. Accordingly, TfOH, a strong acid, was used to substitute BF_3, and **55** was reduced to **53** successfully. Optimum results were obtained: with a drop of TfOH, 4 equiv of TFA and 2 equiv of Et_3SiH at room temperature, **55** provided **53** in 83% yield as a mixture of **55** and **53**.

The amination of this crowded aryl iodide was also challenging. By the general procedure with BINAP/Pd as the catalyst to make the diamine, **55** did not react with (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine, and the mixture of **55** and **53** only gave monocoupled amine (with **53**) most likely because **53** is bulkier than other halobenzenes in our general syntheses. Increasing the temperature to 140 °C in toluene or 150 °C in xylene and microwave irradiation at 140 °C still afforded monocoupled amine. BINAP is thought to inhibit the formation of both catalytically inactive palladium bis(amine) aryl halide complexes and bridging amido complexes which resist reductive elimination.[50] For a bulky aryl iodide, we reasoned that a less bulky phosphine ligand might promote this amination. To test this idea, several catalysts, including $Pd(dppf)Cl_2$, 2-(2'-di-tert-butylphosphine)biphenylpalladium(II) acetate, $Pd(OAc)_2$ with 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate, $Pd(OAc)_2$ with 1,2-bis(diphenylphosphino)ethane, $Pd(OAc)_2$ with PCy_3, $Pd(PPh_3)_4$ and $Pd(P\textit{t}\text{-}Bu_3)_2$, were tried in the coupling reaction of iodobenzene **53** and monocoupled amine. The reactions were tracked and

compared by TLC, and only Pd(P*t*-Bu$_3$)$_2$ catalyzed this reaction. Moreover, Pd(P*t*-Bu$_3$)$_2$ catalyzed the reaction of **53** and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine directly, and diamine **49j** was achieved in 40% yield. General cyclization of **49j** afforded imidazolinium salt **48j** in 46% yield.

Crystal data of imidazolinium salts 48b–48d. As shown in Figure 3, the crystal structure of **48b** shows that the phenyl groups *ortho* to the nitrogen orient *anti* to the phenyl groups on the imidazole ring. However, in the crystal structure, the benzyl groups in **48c** and cyclohexyl groups in **48d** stay *cis* to the phenyl groups on the imidazole ring. However, NOE spectroscopy of **48d** and **48g** in CD_2Cl_2 at room temperature shows some interaction between the benzyl hydrogens on the *ortho*-substituents and the hydrogens on the imidazole ring. Therefore, the cyclohexyl groups in **48d** and the isopropyl groups in **48g** should somewhat orient *anti* to the phenyl groups on the imidazole ring in the solvent. This *cis* conformation may be due to packing forces within the crystal or a strong CH-π attraction between the benzyl hydrogens on the *ortho*-substituents and the phenyl groups on the imidazole ring.

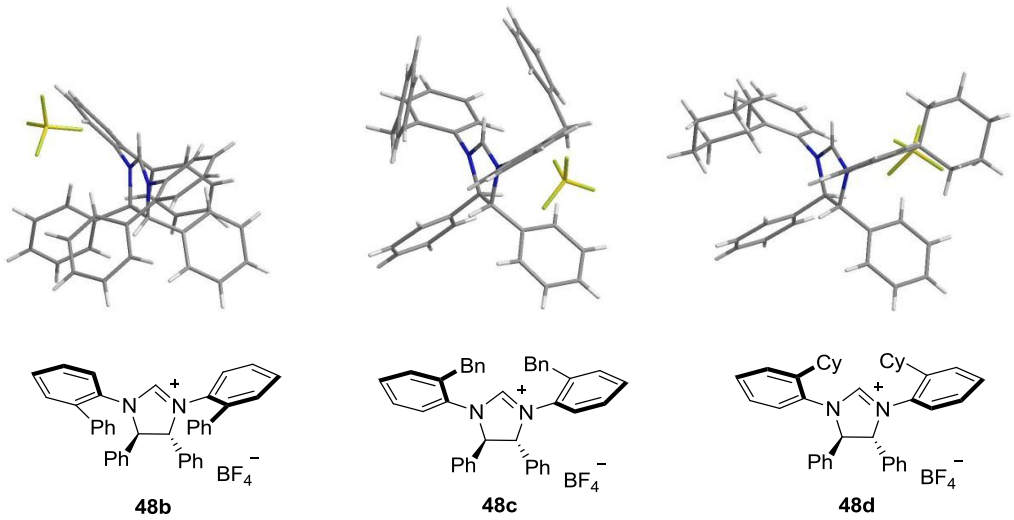


Figure 3. Crystal structures of imidazolinium salts **48b–48d**

Testing imidazolinium salt 48b in the asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl). The palladium sources were screened first (Table 2). The oxindole reaction was carried out in dioxane with 10 mol % equiv of **48b** and palladium, 1.5 equiv of NaO*t*-Bu at 60 ℃ for 17 h. $Pd(dba)_2$ was the best and provided the oxindole in 63% yield with 34% ee (entry 1).

Table 2. Asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) with **48b** and different palladium sources

Entry	Pd	Yield[a] (%)	Ee[b] (%)
1	$Pd(dba)_2$	63	34
2	$Pd(PPh_3)_4$	70	2
3	$Pd(OAc)_2$	42	22

[a]The yield of oxindole **A** was calculated from isolated product after chromatography. [b]The ee was determined by chiral OD-H HPLC.

Different solvents at different temperatures were also screened for the asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) with 10 mol % of **48b** and $Pd(dba)_2$ for around 14 h (Table 3). THF was the most suitable solvent in this reaction (entry 2, 38% yield and 63% ee at room temperature). The reaction could not take place in DME at room temperature (entry 9), although it was effective in Hartwig's report.[13]

Different bases (2 equiv) such as KO*t*-Bu, LiO*t*-Bu, NaH, NaOMe were also tested in the asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) with 10 mol % of **48b** and $Pd(dba)_2$ in THF at room temperature. Unfortunately, no reaction occurred with these bases. Therefore NaO*t*-Bu was the best base for this reaction.

The need for NaO*t*-Bu was also screened in the asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) with 10 mol % of **48b** and $Pd(dba)_2$ in THF at room temperature for approximately 22 h (Table 4). The ee increased when more NaO*t*-Bu was used. An enolate intermediate was

expected to form and directly be involved in the enantiomer selectivity. We supposed that NaO*t*-Bu created more enolate intermediate. To test this hypothesis, $ZnCl_2$ was added to the oxindole reaction, which could coordinate with the oxygen of the carbonyl and increase formation of the enolate intermediate (entry 5). The ee increased slightly, but the yield did not improve (69% ee with 33% yield compared with 63% ee with 38% yield without the addition of $ZnCl_2$).

Table 3. Asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) with **48b** in different solvents

Entry	Solvent	NaO*t*-Bu (equiv)	T (℃)	Yield[a] (%)	Ee[b] (%)
1	THF	2	5	0	-
2	THF	3	23	38	63
3	toluene	3	23	23	60
4	CH_2Cl_2	3	23	13	59
5	Et_2O	3	23	19	2
6	EtOH	3	23	0	-
7	$CHCl_3$	3	23	0	-
8	CH_3CN	3	23	0	-
9[c]	DME	1.5	23	0	-
10	dioxane	1.5	40	32	26
11	THF	1.5	40	45	58
12	toluene	1.5	40	42	57

[a]The yield of oxindole **A** was calculated from isolated product after chromatography. [b]The ee was determined by chiral OD-H HPLC. [c]Reaction run with 5% equiv of **48b** and $Pd(dba)_2$.

Finally, the asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) was carried out with 10 mol% **48b** and $Pd(dba)_2$ in the presence of 3 equiv of NaO*t*-Bu in THF at different temperatures (Table 5). When the temperature increased, the yield increased, and the ee reached the highest level (68%) at 40 ℃, but not at 23 ℃ (lower temperature).

Table 4. Asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) with **48b** and different equivalents of NaO*t*-Bu

Entry	NaO*t*-Bu (equiv)	Yield[a] (%)	Ee[b] (%)
1	1.5	26	48
2	3	38	63
3	4.5	29	72
4	10.5	35	77
5[c]	3	33	69
6[d]	3	27	65

[a]The yield of oxindole **A** was calculated from isolated product after chromatography. [b]The ee was determined by chiral OD-H HPLC. [c]Reaction run with $ZnCl_2$ (0.17 equiv). [d]Reaction run with 20 mol % of **48b** and 10 mol % of $Pd(dba)_2$.

Table 5. Asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) with **48b** at different temperatures

Entry	Solvent	T (°C)	Time[c] (h)	Yield[a] (%)	Ee[b] (%)
1	THF	23	23	38	63
2	THF	40	20	35	68
3	THF	60	2	50	63
4	THF	80	6	74	53
5[d]	THF	40	20	25	49
6	toluene	80	6	64	46

[a]The yield of oxindole **A** was calculated from isolated product after chromatography. [b]The ee was determined by chiral OD-H HPLC. [c]Reaction time was not optimized. [d]Reaction run with 0.2 equiv of NaI.

With **48b**, the optimized results of the asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) were 68% ee and 35% yield at 40 °C (Table 5, entry 2). There were still problems with this catalyst – low yields and high catalyst loading. Several efforts were tried to improve this catalyst system.

1. The ratio of **48b** and $Pd(dba)_2$ was increased to 2 (Table 4, entry 6); the ee did not change but the yield decreased to 27%. This may be due to the formation of dicarbene palladium complex which is difficult to dissociate to form the effective catalyst.

2. To the reaction was added 0.2 equiv of NaI (Table 5, entry 5), but the yield (25%) and ee (49%) decreased.

3. Toluene was tried as the solvent, but the reaction was less effective (64% yield, 46% ee) than when THF was used (74% yield, 53% ee) at 80 ℃ (Table 5, entry 6).

4. To the reaction was added 10 mol % of **48b** and $Pd(dba)_2$ in two identical portions; the second portion did not improve the yield or show any additional effect on the reaction.

In conclusion, imidazolinium salt **48b** with $Pd(dba)_2$ in THF is a moderately effective catalyst system for the asymmetric oxindole reaction. It is most likely that the *ortho* phenyl group is too close to the reaction center. Thus the reaction center is too crowded to facilitate oxidative addition. This may also have contributed to a rather low yield in the synthesis of imidazolinium salt **48b**. Therefore we sought a new NHC ligand. For the new design, we chose to replace the phenyl group with a group that could move away from the metal coordination site. 2-Benzyl-bromobenzene and 2-cyclohexyl-bromobenzene are commercially available, and the flexibility of the benzyl (imidazolinium salt **48c**, Scheme 10) and cyclohexyl (imidazolinium salt **48d**,[27d] Scheme 10) groups will make the palladium center less crowded.

Testing imidazolinium salts 48c and 48d in the asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl). Salt **48c** was used under the same conditions as **48b** (Table 4, entry 3), but the ee of the product dropped to 39%, almost half of that observed with **48b** (72% ee). The benzyl group, the selectivity controlling group, is too flexible and the bulky phenyl part of the benzyl group is not close enough to the reaction center. Accordingly, it is not surprising that the NHC ligand from **48d** (with a cyclohexyl group) is an excellent ligand.

As shown in Table 6, the asymmetric oxindole reaction (eq 1, Ar = 1-naphthyl) was carried out with 10 mol % of **48d** and $Pd(dba)_2$ and 3 equiv of NaO*t*-Bu in THF at different temperatures. The yields remained in the range of 80% to 90% at all temperatures. However, the best ee was 78% at 60 ℃ (entry 4) which was close to that at 80 ℃ (ee 77%, entry 6) but superior than those at low temperatures (entries 1-3). This phenomenon is very similar to that of **48b** which achieved the highest ee at 40 ℃ but not at room temperature.

Table 6. Asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) with **48d** at different temperatures

Entry	T(°C)	Time[c] (h)	Yield[a] (%)	Ee[b] (%)
1	23	40	80	65
2	40	18	88	64
3	50	16	80	74
4	60	2	89	78
5	70	2	87	75
6	80	2	90	77

[a]The yield of oxindole **A** was calculated from isolated product after chromatography. [b]The ee was determined by chiral OD-H HPLC. [c]The reaction time was not optimized.

We had shown that the amount of NaO*t*-Bu was important for the enantioselectivity in the asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) with **48b**, therefore we also tested the effect of NaO*t*-Bu in the same reaction with 10 mol % of **48d** and $Pd(dba)_2$ (Table 7). As expected, the yields were almost the same for different amounts of NaO*t*-Bu, but the ee became better when more NaO*t*-Bu was used. There was not much difference between the ee achieved with 3 and 4.5 equiv of NaO*t*-Bu (entries 2 and 5), therefore, 3 equiv of NaO*t*-Bu was chosen as the best for this asymmetric oxindole reaction.

Table 7. Asymmetric oxindole synthesis (eq 1, Ar = 1-naphthyl) with **48d** and different equivalents of NaO*t*-Bu

Entry	NaO*t*-Bu (equiv)	Time (h)	Yield[a] (%)	Ee[b] (%)
1	1.5	2	88	72
2	3	2	89	78
3[c]	3	3	84	80
4[d]	3	14	82	77
5	4.5	2	91	79

[a]The yield of oxindole **A** was calculated from isolated product after chromatography. [b]The ee was determined by chiral OD-H HPLC. [c]Reaction run with 5 mol % of **48d** and $Pd(dba)_2$. [d]Reaction run with 1 mol % of **48d** and $Pd(dba)_2$.

In conclusion, the best catalysis process we found for the asymmetric oxindole reaction (eq 1, Ar = 1-naphthyl) would utilize **48d** and $Pd(dba)_2$ in a ratio of 1:1, with 3 equiv of NaO*t*-Bu in THF at 60 °C. To probe the reactivity of **48d**, the catalyst loading was decreased to 5 mol % and 1 mol % (Table 7, entries 3 and 4), and the yield and ee were almost unchanged. Different substrates were tested with 1 mol % of **48d**, $Pd(dba)_2$ and 3 equiv of NaO*t*-Bu in THF at 60 °C

for 14 h (oxindole **B**, Ar = phenyl, ee 51%, yield 99%; oxindole **C**, Ar = 4-isobutyl phenyl, ee 58%, yield 97%). However, we were not satisfied with the results of the substrates with phenyl group, and expected more room to optimize them.

Optimization of the asymmetric oxindole synthesis (eq 1, Ar = phenyl) with 48d. As shown in Table 8, the solvents, the palladium sources, the bases and the temperatures were screened. Toluene, a less polar solvent, was superior to THF in this reaction (entries 4 and 8). The equivalent of NaO*t*-Bu had no effect on the enantioselectivity in toluene because of the low solubility of NaO*t*-Bu in toluene (entries 8 and 12). Decreasing the temperature slightly optimized the ee but prolonged the reaction time from 2 h at 60 °C (ee 67%, yield 98%, entry 12) to 12 h at room temperature (ee 70%, yield 94%, entry 13) when 5 mol% of **48d** and $Pd(dba)_2$ with 1.5 equiv of NaO*t*-Bu were used in toluene. These optimized conditions at room temperature also improved the ee of the substrate (oxindole **C**, Ar = 4-isobutylphenyl) to 66% in 94% yield in 12 h.

Exploration of the steric and electronic effects of the ligand toward the asymmetric oxindole synthesis (eq 1, Ar = phenyl). To investigate the steric effect of the NHC ligand on the asymmetric oxindole reaction, a series of (4*R*,5*R*)-1,3-bis(*ortho*-substitutedphenyl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborates with different *ortho*-substituents **48b**–**48d**, **48e** (no substituent)[27g], **48f** (*ortho*-methyl),[25] **48g** (*ortho*-isopropyl)[25] and **48h** (*ortho*-methyl-*meta*-phenyl) were tested in the oxindole reaction (eq 1, Ar = phenyl, Table 9, entries 1-7), and their enantioselectivities were compared. The enantioselectivity and reactivity of the NHC ligand increased as the steric bulk of the *ortho*-substituent increased. Imidazolinium salt **48h** with the additional *meta*-phenyl group showed better enantioselectivity and reactivity than

48f with the *ortho*-methyl group. The enantioselectivity and reactivity of **48g** with the *ortho*-isopropyl group were similar to those of **48d** with *ortho*-cyclohexyl group.

Table 8. Optimization of the asymmetric oxindole synthesis (eq 1, Ar = phenyl) with **48d**[a]

Entry	Solvent	Pd	Base	T (℃)	Time (h)	Yield[b] (%)	Ee[c] (%)
1	THF	$Pd(PPh_3)_4$	NaO*t*-Bu	23	-	-	-
2	THF	$Pd(OAc)_2$	NaO*t*-Bu	23	17	44	57
3	THF	$Pd(dba)_2$	NaO*t*-Bu	23	17	79	59
4	THF	$Pd(dba)_2$	NaO*t*-Bu	60	3	97	54
5	DME	$Pd(dba)_2$	NaO*t*-Bu	60	3	-	-
6	dioxane	$Pd(dba)_2$	NaO*t*-Bu	60	3	97	49
7	heptane	$Pd(dba)_2$	NaO*t*-Bu	60	2	97	60
8	toluene	$Pd(dba)_2$	NaO*t*-Bu	60	2	98	67
9	toluene	$Pd(dba)_2$	KO*t*-Bu	60	3	96	48
10	toluene	$Pd(dba)_2$	LiO*t*-Bu	60	3	trace	-
11	toluene	$Pd(dba)_2$	NaOMe	60	3	-	-
12[d]	toluene	$Pd(dba)_2$	NaO*t*-Bu	60	2	97	67
13[d]	toluene	$Pd(dba)_2$	NaO*t*-Bu	23	12	94	70

[a]Reaction run with 5 mol % of **48d**, the palladium source and 3 equiv of the base. [b]The yield of oxindole **B** was calculated from isolated product after chromatography. [c]The ee was determined by chiral OD-H HPLC. [d]Reaction run with 1.5 equiv of NaO*t*-Bu.

To examine the electronic effect of the NHC ligand on this asymmetric oxindole reaction (eq 1, Ar = phenyl), imidazolinium salt **48i** (*o*,*m*,*p*-trimethoxy) was tested and found to catalyze the reaction at 80 °C only in 6% yield and 3% ee. Therefore the steric bulk of the *ortho*-substituent has a large effect on the enantioselectivity and reactivity of the NHC ligand. We decided to make imidazolinium salt **48j** with larger *o*-2,4-dimethylpentan-3-yl group (Scheme 10). Unfortunately, the enantioselectivity of **48j** in the oxindole reaction (eq 1, Ar = phenyl) was only 50% with 94% yield (Table 9, entry 9).

Table 9. Asymmetric oxindole synthesis (eq 1, Ar = phenyl) with different NHC precursors[a]

Entry	NHC precursor	Yield[b] (%)	Ee[c] (%)
1	**48b** (*o*-phenyl)	29	48
2	**48c** (*o*-benzyl)	38	54
3	**48d** (*o*-cyclohexyl)	94	70
4	**48e** (no substituent)	38	11
5	**48f** (*o*-methyl)	63	39
6	**48g** (*o*-isopropyl)	92	68
7	**48h** (*o*-methyl-*m*-phenyl)	79	48
8[d]	**48i** (*o*,*m*,*p*-trimethoxy)	6	3
9	**48j** (*o*-2,4-dimethylpentan-3-yl)	94	50
10[e]	**56**	97	18
11[f]	**57**	14	5

[a]Reaction run with 5 mol % of the imidazolinium salt, $Pd(dba)_2$ and 1.5 equiv of NaO*t*-Bu in toluene at room temperature for 12 h. [b]The yield of oxindole **B** was calculated from isolated product after chromatography. [c]The ee was determined by chiral OD-H HPLC. [d]Reaction run at 80 °C for 3 h. [e]Reaction run at 60 °C for 1 h. [f]Reaction run for 6.5 h.

1.3 EXPLORATION OF IMIDAZOLINIUM SALTS WITH THE CHIRAL CONTROLLING GROUP (3-METHYLBUTAN-2-YL) LOCATED ON THE *ORTHO* POSITION OF THE *N*-ARYL RING

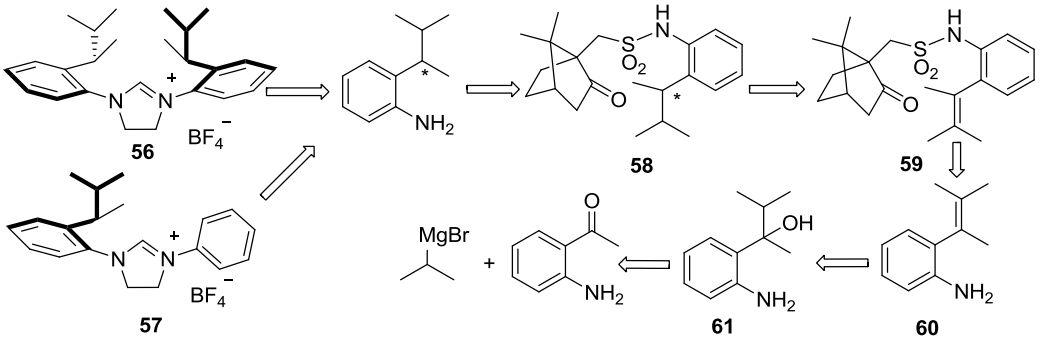
Such chiral *ortho* substituents have not been examined for control in NHC ligands (Scheme 11, salts **56** and **57**).

Attempted synthesis of chiral 2-(3-methylbutan-2-yl)aniline (a required reactant for the synthesis of 56 and 57). Although 2-(3-methylbutan-2-yl)aniline has been made by Harmata,[51] we envisioned applying our procedure (hydrogenation of styrenes) toward its synthesis. As shown in Scheme 11, the chiral 2-(3-methylbutan-2-yl)aniline would be achieved from (*R*)-camphorsulfonylamide **58** by crystallization of the diastereomeric sulfonylamide and cleavage of the amide bond. The asymmetric hydrogenation of (*R*)-camphorsulfonylamide **59** to give **58** would call for the tactic we used to construct **53** from **55**. Amide **59** would be formed by regular amidation of (*R*)-camphorsulfonyl chloride and aniline **60**. Aniline **60** would undoubtedly call on the general procedure we used to make styrene **55** (from benzyl alcohol **61** which could be achieved from 1-(2-aminophenyl)ethanone). Here, (*R*)-camphorsulfonyl group would work as an auxiliary which would not only help separate the diastereomeric sulfonylamide, but also enantioselectively hydrogenate the styrene moiety.

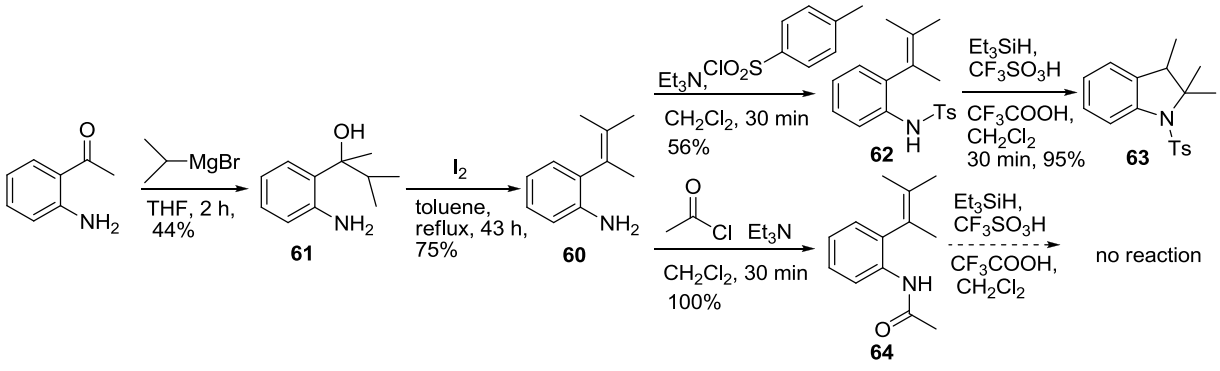
As shown in Scheme 12, the treatment of 1-(2-aminophenyl)ethanone with isopropylmagnesium bromide furnished benzyl alcohol **61** in 44% yield.[52] The dehydration of **61** with iodine gave styrene **60** in 75% yield.[53] As expected, the hydrogenation of this bulky styrene derivative **60** with conventional heterogeneous (Pd/C 10% in EtOH with 50 psi H_2) or homogeneous catalysts (Wilkinson's catalyst in THF and *t*-BuOH with 50 psi H_2) was not successful. Direct hydrogenation of styrene with Et_3SiH, TFA and one drop of TfOH also failed

- most likely because of the basic amino group. As planned in the retrosynthesis, the amino group would be protected by a (*R*)-camphorsulfonyl group. But before using this complex protecting group, *p*-toluenesulfonyl group was tried for easy structural analysis of the product by ^{1}H NMR spectroscopy. The treatment of styrene **60** with *p*-toluenesulfonyl chloride afforded sulfonylamide **62** in 56% yield.[52] Interestingly, when sulfonylamide **62** was treated with Et_3SiH, TFA and one drop of TfOH, indoline derivative **63** was achieved in 95% yield. This product is most likely derived from the protonation of the double bond followed by the intramolecular attack of the amino group. Then we chose to protect the amino group with acetyl group. Aniline **60** was treated with acetyl chloride to give acetamide **64** quantitatively. Unfortunately, under the general hydrogenation conditions we had developed, no reaction occurred with **64**. Finally, we turned back and made 2-(3-methylbutan-2-yl)aniline with Harmata's procedure.

Scheme 11. Retrosynthesis of chiral 2-(3-methylbutan-2-yl)aniline

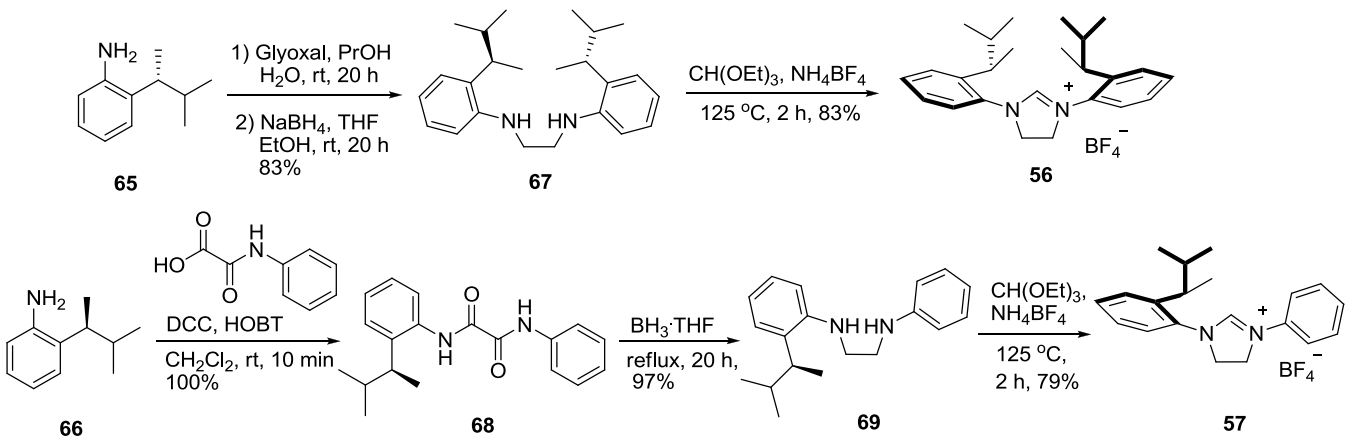


Scheme 12. Attempted synthesis of chiral 2-(3-methylbutan-2-yl)aniline



Synthesis of imidazolinium salts 56 and 57. As shown in Scheme 13, anilines **65** and **66** were resolved by separation (via crystallization) of the amide diastereomers prepared from (*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid and 2-(3-methylbutan-2-yl)aniline. The treatment of **65** with glyoxal provided the diimine which was reduced with $NaBH_4$ to give diamine **67** in 83% overall yield. General cyclization of **67** afforded imidazolinium salt **56** in 83% yield. The amidation of **66** with 2-oxo-2-(phenylamino)acetic acid gave diamide **68** quantitatively. Following reduction of **68** with BH_3 provided diamine **69** in 97% yield.[54] General cyclization of **69** afforded imidazolinium salt **57** in 79% yield.

Scheme 13. Synthesis of imidazolinium salts **56** and **57**



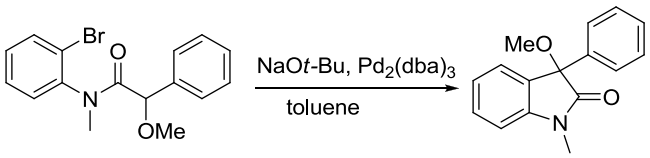
Testing 56 and 57 in the asymmetric oxindole synthesis (eq 1, Ar = phenyl). The catalyst provided by **56** could not catalyze the oxindole reaction at room temperature and afforded only 18% ee with 97% yield at 60 °C (Table 9, entry 10). The low reactivity of **56** at room temperature is most likely due to the overcrowding of the ligand. The less hindered NHC precursor **57** with only one *ortho* substituent did catalyze the oxindole reaction at room temperature, but gave disappointing results (14% yield, 5% ee, Table 9, entry 11).

1.4 EXPLORATION OF NHC LIGANDS IN THE ASYMMETRIC SYNTHESIS OF 3-ALKOXY-3-ARYLOXINDOLES

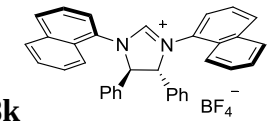
Optimization of the asymmetric synthesis of α-methoxy-α-phenyloxindoles (eq 2). Different solvents were first screened (Table 10). With 5 mol % of **48d** and $Pd(dba)_2$, 3 equiv of NaO*t*-Bu at room temperature for 26 h, the oxindole reaction did not occur in MeCN, DME, Et_2O and 1,2-dichloroethane, but gave the product in toluene (23% ee, 16% yield) and CH_2Cl_2 (racemic, 14% yield). Different NHC precursors (10 mol %) were then tested in this oxindole reaction with 5 mol % of $Pd_2(dba)_3$ and 3 equiv of NaO*t*-Bu in toluene at 60 ℃, and the results are summarized in Table 10. NHC precursors **48d** and **48g** were less effective in this reaction (7% and 2% ee, respectively, entries 1 and 2) than in the α-methyl-α-aryl oxindoles reaction. Imidazolinium salt **48k** with a 1-naphthyl group as the N-substituent provided the product in 49% yield with 34% ee (entry 9). Although **48j** was not as good as **48d** in the α-methyl-α-aryl oxindole reaction, it outperformed **48d** dramatically in this reaction and provided the product in 99% yield with 54% ee (entry 5). With **48j**, the ee increased slightly (61% at 40 ℃) at lower temperatures (entries 5–7), but the yield decreased dramatically (18% at 40 ℃). The ee and yield decreased obviously when the equivalent of NaO*t*-Bu decreased to 1.5 at 60 ℃ (entry 8).

Expansion of the substrate scope (3-alkoxy-3-aryloxindoles). The optimized cyclization conditions (5 mol % of $Pd_2(dba)_3$, 10 mol % of **48j** and 3 equiv of NaO*t*-Bu in toluene at 60 ℃) were applied to three more substrates (Table 11). The ee and yield of the product provided by the chloroaryl substrate (20% ee, 29% yield, entry 2) decreased dramatically in comparison with those of the bromoaryl substrate (54% ee, 99% yield, entry 1). The benzyl protecting group on the substrates also decreased the ee of the products (entries 3 and 4).

Table 10. Asymmetric synthesis of 3-methoxy-3-phenyloxindole with different NHC precursors

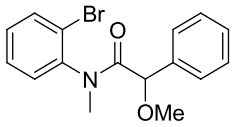
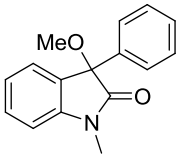
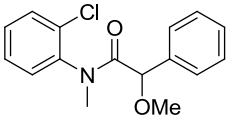
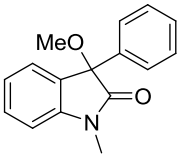
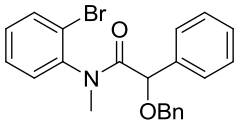
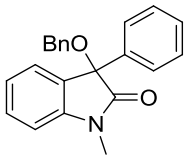
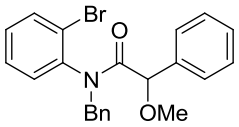
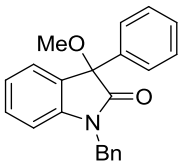


(**2**)

Entry	NHC precursor	T (℃)	Time (h)	Yield[a] (%)	Ee[b] (%)
1	**48d** (*o*-cyclohexylphenyl)	60	2.5	79	7
2	**48g** (*o*-isopropylphenyl)	60	1.5	100	2
3	**48h** (*o*-methyl-*m*-phenylphenyl)	60	3	51	19
4	**48i** (*o*,*m*,*p*-trimethoxyphenyl)	60	4	26	10
5	**48j** (*o*-2,4-dimethylpentan-3-yl-phenyl)	60	2.5	99	54
6	**48j**	50	3	65	53
7	**48j**	40	4	18	61
8[c]	**48j**	60	2.5	10	40
9	**48k** 	60	3.5	49	34

[a]The yields were based on the crude ^{1}H NMR spectra of the reaction mixtures. [b]The ee was determined by chiral OD-H HPLC. [c]Reaction run with 1.5 equiv of NaO*t*-Bu.

Table 11. Asymmetric synthesis of 3-alkoxy-3-phenyloxindoles with **48j**

Entry	Reactant	Product	Time (h)	Yield[a] (%)	Ee[b] (%)
1			2.5	99	54
2			1.5	29	20
3			1	94	20
4			0.5	94	12

[a]The yield was calculated from isolated product after chromatography except entry 1 which was based on the crude ^{1}H NMR spectra of the reaction mixture. [b] The ee was determined by chiral OD-H HPLC.

1.5 MECHANISM OF ASYMMETRIC OXINDOLE SYNTHESIS

Imidazolinium salt **48d** (*o*-cyclohexyl group) provided the most efficient catalyst for the asymmetric α-methyl-α-aryl oxindole synthesis until 2007, when Kündig's ligands increased the ee (79–95%) though also increased the reaction time (24–36 h).[55] For α-methyl-α-1-naphthyl oxindole (more hindered substrate), **48d** compared with Kündig's ligands. In 2008, (4*S*,5*S*)-1,3-

bis(substituted-1-naphthyl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborates (similar to our NHC salts, N-naphthyl vs N-phenyl) were reported by Dorta's group and gave similar reactivity and enantioselectivity to **48d**.[56] The diastereomers of palladium complexes (NHC)Pd(cin)Cl from Dorta's NHC salts (caused by the rotation of the N-naphthyl bond) were separated and increased the ee up to 89%. Therefore, the relatively moderate ee provided by our NHC ligands may also be due to the rotation of the N-aryl bond. In 2009, the NHC ligand with IBIOX[(-)-menthyl] group from Glorius's group was found complementary to the ones obtained by Kündig, and it provided higher ee (>92%) for more hindered substrates.[57]

Regardless of this progress in improving the enantioselectivity of the oxindole reaction, there are still some data that cannot be explained. A detailed mechanism of the asymmetric oxindole synthesis is much needed.

Some of the facts in hands will now be enumerated:

(1) The enantioselectivity and reactivity of our NHC ligands increased as the steric bulk of the *ortho*-substituent increased (Table 9). However, imidazolinium salt **48j** (ortho-2,4-dimethylpentan-3-yl, bulkier) provided lower ee (50%) than **48d** (ortho-cyclohexyl, 70% ee).

(2) With our ligands in THF, the ee reached highest at a certain temperature, but not at a lower temperature (Tables 5 and 6).

(3) With our ligands in THF, the ee increased as the equivalent of NaO*t*-Bu increased (Tables 4 and 7).

(4) An iodoaryl substrate was reported by the Hartwig group to provide the product with lower ee (40%), in comparison with bromoaryl (70%) and chloroaryl (58%) substrates.[13] We also found that NaI, an additive to the oxindole reaction, also decreased the ee from 68 % to 49% (Table 5, entries 2 and 5).

(5) C(1)-Fluoro and C(1)-methyl substrates were found by the Kündig group to give significantly lower ee with their ligand, in comparison with nonsubstituted substrates (Figure 4).[55b]

(6) A C(4)-methyl substrate was reported by the Dorta group to provide dramatically lower ee (8%) with their ligand, in comparison with nonsubstituted substrates (91%) (Figure 4).[56]

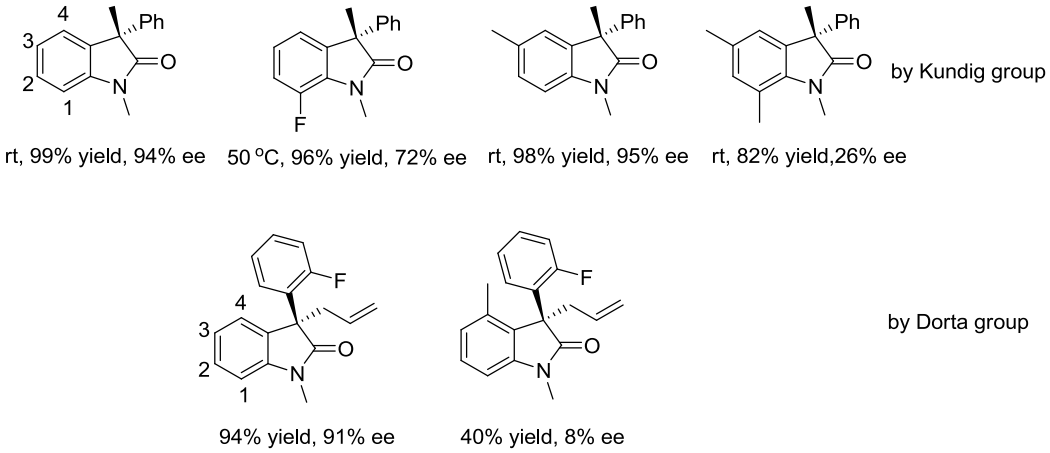


Figure 4. Palladium-catalyzed α-arylation of substrates with substituents at the N-aryl ring

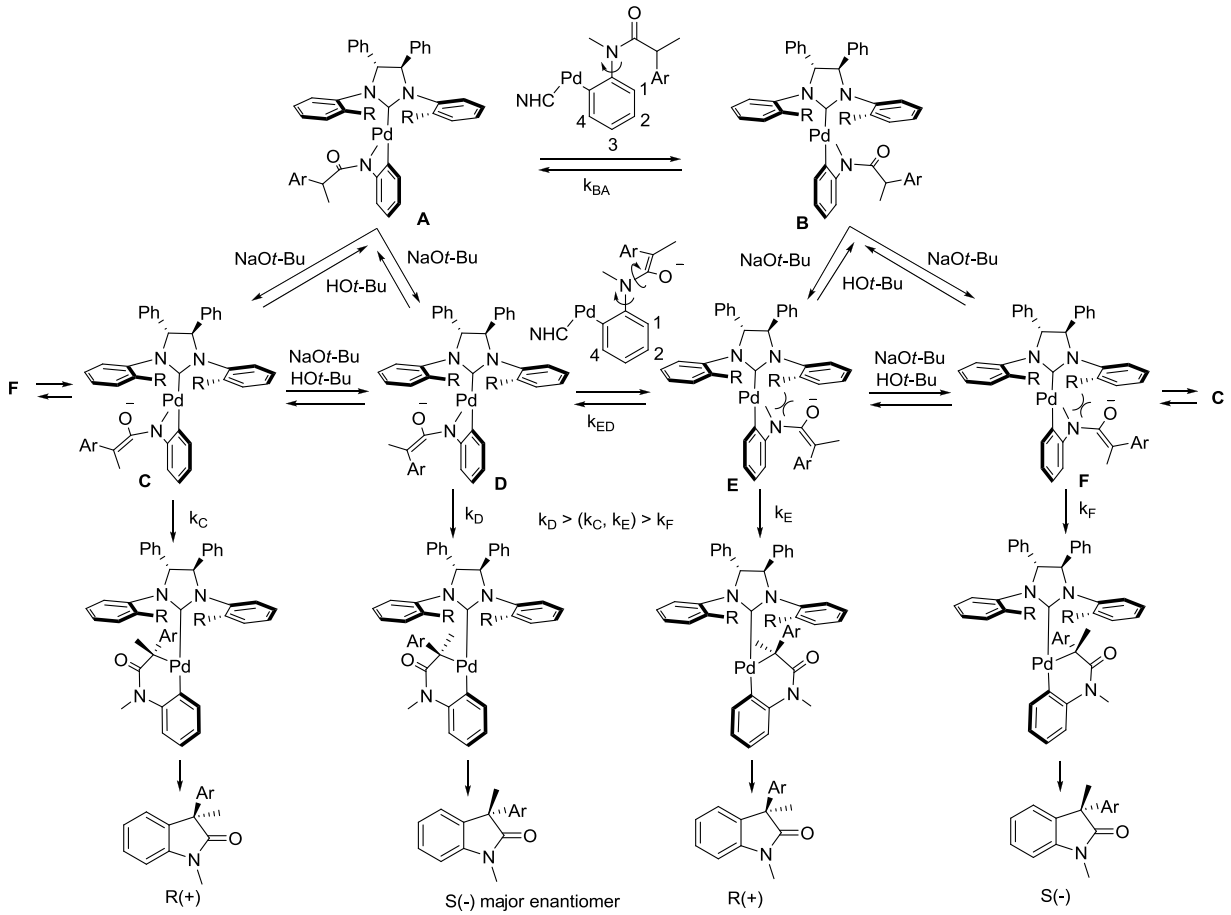
A mechanism for the oxindole reaction was proposed by Hartwig in 2001,[13] and the oxidative addition was proven to be the rate-determining step. However, the key step to control the asymmetric outcome of the synthesis is still unclear, and determining this is important for future ligand design and optimization of the reaction conditions. Here, we propose that the rotation barrier of the N-aryl bond in the oxidative addition products is crucial for the enantioselectivity of the oxidole synthesis, and this rotation of the N-aryl bond has been discussed by Curran in the asymmetric oxindole synthesis from *o*-iodoacrylanilides by Heck and radical cyclizations.[58]

As shown in Scheme 14, the oxidative addition provides palladium complexes **A** and **B**. The NHC ligand orients opposite to the anilide with the NHC-ring vertical to the Pd-phenyl ring. By deprotonation of the anilide with NaO*t*-Bu, **A** affords Z-enolate **C** and E-enolate **D**, and **B**

affords Z-enolate **F** and E-enolate **E**. Z,E-Enolates(**C** and **D**, **E** and **F**) can be interconverted by a protonation–rotation of the C-carbonyl bond–deprotonation cycle. We propose that the reductive elimination step may be faster than the palladacycle formation, and the rates for the formation of the *S*(-) and *R*(+) oxindoles are

$$d[S]/dt = k_D[\mathbf{D}] + k_F[\mathbf{F}] \qquad d[R]/dt = k_C[\mathbf{C}] + k_E[\mathbf{E}]$$

Scheme 14. Proposed mechanism for asymmetric oxindole synthesis



The trajectory for the coordination of the enolate to the palladium is blocked by the R group in **E** and **F**, which results in higher activation energy for the palladacycle formation from **E** and **F** than it from **C** and **D**; and the coordination of E-enolate to the palladium is prefered over Z-enolate because of the steric hinderance from the NHC group. Thus, the order of the rate constants for complexes **C**, **D**, **E** and **F** to give oxindoles would be $k_D > (k_C, k_E) > k_F$. This is also

supported by the result that *S*(-) oxindole is the major enantiomer produced. To increase the enantioselectivity of the reaction, the concentration of **D** should be increased while the concentration of **E** should be decreased. The direct way to achieve this is the enantioselective formation of **A** in the oxidative addition step, a possibility that was proposed by Curran to be the stereocontrolling step in the asymmetric oxindole synthesis from *o*-iodoacrylanilides by Heck cyclization.[58a] If the oxidative addition is not so enantioselective, the conversion of **E** to **D** is then crucial for the enantioselectivity of the oxindole reaction. Complex **E** will cyclize to give *R*(-) oxindole or convert to **D**. To increase the enantioselectivety, the rate of the conversion from **E** to **D** should be increased (lowering the activation energy) to the point that it is faster than the cyclization rate of **E**.

Complexes **D** and **E**, **C** and **F** can be interconverted by more than one pathway. Complexes **D** and **E** interconvert directly by the rotation of the N-aryl bond, as do complexes **C** and **F**. Intermediate pairs **C/D** and **E/F** may also interconvert through a protonation–deprotonation process involving the oxidative addition products **A** and **B**, respectively. Thus there are two paths from **D** to **E** and from **C** to **F**. For example, intermediates **D** and **E** may interconvert directly by rotation of the enolate N-aryl bond, or may interconvert through the pathway **D** to **A** to **B** to **E**. During any required rotation, the NHC ligand may bend to reduce steric hindrance. Because rates of deprotonation and protonation are fast, the rate of the formation of **D** from **E** (or **A** from **B**) is

$$d[\mathbf{D}]/dt = d[\mathbf{A}]/dt = k_{ED}[\mathbf{E}] + k_{BA}[\mathbf{B}]$$

The rotation barrier of the N-aryl bond was proposed by Simpkins to be smaller in the enolate state than it in the amide state ($k_{ED} > k_{BA}$), due to the easy rotation of the amide C-N bond in the enolate state.[59] Enolate **E** and amide **B** can be interconverted by a deprotonation–

protonation cycle. Increasing the amount of NaO*t*-Bu will increase the concentration of **E** at the expense of **B**, which will result in increasing the rate of the formation of **D** from **E** and increase the enantioselectivity of the reaction. This mechanism is appealing because it does explain the experimental facts described in Tables 4 and 7: increasing the equivalent of NaO*t*-Bu increased the ee of the oxindole.

To test the base effect on the rotation barriers of the N-aryl bond in **D/E** and **A/B**, we prepared bromoacetylanilide **70** and bromophenylacetylanilide **71** from ((1*S*)-1-phenylethyl)(2-bromophenyl)amine (Scheme 15). The rotation barrier of the N-aryl bond in the presence of NaO*t*-Bu in THF was studied with Exchange Spectroscopy (EXSY) using a NOESY sequence with the Aguirre *et al.* phase-cycling method (Table 12).[60] The 2D EXSY spectroscopy of benzyl hydrogen germinal to nitrogen was used to calculate the rotation barrier with Abel's method.[61] For anilide **70**, the rotation barrier at 323 K dropped significantly from 92.7 and 91.4 kJ/mol to 86.3 and 83.8 kJ/mol when one equivalent of NaO*t*-Bu was added. Ten equivalents of NaO*t*-Bu further decreased the rotation barrier to 84.9 and 82.8 kJ/mol. For anilide **71** with an additional phenyl substituent, the rotation barrier can only be measured precisely at higher temperature with EXSY (330 K, 95.5 and 93.5 kJ/mol). At this temperature, the addition of one equivalent of NaO*t*-Bu made a cloudy precipitate with broad ^{1}H NMR peaks, most likely due to the formation of sodium enolate (several small peaks were around δ5 ppm in ^{1}H NMR spectroscopy which may belong to the benzylidene hydrogen) and quick rotation of the N-aryl bond (rotation barrier 76.4 and 74.2 kJ/mol). Compared with anilide **70**, the α-hydrogen of anilide **71** with an additional phenyl group is more acidic[62] which results in more enolate formation and a lower rotation barrier.

Scheme 15. Synthesis of anilides **70** and **71**

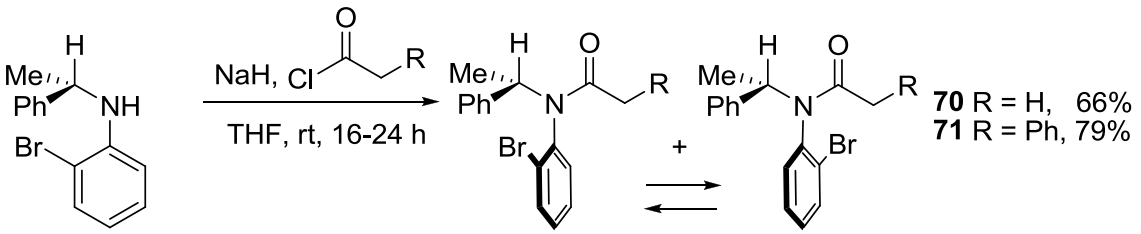


Table 12. Rotation barrier in anilides **70** and **71** measured by 2D EXSY[a] in THF-d[8]

Entry	Anilide	T (K)	NaO*t*-Bu (equiv)	ΔEa(major–minor) (kJ/mol)	ΔEa(minor–major) (kJ/mol)
1[b]	**70**	323	0	92.7	91.4
2	**70**	323	1	86.3	83.8
3[c]	**70**	323	10	84.9	82.8
4	**70**	313	1	86.0	84.3
5[b]	**71**	330	0	95.5	93.5
6[d]	**71**	330	1	76.4	74.2

[a]Measured with 0.5 mol/L anilides, 600 ms mixing time and 8 scans. [b]32 scans. [c]0.08 mol/L anilides. [d]50 ms mixing time.

Higher temperatures may also increase the formation of **E** from **B** due to the endothermic deprotonation, decrease the rotation barrier and increase the enantioselectivity of the oxindole reaction. However, the rotation barrier of anilide **70** in the presence of one equivalent of NaO*t*-Bu does not change so obviously at 313 K and 323K (Table 12, entries 2 and 4). The decreasement of the rotation barrier caused by the enolate formation at higher temperature may be offset by the entropy effect, which may increase the rotation barrier at higher temperature.

Increasing the rotation barrier from **E** to **D** decreases the enantioselectivity of the oxindole reaction. The bulkier ligand from **48j** (ortho-2,4-dimethylpentan-3-yl), in comparison with the ligand from **48d** (ortho-cyclohexyl)); the incorporation of bulky iodide ligand in

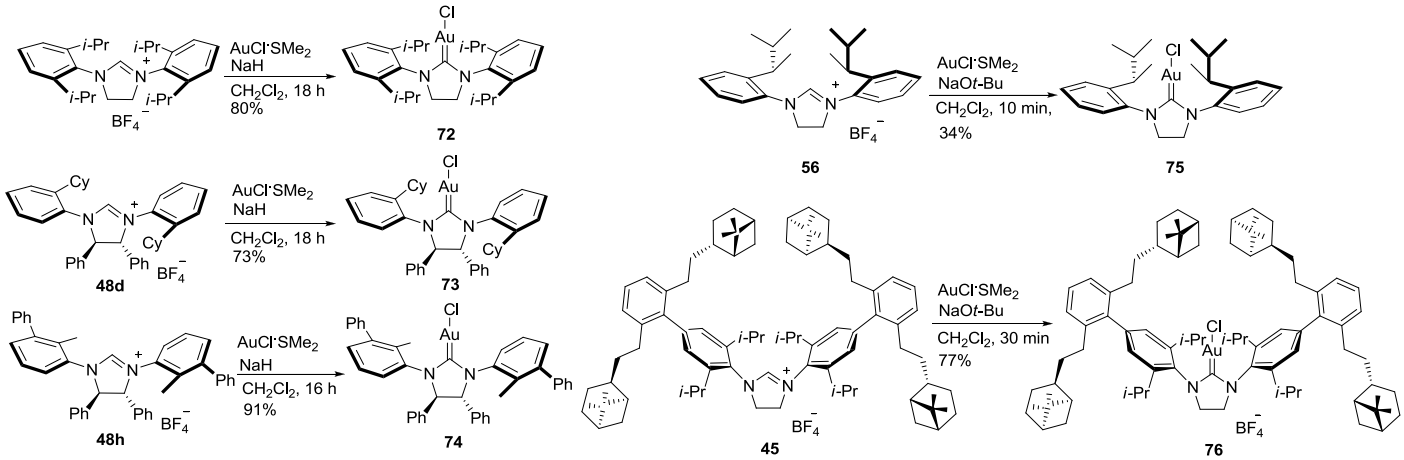
palladium complex **B**; the C(1) substituent[58] and C(4) substituent (prevents the bending of the NHC ligand) on the N-aryl ring, all may increase the rotation barrier and result in the low ee of the products.

In conclusion, the rotation barrier of the N-aryl bond in the oxidative addition products could be important for the enantioselectivity of the oxindole reaction, which supports our hypothesis that the reductive elimination may be faster than the palladacycle formation and not the stereocontrolling step. If the ligand cannot provide a good enantioselectivity in the oxidative addition step, lowering the rotation barrier of the N-aryl bond in the oxidative addition products could also increase the enantioselectivity of the oxindole synthesis.

1.6 ASYMMETRIC PYRROLIDINE SYNTHESIS WITH NHC-GOLD CATALYSTS

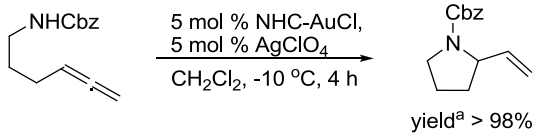
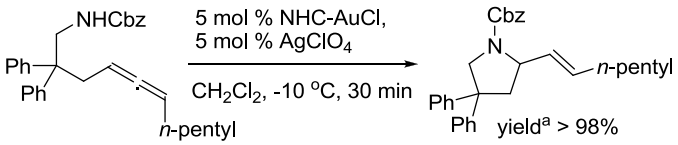
Synthesis of NHC-gold catalysts 72–76. As shown in Scheme 16, the required NHC-gold catalysts **72**–**76** were achieved in 34%–91% yield from imidazolinium salts and AuCl·SMe_2 with NaH or NaO*t*-Bu in CH_2Cl_2 at room temperature. [63]

Scheme 16. Synthesis of NHC-gold catalysts **72**–**76**



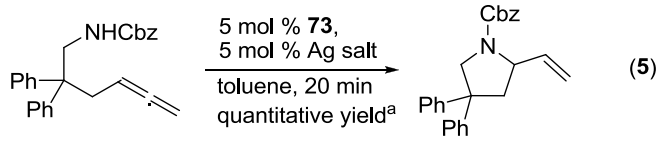
Testing NHC-gold catalysts in the asymmetric cyclization of Cbz-aminoallenes to *N*-Cbz-pyrrolidines. [64] As shown in Table 13, both **73** and **74** catalyzed two reactions (eq 3 and 4) quantitatively, but provided 2-vinyl-*N*-Cbz-pyrrolidine with only 22% and 13% ee, respectively (entry 1). Both ligands gave racemic 2-((*E*)hept-1-enyl)-4,4-diphenyl-*N*-Cbz-pyrrolidine (entry 2). Complex **73** was then examined in the reaction of 2-vinyl-4,4-diphenyl-*N*-Cbz-pyrrolidine (eq 5), and the silver salts were screened (Table 14). All silver salts catalyzed the reaction quantitatively, and $AgClO_4$ was the best choice (13% ee). Under the same conditions ($AgClO_4$ in toluene), **76** compared with **73** and gave 2-vinyl-4,4-diphenyl-*N*-Cbz-pyrrolidine with 12% ee. We were interested in the application of **76** in this reaction and screened the solvents with **76** (Table 15). The best results were 15% ee (yield > 95%) in *o*-xylene at room temperature for 90 min. Imidazolinium salt **56** was also examined in this reaction, and to our surprise, it outperformed other NHC precursors. With only 1.7 mol % of NHC-gold catalyst **75** and $AgClO_4$, the reaction in toluene at room temperature for 24 h provided 2-vinyl-4,4-diphenyl-*N*-Cbz-pyrrolidine almost quantitatively with 21% ee.

Table 13. Asymmetric pyrrolidine synthesis with **73** and **74**

Entry	Reaction		Ee[b] with **73** (%)	Ee[b] with **74** (%)
1		(**3**)	22	13
2		(**4**)	0	0

[a]The yield was calculated from the ^{1}H NMR spectroscopy of the crude reaction mixture. [b]The ee was determined by chiral OD-H HPLC.

Table 14. Asymmetric pyrrolidine synthesis with **73** and different silver salts

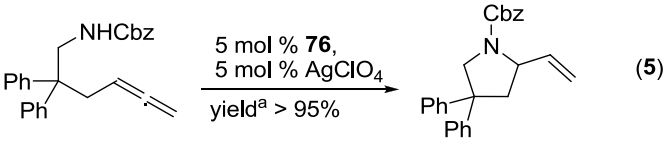


(**5**)

Entry	Ag	Ee[b] (%)
1	$AgClO_4$	13
2	$AgBF_4$	10
3	$AgPF_6$	5
4	AgOTf	10
5	$AgAsF_6$	3
6	$AgSbF_6$	1

[a]The yield was calculated from isolated product after chromatography. [b]The ee was determined by chiral OD-H HPLC.

Table 15. Asymmetric pyrrolidine synthesis with **76** in different solvents



(**5**)

Entry	Solvent	Time (min)	Ee[b] (%)
1	toluene	90	12
2	CH_2Cl_2	15	4
3	THF	15	0
4	*o*-xylene	90	15
5	*p*-xylene	90	12
6	*m*-xylene	90	11
7	benzene	90	13
8	mesitylene	90	9

[a]The yield was calculated from isolated product after chromatography or the ^{1}H NMR spectroscopy of the crude reaction mixture. [b]The ee was determined by chiral OD-H HPLC.

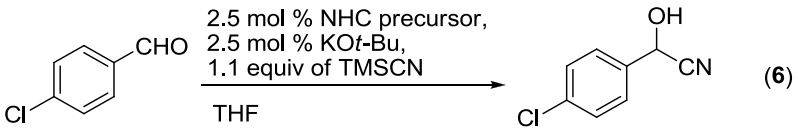
In conclusion, imidazolinium salts **45**, **48d**, **48h, 56** were examined in the gold-catalyzed asymmetric cyclization of Cbz-aminoallenes to *N*-Cbz-pyrrolidines. Their reactivities were excellent, and the yields of the products were almost quantitative. However, their enantioselectivities were moderate or very poor.

1.7 ASYMMETRIC CYANOSILYLATION OF ALDEHYDES WITH NHC CATALYSTS

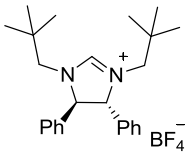
As shown in Table 16, different NHC precursors were examined in the asymmetric cyanosilylation of 4-chlorobenzaldehyde at 60 ℃.[65] Imidazolinium salt **57** was the best (90% yield, 12% ee (entry 4)). When the reaction temperature was decreased to 23 ℃, both yield and ee of the reaction with **57** decreased to 17% and 10%, respectively (entry 5). Imidazolinium salt **77**[29c] (entry 8) outperformed **48b** and **48c** (entries 6 and 7) in this reaction at 23 ℃ and gave the product in 88% yield with 4% ee.

In conclusion, imidazolinium salts **48b**, **48c**, **48d**, **48h**, **56**, **57** and **77** were examined in the asymmetric cyanosilylation of 4-chlorobenzaldehyde. Unfortunately, the enantioselectivities of these ligands in this reaction were poor.

Table 16. Asymmetric cyanosilylation of 4-chlorobenzaldehyde with different NHC precursors



(**6**)

Entry	NHC precursor	T (℃)	Time (h)	Yield[a] (%)	Ee[b] (%)
1	**48d** (*o*-cyclohexyl)	60	6	23	0
2	**48h** (*o*-methyl-*m*-phenyl)	60	6	36	6
3	**56**	60	6	26	0
4	**57**	60	0.5	90	12
5	**57**	23	1	17	10
6	**48b** (*o*-phenyl)	23	24	16	0
7	**48c** (*o*-benzyl)	23	24	20	0
8	 **77**	23	3	88	4

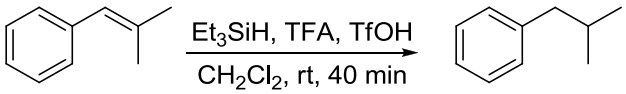
[a]The yield was calculated from isolated product after chromatography. [b]The ee was determined by chiral OD-H HPLC.

1.8 HYDROGENATION OF STYRENE DERIVATIVES WITH ET_3SIH AND TFA

Optimization of reaction conditions. In our synthesis of imidazolinium salt **48j**, the procedure from **55** to **53** with Et_3SiH and TFA is efficient to hydrogenate bulky styrenes. To test the possibility of applying the procedure to other styrene derivatives, the equivalents of Et_3SiH and TFA were optimized (Table 17). Because of its accessibility, β,β-dimethylstyrene was used in this optimization. 1.05 Equiv of Et_3SiH and 2.1 equiv of TFA with one drop of TfOH (0.04

mL) in CH_2Cl_2 at room temperature for 40 min were found the most suitable conditions, and 1-isobutylbenzene was formed in 93% yield.

Table 17. Hydrogenation of β,β-dimethylstyrene with different equivalents of Et_3SiH and TFA

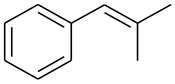
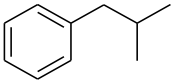
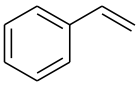
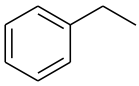
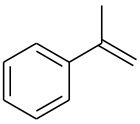
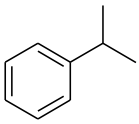
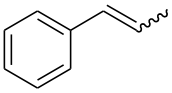
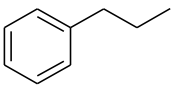
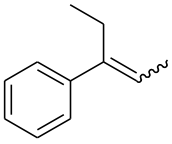
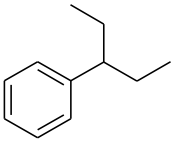
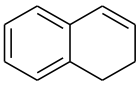
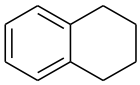
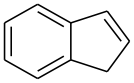
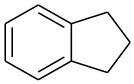
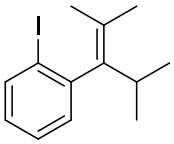
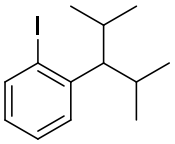
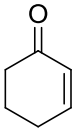


Entry	Et_3SiH (equiv)	TFA (equiv)	Yield[a] (%)
1	5	5	100
2	1.2	2.4	96
3	1.2	1.2	78
4	1.5	1.5	88
5	1.05	2.1	93

[a]Reaction run with β,β-dimethylstyrene (0.25 mmol) and TfOH (one drop, 0.04 mL) in CH_2Cl_2 (0.6 mL) for 40 min, and the yield was calculated from the ^1H NMR spectroscopy of the crude mixture.

Expansion of the substrate scope. With these optimized conditions in hand, the substrate scope was then explored (Table 18). Styrene and monosubstituted styrenes polymerized easily and gave the corresponding products in only approximately 34% yield (entries 2–4). Disubstituted styrenes reacted efficiently and furnished the products almost quantitatively (entries 1 and 5). 1,2-Dihydronaphthalene also gave a quantitative yield of 1,2,3,4-tetrahydronaphthalene (entry 6), but 1*H*-indene provided 2,3-dihydro-1*H*-indene in only 33% yield probably because the benzyl cation intermediate cannot adopt a conformation to be coplanar with the benzene ring, which will stabilize the benzyl cation (entry 7). Styrene **55** is also too bulky to develop a stable benzyl cation and provided **53** in only 38% yield (entry 8). Cyclohexenone and cyclohexene did not react most likely due to the difficulty to develop a stable cation (entries 9 and 10).

Table 18. Scope of the hydrogenation of styrene derivatives with Et_3SiH and TFA

Entry	Reactant	Product	Yield[a] (%)
1			93
2			35
3			33
4			34
5			100
6			100
7			33
8			38
	55	**53**	
9		-	-
10		-	-

[a]The yield was calculated from the ^1H NMR spectroscopy of the crude mixture.

In conclusion, the procedure of the hydrogenation of styrene **55** to **53** by Et_3SiH, TFA and TfOH can be applied to other styrene derivatives. High yield will be achieved if the substrate can develop a stable cation. It is a simple and efficient procedure to hydrogenate bulky styrene derivatives.

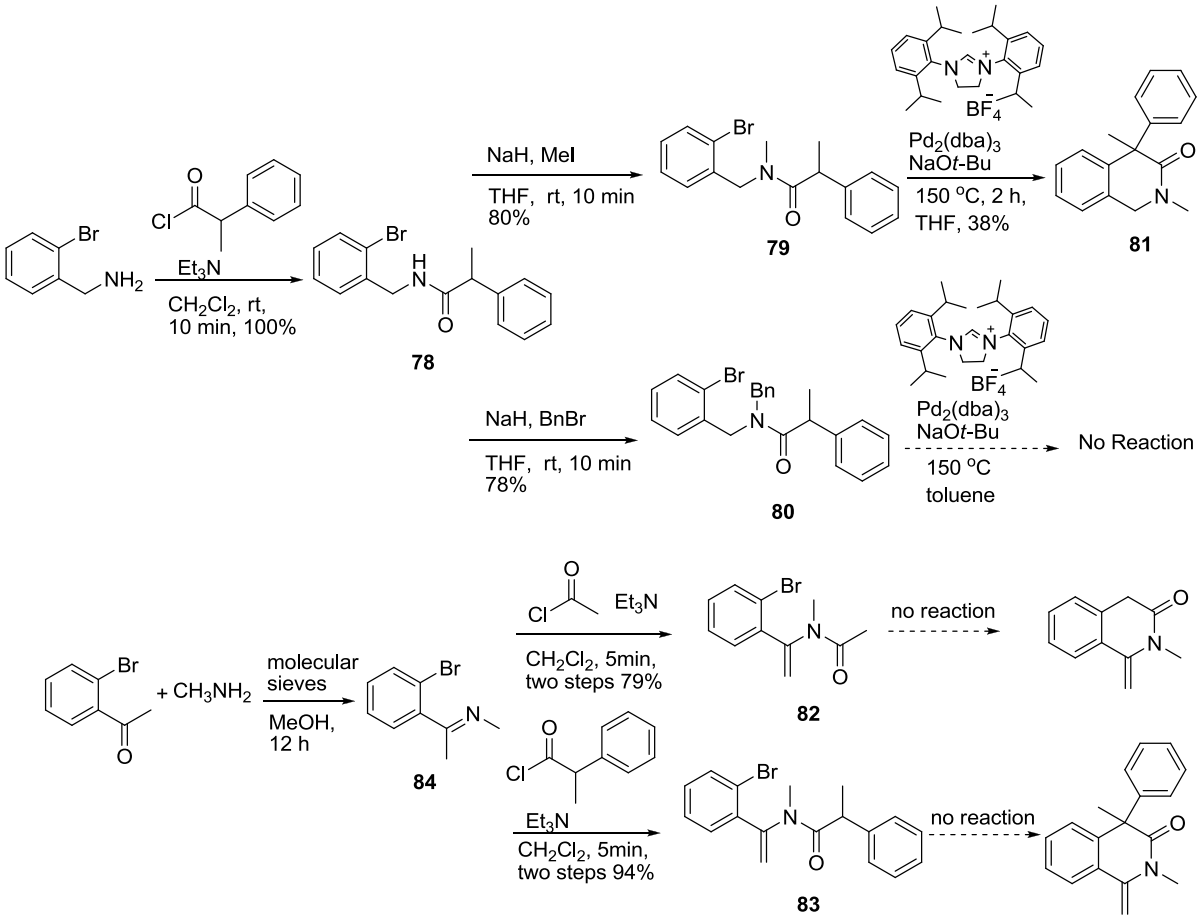
1.9 EXPLORATION OF PALLADIUM-CATALYZED INTRAMOLECULAR ARYLATION IN THE SYNTHESIS OF 1,2-DIHYDROISOQUINOLIN-3(4*H*)-ONE

The palladium-catalyzed intramolecular arylation of anilide enolates has been developed for the synthesis of oxindoles[13, 66] and other five- and six-membered ring compounds.[67] After having studied NHC ligands in the asymmetric synthesis, we turned our interest in the application of this procedure in a six-membered ring formation (additional methylene group between phenyl and amino groups compared to the oxindole). As shown in Scheme 17, the amidation of (2-bromophenyl)methanamine with 2-phenylpropanol chloride provided amide **78** quantitatively. The methylation of **78** with MeI gave *N*-methyl amide **79** in 80% yield, and the benzylation of **78** with benzyl bromide afforded *N*-benzyl amide **80** in 78% yield.[13] Under the oxindole reaction conditions (1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate, $Pd_2(dba)_3$ and NaO*t*-Bu in toluene at 150 ℃ overnight), **79** afforded cyclization product **81** in 32% yield, while no reaction occurred with **80**. The yield of **81** increased to 38% in only 2 h when the solvent was changed to THF.

Expecting that the sp^2 hybridized carbon would bring two reactive components in the molecular together to facilitate the cyclization, we prepared amide **82** and **83** (Scheme 17). The treatment of 1-(2-bromophenyl)ethanone with methanamine afforded imine **84**[68] which gave

acetamide **82** in 79% yield and 2-phenylpropanamide **83** in 94% yield. Unfortunately, under the oxindole reaction conditions (1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate, $Pd_2(dba)_3$ and NaO*t*-Bu in toluene at 200 ℃ or in dioxane at 120 ℃), no reactions occurred with amides **82** or **83**.

Scheme 17. Synthesis of 1,2-dihydroisoquinolin-3(4*H*)-one derivertives

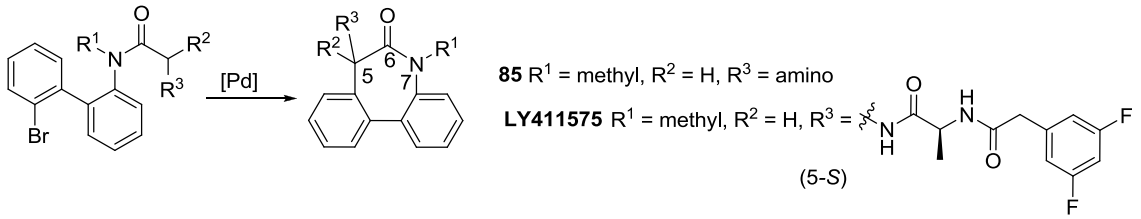


In conclusion, the procedure of palladium-catalyzed intramolecular arylation was applied to the synthesis of 1,2-dihydroisoquinolin-3(4*H*)-one. This procedure is not as efficient as it in the synthesis of oxindoles.

2.0 SYNTHESIS OF DIBENZAZEPINONES BY PALLADIUM–CATALYZED INTRAMOLECULAR ARYLATION OF *O*-(2'-BROMOPHENYL)ANILIDE ENOLATES

γ-Secretase inhibitor LY411575,[69,70] a potential drug candidate for Alzheimer's disease, is known to reduce brain and CSF levels of β-peptides. As the core structure of LY411575, α-substituted dibenzazepinones have an interesting gear-like structure.[71,72] Prior syntheses of dibenzazepinones have been based upon the Friedel-Crafts alkylation,[73a,73b] the palladium-catalyzed borylation-Suzuki reaction,[72] the cyclization of hydroxylamide in neat trifluoromethanesulfonic acid,[73c] the intramolecular Staudinger-aza-Wittig reaction of α-azido pentafluorophenyl ester,[73d] and the hydrogenation of methyl 2-nitro-2'-biphenylacetate.[73e] Some of these methods suffer from low yields, or produce byproducts that are difficult to separate from the target molecule. We became interested in exploring the potential of palladium-catalyzed intramolecular arylation for the seven-membered ring formation and its utility in the synthesis of aminodibenzazepinone **85** (Scheme 18).

Scheme 18. Synthesis of dibenzazepinones by palladium-catalyzed intramolecular arylation



2.1 SYNTHESIS OF DIBENZAZEPINONE PRECURSORS

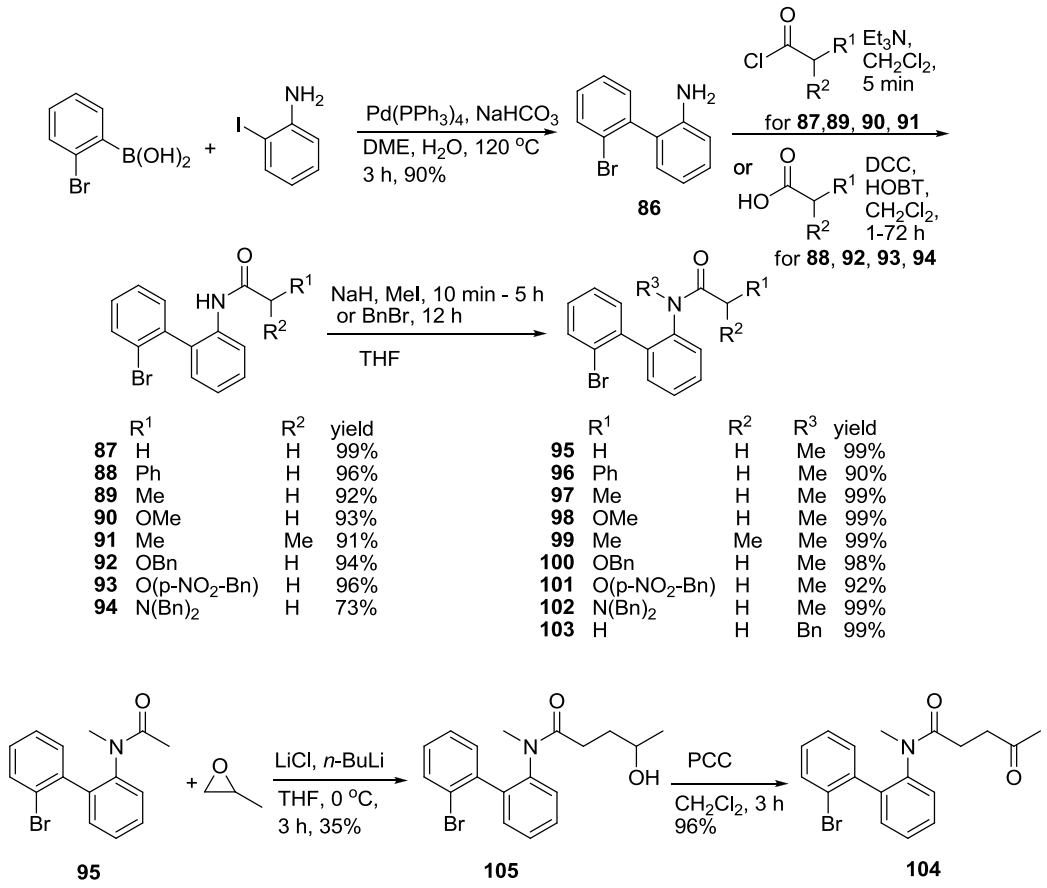
As shown in Scheme 19, the Suzuki coupling of 2-bromophenylboronic acid and 2-iodoaniline afforded 2-amino-2'-bromobiphenyl **86** in 90% yield. The amidation of **86** with acyl chlorides or carboxylic acids gave amides **87**–**94** in generally excellent yields. The methylation of **87**–**94** with methyl iodide or the benzylation of **87** with benzyl bromide provided the desired *N*-alkyl amides **95**–**103** as dibenzazepinone precursors in uniformly excellent yields. However, the synthesis of *N*-methyl-4-oxopentanamide **104** was challenging. The amidation of **86** with 4-oxopentanoic acid and DCC was not successful. To make a more reactive acyl chloride, 4-oxopentanoic acid was treated with $SOCl_2$, but only 5-chloro-5-methyl-dihydrofuran-2(3*H*)-one was achieved. This lactone is most likely derived from intramolecular lactonizaion of acyl chloride. An alternative route was explored. The treatment of amide **95** with 2-methyloxirane and *n*-BuLi afforded alcohol **105** in 35% yield[74] which was oxidized with PCC to give ketone **104** in 96% yield.[75]

2.2 OPTIMIZATION OF REACTION CONDITIONS

As shown in Table 19, two general catalysis systems were screened with acetamide **95**. The treatment of **95** with 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate,[13] palladium acetate, and NaO*t*-Bu in toluene at 100 °C for 20 min gave dibenzazepinone **106** in 78% yield (entry 1). The use of tricyclohexylphosphonium tetrafluoroborate[67a] with palladium acetate increased the yield of **106** to 90% in 10 min (entry 2), and generated a byproduct identified as 9-methyl-9*H*-carbazole **107** (6% yield). This byproduct

is presumed to arise by cleavage of the amide to the aniline by NaO*t*-Bu followed by the palladium-catalyzed intramolecular amination. Changing the solvent to dioxane decreased the yield of **106** to 45% (entry 3). To further explore the efficiency of the catalysis system of tricyclohexylphosphonium tetrafluoroborate, the catalytic loading was lowered to 5 mol % with 1.5 equiv of NaO*t*-Bu (entry 4). However, the yield of **106** dropped to 61%.

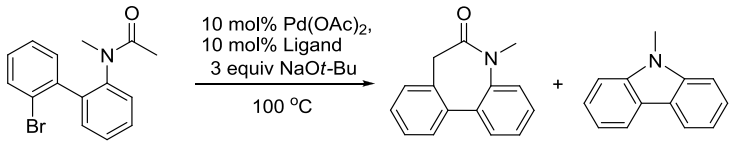
Scheme 19. Synthesis of amides **95**–**104**



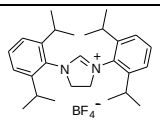
	R^1	R^2	yield
87	H	H	99%
88	Ph	H	96%
89	Me	H	92%
90	OMe	H	93%
91	Me	Me	91%
92	OBn	H	94%
93	O(p-NO_2-Bn)	H	96%
94	$N(Bn)_2$	H	73%

	R^1	R^2	R^3	yield
95	H	H	Me	99%
96	Ph	H	Me	90%
97	Me	H	Me	99%
98	OMe	H	Me	99%
99	Me	Me	Me	99%
100	OBn	H	Me	98%
101	O(p-NO_2-Bn)	H	Me	92%
102	$N(Bn)_2$	H	Me	99%
103	H	H	Bn	99%

Table 19. Optimization of the synthesis of dibenzazepinone **106**



95 **106** **107**

Entry	Ligand Precursor	Solvent	Time (min)	Yield[a] (%)
1		toluene	20	78
2	$HPCy_3BF_4$	toluene	10	90
3[b]	$HPCy_3BF_4$	toluene	10	61
4	$HPCy_3BF_4$	dioxane	10	45

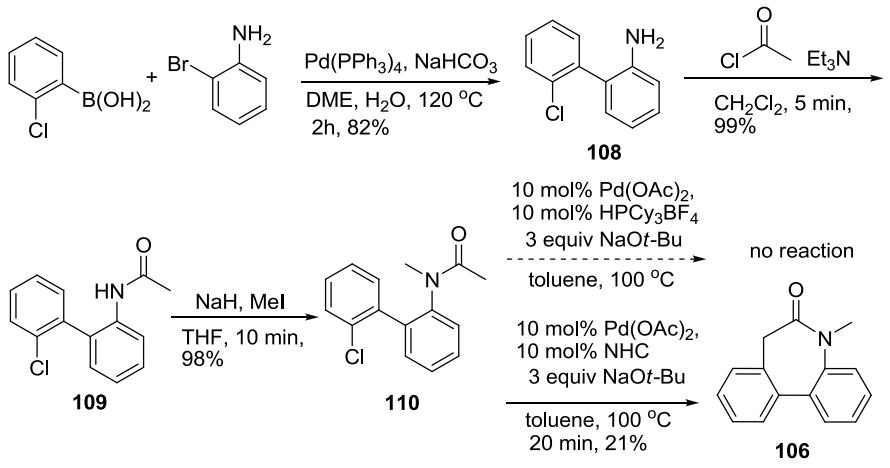
[a]The yield of **106** was calculated from isolated product after chromatography. [b]Reaction run with 5 mol % of the catalyst.

2.3 EXPLORATION OF THE REACTION WITH CHLOROARYL SUBSTRATES

For reasons related to materials cost, the possibility of using a chloroaryl substrate in place of the bromoaryl substrate was explored. As shown in Scheme 20, the synthesis of 2'-chloro-2-aminobiphenyl **108** from 2-chlorophenylboronic acid and 2-bromoaniline, which are less expensive starting materials, proceeded with the same efficiency as found for the bromoaryl analog (82% yield). Following amidation of **108** with acetyl chloride and methylation of amide **109** with methyl iodide gave *N*-methyl amide **110** in quantitative overall yield. Unfortunately, with chloroaryl substrate **110**, the catalysis system of tricyclohexylphosphonium

tetrafluoroborate provided no product; 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate under the same conditions for 20 min gave **106** in only 21% yield.

Scheme 20. Synthesis of dibenzazepinone **106** from chloroaryl substrates



2.4 EXPANSION OF THE SUBSTRATE SCOPE

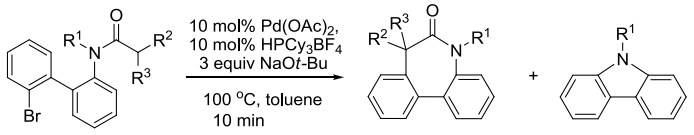
The optimized cyclization conditions were applied to more substrates (Table 20). A phenyl group in the alpha position of the amide was well tolerated; the yield of α-phenyldibenzazepinone **111** was almost quantitative (entry 2). In contrast, α-methyl and α-methoxy substrates **97** and **98** (entry 3 and 4) afforded relatively low yields of the dibenzazepinone and the product was accompanied by the byproduct 9-methyl-9H-carbazole. The incorporation of two methyl groups at the alpha position inhibited the reaction; α,α-dimethyldibenzazepinone **114** was formed in only 8% yield and 54% conversion (entry 5). The *N*-benzyl amide **103** was investigated as an alternative to *N*-methyl amide **95** because the product amide may be readily deprotected. The benzyl and methyl amides behaved similarly. *N*-Benzyl protected dibenzazepinone **115** was isolated in 84% yield along with 9-benzyl-9H-carbazole in

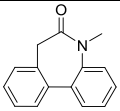
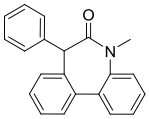
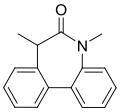
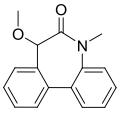
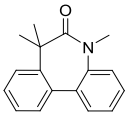
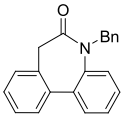
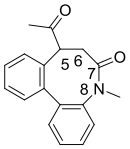
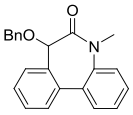
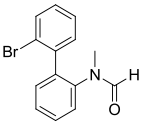
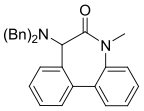
16% yield (entry 6). Interestingly, amide **104** with 2-oxopropyl group on the alpha position of the amide did not give the desired dibenzazepinone derivative, but provided an eight-membered ring product **116** in 20% yield most likely because the intermediate anion is more stable on carbon 5 than on carbon 6 (entry 7).

Under the standard conditions using 3 equiv of base, an interesting byproduct was formed (47% yield) in the reaction of α-benzyloxyamide **100**. This byproduct has a chemical composition identical to that of the desired product **117**. At first thought, it could be a benzyl C-H bond activation product **118** (Scheme 21). A nitro group at the *para* position of the benzyl group will increase the acidity of benzyl hydrogen, therefore the yield of the benzyl C-H bond activation product was expected to increase. However, amide **101**, a *para*-nitro benzyl analog of **100**, did not give the desired benzyl C-H bond activation product but afforded formylamide **119** in 24% yield and 9-methyl-9*H*- carbazole in 47% yield. To further prove the structure of **118**, we decided to prepare it by an alternative route.

As shown in Scheme 21, the amidation of 2-bromoaniline with α-chloroacetyl chloride afforded amide **120** in 98% yield. The methylation of **120** with MeI followed by the treatment with NaI in acetone gave *N*-methylamide **121** in total 30% yield. The treatment of amide **121** with (2-bromophenyl)(phenyl)methanol furnished α-ether-aceticamide **122** in 98% yield. Unfortunately, further cyclization of **122** with the Ullmann coupling procedures ($Pd(PPh_3)_4$ and Cu in DMSO at 85 °C,[76] Cu in solvents (DMSO, DMF or pyridine) at 110 °C or 150 °C, $Pd(PPh_3)_4$ and Sn_2Me_6 in dioxane at 150 °C,[77] Zn and $CuBr{\cdot}SMe_2$ in THF) was unsuccessful. We proposed that the amide structure in **122** prevented the approaching of the two bromoarene moieties. Thus, **122** was reduced with $BH_3{\cdot}SMe_2$[78] to give amine **123** in 99% yield. The unknown byproduct was reduced to the amine as well with $BH_3{\cdot}SMe_2$ in 98% yield. We

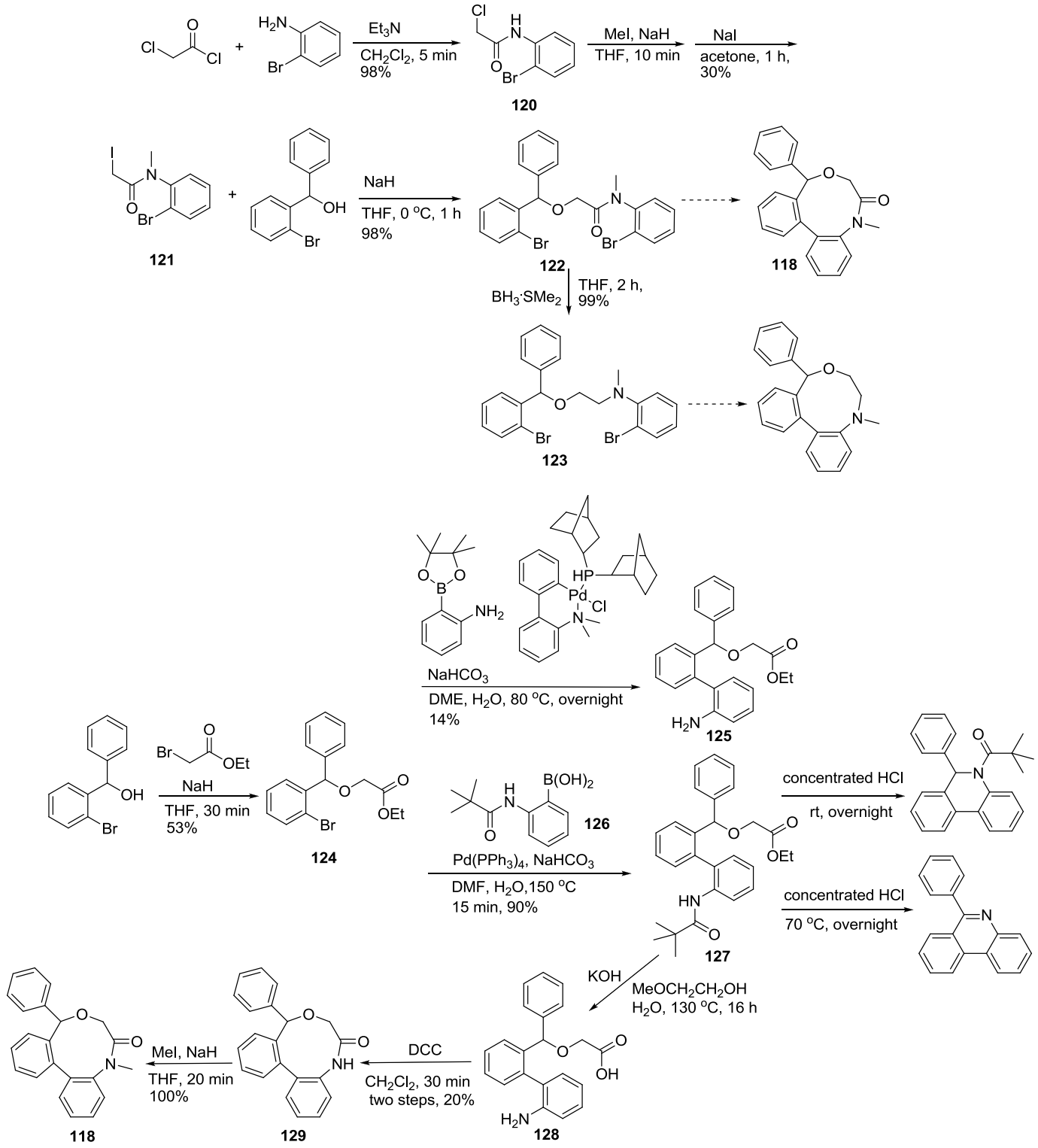
Table 20. Scope of the intramolecular arylation pathway to dibenzazepinones



Entry	Reactant	Product	Yield[a] (%)	**107**[a] (%)	Conversion[b] (%)
1	**95**	 **106**	90	6	96
2	**96**	 **111**	99	-	100
3	**97**	 **112**	45	34	80
4	**98**	 **113**	56	15	86
5	**99**	 **114**	8	15	54
6	**103**	 **115**	84	16	100
7[c]	**104**	 **116**	20	17	97
8[d]	**100**	 **117**	81	7	100
9	**101**	 **119**	24	47	100
10	**102**	 **135**	93	-	100
11[e]	**102**	**135**	91	-	98

[a]The yield was calculated from isolated product after chromatography. [b]The conversion was based on the isolated starting material. [c]Reaction run for 20 min. [d]Reaction run with 1.5 equiv of NaO*t*-Bu. [e]Reaction run with 3 mol% of the catalyst for 15 min.

Scheme 21. Synthesis of lactam **118**



expected that the intramolecular Ullmann coupling of **123** would provide a product with the same ^{1}H NMR spectrum as that of the amine produced from the reduction of the unknown byproduct. However, the intramolecular Ullmann coupling of **123** still failed with the common methods (Cu in DMF at 150 °C; $Pd(PPh_3)_4$ and Sn_2Me_6 in dioxane at 150 °C; Zn and $CuBr{\cdot}SMe_2$ in THF; *t*-BuLi, CuCN and 1,3-dinitrobenzene in MeTHF). We then proposed that the monoborylation of **123** followed by the intramolecular Suzuki coupling would cyclize the ring. However, no reaction occurred under the Miyaura borylation reaction conditions ($Pd(dppf)Cl_2$ and KOAc in DME at 150 °C).

The amine from the reduction of the unknown byproduct was then expected to react with a strong acid to give a salt which can be recrystallized and characterized by X-ray diffraction. However, no reaction occurred with p-toluenesulfonic acid, and fluoboric acid etherate provided a salt which could not be recrystallized with MeOH and DME.

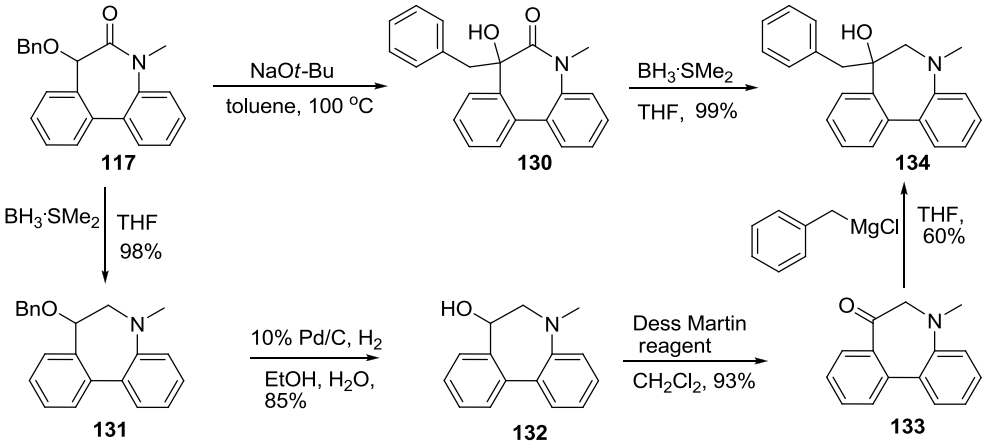
We then sought a new synthesis of **118** (Scheme 21). The treatment of (2-bromophenyl)(phenyl)methanol with ethyl 2-bromoacetate afforded ether **124** in 53% yield. The Suzuki coupling of **124** and 2-aminophenylboronate gave 1,1'-disubstituted biphenyl **125** in only 14% yield. Because of this low yield, we chose phenylboronic acid **126** as the substitution for 2-aminophenylboronate, and the Suzuki coupling reaction furnished 1,1'-disubstituted biphenyl **127** in 90% yield. Unfortunately, the deprotection of the amino group on **127** with concentrated HCl at 70 ℃ and room temperature only afforded 6-phenylphenanthridine[79] and 5-pivaloyl-5,6-dihydro-6-phenyl-phenanthridine, respectively. 6-Phenylphenanthridine is most likely derived from the cleavage of the pivaloyl amide moiety in 5-pivaloyl-5,6-dihydro-6-phenyl-phenanthridine followed by the oxidation with molecular oxygen, and 5-pivaloyl-5,6-dihydro-6-phenyl-phenanthridine is most likely achieved from intramolecular S_N1 substitution of **127**.

Fortunately, the hydrolysis of **127** with KOH deprotected the amino and carboxylic acid groups successfully, and the resulting intermediate **128** was cyclized with DCC to provide lactam **129** in 20% yield. Further methylation of **129** with MeI gave *N*-methyl-lactam **118** quantitatively. We found that the ^{1}H NMR spectrum of the unknown byproduct from the reaction of α-benzyloxyamide **100** is different from that of **118**. The unknown byproduct is not **118**.

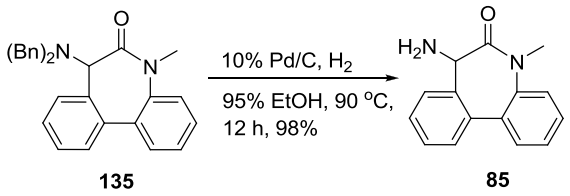
The IR spectra of the unknown byproduct exhibits a broad peak at 3387 cm^{-1}. Therefore it could be α-hydroxy-α-benzyl dibenzazepinone **130**, a 1,2 Wittig rearrangement product.[80] This byproduct was also produced by the reaction of the desired product **117** with NaO*t*-Bu alone in toluene at 100 ℃ (Scheme 22). To confirm the structure of **130**, **117** was reduced to amine **131** (Scheme 22). Following debenzylation of **131**,[81] Dess-Martin oxidation[82] of alcohol **132** and the treatment of aldehyde **133** with benzylmagnesium chloride afforded amine **134**, which was identical to the amide reduction product of **130**. The reaction conditions were then modified for the formation of **117**. α-Benzyloxydibenzazepinone **117** was formed in 81% yield with 4% **130** when the amount of NaO*t*-Bu was reduced to 1.5 equiv, and the reaction was run in toluene for 10 min (Table 20, entry 8).

Because of our interest in the γ-secretase inhibitor, it was significant to find that α-dibenzylaminoamide **102** cyclized efficiently to afford α-dibenzylaminodibenzazepinone **135** in 93% yield (Table 20, entry 10). Lowering the catalyst loading to 3 mol% had little effect, and provided the desired product in 15 min in 91% yield (Table 20, entry 11).

Scheme 22. Rearrangement of α-benzyloxydibenzazepinone **117**



α-Dibenzylaminodibenzazepinone **135** was debenzylated quantitatively through hydrogenolysis to afford α-aminodibenzazepinone **85** (eq 6). The complete synthesis of α-aminodibenzazepinone **85** by this approach requires five steps from 2-bromophenylboronic acid and 2-iodoaniline and proceeds in 60% overall yield. Significant increases in overall yield can be achieved by optimizing the step involving coupling of 2'-bromo-2-aminobiphenyl **86** with dibenzylaminoacetic acid.



(**6**)

3.0 CONCLUSIONS

Chiral *N*-heterocyclic carbene (NHC) ligands were designed and explored in three asymmetric syntheses (oxindole synthesis, pyrrolidine synthesis and cyanosilylation of aldehydes). The NHC ligands with the chiral controlling group located on the *ortho* position of the *N*-aryl ring were introduced but need further improvement. The ligand generated from (4*R*,5*R*)-1,3-bis(*ortho*-cyclohexylphenyl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborates **48d** provided the best asymmetric oxindole synthesis in this study: yields of oxindoles up to 99% with enantioselectivities (ee) up to 80% were achieved in 3 h; **48d** can be prepared in only two steps; with only 1 mol % of **48d**, the reaction still afforded oxindoles with good ee and yield.

Although the NHC ligands from Kündig and Glorius's groups provided better enantioselectivities than **48d** in the oxindole synthesis, there are some data (low ee) that cannot be explained. A mechanism for this asymmetric oxindole synthesis was proposed. The rotation barrier of the N-aryl bond in the oxidative addition products was found crucial for the enantioselectivity. These data can be explained that increasing the rotation barrier would decrease the enantioselectivity, and vice versa. Future work will be focused on the optimization of the mechanism which will provide a guide for the ligand design and optimization of the reaction conditions.

The intramolecular α-arylation of amide enolates has been applied successfully to the formation of seven-membered ring compounds. These reactions provide a new route to the synthesis of substituted dibenzazepinones. The procedure is efficient, and especially useful for the synthesis of α-aminodibenzazepinone. We anticipate that with the appropriate asymmetric ligand or chiral amino protecting group, α-aminodibenzazepinone may be made directly with high enantiomeric excess, thus eliminating the need for resolution of this important target.

4.0 EXPERIMENTAL

General Information. Commercially available reagents and solvents were used as received without further purification. Reactions at "room temperature" were conducted under ambient laboratory conditions T = 20–27 ℃, p = 720–770 mmHg. References to "removal of volatile components" refer to rotary evaporation of the sample at 25–65 ℃ *in vacuo* (18–25 mmHg). Thin layer chromatography (TLC) was performed on silica gel 60 F254 glass backed plates with a layer thickness of 0.25 mm manufactured by EMD. Silica gel columns for flash chromatography, according to the method of Still, were prepared with SILICYCLE silica gel (SiliaFlash P60, 230-240 mesh). ^{1}H NMR spectra were recorded on a Bruker Avance 300 at 300 MHz, a Bruker Avance III 400 at 400 MHz, a Bruker Avance III 500 at 500 MHz and a Bruker DRX 500 at 500 MHz, and chemical shifts were given in parts per million (ppm) on the delta scale (δ) using solvent peak as a reference value (Me_4Si = 0.00, CD_2Cl_2 = 5.32, $CDCl_3$ = 7.24 or 7.27). ^{13}C NMR spectra were recorded on a Bruker Avance 300, a Bruker Avance III 400 and a Bruker Avance III 500 at 75 MHz, and chemical shifts are given in parts per million (ppm) on the delta scale (δ) using deuterated solvents as internal standards ($CDCl_3$ = 77.23; CD_2Cl_2 = 53.80), and the coupling constant values (*J*) are in Hertz. Abbreviations for NMR data: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triples; dq = doublet of quartets; tt = triplet of triplets; m = multiplet; br = broad. 2D EXSY data were acquired with Bruker Avance III 500 at 500 MHz, and peak volumes were integrated using

Bruker TopSpin 3.0. Optical rotations were measured with Perkin-Elmer 241 digital polarimeter with sodium lamp. High resolution and low resolution mass spectra were recorded of a VG 7070 spectrometer. Infrared (IR) spectra were collected on an Avatar 360 Nicolet FT-IR spectrometer. Samples for IR were prepared as a thin film on a NaBr plate by dissolving the sample in CH_2Cl_2 and then evaporating the CH_2Cl_2.

Examination of Imidazolinium Salts in the Asymmetric Synthesis of Oxindoles (Chapters 1.1–1.4). The detailed synthesis and characterization of substrates and oxindoles are described in the papers from Hartwig[13] and Marsden groups.[67a] To a flask in a dry box was added $Pd(dba)_2$ (4.3 mg, 0.0075 mmol), imidazolinium salt (0.0075 mmol) and NaO*t*-Bu (0.225–1.575 mmol). The flask was sealed with a septum, removed from the dry box and added the solvent (1 mL). After being stirred at rt for 10 min, a solution of 2-bromoanilide (0.15 mmol) in the solvent (1 mL) was added, and the resulting mixture was degassed in a dry ice-acetone bath, back filled with nitrogen and stirred at the temperature indicated in Chapters 1.1–1.4. After the reaction was over (as determined by TLC), the solvent was evaporated under reduced pressure. The resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) and analyzed by HPLC (Chiralcel OD-H, hexanes/*i*-PrOH = 90/10, detection at 254 nm). For 1,3-dimethyl-3-(1-naphthyl)oxindole, flow rate = 0.92 mL/min: t_R = 12.28 min, 27.99 min; for 1,3-dimethyl-3-phenyloxindole, flow rate = 0.92 mL/min: t_R = 7.46 min, 8.46 min; for 1,3-dimethyl-3-(4-isobutylphenyl)oxindole, flow rate = 0.92 mL/min: t_R = 5.80 min, 6.38 min; for 1-methyl-3-methoxy-3-phenyloxindole, flow rate = 0.3 mL/min: t_R = 25.34 min, 26.15 min; for 1-methyl-3-benzoxy-3-phenyloxindole, flow rate = 1 mL/min: t_R = 6.68 min, 8.06 min; for 1-benzyl-3-methoxy-3-phenyloxindole, flow rate = 1 mL/min: t_R = 7.96 min, 8.48 min.

Examination of NHC catalysts in the Asymmetric Cyclization of Cbz-Aminoallenes to *N*-Cbz-Pyrrolidines (Chapter 1.6). The detailed synthesis and characterization of Cbz-aminoallenes and *N*-Cbz-pyrrolidines are described in the paper from Windenhoefer group.[64] A solution of NHC-AuCl (0.005 mmol) and $AgClO_4$ (0.005 mmol) in CH_2Cl_2 (0.5 mL) covered by an aluminum foil was stirred at rt for 10 min and cooled to 0 ℃. A solution of Cbz-aminoallenes **(**0.1 mmol) in CH_2Cl_2 (0.5 mL) was added, and the mixture was stirred at the temperature indicated in Chapter 1.6. After the reaction was over (as determined by TLC), the solvent was evaporated under reduced pressure. The resulting crude product was examined by NMR spectroscopy (yield) and analyzed by HPLC (Chiralcel OD-H, flow rate = 1 mL/min, detection at 254 nm). For 2-vinyl-*N*-Cbz-pyrrolidine, hexanes/*i*-PrOH = 99/1: t_R = 12.94 min, 14.09 min; for 2-((*E*)hept-1-enyl)-4,4-diphenyl-*N*-Cbz-pyrrolidine, hexanes/*i*-PrOH = 99/1: t_R = 14.93 min, 19.68 min; for 2-vinyl-4,4-diphenyl-*N*-Cbz-pyrrolidine, hexanes/*i*-PrOH = 95/5: t_R = 9.87 min, 11.26 min.

Examination of NHC Catalysts in the Asymmetric Cyanosilylation of 4-Chlorobenzaldehyde (Chapter 1.7).[65] To a solution of imidazolinium salt (0.0075 mmol) in THF (0.9 mL) was added KO*t*-Bu (0.1 M in THF, 75 μL), and the mixture was stirred at rt for 30 min. A solution of 4-chlorobenzaldehyde (42 mg, 0.3 mmol) in THF (0.6 mL) was added, followed by TMSCN (33 mg, 0.33 mmol), and the mixture was stirred at the temperature indicated in Chapter 1.7. After the reaction was over (as determined by TLC), the mixture was quenched with HCl solution (0.1 M, 0.5 mL) and extracted with ethyl acetate. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc

= 3/1) and analyzed by HLPC (Chiralcel OD-H, hexanes/ *i*-PrOH = 95/5, flow rate = 1 mL/min, detection at 254 nm): t_R = 16.62 min, 18.40 min.

2-Methyl-3-phenyl-bromobenzene. To a solution of phenylboronic acid (210 mg, 1.73 mmol), 2,6-dibromotoluene (410 mg, 1.64 mmol), $Pd(PPh_3)_4$ (95 mg, 0.082 mmol) in DME (2 mL) was added a solution of $NaHCO_3$ (414 mg, 4.92 mmol) in H_2O (2 mL), and the mixture was degassed in a dry ice-acetone bath and back filled with nitrogen. After being stirred at 110 ℃ for 23 h, the mixture was cooled to rt and extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the crude product was purified by flash chromatography (SiO_2, pentane) to give the product (261 mg, 65%) as an oil: IR (cm^{-1}) 3059, 2360, 1452, 1425, 1041, 759; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.47–7.35 (m, 3H), 7.32–7.29 (m, 2H), 7.21 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 141.6, 135.3, 131.8, 131.5, 129.1, 129.0, 128.1, 127.1, 126.7, 126.2, 21.0; HRMS (EI) *m*/*e* calcd for $C_{13}H_{11}Br$ (M^+) 246.0044, found 246.0039.

2-Bromoisophthalic acid (24).[83] A solution of 2-bromo-1,3-dimethylbenzene (24.88 g, 134.4 mmol) and $KMnO_4$ (45 g, 283 mmol) in *t*-BuOH/H_2O (1/1, 250 mL) was refluxed for 1 h and cooled to rt. Additional $KMnO_4$ (45 g, 283 mmol) and *t*-BuOH/H_2O (1/1, 100 mL) were added, and the mixture was refluxed overnight. After being cooled to rt, the mixture was filtered. The solvent was evaporated under reduced pressure until most alcohol was removed, and H_2O was added to bring the volume to 150 mL. Concentrated HCl was added slowly, and the resulting white precipitate was filtered and dissolved in a saturated aqueous Na_2CO_3 solution. The solution was washed with Et_2O and acidified with concentrated HCl. The white precipitate

was filtered and dried to afford **24** (17 g, 52%) as a white solid: ^{1}H NMR (300 MHz, DMSO) δ 7.70 (dd, *J* = 0.6, 7.6 Hz, 2H), 7.54 (dd, *J* = 7.1, 8.1 Hz, 1H).

2,6-Dihydroxymethylbromobenzene (25).[84] To a solution of 2-bromoisophthalic acid **24** (10.27 g, 41.93 mmol) in THF (220 mL) at 0 ℃ was added BH_3 in THF (1.0 M , 109 mL, 109 mmol) dropwise. The resulting mixture was agitated by ultrasound at rt for 2 h. THF/H_2O (1/1, 100 mL) was added, and the H_2O layer was saturated with K_2CO_3 and extracted with THF. The extracts were combined, dried over K_2CO_3 and filtered. Removal of volatile components from the filtrate afforded **25** (9.06 g, 99%) as a white solid: ^{1}H NMR (300 MHz, DMSO) δ 7.43 (m, 3H), 5.39 (t, *J* = 5.6 Hz, 2H), 4.52 (d, *J* = 5.6 Hz, 4H).

4-Bromo-2,6-diisopropylbenzenamine (27). [85] To a solution of 2,6-diisopropylbenzenamine (32.5 g, 183 mmol) in CH_2Cl_2/MeOH (1/1, 173 mL) at rt was added a solution of bromine (9.57 mL, 187 mmol) in CH_2Cl_2/MeOH (1/1, 86 mL) dropwise over 1.5 h, and the mixture was stirred for 22 h. The solvent was evaporated under reduced pressure, and the resulting crystalline residue was washed with hexanes/CH_2Cl_2 (2/1, 240 mL), neutralized with 20% aqueous NaOH solution (200 mL), and extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. Removal of volatile components from the filtrate provided **27** (40.5 g, 87%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (s, 2H), 3.69 (s, 2H), 2.88 (heptet, *J* = 6.8 Hz, 2H), 1.24 (d, *J* = 6.8 Hz, 12H).

***N*-(4-Bromo-2,6-diisopropylphenyl)ethane-1,2-diimine (28).** To a solution of aniline **27** (18.4 g, 71.8 mmol) in *n*-propanol (50 mL) at rt was added 40% aqueous oxalaldehyde (5.21 g, 35.9 mmol), *n*-propanol (5 mL) and H_2O (12.5 mL), and the mixture was stirred at rt for 14 h and 70 ℃ for 4 h. H_2O (50 mL) was added, and the mixture was cooled to rt. The resulting yellow precipitate was filtered, washed with H_2O/*n*-propanol (1/1, 30 mL) and dried *in vacuo* to

afford **28** (15.2 g, 80%) as a yellow solid: IR (cm^{-1}) 2963, 1629, 1461, 1175, 865, 720; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 2H), 7.27 (s, 4H), 2.94 (heptet, *J* = 6.9 Hz, 4H), 1.19 (d, *J* = 7.5 Hz, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 147.1, 139.3, 126.7, 119.0, 28.6, 23.6; HRMS (EI) *m*/*e* calcd for $C_{26}H_{34}N_2Br_2$ (M^+) 532.1089, found 532.1066.

***N*-(4-Bromo-2,6-diisopropylphenyl)ethane-1,2-diamine (29).** To a solution of diimine **28** (7.0 g, 13.1 mmol) in THF (45 mL) and EtOH (45 mL) at 0 ℃ was added $NaBH_4$ (2.0 g, 52.4 mmol) slowly over 1 h, and the mixture was stirred at rt for 12 h, 70 ℃ for 0.5 h and cooled in an ice bath. H_2O (10 mL) was added, followed by HCl (3 M, 60 mL) slowly, and the resulting white precipitate was filtered, washed with Et_2O and dissolved in an aqueous NaOH solution. The solution was extracted with Et_2O, and the extracts were combined, dried over $MgSO_4$ and filtered. Removal of volatile components from the filtrate gave **29** (6.5 g, 92%) as a white solid: IR (cm^{-1}) 3363, 2961, 1580, 1461, 1198, 1092, 726; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 4H), 3.39 (heptet, *J* = 6.9 Hz, 4H), 3.30 (br, 2H), 3.13 (s, 4H), 1.28 (d, *J* = 6.9 Hz, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 142.2, 126.8, 117.4, 52.0, 27.9, 24.2; HRMS (EI) *m*/*e* calcd for $C_{26}H_{38}N_2Br_2$ (M^+) 536.1402, found 536.1425.

***N*-(4-Pinacolatoboronyl-2,6-diisopropylphenyl)ethane-1,2-diamine (30).** A mixture of bis(pinacolato)diboron (533 mg, 2.1 mmol), diamine **29** (517 mg, 0.96 mmol), KOAc (565 mg, 5.76 mmol), $Pd(dppf)Cl_2$ (54.9 mg, 0.067 mmol) and DME (6 mL) in a 10 mL microwave tube was degassed at -15 °C and irradiated in a microwave reactor at 150 °C, 250 W for 35 min. After being cooled to rt, the mixture was filtered. After removal of volatile components from the filtrate, the crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 8/1) to give **30** (537 mg, 88%) as a white solid: IR (cm^{-1}) 2966, 1603, 1462, 1373, 1144, 966, 850, 732; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 4H), 3.51 (s, 2H), 3.32 (heptet, *J* = 6.6 Hz, 4H), 3.19 (s,

4H), 1.33 (s, 24H), 1.29 (d, J = 6.6 Hz, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 140.9, 130.5, 83.4, 52.1, 27.9, 24.9, 24.2; HRMS (EI) *m*/*e* calcd for $C_{38}H_{62}B_2N_2O_4$ (M^+) 632.4896, found 632.4905.

2,6-Bis((*tert*-butyldimethylsilyloxy)methyl)bromobenzene (31). To a solution of imidazole (15.0 mg, 0.22 mmol) and diol **25** (21.7 mg, 0.10 mmol) in DMF (1 mL) at 0 ℃ was added TBSCl (33.2 mg, 0.22 mmol), and the mixture was stirred at rt for 1 h. Saturated aqueous NH_4Cl solution (1 mL) was added and the resulting mixture was extracted with hexanes. The extracts were combined, dried over $MgSO_4$ and filtered. Removal of volatile components from the filtrate afforded **31** (40 mg, 90%) as a white solid: IR (cm^{-1}) 2952, 2929, 2856, 1468, 1254, 1120, 909, 838, 778; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.37 (m, 1H), 4.74 (s, 4H), 0.96 (s, 18H), 0.19 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 127.1, 126.0, 119.7, 64.9, 26.0, 18.4, 4.9; HRMS (EI) *m*/*e* calcd for $C_{19}H_{34}O_2Si_2Br$ (M^+) 429.1281, found 429.1286.

***N*-(4-(2,6-Bis(Boc-L-proline-carboxyl-methylene))phenyl-2,6-diisopropyl-phenyl)ethane-1,2-diamine (34).** To a solution of Boc-L-proline (580 mg, 2.70 mmol), DMAP (10.6 mg), tetraol **33** (400 mg, 0.61 mmol) in THF (4 mL) at -10 °C was added a solution of DCC (556 mg, 2.70 mmol) in THF (3 mL) over 1 h, and the mixture was stirred at rt for 1 h. Et_2O (5 mL) was added, and the resulting precipitate was filtered and washed with Et_2O. After removal of volatile components from the filtrate, the crude product was purified by flash chromatography (SiO_2, CH_2Cl_2, then hexanes/EtOAc = 1/1) to afford **34** (780 mg, 89%) as a white solid: IR (cm^{-1}) 2967, 1747, 1698, 1452, 1398, 1162, 917, 732; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.49 (m, 4H), 7.41 (m, 2H), 6.97 (m, 4H), 5.03 (m, 8H), 4.40–4.19 (m, 4H), 3.48–3.33 (m, 12H), 3.20 (s, 4H), 2.20–2.16 (m, 4H), 1.92–1.81 (m, 12H), 1.43 (s, 14H), 1.30–1.27 (m, 46H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ. 173.2, 173.0, 154.6, 154.0, 143.3, 143.1, 135.2, 135.1,

134.9, 132.6, 128.6, 128.4, 128.1, 127.9, 127.8, 125.1, 125.0, 80.1, 64.8, 59.5, 59.4, 52.7, 47.0, 46.7, 31.2, 30.3, 28.5, 28.4, 28.2, 24.8, 24.5, 24.4, 23.9; HRMS (ES) *m*/*e* calcd for $C_{82}H_{116}N_6O_{16}Na$ (MNa^+) 1463.8346, found 1463.8356.

2,6-Bis(Boc-L-proline-carboxylmethylene))bromobenzene (22). By the same procedure as **34**, diol **25** (543 mg, 2.5 mmol), Boc-L-proline (1098 mg, 5.1 mmol), DMAP (23 mg) and DCC (1057 mg, 5.1 mmol) in THF (20 mL) at -10 ℃ for 5.5 h, 0 ℃ for 0.5 h and rt for 1 h gave **22** (1.35 g, 89%) as a white solid: IR (cm^{-1}) 2976, 1751, 1700, 1398, 1161; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 3H), 5.31 (m, 4H), 4.38 (m, 2H), 3.53–3.47 (m, 4H), 2.21–2.02 (m, 2H), 2.02–1.89 (m, 6H), 1.44 (s, 8H), 1.35 (s, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 172.8, 154.6, 154.0, 136.3, 136.1, 135.8, 129.8, 129.6, 127.7, 124.5, 80.2, 80.1, 77.4, 66.5, 59.4, 59.1, 46.8, 46.5, 31.2, 30.2, 28.6, 28.5, 24.6, 23.8; HRMS (ES) *m*/*e* calcd for $C_{28}H_{39}N_2O_8NaBr$ (MNa^+) 633.1787, found 633.1799.

General procedure for the Suzuki Coupling.[60] A solution of $Pd(PPh_3)_4$ (31 mg, 0.027 mmol), bromobenzene (0.54 mmol), pinacolatoboronylbenzene (0.60 mmol) in DME (3 mL) in a 10 mL microwave tube was degassed in an dry ice-acetone bath and warmed to rt. A solution of $NaHCO_3$ (151 mg, 1.8 mmol) in H_2O (2 mL) was added, and the mixture was degassed again in the dry ice-acetone bath and irradiated in a microwave reactor at 140 ℃, 250 W for 20 min. After being cooled to rt, the mixture was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 8/1).

***N*-(4-(2,6-Bishydroxylmethyl)phenyl-2,6-diisopropylphenyl)ethane-1,2-diamine (33).** By the general procedure, after irradiation in a microwave reactor at 140 ℃, 250 W for 20 min, diamine **30** (190 mg, 0.3 mmol), $Pd(PPh_3)_4$ (31 mg, 0.027 mmol), bromobenzene **31** (240 mg,

0.54 mmol) and $NaHCO_3$ (151 mg, 1.8 mmol) provided a crude product. The crude product was added a solution of TBAF (640 mg, 2.03 mmol) in THF (3 mL), and the mixture was stirred at rt for 2 h. The solvent was evaporated under reduced pressure, and the residue was washed with Et_2O and dissolved in EtOAc. The solution was washed with H_2O and brine, dried over $MgSO_4$ and filtered. Removal of volatile components from the filtrate afforded **33** (150 mg, 85%) as a white solid: IR (cm^{-1}) 3319, 2961, 1461, 1443, 1063, 731; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.51 (m, 4H), 7.44 (m, 2H), 6.97 (s, 4H), 4.41 (s, 8H), 3.53 (heptet, *J* = 6.9 Hz, 4H), 3.26 (s, 4H), 1.26 (d, *J* = 7.2 Hz, 24H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 143.3, 142.9, 140.7, 139.9, 133.3, 127.9, 126.9, 124.8, 63.6, 52.6, 28.1, 24.4; HRMS (EI) *m*/*e* calcd for $C_{42}H_{56}N_2O_4$ (M^+) 652.4240, found 652.4266.

***N*-(4-(2,6-Bismethyl)phenyl-2,6-diisopropylphenyl)ethane-1,2-diamine (38).** By the general procedure, after irradiation in a microwave reactor at 140 ℃, 250 W for 20 min, *N*-(4-diamine **30** (44 mg, 0.070 mmol), $Pd(PPh_3)_4$ (7 mg, 0.006 mmol), 2,6-dimethylbromobenzene (22 mg, 0.119 mmol) and $NaHCO_3$ (30 mg, 0.36 mmol) gave **38** (35 mg, 99%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (m, 6H), 6.89 (s, 4H), 3.69 (heptet, *J* = 6.9 Hz, 4H), 3.50 (s, 4H), 1.98 (s, 12H), 1.26 (d, *J* = 6.6 Hz, 24H).

***N*-(4-(2,6-Bismethoxymethyl)phenyl-2,6-diisopropylphenyl)ethane-1,2-diamine (39).** By the general procedure, after irradiation in a microwave reactor at 140 ℃, 250 W for 20 min, diamine **30** (63 mg, 0.099 mmol), bromobenzene **37** (43.5 mg, 0.178 mmol), $NaHCO_3$ (49.6 mg, 0.59 mmol) and $Pd(PPh_3)_4$ (10.2 mg, 0.0089 mmol) afforded **39** (60 mg, 95%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 4H), 7.44 (m, 2H), 6.97 (s, 4H), 4.41 (s, 8H), 3.53 (heptet, *J* = 6.9 Hz, 4H), 3.26 (s, 4H), 1.26 (d, *J* = 7.2 Hz, 24H).

***N*-(4-(2,6-Bis(((*S*)-1-phenylethoxy)methyl)phenyl)-2,6-diisopropyl-phenyl)ethane-1,2-diamine (44).** By the general procedure, after irradiation in a microwave reactor at 140 ℃, 250 W for 22 min, diamine **30** (260 mg, 0.41 mmol), $Pd(PPh_3)_4$ (48 mg, 0.041 mmol), bromobenzene **43** (350 mg, 0.82 mmol) and $NaHCO_3$ (207 mg, 2.47 mmol) provided **44** (298 mg, 67%) as a white solid: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.47–7.15 (m, 26H), 6.85 (s, 4H), 4.33 (q, *J* = 6.4 Hz, 4H), 4.15 (d, *J* = 11.6 Hz, 2H), 4.04 (d, *J* = 11.6 Hz, 2H), 3.46 (heptet, *J* = 6.9 Hz, 4H), 3.23 (s, 4H), 1.34 (d, *J* = 6.4 Hz, 12H), 1.19 (d, *J* = 2.4 Hz, 12H), 1.16 (d, *J* = 2.4 Hz, 12H).

***N*-(4-(2,6-Bis(2-(1*S*,2*S*,5*S*)-myrtylethyl))phenyl-2,6-diisopropylphenyl)ethane-1,2–diamine (47).** By the general procedure, after irradiation in a microwave reactor at 140 ℃, 250 W for 30 min, diamine **30** (329 mg, 0.52 mmol), $Pd(PPh_3)_4$ (48 mg, 0.041 mmol), 2,6-bis(2-(1*S*,2*S*,5*S*)-myrtyl-ethyl)phenyl bromide **46** (458 mg, 1.0 mmol) and $NaHCO_3$ (262 mg, 3.12 mmol) afforded **47** (450 mg, 80%) as a white solid: $[\alpha]^{20}_D$ +3.83 (*c* 73, $CHCl_3$); IR (cm^{-1}) 2959, 2927, 2865, 1459, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.16 (m, 2H), 7.10 (d, *J* = 6.9 Hz, 4H), 6.93 (s, 4H), 3.50 (heptet, *J* = 6.8 Hz, 4H), 3.23 (s, 4H), 2.45–2.26 (m, 8H), 1.91–1.84 (m, 4H), 1.80–1.58 (m, 16H), 1.53–1.40 (m, 10H), 1.29 (dd, *J* = 6.7, 2.2 Hz, 24H), 1.23–1.20 (m, 8H), 1.13 (s, 12H), 0.98–0.83 (m, 8H), 0.73 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 141.7, 141.5, 135.1, 127.0, 126.6, 125.2, 52.8, 45.9, 40.9, 39.3, 38.8, 34.9, 32.1, 27.8, 26.8, 24.5, 23.5, 22.0, 20.1; HRMS (ES) *m*/*e* calcd for $C_{82}H_{121}N_2$ (MH^+) 1133.9530, found 1133.9510.

2,6-Bis(methoxymethyl)bromobenzene (37).[86] A solution of diol **25** (87 mg, 0.4 mmol), 60% NaH in mineral oil (48 mg, 1.2 mmol) in THF (2 mL) was stirred at rt for 1 h. MeI (60 μL, 0.96 mmol) was added, and the mixture was stirred at rt for 14 h. H_2O (0.5 mL) was added, and the mixture was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$

and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 20/1) to provide **37** (90 mg, 92%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.28 (m, 3H), 4.53 (s, 4H), 3.45 (s, 6H).

(*S*)-1-Phenylethanol (41).[87] To a suspension of $LiAlH_4$ (0.7 g, 18.3 mmol) in THF (25 mL) at 0 ℃ was added a solution of (*R*)-styrene oxide (2.0 g, 16.6 mmol) in THF (25 mL) slowly, and the mixture was stirred at rt for 1.5 h and cooled in an ice bath. H_2O (10 mL) was added, followed by HCl (3 M, 25 mL) slowly, and the resulting mixture was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. Removal of volatile components from the filtrate afforded **41** (2.0 g, 99%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.11 (m, 5H), 5.92 (m, 1H), 1.50 (d, *J* = 7.2 Hz, 3H).

2,6-Bis(bromomethyl)bromobenzene (42).[88] A solution of 2,6-dimethylbromobenzene (200 mg, 1.08 mmol), NBS (424 mg, 2.38 mmol) in MeOAc (5.4 mL) was irradiated to reflux by an incandescent light for 18 h. The solvent was evaporated under reduced pressure, and the residue was washed with hot hexanes. The hexanes solution was concentrated to 10 mL and put in an ice-acetone bath. The resulting white crystalline precipitate was filtered and washed with cold hexanes. Further purification of the crude crystalline product by flash chromatography (SiO_2, hexanes/EtOAc = 20/1) provided **42** (230 mg, 63%) as a white solid: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.45 (m, 2H), 7.34 (m, 1H), 4.67 (s, 4H).

2,6-Bis(((S)-1-phenylethoxy)methyl)bromobenzene (43). To a suspension of 60% NaH in mineral oil (196 mg, 4.9 mmol) in THF (10 mL) at 0 ℃ was added a solution of (*S*)-1-phenylethanol **41** (287 mg, 2.34 mmol) in THF (5 mL) dropwise, and the mixture was stirred at rt for 25 min and cooled in an ice bath. To this solution was added a solution of benzylbromide **42** (365 mg, 1.07 mmol) and Bu_4I (10 mg) in THF (10 mL) which was previously stirred at rt for

50 min, and the resulting mixture was stirred at rt for 30 min, 70 ℃ for 16 h and cooled to rt. Saturated aqueous NH_4Cl solution (1.5 mL) was added, followed by H_2O (20 mL), and the mixture was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexane/EtOAc = 20/1) to give **43** (368 mg, 81%) as a white solid: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.37–7.20 (m, 13H), 4.60 (q, *J* = 6.5 Hz, 2H), 4.37 (s, 4H), 1.50 (d, *J* = 6.5 Hz, 6H).

2-(2,6-Dimethyl)phenyl-iodobenzene (50). To flame dried Mg (510 mg, 21 mmol) was added THF (35 mL), followed by 2,6-dimethylbromobenzene (1.47 mL, 11 mmol) and 1,2-dibromoethane (10 μL), and the mixture was stirred at 40 ℃ for 1 h. A solution of 2-bromo-iodobenzene (1.29 mL, 10 mmol) in THF (15 mL) was added over 5 h, and the mixture was stirred for 1 h. After being cooled in an ice bath, I_2 (3810 mg, 15 mmol) was added, and the mixture was warmed to rt for 1 h. Aqueous $Na_2S_2O_3$ solution was added to consume unreacted I_2, and the resulting colorless mixture was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes) to provide **50** (2.30 g, 75%) as a white solid: IR (cm^{-1}) 3046, 2940, 2914, 2852, 1581, 1555, 1460, 1377, 1013, 1000, 778, 762; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.01 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.26–7.06 (m, 4H), 1.99 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 139.5, 136.0, 130.0, 129.0, 128.9, 128.1, 127.6, 20.5; HRMS (EI) *m*/*e* calcd for $C_{14}H_{13}I$ (M^+) 308.0062, found 308.0073.

General Procedure for the Buchwald–Hartwig Coupling of Bromobenzenes with (1*R*,2*R*)-1,2-Diphenylethane-1,2-diamine. A solution of BINAP (622 mg, 1 mmol) in toluene (80 mL) was degassed in a dry ice-acetone bath, back filled with nitrogen and stirred at 80 ℃

until BINAP was dissolved. After being cooled to rt, a solution of $Pd(OAc)_2$ (112 mg, 0.5 mmol) in toluene (10 mL) was added, and the resulting mixture was stirred for 10 min. A solution of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (1061 mg, 5 mmol) and iodobenzenes or bromobenzenes (10 mmol) in toluene (30 mL) was added, followed by NaO*t*-Bu (1920 mg, 20 mmol), and the resulting mixture was degassed in a dry ice-acetone bath, back filled with nitrogen and stirred at 110 ℃. After the reaction was over (as determined by TLC), hexanes (400 mL) was added, and the resulting mixture was purified by flash chromatography (SiO_2, hexanes/EtOAc = 1/1).

***N*1-(2-(2,6-Dimethyl)phenylphenyl)-*N*1-*N*2-(1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (51).** By the general procedure, BINAP (5.6 mg, 0.009 mmol), $Pd(OAc)_2$ (1 mg, 0.0045 mmol), (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (31.8 mg, 0.15 mmol), iodobenzene **50** (46.2 mg, 0.15 mmol) and NaO*t*-Bu (29 mg, 0.3 mmol) in toluene (2.7 mL) at 150 ℃ for 4.5 h gave **51** (28 mg, 48%) as an oil after chromatography (SiO_2, hexanes/EtOAc = 5/1): ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.34–7.20 (m, 11H), 7.11 (dd, *J* = 5.1, 2.0 Hz, 2H), 6.97 (td, *J* = 8.1, 1.6 Hz, 1H), 6.82 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.63 (td, *J* = 7.4, 1.1 Hz, 1H), 6.20 (d, *J* = 8.1 Hz, 1H), 4.65 (d, *J* = 5.6 Hz, 1H), 4.44 (dd, *J* = 5.8, 3.6 Hz, 1H), 4.24 (d, *J* = 3.5 Hz, 1H), 2.13 (s, 3H), 1.64 (s, 3H); LRMS (API-ES) (MH^+) 393.

***N*1-(2-(2,6-Dimethyl)phenylphenyl)-*N*2-2,6-dimethyl)phenyl-*N*1-*N*2-(1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (52).** By the general procedure, BINAP (6.2 mg, 0.01 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), 2,6-dimethylbromobenzene (18.7 mg, 0.1 mmol), diamine **51** (20 mg, 0.05 mmol) and NaO*t*-Bu (10 mg, 0.1 mmol) in toluene (2.0 mL) at 120 ℃ for 13 h afforded **52** (20 mg, 81%) as an oil after flash chromatography (SiO_2, hexanes/EtOAc = 20/1): ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.21–6.72 (m, 18H), 6.64 (t, *J* = 7.4 Hz, 1H), 4.95 (d, *J* = 0.3 Hz,

1H), 4.74 (dd, *J* = 7.5, 3.0 Hz, 1H), 4.40 (d, *J* = 6.0 Hz, 1H), 3.55 (s, 1H), 2.09 (s, 3H), 1.96 (s, 3H), 1.88 (s, 6H).

***N*-(2-Benzylphenyl)-*N*-(1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (49c).** By the general procedure, BINAP (144 mg, 0.23 mmol), $Pd(OAc)_2$ (26 mg, 0.115 mmol), 2-benzylbromobenzene (1000 mg, 4.0 mmol), (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (409 mg, 1.93 mmol) and NaO*t*-Bu (556 mg, 5.79 mmol) in toluene (60 mL) at 110 ℃ for 18 h gave **49c** (950 mg, 91%) as an oil after flash chromatography: $[\alpha]^{23}_D$ +157 (*c* 2.65, CH_2Cl_2); IR (cm^{-1}) 3400, 3026, 2906, 1603, 1585, 1506, 1452, 1310, 1267, 908, 732; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.17 (m, 6H), 7.11–6.97 (m, 12H), 6.95 (t, *J* = 7.8 Hz, 2H), 6.78 (d, *J* = 7.8 Hz, 4H), 6.65 (t, *J* = 7.2 Hz, 2H), 6.29 (d, *J* = 8.1 Hz, 2H), 4.52 (S, 2H), 4.25 (br, 2H), 3.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 139.6, 139.4, 131.4, 130.8, 130.2, 129.7, 129.3, 129.2, 129.0, 128.8, 128.7, 128.5, 128.4, 128.3, 127.7, 127.5, 127.3, 126.8, 126.6, 126.1, 125.9, 125.7, 122.4, 117.7, 112.5, 63.0, 38.3; HRMS (EI) *m*/*e* calcd for $C_{40}H_{37}N_2$ (MH^+) 545.2957, found 545.2934.

***N*-(2-Methyl-3-phenylphenyl)-*N*-(1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (49h).** By the general procedure, BINAP (27.4 mg, 0.044 mmol), $Pd(OAc)_2$ (5.0 mg, 0.022 mmol), (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (93.5 mg, 0.44 mmol), 2-methyl-3-phenyl-bromobenzene (229 mg, 0.926 mmol) and NaO*t*-Bu (127 mg, 1.32 mmol) in toluene (10 mL) at 110 ℃ for 4 h gave **49h** (223 mg, 93%) as a white solid after flash chromatography (SiO_2, hexanes/EtOAc = 10/1): $[\alpha]^{23}_D$ +170 (*c* 1.0, CH_2Cl_2); IR (cm^{-1}) 3415, 3027, 1583, 1467, 760; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.23 (m, 20H), 6.95 (t, *J* = 8.1 Hz, 2H), 6.61 (d, *J* = 7.2 Hz, 2H), 6.32 (d, *J* = 8.1 Hz, 2H), 4.76 (s, 2H), 4.61 (br, 2H); 2.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 142.5, 142.4, 140.0, 129.4, 128.7, 127.9, 127.7, 127.2 , 126.6, 125.9, 120.3, 119.7, 110.8, 64.2, 14.4; HRMS (ES) *m*/*e* calcd for $C_{40}H_{37}N_2$ (MH^+) 545.2957, found 545.2955.

***N*-(2,3,4-Trimethoxyphenyl)-*N*-(1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (49i).** By the general procedure, BINAP (62.2 mg, 0.1 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), 2,3,4-trimethoxybromobenzene[89] (519 mg, 2.1 mmol), (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (212 mg, 1.0 mmol) and NaO*t*-Bu (288 mg, 3.0 mmol) in toluene (10 mL) at 115 ℃ for 5 h gave **49i** (123 mg, 23%) as a pale yellow solid after flash chromatography: $[\alpha]^{23}_{D}$ +96 (*c* 0.85, CH_2Cl_2); IR (cm^{-1}) 3380, 2936, 1497, 1269, 1094; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.17 (m, 10H), 6.35 (d, *J* = 9.0 Hz, 2H), 5.96 (d, *J* = 9.0 Hz, 2H), 4.97 (s, 2H), 4.52 (s, 2H), 3.85 (s, 6H), 3.73 (s, 6H), 3.68 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 142.8, 141.5, 140.6, 135.8, 128.6, 128.3, 127.6, 127.4, 107.8, 106.5, 64.6, 61.0, 60.6, 56.6; HRMS (EI) *m*/*e* calcd for $C_{32}H_{36}N_2O_6$ (M^+) 544.2573, found 544.2571.

General Procedure for the Cyclization of Diamines to Imidazolinium Salts. A mixture of $CH(OEt)_3$ (5 mL, 30 mmol), NH_4BF_4 (189 mg, 1.8 mmol) and the diamine (1.5 mmol) was stirred at 125 ℃. After the reaction was over (as determined by TLC), the crude product was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOH = 20/1).

***N*,*N*-(4-(2,6-Bis(Boc-L-proline carboxylmethylene))phenyl-2,6-diisopropylphenyl) imidazolinium tetrafluoroborate (21).** By the general procedure, diamine **34** (500 mg, 0.35 mmol), $CH(OEt)_3$ (2.0 mL, 10.4 mmol) and NH_4BF_4 (37 mg, 0.35 mmol) at 125 °C for 1.5 h afforded **21** (410 mg, 77%) as a white solid: IR (cm^{-1}) 2972, 2879, 2253, 1747, 1695, 1629, 1453, 1400, 1367, 1301, 1265, 1162, 915, 771, 731; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.94–8.81 (m, 1H), 7.62–7.52 (m, 2H), 7.52–7.40 (m, 4H), 7.37–7.22 (m, 4H), 5.22–4.78 (m, 8H), 4.78–4.58 (m, 4H), 4.32–3.78 (m, 4H), 3.50–2.95 (m, 12H), 2.28–1.76 (m, 16H), 1.51–1.13 (m, 60H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 173.1, 173.0, 172.6, 172.0, 171.5, 159.8, 159.5, 154.8, 154.7, 154.5, 153.8, 147.0, 146.8, 146.6, 146.4, 141.4, 141.2, 140.4, 140.0, 139.6, 135.1, 134.8, 134.4,

134.2, 134.0, 130.2, 129.8, 129.7, 129.4, 129.2, 128.7, 127.3, 127.1, 126.0, 125.3, 79.8, 79.6, 72.1, 66.1, 65.4, 64.3, 59.4, 59.3, 58.9, 58.8, 58.4, 54.7, 46.9, 46.7, 31.2, 30.2, 29.9, 29.7, 28.4, 28.3, 25.5, 25.1, 24.7, 24.3, 24.0, 23.8; HRMS (ES) *m*/*e* calcd for $C_{83}H_{115}N_6O_{16}$ ($M^+BF_4^-$) 1451.8370, found 1451.8365.

***N*,*N*-(4-Pinacolatoboronyl-2,6-diisopropylphenyl)imidazolinium tetrafluoroborate (26).** By the general procedure, diamine **30** (127 mg, 0.2 mmol), $CH(OEt)_3$ (1 mL, 6 mmol) and NH_4BF_4 (27 mg, 0.26 mmol) at 125 ℃ for 0.5 h provided **26** (126 mg, 85%) as a white solid after washing with hexanes: IR (cm^{-1}) 2969, 1628, 1597, 1373, 1321, 1265, 1148, 1058, 724; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.91 (s, 1H), 7.71 (s, 4H), 4.56 (s, 4H), 3.03 (heptet, *J* = 6.9 Hz, 4H), 1.43 (d, *J* = 6.9 Hz, 12H), 1.35 (s, 24H), 1.28 (d, *J* = 6.6 Hz, 12H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 158.4, 146.6, 131.8, 131.6, 84.8, 54.5, 29.6, 25.2, 25.1, 24.0; HRMS (ES) *m*/*e* calcd for $C_{39}H_{61}N_2O_4B_2$ ($M^+BF_4^-$) 643.4817, found 643.4777.

***N*,*N*-(4-(2,6-Bismethyl)phenyl-2,6-diisopropylphenyl)imidazolinium tetrafluoroborate (35).** By the general procedure, diamine **38** (18 mg, 0.031 mmol), $CH(OEt)_3$ (0.2 mL, 0.92 mmol) and NH_4BF_4 (3.2 mg, 0.031 mmol) at 125 ℃ for 1 h afforded **35** as a white solid after washing with hexanes: ^1H NMR (300 MHz, CD_2Cl_2) δ 7.94 (s, 1H), 7.22–7.11 (m, 10H), 4.71 (s, 4H), 3.12 (heptet, *J* = 6.8 Hz, 4H), 2.06 (s, 6H), 1.99 (s, 6H), 1.44 (d, *J* = 6.8 Hz, 12H), 1.31 (d, *J* = 6.8 Hz, 12H).

***N*,*N*-(4-(2,6-Bismethoxymethyl)phenyl-2,6-diisopropylphenyl)imidazolinium tetrafluoroborate (36).** By the general procedure, diamine **39** (58 mg, 0.082 mmol), $CH(OEt)_3$ (0.4 mL, 2.4 mmol) and NH_4BF_4 (9.5 mg, 0.09 mmol) at 125 ℃ for 1 h afforded **36** (30 mg, 50%) as a white solid after washing with Et_2O: IR (cm^{-1}) 3048, 2966, 2928, 2823, 1630, 1449, 1264, 1194, 1095, 1061, 729; ^1H NMR (300 MHz, CD_2Cl_2) δ 8.15 (s, 1H), 7.53–7.40 (m, 6H),

7.22 (s, 4H), 4.71 (s, 4H), 4.08 (s, 4H), 4.02 (s, *4*H), 3.24 (s, 6H), 3.20 (s, 6H), 3.13 (heptet, *J* = 6.6 Hz, 4H), 1.49 (d, *J* = 6.6 Hz, 12H), 1.37 (d, *J* = 6.9 Hz, 12H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 158.4, 145.7, 141.8, 140.0, 136.4, 136.2, 128.3, 128.2, 128.0, 127.9, 126.7, 72.5, 72.4, 58.2, 58.0, 54.5, 29.3, 24.9, 23.6; HRMS (ES) *m*/*e* calcd for $C_{47}H_{63}N_2O_4$ ($M^+BF_4^-$) 719.4788, found 719.4725.

***N*,*N*-(4-(2,6-Bis(((*S*)-1-phenylethoxy)methyl)phenyl)-2,6-diisopropylphenyl)imidazolinium tetrafluoroborate (40).** By the general procedure, diamine **44** (270 mg, 0.25 mmol), $CH(OEt)_3$ (1.3 mL, 7.6 mmol) and NH_4BF_4 (32 mg, 0.3 mmol) at 125 ℃ for 1.75 h afforded **40** (200 mg, 68%) as a white solid: IR (cm^{-1}) 3031, 2969, 2929, 2871, 1629, 1452, 1264, 1093, 911, 762, 732; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.84 (s, 1H), 7.53–7.42 (m, 6H), 7.36–7.20 (m, 20H), 7.15 (s, 4H), 4.73 (s, 4H), 4.42 (heptet, *J* = 6.6 Hz, 4H), 4.13–3.97 (m, 8H), 3.07–3.01 (m, 4H), 1.42–1.32 (m, 24H), 1.23–1.20 (m, 12H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 158.4, 146.2, 144.3, 144.0, 142.2, 139.6, 137.0, 136.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.8, 127.6, 126.9, 126.7, 126.5, 126.4, 78.0, 77.6, 68.5, 68.4, 54.9, 29.5, 25.2, 25.1, 24.3, 24.2, 24.0, 23.9; HRMS (ES) *m*/*e* calcd for $C_{75}H_{87}N_2O_4$ ($M^+BF_4^-$) 1079.6666, found 1079.6709.

***N*,*N*-(2-Phenylphenyl)-(4*R*,5*R*)-4,5-diphenylimidazolinium tetrafluoroborate (48b).**[90] By the general procedure, diamine **49b**[91] (826 mg, 1.6 mmol), $CH(OEt)_3$ (2.4 mL, 14.4 mmol) and NH_4BF_4 (202 mg, 1.92 mmol) at 120 ℃ for 5 h afforded **48b** (396 mg, 41%) as a white solid after flash chromatography and recrystallization from DME and CH_2Cl_2: mp 245–267 ℃.

***N*,*N*-(2-Benzylphenyl)-(4*R*,5*R*)-4,5-diphenylimidazolinium tetrafluoroborate (48c).** By the general procedure, **49c** (816 mg, 1.5 mmol), $CH(OEt)_3$ (5.0 mL, 30.0 mmol) and NH_4BF_4 (189 mg, 1.8 mmol) at 120 ℃ for 5 h provided **48c** (802 mg, 84%) as a white solid after flash

chromatography and recrystallization from EtOAc and CH_2Cl_2: mp 184–186 °C; $[\alpha]^{23}_D$ +290 (*c* 2.5, CH_2Cl_2);. IR (cm^{-1}) 3063, 1616, 1059, 762; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.99 (s, 1H), 7.47–7.38 (m, 8H), 7.36–7.29 (m, 8H), 7.27–7.16 (m, 8H), 7.08–7.04 (m, 4H), 5.71 (s, 2H), 4.06 (s, 4H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 157.7, 139.2, 136.3, 133.1, 133.0, 132.8, 130.7, 129.9, 129.4, 128.8, 128.7, 128.6, 128.5, 127.3, 76.1, 37.8; HRMS (ES) *m*/*e* calcd for $C_{41}H_{35}N_2$ ($M^+BF_4^-$) 555.2800, found 555.2789.

***N*,*N*-(2-Cyclohexylphenyl)-(4*R*,5*R*)-4,5-diphenylimidazolinium tetrafluoroborate (48d).**[27d] By the general procedure, diamine **49d**[27d] (678 mg, 1.28 mmol), $CH(OEt)_3$ (4.3 mL, 25.6 mmol) and NH_4BF_4 (162 mg, 1.54 mmol) at 120 °C for 5 h afforded **48d** (580 mg, 72%) as a white solid after flash chromatography and recrystallization from dioxane: mp 118–138 °C.

***N*,*N*-(2-Methyl-3-phenylphenyl)-(4*R*,5*R*)-4,5-diphenylimidazolinium tetrafluoroborate (48h).** By the general procedure, **49h** (218 mg, 0.4 mmol), $CH(OEt)_3$ (1.4 mL, 8 mmol) and NH_4BF_4 (42 mg, 0.4 mmol) at 125 °C for 3 h gave **48h** (201 mg, 79%) as a hard foam after flash chromatography: $[\alpha]^{23}_D$ +237 (*c* 1.24, CH_2Cl_2); IR (cm^{-1}) 3061, 1616, 1058, 762; ^1H NMR (300 MHz, CD_2Cl_2) δ 8.77 (s, 1H), 7.49–7.36 (m, 18H), 7.30–7.24 (m, 8H), 5.91 (s, 2H), 2.35 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 158.2, 145.1, 140.6, 133.8, 133.7, 132.0, 130.9, 130.1, 129.5, 128.7, 127.9, 127.3, 126.6, 76.5, 16.7; HRMS (ES) *m*/*e* calcd for $C_{41}H_{35}N_2$ ($M^+BF_4^-$) 555.2800, found 555.2803.

***N*,*N*-2,3,4-Trimethoxyphenyl-(4*R*,5*R*)-4,5-diphenylimidazolinium tetrafluoroborate (48i).** By the general procedure, **49i** (100 mg, 0.184 mmol), $CH(OEt)_3$ (0.77 mL, 4.6 mmol) and NH_4BF_4 (21 mg, 0.2 mmol) at 125 °C for 3 h gave **48i** (81 mg, 69%) as a hard foam after flash chromatography: $[\alpha]^{23}_D$ +286 (*c* 1.5, CH_2Cl_2); IR (cm^{-1}) 2943, 1620, 1493, 1271, 1057; 1H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.45–7.37 (m, 10H), 7.09 (d, J = 9.0 Hz, 2H), 6.57 (d, J = 9.0

Hz, 2H), 5.74 (s, 2H), 4.08 (s, 6H), 3.84 (s, 6H), 3.79 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 155.0, 148.3, 142.0, 135.5, 130.2, 129.8, 127.9, 122.0, 120.1, 107.2, 75.8, 61.9, 61.2, 56.2; HRMS (ES) m/e calcd for $C_{33}H_{35}N_2O_6$ ($M^+BF_4^-$) 555.2495, found 555.2499.

***N*,*N*-2-(2,4-Dimethylpentan-3-yl)phenyl-(4*R*,5*R*)-4,5-diphenylimidazolinium tetrafluoroborate (48j).** By the general procedure, **49j** (220 mg, 0.392 mmol), $CH(OEt)_3$ (2 mL, 11.76 mmol), NH_4BF_4 (42 mg, 0.4 mmol) and 1 drop of HCOOH at 125 ℃ for 3 h provided **48j** (118 mg, 46%) as a white solid with some impurity after flash chromatography which is difficult to be purified: $[\alpha]^{23}_D$ +214 (*c* 2.8, CH_2Cl_2); IR (cm^{-1}) 2964, 1615, 1058, 758; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.50–7.38 (m, 10H), 7.36 (d, *J* = 7.5 Hz, 4H), 7.28–7.20 (m, 4H), 5.61 (s, 2H), 2.59 (dd, *J* = 9.0, 5.4 Hz, 2H), 2.38–2.27 (m, 2H), 2.23–2.12 (m, 2H), 1.04 (d, *J* = 6.6 Hz, 6H), 0.96 (d, *J* = 6.6 Hz, 6H), 0.77 (d, *J* = 6.9 Hz, 6H), 0.75 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 139.6, 134.8, 133.2, 131.0, 130.5, 130.2, 130.1, 129.5, 128.0, 127.6, 78.1, 52.1, 30.2, 30.0, 22.3, 21.6, 18.0; HRMS (ES) *m*/*e* calcd for $C_{41}H_{51}N_2$ ($M^+BF_4^-$) 571.4052, found 571.4011.

1,3-Bis((*R*)-1-(3-methylbutan-2-yl)phenyl)imidazolinium tetrafluoroborate (56). By the general procedure, diamine **67** (150 mg, 0.425 mmol), $CH(OEt)_3$ (2.1 mL, 12.75 mmol) and NH_4BF_4 (49 mg, 0.468 mmol) at 125 ℃ for 4 h gave **56** (159 mg, 83%) as a pale yellow foam after flash chromatography: $[\alpha]^{23}_D$ -106 (*c* 7.7, CH_2Cl_2); IR (cm^{-1}) 3064, 2964, 2874, 2360, 1638, 1489, 1266, 1038, 766, 734; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.8, 0.9 Hz, 2H), 7.65 (s, 1H), 7.46–7.7.41 (m, 2H), 7.35–7.32 (m, 2H), 7.29–7.23 (m, 2H), 4.66–4.47 (m, 4H), 2.55–2.45 (m, 2H), 1.89–1.80 (m, 2H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.09 (d, *J* = 6.6 Hz, 6H), 0.73 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 144.1, 133.4, 131.0, 128.0, 127.9, 127.7, 54.2,

41.2, 34.6, 22.1, 20.6, 20.5; HRMS (ES) *m*/*e* calcd for $C_{25}H_{35}N_2$ ($M^+BF_4^-$) 363.2800, found 363.2836.

1-((*S*)-(2-(3-Methylbutan-2-yl)phenyl)-3-phenylimidazolinium tetrafluoroborate (57). By the general procedure, diamine **69** (126 mg, 0.447 mmol), $CH(OEt)_3$ (2.3 mL, 13.41 mmol) and NH_4BF_4 (51.6 mg, 0.492 mmol) at 125 ℃ for 2 h gave **57** (134 mg, 79%) as a crystal after flash chromatography and recrystallization with EtOAc: mp 174–176 ℃; $[\alpha]^{23}_D$ +62 (*c* 1.1, CH_2Cl_2); IR (cm^{-1}) 3069, 2962, 2360, 2340, 1061, 753; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.63 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.47–7.22 (m, 8H), 4.71–4.64 (m, 2H), 4.54–4.35 (m, 2H), 2.48–2.39 (m, 1H), 1.86–1.74 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 144.2, 135.6, 133.7, 131.3, 130.4, 128.4, 128.1, 127.9, 127.8, 119.6, 77.4, 54.2, 50.0, 41.2, 34.7, 22.1, 20.5; HRMS (ES) *m*/*e* calcd for $C_{20}H_{25}N_2$ ($M^+BF_4^-$) 293.2018, found 293.2038.

***N*,*N*-(4-Boronic acidic-2,6-diisopropylphenyl)-imidazolinium tetrafluoroborate (32).** A solution of $NaIO_4$ (205 mg, 0.96 mmol), imidazolinium salt **26** (117 mg, 0.16 mmol) and NH_4OAc (55 mg, 0.70 mmol) in acetone (6.4 mL) and H_2O (6.4 mL) was stirred at rt for 19 h. Acetone was evaporated under reduced pressure, and the residue was added CH_2Cl_2 (10 mL). The resulting precipitate was filtered, washed with H_2O and CH_2Cl_2 to afford **32** (90 mg, 99%) as a white solid: IR (cm^{-1}) 3405, 2964, 1618, 1590, 1368, 846; ^1H NMR (300 MHz, DMSO) δ 9.40 (s, 1H), 8.30 (s, 4H), 7.80 (s, 4H), 4.52 (s, 4H), 3.08 (heptet, *J* = 6.6 Hz, 4H), 1.36 (d, *J* = 6.6 Hz, 12H), 1.19 (d, *J* = 6.6 Hz, 12H); ^{13}C NMR (75 MHz, MeOD) 145.9, 131.0, 72.7, 59.1, 55.0, 30.2, 25.6, 24.1; HRMS (ES) *m*/*e* calcd for $C_{27}H_{41}B_2N_2O_4$ ($M^+BF_4^-$) 479.3252, found 479.3206.

2-(2,4-Dimethylpent-2-en-3-yl)iodobenzene (55). To a solution of 3-(2-iodophenyl)-2,4-dimethylpentan-3-ol[9] (1.59 g, 5 mmol) in CH_2Cl_2 (5 mL) was added $BF_3{\cdot}Et_2O$ (0.63 mL, 5.02 mmol) dropwise at 0 ℃, and the mixture was stirred at rt for 10 min. After removal of volatile components from the mixture, the resulting crude product was purified by flash chromatography (SiO_2, hexanes) to provide **55** (1.44 g, 96%) as a colorless liquid: IR (cm^{-1}) 2961, 2928, 1461, 1012, 754; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.28 (td, *J* = 7.5, 1.2 Hz, 1H), 7.01 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.91 (td, *J* = 7.8, 1.8 Hz, 1H), 3.06 (heptet, *J* = 6.9 Hz, 1H), 1.82 (S, 3H), 1.35 (S, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 141.6, 139.0, 129.7, 128.9, 127.5, 127.4, 103.0, 30.4, 22.8, 22.4, 20.4, 19.4; HRMS (EI) *m*/*e* calcd for $C_{13}H_{17}I$ (M^+) 300.0375, found 300.0372.

2-(2,4-Dimethylpentan-3-yl)iodobenzene (53). To a solution of CF_3COOH (0.75 mL, 10 mmol), Et_3SiH (0.8 mL, 5 mmol), CF_3SO_3H (0.02 mL) in CH_2Cl_2 (2.5 mL) was added a solution of styrene **55** (750 mg, 2.5 mmol) in CH_2Cl_2 (2.5 mL) slowly at 0 ℃ for 5 min, and the mixture was stirred at rt for 1 h. After removal of volatile components from the mixture, the residue was filtered through a pad of silica gel with hexanes to give a mixture (0.74 g, 98%) of **53** (83%) and **55** (15%) as a colorless liquid which was used directly in the next step: ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.12 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.88 (td, *J* = 8.1, 1.5 Hz, 1H), 2.83 (t, *J* = 7.5 Hz, 1H), 2.17 (heptet, *J* = 6.9 Hz, 2H), 0.94 (d, *J* = 6.9 Hz, 6H), 0.78 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 128.7, 127.7, 127.6, 60.5, 30.7, 21.3, 19.5; HRMS (EI) *m*/*e* calcd for $C_{13}H_{19}I$ (M^+) 302.0532, found 302.0539.

***N*-(2-(2,4-Dimethylpentan-3-yl)phenyl)-*N*-(1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (49j).** A solution of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (255 mg, 1.2 mmol), the mixture of **53** and **55** from last step (976 mg, 2.52 mmol), NaO*t*-Bu (346 mg, 3.6 mmol), $Pd(Pt\text{-}Bu_3)_2$

(245 mg, 0.48 mmol) in toluene (24 mL) was degassed in a dry ice-acetone bath, back filled with nitrogen and stirred at 110 ℃ for 6 h. After being cooled to rt, brine (10 mL) was added, and the organic layer was separated, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (florisil, hexanes) to provide **49j** (268 mg, 40%) as a white foam with some impurity which is difficult to be purified: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.2 Hz, 4H), 7.34 (t, *J* = 7.2 Hz, 6H), 7.26–7.20 (m, 4H), 6.93 (dd, *J* = 6.9, 0.9 Hz, 2H), 6.86 (t, *J* = 6.9 Hz, 2H), 6.63 (t, *J* = 7.2 Hz, 2H), 6.18 (d, *J* = 8.1 Hz, 2H), 4.72 (s, 2H), 4.57 (s, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.24 (heptet, *J* = 6.6 Hz, 2H), 2.08 (heptet, *J* = 6.6 Hz, 2H), 1.05 (d, *J* = 6.6 Hz, 6H), 0.83 (d, *J* = 6.6 Hz, 6H), 0.81 (d, *J* = 6.6 Hz, 6H), 0.47 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 140.7, 129.1, 128.4 , 128.2, 127.8, 127.1, 126.0, 117.5, 113.1, 64.4, 50.2, 30.2, 29.9, 22.0, 21.6, 20.3, 18.6; HRMS (ES) *m*/*e* calcd for $C_{40}H_{53}N_2$ (MH^+) 561.4209, found 561.4229.

2-(2-Aminophenyl)-3-methylbutan-2-ol (61). [92] To a mixture of frame-dried magnesium turning (438 mg, 18 mmol) and THF (40 mL) was added isopropylbromide (2.77 g, 22.5 mmol), and the mixture was stirred at rt until magnesium turning was dissolved. 2-Aminophenylmethylketone (2.03 g, 15 mmol) was added slowly, and the mixture was stirred for 2 h. HCl (0.1 N, 5 mL) was added, and the resulting mixture was extracted with ethyl acetate. The extracts were combined, washed with H_2O, brine, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 2/1) to give **61** (1.18 g, 44%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06–7.02 (m, 2H), 6.69–6.61 (m, 2H), 4.68 (br, 2H), 2.05 (s, 1H), 1.53 (s, 3H), 1.28 (heptet, *J* = 7.2 Hz, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.67 (d, *J* = 6.9 Hz, 3H).

2-(3-Methylbut-2-en-2-yl)aniline (60). A solution of benzyl alcohol **61** (1.11 g, 6.17 mmol) and I_2 (18 mg, 0.07 mmol) in toluene (5 mL) was refluxed for 43 h. After being cooled to rt, Na_2SO_3 (44 mg, 0.35 mmol) was added, and the mixture was stirred for 10 min, washed with H_2O, brine, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **60** (0.76 g, 75%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 3.61 (br, 2H), 1.89 (s, 3H), 1.83 (s, 3H), 1.52 (s, 3H).

4-Methyl-*N*-(2-(3-methylbut-2-en-2-yl)phenyl)benzenesulfonamide (62). To a solution of aniline **60** (370 mg, 2.2 mmol) and *p*-tosyl chloride (504 mg, 2.64 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (668 mg, 6.6 mmol), and the mixture was stirred at rt for 30 min. Saturated aqueous NH_4Cl solution (10 mL) was added, and the mixture was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 10/1) to give **62** (390 mg, 56%) as a solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.26–7.15 (m, 3H), 7.04 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 6.62 (s, 1H), 2.36 (s, 3H), 1.80 (s, 3H), 1.53 (s, 3H), 1.32 (s, 3H).

2,2,3-Trimethyl-1-p-tosylindoline (63). To a solution of CF_3COOH (199 mg, 1.75 mmol) and Et_3SiH (203 mg, 1.75 mmol) in CH_2CH_2 (1 mL) was added a drop of CF_3SO_3H at 0 ℃, followed by a solution of amide **62** (370 mg, 1.16 mmol) in CH_2CH_2 (2 mL), and the mixture was stirred at rt for 10 min. The solvent was evaporated under reduced pressure, and the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 10/1) to give **63** (345 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.1

Hz, 1H), 7.26–7.21 (m, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 3.02 (q, *J* = 6.9 Hz, 1H), 2.38 (s, 3H), 1.64 (s, 3H), 1.39 (s, 3H), 1.16 (d, *J* = 6.9 Hz, 3H).

***N*-(2-(3-Methylbut-2-en-2-yl)phenyl)acetamide (64).** To a solution of aniline **60** (430 mg, 2.62 mmol) and Et_3N (478 mg, 4.72 mmol) in CH_2Cl_2 (10 mL) was added acetyl chloride (309 mg, 3.93 mmol) slowly, and the mixture was stirred at rt for 30 min. Saturated aqueous NH_4Cl solution (10 mL) was added, and the organic layer was separated, washed with H_2O, brine, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **64** (540 mg, 100%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.1 Hz, 1H), 7.42 (br, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 6.6 Hz, 1H), 2.23 (s, 3H), 1.91 (s, 3H), 1.89 (s, 3H), 1.49 (s, 3H).

Resolution of 2-(3-methylbutan-2-yl)benzenamine 65 and 66. To a solution of racemic 2-(3-methylbutan-2-yl)benzenamine (820 mg, 5.0 mmol), (*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (1265 mg, 5.5 mmol) and 1-hydroxybenzotriazole (HOBT) (744 mg, 5.5 mmol) in CH_2Cl_2 (45 mL) was added a solution of DCC (1139 mg, 5.5 mmol) in CH_2Cl_2 (5 mL) slowly at 0 ℃ for 30 min. After being warned to rt slowly in 30 min, the mixture was filtered. After removal of volatile components from the filtrate, the crude product was purified by flash chromatography (SiO_2, CH_2Cl_2) to give (2*S*)-2-(6-methoxynaphthalen-2-yl)-*N*-(2-(3-methylbutan-2-yl)phenyl)propanamide (1.32 g, 71%) as a white solid. This amide was recrystallized (CH_2Cl_2/hexanes = 1/5) several times (the purity was determined by the ^{1}H NMR spectroscopy) to give (*S*)-2-(6-methoxynaphthalen-2-yl)-*N*-(2-((*S*)-3-methylbutan-2-yl)phenyl) propanamide as a crystal (the configuration of the amide was determined by the X-ray

diffraction): mp 147–148 ℃; $[\alpha]^{23}_{D}$ +53 (*c* 3.76, CH_2Cl_2); IR (cm^{-1}) 3267, 2966, 1651, 1515, 1029, 764; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.72 (m, 4H), 7.46 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.20–7.11 (m, 3H), 7.09–7.02 (m, 2H), 7.00 (br, 1H), 3.95–3.88 (m, 4H), 1.81–1.74 (m, 1H), 1.73 (d, *J* = 7.2 Hz, 3H), 1.36–1.26 (m, 1H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.48 (d, *J* = 6.6 Hz, 3H), 0.33 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 158.2, 138.7, 136.3, 134.8, 134.2, 129.4, 129.3, 128.2, 127.0, 126.7, 126.5, 126.2, 125.5, 123.8, 119.7, 105.9, 55.5, 48.2, 40.2, 33.6, 21.2, 19.5, 18.1, 18.0; HRMS (ES) *m*/*e* calcd for $C_{25}H_{29}NO_2$ (MNa^+) 398.2096, found 398.2059; (*S*)-2-(6-methoxynaphthalen-2-yl)-*N*-(2-((*R*)-3-methylbutan-2-yl)phenyl)propanamide as a feather-like white solid: $[\alpha]^{23}_{D}$ +17 (*c* 1.7, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.73 (m, 4H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.21–7.11 (m, 3H), 7.08–7.04 (m, 2H), 6.97 (br, 1H), 3.97–3.90 (m, 4H), 1.89–1.76 (m, 1H), 1.75 (d, *J* = 7.2 Hz, 3H), 1.38–1.27 (m, 1H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.50 (d, *J* = 6.6 Hz, 3H), 0.30 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 158.2, 138.2, 136.1, 134.8, 134.3, 129.4, 129.3, 128.3, 127.0, 126.7, 126.6, 126.3, 125.3, 123.5, 119.7, 105.9, 55.6, 48.3, 40.2, 33.5, 21.2, 19.4, 18.0, 17.8.

A solution of (*S*)-2-(6-methoxynaphthalen-2-yl)-*N*-(2-((*R*)-3-methylbutan-2-yl)phenyl) propanamide (490 mg, 1.3 mmol) and NaOH (2080 mg, 52 mmol) in EtOH (13 mL) was refluxed at 100 ℃ for 40 h and concentrated under reduced pressure. H_2O was added, and the mixture was extracted with hexanes. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the crude product was purified by flash chromatography (SiO_2, Et_2O/hexanes = 1/2) to give aniline **65** (172 mg, 81%) as an oil: $[\alpha]^{23}_{D}$ +3.8 (*c* 1.64, CH_2Cl_2); HPLC, Chiralcel OD-H, hexanes/*i*-PrOH = 95/5, flow rate = 0.95 mL/min, detection at 254 nm, t_R = 7.68 min (minor), 8.20 min (major), ee = 95%.

By the same procedure as aniline **65**, (*S*)-2-(6-methoxynaphthalen-2-yl)-*N*-(2-((*S*)-3-methylbutan-2-yl)phenyl)propanamide (410 mg, 1.09 mmol) and NaOH (2180 mg, 54.5 mmol) in EtOH (12 mL) at 100 ℃ for 40 h provided aniline **66** (160 mg, 90%) as an oil: $[\alpha]^{23}_{D}$ -2.3 (*c* 5.4, CH_2Cl_2); HPLC, Chiralcel OD-H, hexanes/*i*-PrOH = 95/5, flow rate = 0.95 mL/min, detection at 254 nm, t_R = 7.68 min (major), 8.20 min (minor), ee = 98%.

***N*1,*N*2-Di((*R*)-1-(3-methylbutan-2-yl))phenylethane-1,2-diamine (67).** To a solution of aniline **65** (172 mg, 1.05 mmol) in PrOH (0.7 mL) was added a solution of glyoxal (40% H_2O solution, 76 mg, 0.524 mmol) in PrOH (0.1 mL) and H_2O (0.23 mL), and the mixture was stirred at rt for 5 h. Hexanes was added, and the organic layer was separated, washed with H_2O, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the crude product was dissolved in THF (1.5 mL) and EtOH (1.5 mL). $NaBH_4$ (93 mg, 2.47 mmol) was added slowly at 0 ℃ in 1 h, and the resulting mixture was stirred at rt for 4 h. H_2O (0.3 mL) was added, followed by HCl (3 M, 2.5 mL), and the resulting white precipitate was collected and dissolved in a mixture of NaOH (1 M, 10 mL) and Et_2O (10 mL). The organic layer was separated, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the crude product was purified by flash chromatography (SiO_2, EtOAc/hexanes = 1/10) to give **67** (152 mg, 83%) as an oil: $[\alpha]^{23}_{D}$ +1.7 (*c* 7.7, CH_2Cl_2); HPLC, Chiralcel OD-H, hexanes/*i*-PrOH = 95/5, flow rate = 0.95 mL/min, detection at 254 nm, t_R = 5.98 min (major), 6.58 min (minor), ee = 99%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15–7.07 (m, 4H), 6.79–6.72 (m, 4H), 3.90 (br, 2H), 3.50–3.43 (m, 4H), 2.49–2.40 (m, 2H), 1.90–1.79 (m, 2H), 1.19 (d, *J* = 6.9 Hz, 6H), 0.92 (d, *J* = 6.6 Hz, 6H), 0.83 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 132.0, 127.0, 126.7, 118.0, 111.2, 44.0, 39.5, 32.8, 21.8, 19.6, 17.4; HRMS (ES) *m*/*e* calcd for $C_{24}H_{37}N_2$ (MH^+) 353.2957, found 353.2939.

(*S*)-*N*1-(2-(3-Methylbutan-2-yl)phenyl)-*N*2-phenyloxalamide (68). To a solution of aniline **66** (80 mg, 0.487 mmol), 2-anilino-2-oxoacetic acid (97 mg, 0.585 mmol) and HOBT (80 mg, 0.585 mmol) in CH_2Cl_2 (6 mL) was added a solution of DCC (121 mg, 0.585 mmol) in CH_2Cl_2 (4 mL) slowly in 10 min, and the resulting precipitate was filtered. After removal of volatile components from the filtrate, the crude product was purified by flash chromatography (SiO_2, EtOAc/hexanes = 1/3) to give **68** (151 mg, 100%) as a white solid: $[\alpha]^{23}_D$ +2.5 (*c* 1.6, CH_2Cl_2); IR (cm^{-1}) 3269, 1666, 1512, 1444, 756; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (br, 1H), 9.39 (br, 1H), 8.00–7.96 (m, 1H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.30–7.20 (m, 4H), 2.74–2.65 (m, 1H), 1.90–1.79 (m, 1H), 1.29 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 157.9, 138.7, 136.5, 133.6, 129.5, 127.7, 126.7, 126.4, 125.8, 122.8, 120.1, 40.7, 34.3, 21.4, 20.0, 18.2; HRMS (EI) *m*/*e* calcd for $C_{19}H_{22}N_2O_2$ (M^+) 310.1681, found 310.1679.

***N*1-(*S*)-2-(3-Methylbutan-2-yl)phenyl-*N*2-phenylethane-1,2-diamine (69).** A mixture of diamide **68** (150 mg, 0.482 mmol) and BH_3 (1M in THF, 3.86 mL, 3.86 mmol) was refluxed for 20 h. After being cooled to rt, MeOH (2 mL) was added, and the resulting mixture was stirred for 10 min. After removal of volatile components from the mixture, the crude product was purified by flash chromatography (SiO_2, EtOAc/hexanes = 1/5) to give **69** (132 mg, 97%) as an oil: $[\alpha]^{23}_D$ -8.1 (*c* 1.75, CH_2Cl_2); HPLC, Chiralcel OD-H, hexanes/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, detection at 254 nm, t_R = 14.40 min (major), 17.16 min (minor), ee = 99%; IR (cm^{-1}) 3408, 2960, 1602, 1504, 1310, 1257, 748; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.17 (m, 2H), 7.14–7.07 (m, 2H), 6.78–6.65 (m, 5H), 3.88 (br, 2H), 3.43 (br, 4H), 2.49–2.39 (m, 1H), 1.90–1.75 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 145.3, 132.0, 129.6, 127.0, 126.7, 118.0, 117.9, 113.3, 111.2,

43.9, 43.4, 39.2, 33.0, 21.8, 19.6, 17.2; HRMS (EI) *m*/*e* calcd for $C_{19}H_{26}N_2$ (M^+) 282.2096, found 282.2087.

***N*-(2-Bromophenyl)-*N*-((*S*)-1-phenylethyl)-acetamide (70).** A solution of (*S*)-2-bromo-*N*-(1-phenylethyl)-aniline (552 mg, 2.0 mmol) and NaH (60% in mineral oil, 82 mg, 2.04 mmol) in THF (20 mL) was stirred at 50 ℃ for 10 min and cooled to room temperature. Acetyl chloride (171 μL, 2.4 mmol) was added drop wise, and the resulting mixture was stirred for 16 h. After being quenched with saturated NH_4Cl solution (H_2O), the mixture was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to provide **70** (421 mg, 66%) as an oil: IR (cm^{-1}) 3493, 3306, 2978, 1662, 1382, 1310, 1091, 1030, 772, 728; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.5, 1.0 Hz, 0.7H), 7.47 (dd, *J* = 8.0, 1.5 Hz, 0.3H), 7.40 (td, *J* = 7.5, 1.5 Hz, 0.3H), 7.33–7.28 (m, 3.7H), 7.20–7.07 (m, 3.3H), 6.45 (dd, *J* = 8.0, 1.5 Hz, 0.7H), 6.31 (q, *J* = 7.5 Hz, 0.7H), 5.96 (q, *J* = 7.0 Hz, 0.3H), 1.82 (s, 2.1H), 1.80 (s, 0.9H), 1.66 (d, *J* = 7.0 Hz, 0.9H), 1.40 (d, *J* = 7.0 Hz, 2.1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 170.1, 142.4, 139.3, 139.0, 138.9, 134.0, 133.9, 131.8, 131.7, 129.8, 129.4, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 126.6, 126.4, 55.7, 53.2, 23.6, 23.4, 19.8, 16.4; HRMS (ES) *m*/*e* calcd for $C_{16}H_{17}NOBr$ (MH^+) 318.0494, found 318.0482.

***N*-(2-Bromophenyl)-*N*-((*S*)-1-phenylethyl)-phenylacetamide (71).** A solution of (*S*)-2-bromo-*N*-(1-phenylethyl)-aniline (670 mg, 2.42 mmol) and NaH (60% in mineral oil, 99 mg, 2.47 mmol) in THF (20 mL) was stirred at 50 ℃ for 10 min and cooled to room temperature. 2-Phenylacetyl chloride (0.38 mL, 2.91 mmol) was added drop wise, and the reulting mixture was stirred for 24 h. After being quenched with saturated NH_4Cl solution (H_2O), the mixture was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal

of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 10/1) to afford **71** (756 mg, 79%) as an oil: IR (cm^{-1}) 3030, 2979, 1731, 1660, 1473, 1383, 1240, 1030, 769, 727; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.1, 1.5 Hz, 0.7H), 7.53 (dd, *J* = 7.8, 1.5 Hz, 0.3H), 7.34–7.01 (m, 12.3H), 6.37 (q, *J* = 7.2 Hz, 0.7H), 6.29 (dd, *J* = 7.8, 1.5 Hz, 0.7H), 6.01 (q, *J* = 7.2 Hz, 0.3H), 3.56 (d, *J* = 15.3 Hz, 0.7H), 3.50 (d, *J* = 15.3 Hz, 0.3H), 3.29 (d, *J* = 15.0 Hz, 0.7H), 3.28 (d, *J* = 15.3 Hz, 0.3H), 1.67 (d, *J* = 6.9 Hz, 0.9H), 1.43 (d, *J* = 7.2 Hz, 2.1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.5, 142.3, 139.0, 138.6, 138.1, 135.3, 135.2, 133.9, 133.8, 132.4, 129.9, 129.4, 129.3, 128.4, 128.3, 128.0, 127.9, 127.9, 127.8, 127.6, 126.7, 126.5, 56.2, 53.5, 42.6, 42.5, 19.7, 16.4; HRMS (ES) *m*/*e* calcd for $C_{22}H_{21}NOBr$ (MH^+) 394.0807, found 394.0816.

Gold, [1,3-bis[2,6-diisopropylphenyl]-2-imidazolidinylidene]chloro- (72).[93] A solution of 1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (4.8 mg, 0.01 mmol), AuCl·SMe_2 (3.1 mg, 0.0105 mol) and NaH (0.26 mg, 0.0105 mmol) in CH_2Cl_2 (1 mL) covered by aluminum foil was stirred at rt for 18 h and filtered through celite. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **72** (80%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 4H), 4.08 (s, 4H), 3.15 (heptet, *J* = 6.6 Hz, 4H), 1.43 (d, *J* = 6.6 Hz, 12H), 1.35 (d, *J* = 6.6 Hz, 3H).

Gold, [1,3-bis(2-cyclohexylphenyl)-(4*R*,5*R*)-4,5-diphenylimidazolidinylidene]chloro- (73). A solution of imidazolinium salt **48d** (300 mg, 0.32 mmol), AuCl·SMe_2 (100 mg, 0.352 mmol) and NaH (12 mg, 0.48 mmol) in CH_2Cl_2 (10 mL) covered by aluminium foil was stirred at rt for 18 h and filtered through celite. To the filtrate was added activated carbon, and the mixture was stirred for 20 min and filtered through celite. After removal of volatile components

from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **73** (179 mg, 73%) as a white solid: IR (cm^{-1}) 2926, 2850, 1468, 911, 732; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.19 (m, 15.5H), 7.05–6.85 (m, 2.5H), 5.40–5.34 (m, 0.6H), 5.28–5.21 (m, 0.5H), 5.12 (s, 0.9H), 3.16–3.09 (m, 0.5H), 2.97–2.94 (m, 0.9H), 2.72–2.66 (m, 0.5H), 2.55–2.52 (m, 0.7H), 2.35–2.31 (m, 1.4H), 2.08–0.86 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 194.0, 146.4, 145.0, 138.1, 137.8, 137.1, 136.7, 135.9, 131.2, 131.1, 129.7, 129.6, 129.4, 129.3, 128.8, 128.4, 128.0, 127.9, 127.8, 127.7, 127.0, 126.7, 79.5, 78.8, 39.4, 39.2, 38.8, 35.0, 34.9, 34.6, 34.5, 27.8, 27.5, 27.3, 27.2, 27.0, 26.4, 26.3; HRMS (ES) *m*/*e* calcd for $C_{39}H_{42}N_2Au$ (M^+Cl) 735.3014, found 735.3038.

Gold, [1,3-bis(2-methyl-3-phenylphenyl)-(4*R*,5*R*)-4,5-diphenylimidazolidinylidene] chloro- (74). A solution of imidazolinium salt **48h** (97 mg, 0.15 mmol), AuCl·SMe_2 (49 mg, 0.165 mol) and NaH (27 mg, 1.125 mmol) in CH_2Cl_2 (5 mL) covered by aluminum foil was stirred at rt for 16 h and filtered through celite. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 2/1) to give **74** (107 mg, 91%) as a white solid: IR (cm^{-1}) 3061, 3032, 2236, 1473, 911, 762, 727; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.23 (m, 20H), 7.23–7.04 (m, 6H), 5.41–5.31 (br, 2H), 2.42 (br, 4H), 2.06 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 144.7, 144.1, 141.1, 138.0, 137.6, 135.8, 134.4, 132.5, 130.7, 130.4, 129.6, 129.4, 128.3, 127.7, 127.4, 126.4, 125.0, 78.9, 75.0, 60.5, 21.2, 17.4, 17.0, 14.4; HRMS (ES) *m*/*e* calcd for $C_{41}H_{34}N_2Au$ (M^+Cl) 751.2388, found 751.2418.

Gold, [1,3-bis[2-(*R*)-1-(3-methylbutan-2-yl)phenyl] imidazolidinylidene]chloro- (75). A solution of imidazolinium salt **56** (4.5 mg, 0.01 mmol), AuCl·SMe_2 (3.5 mg, 0.012 mol) and NaO*t*-Bu (1.5 mg, 0.015 mmol) in CH_2Cl_2 (0.6 mL) covered by aluminum foil was stirred at rt

for 10 min and filtered through celite. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **75** (2 mg, 34%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.28 (m, 8H), 4.20–3.93 (m, 4H), 2.70–2.55 (m, 1.78H), 2.36 (br, 0.22H), 1.98–1.82 (m, 2H), 1.46–0.76 (m, 18H).

Gold, [1,3-bis[4-(2,6-bis(2-(1*S*,2*S*,5*S*)-myrtylethyl))phenyl-2,6-diisopropylphenyl] imidazolidinylidene]chloro- (76). A solution of imidazolinium salt **45** (142 mg, 0.115 mmol), AuCl·SMe_2 (38 mg, 0.127 mol) and NaO*t*-Bu (33 mg, 0.345 mmol) in CH_2Cl_2 (2 mL) covered by aluminum foil was stirred at rt for 30 min and filtered through celite. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 10/1) to give **76** (121 mg, 77%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.20 (m, 2H), 7.13–7.09 (m, 8H), 4.14 (s, 4H), 3.18 (heptet, *J* = 6.6 Hz, 4H), 2.39–2.20 (m, 8H), 1.96–0.74 (m, 92H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 142.1, 142.0, 141.0, 140.8, 132.8, 127.7, 127.0, 126.6, 126.4, 126.3, 53.8, 46.5, 46.1, 41.4, 41.2, 39.8, 39.6, 39.4, 38.8, 35.1, 34.7, 32.4, 31.8, 29.3, 27.1, 27.0, 25.3, 25.2, 24.8, 24.6, 24.5, 23.8, 22.4, 22.2, 20.5, 20.3.

***N*-(2-Bromobenzyl)-2-phenylpropanamide (78).** To a solution of (2-bromophenyl) methanamine (558 mg, 3 mmol) and Et_3N (310 mg, 3.06 mmol) in CH_2Cl_2 (10 mL) was added a solution of 2-phenylpropanoyl chloride (518 mg, 3.06 mmol) in CH_2Cl_2 (5 mL) slowly at 0 ℃, and the mixture was stirred at rt for 10 min. Saturated aqueous NH_4Cl solution was added, and the resulting mixture was extracted with Et_2O. The extracts were combined, washed with H_2O, brine, dried over $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure to give **78** (950 mg, 100%) as an oil which was used directly in the next step: IR (cm^{-1}) 3287, 3063, 1650, 1545, 1234, 1026, 747; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.8 Hz, 1H), 7.37–7.20

(m, 7H), 7.14–7.08 (m, 1H), 5.88 (br, 1H), 4.44 (dd, *J* = 6, 0.9 Hz, 2H), 3.63 (q, *J* = 7.2 Hz, 1H), 1.55 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 141.3, 137.4, 132.9, 130.2, 129.2, 129.1, 127.9, 127.8, 127.6, 123.7, 47.3, 44.1, 18.6.

***N*-(2-Bromobenzyl)-*N*-methyl-2-phenylpropanamide (79).** By the general procedure, amide **78** (475 mg, 1.5 mmol), NaH 60% in mineral oil (36 mg, 1.5 mmol), MeI (256 mg, 1.8 mmol) in THF (7.5 mL) for 1 h afforded **79** (398 mg, 80%) as a white solid after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 2927, 1642, 1404, 1288, 748; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.2, 1.2 Hz, 0.48H), 7.53 (dd, *J* = 7.8, 1.2 Hz, 0.52H), 7.37–7.11 (m, 6.5H), 7.11 (td, *J* = 7.5, 1.8 Hz, 0.5H), 7.00 (dd, *J* = 7.5, 1.5 Hz, 0.56H), 6.92 (d, *J* = 7.5 Hz, 0.44H), 4.91 (d, *J* = 7.2 Hz, 0.5H), 4.84 (d, *J* = 18 Hz, 0.55H), 4.66 (d, *J* = 17.4 Hz, 0.5H), 4.32 (d, *J* = 18 Hz, 0.45H), 4.00 (q, *J* = 6.6 Hz, 0.54H), 3.74 (q, *J* = 6.9 Hz, 0.46H), 3.00 (s, 1.38H), 2.87 (s, 1.62H), 1.51 (d, *J* = 6.9 Hz, 1.62H), 1.44 (d, *J* = 6.9 Hz, 1.38H); HRMS (EI) *m*/*e* calcd for $C_{17}H_{18}NOBr$ (M^+) 331.0572, found 331.0579.

***N*-(2-Bromobenzyl)-*N*-benzyl-2-phenylpropanamide (80).** By the general procedure, amide **78** (475 mg, 1.5 mmol), NaH 60% in mineral oil (36 mg, 1.5 mmol), BnBr (308 mg, 1.8 mmol) in THF (7.5 mL) for 2 h afforded **80** (478 mg, 78%) as an oil after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 2973, 1653, 1452, 1214, 1028, 752; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.8, 1.2 Hz, 0.54H), 7.49 (dd, *J* = 7.8, 1.2 Hz, 0.46H), 7.38–6.95 (m, 13H), 5.21 (t, *J* = 15 Hz, 1H), 4.72 (d, *J* = 17.4 Hz, 0.46H), 4.64 (d, *J* = 18.6 Hz, 0.54H), 4.29–4.12 (m, 2H), 3.93 (q, *J* = 6.6 Hz, 0.46H), 3.74 (q, *J* = 6.9 Hz, 0.54H), 1.50 (d, *J* = 6.9 Hz, 1.38H), 1.47 (d, *J* = 6.9 Hz, 1.62H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 174.8, 141.8, 141.6, 137.4, 136.8, 136.6, 136.0, 133.3, 133.0, 129.2, 129.1, 128.8, 128.7, 128.2, 128.0, 127.8, 127.7,

127.6, 127.3, 127.2, 127.1, 126.4, 123.7, 122.8, 50.8, 50.6, 49.5, 49.2, 43.6, 43.5, 21.2, 21.1; HRMS (ES) *m*/*e* calcd for $C_{16}H_{16}NONaBr$ (MNa^+) 340.0313, found 340.0288.

2,4-Dimethyl-4-phenyl-1,2-dihydroisoquinolin-3(4*H*)-one (81). A solution of 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (3.6 mg, 0.0075 mmol), $Pd_2(dba)_3$ (3.5 mg, 0.00375 mmol) and NaO*t*-Bu (22 mg, 0.225 mmol) in THF (1 mL) was stirred at rt for 10 min. A solution of amide **79** (25 mg, 0.075 mmol) in THF (0.5 mL) was added, and the mixture was degassed by an oil pump in a dry ice-acetone bath. After being stirred at 120 ℃ for 2h, the mixture was cooled to rt and purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **81** (7.2 mg, 38%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.18 (m, 7H), 7.02–6.98 (m, 2H), 4.21–4.06 (m, 2H), 3.10 (s, 3H), 1.92 (s, 3H).

***N*-(1-(2-Bromophenyl)vinyl)-*N*-methylacetamide (82).** A mixture of molecular sieves (0.5 g), 2-bromoacetophenone (100 mg, 0.5 mmol) and methylamine (2 M in MeOH, 1.5 mL, 3 mmol) was stirred at rt for 12 h and filtered. The filtrate was concentrated under reduced pressure, and the residue was dried by an oil pump. CH_2Cl_2 (3 mL) and Et_3N (61 mg, 0.6 mmol) was added at rt, followed by acetyl chloride (47 mg, 0.6 mmol) slowly at 0 °C, and the mixture was stirred at rt for 5 min, quenched with saturated aqueous NH_4Cl solution and extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **82** (100 mg, 79%) as an oil: IR (cm^{-1}) 3493, 3305, 2936, 1660, 1373, 1025, 902, 768; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.8 Hz, 1H), 7.35–7.33 (m, 2H), 7.24–7.19 (m, 1H), 5.38 (br, 1H), 5.30 (s, 1H), 2.97 (br, 3H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 141.8, 136.6, 136.0, 133.2, 133.0, 129.1, 129.0, 128.8, 128.7, 128.0,

127.8, 127.7, 127.6, 127.1, 127.0, 123.7, 122.7, 53.8, 51.32, 43.7, 43.4, 35.4, 35.0, 21.0; HRMS (EI) *m*/*e* calcd for $C_{11}H_{12}NOBr$ (M^+) 253.0102, found 253.0100.

***N*-(1-(2-Bromophenyl)vinyl)-*N*-methyl-2-phenylpropanamide (83).** A mixture of 2-bromoacetophenone (100 mg, 0.5 mmol), methylamine (2 M in MeOH, 1.5 mL, 3 mmol) and molecular sieves (0.5 g) was stirred at rt for 12 h and filtered. The filtrate was concentrated under reduced pressure, and the residue was dried by an oil pump. CH_2Cl_2 (2 mL) and Et_3N (56 mg, 0.55 mmol) was added at rt, followed by a solution of 2-phenylpropanoyl chloride (93 mg, 0.55 mmol) in CH_2Cl_2 (1 mL) slowly at 0 °C, and the mixture was stirred at rt for 5 min, quenched with saturated aqueous NH_4Cl solution and extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **83** (160 mg, 94%) as an oil: IR (cm^{-1}) 2970, 1657, 1376, 766; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 1H), 7.32-7.14 (m, 8H), 5.37 (br, 1H), 5.16 (s, 1H); 4.18 (br, 1H), 3.03 (br, 3H), 1.43 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1, 131.0, 130.2, 127.8, 126.9, 43.6, 21.5; HRMS (EI) *m*/*e* calcd for $C_{18}H_{18}NOBr$ (M^+) 343.0572, found 343.0572.

[1,1'-Biphenyl]-2-amine, 2'-bromo- (86).[94] A solution of 2-iodoaniline (3.48 g, 15.89 mmol), 2-bromophenylboronic acid (3.67 g, 18.27 mmol), $Pd(PPh_3)_4$ (550 mg, 0.48 mmol) and $NaHCO_3$ (4.0 g, 47.7 mmol) in DME (45 mL) was stirred at rt for 5 min. H_2O (23 mL) was added, and the resulting mixture was degassed by an oil pump in a dry ice-acetone bath, sealed and stirred at 120 ℃ for 3 h. After being cooled to rt, the mixture was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **86** (3.53 g, 90%) as a pale yellow solid: ^1H NMR (300 MHz,

$CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 1H), 7.47–7.31 (m, 2H), 7.27–7.19 (m, 2H), 7.06 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.87 (td, *J* = 7.5, 0.9 Hz, 1H), 6.81 (dd, *J* = 8.1, 0.9 Hz, 1H), 3.54 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 140.2, 133.3, 132.0, 130.4, 129.4, 129.3, 128.0, 127.3, 124.4, 118.4, 115.7.

[1,1'-Biphenyl]-2-amine, 2'-chloro- (108).[95] A solution of 2-bromoaniline (516 mg, 3.0 mmol), 2-chlorophenylboronic acid (562 mg, 3.6 mmol), $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) and $NaHCO_3$ (756 mg, 9.0 mmol) in DME (7 mL) was stirred at rt for 5 min. H_2O (7 mL) was added, and the resulting mixture was degassed by oil pump in a dry ice-acetone bath, sealed and stirred at 120 ℃ for 2 h. After being cooled to rt, the mixture was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to provide **108** (501 mg, 82%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 1H), 7.38–7.23 (m, 3H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 3.52 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 138.1, 134.0, 133.1, 131.6, 131.0, 130.3, 129.5, 128.9, 128.4, 128.2, 128.1, 126.3, 125.4, 119.5, 117.3, 116.6, 114.6.

General Procedure for the Acylation of 2-Arylanilines with Acyl Chlorides. To a solution of 2-arylaniline (2.0 mmol) and Et_3N (0.34 mL, 2.4 mmol) in CH_2Cl_2 (10 mL) was added acyl chloride (2.4 mmol) slowly at 0 ℃ and stirred at rt for 5 min. Saturated aqueous NH_4Cl solution was added, and the resulting mixture was stirred for 10 min. The organic layer was separated, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography.

[1,1'-Biphenyl]-2-acetamide, 2'-bromo- (87). By the general procedure, aniline **86** (1.0 g, 4.0 mmol), Et_3N (0.67 mL, 4.8 mmol), acetyl chloride (0.34 mL, 4.8 mmol) in CH_2Cl_2 (20 mL) for 5 min provided **87** (1.15 g, 99%) as an oil after flash chromatography (SiO_2, hexanes/EtOAc = 1/1): IR (cm^{-1}) 3421, 3286, 3056, 1670, 1520, 1442, 1369, 1294, 1027, 1005, 754; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.1 Hz, 1H), 7.71–7.69 (m, 1H), 7.42–7.37 (m, 2H), 7.29–7.25 (m, 2H), 7.21–7.13 (m, 2H), 6.86 (br, 1H), 1.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 138.9, 135.1, 133.3, 132.0, 130.1, 130.0, 129.3, 129.1, 128.1, 124.4, 124.0, 122.2, 24.6; HRMS (EI) *m*/*e* calcd for $C_{14}H_{12}NOBr$ (M^+) 289.0102, found 289.0101.

[1,1'-Biphenyl]-2-propionamide, 2'-bromo- (89). By the general procedure, aniline **86** (248 mg, 1.0 mmol), Et_3N (0.17 mL, 1.2 mmol), propionyl chloride (0.10 mL, 1.2 mmol) in CH_2Cl_2 (10 mL) for 5 min provided **89** (278 mg, 92%) as an oil after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 3296, 2976, 1672, 1442，754; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.8 Hz, 1H), 7.70–7.67 (m, 1H), 7.41–7.34 (m, 2H), 7.28–7.22 (m, 2H), 7.18–7.11(m, 2H), 6.92 (br, 1H), 2.20 (q, *J* = 7.5 Hz, 2H), 1.05 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 138.8, 135.1, 133.1, 131.9, 129.9, 129.0, 128.0, 124.1, 123.9, 121.9, 30.7, 9.5; HRMS (EI) *m*/*e* calcd for $C_{15}H_{14}NOBr$ (M^+) 303.0259, found 303.0270.

[1,1'-Biphenyl]-2-methoxyacetamide, 2'-bromo- (90). By the general procedure, aniline **86** (248 mg, 1.0 mmol), Et_3N (0.17 mL, 1.2 mmol), methoxyacetyl chloride (0.11 mL, 1.2 mmol) in CH_2Cl_2 (10 mL) for 5 min provided **90** (298 mg, 93%) as an oil after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 3369, 2936, 1693, 1526, 1303, 1111, 757; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.1 Hz, 1H), 8.08 (br, 1H), 7.71–7.68 (m, 1H), 7.46–7.37 (m, 2H), 7.29–7.24 (m, 2H), 7.17–7.14 (m, 2H), 3.84 (d, *J* = 1.2 Hz, 2H), 3.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 138.5,134.5,133.0, 131.7, 131.5, 129.8, 129.7, 129.0, 127.9,

124.2, 124.0, 120.9, 72.1, 59.3; HRMS (EI) *m*/*e* calcd for $C_{15}H_{14}NO_2Br$ (M^+) 319.0208, found 319.0207.

[1,1'-Biphenyl]-2-isobutyramide, 2'-bromo- (91). By the general procedure, aniline **86** (248 mg, 1.0 mmol), Et_3N (0.17 mL, 1.2 mmol), isobutyryl chloride (0.13 mL, 1.2 mmol) in CH_2Cl_2 (10 mL) for 5 min provided **91** (289 mg, 91%) as an oil after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 3424, 3298, 2968, 1676, 1517, 1285, 754; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.1 Hz, 1H), 7.72–7.67 (m, 1H), 7.43–7.36 (m, 2H), 7.29–7.24 (m, 2H), 7.19–7.12 (m, 2H), 6.92 (br, 1H), 2.36 (heptet, *J* = 6.9 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 138.8, 135.1, 133.1, 132.0, 131.9, 129.9, 129.7, 129.0, 128.0, 124.2, 123.9, 121.9, 36.5, 19.3; HRMS (EI) *m*/*e* calcd for $C_{16}H_{16}NOBr$ (M^+) 317.0415, found 317.0410.

[1,1'-Biphenyl]-2-acetamide, 2'-chloro- (109). By the general procedure, aniline **108** (475 mg, 2.33 mmol), Et_3N (0.39 mL, 2.8 mmol), acetyl chloride (0.2 mL, 2.8 mmol) in CH_2Cl_2 (10 mL) for 5 min provided **109** (570 mg, 99%) as an oil after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 3421, 3283, 3058, 1670, 1521, 1442, 1293, 1036, 754; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.1 Hz, 1H), 7.49–7.46 (m, 1H), 7.39–7.23 (m, 4H), 7.18–7.15 (m, 2H), 7.10 (br, 1H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 136.7, 135.2, 133.5, 131.9, 130.5, 130.2, 129.8, 129.6, 128.8, 127.3, 124.4, 122.5, 24.2; HRMS (EI) *m*/*e* calcd for $C_{14}H_{12}NOCl$ (M^+) 245.0607, found 245.0610.

[1,1'-Biphenyl]-2-(2-chloroacetamide), 2'-bromo- (120). By the general procedure, aniline **86** (124 mg, 0.5 mmol), Et_3N (60.7 mg, 0.6 mmol), 2-chloroacetyl chloride (68 mg, 0.6 mmol) in CH_2Cl_2 (5 mL) for 10 min provided **120** (167 mg, 100%) as an oil after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 3378, 3058, 1689, 1529, 1446, 1307,

756; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.4 Hz, 1H), 8.08 (br, 1H), 7.73-7.70 (m, 1H), 7.46-7.39 (m, 2H), 7.31-7.26 (m, 2H), 7.24-7.18 (m, 2H), 4.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 138.2, 134.3, 133.3, 132.2, 131.8, 130.2, 130.0, 129.2, 128.2, 125.1, 124.1, 121.1, 43.1; HRMS (EI) *m*/*e* calcd for $C_{14}H_{11}NOClBr$ (M^+) 322.9713, found 322.9719.

[1,1'-Biphenyl]-2-phenylacetamide, 2'-bromo- (88). To a solution of aniline **86** (350 mg, 1.4 mmol), phenylacetic acid (209 mg, 1.54 mmol) and 1-hydroxybenzotriazole (HOBT) (209 mg, 1.54 mmol) in CH_2Cl_2 (10 mL) was added a solution of DCC (318 mg, 1.54 mmol) in CH_2Cl_2 (4 mL) slowly at rt in 1 h, stirred for 36 h and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **88** (490 mg, 96%) as an oil: IR (cm^{-1}) 3381, 3307, 3060, 1685, 1519, 1443, 1303, 754; ^{1}H NMR (300 MHz, $CDCl_3$) major conformer: δ 8.32 (d, *J* = 8.1 Hz, 1H), 7.48 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.41 (td, *J* = 7.2, 1.5 Hz, 1H), 7.25–7.08 (m, 6H), 7.13–6.93 (m, 4H), 6.80 (br, 1H), 3.59 (s, 1H), 3.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 138.3, 135.0, 133.7, 133.2, 131.6, 131.2, 129.7, 129.4, 129.3, 129.1, 127.8, 127.6, 124.2, 123.8, 121.0, 45.1; HRMS (EI) *m*/*e* calcd for $C_{20}H_{16}NOBr$ (M^+) 365.0415, found 365.0410.

[1,1'-Biphenyl]-2-benzyloxyacetamide, 2'-bromo- (92). To a solution of aniline **86** (744 mg, 3.0 mmol), benzyloxyacetic acid (600 mg, 3.6 mmol) and HOBT (492 mg, 3.6 mmol) in CH_2Cl_2 (24 mL) was added a solution of DCC (750 mg, 3.6 mmol) in CH_2Cl_2 (6 mL) slowly at rt in 1 h, stirred for 1 h and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **92** (1.11 g, 94%) as an oil: IR (cm^{-1}) 3376, 3065, 2869, 1693, 1526, 1026, 738; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.1 Hz, 1H), 8.20 (br, 1H), 7.55 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.44–7.37 (m, 1H), 7.33–7.09 (m, 8H), 7.06–6.98 (m, 2H), 4.39–4.29 (m, 2H), 4.03–3.91 (m, 2H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 167.5, 138.5, 136.6, 134.6, 133.1, 131.7, 131.5, 129.9, 129.2, 128.5, 128.0, 127.9, 127.6, 124.3, 124.0, 120.9, 73.2, 69.7; HRMS (EI) *m*/*e* calcd for $C_{21}H_{18}NO_2Br$ (M^+) 395.0521, found 395.0538.

[1,1'-Biphenyl]-2-dibenzylaminoacetamide, 2'-bromo- (94). To a solution of aniline **86** (124 mg, 0.5 mmol), dibenzylaminoacetic acid (153 mg, 0.6 mmol) and HOBT (82 mg, 0.6 mmol) in CH_2Cl_2 (4 mL) was added a solution of DCC (125 mg, 0.6 mmol) in CH_2Cl_2 (1 mL) at rt in 1 h, stirred for 72 h and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **94** (176 mg, 73%) as an oil: IR (cm^{-1}) 3336, 3061, 3029, 2923, 2831, 2246, 1692, 1583, 1514, 1445, 910, 750; ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 7.82 (dd, *J* = 7.2, 0.6 Hz, 1H), 7.54 (td, *J* = 6.9, 1.2 Hz, 1H), 7.43–7.33 (m, 3H), 7.31–7.19 (m, 6H), 7.17–7.13 (m, 2H), 6.99–6.94 (m, 4H), 3.52 (d, *J* = 13.5 Hz, 2H), 3.44 (d, *J* = 13.5 Hz, 2H), 3.18 (d, *J* = 16.5 Hz, 1H), 3.04 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 139.4, 136.9, 135.2, 133.4, 132.1, 131.4, 130.3, 130.1, 129.2, 129.1, 128.7, 128.0, 127.6, 124.7, 124.1, 121.2, 58.9, 57.6; HRMS (EI) *m*/*e* calcd for $C_{28}H_{26}N_2OBr$ (MH^+) 485.1228, found 485.1217.

[1,1'-Biphenyl]-2-(2-(4-nitrobenzyloxy)-acetamide), 2'-bromo- (93). To a solution of aniline **86** (248 mg, 1 mmol), 4-nitrobenzyloxyacetic acid (254 mg, 1.2 mmol) and HOBT (163 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) was added DCC (248 mg, 1.2 mmol) at rt slowly, and the mixture was stirred for 4 h and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 1/1) to give **93** (420 mg, 96%) as a white solid: IR (cm^{-1}) 3360, 2904, 1687, 1522, 1347, 1108, 768; ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.1 Hz, 1H), 8.17–8.13 (m, 3H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.43 (td, *J* = 8.1, 1.5 Hz, 1H), 7.37 (t, *J* = 8.4 Hz, 1H), 7.28 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.22–

7.11 (m, 5H), 4.56–4.45 (m, 2H), 4.12–4.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 147.4, 144.1, 138.4, 134.3, 132.8, 131.8, 131.3, 129.9, 129.8, 129.1, 127.9, 127.4, 124.4, 123.8, 123.7, 123.6, 120.8, 71.8, 70.2; HRMS (EI) *m*/*e* calcd for $C_{21}H_{17}N_2O_4Br$ (M^+) 440.0372, found 440.0370.

General Procedure for the Methylation of Amides with Methyl Iodide. A mixture of amide (1.0 mmol) and NaH 60% in mineral oil (42 mg, 1.05 mmol) was added THF (10 mL) at rt and stirred for 10 min. MeI (0.075 mL, 1.2 mmol) was added, and the resulting mixture was stirred for 10 min. After removal of volatile components from the mixture, the resulting crude product was purified by flash chromatography.

[1,1'-Biphenyl]-2-(*N*-methyl-acetamide), 2'-bromo- (95). By the general procedure, amide **87** (1.01 g, 3.48 mmol), NaH 60% in mineral oil (147 mg, 3.65 mmol), MeI (593 mg, 4.18 mmol) in THF (25 mL) for 10 min afforded **95** (1.05 g, 99%) as a white solid after flash chromatography (SiO_2, hexanes/EtOAc = 1/1): IR (cm^{-1}) 3066, 1658, 1467, 1373, 757; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.63 (m, 1H), 7.48–7.38 (m, 2H), 7.38–7.30 (m, 2H), 7.29–7.09 (m, 3H), 3.09 (s, 1.04H), 2.96 (s, 0.31H), 2.84 (s, 1.65H), 2.17 (s, 0.14H), 2.01 (s, 0.32H), 1.98 (s, 1.54H), 1.86 (s, 1.0H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.5, 142.7, 142.3, 142.0, 139.3, 138.8, 133.6, 133.3, 132.7, 132.5, 131.9, 131.4, 130.3, 129.7, 129.5, 129.4, 129.3, 128.7, 128.5, 128.4, 127.9, 127.7, 127.3, 123.5, 123.3, 77.43, 38.9, 38.4, 36.0, 31.1, 22.7, 22.0; HRMS (EI) *m*/*e* calcd for $C_{15}H_{14}NOBr$ (M^+) 303.0259, found 303.0268.

[1,1'-Biphenyl]-2-(*N*-methyl-phenylacetamide), 2'-bromo- (96). By the general procedure, amide **88** (480 mg, 1.32 mmol), NaH 60% in mineral oil (53 mg, 1.32 mmol), MeI (225 mg, 1.59 mmol) in THF (5 mL) for 10 min afforded **96** (451 mg, 90%) as a white solid after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 3060, 1658, 1373, 753; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.71–7.58 (m, 1H), 7.45–7.09 (m, 11.4H), 6.85–6.80 (m, 0.6H), 3.70–3.50 (m, 1.6H), 3.37–3.32 (m, 0.4H), 3.15 (s, 1 H), 2.99 (s, 0.3H), 2.86 (s, 1.7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 170.9, 142.1, 142.0, 141.6, 139.1, 139.0, 138.9, 135.8, 135.3, 134.5, 133.8, 133.2, 132.9, 132.5, 131.7, 131.4, 130.4, 129.8, 129.7, 129.5, 129.4, 129.1, 129.0, 128.8, 128.7, 128.6, 128.4, 128.1, 127.9, 127.6, 127.5, 127.4, 127.0, 126.8, 126.6, 123.5, 123.3, 77.43, 41.1, 41.0, 38.9, 36.4; HRMS (EI) *m*/*e* calcd for $C_{21}H_{18}NOBr$ (M^+) 379.0572, found 379.0575.

[1,1'-Biphenyl]-2-(*N*-methyl-propionamide), 2'-bromo- (97). By the general procedure, amide **89** (249 mg, 0.82 mmol), NaH 60% in mineral oil (35 mg, 0.86 mmol), MeI (140 mg, 0.99 mmol) in THF (10 mL) for 10 min afforded **97** (257 mg, 99%) as a white solid after flash chromatography (SiO_2, hexanes/EtOAc = 1/1): IR (cm^{-1}) 3058, 2974, 2936, 1660, 1464, 1378, 1285, 753; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67–7.60 (m, 1H), 7.45–7.37 (m, 2H), 7.37–7.28 (m, 2H), 7.27–7.05 (m, 3H), 3.11 (s, 1.08H), 2.97 (s, 0.35H), 2.85 (s, 1.57H), 2.35–2.18 (m, 0.7H), 2.18–2.04 (m, 1.3H), 1.14 (t, *J* = 7.2 Hz, 1.54H), 1.03 (t, *J* = 7.2 Hz, 0.40H), 0.95 (t, *J* = 6.9 Hz, 1.06H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 173.7, 142.3, 142.2, 141.7, 139.8, 139.1, 139.0, 138.7, 133.4, 133.1, 132.5, 132.3, 131.5, 131.2, 130.1, 129.5, 129.4, 129.2, 129.1, 128.5, 128.3, 128.2, 127.7, 127.4, 127.1, 127.0, 123.3, 123.1, 38.3, 38.0, 35.9, 27.6, 27.4, 26.9, 9.9, 9.7, 9.1; HRMS (EI) *m*/*e* calcd for $C_{16}H_{16}NOBr$ (M^+) 317.0415, found 317.0421.

[1,1'-Biphenyl]-2-(*N*-methyl-methoxyacetamide), 2'-bromo- (98). By the general procedure, amide **90** (275 mg, 0.86 mmol), NaH 60% in mineral oil (36 mg, 0.90 mmol), MeI (147 mg, 1.03 mmol) in THF (8 mL) for 10 min afforded **98** (286 mg, 99%) as an oil after flash chromatography (SiO_2, hexanes/EtOAc = 1/1): IR (cm^{-1}) 3058, 2925, 2820,1676, 1465, 1330, 1103, 754; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68–7.63 (m, 1H), 7.48–7.40 (m, 2H), 7.39–7.17 (m, 5H), 4.09–3.93 (m, 0.75H), 3.88– 3.79 (m, 1.25H), 3.37 (s, 1.45H), 3.28 (s, 0.52H), 3.27 (s,

1.0H), 3.13 (s, 1.1H), 2.98 (s, 0.40H), 2.85 (s, 1.53H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 168.7, 141.3, 140.3, 139.8, 139.5, 138.8, 138.6, 138.5, 138.4, 133.4, 133.0 132.6, 132.4, 131.4, 131.2, 131.0, 129.9, 129.5, 129.2, 129.1, 129.0, 128.6, 128.1, 128.0, 127.9, 127.4, 127.1, 126.9, 123.1, 122.8, 71.0, 70.6, 70.2, 59.1, 58.7, 38.2, 36.7, 35.7; HRMS (EI) *m*/*e* calcd for $C_{16}H_{16}NO_2Br$ (M^+) 333.0364, found 333.0377.

[1,1'-Biphenyl]-2-(*N*-methyl-isobutyramide), 2'-bromo- (99). By the general procedure, amide **91** (260 mg, 0.82 mmol), NaH 60% in mineral oil (35 mg, 0.86 mmol), MeI (140 mg, 0.99 mmol) in THF (10 mL) for 10 min afforded **99** (268 mg, 99%) as a white solid after flash chromatography (SiO_2, hexanes/EtOAc = 1/1): IR (cm^{-1}) 2968, 1658, 1466, 1386, 1102, 752; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.48–7.24 (m, 5H), 7.24–7.09 (m, 2H), 3.21 (s, 1.2H), 3.07 (s, 0.3H), 2.89 (s, 1.5H), 2.76 (heptet, *J* = 6.9 Hz, 0.1H), 2.62–2.46 (m, 0.9H), 1.13 (d, *J* = 6.6 Hz, 1.5H), 1.09 (d, *J* = 6.6 Hz, 1.5H), 0.94 (d, *J* = 6.6 Hz, 1.37H), 0.81 (d, *J* = 6.6 Hz, 0.35H), 0.69 (d, *J* = 6.6 Hz, 1.28H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 177.2, 142.4, 142.2, 141.8, 139.8, 139.2, 138.9, 138.5, 133.5, 133.0, 132.8, 132.1,131.8, 131.3, 130.9, 130.6, 129.6, 129.4, 129.3, 129.1, 128.0, 127.8, 127.3, 127.2, 126.9, 123.3, 38.8, 37.9, 36.2, 31.5, 30.9, 30.3, 20.6, 20.1, 19.6,18.9,18.8, 18.7; HRMS (EI) *m*/*e* calcd for $C_{17}H_{18}NOBr$ (M^+) 331.0572, found 331.0565.

[1,1'-Biphenyl]-2-(*N*-methyl-benzyloxyacetamide), 2'-bromo- (100). By the general procedure, amide **92** (1.04 g, 2.63 mmol), NaH 60% in mineral oil (110 mg, 2.77 mmol), MeI (448 mg, 3.16 mmol) in THF (30 mL) for 10 min afforded **100** (1.056 g, 98%) as an oil after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 3060, 2925, 1673, 1026, 751; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.58 (m, 1H), 7.42–7.14 (m, 11.4H), 7.05 (dd, *J* = 7.2, 1.8 Hz, 0.6H), 4.63–4.33 (m, 2H), 4.14–3.87 (m, 2H), 3.12 (s, 1H), 3.00 (s, 0.4H), 2.86 (s, 1.6H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 169.7, 169.0, 141.6, 140.6, 140.2, 139.8, 139.0, 138.9, 138.7, 138.6, 137.9, 137.5, 133.6, 133.1, 132.7, 132.5, 131.6, 131.5, 131.2, 130.3, 129.6, 129.4, 128.8, 128.4, 128.3, 128.1, 128.0, 127.9, 127.6, 127.4, 127.3, 127.2, 123.3, 123.1, 73.2, 73.0, 72.9, 69.0, 68.2, 38.5, 37.2, 36.0; HRMS (ES) *m*/*e* calcd for $C_{22}H_{20}NO_2NaBr$ (MNa^+) 432.0575, found 432.0548.

[1,1'-Biphenyl]-2-(2-(4-nitrobenzyloxy)-*N*-methyl-acetamide), 2'-bromo- (101). By the general procedure, amide **93** (0.40 g, 0.91 mmol), NaH 60% in mineral oil (37 mg, 0.91 mmol) and MeI (157 mg, 1.1 mmol) in THF (5 mL) for 5 h afforded **101** (377 mg, 92%) as a white solid after flash chromatography (SiO_2, hexanes/EtOAc = 1/1): IR (cm^{-1}) 3061, 2927, 1672, 1604, 1520, 1346, 1128, 850, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18–8.11 (m, 2H), 7.69 (d, *J* = 7.8 Hz, 0.45H), 7.62 (d, *J* = 9 Hz, 0.55H), 7.50–7.19 (m, 8.5H), 7.14 (dd, *J* = 7.2, 1.2 Hz, 0.5H), 4.76–4.46 (m, 2H), 4.26–4.13 (m, 0.6H), 4.06–3.90 (m, 1.4H), 3.17 (s, 1.4H), 3.06 (m, 0.3H), 2.89 (m, 1.3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 168.6, 147.4, 147.3, 145.7, 145.4, 145.3, 145.2, 141.3, 140.2, 139.9, 138.9, 138.8, 138.6, 138.5, 133.5, 133.2, 132.9, 132.6, 131.5, 131.4, 131.2, 130.4, 130.2, 130.0, 129.8, 129.5, 129.3, 129.0, 128.8, 128.3, 128.2, 128.1, 127.9, 127.8, 127.5, 127.4, 127.0, 123.5, 123.4, 123.3, 122.9, 72.0, 71.6, 69.2, 68.8, 68.6, 48.8, 38.5, 37.1, 36.1, 33.9, 25.7, 25.0; HRMS (ES) *m*/*e* calcd for $C_{22}H_{20}N_2O_4Br$ (MH^+) 455.0606, found 455.0576.

[1,1'-Biphenyl]-2-(*N*-methyl-dibenzylaminoacetamide), 2'-bromo- (102). By the general procedure, amide **94** (166 mg, 0.34 mmol), NaH 60% in mineral oil (15 mg, 0.36 mmol), MeI (58 mg, 0.41 mmol) in THF (4 mL) for 10 min afforded **102** (170 mg, 99%) as an oil after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 3060, 3027, 2919, 1664, 1464, 749; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 0.5H), 7.48 (d, *J* = 8.1 Hz, 0.3H), 7.43–7.07 (m, 15.7H), 6.96–6.89 (m, 0.5H), 6.88 (d, *J* = 7.5 Hz, 0.5H), 6.60 (d, *J* = 7.2 Hz, 0.5H),

3.98–3.01 (m, 7.5H), 2.82 (s, 1.50H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 171.0, 170.7, 142.1, 141.3, 140.6, 140.1, 139.9, 139.8, 139.1, 138.9, 138.8, 138.7, 133.7, 133.1, 132.8, 132.3, 131.5, 131.0, 130.3, 130.1, 129.5, 129.4, 129.3, 129.0, 128.7, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.2, 127.1, 126.8, 123.4, 123.2, 123.0, 77.4, 58.3, 58.0, 57.4, 56.2, 53.5, 53.2, 38.7, 37.9, 35.9; HRMS (ES) *m*/*e* calcd for $C_{29}H_{28}N_2OBr$ (MH^+) 499.1385, found 499.1381.

[1,1'-Biphenyl]-2-(*N*-methyl-acetamide), 2'-chloro- (110). By the general procedure, amide **109** (271 mg, 1.1 mmol), NaH 60% in mineral oil (47 mg, 1.155 mmol), MeI (188 mg, 1.32 mmol) in THF (7 mL) for 10 min afforded **110** (280 mg, 98%) as a white solid after flash chromatography (SiO_2, hexanes/EtOAc = 1/1): IR (cm^{-1}) 3069, 1658, 1373, 1031, 760; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.33 (m, 5H), 7.33–7.23 (m, 3H), 7.15 (br, 1H), 3.04 (s, 1.15H), 2.96 (s, 0.44H), 2.85 (s, 1.41H), 2.01–2.00 (m, 0.25H), 1.94 (s, 1.50H), 1.86 (s, 1.25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.3, 142.4, 142.0, 137.2, 136.9, 133.0, 132.2, 131.5, 131.2, 130.3, 129.9, 129.4, 129.1, 128.4, 128.2, 127.8, 127.2, 126.9, 126.5, 37.9, 35.9, 22.5, 22.2, 21.9; HRMS (EI) *m*/*e* calcd for $C_{15}H_{14}NOCl$ (M^+) 259.0764, found 259.0763.

[1,1'-Biphenyl]-2-(*N*-benzyl-acetamide), 2'-bromo- (103). A mixture of amide **87** (290 mg, 1.0 mmol) and NaH 60% in mineral oil (42 mg, 1.05 mmol) was added THF (10 mL) at rt and stirred for 10 min. Benzyl bromide (205 mg, 1.2 mmol) was added, and the resulting mixture was stirred for 12 h. After removal of volatile components from the mixture, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 1/1) to give **103** (371 mg, 99%) as a white solid: IR (cm^{-1}) 3060, 1658, 1386, 751; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74–7.65 (m, 1H), 7.40–7.32 (m, 3H), 7.32–7.22 (m, 3H), 7.21–7.16 (m, 5H), 6.88 (d, *J* = 7.8 Hz, 0.24H), 6.75 (d, *J* = 7.8 Hz, 0.76H), 5.44 (d, *J* = 18.0 Hz, 0.22H), 5.27 (d, *J* = 14.1 Hz, 0.78H), 3.90 (d, *J* = 14.4 Hz, 0.22H), 3.45 (d, *J* = 14.4 Hz, 0.78H), 2.10 (s, 0.21H), 2.04 (s,

2.14H), 1.95 (s, 0.65H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 139.9, 139.1, 138.7, 137.4, 133.6, 132.8, 131.4, 130.8, 130.4, 130.1, 129.8, 129.4, 129.1, 128.9, 128.5, 128.3, 128.0, 127.8, 127.4, 123.4, 52.9, 50.7, 23.4, 23.0; HRMS (EI) *m*/*e* calcd for $C_{21}H_{18}NOBr$ (M^+) 379.0572, found 379.0556.

[1,1'-Biphenyl]-2-(*N*-methyl-4-hydroxypentanamide), 2'-bromo- (105). To a solution of LiCl (544 mg, 12.828 mmol) and diisopropylamine (454 mg, 4.49 mmol) in THF (15 mL) in a dry ice-acetone bath was added *n*-BuLi (1.6 M in hexane, 2.8 mL, 4.49 mmol), and the resulting mixture was stirred at 0 °C for 10 min and cooled in the dry ice-acetone bath. A solution of amide **95** (650 mg, 2.138 mmol) in THF (5 mL) was added slowly, and the resulting mixture was stirred in the dry ice-acetone bath for 1 h, 0 °C for 15 min, 23 °C for 5 min and cooled to 0 °C. Propene oxide (621 mg, 10.69 mmol) was added, and the resulting mixture was stirred at 0 °C for 3 h. Saturated aqueous NH_4Cl solution was added, and the mixture was extracted with EtOAc. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, EtOAc) to give **105** (272 mg, 35%) as an oil: (IR (cm^{-1}) 3421, 2966, 1641, 1499, 1386, 1132, 754; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.62 (m, 1H), 7.45-7.14 (m, 7H), 3.76-3.53 (m, 2H), 3.11 (s, 1H), 3.02 (s, 0.15H), 3.00 (s, 0.35H), 2.84 (s, 1.5H), 2.43-2.10 (m, 2H), 1.85-1.51 (m, 2H), 1.16-1.12 (m, 1.8H), 1.07-1.04 (m, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 174.3, 173.7, 173.6, 141.9, 141.4, 141.3, 141.2, 139.5, 139.0, 138.8, 138.6, 138.5, 133.4, 133.0, 132.6, 132.3, 131.5, 131.4, 131.1, 130.3, 129.6, 129.4, 129.2, 129.1, 128.9, 128.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.5, 127.2, 123.2, 123.0, 67.6, 67.3, 67.2, 38.6, 36.0, 34.3, 34.2, 34.1, 33.5, 33.4, 31.4, 31.2, 31.1, 30.6, 30.3, 30.1, 23.8, 23.6, 23.4, 23.2; HRMS (EI) *m*/*e* calcd for $C_{18}H_{21}NO_2Br$ (MH^+) 362.0756, found 362.0752.

[1,1'-Biphenyl]-2-(*N*-methyl-4-oxopentanamide), 2'-bromo- (104). A solution of amide **105** (260 mg, 0.718 mmol) and PCC (310 mg, 1.436 mmol) in CH_2Cl_2 (7 mL) was stirred at rt for 3 h and filtered through celite. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 1/1) to give **104** (249 mg, 96%) as a solid: IR (cm^{-1}) 3496, 3059, 2920, 1716, 1657, 1465, 1165, 1026, 755; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 0.85H), 7.46–7.30 (m, 5.65H), 7.25–7.19 (m, 1.5H), 3.11 (s, 0.8H), 2.99 (s, 0.13H), 2.96 (s, 0.27H), 2.80 (s, 1.8H), 2.79–2.22 (m, 4H), 2.18 (s, 2H), 2.12 (s, 0.25H), 2.10 (s, 0.75H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 172.4, 171.6, 141.9, 141.2, 139.0, 138.7, 138.4, 133.4, 133.0, 132.4, 131.6, 131.4, 131.2, 130.8, 129.6, 129.5, 129.3, 129.0, 128.8, 128.7, 128.6, 128.5, 128.3, 127.8, 127.7, 127.2, 123.2, 38.8, 38.5, 38.3, 37.7, 35.9, 30.2, 30.1, 29.9, 28.8, 28.4, 27.5; HRMS (EI) *m*/*e* calcd for $C_{18}H_{18}NO_2Br$ (M^+) 359.0521, found 359.0508.

General Procedure for the Palladium-Catalyzed Cyclization of Dibenzazepinones. A solution of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), $HPCy_3BF_4$ (5.6 mg, 0.015 mmol) and NaO*t*-Bu (44 mg, 0.45 mmol) in toluene (1 mL) was stirred at rt for 10 min and cooled in a dry ice-acetone bath. The amide as dibenzazepinone precursor (0.15 mmol) in toluene (0.5 mL) was added, and the resulting mixture was degassed by oil pump and refilled with argon. After stirred at 100 ℃ for 10 min, the mixture was cooled to rt and purified by flash chromatography.

5-Phenyl-*N*-methyl-dibenzazepin-6-one (111). By the general procedure, amide **96** (57 mg, 0.15 mmol) gave **111** (44.5 mg, 99%) as a film after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 2920, 1662, 1366, 705; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.70 (m, 0.7H), 7.66–7.59 (m, 1.3H), 7.53–7.46 (m, 2.4H), 7.46–7.28 (m, 3.6H), 7.21–7.18 (m, 0.4H), 7.10–7.04 (m, 0.6H), 6.99–6.87 (m, 3H), 6.71–6.66 (m, 1H), 5.35 (s, 0.6H), 4.65 (s, 0.4H),

3.40 (s, 1.9H), 3.36 (s, 1.1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 170.8, 142.2, 140.7, 139.3, 138.0, 136.7, 136.6, 136.0, 135.7, 134.6, 134.3, 131.8, 130.7, 130.3, 129.8, 129.4,128.9, 128.7, 128.6, 128.5, 128.2, 128.1, 127.9, 127.6, 127.3, 126.4, 126.2, 125.6, 125.0, 122.7, 122.4, 60.5, 51.5, 37.3, 36.7, 29.9; HRMS (EI) *m*/*e* calcd for $C_{21}H_{17}NO$ (M^+) 299.1310, found 299.1309.

5-Methoxy-*N*-methyl-dibenzazepin-6-one (113). By the general procedure, amide **98** (50 mg, 0.15 mmol) gave **113** (21 mg, 56%) as a film after flash chromatography (SiO_2, hexanes/EtOAc = 1/2): IR (cm^{-1}) 3066, 2926, 2831, 1680, 1440, 1212, 1092, 984, 767, 743; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.5 Hz, 1H), 7.63 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.58 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.54–7.32 (m, 5H), 5.03 (s, 0.05H), 4.54 (s, 0.95H), 3.56 (s, 2.86H), 3.42 (s, 0.14H), 3.35 (s, 2.86H), 3.03 (s, 0.14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 140.8, 137.3, 133.8, 133.5, 130.0, 129.5, 129.0, 128.9, 128.1, 127.9, 125.8, 122.9, 122.8, 78.7, 58.4, 36.5; HRMS (EI) *m*/*e* calcd for $C_{16}H_{15}NO_2$ (M^+) 253.1103, found 253.1100.

5,5-Dimethyl-*N*-methyl-dibenzazepin-6-one (114). By the general procedure, amide **99** (50 mg, 0.15 mmol) gave **114** (3 mg, 8%) as a film after flash chromatography (SiO_2, hexanes/EtOAc = 1/1): IR (cm^{-1}) 2926, 1651, 1598, 758, 735; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.52 (m, 3H), 7.45–7.38 (m, 3H), 7.29–7.24 (m, 2H), 3.37 (s, 3H), 1.79 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 143.9, 141.9, 136.8, 135.4, 130.0, 129.9, 128.6, 128.5, 127.5, 125.3, 125.1, 122.0, 46.2, 38.5, 26.8, 23.2; HRMS (EI) *m*/*e* calcd for $C_{17}H_{17}NO$ (M^+) 251.1310, found 251.1305.

***N*-benzyl-dibenzazepin-6-one (115).** By the general procedure, amide **103** (57 mg, 0.15 mmol) gave **115** (38 mg, 84%) as a film after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1})3063， 3029， 1669， 1440， 763， 738; 1H NMR (300 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2H), 7.43–7.37 (m, 3H), 7.37–7.20 (m, 3H), 7.14–7.08 (m, 3H), 6.92–6.87 (m, 2H),

5.19 (d, *J* = 15.6 Hz, 1H), 4.94 (d, *J* = 15.6 Hz, 1H), 3.68 (d, *J* = 12.3 Hz, 1H), 3.55 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 140.7, 137.6 137.5, 136.7, 135.5, 135.4, 135.1, 135.0, 134.9, 131.4, 131.3, 131.2, 130.1, 130.0, 129.6, 129.5, 129.2, 129.1, 129.0, 128.9, 128.2, 128.1, 128.0, 127.8, 127.5, 127.4, 127.0, 126.9, 126.8, 126.7, 126.0, 125.9, 124.9, 124.8, 124.7, 124.5, 124.4, 122.3, 122.2, 53.8, 51.9, 50.0, 44.1, 42.4, 42.3, 40.6; HRMS (EI) *m*/*e* calcd for $C_{21}H_{17}NO$ (M^+) 299.1310, found 299.1301.

5,6-Dihydro-8-methyl-5-acetyl-dibenzazocin-7(8H)-one (116). By the general procedure, amide **104** (54 mg, 0.15 mmol) gave **116** (8 mg, 20%) as a film after flash chromatography (SiO_2, hexanes/EtOAc = 1/1): IR (cm^{-1}) 1714, 1661, 768; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.44 (m, 1H), 7.40–7.33 (m, 4H), 7.29–7.22 (m, 2H), 7.13 (dt, *J* = 6.6, 1.5 Hz, 1H), 4.11 (t, *J* = 9.6 Hz, 1H), 3.20 (dd, *J* = 12.9, 9.0 Hz, 1H), 2.94 (s, 3H), 2.53 (dd, *J* = 12.9, 9.9 Hz, 1H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7, 172.3, 142.6, 139.8, 138.2, 135.8, 132.6, 131.2, 130.8, 129.8, 129.2, 128.4, 128.3, 125.9, 56.5, 35.7, 35.0, 28.3; HRMS (EI) *m*/*e* calcd for $C_{18}H_{17}NO_2$ (M^+) 279.1259, found 279.1249.

5-Benzyloxy-*N*-methyl-dibenzazepin-6-one (117). By the general procedure, $Pd(OAc)_2$ (13.6 mg, 0.06 mmol), $HPCy_3BF_4$ (22.4 mg, 0.06 mmol), amide **100** (248 mg, 0.6 mmol) and NaO*t*-Bu (86.4 mg, 0.9 mmol) in toluene (6 mL) gave **117** (160 mg, 81%) as a film after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 3063, 2926，1680，743; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8 Hz, 1H), 7.60–7.22 (m, 12H), 4.97 (d, *J* = 11.7 Hz, 1H), 4.75 (s, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 140.8, 138.0, 137.5, 133.8, 133.5, 130.0, 128.9, 128.9, 128.5, 128.0, 127.9, 127.9, 127.8, 125.8, 123.4, 122.8, 76.7, 72.2, 36.6; HRMS (EI) *m*/*e* calcd for $C_{22}H_{19}NO_2$ (M^+) 329.1416, found 329.1416.

[1,1'-Biphenyl]-2-(*N*-methylformamide), 2'-bromo- (119). By the general procedure, amide **101** (91 mg, 0.2 mmol) in toluene (2 mL) gave **119** (14 mg, 20%) as a film after flash chromatography (SiO_2, hexanes/EtOAc = 1/1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.67 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.51–7.30 (m, 5H), 7.29–7.18 (m, 2H), 2.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 163.4, 140.4, 139.6, 133.4, 132.0, 131.8, 131.4, 129.8, 129.6, 129.0, 128.9, 128.8, 128.4, 128.0, 127.8, 127.7, 127.6, 127.2, 123.6, 33.3; MS (ES) *m*/*e* (MNa^+) 312.0

5-Dibenzylamino-*N*-methyl-dibenzazepin-6-one (135). By the general procedure, amide **102** (75 mg, 0.15 mmol) gave **135** (58 mg, 93%) as a film after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 3061, 3027, 2925，2245，1656，732; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.24 (m, 7H), 7.17–7.08 (m, 7H), 6.73–6.67 (m, 4H), 4.67 (s, 1H), 3.42 (d, *J* = 14.1 Hz, 2H), 3.19 (s, 3H), 3.17 (d, *J* = 14.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 141.4, 137.1, 137.0, 136.4, 134.0, 130.4, 129.8, 129.7, 129.4, 129.0, 128.7, 128.0, 127.0, 124.6, 121.9, 77.9, 54.9, 37.5; HRMS (EI) *m*/*e* calcd for $C_{29}H_{26}N_2O$ (M^+) 418.2045, found 418.2042.

***N*-(2-Bromophenyl)-2-iodo-*N*-methylacetamide (121).** To a solution of amide **120** (1.45 g, 5.83 mmol) and MeI (1.66 g, 11.67 mmol) in THF (30 mL) was added 60% NaH in mineral oil (257 mg, 6.42 mmol) slowly, and the mixture was stirred at rt for 10 min. Saturated aqueous NH_4Cl solution was added, and the resulting mixture was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give a product (560 mg) as a mixture of *N*-(2-bromophenyl)-2-iodo-*N*-methylacetamide and *N*-(2-bromophenyl)-2-chloro-*N*-methylacetamide. To this mixture was added acetone (10 mL) and Sodium iodide (2.6 g, 17.3 mmol), and the resulting mixture was stirred at rt for 1 h. The solvent was evaporated under reduced pressure, and the residue was

dissolved in Et_2O. The resulting solvent was dried over $MgSO_4$ and filtered. Removal of volatile components from the filtrate provided **121** (601 mg, 30%) as a colorless oil: IR (cm^{-1}) 3057, 2931, 1664, 1476, 1373, 1111, 1049, 767, 729; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.52 (m, 2H), 7.35 (m, 1H), 3.66 (d, *J* = 10.2 Hz, 1H), 3.39 (d, *J* = 10.2 Hz, 1H), 3.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 142.0, 134.1, 130.5, 129.6, 129.2, 123.1, 36.9, -2.5; HRMS (EI) *m*/*e* calcd for C_9H_9NOBrI (M^+), 352.8912, found 352.8924.

***N*-(2-Bromophenyl)-2-((2-bromophenyl)(phenyl)methoxy)-*N*-methylacetamide (122).** To a solution of (2-bromophenyl)(phenyl)methanol (295 mg, 1.12 mmol) and amide **121** (396 mg, 1.12 mmol) in THF (1 mL) was added 60% NaH in mineral oil (50 mg, 1.23 mmol) at 0 ℃, and the mixture was stirred at rt for 1 h. After removal of volatile components from the mixture, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to provide **122** (535 mg, 98%) as a colorless oil: IR (cm^{-1}) 3061, 2928, 1682, 1476, 1114, 758, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56–7.51 (m, 1H), 7.48–7.42 (m, 2 H), 7.37–7.33 (m, 2H), 7.26–7.10 (m, 7H), 7.08 (td, *J* = 7.8, 1.5 Hz, 1H), 5.88 (s, 0.5H), 5.84 (s, 0.5H), 3.88 (m, 2H), 3.20 (s, 1.5H), 3.19 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 168.6, 141.0, 140.9, 140.3, 140.2, 139.8, 139.7, 134.0, 133.8, 132.6, 132.5, 130.1, 130.0, 129.8, 129.7, 129.0, 128.9, 128.7, 128.5, 128.2, 127.8, 127.7, 127.6, 123.4, 123.2, 123.1, 123.0, 114.6, 81.7, 81.6, 67.1, 66.9, 36.0; HRMS (ES) *m*/*e* calcd for $C_{22}H_{19}NO_2NaBr_2$ (MNa^+), 509.9680, found 509.9690.

2-Bromo-*N*-(2-((2-bromophenyl)(phenyl)methoxy)ethyl)-*N*-methylbenzenamine (123). To a solution of amide **122** (250 mg, 0.513 mmol) in THF (6 mL) was added borane-dimethylsulfide (2 M in THF, 1 mL, 2.05 mmol) at rt, and the mixture was stirred for 2 h. Aqueous NaOH solution (1 M, 1 mL) was added, and the mixture was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtrated. After removal of volatile components

from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to provide **123** (240 mg, 99%) as a colorless oil: IR (cm^{-1}) 2865, 1586, 1476, 1046, 1024, 754, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.46 (m, 3H), 7.37–7.33 (m, 2H), 7.29–7.15 (m, 5H), 7.09–7.03 (m, 2H), 6.86–6.80 (m, 1H), 5.75 (s, 1H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.36 (t, *J* = 6.0 Hz, 2H), 2.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 141.4, 140.9, 134.0, 133.9, 132.8, 129.1, 128.8, 128.4, 128.1, 127.9, 127.7, 127.5, 124.1, 123.5, 122.2, 119.8, 82.1, 67.5, 55.5, 42.1; HRMS (EI) *m*/*e* calcd for $C_{22}H_{21}NOBr_2$ (M^+) 472.9990, found 472.9975.

Ethyl 2-((2-bromophenyl)(phenyl)methoxy)acetate (124). To a solution of (2-bromophenyl)(phenyl)methanol (720 mg, 2.73 mmol) in THF (30 mL) was added 60% NaH in mineral oil (110 mg, 2.73 mmol) at 0 °C, and the mixture was stirred for 10 min. Ethyl 2-bromoacetate (547 mg, 3.276 mmol) was added, and the resulting mixture was stirred at rt for 30 min. Saturated aqueous NH_4Cl solution was added, and the mixture was extracted with EtOAc. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 10/1) to provide **124** (501 mg, 53%) as a colorless oil: IR (cm^{-1}) 1754, 1206, 1118, 1025, 755; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.44–7.41 (m, 2H), 7.37–7.23 (m, 4H), 7.17 (td, *J* = 7.8, 1.8 Hz, 1H), 4.25 (quartet, *J* = 7.2 Hz, 2H), 4.16 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 140.2, 139.8, 133.0, 129.5, 128.8, 128.6, 128.1, 128.0, 127.8, 123.7, 82.0, 66.3, 61.1, 14.3; HRMS (ES) *m*/*e* calcd for $C_{17}H_{17}O_3NaBr$ (MNa^+) 371.0259, found 371.0262.

Ethyl 2-((2-(2-aminophenyl)phenyl)(phenyl)methoxy)acetate (125). To a solution of 2-aminophenylboronicacidpinacolester (277 mg, 1.265 mmol), bromobenzene **124** (320 mg, 0.917 mmol), chloro(di-2-norbornylphosphino)(2'-dimethylamino-1,1'-biphenyl-2-yl)palladium

(II) (52 mg, 0.0917 mmol) in DME (5 mL) was added a solution of $NaHCO_3$ in H_2O (5 mL), and the mixture was degassed by an oil pump in a dry ice-acetone bath and stirred at 80 °C overnight. After being cooled to rt, the mixture was extracted with EtOAc. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to provide **125** (47 mg, 14%) as a colorless oil: IR (cm^{-1}) 3466, 3371, 2926, 1752, 1617, 1206, 1118, 751, 700; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78-7.72 (m, 0.8H), 7.68-7.64 (m, 0.2H), 7.45-7.30 (m, 2.7H), 7.24-7.06 (m, 6.3H), 7.02 (dd, *J* = 8.1, 1.2 Hz, 0.4H), 6.86-6.63 (m, 1.6H), 5.50 (s, 0.3H), 5.44 (s, 0.4H), 4.52 (m, 0.3H), 4.17-4.12 (m, 2H), 4.05-3.96 (m, 2H), 3.45 (br, 2H), 1.27-1.20 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.3, 144.7, 143.8, 140.9, 140.4, 140.3, 138.2, 138.1, 131.1, 130.6, 130.5, 130.2, 129.1, 129.0, 128.9, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.4, 127.2, 126.2, 118.4, 115.8, 115.4, 115.3, 80.9, 80.3, 77.4, 68.0, 66.6, 66.2, 61.0, 60.9, 14.4; HRMS (EI) *m*/*e* calcd for $C_{23}H_{23}NO_3$ (M^+) 361.1678, found 361.1670.

Ethyl 2-((2-(2-pivalamidophenyl)phenyl)(phenyl)methoxy)acetate (127). A solution of 2-pivalamidophenylboronic acid (304 mg, 1.375 mmol), bromobenzene **124** (400 mg, 1.146 mmol), $Pd(PPh_3)_4$ (66 mg, 0.0573 mmol) and $NaHCO_3$ (289 mg, 3.438 mmol) in DMF (4 mL) and H_2O (0.8 mL) was degassed by an oil pump in a dry ice-acetone bath and stirred at 150 °C for 15 min. After being cooled to rt, the mixture was extracted with EtOAc. The extracts were washed with water, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to provide **127** (456 mg, 90%) as a colorless oil: IR (cm^{-1}) 3430, 2962, 1754, 1687, 1483, 1205, 1118, 762; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 8.1, 0.9 Hz, 0.5H), 8.19 (dd, *J* = 8.1, 0.9 Hz, 0.5H), 8.01 (dd, *J* = 8.1, 0.9 Hz, 0.5H), 7.63 (dd, *J* = 8.1, 1.2 Hz,

0.5H), 7.53 (td, J = 8.1, 1.2 Hz, 0.5H), 7.47 (br, 1H), 7.45–7.33 (m, 2H), 7.30–7.22 (m, 2.5H), 7.19–7.07 (m, 4.5H), 6.92–6.87 (m, 1.5H), 4.21 (quartet, J = 7.2 Hz, 1H), 4.13 (quartetd, J = 7.2,1.8 Hz, 1H), 4.03–4.89 (m, 1H), 3.89 (d, J = 15.3 Hz, 0.5H), 3.72 (d, J = 15.3 Hz, 0.5H), 1.26 (t, J = 7.2 Hz, 1.5H), 1.20 (t, J = 7.2 Hz, 1.5H), 1.02 (s, 4.5H), 0.69 (s, 4.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 176.0, 170.1, 169.8, 141.1, 140.1, 139.8, 139.7, 137.2, 136.5, 136.0, 132.2, 130.5, 130.1, 130.0, 129.9, 129.8, 129.3, 129.2, 129.0, 128.8, 128.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 126.7, 124.8, 124.2, 123.8, 122.4, 122.1, 121.3, 80.8, 80.3, 66.2, 66.0, 61.0, 60.9, 39.7, 39.4, 27.3, 27.1, 14.4, 14.3; HRMS (ES) m/e calcd for $C_{28}H_{31}NO_4Na$ (MNa^+) 468.2151, found 468.2146.

5,6,8,9-Tetrahydro-5-phenyl-dibenz-6-oxazonin-8-one (129). A solution of KOH (566 mg, 10.11 mmol), **127** (150 mg, 0.337 mmol) in 2-methoxylethanol (2 mL) and H_2O (0.2 mL) was stirred at 130 °C for 16 h and cooled to rt. The PH of the mixture was adjusted to 1 with aqueous HCl solution (2 M), and the resulting mixture was extracted with EtOAc. The extracts were combined, washed with H_2O, brine, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product (80 mg) was added CH_2Cl_2 (2 mL), followed by a solution of DCC (50 mg) in CH_2Cl_2 (1 mL). The mixture was stirred at rt for 30 min and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **129** (21 mg, 20%) as a colorless oil: IR (cm^{-1}) 3059, 2906, 1667, 1115, 759; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.45 (m, 0.5H), 7.42–7.34 (m, 2.8H), 7.32–7.16(m, 3.7H), 7.10–7.05 (m, 3.6H), 7.00 (t, J = 7.5 Hz, 1H), 6.78–6.74 (m, 1.6H), 6.52(dd, J = 7.5, 1.2 Hz, 0.8H), 5.47 (s, 0.8H), 5.35 (s, 0.2H), 4.75 (d, J = 17.1 Hz, 0.8H), 4.24 (d, J = 17.1 Hz, 0.8H), 4.22 (d, J = 13.2 Hz, 0.2H), 4.09 (d, J = 13.2 Hz, 0.2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 141.4, 139.0, 138.6, 135.8, 130.8, 130.1,

129.9, 128.8, 128.3, 128.2, 127.7, 127.0, 126.6, 126.2, 125.7, 125.0, 87.4, 71.7; HRMS (ES) *m*/*e* calcd for $C_{21}H_{17}NO_2Na$ (MNa^+) 338.1157, found 338.1131.

5,6,8-Tetrahydro-5-phenyl -*N*-methyl-dibenz-6-oxazonin-8-one (118). A solution of lactam **129** (18 mg, 0.057 mmol), 60% NaH in mineral oil (2.5 mg, 0.0627 mmol) in THF (1 mL) was stirred at rt for 10 min. MeI (9.7 mg, 0.0686 mmol) was added, and the resulting mixture was stirred at rt for 20 min. After removal of volatile components from the mixture, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 1/1) to give **118** (19 mg, 100%) as a colorless oil: IR (cm^{-1}) 3060, 2921, 1655, 758, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.52 (m, 0.4H), 7.39–7.29 (m, 4.5H), 7.22 (d, *J* = 8.1 Hz, 1.7H), 7.17–7.09 (m, 3.9H), 6.88–6.82 (m, 2.5H), 5.49 (s, 0.87H), 5.23 (s, 0.13H), 4.63 (d, *J* = 15.6 Hz, 0.87H), 4.23 (d, *J* = 15.6 Hz, 1H), 4.97 (d, *J* = 12.6 Hz, 0.13H), 2.91 (s, 0.4H), 2.87 (s, 2.6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 142.2, 141.9, 139.9, 138.7, 137.0, 130.3, 129.4, 129.2, 128.9, 128.4, 128.0, 127.5, 127.2, 126.2, 126.1, 125.2, 87.5, 73.5, 38.4; HRMS (ES) *m*/*e* calcd for $C_{22}H_{19}NO_2Na$ (MNa^+) 352.1313, found 352.1301.

5-Benzyl-5-hydroxy-*N*-methyl-dibenzazepin-6-one (130). In the cyclization reaction of **100**, **130** (4% yield) was separated as a film after flash chromatography (SiO_2, hexanes/EtOAc = 3/1): IR (cm^{-1}) 3387, 2926， 1644， 1352, 763, 736; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.69 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.60–7.41 (m, 4H), 7.41 (td, *J* = 8.1, 1.2 Hz, 2H), 7.17–7.12 (m, 3H), 6.91–6.86 (m, 2H), 5.27 (s, 1H), 3.39 (s, 3H), 2.73–2.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 143.0, 140.6, 136.6, 135.0, 134.0, 130.4, 130.0, 129.4, 128.9, 128.9, 128.4, 128.0, 126.8, 126.3, 125.6, 122.7, 78.2, 41.2, 38.6; HRMS (EI) *m*/*e* calcd for $C_{22}H_{19}NO_2$ (M^+) 329.1416, found 329.1409.

5-Benzyloxy-*N*-methyl-dihydrodibenzazepine (131). To a solution of dibenzazepinone **117** (160 mg, 0.486 mmol) in THF (6 mL) was added a solution of $BH_3 \cdot Me_2S$ in THF (2 M, 1 mL) at rt and stirred for 2 h. NaOH solution in H_2O (1 M, 2 mL) was added, and the mixture was stirred for 10 min. THF was evaporated under reduced pressure, and the residue was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **131** (150 mg, 98%) as an oil: IR (cm^{-1}) 3062, 2860, 1596, 1492, 1444, 1181, 755, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.54 (m, 1H), 7.40–7.19 (m, 10H), 7.12 (td, *J* = 7.5, 1.8 Hz, 1H), 7.04 (dd, *J* = 7.8, 0.6 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.50 (m, 1H), 4.29 (d, *J* = 11.7 Hz, 1H), 3.62–3.47 (m, 2H), 2.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 139.2, 138.5, 138.4, 134.9, 129.0, 128.9, 128.7, 128.5, 127.8, 127.7, 127.5, 127.4, 123.6, 122.7, 118.3, 77.4, 71.8, 68.8, 41.8; HRMS (EI) *m*/*e* calcd for $C_{22}H_{21}NO$ (M^+) 315.1623, found 315.1609.

5-Hydroxy-*N*-methyl-dihydrodibenzazepine (132). To a solution of dibenzazepine **131** (90 mg, 0.285 mmol) in 95% ethanol (3 mL) was added 10% palladium on carbon (30 mg, 0.0285 mmol) and stirred at 80 ℃ under H_2 (1 atm) for 14 h. After cooled to rt, the mixture was filtered through celite. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **132** (54 mg, 85%) as an oil: IR (cm^{-1}) 3345, 2803, 1485, 1443, 1065, 756, 733; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.47 (m, 1H), 7.36–7.28 (m, 5H), 7.12 (td, *J* = 7.8, 1.5 Hz, 1H), 7.05 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.71 (m, 1H), 3.51 (m, 1H), 3.38 (m, 1H), 2.71 (s, 3H), 2.18 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 141.3, 137.7, 134.7, 129.3, 129.0, 128.5, 127.8, 127.7, 122.9, 122.8, 118.4, 70.2, 70.0, 41.8; HRMS (EI) *m*/*e* calcd for $C_{15}H_{15}NO$ (M^+) 225.1154, found 225.1145.

***N*-Methyl-dibenzazepin-5-one (133).** To a solution of Dess Martin reagent (122 mg, 0.289 mmol) in CH_2Cl_2 (3 mL) was added a solution of dibenzazepine **132** (50 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) at 0 ℃ and stirred for 30 min. NaOH solution in H_2O (1 M, 1 mL) was added, and the resulting mixture was stirred at rt for 5 min and extracted with EtOAc. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **133** (46 mg, 93%) as a solid: IR (cm^{-1}) 3062, 2830, 1680, 1596, 1300, 757, 732; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86–7.82 (m, 1H), 7.64–7.58 (m, 1H), 7.52–7.36 (m, 4H), 7.23–7.16 (m 2H), 3.95 (s, 2H), 2.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 150.2, 139.2, 137.4, 133.6, 133.0, 130.9, 130.3, 129.6, 128.6, 127.8, 124.3, 117.3, 72.2, 42.0; HRMS (EI) *m*/*e* calcd for $C_{15}H_{13}NO$ (M^+) 223.0997, found 223.0995.

5-Benzyl-5-hydroxy-*N*-methyl-dihydrodibenzazepine (134). The synthesis from dibenzazepinone **130:** to a solution of **130** (6 mg, 0.0183 mmol) in THF (0.5 mL) was added $BH_3 \cdot Me_2S$ (7.3 μL) at rt and stirred for 1.5 h. NaOH solution in H_2O (1 M, 1 drop) was added, and the mixture was stirred for 10 min. After removal of volatile components from the mixture, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **134** (5.7 mg, 99%) as an oil: IR (cm^{-1}) 3556, 2924, 1496, 1443, 761, 737; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 4.8 Hz, 1H), 7.47 (dd, *J* = 4.5, 0.6 Hz, 1H), 7.42–7.39 (m, 2H), 7.37 (td, *J* = 5.1, 0.9 Hz, 1H), 7.31 (td, *J* = 4.8, 1.2 Hz, 1H), 7.16–7.11 (m, 4H), 7.08 (d, *J* = 4.8 Hz, 1H), 6.75–6.74 (m, 2H), 3.56 (d, *J* = 6.9 Hz, 1H), 3.37 (d, *J* = 6.9 Hz, 1H), 2.98 (d, *J* = 8.4 Hz, 1H), 2.78 (s, 3H), 2.69 (d, *J* = 8.1 Hz, 1H), 2.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 143.0, 137.6, 136.4, 136.2, 130.7, 130.0, 129.2, 128.9, 128.3, 128.0, 127.5, 127.0, 124.6, 123.1,

118.0, 75.4, 74.2, 46.5, 42.1; HRMS (ES) *m*/*e* calcd for $C_{22}H_{22}NO$ (MH^+) 316.1701, found 316.1692.

The synthesis from dibenzazepinone **133:** to a solution of **133** (28 mg, 0.125 mmol) in THF (2 mL) was added a solution of benzylmagnesium chloride (2 M in THF, 69 μL, 0.138 mmol) slowly at rt, stirred for 15 min and added a drop of H_2O. After removal of volatile components from the mixture, the resulting crude product was purified by flash chromatography (SiO_2, hexanes/EtOAc = 3/1) to give **134** (23.6 mg, 60%) as an oil.

5-Amino-*N*-methyl-dibenzazepin-6-one (85).[96] A solution of dibenzazepinone **135** (30 mg, 0.072 mmol) and 10% palladium on carbon (6.5 mg, 0.0061 mmol) in ethanol (95%, 6 mL) was stirred under H_2 (1 atm, balloon) at 90 ℃ for 12 h. After cooled to rt, the mixture was filtered, and the filtrate was extracted with Et_2O. The extracts were combined, dried over $MgSO_4$ and filtered. After removal of volatile components from the filtrate, the resulting crude product was purified by flash chromatography (SiO_2, Et_2O/EtOH = 10/1) to give **85** (16.7 mg, 98%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.30 (m, 8H), 4.36 (s, 1H), 3.35 (s, 3H), 2.25 (br, 2H).

5-Pivaloyl-5,6-dihydro-6-phenyl-phenanthridine. A solution of **127** (20 mg, 0.045 mmol) in aqueous HCl (6 M, 0.4 mL) was stirred at rt overnight. Aqueous NaOH solution (1 M, 2.5 mL) was added, and the mixture was extracted with ethyl acetate. The extracts were combined, dried over $MgSO_4$ and filtered. Removal of volatile components from the filtrate afforded the product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.70–7.63 (m, 1H), 7.50–7.44 (m, 1H), 7.40–7.38 (m, 2H), 7.35–7.32 (m, 1H), 7.18–7.07 (m, 7H) 6.70 (s, 1H), 1.30 (s, 9H).

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