7-2015

Asymmetric Synthesis and Transition Metal-Catalyzed Cross-Coupling Arylations of Selected Organolithiums

Barry Kyle Sharp
University of Arkansas, Fayetteville

Asymmetric Synthesis and Transition Metal-Catalyzed Cross-Coupling Arylations of Selected Organolithiums

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in Chemistry

By

Barry Kyle Sharp
University of Arkansas
Bachelor of Science in Chemistry, 2009

July 2015
University of Arkansas

This dissertation is approved for recommendation to the Graduate Council.

_____
Matt McIntosh, Ph.D.
Committee Chair

_____
Neil Allison, Ph.D.
Committee Member

_____
Nan Zheng, Ph.D.
Committee Member

_____
James F. Hinton, Ph.D.
Committee Member

Abstract

My former boss, Dr. Gawley, always loved to say, “The world is chiral” (*à la* Pasteur). From DNA and proteins to hands and feet, it is obviously true. Also, a wide variety of chemical products exist as single enantiomers. Advances in chemical technology have greatly accelerated asymmetric synthesis in the past quarter century, and namely, organolithiums, have been shown to provide a versatile route to chiral natural products and biologically active molecules. Versatility arises from the array of methods that produce a chiral organolithium. Dynamic thermodynamic resolution (DTR) is considered one of the most practical methods, but among the others are asymmetric deprotonation and tin-lithium exchange. The selected targets for this investigation using chiral organolithiums, 2,3-dehydropyridones and chiral tertiary alcohols, are important building blocks for enantioselective synthesis. Practicality ultimately begins and ends with cost efficiency, and catalysis is generally a good place to start. Catalytic dynamic resolution (CDR), as well as conventional transition metal-catalyzed cross-coupling, has been applied with the intention of expanding the scope of organolithiums in asymmetric synthesis. The dynamic resolution of the ethylene and propylene ketal of *N*-Boc-2-lithio-4-oxopiperidine was investigated and resulted in a number of novel piperidine derivatives, and arylation of alkyl and benzyl carbamates *via* Negishi and Stille-type cross-coupling gave a number of novel tertiary alcohol precursors.

Acknowledgements

I would like to thank the late and great Dr. Gawley and his wife Lorraine, Dr. McIntosh and Karen, Nan, Drs. Allison and Hinton, Marv Lester and Jerry Holmsley, DT, and everyone who has been kind to me from the chemistry department.

Dedication

To my Parents and late grandparents.

Chapter 1: Asymmetric Synthesis of Organolithiums 1
1.1 Tin-Lithium Exchange 3
1.1.1 Tin-lithium Exchange of α-Aminoorganostannanes 6
1.2 Piperidines 10
1.2.1 Asymmetric Deprotonation of *N*-Boc-piperidine 10
1.2.2 Dynamic Resolution 19
1.2.3 2,3-Dihydropyridones 30
1.2.4 Investigations of the Ethylene Ketal of N-Boc-4-oxo-piperidine 32
1.3 α–Alkoxyorganolithiums 34
1.3.1 Tin-lithium Exchange of α–Alkoxyorganostannanes 35
1.3.2 Carbamates 38
1.4 Statement of the Problem 46
1.5 Results/Discussion 47
1.5.1. Piperidines 47
1.5.2. α–Alkoxyorganolithiums 60
1.6 Experimental Procedures 64
1.7. References 68

Chapter 2: Transition-metal catalyzed cross-coupling arylation 75
2.1 Cross-Coupling Arylations 75
2.1.1 Stille cross-coupling arylations 77
2.1.2 Negishi cross-coupling arylations 83
2.2 Chiral Diarylmethanols 87
2.2.1 Organometallic Additions to Aldehydes 87
2.2.2 Asymmetric Reduction of Ketones 92
2.3 Statement of the problem 96
2.4 Results/Discussion 97
2.5 Experimental Procedures 101
2.6. References 103

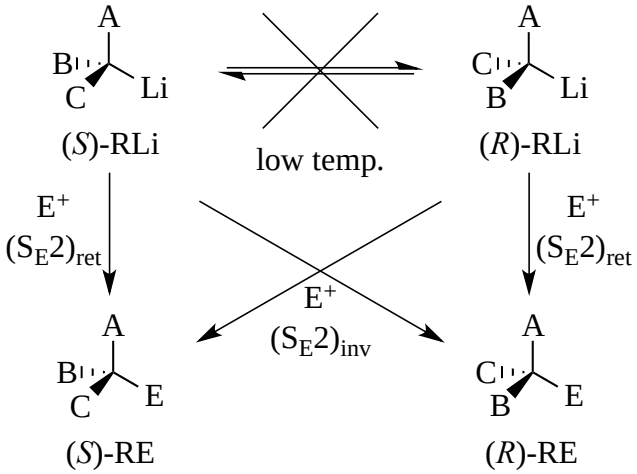
Chapter 1: Asymmetric Synthesis of Organolithiums

When designing a synthesis, several aspects must be considered. One of the most important and challenging requirements in chemical industries is the demand for enantioselectivity. There are a large number of medicinal, pharmaceutical, cosmetic, pesticidal, nutritional, and flavoring molecules that are marketed as single enantiomers.[1] Thus, there is an economic advantage for companies that manufacture these products to invest in improving this area of synthesis. In addition to the economic incentives, there are the illustrious goals of idealizing human existence, such as disease and hunger eradication, sustainable energy, painlessness, immortality, so on and so forth. Naturally, with such important tasks at hand, a diverse history of enantioselective methodologies exists in the literature.[2] One of the most capable and widespread approaches, as well as the most challenging in terms of understanding reactivity and developing laboratory techniques, is organolithiums.[3]

Organolithiums have several properties that give distinct advantages for inducing enantioselectivity. One of the most important properties of stereogenic C–Li carbons is their configurational stability at low temperatures. The resulting carbon-lithium bond is mostly ionic in nature, which lends itself to a configurational stability that is partially determined (for better or worse) by other polar interactions, such as coordination to external and internal ligands. A fundamental requirement for the utility of the chiral carbanion in asymmetric synthesis is that it be configurationally stable on a timescale relative to the rate of another chemical transformation in which the stereochemical integrity preserved (***Scheme 1.1.1***). A number of α-amino- and α-alkoxyorganolithiums, specifically those derived from piperidines and carbamates, have shown remarkable stability and as such, have been widely studied and exploited.[1, 4] Several mechanistic

studies that have focused on determining the solution structures and aggregation states shed light on the origin of the enantioselectivity of organolithium chemistry.[5]

Scheme 1.1.1. Configurational stability of organolithiums at low temperature

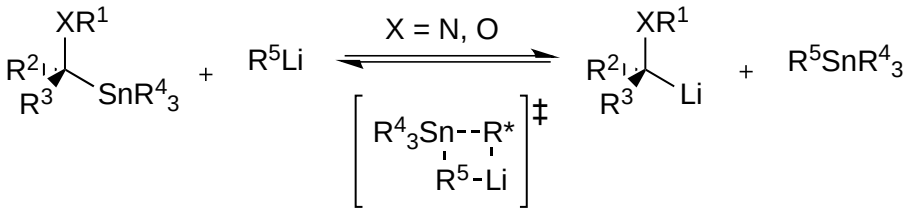


Another beneficial property of the carbanion is its high reactivity with electrophiles, even at cryogenic temperatures, allowing access to a variety of transformations *via* bimolecular electrophilic substitution with retention $(S_E2)_{ret}$ or inversion $(S_E2)_{inv}$.[6] A "one-size-fits-all" methodology for asymmetric manipulations using chiral organolithiums is lacking, and consequently, traditional preparations of enantiomerically enriched organolithiums have various limitations, such as substrate and functional group compatibility. In order to harness the utility of organolithiums, a robust knowledge of the literature pertaining to their specific generation and reactivity over a broad range of substrates is necessary.

1.1 Tin-Lithium Exchange

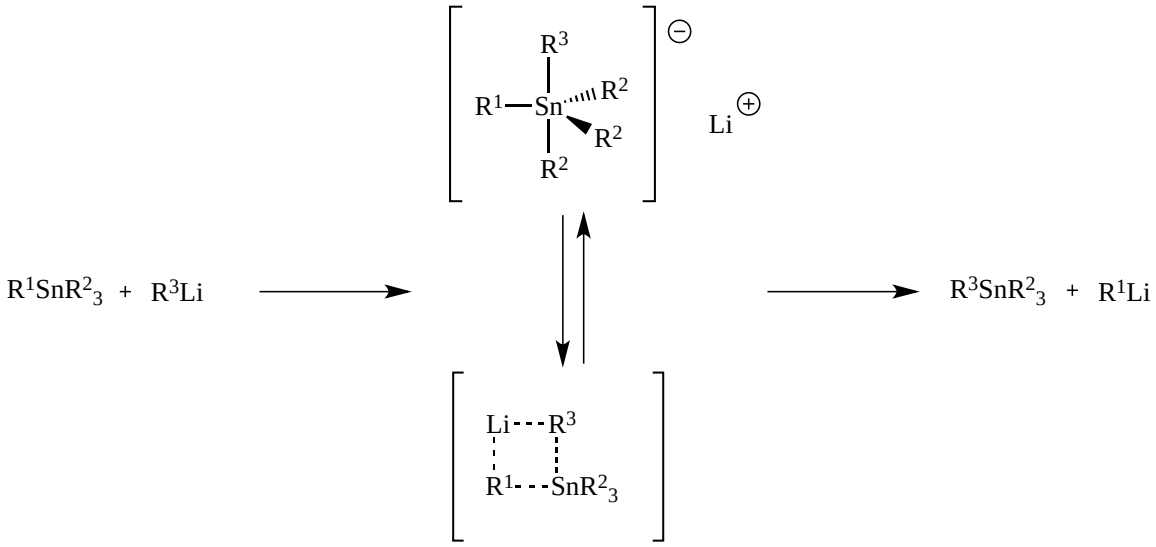
The transmetallation of tin to lithium has proven to be a very useful tool for the formation of organolithiums.[7] The exchange has garnered interest for several decades but is still not well understood. Seyferth and Weiner first reported the exchange in 1959.[8] C&E News later reported that the process was being used in the U.S.S.R. for stereospecific polymer production, which led to research groups in the free world beginning research on tin-lithium exchange. Since then, several investigations into the mechanism have been undertaken. It has been generally accepted that the exchange is retentive relative to absolute configuration and proceeds through a four-membered transition state, where the most thermodynamically stable carbanion that can be formed by the substituents on the stannane is transferred to the lithium (***Scheme 1.1.2***). The equilibrium is shifted toward the more stable carbanion by using linear alkyl groups on the tin except the transferred substituent that would be more favorably exchanged with the alkyl group on the lithium, leading to an unreactive tetraalkyltin and the desired organolithium. A study of the relative stabilities of organolithiums by Macdonald and McGarvey showed that α-induction by α-heteroatoms significantly lowers the ground state energy of the organolithium, which makes the exchange from tin to lithium more favorable.[9]

Scheme 1.1.2. Generalized tin-lithium exchange reaction



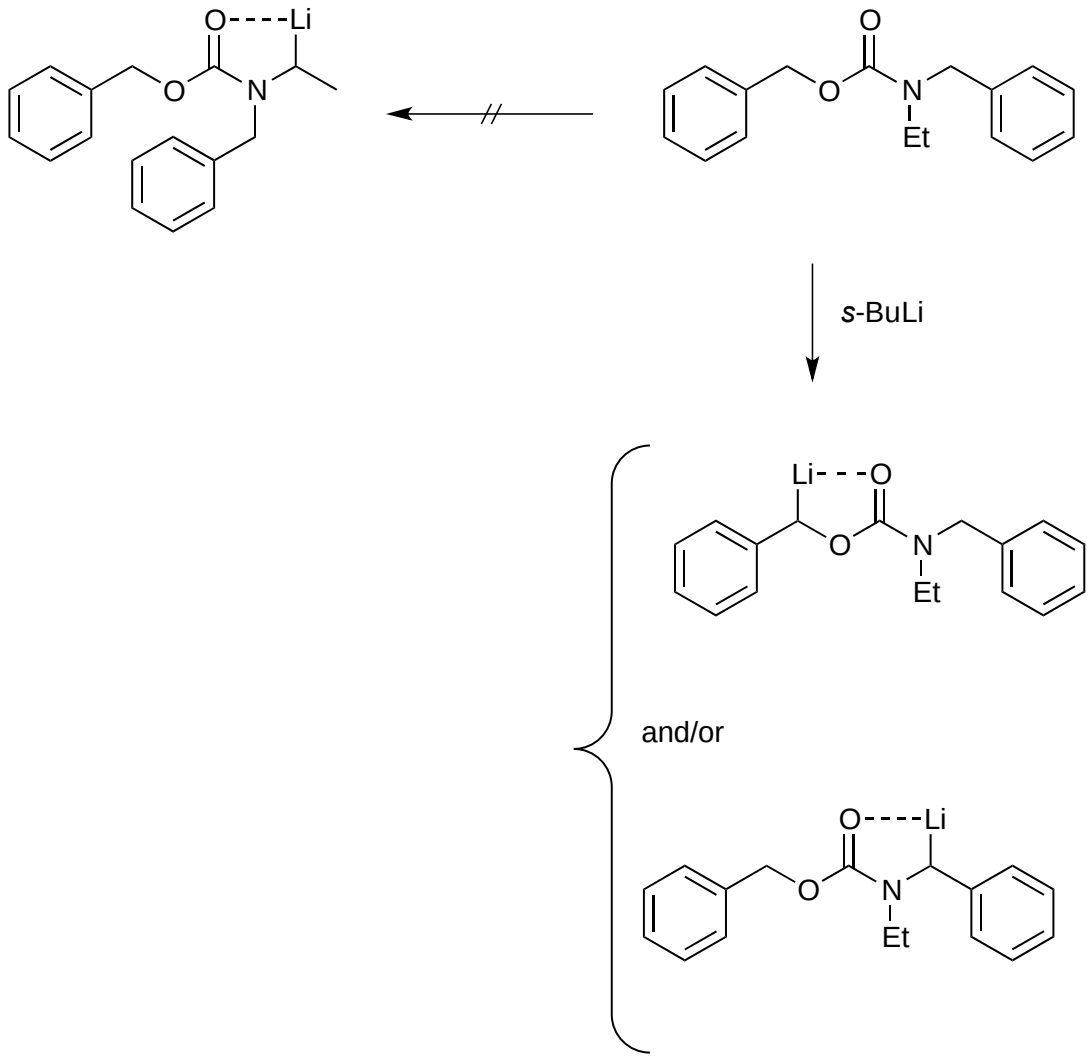
Later ^{1}H NMR experiments by Hans Reich showed evidence of an "ate" intermediate complex during the exchange, where the alkyl group of the organolithium is added to the tin, and forms a hypervalent pentaorganostannate with lithium as the counter ion (***Figure 1.1.1***).[10] The driving force to products can be amplified by chelation of the organolithium to another intramolecular heteroatom (*vide infra*).

Figure 1.1.1. Tin-lithium exchange intermediates

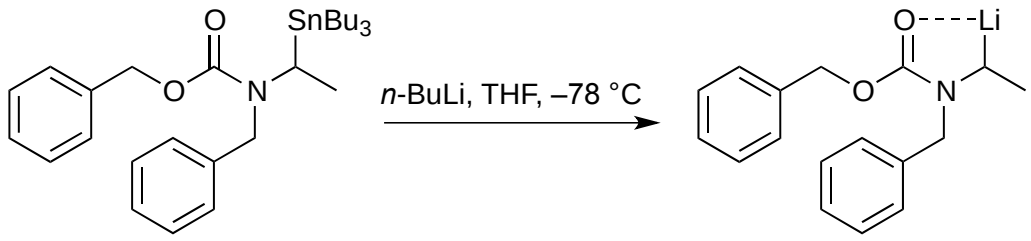


Tin-lithium exchange is especially useful for preparing organolithiums where alternative routes, such as direct deprotonation, are difficult or impossible. For example, it has the ability to deliver lithiation at a specific site, as well as overcome the kinetic barrier to deprotonation (***Scheme 1.1.3***). The benzylic hydrogens are more acidic, and would be preferentially removed by *s*-BuLi. However, if a substitution on the methylene α to nitrogen is desired, then an organostannane would provide the only access to this transformation, *via* transmetallation with *n*-BuLi.[11]

Scheme 1.1.3a. Undesired Deprotonative Lithiation



Scheme 1.1.3b. Desired Tin-Lithium Exchange



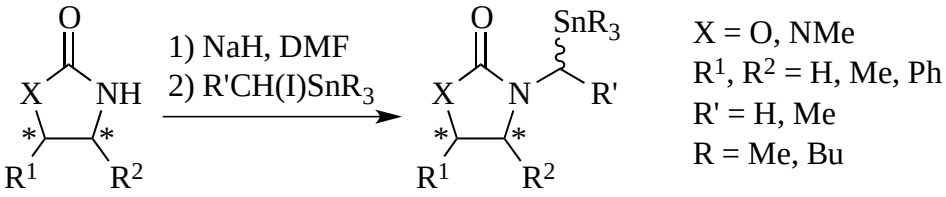
A number of α-heteroatom organostannane synthesis procedures are available for preparation of these configurationally stable, versatile compounds, further emphasizing the utility of organolithiums (*vide infra*).

1.1.1 Tin-lithium Exchange of α-Aminoorganostannanes

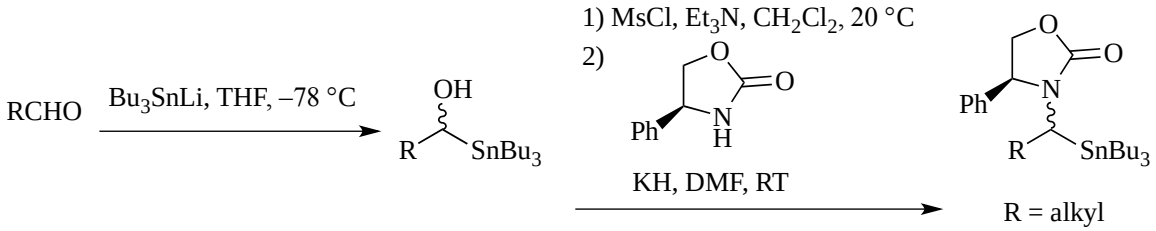
[*Tin-lithium exchange of α–alkoxyorganolithiums will be discussed in Sec 1.3.1*]

The first non-racemic α-aminoorganostannanes were made by S_N2 reactions on α-iodoorganostannanes by chiral oxazolidin-2-ones and imidazolidin-2-ones by Pearson and Lindbeck in 1991 (***Scheme 1.1.4***),[12] and later extended to α-mesyloxystannanes by Nakai and coworkers in 1998 (***Scheme 1.1.5***).[13] These methods exploit the addition of chiral auxiliaries, which form a mixture of diastereomers that can be separated by chromatography. Pure enantiomers can then be obtained after removal of the auxiliary.

Scheme 1.1.4. Pearson and Linbeck's *N*-alkylation with α-iodoalkylstannanes

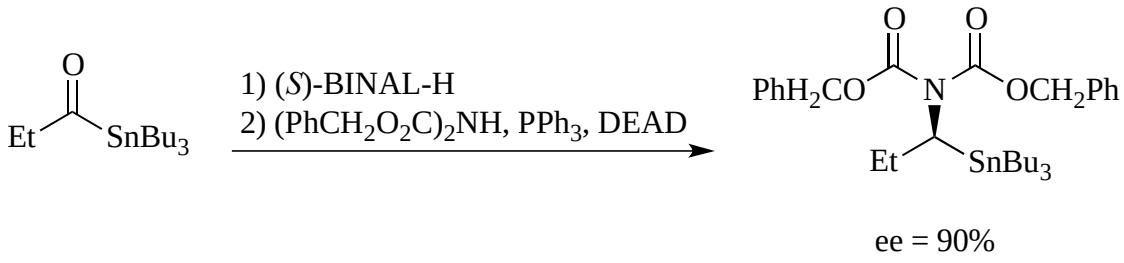


Scheme 1.1.5. Nakai's *N*-alkylation with α-mesyloxystannanes



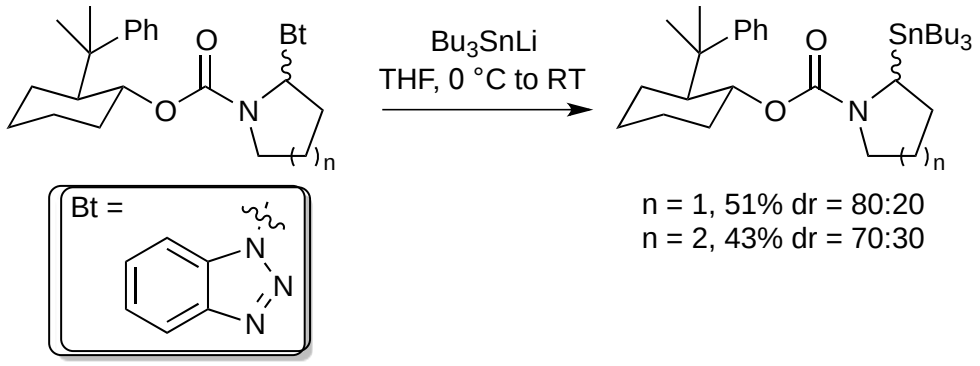
Chong and co-workers reported the first enantioselective synthesis of α-aminoorganostannanes using a BINAL reduction of acylstannanes followed by a Mitsunobu reaction (***Scheme 1.1.6***).[14]

Scheme 1.1.6. Chong's enantioselective synthesis of α-aminoorganostannanes

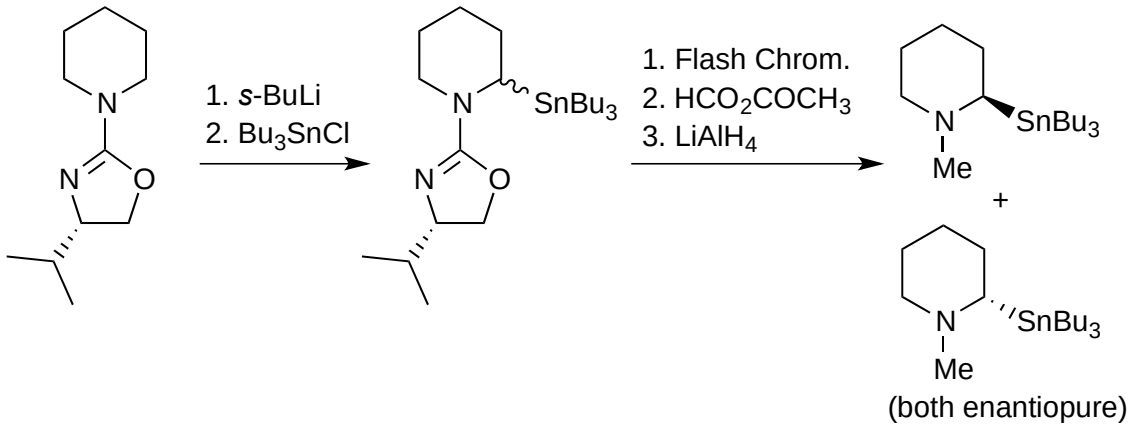


Gawley et al. used an S_N2 methodology directed by a chiral auxiliary, trans-cumylcyclohexanol (TCC), to give α-stannylpyrrolidine and –piperidine derivatives (***Scheme 1.1.7a***).[15] This work was a follow up to a previous report of a deprotonation using a chiral piperidinooxazoline, which similarly gave a single diastereomer of a piperidinostannane after separation by column chromatography (***Scheme 1.1.7b***).[16] Again, separation of diastereomers by chromatography is not ideal, but both of these methods allow access to either enantiomer of the piperidinostannane by choosing the appropriate stereoisomer of the chiral auxiliary.

Scheme 1.1.7a. Gawley's addition of lithium tributylstannane onto *N*-acyl pyrrolidine



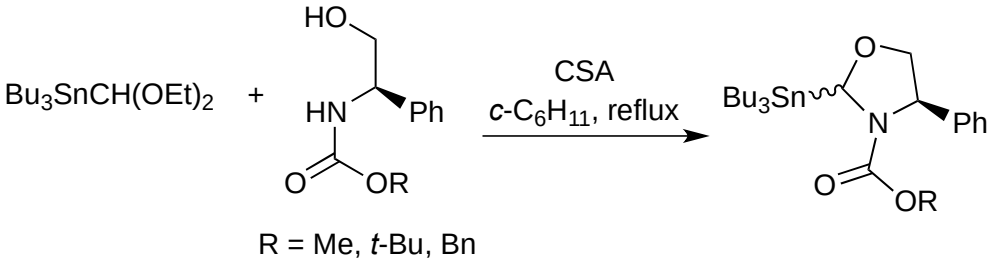
Scheme 1.1.7b. Gawley's addition of tributylstannanyl chloride to piperidinooxazoline



Peter Beak developed access to enantioenriched pyrrolidinostannanes directly by an asymmetric deprotonation, followed by electrophilic quenching with tributylstannane chloride (vide infra, ***Sec. 1.2.1***).

The French groups of Grognec and Quintard developed a more facile synthesis of very similar α-amino tin oxazolidin-2-ones from phenylglycinol (***Scheme 1.1.7c***).[17]

Scheme 1.1.7c. Grognec and Quintard's oxazolidin-2-ones

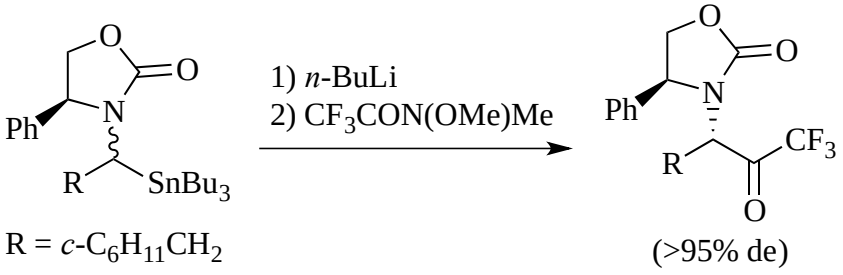


R = Me, *t*-Bu, Bn

There have been a number of biologically active molecules synthesized demonstrating the utility of α-aminoorganostannanes as building blocks toward chiral amines.[7]

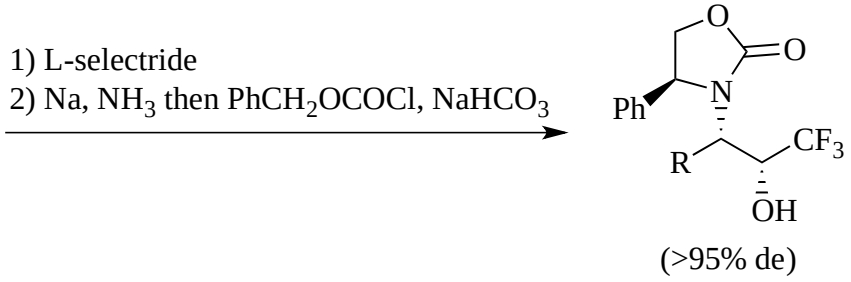
Nakai and coworkers used the methodology originally published by Pearson and Lindbeck (*vide supra*) to make β-amino alcohols, which are ubiquitous in natural products (***Scheme 1.1.8***).[13]

Scheme 1.1.8. Nakai's synthesis of β-amino alcohols



R = *c*-$C_6H_{11}CH_2$

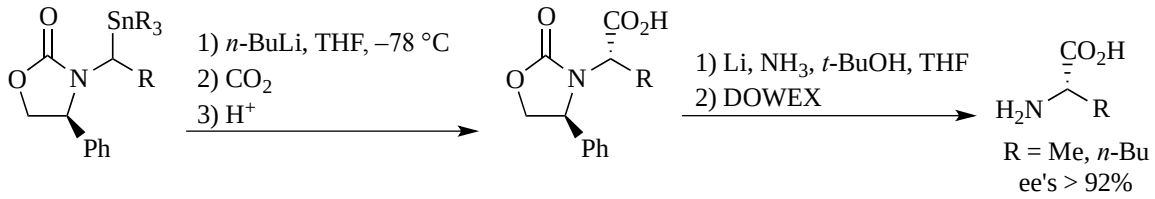
(>95% de)



(>95% de)

Fournet and coworkers also used this methodology to make highly enantioenriched α-amino acids (***Scheme 1.1.9***).[18]

Scheme 1.1.9. Fournet's enantioselective synthesis of α-amino acids



1.2 Piperidines

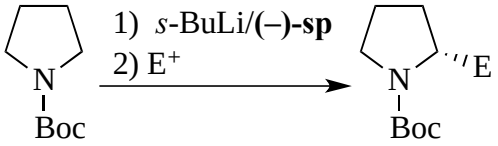
Piperidine rings are present in the backbones of a wide range of natural products and biologically active molecules.[19] There are several approaches that exploit the characteristics of chiral organolithiums discussed above in the asymmetric synthesis of piperidines. Chiral piperidine derivatives can be made directly *via* tin-lithium exchange (*vide supra*), asymmetric deprotonation, or dynamic resolution.

1.2.1 Asymmetric Deprotonation of *N*-Boc-piperidine

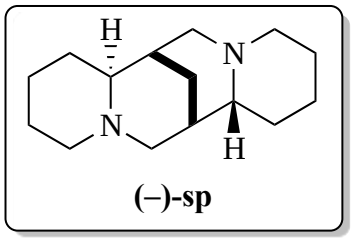
The development of organolithiums in the asymmetric deprotonation of *N*-acyl-heterocycles has led to a wide range of powerful, stereoselective processes.[20] The organolithium that arises from a deprotonative lithiation is configurationally stable at low temperature and can often be electrophilically quenched with stereochemical integrity maintained.

It was reported in the mid-90's that the asymmetric deprotonation of *N*-Boc-pyrrolidine, the next smaller homologue of *N*-Boc-piperidine, can proceed with high enantioselectivity (***Scheme 1.2.1***).[5c] Deprotonation selectively removes the pro-S hydrogen *via* a ternary complex of the chiral base formed by isopropyllithium and (–)-sparteine (**(–)-sp**), and *N*-Boc-pyrrolidine *via* a well-characterized mechanism.[21] Computational studies showed that the most favorable ternary complex and transition state both suggested the stereochemical course was determined principally by sterics, as opposed to electronics. The chiral base complex first associates with the carbonyl oxygen of *N*-Boc-pyrrolidine, which places the alkyl group of the organolithium base directly above the proximal α-amino carbon. This process is termed the complex-induced proximity effect, (CIPE), where the proximal carbonyl oxygen directs the regioselective deprotonative lithiation.[22] The difference between the lowest activation energy for the transition state of pro-*S* and pro-*R* proton transfer was ~1 kcal/mol. The pro-*S* hydrogen is the least sterically hindered because the distance between non-bonding hydrogen atoms on (–)-sp and the piperidine ring during the transfer of the pro-*S* proton to the alkyl group on the organolithium base is longer than the distance between the non-bonding hydrogens on (–)-sp and the piperidine ring in the transfer of the pro-*R* proton. The highly enantioselective synthesis of a number of pyrrolidine derivatives are available by asymmetric deprotonation.[3b] The expansion of this system to *N*-Boc-piperidine was not as straightforward as one might have expected.

Scheme 1.2.1. Asymmetric deprotonation of *N*-Boc-pyrrolidine



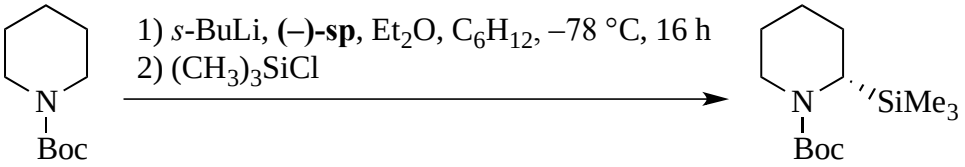
E = $Si(CH_3)_3$, $(C_6H_5)_2COH$, CO_2H, CH_3, $Sn(C_4H_9)_3$, CH_2OH, $(CH_3)_2COH$



(–)-sp

Marginal success in the asymmetric deprotonation of *N*-Boc-piperidine was reported by the Beak group using the same procedure they developed for *N*-Boc-pyrrolidine.[23] The deprotonation proved to be slow (~16 h) and yielded only 8% of the desired product (**1**), but it gave the *S* enantiomer with moderate er (87:13) (***Scheme 1.2.2***).

Scheme 1.2.2. Beak's Asymmetric Deprotonation of *N*-Boc-Piperidine



8% yield, 87:13 er

(*S*)-1

Due to the long reaction time, the major product was formed from the competing reaction of *s*-BuLi attacking on the Boc group (***Figure 1.2.1***). Computational studies predicted that, of the four α-amino hydrogen atoms, the least acidic was the equatorial, pro-*S* that led to the major stereoisomer formed (***Figure 1.2.2***).

Figure 1.2.1. Byproducts of BuLi attack on the Boc group

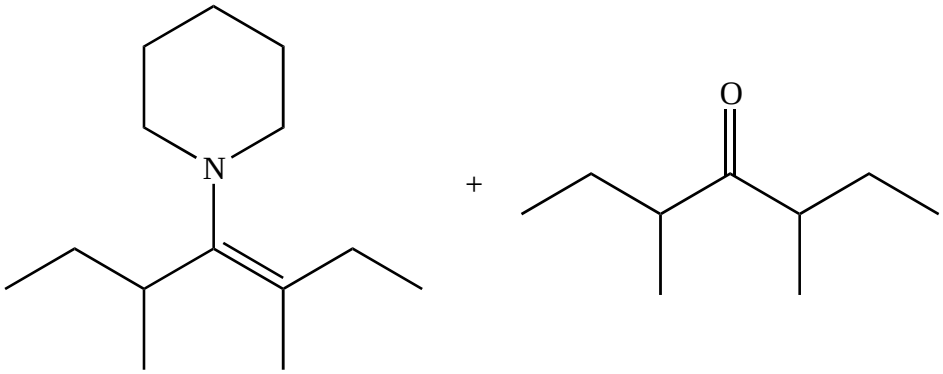
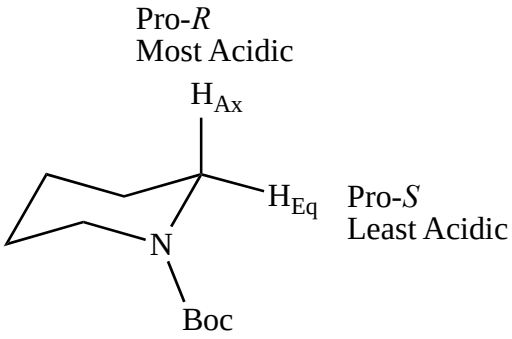
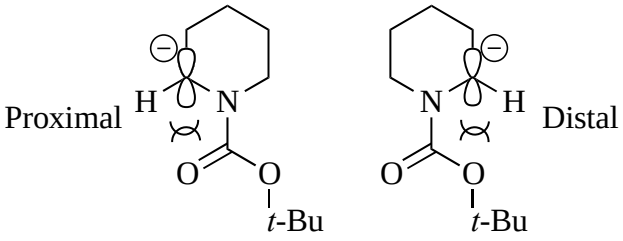


Figure 1.2.2. Calculated relative acidities of α-amino protons



The calculations suggest that the carbanion resulting from abstraction of an axial proton would have the optimal charge distribution through the pi system of the carbonyl, which would also be oriented distal to the carbonyl oxygen to further reduce repulsive interactions (***Figure 1.2.3***).

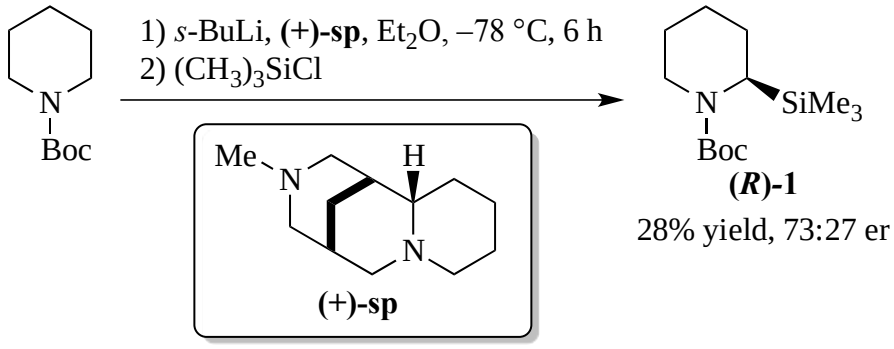
Figure 1.2.3. Optimal charge distribution after abstraction of axial proton



Since this deprotonation is obviously not the one that leads to the major stereoisomer, a similar ternary complex, as proposed for *N*-Boc-pyrrolidine, was investigated computationally. The lowest ground state energy of the ternary complex and the lowest activation energy of the transition state of the pro-*S* and pro-*R* proton transfers are not significant and neither would be relatively favorable. These calculations agree with the experimental results that the high kinetic barrier to deprotonation accounts for the long reaction time, and the lower enantioselectivity arises from the similar activation energies of competing stereochemical pathways.

O'Brien tested the reactivity of several diamine / *s*-BuLi complexes, and one, later referred to as O'Brien's (+)-sparteine surrogate [**(+)-sp**] due to its opposite stereoselectivity relative to (–)-sp, was more reactive than (–)-sp, even though the two have similar steric bulkiness.[24] The competitive deprotonation of *N*-Boc-pyrrolidine using (–)-sp, which gives 95:5 *S:R*, and (+)-sp, which gives 5:95 *S:R*, was used to determine the relative reactivity of the two diamine ligands. The product of the competition was 10:90 *S:R*. The increased reactivity of (+)-sp relative to (–)-sp for the deprotonative lithiation of *N*-Boc-pyrrolidine was anticipated to perform similarly in the deprotonative lithiation of other substrates that are not as facile as *N*-Boc-pyrrolidine, such as *N*-Boc-piperidine. O'Brien used his surrogate in the asymmetric deprotonation of *N*-Boc-piperidine to obtain an increased yield (28%), but lower selectivity (73:27 er) favoring the *R* enantiomer (***Scheme 1.2.3***).

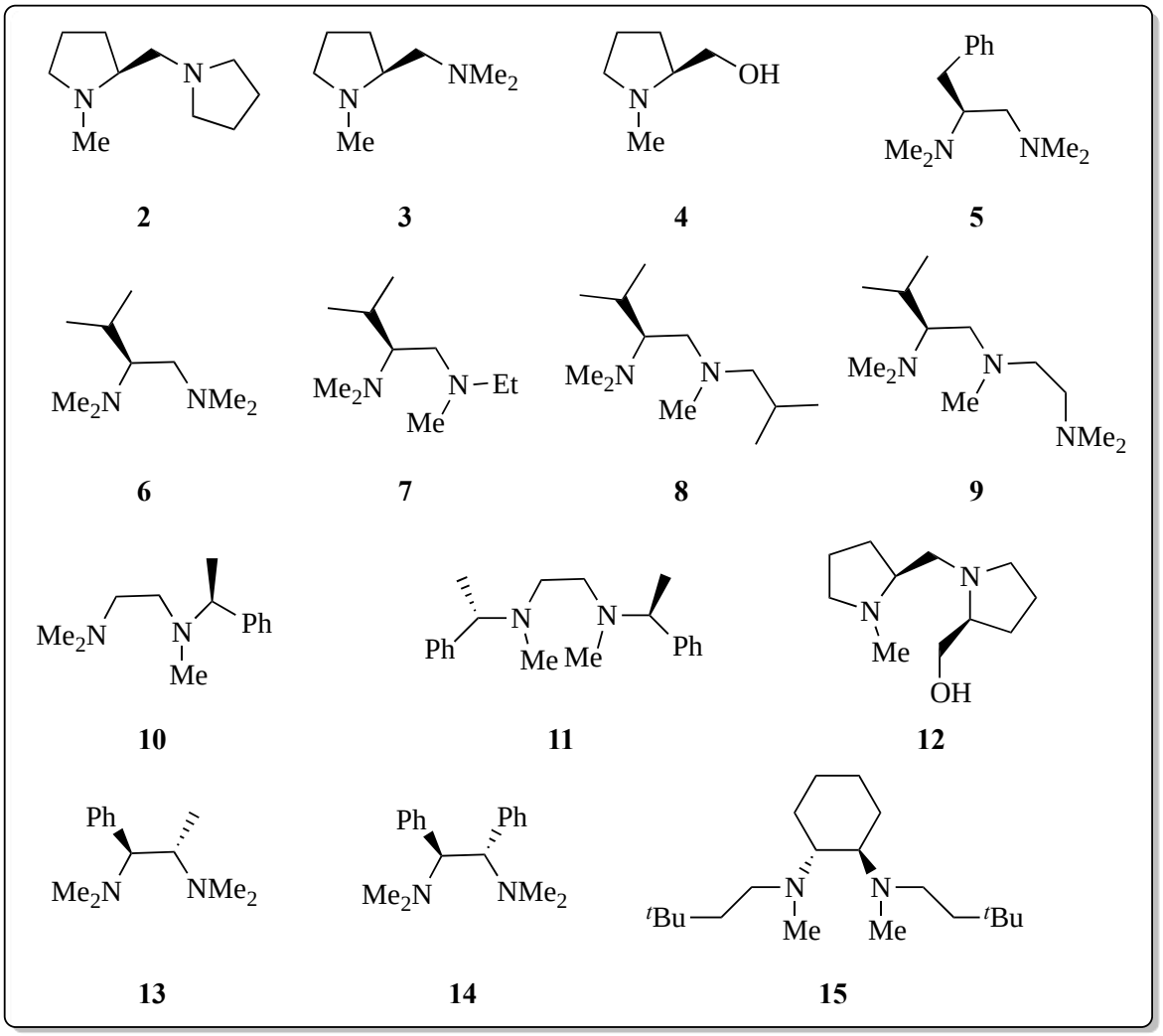
Scheme 1.2.3. O'Brien's Asymmetric Deprotonation of *N*-Boc-piperidine



In 1990, Beak showed that efficient proton abstraction could occur using s-BuLi and the achiral ligand, *N,N,N',N'*-tetramethylethylenediamine (TMEDA), but obviously led to racemic products. TMEDA leads to higher yields by stabilizing the carboanion.[25]

In 2007, the O'Brien and Coldham groups jointly investigated several chiral TMEDA derivatives, as well as a few other chiral ligands derived from amino acids, in the asymmetric deprotonation of *N*-Boc-piperidine.[26] Minimal success was achieved using the ligands in ***Figure 1.2.4*** instead of (+)-sp. The best results were achieved with **5** giving 50% yield, but only 65:35 er, and **15** giving 90:10 er, but only 13% yield.

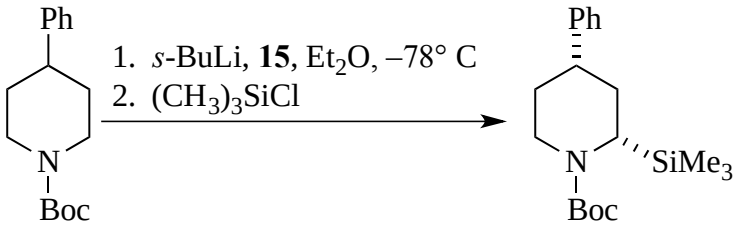
Figure 1.2.4. O'Brien and Coldham ligands investigated in the asymmetric deprotonation of *N*-Boc-piperidine



In 1993, Beak demonstrated that *N*-Boc-4-phenylpiperidine is more reactive than *N*-Boc-piperidine in deprotonative lithiation.[27] Interestingly, racemic deprotonation followed by electrophilic substitution of this substrate gives only the *cis*-diastereomers and none of the *trans*. Assuming that the reaction proceeds similarly as with *N*-Boc-piperidine, such that the equatorial proton is abstracted, followed by retentive electrophilic quench, then the axial proton is virtually not abstracted. Therefore, conversion between the *cis*-enantiomers is only possible by a rotation

of the Boc group, which is known to be very slow at low temperatures (several hours). The authors reasoned that a kinetic resolution (KR) should be possible using a chiral ligand if one diastereomeric rotamer is more reactive than the other. If a kinetic resolution is controlling the stereochemical course, then allowing the reaction to progress to less than 50% yield would lead to an increase in selectivity because only the diastereomer that reacts faster (*cis*) will be converted to product. The addition of a chiral ligand would influence the stereoselectivity of the active diastereomers toward formation of products. The KR of this substrate indeed gave the most successful result by using ligand **15** to give 48% yield and 87:13 er of the *cis*-diastereomers (***Scheme 1.2.4***).[26]

Scheme 1.2.4. Kinetic Resolution of *N*-Boc-4-phenylpiperidine

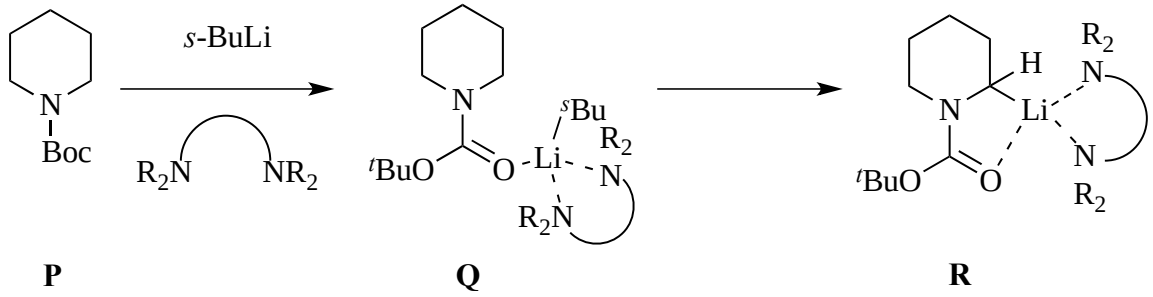


48%, 87:13 er

Recently, the O'Brien and Coldham groups collaborated again to optimize their procedure for the asymmetric deprotonation of *N*-Boc-piperidine using (+)-sp.[28] They used React-IR to provide experimental support for the formation of a ternary complex prior to deprotonative lithiation. The reaction proceeds first by the chiral base complex coordinating to the carbonyl of the Boc group (CIPE, vide supra), as shown by a lowering of the carbonyl absorption frequency (**Q** in ***Scheme 1.2.2***). The React-IR showed the less reactive (–)-sp maintaining about a 50:50 ratio of the non-lithiated species (**P** in ***Scheme 1.2.2***) and the pre-lithiation species (**Q** in ***Scheme 1.2.2***), with

only minimal amounts proceeding to the desired organolithium species **(R** in ***Scheme 1.2.2***). This result is consistent with the very low yields of asymmetric deprotonation using (–)-sp observed by Beak.[23]

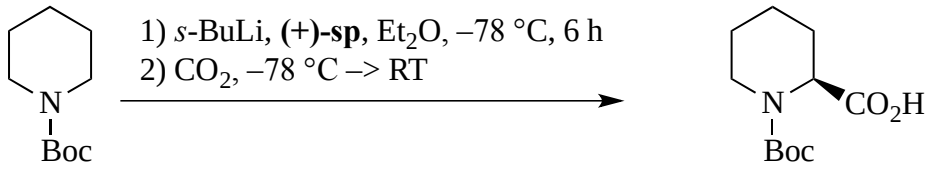
Scheme 1.2.5. CIPE in the Asymmetric Deprotonation of *N*-Boc-piperidine



P **Q** **R**

The reaction conditions were optimized using (+)-sp to give good yields and selectivities with several electrophiles, which is an impressive approach to make (*R*)-*N*-Boc-2-pipecolic acid, where E^+ is CO_2, in 88:12 er with a yield of 92% (***Scheme 1.2.6***). The authors reported a decrease in enantioselectivity when more bulky electrophiles were used, *e.g.* $PhMe_2SiCl$. They speculated that these more sterically hindered electrophiles reacted at temperatures that were competitive with racemization. Also, the lower er obtained in O'Brien's previous work with (+)-sp on *N*-Boc-piperidine can be rationalized by the crowding of the carbanion by using 2.4 equivalents of the chiral diamine.[24] A significant disadvantage of using (+)-sp is that only one enantiomer is readily accessible.

Scheme 1.2.6. Optimized Asymmetric Deprotonation of *N*-Boc-piperidine



(*R*)-*N*-Boc-2-pipecolic acid
92% yield, 88:12 er

1.2.2 Dynamic Resolution

Without question, Peter Beak would be the first bust carved into the Mt. Rushmore of asymmetric substitution by dynamic resolution. He has laid a sturdy, encompassing foundation for inducing enantioselecivity by manipulation of reaction conditions to accentuate kinetic and thermodynamic differences of diastereomeric complexes.[3]

A resolution occurs whenever diastereomeric complexes can be isolated based on their relative ground state energies, the activation energy required for conversion to product, and/or the barrier to stereoisomerization. The racemic organolithium is made by either deprotonation or transmetallation from tin. Addition of a chiral ligand to coordinate the organolithium forms a mixture of diastereomers ((*R*)-RLiL* and (*S*)-RLiL*). When one diastereomer reacts faster than the other, and they do not interconvert, this is a classical kinetic resolution (***Figure 1.2.5a***). The enantioenrichment of the products, ((*R*)-RE, (*S*)-RE), depends on the extent to which the reaction is allowed to proceed.

When one diastereomer reacts faster than the other and the stereoisomerization is rapid, then a dynamic kinetic resolution (DKR), controlled by the Curtin-Hammett principle, is possible. The product ratio is determined by the relative rates of reaction with the electrophile. The electrophilic quench occurs by slow addition or repeated substoichiometric additions of

electrophile to allow for the equilibration. DKR requires the barrier for interconversion between diastereomers is lower than E^+ quench.

The third type of resolution is dynamic thermodynamic resolution, where the diastereomeric complexes are warmed to allow for equilibration to the thermodynamically more stable isomer prior to rapid freezing of the equilibration and electrophilic quench. The er of products is determined by the thermodynamic equilibrium of the diastereomers (***Figure 1.2.5b***).

Figure 1.2.5a. Kinetic Resolution

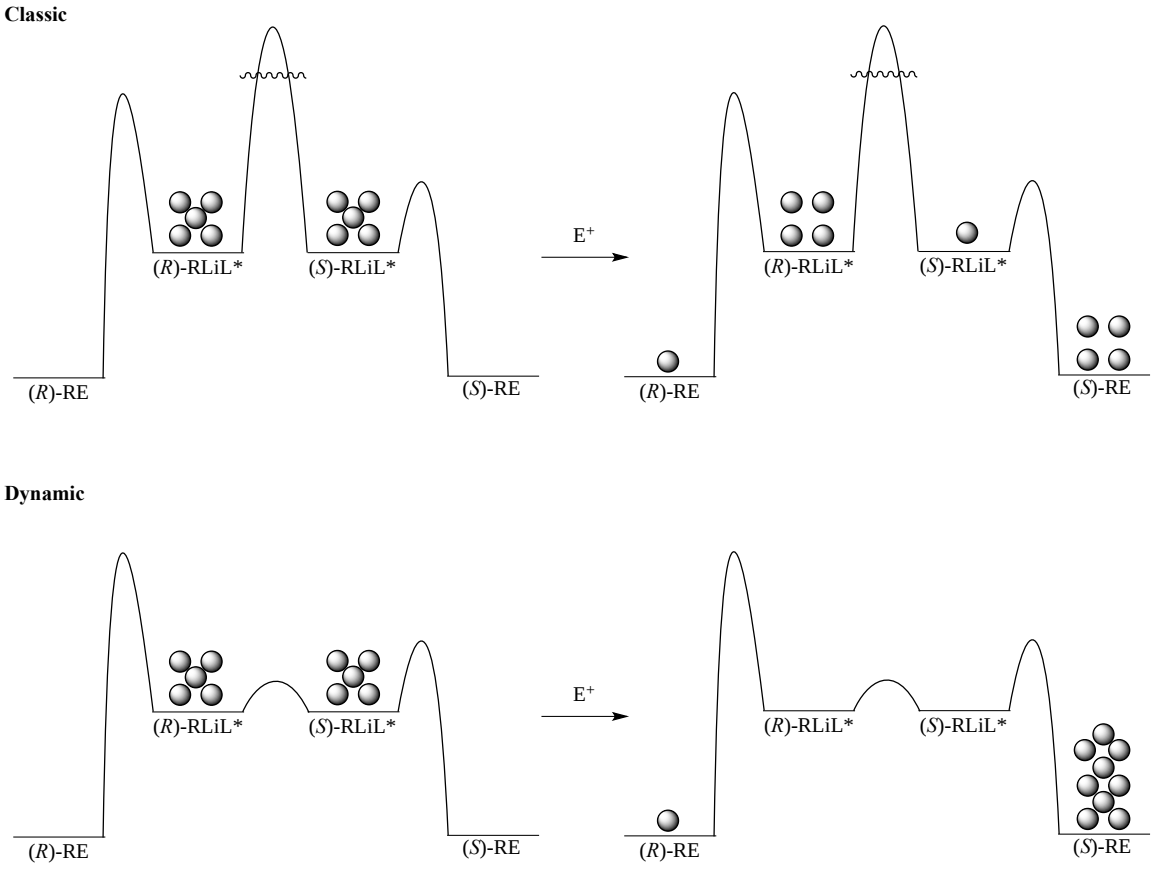
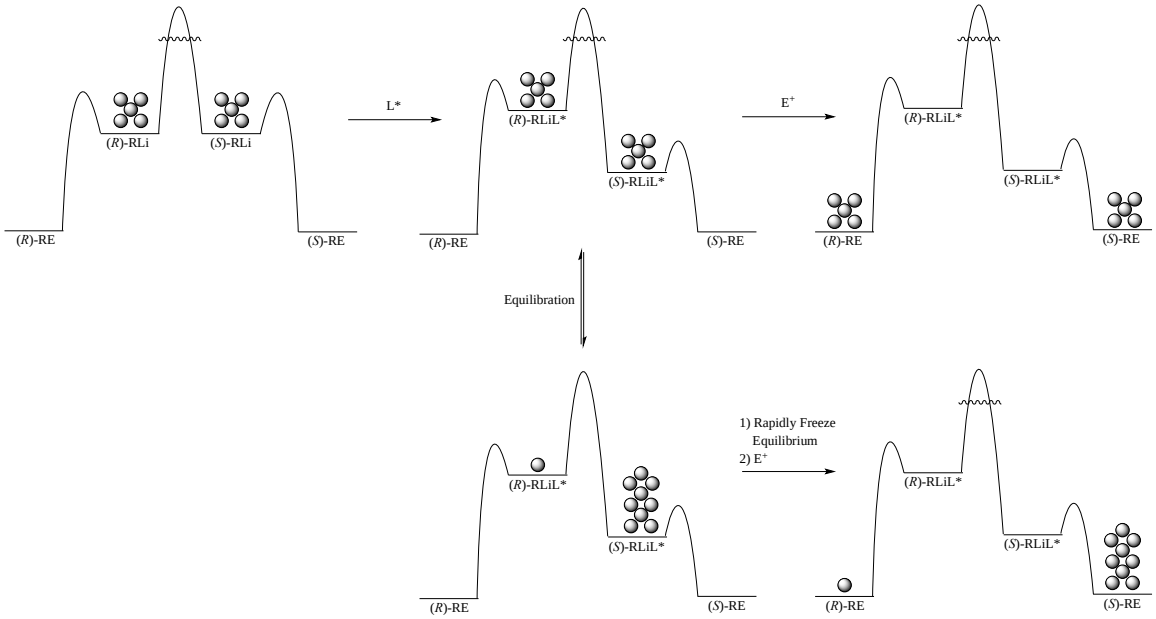


Figure 1.2.5b. Dynamic Thermodynamic Resolution



A key requirement for a dynamic thermodynamic resolution to be realized experimentally is configurational stability at the Li-C stereocenter at low temperature and configurational instability at higher temperatures. Warming the population of diastereomers allows the barrier to interconversion to be overcome, so the population can reach the thermodynamic equilibrium. The reaction mixture must be rapidly cooled to stop interconversion and restore configurational stability, followed by quenching with an electrophile to give the enriched products, ((*R*)-RE, (*S*)-RE). This requires that the barrier for interconversion between diastereomers be higher than the barrier for electrophilic quench.

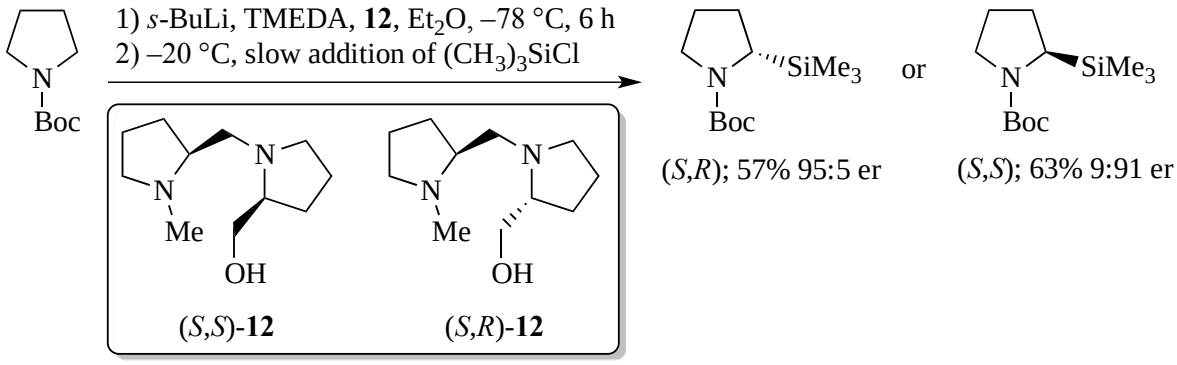
If the more stable diastereomer is also the most reactive towards electrophilic quench, then kinetic and thermodynamic control can be used in tandem. Substoichiometric amounts of electrophile can be added at low temperature after resolution, followed by subsequent cycles of warming to equilibration and rapid cooling prior to another substoichiometric addition of

electrophile.

On the other hand, if the more stable diastereomer is less reactive towards electrophilic quench, then a substoichiometric amount of a sacrificial electrophile can be added to consume the less populated, more reactive stereoisomer. A highly reactive sacrificial electrophile is complemented by a less reactive electrophile that leads to the desired product for maximum enantioselectivity.

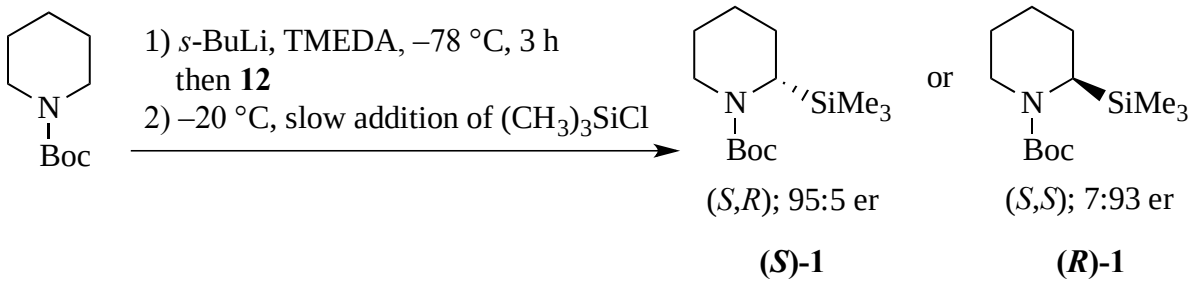
After the initial failures of asymmetric deprotonation on *N*-Boc-piperidine, several dynamic resolutions were published. The first investigations into the dynamic resolution of *N*-Boc-piperidine were by the Coldham group. The DKR of *N*-Boc-2-lithio-pyrrolidine was optimized using the diamino alcohol ligand, (*S*,*R*)-**12** to give the *S* product in 91:9 er, and (*S*,*S*)-**12** gave the *R* product with 95:5 er, both with about 60% yield (***Scheme 1.2.7***).[29] After deprotonation at –78 °C, the temperature was raised to –20 °C in order to allow for the interconversion of diastereomeric complexes. The results of the higher temperature quench showed that the thermodynamically favored diastereomer was less reactive to electrophilic quench because the opposite enantiomer was produced at low temperature (where the interconversion is slower).

Scheme 1.2.7. DKR of *N*-Boc-pyrrolidine



Similar results were shown when the same ligands were used in the DKR of *N*-Boc-piperidine.[30] The (*S*,*R*)-**12** gave the S product in 95:5 er, and (*S*,*S*)-**12** gave the R product with 93:7 er, both with about 60% yield (***Scheme 1.2.8***). Again, the thermodynamically favored diastereomer was less reactive towards electrophilic quench. High stereoselectivity was only achieved using chlorotrimethylsilane, $(CH_3)_3SiCl$, since more reactive electrophiles did not selectively react with either diastereomer.

Scheme 1.2.8. DKR of *N*-Boc-piperidine



Following the promising, but limited DKR, Coldham published the first successful DTR of *N*-Boc-2-lithiopiperidine.[31] Under DTR conditions with **(*S*,*R*)-12**, the *R* product is obtained in 58:42 er, and **(*S*,*S*)-12** favored the formation of the S product with 77:23 er (***Scheme 1.2.9***). The

low selectivity prompted the investigation of several other diamino alcohol ligands' ability to influence a DTR, which are listed in ***Figure 1.2.6***. A handful of ligands showed good enantioselectivity using Me_3SiCl as the control electrophile (***Table 1.2.1***). Using **1**7, the substrate scope was expanded to acylation using DMF (54% yield, 77:23 er), stannylation using Bu_3SnCl, (65% yield, 80:20 er), and allylation using allyl bromide *via* zinc-cuprate transmetallations (47% yield, 79:23 er).

Scheme 1.2.9. Coldham's conditions for DTR of *N*-Boc-piperidine

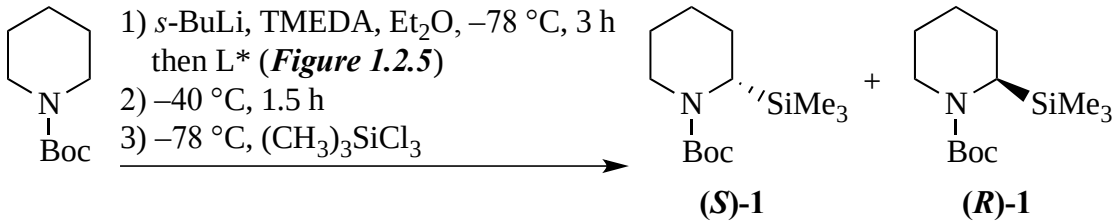


Figure 1.2.6. Coldham's ligands investigated in the DTR of *N*-Boc-piperidine

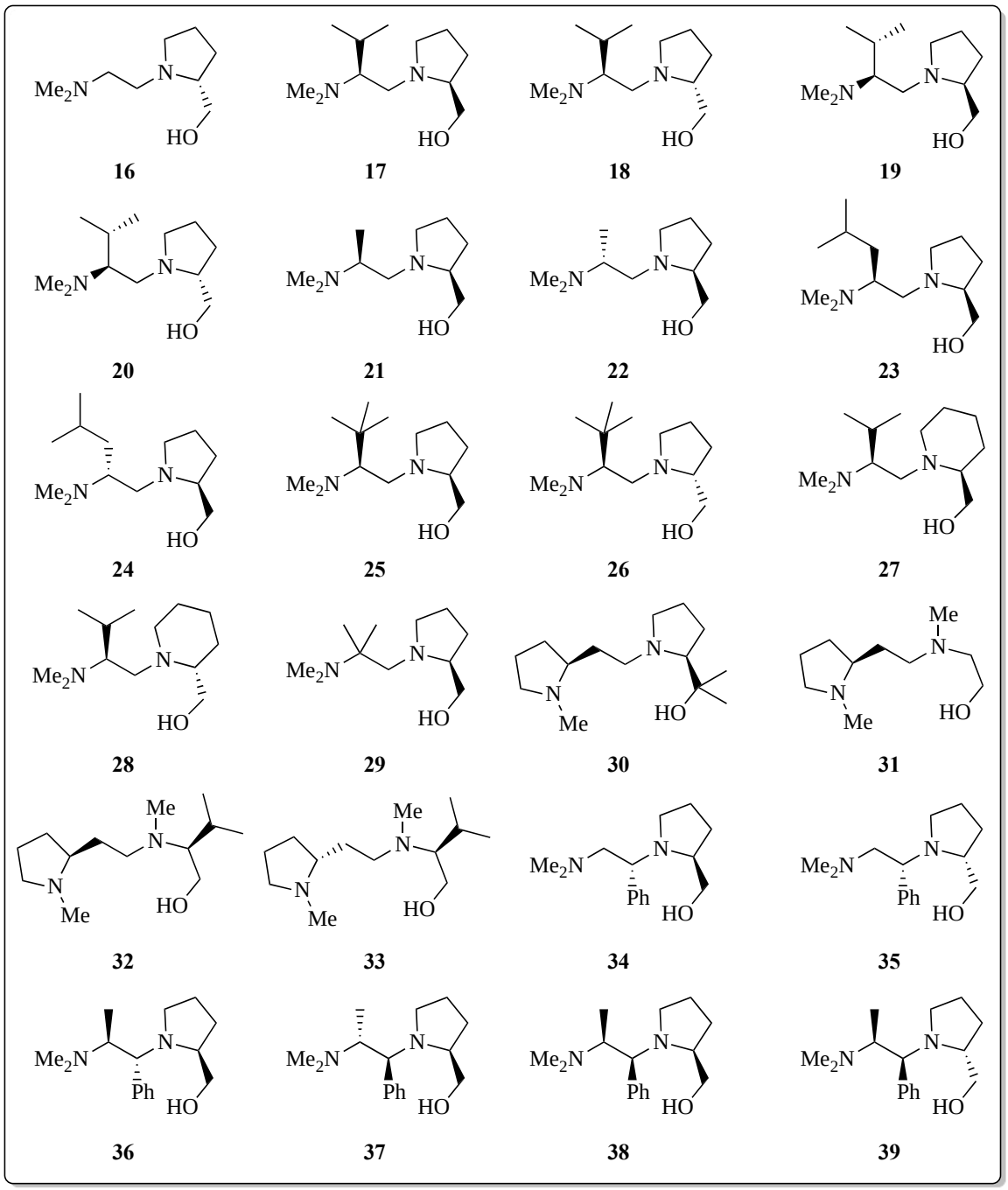
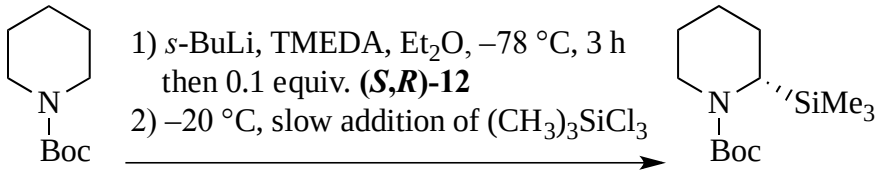


Table 1.2.1. DTR results with diamino alcohol ligands from ***Figure 1.2.6***

L*	***er (S : R)***	***L****	***er (S:R)***
(*S*,*R*)-12	42 : 58	27	56 : 44
(*S*,*S*)-12	77 : 23	28	20 : 80
16	41 : 59	29	55 : 45
17	80 : 20	30	72 : 28
18	15 : 85	31	46 : 54
19	82 : 18	32	55 : 45
20	22 : 78	33	50 : 50
21	51 : 49	34	52 : 48
22	51 : 49	35	51 : 49
23	85 : 15	36	57 : 43
24	49 : 51	37	51 : 49
25	65 : 35	38	81 : 19
26	23 : 77	39	30 : 70

Recently, the procedure was optimized, using ligand **23** in ***Figure 1.2.6***, to obtain (*S*)-*N*-Boc-2-pipecolic acid, 62% yield and 87:13, where E^+ is CO_2.[32] The authors also reported a catalytic dynamic kinetic resolution, again only viable with Me_3SiCl, using (*S*,*R*)-12 to obtain **(*S*)-1** with 96:4 er (***Scheme 1.2.10***). This shows that ligand exchange between the achiral and chiral ligands occurs rapidly, and the minor diastereomer reacted much faster than the major.

Scheme 1.2.10. Catalytic DKR of *N*-Boc-piperidine

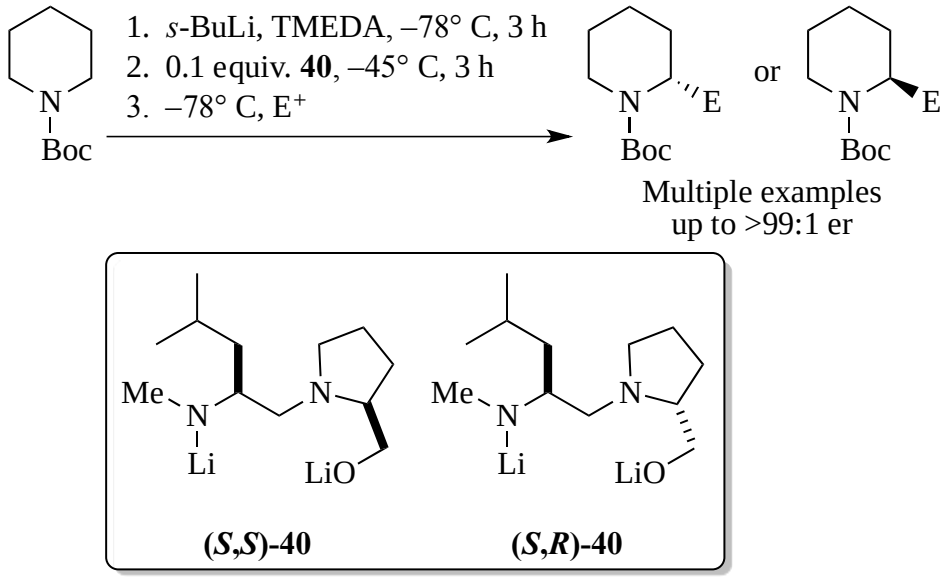


(*S*)-1

In 2010, Beng and Gawley published the DTR of *N*-Boc-piperidine, using diastereomeric dilithio-diamino alkoxide ligands, **40**, to give **1** with up to 96:4 er (*S:R*) and 2:98 (*S:R*) with either diastereomer of the ligand respectively.[33] The differences in free energy barriers for racemization and resolution in the presence of the achiral and chiral ligands respectively, allow for the possibility of catalysis of the resolution. As shown by their previous example of *N*-trimethylallylpiperidine, a plot of $\Delta G^{\ddagger}$ vs. temperature gives the crossover point, below which resolution is faster than racemization.[5e] If exchange between achiral and chiral ligands occurs rapidly and a configurationally stabile complex with the achiral ligand is formed, then resolution using a catalytic amount of the chiral ligand is possible.

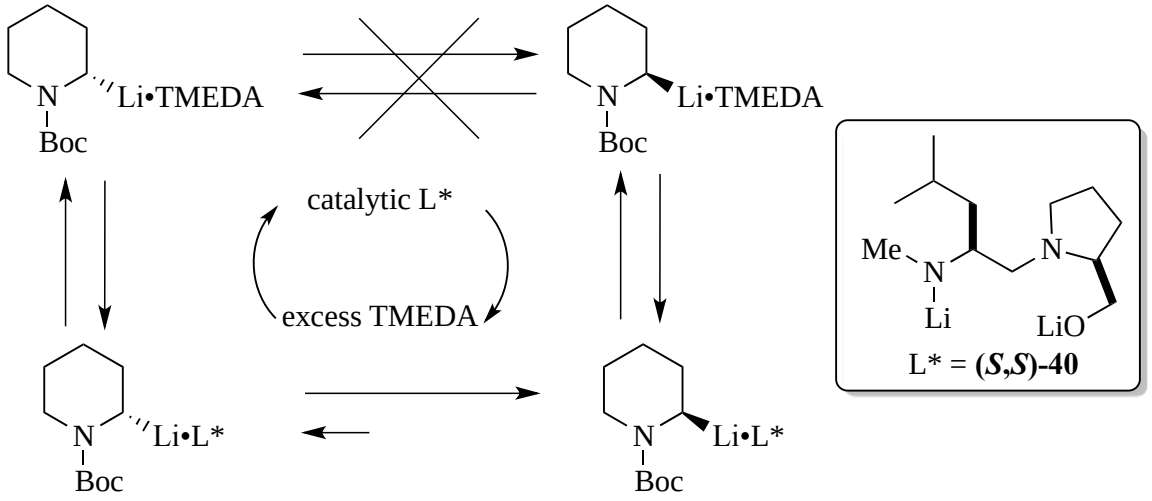
The subsequent catalytic dynamic resolution (CDR) achieved up to >99:1 er with multiple electrophiles using either diastereomer of the chiral ligand (***Scheme 1.2.11***). The scope of reactions includes acylations, alkylations, allylations, arylations, and vinylations.[33-34]

Scheme 1.2.11. Gawley's CDR of *N*-Boc-piperidine



Recently, Gawley and Williard reported a comprehensive investigation into the mechanism of CDR.[5d] An excess of achiral ligand, TMEDA, was shown to be the key ingredient for CDR of *N*-Boc-piperidine as the excess (4 equiv.) accelerates resolution and retards racemization. Analysis of ^{6}Li NMR did not yield a well-defined solution structure of the organolithium, but showed that the racemic and enantiopure aggregations were different and those dynamic phenomena were exhibited at temperatures above –60 °C. Fractional kinetic orders of the chiral ligand indicate a deaggregation event for the transition state. From this data, a catalytic cycle was proposed (***Scheme 1.2.12***).

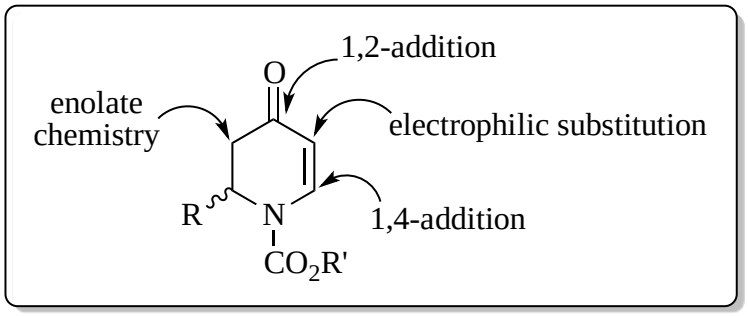
Scheme 1.2.12. Proposed catalytic cycle for the CDR of N-Boc-2-lithiopiperidine



1.2.3 2,3-Dihydropyridones

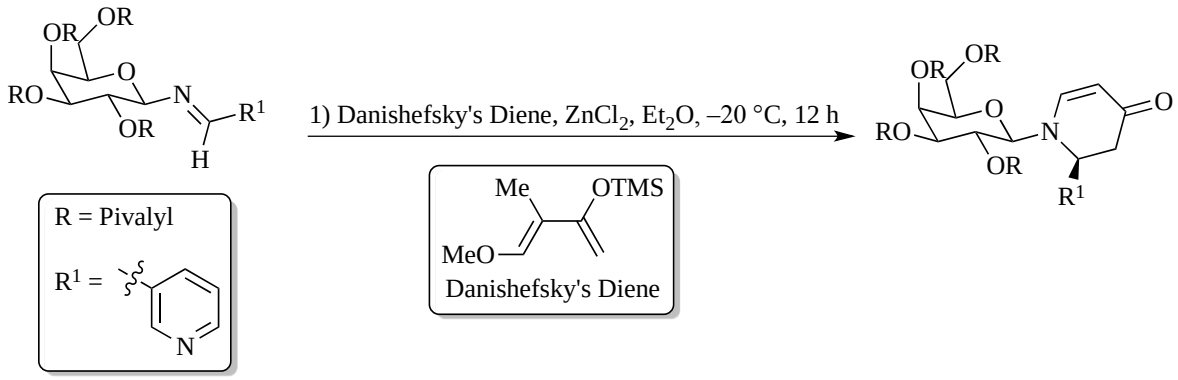
The highly functionalized piperidine derivatives, 2,3-dihydropyridones, have been used as intermediates in the syntheses of a wide variety of alkaloids and other natural products (***Figure 1.2.7***).[35] These substrates are facilely accessible *via* asymmetric derivation of 4-oxopiperidine (***Section 1.4***).

Figure 1.2.7. Functionalization of 2,3-dihydropyridones



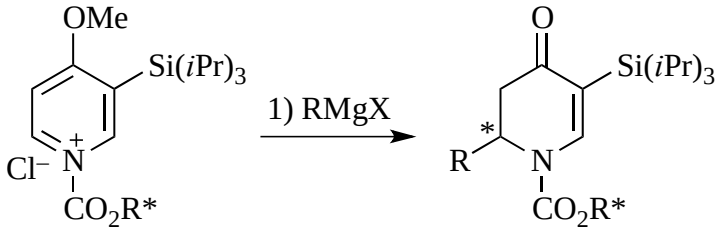
An early example of a stereoselective synthesis of a 2,3-dihydropyridone was by Kunz in 1989 *via* an *aza*-Diels-Alder reaction.[36] The stereoselectivity is controlled by preferential attack on the *si* face of the aldimine, and the major product has *S* configuration. His system was limited to aryl dienophiles, with very long reaction times, and required separation of diastereomers. One interesting example of using a 2,3-dihydropyridone as an intermediate was in the synthesis of (*S*)-anabasin, employing a chiral Schiff base as the dienophile and Danishefsky's diene (***Scheme 1.2.13***). The chiral auxiliary can be removed almost quantitatively to give up to 92% yield, and >20:1 er (*S*:*R*).

Scheme 1.2.13. Kunz' *aza*-Diels-Alder reaction to make 2,3-dihydropyridones



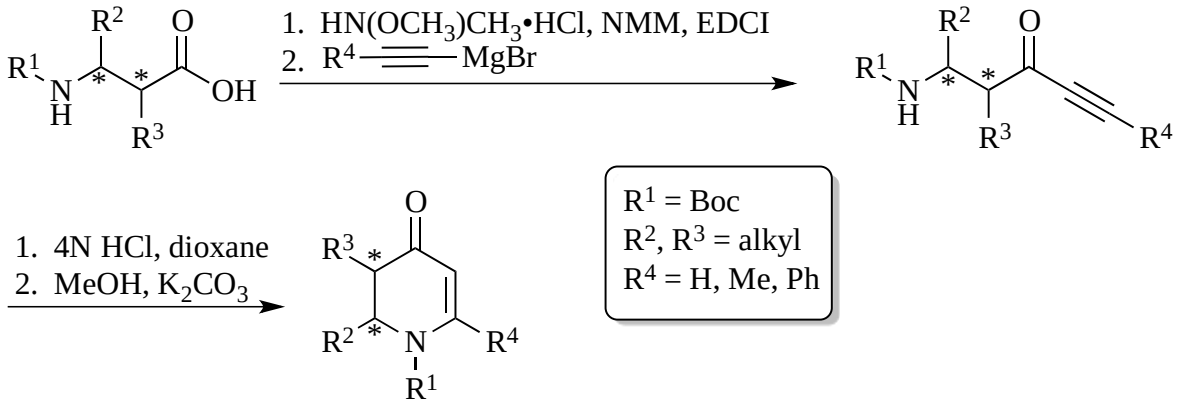
Additionally, the Comins group has made several enantio-enriched 2,3-dihydropyridones by nucleophilic addition of Grignard reagents to chiral pyridinium salts, where the asymmetric induction was determined by the chiral auxiliary CO_2R^*, where R* is menthol or a derivative (***Scheme 1.2.14***).[37]

Scheme 1.2.14. Comins' 2,3-dihydropyridone synthesis



Recently, Georg *et al.* synthesized several 2,3-dihydropyridones *via* cyclizations using β-amino acids (***Scheme 1.2.15***).[38] Her procedure was mainly limited to bicyclic products, but an er of >95:5 could be achieved.

Scheme 1.2.15. Georg's 2,3-dihydropyridone synthesis

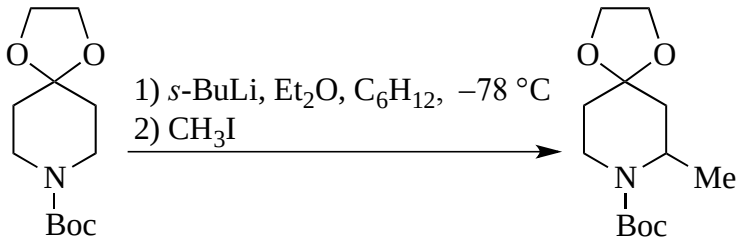


1.2.4 Investigations of the Ethylene Ketal of N-Boc-4-oxo-piperidine

There have been minimal attempts of the asymmetric deprotonation of the ethylene ketal of *N*-Boc-4-oxo-piperidine, **41**, of which very moderate results have been reported.

Initial investigation by Beak used the same procedure for deprotonation of *N*-Boc-piperidine on **41** to give 74% of the racemic product using MeI as the electrophile (***Scheme 1.2.16***).[25]

Scheme 1.2.16. Beak's racemic deprotonation of the ethylene ketal of *N*-Boc-4-oxopiperidine

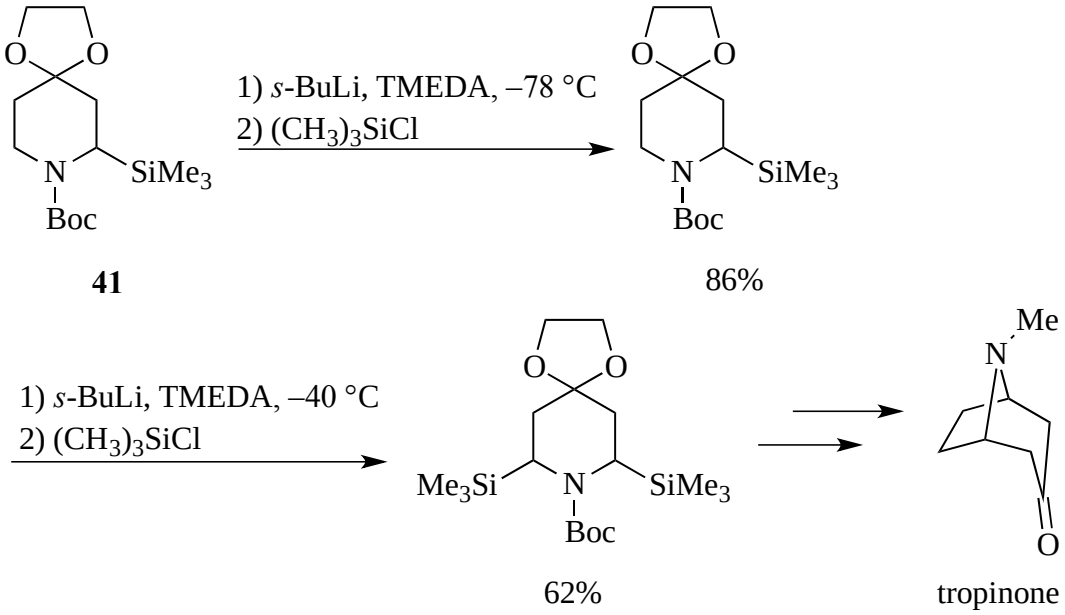


41 74%

The only attempt at an asymmetric deprotonation was a joint effort by the Coldham and O'Brien groups.[26] Using **5** from ***Figure 1.2.1***, gave 60:40 er with 47% yield, but the absolute configuration was not determined. The authors commented that the substrate might not be amenable to a resolution.

Laha recently used **41** in the synthesis of cocaine antagonists, such as tropinone, but was not concerned with enantioselectivity.[39] She used tandem deprotonations followed by electrophilic quench with $(CH_3)_3SiCl$ to make the ethylene ketal of *N*-Boc-2,6-bis(trimethylsilyl)-4-oxopiperidine, with 86% yield for the first step, and 66% yield, after warming to –40 °C for the second (***Scheme 1.2.17***).

Scheme 1.2.17. Laha's synthesis of tropinone



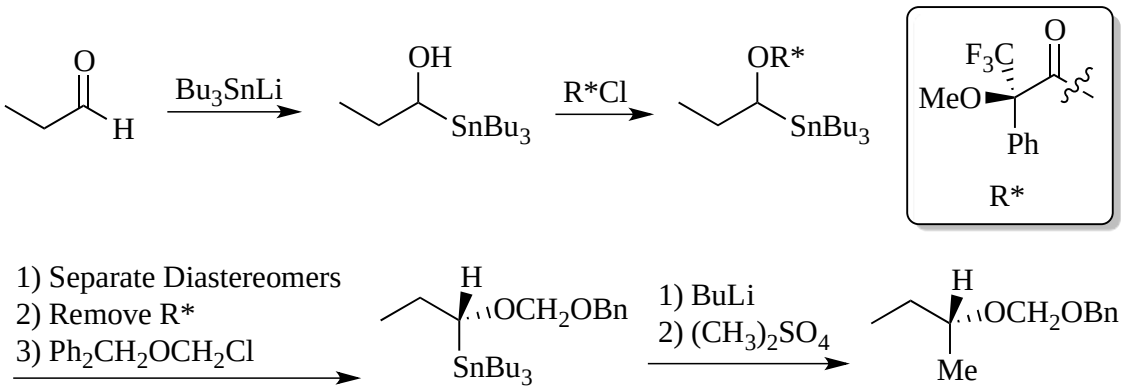
1.3 α–Alkoxyorganolithiums

Enantiopure α–alkoxyorganolithiums provide derivatives that have been widely used in the asymmetric synthesis of natural products and biologically active molecules.[40] A number of methods are available to produce enantiopure α–alkoxyorganolithiums by tin-lithium exchange, as well as direct routes to carbamate derivatives by asymmetric deprotonation and dynamic resolution.

1.3.1 Tin-lithium Exchange of α–Alkoxyorganostannanes

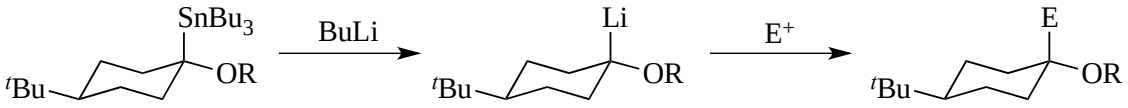
Access to configurationally stable α–alkoxyorganolithiums was pioneered by Still and Sreekumar and opened the door to their use in organic synthesis.[41] They used chiral α–alkoxyorganostannanes made from 1,2-addition of tri-n-butylstannyllithium to aldehydes. The resulting alcohols were esterified with Mosher's acid, and the resulting diastereomers were separated by column chromatography. Hydrolysis of the chiral auxiliary, followed by protection of the alcohol to a MOM or BOM ether led to the enantiopure α–alkoxyorganostannane. They showed that at temperatures below –78 °C tin-lithium exchange and subsequent electrophilic substitution proceeds without the loss of stereochemical integrity (***Scheme 1.3.1***).

Scheme 1.3.1. Still and Sreekumar's pioneering use of chiral α–alkoxyorganostannanes



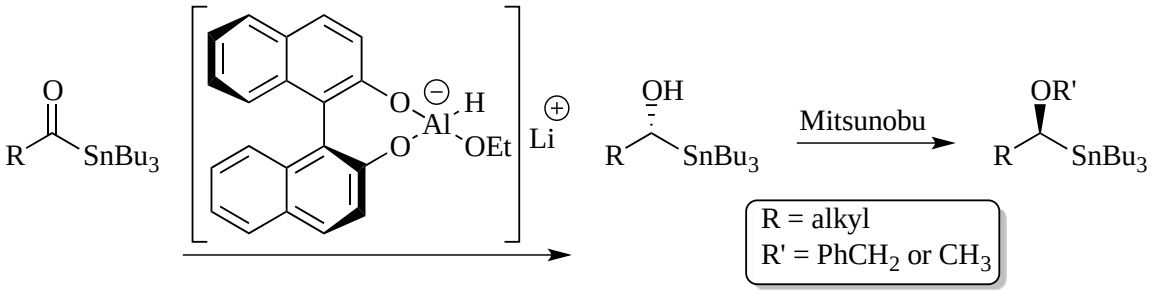
In a remarkable display of configurational stability, additional studies by Macdonald and McGarvey showed that both diastereomeric α–alkoxyorganostannanes derived from 4-*tert*-butyl-cyclohexanone underwent tin-lithium exchange and subsequent electrophilic quench with MeI with complete stereoretention (***Scheme 1.3.2***).[9]

Scheme 1.3.2. Macdonald and McGarvey's use of α–alkoxyorganostannanes



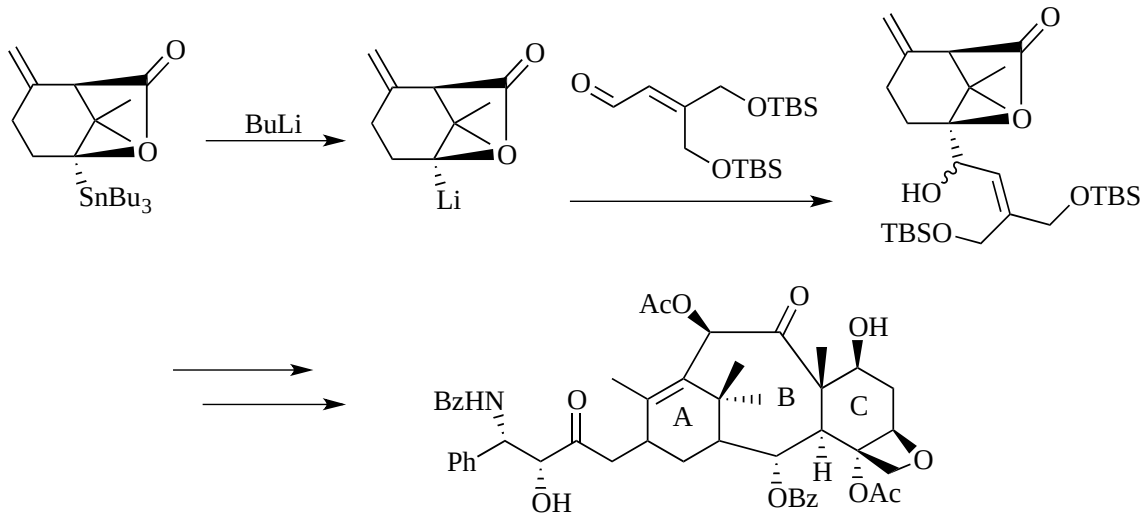
Efforts to improve the synthesis of enantiopure α–alkoxyorganostannane were developed by Chong and coworkers employing an asymmetric reduction of acyl stannanes with BINAL-H.[42] Subsequent Mitsunobu esterification led to α–alkoxyorganostannanes with 80 to 96 % ee (***Scheme 1.3.3***). Remorsefully, problems with the cost of BINAL and reproducibility of scale-up forced the authors to revert to a chromatographic separation of diastereomers *via* a sequence of chiral auxiliary addition/removal.

Scheme 1.3.3. Chan and Chong's improved synthesis of α–alkoxyorganostannanes



Though limited by preparative methods, the synthetic utility of α–alkoxyorganostannanes has been well demonstrated. Liu and coworkers used an α–alkoxyorganolithium made from the lithiodestannylation of stannyl lactone in ***Scheme 1.3.4*** for the addition of an aldehyde that gives the alcohol intermediate in the preparation of the ABC system in Taxol.[43]

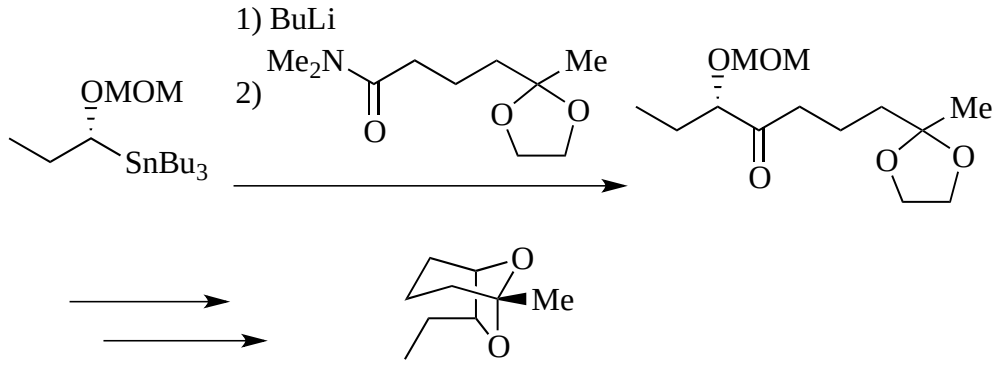
Scheme 1.3.4. Liu's synthesis of the Taxol ABC system



Taxol ABC system

Another α–alkoxyorganostannane was employed by Chong as an α–alkoxyorganolithium precursor, which adds to *N*,*N*-dimethylamides giving a ketone intermediate towards the enantioselective total synthesis of (+)-endo-brevicomin (***Scheme 1.3.5***).[44]

Scheme 1.3.5. Chong's synthesis of (+)-endo-brevicomin

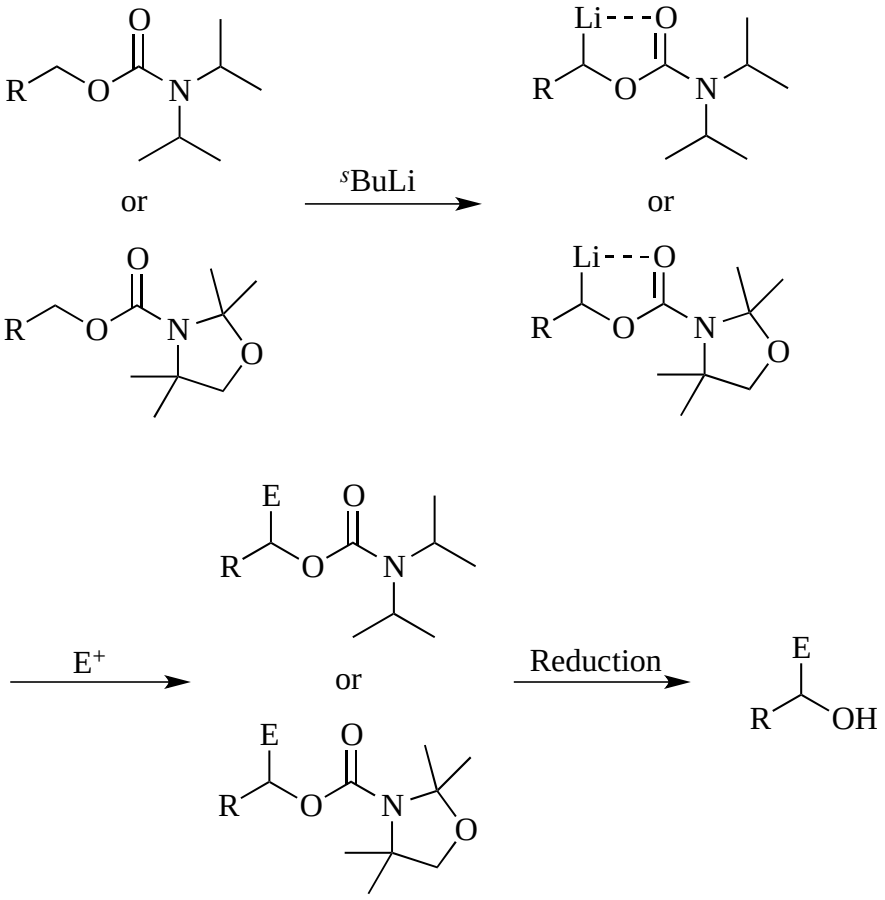


(+)-*endo*-brevicomin

1.3.2 Carbamates

Dieter Hoppe has developed highly enantioselective syntheses of a number of types of carbamates. Due to the fact that facile routes to non-mesomerically stabilized α–alkoxyorganolithiums were not available by deprotonation, such as dialkyl ethers and alkyl carboxylates, Hoppe developed a method for deprotonation using the carbamate functionality.[45] Like other carboxylates, the carbonyl oxygen chelates the α–alkoxyorganolithium, but the α–protons are sufficiently more acidic to the extent that deprotonation is synthetically useful. The *N*,*N*-diisopropyl alkyl carbamates can be reduced to the alcohol by DIBAL-H (***Scheme 1.3.6***).

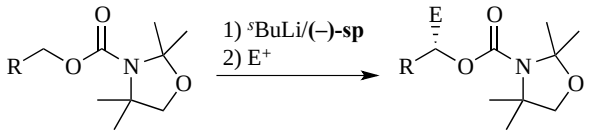
Scheme 1.3.6. Electrophilic Substitution of *N*,*N*-dialkylcarbamates to make alcohols



1.3.2.1 Asymmetric Deprotonation of aliphatic carbamates

The deprotonative lithiation of alkyl carbamates proceeds smoothly in non-polar solvents using *s*-BuLi and TMEDA. Replacing TMEDA with (–)-sp rendered the deprotonation asymmetric. There are a number of highly enantioenriched alkyl carbamate derivatives that are available by asymmetric deprotonation with (–)-sp (***Scheme 1.3.7***).[4, 45-46]

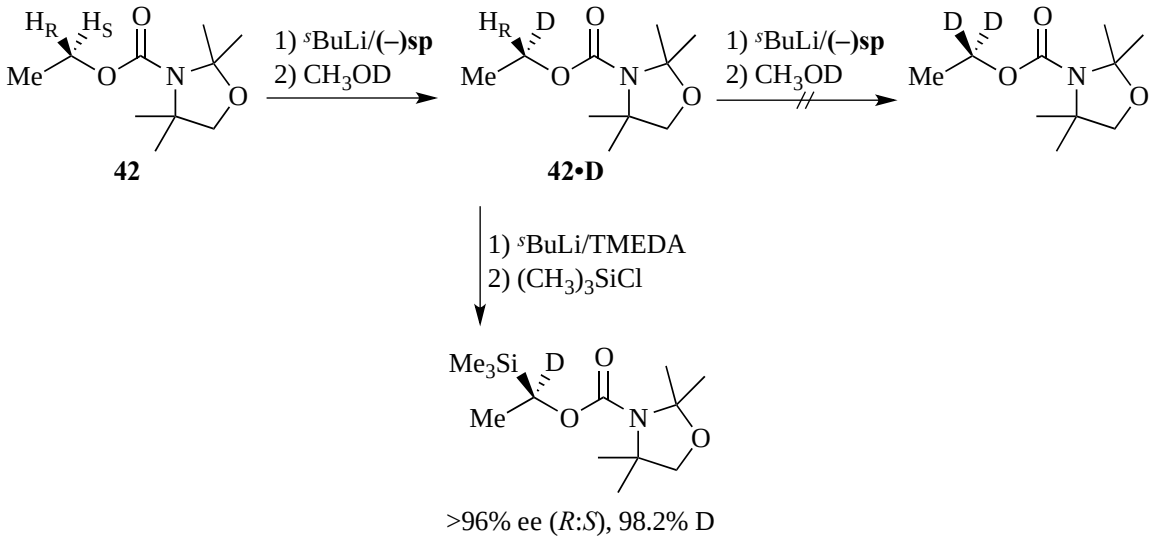
Scheme 1.3.7. Scope of electrophilic substitution on alkyl *N*,*N*-dialkylcarbamates



R = CH_3, $H_3C(CH_2)_6$, $(CH_3)_2CH$, $(CH_3)_2CCH(CH_2)_2$, $PH(CH_2)_2$, *o*-$OMePh(CH_2)_2$, $CpFeCpCH_2$, $(PhCH_2)_2NCH_2$, $TBSOCH_2(CH_2)_3$
E = CO_2CH_3, $Si(CH_3)_3$, $Sn(CH_3)_3$, CH_3, PhCO, $^nBu_3Sn$

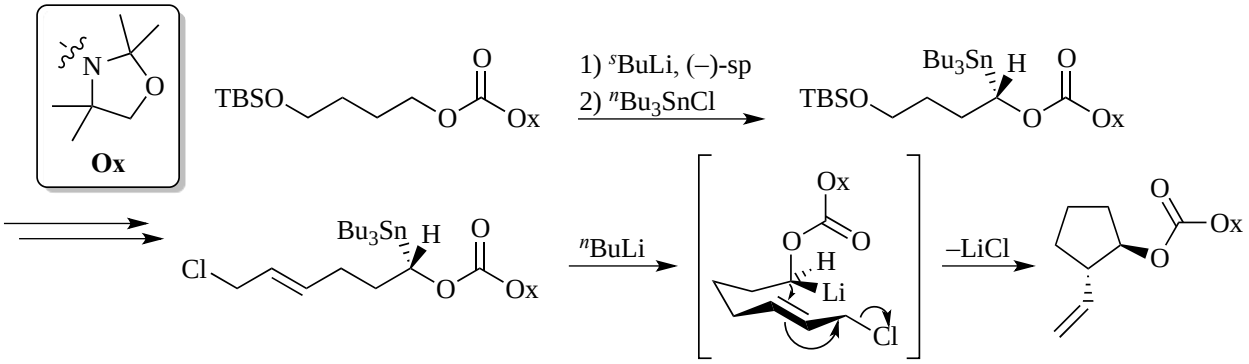
Computational studies showed a large kinetic preference for the abstraction of the pro-*S* proton.[47] In a complementary isotope-effect experiment by Hoppe, the asymmetric deprotonation of **42** with (–)-sp was quenched with CH_3OD (***Scheme 1.3.8***).[48] A subsequent asymmetric deprotonation with (–)-sp on the deuterated compound showed only traces of the desired product. When a racemic deprotonation of the **42•D** was attempted, the product had 96% ee (*R*:*S*), and 98% deuterium incorporation, which showed that (–)-sp would only abstract the pro-*S* proton, and abstraction of the pro-*S* deuterium is very sluggish. Therefore, the stereochemical course of the racemic deprotonation is exclusively dependent on the kinetic isotope effect (k_H/k_D), where the proton is preferentially abstracted over the deuterium. Lithiated **42** is configurationally stable under reaction conditions with both TMEDA and (–)-sp, and the diastereomeric complexes formed by deprotonation do not equilibrate at the reaction temperature.

Scheme 1.3.8. Hoppe's isotope-effect experiment



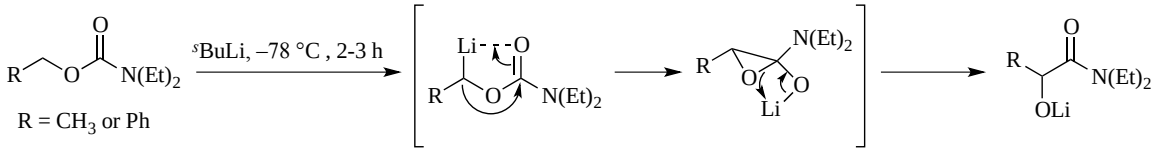
Due to the inherent low acidity of α-protons on alkyl carbamates, functional group compatibility can be an issue for their utility. A pragmatic option called the "stannyl trick", can be applied, which combines asymmetric deprotonation and tin-lithium exchange (***Scheme 1.3.9***).[46g] If the functional group can be protected for deprotonation, the chiral stannane can be prepared. Then, the necessary transformations can be performed, followed by the stereoretentive tin-lithium exchange at a more convenient juncture.

Scheme 1.3.9. Example of the "stannyl trick"



In 1999, the Nakai group in Japan reported a 1,2-carbamoyl rearrangement of a lithiated alkyl carbamate when the reaction temperature was raised to temperatures above –40 °C.[49] This is similar to a Snieckus-type rearrangement of a lithiated alkyl and benzyl carbamates reported by Gawley to make hydroxyl amides at low temperatures.[50] An addition-elimination mechanism was proposed, which leads to an α-hydroxy amide (***Scheme 1.3.10***).

Scheme 1.3.10. "Snieckus-type" rearrangement of *N*,*N*-diisopropyl carbamate

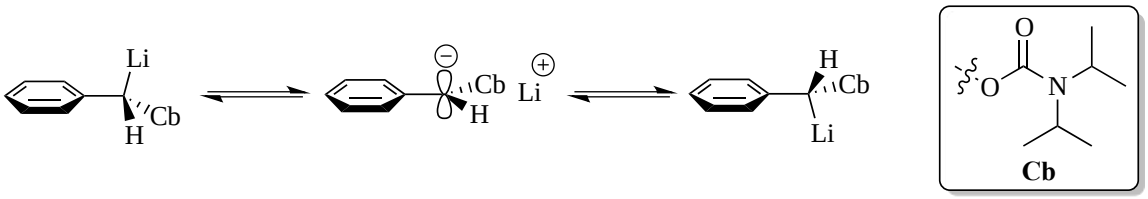


1.3.3.2 Dynamic resolutions of benzyl carbamates

Benzyl-type carbamates are also easily deprotonated using s-BuLi and TMEDA for racemic

substitutions.[5l, m, 51] In contrast to the lithiated alkyl carbamates, the molecular configuration of the benzylic carbanion species is flattened to optimize electron delocalization through the *pi* system, which often leads to the formation of solvent-separated ion pairs (***Scheme 1.3.11***). This leads to a decrease in configurational stability relative to the more tetrahedral lithiated alkyl carbamate, where a more favorable chelation of the organolithium to the carbonyl oxygen raises the barrier to stereoisomerization. In contrast to the alkyl carbamates, the asymmetric deprotonation of benzyl carbamates using (–)-sp resulted in much less enantioselectivities (*vide infra*).[5l]

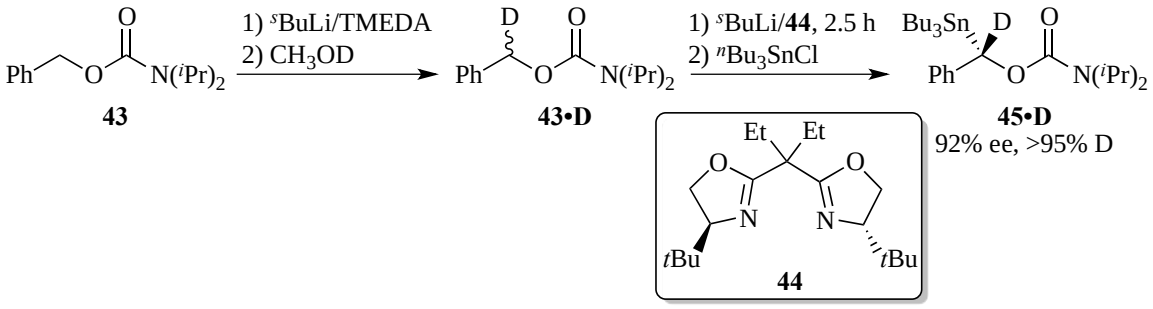
Scheme 1.3.11. Stereoisomerization of benzyl carbamates



The increased configurational lability allows for a dynamic thermodynamic resolution to control the stereochemical course of the reaction. Hoppe proved the stereochemical origin using a similar deuterium labeling experiment as in the alkyl carbamates.[5l] Benzyl carbamate, **43**, was deprotonated with *s*-BuLi and TMEDA, followed by a MeOD quench. The racemic **43•D** was then deprotonated with *s*-BuLi and (*R*,*R*)-diethyl-di-*tert*-butyl(*bis*)oxazoline, **44**, to give *S* enantiomer of the desired organostannane, **45**, with 92% ee using the stannyl electrophile, which reacts with inversion of configuration (*vide infra*), and 95% deuterium incorporation (***Scheme 1.3.12***). This shows that only the proton is removed, and equilibration to the more thermodynamically stable diastereomeric organolithium complex occurs at reaction

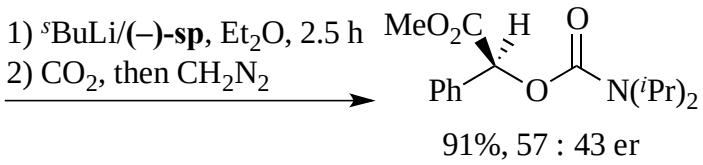
temperatures. Therefore, enantioselectivity is determined by a dynamic thermodynamic resolution (DTR).

Scheme 1.3.12. Isotope experiment on **43**



The Hoppe group has investigated the stereochemical course of the substitution using silylation, stannylation, as well as a number of carbonyl-type electrophiles.[5l] Benzyl-type carbamates were deprotonated or subjected to tin-lithium exchange in the presence of (–)-sp (***Scheme 1.3.13***) or a BOx ligand at –78 °C for 2.5 h, followed by electrophilic quench. The stereochemical pathway is highly dependent on the chiral ligand used. Using (–)-sp, the pro-S proton is preferentially abstracted, but the thermodynamically more stable diastereomer is the pro-R complex. So, the longer the diastereomeric complexes are allowed to equilibrate, the lower the enantioselectivity observed in the products. Using **44**, the kinetic preference for proton abstraction is minimal, but the thermodynamically more stable diastereomer is the pro-S complex. So, the longer the diastereomeric complexes are allowed to equilibrate, the higher enantioselectivity observed in the products.

Scheme 1.3.13. Deprotonation of **43** with (–)-sp



91%, 57 : 43 er

Using **44**, carbonyl-type electrophiles that were investigated (***Scheme 1.3.14***), and the resulting products, with their stereochemical courses are summarized in ***Table 1.3.1***.[5m] The authors argue that the differences in stereochemical course relate back to the flattening of the carbanionic center. The flatter center allows for more electron density on the rear face, from which the attack can occur with the added benefit of avoiding energetically repulsive interactions with the lithium cation. Therefore, electrophiles with energetically low LUMOs (acid, silyl, and stannyl chlorides, aromatic aldehydes and ketones, MeI, CO_2, and allyl bromide) react with inversion. In contrast, electrophiles with energetically higher LUMOs, which are known for aliphatic aldehydes and ketones, have less energetically unfavorable interaction, as well as a more favorable attraction of the lithium cation to their carbonyl oxygen.

Scheme 1.3.14. Electrophilic substitution of **43** by DTR

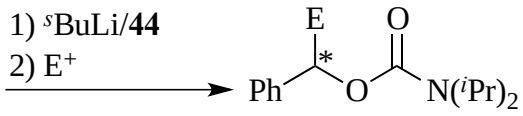


Table 1.3.1. Results of the DTR of **43**

E^+	**Yield (%)**	**ee (%)**	**Inversion/Retention**
Bu_3SnCl	98	98	inversion
Me_3SiCl	67	30	inversion
$H_3COC(O)Cl$	95	91	inversion
$^tBuC(O)Cl$	87	63	inversion
4-$BrC_6H_4C(O)Cl$	24	96	inversion
$(CH_3)_2CO$	28	54	retention
Ph_2CO	81	94	inversion
^tBuCHO	70 (dr 1.1:1)	32	retention
4-BrC_6H_4CHO	80 (dr 1.3:1)	97	inversion

1.4 Statement of the Problem

The overall aim is to apply dynamic resolution to the selected, synthetically important piperidine and carbamate derivatives. The specific goals are as follows:

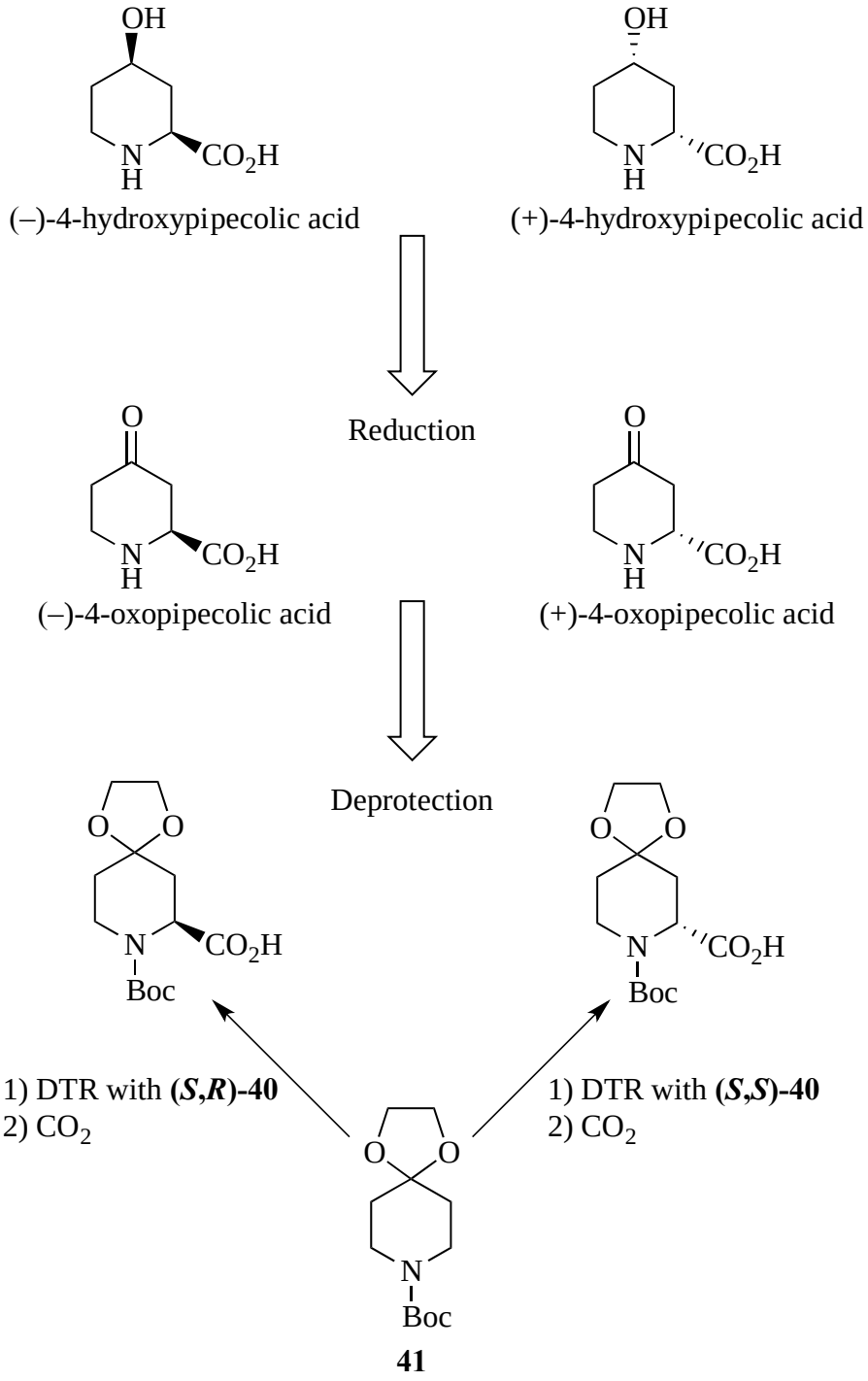
- Investigate the utility of dynamic resolution of the ketal of 2-lithio-4-oxopiperidine, including reproducibility, scope of electrophiles, and application toward the synthesis of natural products and biologically active molecules with pharmaceutical and medicinal applications.
- Investigate the utility of dynamic resolution of *N*,*N*-diisopropyl-2-lithio-hexyl carbamate, including reproducibility, scope of electrophiles, and application toward the synthesis of natural products and biologically active molecules with pharmaceutical and medicinal applications.

1.5 Results/Discussion

1.5.1. Piperidines

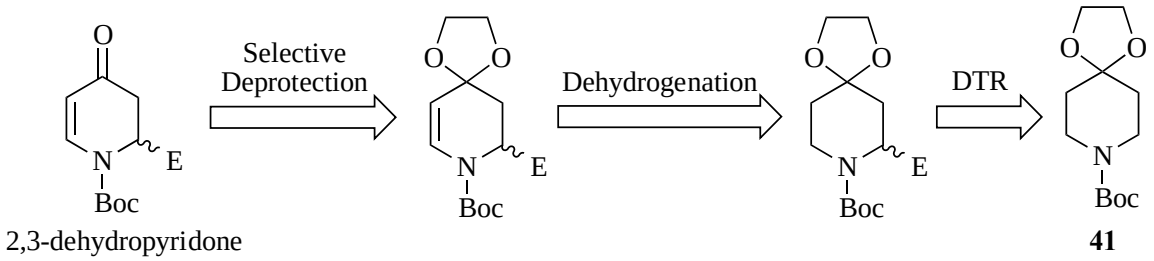
If the recently reported application of dynamic resolution used by Gawley and Beng to make highly enantiopure piperidine derivatives from *N*-Boc-piperidine could be applied to **41**, the utility of this methodology would be significantly enhanced. There are a number of piperidine derivatives with multiple substitutions on the heterocycle that would be accessible in enantiopure form by facile transformations, such as hydroxypipecolic acids ((–)-4-hydroxypipecolic acid cost over $500 per gram and (+)-4-hydroxypipecolic acid is not commercially available). The asymmetric addition of CO_2 by DTR with either enantiomer of **40** gives either enantiomer of masked 4-oxopipecolic acid. Deprotection followed by substrate-induced asymmetric hydrogenation would provide access to either enantiomer of 4-hydroxypipecolic acid (***Scheme 1.5.1***).

Scheme 1.5.1. Asymmetric synthesis of 4-hydroxypipecolic acids



Facile, highly enantioselective synthesis of 2,3-dehydropyridones would also be available by the successful application of this methodology (***Scheme 1.5.2***).

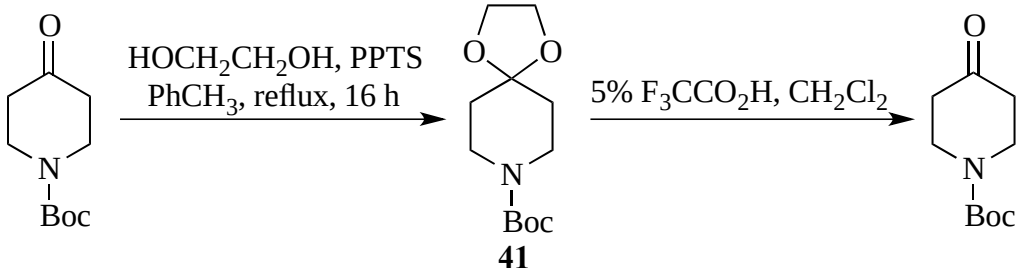
Scheme 1.5.2. Synthesis of 2,3-dehydropyridones



2,3-dehydropyridone **41**

The asymmetric substitution of *N*-Boc-4-oxopiperidine by application of dynamic resolution first requires the protection of the ketone functional group. The most convenient protection method is transformation to an acetal by the pyridinium p-toluenesulfonate (PPTS) catalyzed addition of ethylene glycol to the ketone, which gives the ethylene ketal of *N*-Boc-4-oxopiperidine, **41**. This facile modification proceeds smoothly in almost quantitative yields, and also allows for the facile removal of the protecting group under acidic conditions (***Scheme 1.5.3***).

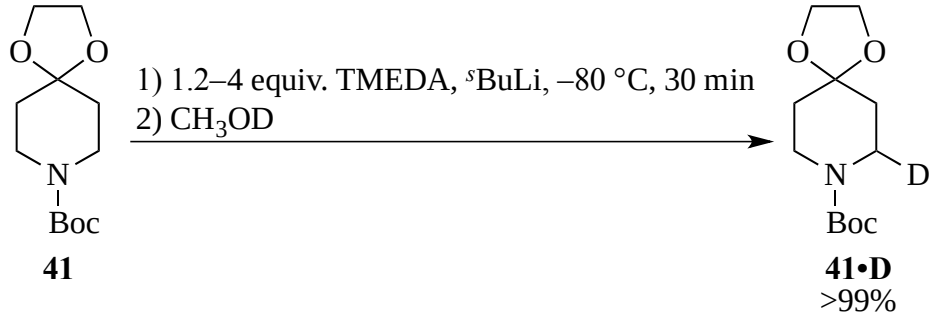
Scheme 1.5.3. Protection and deprotection of *N*-Boc-4-oxopiperidine



41

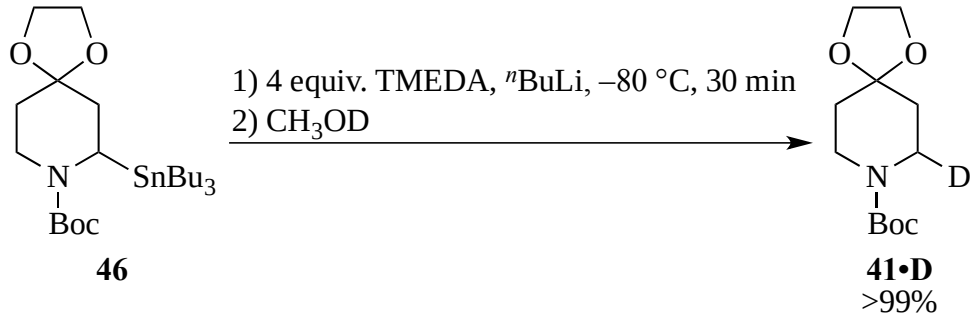
The lithiation of **41** was then optimized (***Scheme 1.5.4***). Using the optimized conditions for the lithiation of *N*-Boc-piperidine as a starting point, the addition order and stoichiometry of the piperidine, TMEDA, and *s*-BuLi were investigated. The standard reaction procedure began with the slow addition of *s*-BuLi to a solution of **41** and TMEDA in Et_2O cooled to –80 °C. If the addition of *s*-BuLi is not sufficiently slow, then the temperature of the solution can quickly rise, leading to an increased decomposition of the substrate by attack on the Boc group by *s*-BuLi. A few drops every 15 to 20 sec is ideal, but reverse addition, where the piperidine is added to a cooled solution of *s*-BuLi, also works efficiently. The formation of *N*-Boc-2-lithio-4-oxopiperidine was determined by quenching an aliquot of the solution with CH_3OD at selected time intervals and looking for deuterium incorporation by GC/MS. These data show that the ethylene ketal of *N*-Boc-4-oxopiperidine is much more reactive toward lithiation than *N*-Boc-piperidine. After 10 min, the deuterium incorporation was >50%, and >80% after 30 min. Additional solvents investigated were THF and hexanes, but neither showed as efficient lithiation as Et_2O. The optimized time for lithiation was determined to be 1 h at a concentration of 0.2 M, with nearly quantitative deuterium incorporation observed by GC/MS. The effect of TMEDA concentration was then probed. There was no significant difference in the efficiency of deprotonation with > 1equiv. of TMEDA.

Scheme 1.5.4. Optimized deprotonative lithiation of **41**



The efficiency with which deprotonative lithiation proceeds provides a much more convenient route to lithiated **41** than tin-lithium exchange, but Beng showed that complete conversion of the ethylene ketal of *N*-Boc-4-oxo-2-tri-*n*-butylstannylpiperidine, **46**, to lithiated **41** occurred after 30 min in the presence of 4 eq. TMEDA (***Scheme 1.5.5***).[52]

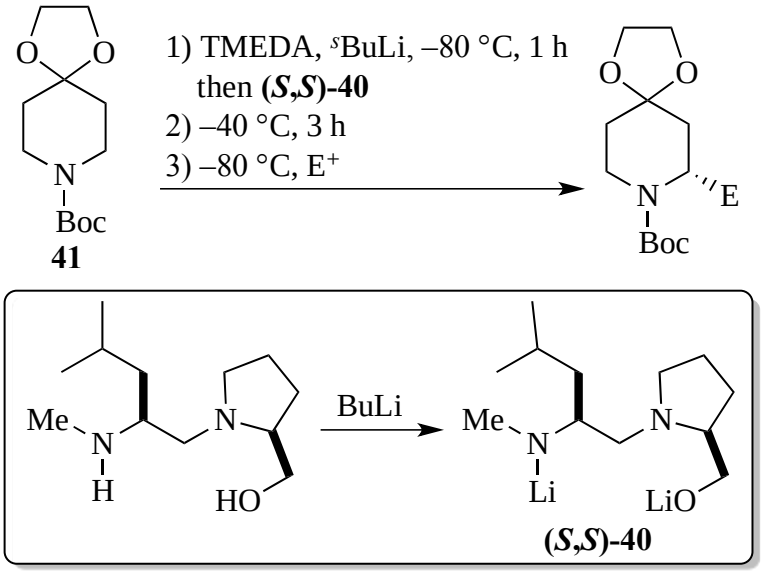
Scheme 1.5.5. Tin-lithium exchange of **46**



To begin the application of dynamic resolution to **41**, the standard DTR conditions for *N*-Boc-piperidine were applied, and temperatures were accurately and precisely maintained by using an internal temperature probe (***Scheme 1.5.6***). A racemic deprotonation was carried out as above, in the same –80 °C bath; the conjugate acid of **40** was deprotonated in Et_2O with either *n*-BuLi or *s*-BuLi. After 1 h, the solutions were combined by cannulation and quickly transferred to a –40 °C

bath. The internal temperature reached reached –40 °C in about 5 min, the solution was then stirred for 3 h, and transferred back to the –80 °C bath. When the internal temperature reached –80 °C, the selected electrophile was added dropwise to maintain the desired temperature. After at least 4 h, CH_3OH was added, and the solution was warmed to ambient temperature. An acidic work-up allowed for the convenient recovery of the chiral ligand from the products.

Scheme 1.5.6. Standard conditions for the DTR of the ethylene ketal of *N*-Boc-4-oxopiperidine



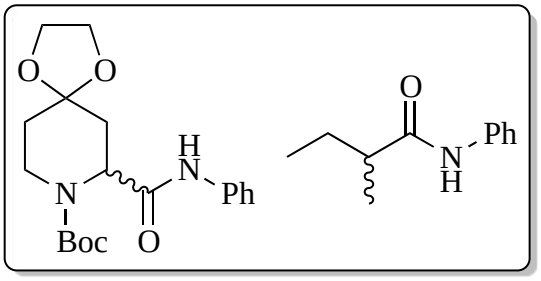
The initial electrophile, phenyl isocyanate (PhNCO), was selected due to an expected ease of analysis of enantiopurity by diode array detection of the chromophore on CSP-SFC. This seemed to be the case, but several setbacks were observed. The racemic side product of the reaction between *s*-BuLi and PhNCO elutes with practically the same elution time as the desired products (***Figure 1.5.1***), so controlling *s*-BuLi addition is critical, which is not a simple matter on low scale reactions. The *s*-BuLi product was easy to remove by column chromatography, but only racemic products were observed after chromatography. Very few non-racemic products were

observed, but at least one reaction unequivocally gave enantiopure product (***Entry 4***, ***Table 1.5.1***).

Table 1.5.1. DTR results for the ethylene ketal

Entry	E^+	TMEDA Equiv.	L*	Substrate Conc. (M)	^{s}BuLi Equiv./ Conc. (M)	Ligand Origination[a]	yield (%)/er
1	PhNCO	1.2	(*S*,*S*)-**40**	0.2	1.2/1.2	–	77/50:50
2	PhNCO	2	(*S*,*S*)-**40**	0.2	1.2/1.2	–	85/50:50
3	PhNCO	4	(*S*,*R*)-**40**	0.2	1.2/1.0	–	85/50:50
4	PhNCO	4	(*S*,*S*)-**40**	0.05	1.2/1.0	–	–/98:2
5	PhNCO	4	(*S*,*S*)-**40**	0.06	1.2/1.3	–	–/50:50
6	PhNCO	4	(*S*,*S*)-**40**	0.1	1.2/1.2	–	90/50:50
7	PhNCO	4	(*S*,*S*)-**40**	0.2	1.2/1.0	–	>95/50:50
8	PhNCO	4	(*S*,*S*)-**40**	0.2	1.2/1.0	Scott	–/50:50
9	PhNCO	4	(*S*,*S*)-**40**	0.2	1.2/1.0	Beng	–/50:50
10	PhNCO	4	(*S*,*S*)-**40**	0.2	1.2/1.0	Abby	–/50:50
11	CbzCl	4	(*S*,*S*)-**40**	0.06	1.2/1.2	–	75/50:50
12	CbzCl	4	(*S*,*S*)-**40**	0.1	1.2/1.2	–	>95/50:50
13	CbzCl	4	(*S*,*S*)-**40**	0.2	1.2/1.1	–	>95/98:2
14	TMSCl	4	(*S*,*S*)-**40**	0.2	1.2/1.1	–	80/50:50

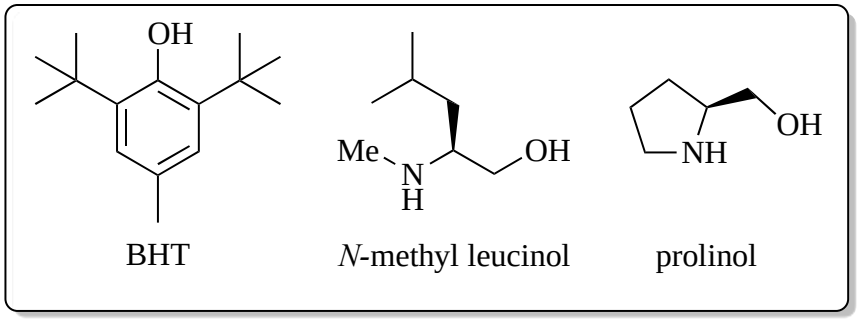
Figure 1.5.1. Overlapping products on CSP-SFC chromatograph



The next electrophile selected for investigation was benzyl chloroformate (CbzCl). The side product from addition of the lithium base to the electrophile in CSP-SFC traces did not obstruct analysis of enantiopurity. Similar results to the PhNCO electrophile were achieved, but a quadruplicate reactions all gave >95:5 er (***Entry 13***, ***Table 1.5.1***). Unfortunately, this was the exception, as the majority of non-racemic products were produced with an er in the 60:40 range. The problem with reproducibility was initially attributed to absolute purity of the chiral ligand, of which several contaminants could be leftover from its synthesis. Butylated hydroxytoluene (BHT) is present in THF and ether as a stabilizer and was present in the starting material and ligand due to using dried, but not distilled solvents. Also, small amounts of *N*-Boc-leucine and the methyl ester of proline could remain if their coupling was incomplete, which are reduced to *N*-methyl-leucinol and prolinol in the final step of ligand synthesis. Any of these contaminants can act as ligands that would coordinate to organolithiums and effect resolution (***Figure 1.5.2***). All contaminants were shown to be removed by recrystallization of ***SS*-40** at -40 °C in ether/hexanes. The Kughelrohr-distilled ligand was dissolved in ether and cooled to –40 °C, followed by lithiation with either *n*-BuLi or *s*-BuLi, and left overnight. The mother liquor was removed and the crystals were washed with cold hexanes. Upon warming, the crystals liquefied to a colorless oil. They were subjected to an acid workup, Kuglerohr-distillation and then

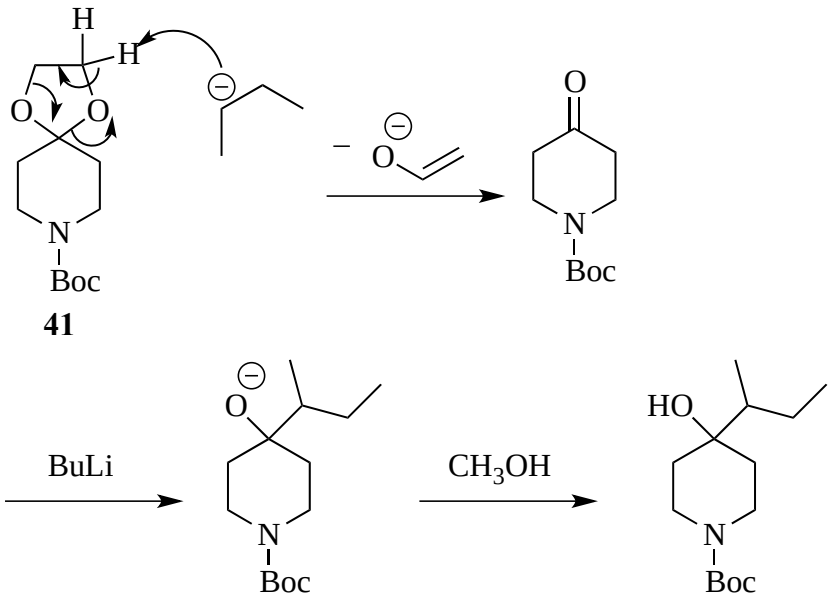
dissolved in freshly distilled ether to make a stock solution. This was the method of preparation for both of the ligands used in successful DTR's. The diastereomer, ***SR*-40**, does not recrystallize under the same conditions.

Figure 1.5.2. Possible contaminants identified from ligand synthesis



The decomposition of the ethylene ketal by a competitive deprotonation α to the oxygen in the ketal ring has been proposed, which would lead to deprotection of the ketone (***Scheme 1.5.7***). This uses another equivalent of s-BuLi to form alkoxides, which in turn is likely affecting aggregation and leading to racemic products. The tertiary alcohol produced when the alkoxide is protonated was observed by GC/MS.

Scheme 1.5.7. Deprotection of the ethylene ketal of N-Boc-4-oxopiperidine by *s*-BuLi



41

Mol. Wt. = 257

An obvious solution was to switch the starting material to the propylene ketal of *N*-Boc-4-oxopiperidine, **47**, which would be less thermodynamically favored to the deprotection similarly to **41**. Initial results of a racemic deprotonation of **47** that was quenched by CbzCl gave the desired product, **48** and did not show any of the tertiary alcohol produced by ketal degradation (***Scheme 1.5.8***).

Scheme 1.5.8. Synthesis and DTR of **47**

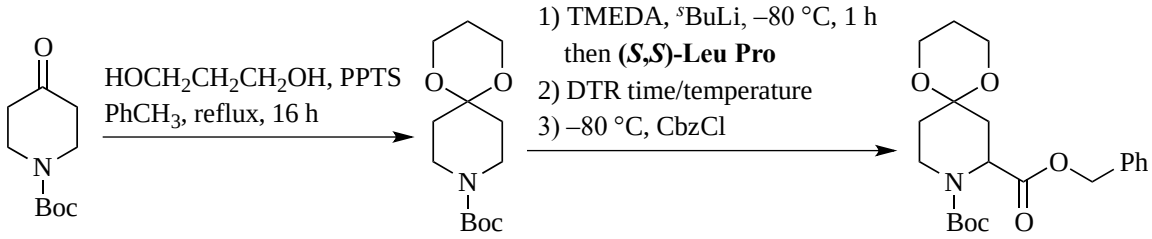


Table 1.5.2. DTR results for the propylene ketal

Entry	Substrate Conc. (M)	^{s}BuLi Equiv./ Conc. (M)	Equilibration time (h)/ temperature (°C)	Additive	Ligand Origination[a]	yield (%)/er
16	0.06	1.2/1.2	3/–40	none	–	–/50:50
17	0.1	1.2/1.2	3/–40	none	–	–/50:50
18	0.2	1.2/1.2	3/–40	none	–	>95/50:50
19	0.5	1.2/1.2	3/–40	none	–	–/50:50
20	0.5	0.9/1.3	3/–40	none	–	–/50:50
21	0.5	1.2/0.8	3/–40	none	–	–/50:50
22	0.2	1.2/1.2	5/–55	none	–	–/50:50
23	0.2	1.2/1.2	4/–40	none	–	–/50:50
24	0.2	1.2/1.0	2/–30	none	–	–/50:50
25	0.2	1.2/1.2	2/–10	none	–	–/50:50
26	0.2	1.2/1.2	1/–10	none	–	–/50:50
27	0.2	1.2/1.2	1/0	none	–	–/50:50
28	0.2	1.2/1.2	3/–40	BHT	–	–/50:50
29	0.2	1.2/1.2	3/–40	NMeLeu	–	–/50:50
30	0.2	1.2/1.2	3/–40	Prolinol	–	–/50:50
31	0.2	1.2/1.2	3/–40	BHT, *N*-Me Leu	–	–/50:50
32	0.2	1.2/1.2	3/–40	BHT, Prolinol	–	–/50:50
33	0.2	1.2/1.2	3/–40	*N*-Me Leu, Prolinol	–	–/50:50
34	0.2	1.2/1.0	3/–40	none	Scott	–/50:50
35	0.2	1.2/1.0	3/–40	none	Beng	–/50:50
36	0.2	1.2/1.0	3/–40	none	Jin Sun	–/50:50
37	0.2	1.2/1.0	3/–40	none	Kylie[b]	–/50:50
38	0.2	1.2/1.0	3/–40	none	Pooja[b]	–/50:50

[a]other than the author; [b]provided unreduced peptide

The reaction conditions were initially focused on replicating the conditions of the handful of successful DTR's of **41** (***Entry 13***, ***Table 1.5.1***). After meticulous repetition of these standard conditions (***Entry 18***, ***Table 1.5.2***), exhaustive variation of concentration, time, temperature, ligand origination, and addition of suspected contaminants were independently performed (***Entry 16-38***, ***Table 1.5.2***). The concentration with respect to piperidine was varied from 0.06–0.5 M, and with respect to *s*-BuLi has been used with 0.9–>10 equiv. of 0.8–1.3 M. The effect of time was monitored from 1–5 h at equilibration temperatures from –55 to 0 °C. The ligand was obtained from a half dozen independent chemists in addition to the author of this dissertation (***Entry 8-10***, ***34-38***, ***Table 1.5.2***). The effect of likely contaminants, including *N*–methyl leucinol, prolinol, and BHT, was examined to determine if impurities in the chiral ligand were required to affect resolution (***Entry 28-33***, ***Table 1.5.2***). The results were diabolically mundane as only racemic products were observed from any resolution of **47**.

After unsuccessful attempts to reproduce the handful of early, positive DTR results on either of the ketals of *N*-Boc-4-oxopiperidine, the reproducibility of the DTR of the original substrate reported by Beng, *N*-Boc-piperidine was investigated. A similar gamut of experimental parameters and modifications was run on *N*-Boc-piperidine as on **41 and 47**, but the results reported by Beng could not be reproduced (***Entry 39-48***, ***Table 1.5.3***).

The dynamic resolution of these substrates has also been unreliable for other members of this group, as well as other groups with similar research interests. Ultimately, the methodology is not applicable in the asymmetric synthesis of piperidine derivatives due to the issues discussed above.

Scheme 1.5.8. DTR conditions for *N*-Boc-piperidine

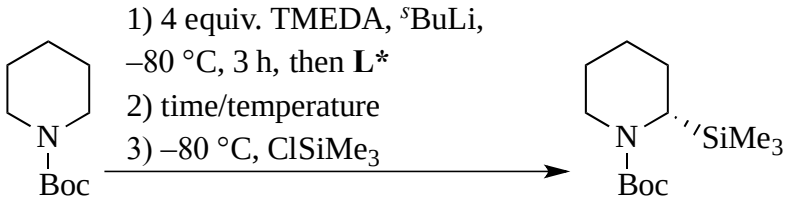
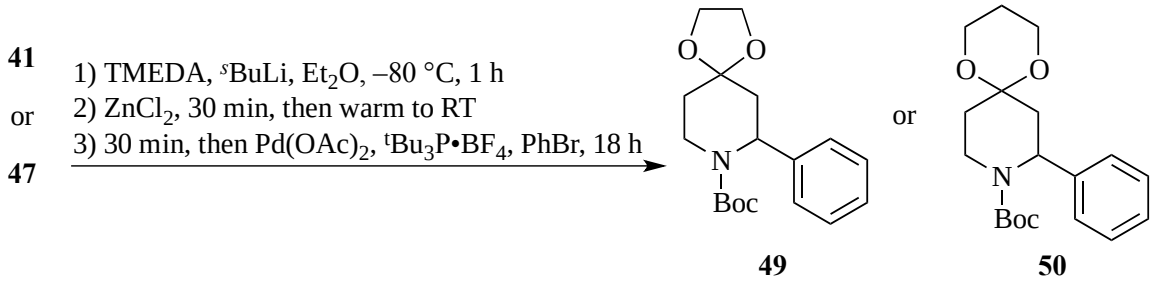


Table 1.5.3. DTR results for *N*-Boc-piperidine

Entry	L*	Additive	Ligand Origination	yield (%)/er
39	**(*S*,*S*)-40**	none	–	>95/50:50
40	**(*S*,*S*)-23**	none	–	–/65:35
41	**(*S*,*S*)-12**	none	–	–/60:40
42	**(*S*,*S*)-40**	BHT	–	–/50:50
43	**(*S*,*S*)-40**	*N*-Me Leu	–	–/50:50
44	**(*S*,*S*)-40**	Prolinol	–	–/50:50
45	**(*S*,*S*)-40**	BHT, *N*-Me Leu	–	–/50:50
46	**(*S*,*S*)-40**	BHT, Prolinol	–	–/50:50
47	**(*S*,*S*)-40**	*N*-Me Leu, Prolinol	–	–/50:50
48	**(*S*,*S*)-40**	none	Scott	–/50:50

During this extensive methodological investigation, a number of novel piperidine derivatives were produced. The racemic Negishi-type cross-coupling arylation of **41** and **47** with bromobenzene gave the desired 2-phenyl piperidine derivatives **49** and **50**, respectively, with up to quantitative conversion to product by GC/MS, and 92% isolated yield (***Scheme 1.5.9.***).

Scheme 1.5.9. Negishi-type cross-coupling arylations



1.5.2. α–Alkoxyorganolithiums

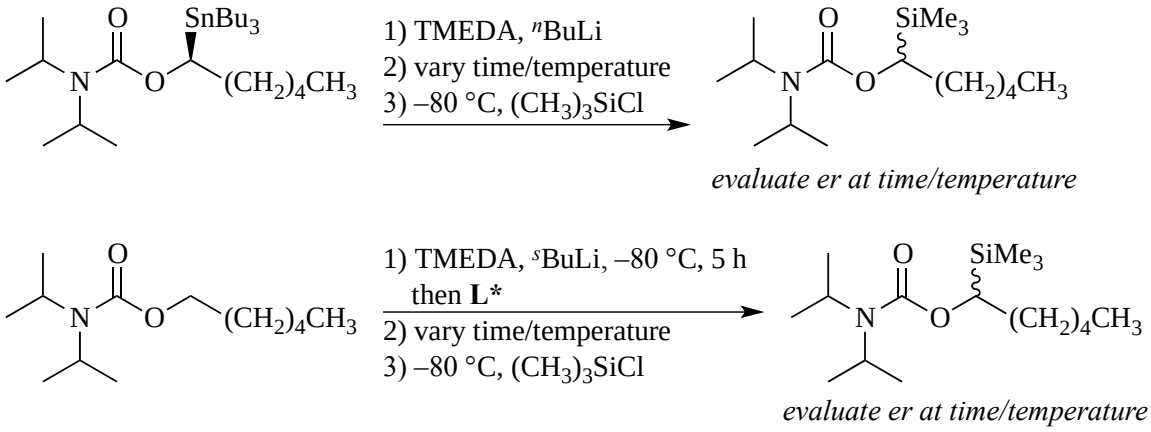
The application of dynamic resolution in the synthesis of highly enantiopure alkyl carbamate derivatives would significantly improve the methods of preparation for chiral alcohol derivatives that are ubiquitous in synthetic chemistry.[40]

In my last conversation with Professor Gawley before his untimely passing, we discussed the nascent stages of applying DTR or CDR methodology on *N*,*N*-diisopropyl hexyl carbamate, **51**.

In order to utilize dynamic resolution for the enantioselective synthesis of carbamates, efforts were made to determine the free energy barriers of racemization and resolution. As Hoppe demonstrated using (–)-sp, asymmetric deprotonation of alkylcarbamates gives highly enantiopure organolithiums, which can be quenched with alkylstannyl chloride electrophiles to give the corresponding organostannane, **52**. Tin-lithium exchange of these highly enantiopure organostannanes at various times and temperatures, followed by electrophilic quench with another electrophile, should give a downward sloping curve relative to er over time, which allows for the determination of the rate of racemization. The rate of resolution is determined by forming racemic lithiated **51**, which is then resolved by a chiral ligand at various times and various temperatures, then quenched with an electrophile to give an upward sloping curve

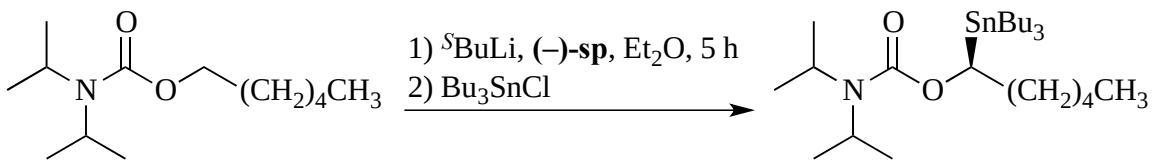
relative to er over time (***Scheme 1.5.8***). The plot of the free energy barriers determined for racemization and resolution will disclose a crossover point. This point is the temperature where resolution is faster than racemization, and subsequently where DTR and CDR are possible.

Scheme 1.5.8. Determination of free energy barriers for racemization and resolution



As shown in ***Scheme 1.5.8***, the asymmetric deprotonation of **51** with (–)-sp was quenched with Bu_3SnCl to give ***S*-52**, assuming an S_E2_{inv} mechanism (*vide supra*), with good yield and high enantioselectivity.

Scheme 1.5.7. Asymmetric deprotonation of CbHx with (–)-sp

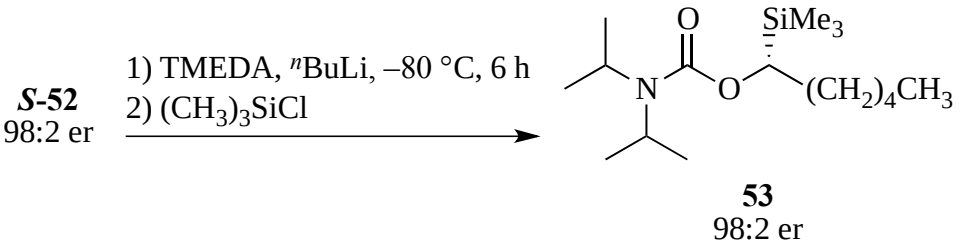


51

***S*-52**
85% yield, 98:2 er (*S*:*R*)

The configurational stability of lithiated **51** was monitored by subjecting ***S*-52** to tin-lithium exchange conditions, and quenching with $(CH_3)_3SiCl$ at different time intervals and monitoring the er of the organosilane, **53**. After 6 h, **53** was obtained without any loss of stereochemical integrity (***Scheme 1.5.8***).

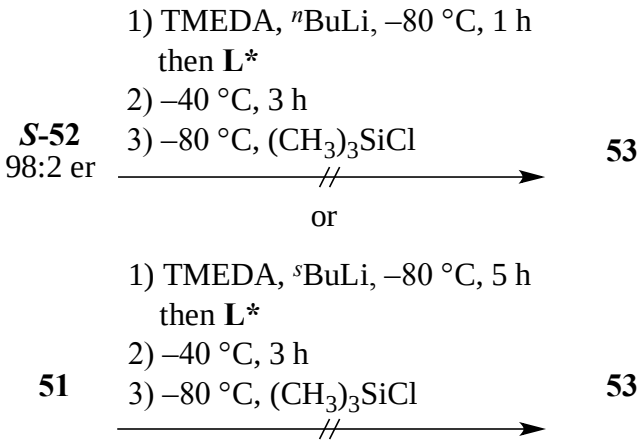
Scheme 1.5.8. Configurational stability of lithiated **51** at low temperature

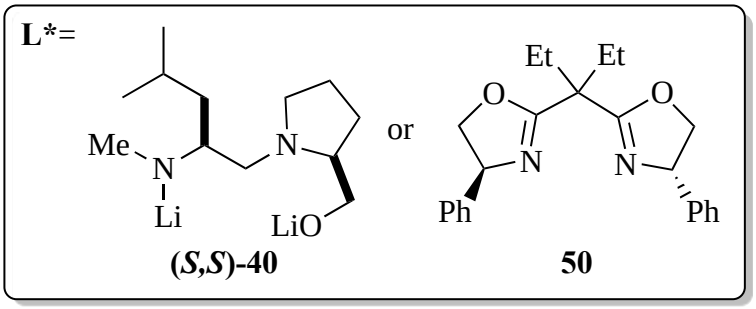


53
98:2 er

This successful asymmetric deprotonation was the height of joy experienced with this investigation. A number of experiments where the enantiopure organostannane was subjected to tin-lithium exchange conditions in the presence of ***SS*-40** or (*R*,*R*)-diethyldiphenyl(bis)oxazoline, **50**, then subjected to standard DTR conditions and quenched with Me_3SiCl gave no desired product (***Scheme 1.5.10***). In fact, any attempt to warm lithiated **51** to temperatures required for resolution resulted in decomposition by way of the "Sniekus-type" rearrangement reported by Nakai and Gawley (*vide supra*). Similar results were observed in the products from a DTR where the lithiated **51** was formed by a racemic deprotonation. With such a fundamental problem, attempts to apply DTR were abandoned.

Scheme 1.5.10. DTR of lithiated **51**





(*S*,*S*)-40 **50**

1.6 Experimental Procedures

Synthesis of the ketal of N-Boc-4-oxo-piperidine

***N*-Boc-4-oxopiperidine**:

To a stirred solution of 4-piperidone hydrochloride monohydrate (1.53 g, 10 mmol) and Et_3N (1.67 mL, 12 mmol), was added tert-butoxycarbonyl anhydride, Boc_2O (2.18 g, 10 mmol) in THF and water (15 mL/5 mL respectively), and stirred for 2 h at room temperature. Then, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with ammonium chloride and brine, dried over magnesium sulfate ($MgSO_4$), and the solvents removed under reduced pressure to give the N-Boc-4-oxopiperidine in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.72 (4H, t, 2 x CH_2), 2.44 (4H, t, 2 x CH_2), 1.50 (9H, s, 3 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 207 (C=O), 154 (Boc C=O), 80 (CCH_3), 41 (2 x CH_2), 28 (2 x CH_2)

Ethylene ketal of *N*-Boc-4-oxo-piperidine:

N-Boc-4-piperidone (2 g, 10 mmol), ethylene glycol (0.744 g, 12 mmol), pyridinium *p*-toluenesulfonate (PPTS, 0.25 g, 1 mmol), and toluene (10 mL) were added to a flask with a Dean-Stark trap attached and refluxed overnight. Then, the solution was partitioned with EtOAc and 2 M NaOH, and the organic layer separated and dried over $MgSO_4$. Then, the solvents were removed under reduced pressure to give a yellow oil that crystallized with time. The crystals were washed with hexanes to give the pure product in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.95 (4H, s, 2 x CH_2), 3.5 (4H, t, 2 x CH_2), 1.65 (4H, t, 2 x CH_2), 1.45 (9H, s, 3 x CH_3)

Propylene ketal of *N*-Boc-4-oxo-piperidine:

N-Boc-4-piperidone (5 g, 19.5 mmol), 1,3-propanediol (2 g, 26.3 mmol), PPTS (0.51 g, 2 mmol), and toluene (50 mL) were added to a flask with a Dean-Stark trap attached and refluxed overnight. Then, the solution was partitioned with EtOAc and 2 M NaOH, and the organic layer separated and dried over $MgSO_4$. Then, the solvents were removed under reduced pressure to give a yellow oil that crystallized with time. The crystals were washed with hexanes to give the pure product in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.9 (4H, s, 2 x CH_2), 3.4 (4H, t, 2 x CH_2), 1.75 (2H, br, CH_2), 1.85 (4H, br, 2 x CH_2), 1.45 (9H, s, 3 x CH_3); ^{13}C NMR (100 MHz) δ = 155 (Boc C=O), 96 (Ketal C), 79 ($C(CH_3)$), 59 (2 x α-O CH_2), 40 (2 x α-N CH_2), 33 (2 x CH_2), 28 (3 x CH_3), 25.4 (CH_2)

Synthesis of (S,S)-N-methyl-leu-pro

***N*-Boc-(*S*)-leucine**:

(*S*)-Leucine (10 g, 76.3 mmol), Boc_2O (20 g, 91.7 mmol), and 200 mL of 2 M NaOH (aq.) were added to a flask and stirred overnight at room temperature followed by addition of 50mL DCM. Then, the aqueous layer was separated and acidified with citric acid, and extracted with DCM (3x 50 mL), dried over $MgSO_4$, and solvents removed by reduced pressure to give 10.26 g (58% yield) white solid product.

(S)*-Proline methyl ester hydrochloride*:

(*S*)-Proline (5.8 g, 50.4 mmol) was stirred in anhydrous MeOH (35 mL) until it dissolved. Then, at 0 °C $SOCl_2$ (4.0 mL, 55.5 mmol) was slowly added, and stirred for 2 hours. The solvents were removed under reduced pressure to give a viscous oil in 86% yield.

N*-Boc-Leu-Pro-OMe*:

N-Boc-Leu (11.6 g, 50 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, EDCI (9.8 g, 50 mmol), and 1-hydroxybenzotrazole, HOBt (7.6 g, 50 mmol) were stirred until dissolved in $CHCl_3$ (200 mL). Then, the proline methyl ester (8.3 g, 50 mmol) in $Et_3N/CHCl_3$ (20 mL/100 mL) was added and stirred overnight at room temperature. Then, the solvents were removed under reduced pressure, and EtOAc (150 mL) was added and stirred for 30 min, followed by filtration of solids. The EtOAc was washed w/ 10% citric acid (3x 100 mL) and then 10% $NaHCO_3$ (3x 50 mL). The organic layer was dried over $MgSO_4$, and evaporated to give 9.88 g (58% yield) of a yellow oil. ^{13}C NMR (75.5 MHz, $CDCl_3$) (mixture of rotamers) δ = 172.6 (C=O of ester), 170.1 and 169.1 (C=O of amide), 156.5 (C=O of carbamate), 80.2 and 79.8 (C), 59.3 and 58.5 (CH), 56.8 and 56.2 (CH), 52.6 (CH_3), 46.7(CH_2), 31.7 (CH), 28.5 (CH_2), 28.1 and 28.0, 27.8 (3 x CH_3), 25.0 and 24.9 (CH_2), 19.4 and 19.0 (CH_3), 18.4 and 18.2 (CH_3)

(*S,S*)-*N*-Me-Leu-Pro

Lithium aluminum hydride, $LiAlH_4$ (8.5 g, 220 mmol) was dissolved in THF (70 mL) at 0 °C. Then, the peptide (9.88 g, 28.9 mmol) in THF (140 mL) was slowly added and stirred at reflux (80 °C) overnight. Then, the solution was cooled to 0 °C, and Et_2O (100 mL) was added. Then, the solution was carefully quenched by slow addition of 50% NaOH (aq.) until all the solids turned white. The solvent was decanted, and the remaining white solid was washed with Et_2O (3x 50 mL). The Et_2O extractions were concentrated to about 100 mL, and extracted with 2 M HCl (aq.) (3x 20 mL). The aqueous extractions were then basified with 50% NaOH (aq.) to pH 14, and extracted with Et_2O (3x 50 mL). The organic layers were combined and dried over $MgSO_4$, and solvent was removed under reduced pressure to give a yellow oil, which was

purified by Kuglerohr distillation to give 2.56 g (42%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.7 (6H), 1.0-1.2 (2H), 1.3-1.7 (5H), 2.2 (3H), 2.2-2.4 (2H), 2.4-2.6 (2H), 2.7-2.9 (1H, NH), 2.9 (2H), 3.1-3.2 (1H), 3.3-3.4 (1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 66.4 (CH), 64.4 (CH_2), 63.6 (CH), 56.7 (CH_2), 56.1 (CH_2), 40.5 (CH), 34.1 (CH_3), 28.3 (CH_2), 24.0 (CH_2), 18.5 (CH_3) and 17.9 (CH_3).

General procedure for racemic, direct electrophilic quenches

To an oven-dried flask, the ethylene or propylene ketal of *N*-Boc-4-oxo-piperidine (1 eq.) or *N*-Boc-piperidine, *N,N,N',N'*-tetramethylethylenediamine, (TMEDA, 4 eq.), and freshly distilled Et_2O were added and stirred at –80 °C. Then, *s*-BuLi (1.2 eq.) was slowly added and stirred for 1 h. Then, the electrophile, E^+ (3 eq.) was added and stirred overnight at –80 °C. Then, MeOH was added and the solution was allowed to warm to room temperature. After aqueous workup, the organic solvents were dried over $MgSO_4$ and removed under reduced pressure.

General procedure for racemic arylation via Negishi-type coupling

To an oven-dried flask, the ethylene or propylene ketal of *N*-Boc-4-oxo-piperidine or *N*-Boc-piperidine (1 eq.), TMEDA (4 eq.), and freshly distilled Et_2O were added and stirred at –80 °C. Then, *s*-BuLi (1.2 eq.) was slowly added and stirred for 1 h. Then, $ZnCl_2$ in Et_2O (0.6 eq.) was added dropwise and stirred for 30 min. Followed by slow warming to ambient temperature, and stirred for 30 min. Then, $Pd(OAc)_2$ (0.04 eq.), *t*-Bu_3P•HBF_4 (0.08 eq.), and PhBr (1.1 eq.) were added and stirred 18 h. Then, NH_4OH was added and stirred 30 min, followed by filtration through Celite™. Then, the organic layer was washed with 1 N HCl and then, twice with H_2O;

then, dried over $MgSO_4$, and the solvent was removed by reduced pressure. *N*-Boc-2-phenylpiperidine $M^+ = 205$, ethylene ketal of *N*-Boc-4-oxo-2-phenylpiperidine $M^+ = 263$

General procedure for the dynamic thermodynamic resolution of the ethylene or propylene ketal of N-Boc-2-lithio-4-oxopiperidine or N-Boc-piperidine with direct electrophilic quench

To an oven-dried flask, the ethylene or propylene ketal of *N*-Boc-4-oxo-piperidine (243 mg, 1 mmol) or *N*-Boc-piperidine, TMEDA (0.6 mL, 4 mmol), and (*S*,*S*)-*N*-methyl-leu-pro (214 mg, 1 mmol) was added and brought to –80 °C. Then, *s*-BuLi (2.5 mL of 1.4 M soln., 3.5 eq.) was added dropwise and stirred for 1 h. Then, the flask was warmed to –45 °C for 3 h. The solution was then rapidly cooled to –80° C, and the electrophile was added within 5 min. Then, acidic MeOH was added and the solution was allowed to slowly warm to room temperature.

1.7. References

1. Gawley, R.E.; Aubé, J., *Principles of Asymmetric Synthesis*. Elsevier: **2012**.

2. (a) Vargas, A.; Mondelli, C.; Baiker, A., Catalysis with Chirally Modified Metal Surfaces; Scope and Mechanisms. In *Catalytic Methods in Asymmetric Synthesis*, John Wiley & Sons, Inc.: **2011**; pp 291-321; (b) Raj, M.; Singh, V.K., Recent Advances on Stereoselective Organocatalytic Reactions. Organocatalytic Synthesis of Natural Products and Drugs. In *Catalytic Methods in Asymmetric Synthesis*, John Wiley & Sons, Inc.: **2011**; pp 413-490; (c) Gonzalo, G. d.; Lavandera, I.; Gotor, V., Recent Advances in Biocatalysis Applied to Organic Synthesis. In *Catalytic Methods in Asymmetric Synthesis*, John Wiley & Sons, Inc.: **2011**; pp 491-527; (d) Freund, M.; Tsogoeva, S. B., Peptides for Asymmetric Catalysis. In *Catalytic Methods in Asymmetric Synthesis*, John Wiley & Sons, Inc.: **2011**; pp 529-578; (e) Ferrer, C.; Verdaguer, X.; Riera, A., Recent Advances in the Metal-Catalyzed Stereoselective Synthesis of Biologically Active Molecules. In *Catalytic Methods in Asymmetric Synthesis*, John Wiley & Sons, Inc.: **2011**; pp 625-670; (f) Chemler, S. R., Stereoselective Nitrogen heterocycle Synthesis Mediated by Chiral Metal Catalysts. In *Catalytic Methods in Asymmetric Synthesis*, John Wiley & Sons, Inc.: **2011**; pp ; (g) Frontmatter. In *Catalytic Methods in Asymmetric Synthesis*, John Wiley & Sons, Inc.: **2011**; pp i-xviii.

3. (a)Lee, W. K.; Park, Y. S.; Beak, P., Dynamic Thermodynamic Resolution: Advantage by Separation of Equilibration and Resolution. *Acc. Chem. Res*., **2009**, *42* (2) 224-234; (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S., Regioselective, diastereoselective, and enantioselective lithiation-substitution sequences: Reaction pathways and synthetic applications. *Acc. Chem. Res*., **1996**, *29* (11), 552-560; (c) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A., Dynamic Thermodynamic Resolution: Control of Enantioselectivity through Diastereomeric Equilibration. *Acc. Chem. Res*., **2000**, *33*, (10), 715-727.

4. Hoppe, D.; Hense, T., Enantioselective synthesis with lithium/(–)-sparteine carbanion pairs. *Angew Chem. Int. Edit*., **1997**, *36* (21), 2283-2316.

5. (a) Anders, E.; Koch, R.; Freunscht, P., Optimization and Application of Lithium Parameters for PM3. *J. Comput. Chem*., **1993**, *14* (11), 1301-1312; (b) Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S. H.; Wiberg, K. B., An experimental and computational investigation of the enantioselective deprotonation of Boc-piperidine. *J. Am. Chem Soc*., **2002**, *124* (9), 1889-1896; (c) Beak, P.; Kerrick, S. T.; Wu, S. D.; Chu, J. X., Complex-Induced Proximity Effects – Enantioselective Syntheses Based on Asymmetric Deprotonations of N-Boc-Pyrrolidines. *J. Am. Chem. Soc*., **1994**, *116* (8), 3231-3239; (d) Beng, T. K.; Tyree, W. S.; Parker, T.; Su, C. C.; Williard, P. G.; Gawley, R. E., Dynamics of Catalytic Resolution of 2-Lithio-N-Boc-Piperidine by Ligand Exchange. *J. Am. Chem. Soc.*, **2012**, *134* (40), 16845-16855; (e) Beng, T. K.; Yousaf, T. I.; Coldham, I.; Gawley, R.E., Enantiomerization Dynamics and a Catalytic Dynamic Resolution of N-Trimethylallyl-2-lithiopyrrolidine. *J. Am. Chem. Soc*., **2009**, *131* (20), 6908; (f) Coldham, I. : Leonori, D.; Beng, T. K.; Gawley, R. E., The barrier to enantiomerization and dynamic resolution of N-Boc-2-lithiopiperidine and the effect of TMEDA. *Chem. Commun*., **2009** (35), 5239-5241; (g) Derwing, C.; Frank, H.; Hoppe, D., Chiral benzyllithium compounds: High configurative stability of (R)- and (S)-1-lithioindan-1-yl N,N-diisopropylcarbamate and unexpected stereochemical course of the substitution reactions. *Eur. J. Org. Chem*., **1999** (12), 3519-3524; (h) Gawley, R. E.; Klein, R.; Ashweek, N. J.; Coldham, I., Structural studies of Li-6 2-lithiopyrrolidines using NMR spectroscopy. *Tetrahedron*, **2005**, *61* (13), 3271-3280; (i) Gawley, R. E.; Low, E.; Zhang, Q. H.; Harris, R., The steric course of S(E)2 reactions of unstabilized alpha-aminoorganolithiums: Distinguishing between SET and polar mechanisms. *J. Am. Chem. Soc*., **2000**, *122* (14), 3344-3350; (j) Hemery, T.; Huenerbein, R.; Frohlich, R.; Grimme, S.; Hoppe, D., Configurationally Labile Enantioenriched Lithiated 3-Arylprop-2-enyl Carbamates: Joint Experimental and Quantum Chemical Investigations on the Equilibrium of Epimers. *J. Org. Chem*., **2010**, *75* (16), 5716-5720; (k) Klein, R.; Gawley, R. E., Configurational and conformational effects on tin-lithium exchange in alpha-aminoorganostannanes by rapid-injections NMR. *J. Am. Chem. Soc.*, **2007**, *129* (14), 4126; (l) Lange, H.; Heunerbein, R.; Frohlich, R.; Grimme, S.; Hoppe, D., Configurationally labile lithiated O-benzyl carbamates: Application in asymmetric synthesis and quantum chemical investigations on the equilibrium of diastereomers. *Chem. Asian J.*, **2008**, *3* (1), 78-87; (m) Lange, H.; Huenerbein, R.; Wibbeling, B.; Frohlich, R.; Grimme, S.; Hoppe, D., Comprehensive experimental and theoretical studies of configurationally labile epimeric diamine complexes of alpha-aminoorganolithiums by C-13, N-15, and Li-6 NMR spectroscopy. *J. Am. Chem. Soc*., **2000**, *122* (39), 9562-9563; (o) Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Coldham, I.; Sanderson, A., Asymmetric

Deprotonation of N-Boc-Piperidine: React IR Monitoring and Mechanistic Aspects. *J. Am. Chem. Soc*., **2010**, *132* (21), 7260; (p) Wiberg, K. B.; Bailey, W. F., A transition state for the enantioselective deprotonation of N-Boc-pyrrolidine with isopropyllithium/(–)-sparteine. *Angew. Chem. Int. Edit.*, **2000**, *39* (12), 2127.

6. Gawley, R. E., Chiral, nonracemic, 2-lithiopiperidines and –pyrrolidines: Remarkably stable "carbanions" with considerable synthetic potential. *Curr. Org. Chem*., **1997**, *1* (1), 71-94.

7. Coeffard, V.; Beaudet, I.; Quintard, J. P.; Le Grognec, E., Preparation of Enantiomerically Enriched alpha-Aminoorganostannanes and their Applications in Stereoselective Synthesis. *Chirality*, **2010**, *22* (10), 864-869.

8. Seyferth, D.; Weiner, M., Communications: Preparation and /Some Reactions of Allyllithium. *J. Org. Chem.*, **1959**, *24* (9), 1395-1396.

9. Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J., Physical properties and synthetic utility of alpha-alkoxyorganolithium species as studied through ligand selectivity in tin-lithium exchange. *J. Am. Chem. Soc*., **1988**, *110* (3), 842-853.

10. Reich, J. J.; Borst, J. P.; Coplien, M. B.; Phillips, N. H., Lithium-tin exchange reaction. Stereochemistry at tin. *J. Am. Chem. Soc.*, **1992**, *114* (16), 6577-6579.

11. Pearson, W. H.; Lindbeck, A. C., Geration of synthetic equivalents of RCH(Li)NH2 for the synthesis of primary amines. Tin-lithium exchange on carbamate-protected (alpha-aminoalkyl)stannanes. *J. Org. Chem*., **1989**, *54* (24), 5651-5654.

12. Pearson, W. H.; Lindbeck, A. C., Stereochemical studies on the chiral, nonconjugated, nitrogen-substituted carbanions generated by tin lithium exchange. *J. Am. Chem. Soc.*, **1991**, *113* (22), 8546-8548.

13. Tomoyasu, T.; Tomooka, K.; Nakai, T., A new approach to asymmetric synthesis of beta-amino alcohols by means of alpha-chirally protected alpha-aminoorganolithiums: preparation and configurational stability. *Synlett*, **1998** (10), 1147.

14. Chong, J. M.; Park, S. B., Enantiomerically enriched tert-Boc-protected alpha-aminoorganolithiums: preparation and configurational stability. *J. Org. Chem.*, **1992**, *57* (8), 2220-2222.

15. Gawley, R. E.; Barolli, G.; Madan, S.; Saverin, M.; O'Connor, S., Nucleophilic synthesis of enantiopure 2-(tributylstannyl)pyrrolidines and piperidines. *Tetrahedron Lett.*, **2004**, *45* (8), 1759-1761.

16. Gawley, R. E.; Zhang, Q., 2-lithio-N-methylpiperidine and 2-lithio-N-methylpyrrolidine: configurationally and chemically stable unchelated alpha-aminoorganolithiums. *J. Am. Chem. Soc.*, **1993**, *115* (16), 7515-7516.

17. Coeffard, V.; Le Grognec, E.; Beoudet, I.; Leat-Crest, V.; Quintard, J. P., Precursors of chiral alpha-amino anions: An improved synthesis of chiral N-(alpha-tributylstannylorgano)oxazolidin-2-ones derived from (R)- or (S)-phenylglycinol. *Synthesis*, **2006** (24), 4151-4158.

18. (a) Jeanjean, F.; Fournet, G.; Le Bars, D.; Gore, J., Synthesis of highly enantio-enriched alpha-amino acids by carboxylation of N-(alpha-lithioalkyl)oxazolidinones. *Eur. J. Org. Chem.*, **2000** (7), 1297-1305; (b) Jeanjean, F.; Perol, N.; Gore, J.; Fournet, G., Asymmetric carboxylation in the synthesis of L-methionine: anew tool for C-11 chemistry. *Tetrahedron Lett.*, **1997**, *38* (43), 7547-7550.

19. (a) Escolano, C.; Amat, M.; Bosch, J., Chiral Oxazolopiperidone lactams: Versatile intermediates for the enantioselective synthesis of piperidine-containing natural products. *Chem. Eur. J.*, **2006**, *12* (32), 8198-8207; (b) Joseph, S.; Comins, D. L., Synthetic applications of chiral 2,3-dihydro-4-pyridones. *Curr. Opin. Drug Discov. Dev.*, **2002**, *5* (6), 870-880.

20. Gawley, R. E.; Siegel, J., *Stereochemical aspects of organolithium compounds*. Wiley-VCH: 2010.

21. Wiberg, K. B.; Bailey, W. F., A transition state for the enantioselective deprotonation of N-Boc-pyrrolidine with isopropyllithium/(–)-sparteine. *Angew. Chem. Int. Edit.*, **2000**, *39* (12), 2127-2129.

22. Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P., Beyond Thermodynamic Acidity: A perspective on the Complex-Induced Proximity Effect (CIPE) in deprotonation reactions. *Angew. Chem. Int. Edit.*, **2004**, *43* (17), 2206-2225.

23. Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B., An experimental and computational investigation of the enantioselective deprotonation of Boc-piperidine. *J. Am. Chem. Soc.*, **2002**, *124* (9), 1889-1896.

24. McGrath, M. J.; Bilke, J. L.; O'Brien, P., Reactivity series for s-BuLi/diamine-mediated lithiation of N-Boc-pyrrolidine: applications in catalysis and lithiation of N-Boc-piperidine. *Chem. Commun.*, **2006** (24), 2607-2609.

25. Beak, P.; Lee, W. K., alpha-Liithioamine synthetic equivalents: syntheses of diastereoisomers from the Boc-piperidines. *J. Org. Chem.*, **1990**, *55* (9), 2578-2580.

26. Coldham, I.; O'Brien, P.; Patel, J. J.; Raimbault, S.; Sanderson, A. J.; Stead, D.; Whittaker, D. T. E., Asymmetric deprotonation of N-Boc-piperidines. *Tetrahedron: Asymmetry*, **2007**, *18* (17), 2113-2119.

27. Beak, P.; Lee, W. K., alpha-Lithioamine synthetic equivalents: syntheses of diastereoisomers from Boc derivatives of cyclic amines. *J. Org. Chem.*, **1993**, *58* (5), 1109-1117.

28. Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Coldham, I.; Sanderson, A., Asymmetric Deprotonation of N-Boc Piperidine: React IR Monitoring and Mechanistic Aspects. *J. Am. Chem. Soc.,* **2010**, *132* (21), 7260-7261.

29. (a) Coldham, I.; Patel, J. J.; Sanchez-Jimenez, G., Dynamic kinetic resolution of N-Boc-2-lithiopyrrolidine. *Chem. Commun.,* **2005** (24), 3083-3085; (b) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Patel, J. J.; Sanchez-Jimenez, G., Dynamic Thermodynamic and Dynamic Kinetic Resolution of 2-Lithiopyrrolidines. *J. Am. Chem. Soc.,* **2006**, *128* (33), 10943-10951.

30. Coldham, I.; Patel, J. J.; Raimbault, S.; Whittaker, D. T. E., Dynamic kinetic and kinetic resolution of N-Boc-2-lithiopiperidine., *Chem. Commun.,* **2007** (43), 4534-4536.

31. Coldham, I.; Raimbault, S.; Chovatia, P. T.; Patel, J. J.; Leonori, D.; Sheikh, N. S.; Whittaker, D. T. E., Dynamic resolution of N-Boc-2-lithiopiperidine. *Chem. Commun*., **2008** (35), 4174-4176.

32. Coldham, I.; Raimbault, S.; Whittaker, D. T. E.; Chovatia, P. T.; Leonori, D.; Patel, J. J.; Sheikh, N. S., Asymmetric substitutions of 2-lithiated N-Boc-piperidine and N-Boc-azepine by dynamic resolution. *Chem. Eur. J*., **2010**, *16* (13), 4082-4090.

33. Beng. T. K.; Gawley, R. E., Highly Enantioselective Catalytic Dynamic Resolution of N-Boc-2-lithiopiperidine: Synthesis of (R)-(+)-N-Boc-pipecolic acid, (S)-(–)-coniine, (S)-(+)-pelletierine, (+)-β-conhydrine, and (S)-(–)-ropivacaine and Formal Synthesis of (–)-lasubine II and (+)-cermizine C. *J. Am. Chem. Soc*., **2010**, *132* (35), 12216-12217.

34. Beng, T. K.; Gawley, R. E., Application of Catalytic Dynamic Resolution of N-Boc-2-lithiopiperidines to the Asymmetric Synthesis of 2-aryl and 2-vinyl piperidines. *Org. Lett*., **2010**, *13* (3), 394-397.

35. Comins, D. L.; Joseph, S. P.; Goehring, R. R., Asymmetric Synthesis of 2-alkyl(aryl)-2,3-dihydro-4-pyridones by Addition of Grignard Reagents to Chiral 1-acyl-4-methoxypyridinium Salts. *J. Am. Chem. Soc.*, **1994**, *116* (11), 4719-4728.

36. Pfrengle, W.; Kunz, H., Hetero-Diels-Alder reactions on a carbohydrate template: stereoselective synthesis of (S)-anabasin. *J. Org. Chem*., **1989**, *54* (18), 4261-4263.

37. Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S., Asymmetric synthesis of 2-alkyl(aryl)-2,3-dihydro-4-pyridones by addition of Grignard reagents to chiral 1-acyl-4-methoxypyridinium salts. *J. Org. Chem*., **1990**, *55* (9), 2574-2576.

38. (a) Niphakis, M. J.; Turunen, B. J.; Georg, G. I., Synthesis of 6- and 7-membered cyclic enaminones: scope and mechanism. *J. Org. Chem*., **2010**, *75* (20), 6793-6805; (b) Turunen, B. J.; Georg, G. I., Amino acid-derived enaminones: a study in ring formation providing valuable asymmetric synthons. *J. Am. Chem. Soc.,* **2006**, *128* (27), 8702-8703.

39. Laha, J. K., Excellent Exo/Endo-Selectivity in the 1-3-dipolar cycloaddition of cyclic azomethine ylide: exploring the facile investigation of cocaine antagonists. *Lett. Org. Chem.*, **2007**, *4* (8), 550-552.

40. Hoppe, D.; Marr, F.; Brüggemann, M., Enantioselective Synthesis by Lithiation Adjacent to Oxygen and Electrophile Incorporation., In *Organolithiums in Enantioselective Synthesis*, Hodgson, D., Ed. Springer Berlin Heidelberg: **2003**; Vol. 5, pp 61-138.

41. Still, W. C.; Sreekumar, C., alpha-Alkoxyorganolithium reagents. A new class of configurationally stable carbanions for organic synthesis. *J. Am. Chem. Soc*., **1980**, *102* (3), 1201-1202.

42. Chan, P. C. M.; Chong, J. M., Asymmetric reduction of acylstannanes. Preparation of enantiomerically enriched alpha-alkoxystannanes. *J. Org. Chem*., **1988**, *53* (23), 5584-5586.

43. Stork, G.; Manabe, K.; Liu, L., An enantioselective construction of the ABC system of taxol. *J. Am. Chem. Soc.*, **1998**, *120* (6), 1337-1338.

44. Chong, J. M.; Mar, E. K., Enantioseletive syntheses of endo- and exo-brevicomin via α-alkoxystannanes. *Tetrahedron*, **1989**, *45* (24), 7709-7716.

45. Hoppe, D.; Hintze, F.; Tebben, P., Chiral Lithium-1-oxyalkanides by asymmetric deprotonation; enantioselective synthesis of 2-hydroxyalkanoic acids and secondary alkanols. *Angew. Chem. Int. Edit. Eng.*, **1990**, *29* (12), 1422-1424.

46. (a) Hintze, F.; Hoppe, D., Enantioselective Synthesis of (S)-1-Methyldodecyl Acetate, A Pheromone of Drosophila mulleri, via (–)-Sparteine-Assisted Deprotonation of 1-Dodecanol. *Synthesis*, **1992**, *1992* (12), 1216-1218; (b) Paetow, M.; Ahrens, H.; Hoppe, D., Chiral α,ω-dioxy-carbanions from 1,3-propanediol and 1,4-butanediol by sparteine-assisted deprotonation. Enantioselective synthesis of 1,3- and 1,4-diols, (R)-pantolactone, and a cyclopropane. *Tetrahedron Lett.*, **1992**, *33* (37), 5323-5326; (c) Schwerdtfeger, J.; Hoppe, D., Stereoselective generation of 1-acyloxy-2-amino carbanions by deprotonation; synthesis of enantiomerically and diastereomerically pure β-amino alcohols. *Angew. Chem. Int. Edit. Eng.*, **1992**, *31* (11), 1505-1507; (d) Sommerfeld, P.; Hoppe, D., Enantioselective generation of 3-amino-1-oxy-substituted carbanions by sparteine-induced deprotonation: asymmetric synthesis of 3-hydroxyalkylamines. *Synlett*, **1992**, *1992* (9), 764-766; (e) Behrens, K.; Frölich, R.; Meyer, O.; Hoppe, D., Enantioselective lithiation and substitution of (E)-cinnamyl N,N-diisopropylcarbamate through use of (–)-sparteine complexes. *Eur. J. Org. Chem*., **1998**, *1998* (11), 2397-2403; (f) Schwerdtfeger, J.; Kolczewski, S.; Weber, B.; Frölich, R.; Hoppe, D., Stereoselective deprotonation of chiral and achiral 2-aminoalkyl carbamates: synthesis of optically active β-amino alcohols via 1-oxy-substituted alkyllithium intermediates. *Synthesis*, **1999**, *1999* (9), 1573-1592; (g) Christoph, G.; Hoppe, D., Asymmetric synthesis of 2-alkenyl-1-cyclopentanols via tin-lithium exchange and intramolecular cycloalkylation. *Org. Lett.*, **2002**, *4* (13), 2189-2192.

47. Würthwein, E. U.; Behrens, K; Hoppe, D., Enantioselective deprotonation of alkyl carbamates by means of (R,R)-1,2-bis(N,N-dimethylamino)cyclohexane/sec-butyllithium—Theory and experiment. *Chem. Eur. J.*, **1999**, *5* (12), 3459-3463.

48. Hoppe, D.; Paetow, M.; Hintze, F., Stereodivergent enantioselective synthesis by exploiting unusually large kinetic H/D isotope effects on deprotonation. *Angew. Chem. Int. Edit. Eng.*, **1993**, *32* (3), 394-396.

49. Tomooka, K.; Shimizu, H.; Inoue, T.; Shibata, H.; Nakai, T., 1,2-Carbamoyl migration on enantio-enriched alpha-lithioalkyl carbamates generated with s-butyllithium/sparteine: steric course and mechanism. *Chem. Lett.*, **1999**, *28* (8), 759-760.

50. Zhange, P. Gawley, R. E., Directed metalation/Snieckus rearrangement of O-benzylic carbamates. *J. Org. Chem.*, **1993**, *58* (12), 3223-3224.

51. Hoppe, D.; Brönneke, A., Synthesis of 1-arylalkyl N,N-dialkylcarabamtes by lithiation and substitution of benzylic-type carbamates. *Synthesis*, **1982** (12), 1045-1048.

52. Beng, T. K., *Dynamics and Catalytic Resolutions of Selected Chiral organolithiums*. University of Arkansas: **2011**.

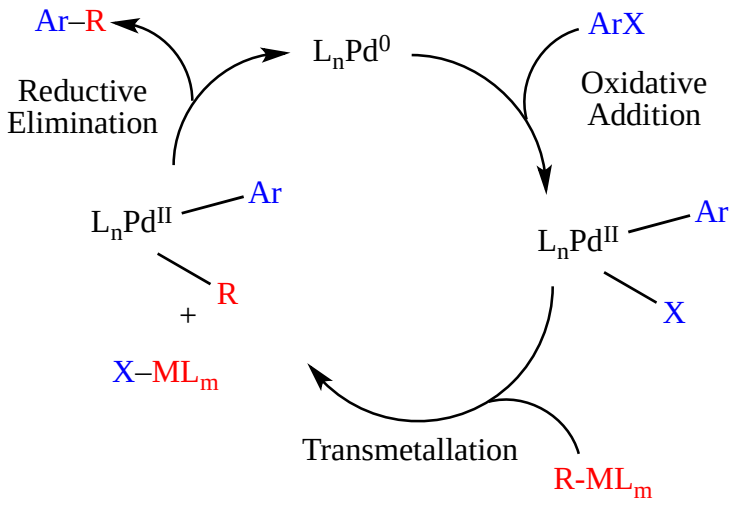
Chapter 2: Transition-metal catalyzed cross-coupling arylation

The utility of enantiopure carbamates as intermediates toward biologically active materials has been demonstrated (vide supra). A curious omission from the library of their derivatives is arylation products. The incorporation of benzene derivatives in natural products that are available from lithiated carbamates has been limited to addition of aryl carbonyls. The direct arylation of benzyl carbamates would significantly expand access to chiral building blocks useful for the synthesis of natural products and biologically active molecules. An important class of intermediates, diarylmethanols, has generally been made by addition of aryl organometallic reagents to aryl aldehydes or by asymmetric reduction of a diaryl ketone. Combining the asymmetric capabilities of organolithiums (Chapter 1) with the practicality of carbamates yields a powerful tool in the hands of skilled synthetic chemists.

2.1 Cross-Coupling Arylations

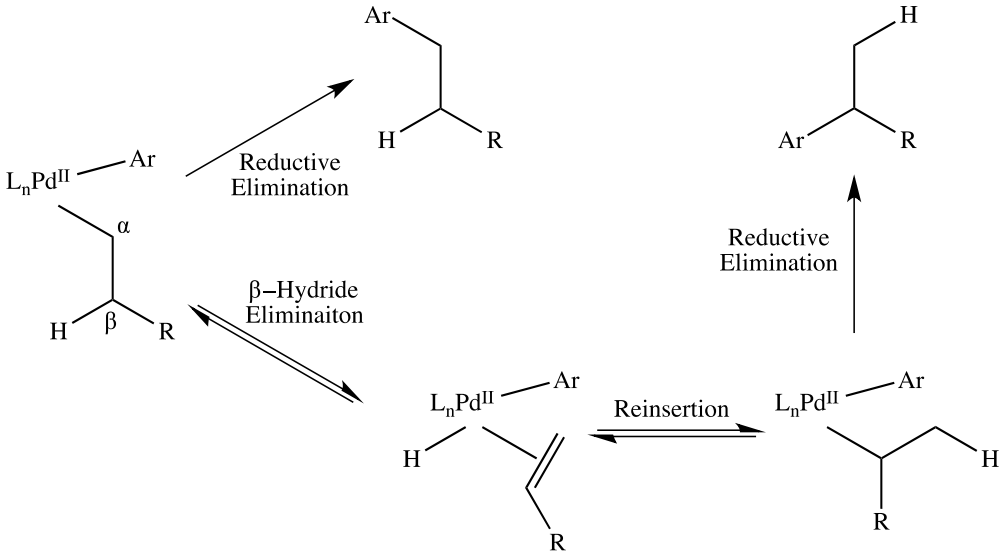
Transition metal-catalyzed cross-coupling reactions have been widely exploited for the formation of Csp^2-Csp^2 and Csp-Csp^2 bonds, but direct arylation of Csp^3 carbons has had inherent difficulties (*vide infra*). The generally accepted catalytic cycle for a typical Pd-catalyzed cross-coupling reaction is (1) oxidative addition of the electrophile to Pd^0, (2) transmetallation, and (3) reductive elimination of the product (***Figure 2.1.1***).

Figure 2.1.1. General catalytic cycle for Pd-catalyzed cross-coupling reactions



If a β-hydride is available for abstraction by a vacant coordination site of the Pd, then a competitive pathway to isomerization *via* β-hydride elimination/reinsertion exists. The elimination leads to coordination with an olefin, followed by another migratory insertion /reductive elimination sequence that could yield a regioisomer (***Scheme 2.1.1***). Manipulation of the steric and electronic properties of ligands on the active catalytic species helps to increase the rate of reductive elimination and minimize this side reaction. Throughout the literature reductive eliminations have been made more favorable by decreasing the electron density on the metal center and/or by increasing the bulkiness of the ligands.[53] Electron-poor complexes are more easily reduced. Alternatively, the high-energy steric interactions are eased by reductive elimination; bulkier ligands make elimination more favorable.

Scheme 2.1.1. Reductive elimination vs. isomerization *via* β–hydride elimination



There are several organometallic nucleophiles that have been used in Pd-catalyzed cross-coupling arylations. Organotins (Stille) and organozincs (Negishi) are especially useful due to their configurational stabilities at higher temperatures and facile transmetallation to Pd.

Recently, advances in the Negishi- and Stille-type couplings have provided access to the formation of Csp^2-Csp^3 bonds, specifically arylation of Csp^3.

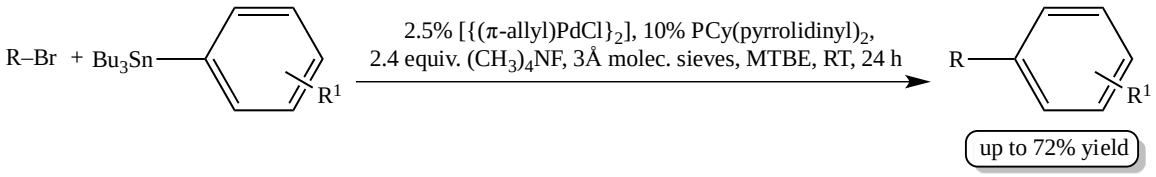
2.1.1 Stille cross-coupling arylations

The Eaborn group reported the first coupling of organostannane reagents and aryl halides in 1976.[54] The reaction was vastly improved and exploited by the group of John K. Stille, for whom the reaction was named, beginning in 1978 and continuing until his untimely death in a plane crash in 1989.[55]

The first Stille-type cross-coupling to form a Csp^2-Csp^3 bond was developed by the Fu group in

2003.[56] The organometallic nucleophile was an aryl tin, which was coupled with primary alkyl halides (***Scheme 2.1.2***).

Scheme 2.1.2. Fu's Csp^2-Csp^3 Stille cross-coupling arylation



The first enantioselective example was reported by the Hoppe group in 2006.[57] A sparteine-induced γ-deprotonation/substitution gave 52 in 94% ee. Pd-catalyzed cross-couplings with aryl iodides and bromides gave **53** and its regioisomer, 54, both with almost complete stereochemical integrity maintained (***Scheme 2.1.3***). The catalytic cycle was proposed to go through an η-3 planar-chiral complex that led to the retentive rearrangement products that most reactions formed (***Scheme 2.1.4***).

Scheme 2.1.3. Hoppe enantioselective Stille cross-coupling arylation of **51**

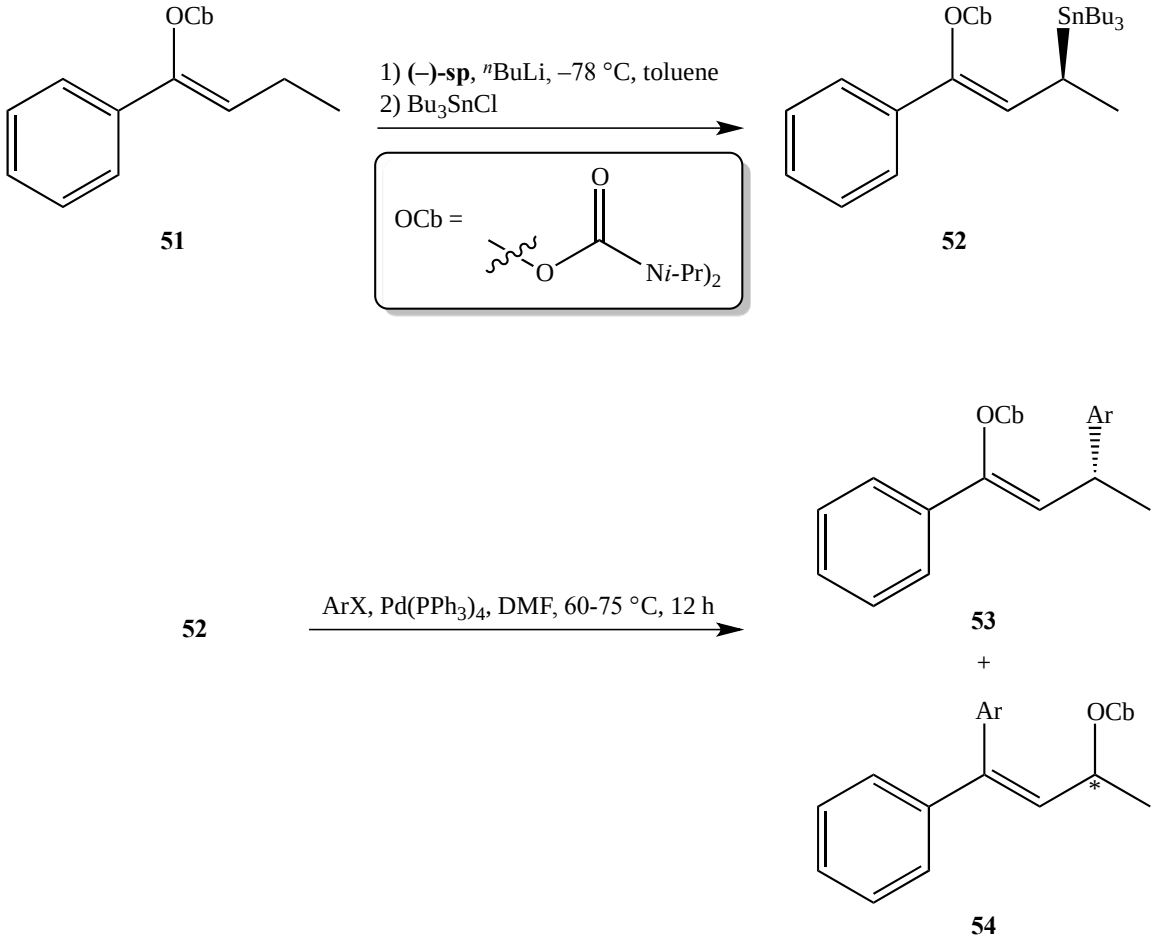
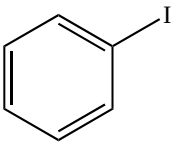
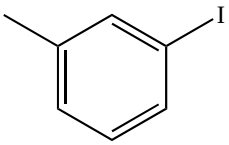
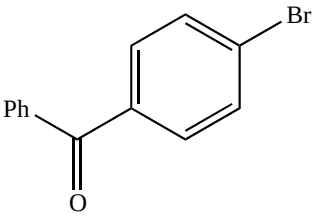
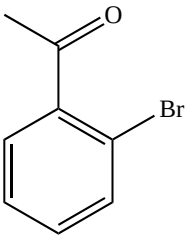
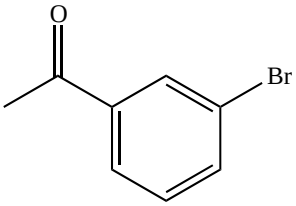
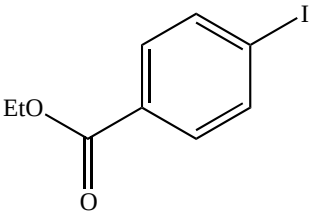
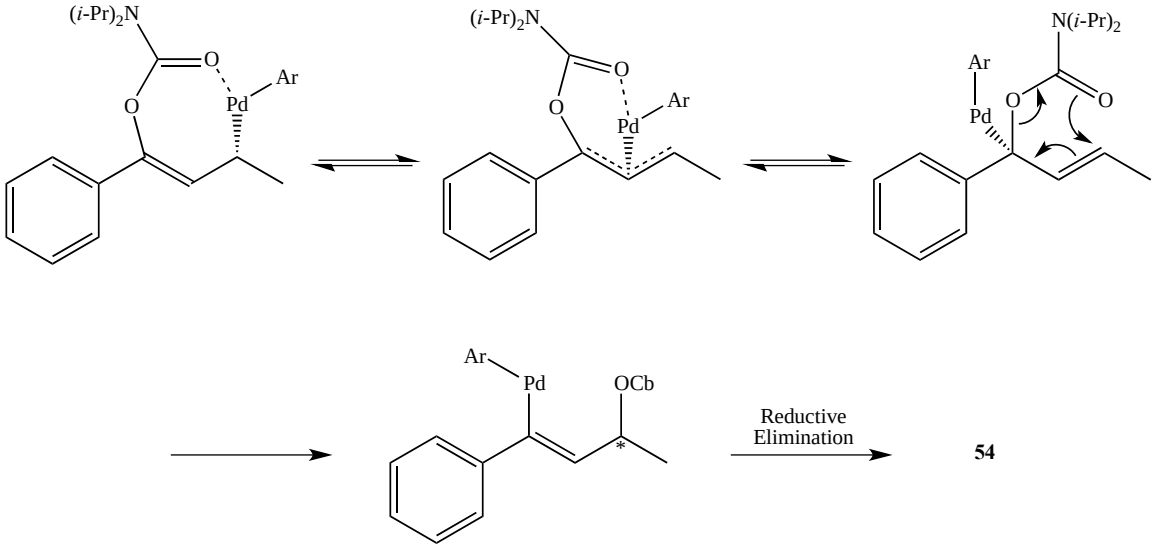


Table 2.1. Hoppe's Stille cross-coupling arylation products

ArX	yield **53** (%)	ee **53** (%)	yield **54** (%)	ee **54** (%)
	44	94	13	94
	41	91	–	–
	51	>90	27	>90
	–	–	67	92
	44	94	25	94
	51	90	29	90

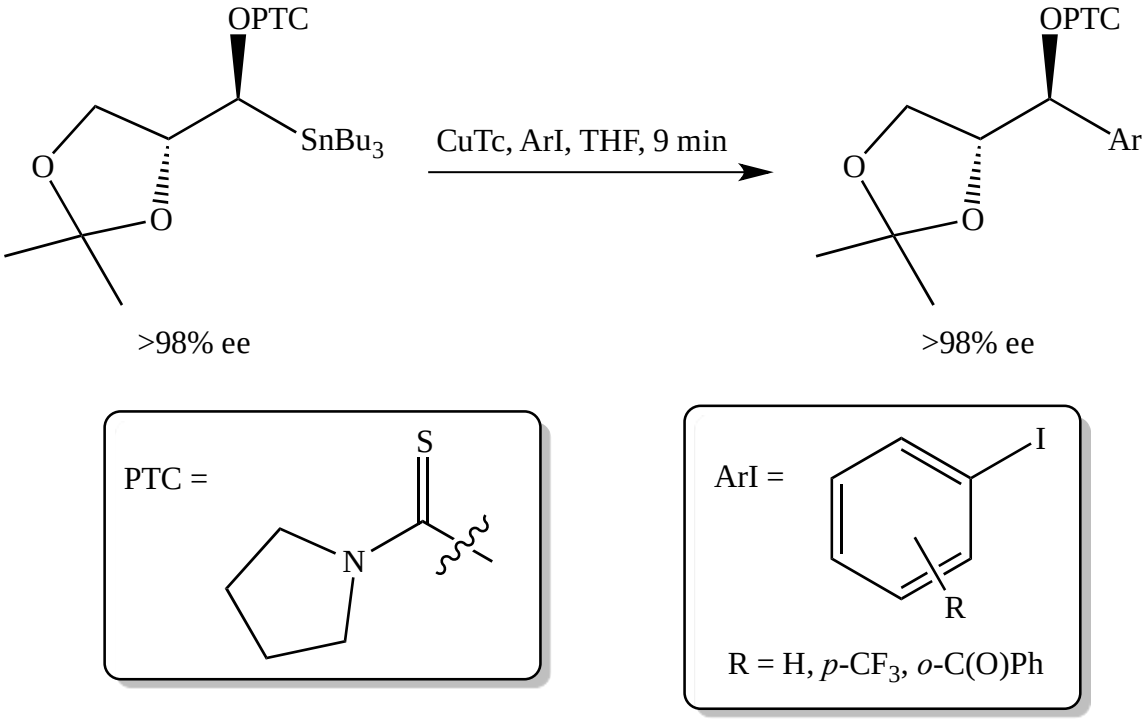
Scheme 2.1.4. Proposed mechanism of regioisomerization



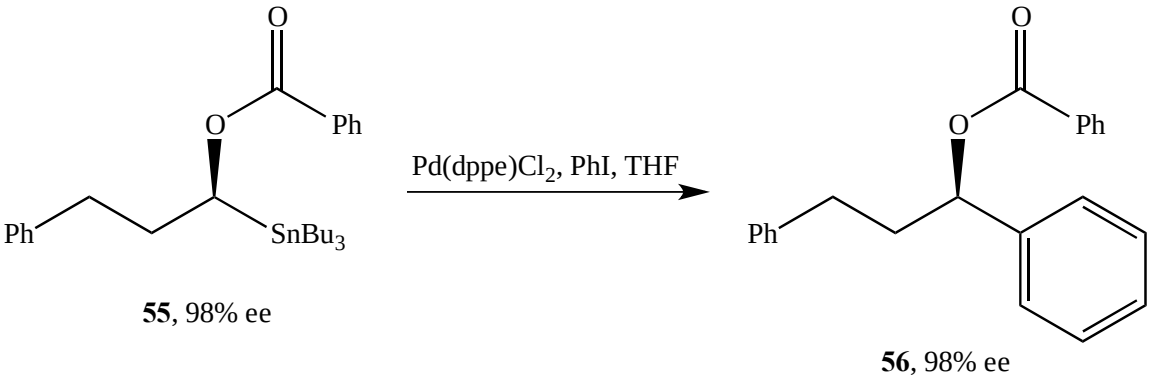
In 2007, the Falck group reported the diastereoselective coupling of (+)-glyceryl stannane (>98% ee) with aryl iodides using the Liebeskind promoter, CuTc (***Scheme 2.1.5***).[58] A number of arylation products were made with >98% de.

In 2010, the same group reported the arylation of an enantioenriched α–alkoxyorganostannane *via* a Pd-catalyzed Stille cross-coupling.[59] Stannyl benzoate (98% ee), **55**, was coupled with iodobenzene to give the desired product, **56**, with complete retention of stereochemical integrity (***Scheme 2.1.6***).

Scheme 2.1.5. Falck's diastereoselective Stille arylation



Scheme 2.1.6. Falck's enantioselective arylation of **55**

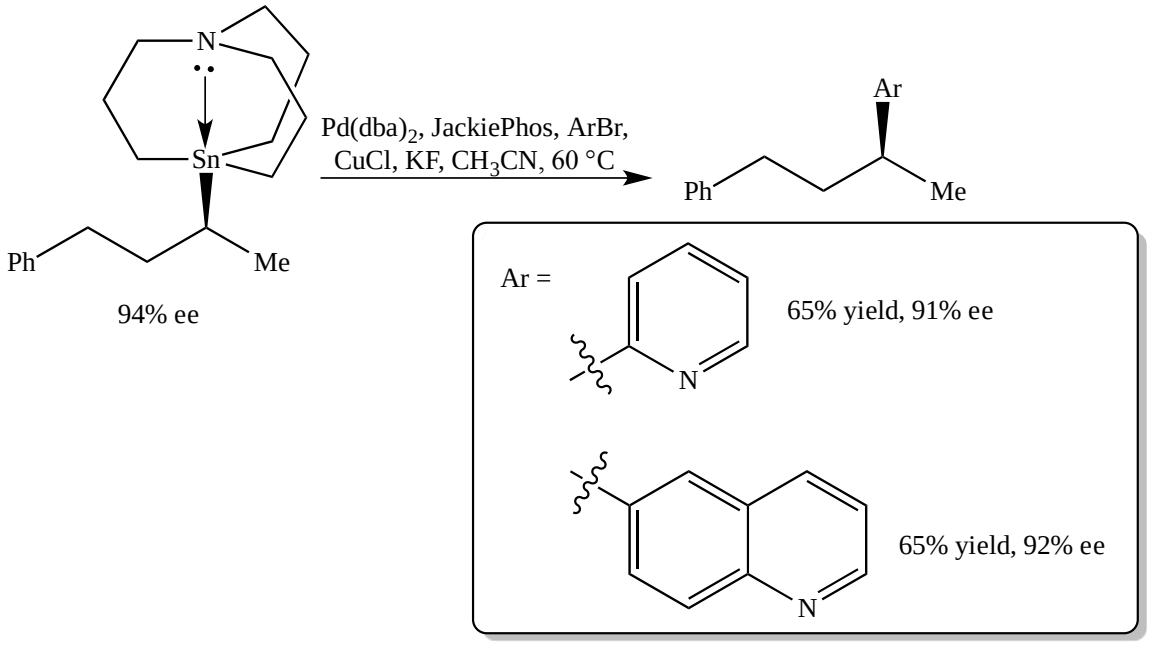


55, 98% ee

56, 98% ee

The Biscoe group has very recently demonstrated the stereoretentive Pd-catalyzed Stille cross-coupling of alkyl azastannatranes with aryl bromides (***Scheme 2.1.7***).[60] The azastannatrane moiety increases the favorability of transmetallation to Pd relative to typical trialkyl stannanes. Internal coordination of the lone pair of the nitrogen to the Sn increases the favorability for the apical substituent to be transmetallated.

Scheme 2.1.7. Biscoe's Stille cross-coupling arylation

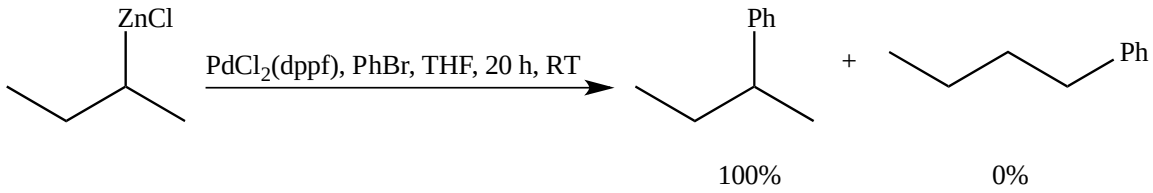


2.1.2 Negishi cross-coupling arylations

The initial attempts to couple secondary organozinc reagents with aryl halides resulted in very low yields of the desired products. The Hayashi group reported an early improvement in 1984.[61] The cross coupling of *s*-BuZnCl with bromobenzene using $PdCl_2$(dppf) gave the desired isomer in 100% yield by GLC (***Scheme 2.1.8***). This ligand has an unusually large cone angle,

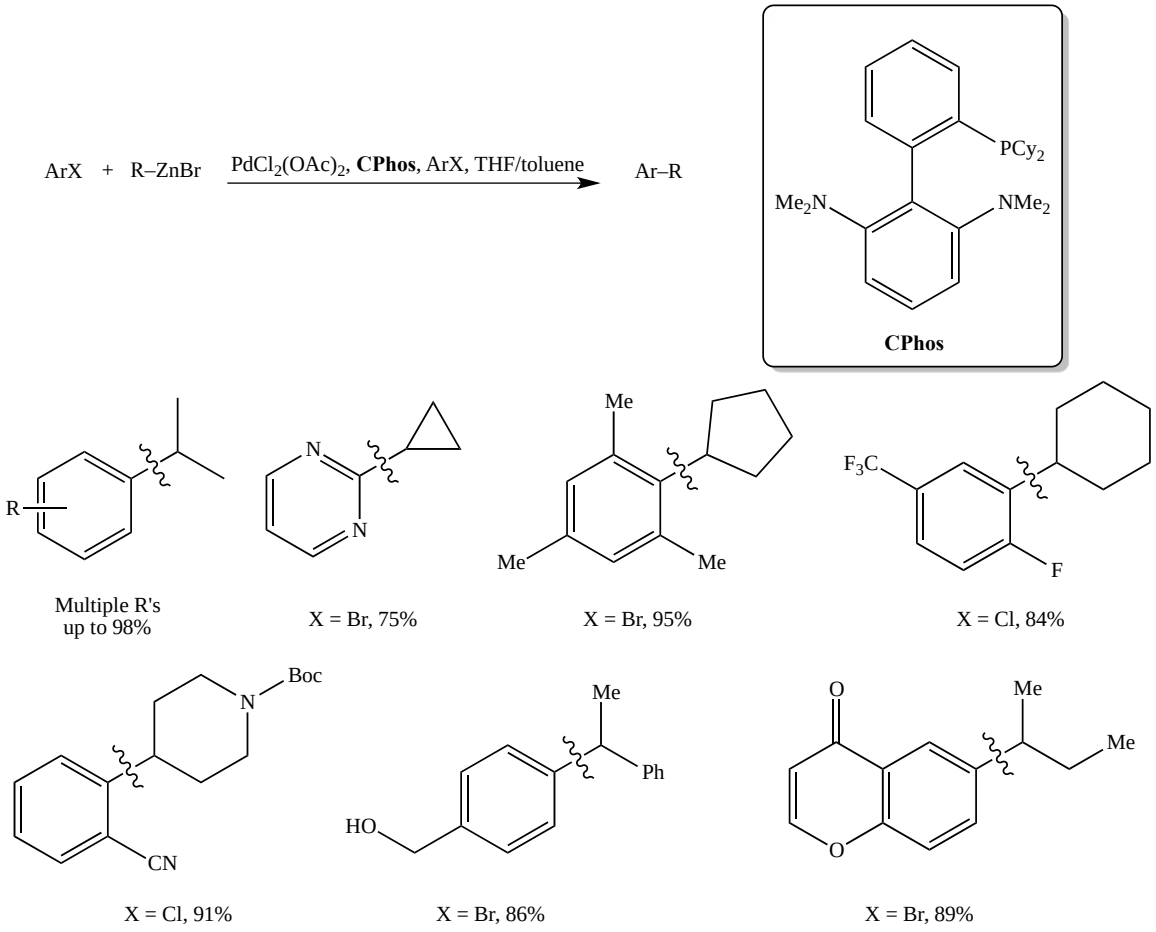
which leads to a more facile reductive elimination; thus isomerization is less favorable.

Scheme 2.1.8. Hayashi's Negishi cross-coupling arylation



The scope of this reaction, in terms of aryl electrophiles and functional group compatibility, was greatly expanded by the Buchwald group in 2009 (***Scheme 2.1.9***).[62] The Pd-catalyzed Negishi cross-coupling of isopropyl ZnBr with aryl bromides and chlorides gave high yields and regioselectivity using CPhos. They reinforced the idea that isomerization is suppressed by an increase in the relative rate of reductive elimination versus β-hydride elimination. If the regioselectivity is controlled by Curtin-Hammett kinetics, then a similar ratio of isomers should be produced by cross-coupling of ArX with isopropyl ZnCl and n-propyl ZnCl, respectively. This ratio was not observed so isomeric Pd-complexes are not equilibrating faster than the relative rates of β-hydride elimination and reductive elimination.

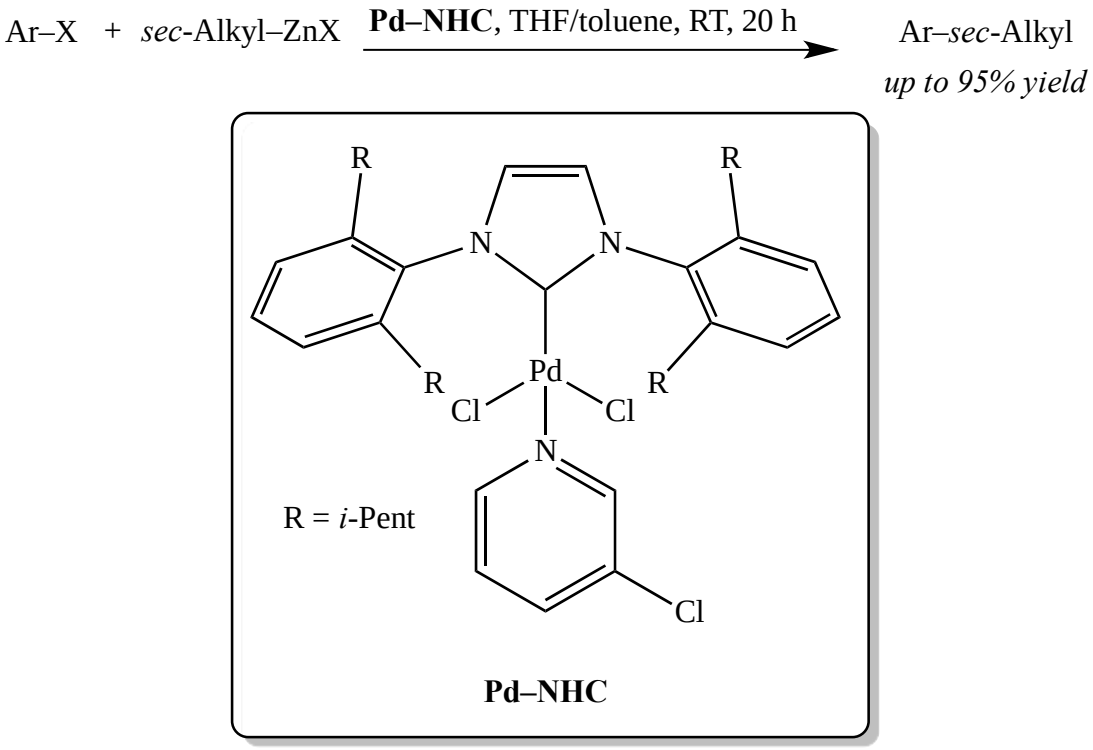
Scheme 2.1.9. Buchwald's Negishi cross coupling arylations



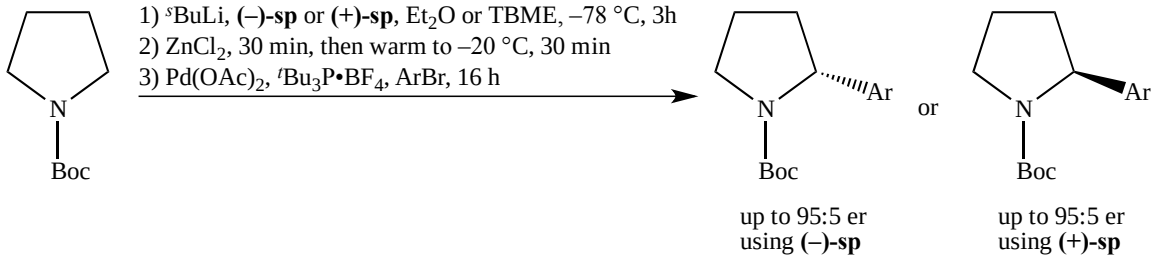
In 2011, the Organ group designed an NHC-catalyst that eliminated the regioisomer under optimized conditions (***Scheme 2.1.10***).[63] NMR studies showed that an increase of steric bulk on the aryl substituents on nitrogen gives the metal center more positive character, which is known to increase the relative rate of reductive elimination compared to more electron-rich centers.

In the same year, a highly effective Negishi cross-coupling was reported by Campos and O'Brien.[64] They utilized the excellent enantioselectivity available *via* an asymmetric deprotonation of *N*-Boc-pyrrolidine with either (–)-sp or (+)-sp, then the chiral organolithium was transmetallated to zinc and coupled with aryl bromides (***Scheme 2.1.11***).

Scheme 2.1.10. Organ's NHC-catalyzed Negishi cross-coupling arylation



Scheme 2.1.11. Negishi cross-coupling arylation of *N*-Boc-pyrrolidine



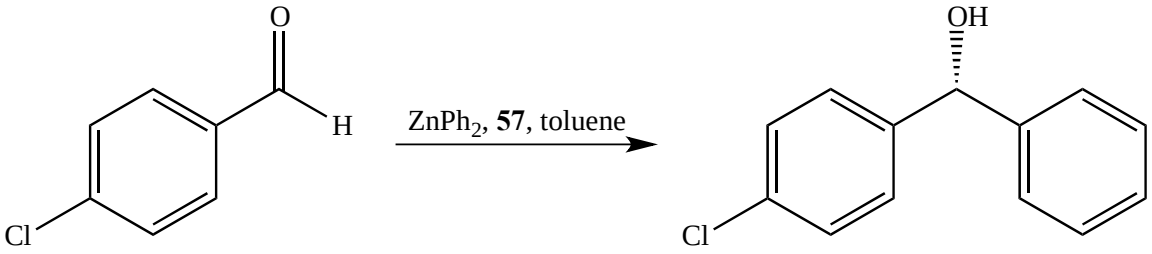
2.2 Chiral Diarylmethanols

Chiral diarylmethanols are ubiquitous and fundamental intermediates in medicinal and pharmaceutical compound synthesis. As with any synthesis, a catalytic approach is preferred. There have been two main strategies toward this end throughout the literature: organometallic addition to aldehydes and asymmetric reduction of ketones.

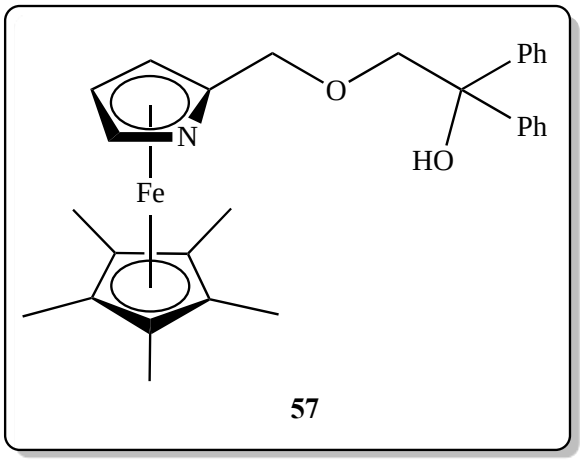
2.2.1 Organometallic Additions to Aldehydes

The Fu group laid the groundwork for the asymmetric aryl addition to aldehydes in 1997.[65] Diphenylzinc was the source of the aryl group that was added to p-chlorobenzaldehyde; the reaction was catalyzed by an azaferrocene derivative. The desired product was formed with 99% yield, but with only 57% ee (*Scheme 2.2.1*).

Scheme 2.2.1. Fu's aryl addition to an aldehyde



99% yield, 57% ee

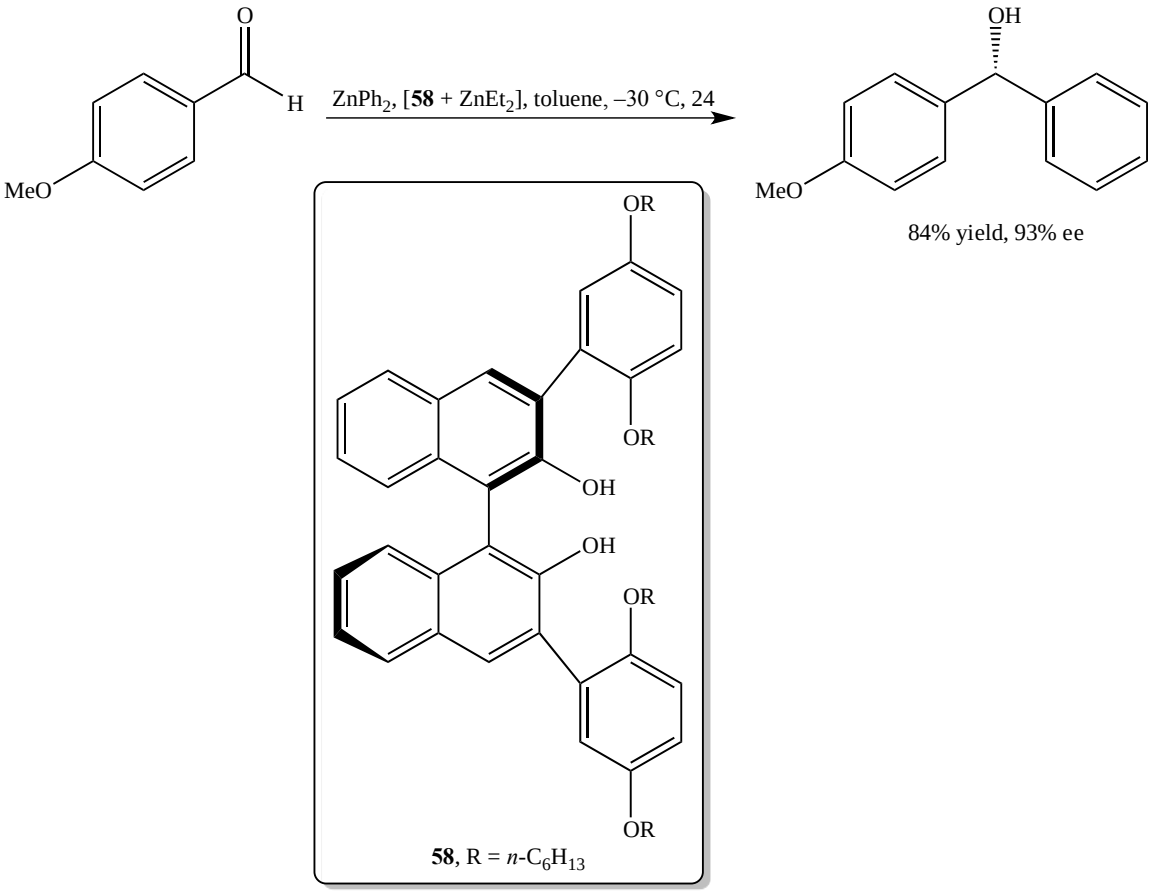


57

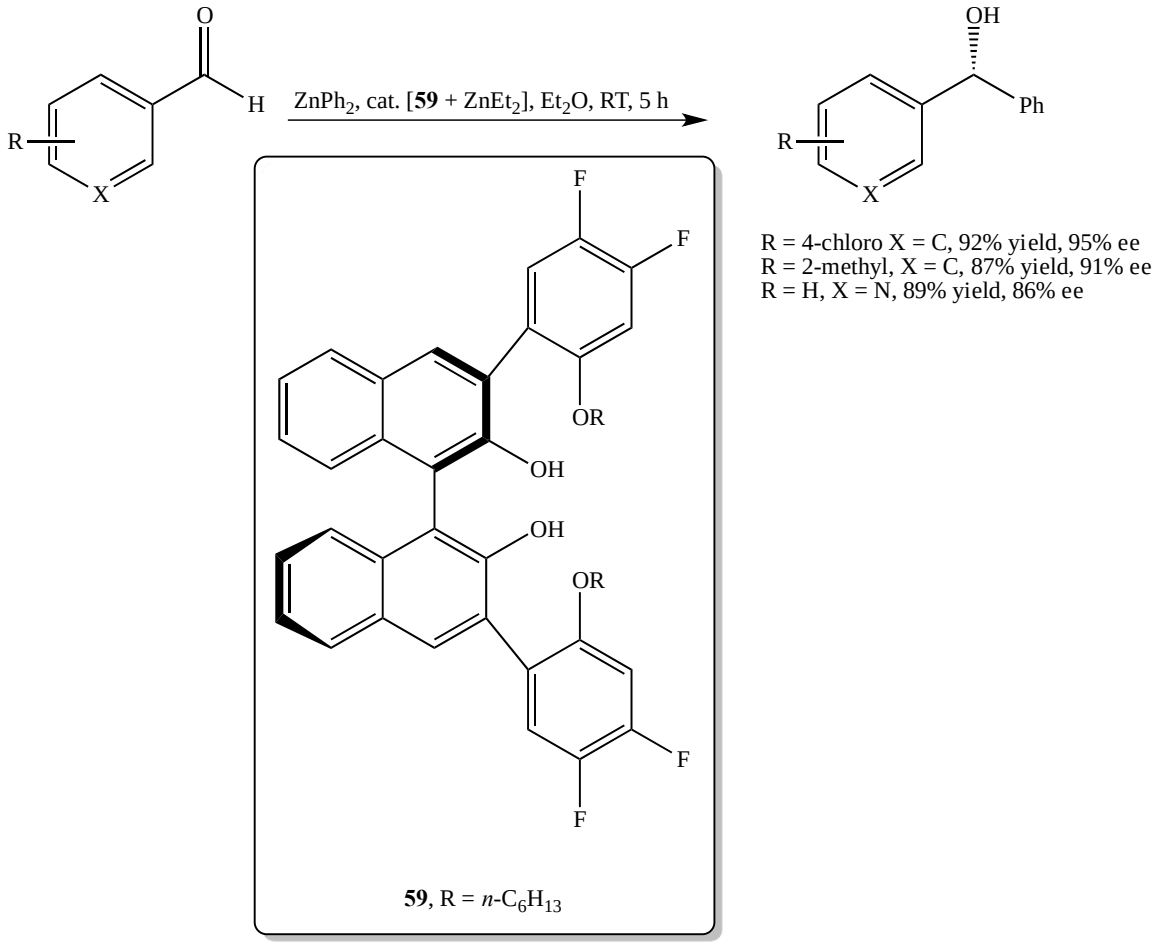
Two years later, the Pu group optimized the addition of diphenylzinc to aryl aldehydes using a chiral BINOL derivative, **58** (*Scheme 2.2.2*).[66] They reported that the phenyl addition to *p*-methoxybenzaldehyde by diphenylzinc occurs in the absence of a Pd catalyst to give racemic products, so increasing the reactivity of the chiral catalyst toward aryl addition relative to the racemic addition is required to improve enantioselectivity. The background reaction was suppressed by increasing the chiral catalyst loading, performing the reaction at lower temperatures and concentrations, and pretreatment of the chiral ligand with diethylzinc. The complex generated from the reaction of diethylzinc and **58** catalyzes the aryl addition better than the complex generated by the reaction of diphenylzinc and **58**. In 2000, incorporation of fluorine into a BINOL derivative was shown to increase catalytic reactivity in the addition of diphenylzinc to a number of aryl aldehydes (*Scheme 2.2.3*).[67] This highly enantioselective

method is limited to unsubstituted aryl zincates.

Scheme 2.2.2. Pu's optimized aryl addition

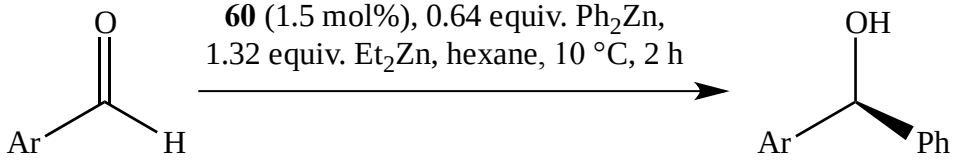


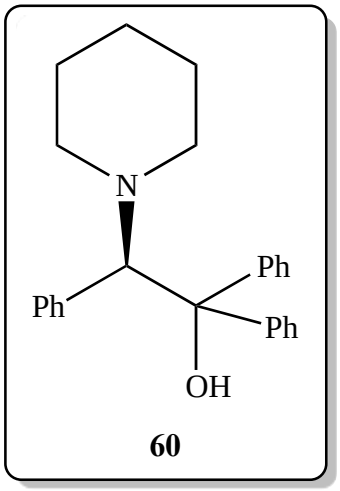
Scheme 2.2.3. Pu's phenyl addition to aryl aldehydes by fluorinated catalyst, **59**



In 2004, the Pericas group reported the phenyl addition to aryl aldehydes, using a piperidine-derivative catalyst, **60**, to give diaryl methanols in good yields and enantioselectivities (***Scheme 2.2.4***).[68] React IR and DFT studies suggested the formation of the mixed zinc species, EtPhZn, which is less reactive than diphenylzinc towards the racemic addition.

Scheme 2.2.4. Pericas's aryl addition to aldehydes



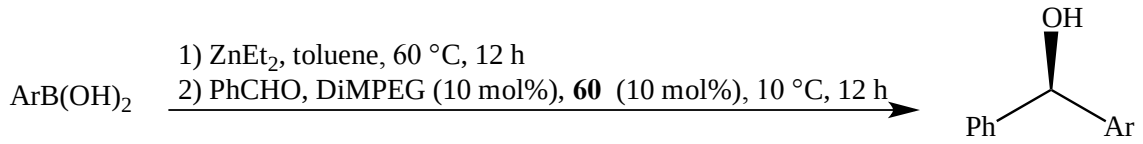


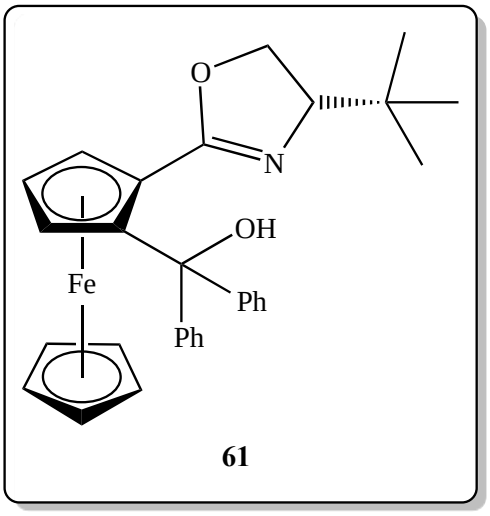
60

Ar	**yield (%)**	**ee (%)**
4-methylphenyl	90	95
4-biphenyl	86	99
2-methylphenyl	85	94
2-fluorophenyl	94	91
3-methoxyphenyl	79	95
2-naphthyl	65	92

In 2002, Bolm reported the development of a method for preparing different aryl zinc compounds, *via* a transmetallation between aryl boronic acids or boranes and alkyl zincs to form the aryl zinc in situ.[69] A number of aryl zinc species were formed and used in the arylation of benzaldehyde, which was catalyzed by the ferrocene-derivative, **61** (***Scheme 2.2.5***). The addition of the poly(ethylene glycol) derivative, DiMPEG, was reported to increase the enantioselectivity.

Scheme 2.2.5. Bolm's Negishi cross-coupling arylation using aryl boronic acid





61

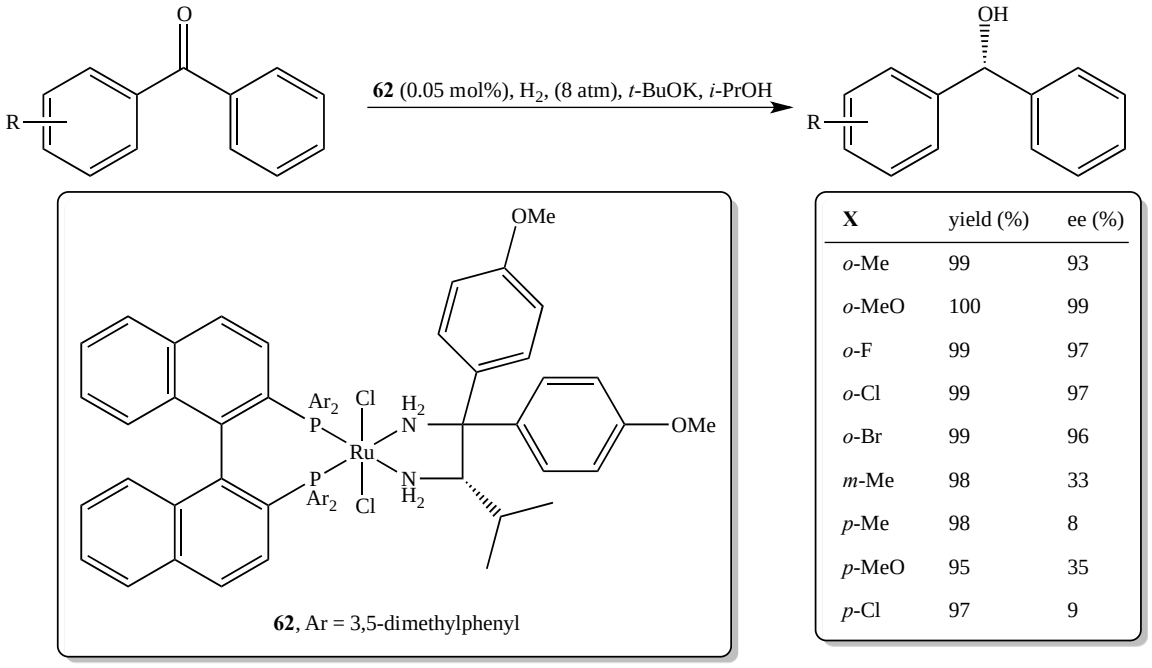
Ar	yield (%)	ee (%)
4-chlorophenyl	61	97
4-biphenyl	75	97
4-methylphenyl	91	96
4-methoxyphenyl	86	90
1-naphthyl	91	85
2-bromophenyl	58	88
4-bromophenyl	48	96

A number of other aryl organometallics have been developed for asymmetric addition to aldehydes, but they are generally limited due to the need to preform stoichiometric amounts of the desired aryl organometallic reagent.[70]

2.2.2 Asymmetric Reduction of Ketones

The application of Noyori's Ru-BINAP catalyst systems to the asymmetric hydrogenation of ketones has allowed access to highly enantioenriched *o*-substituted diarylmethanols (***Scheme 2.2.6***).[71]

Scheme 2.2.5. Noyori's asymmetric reduction of ketones



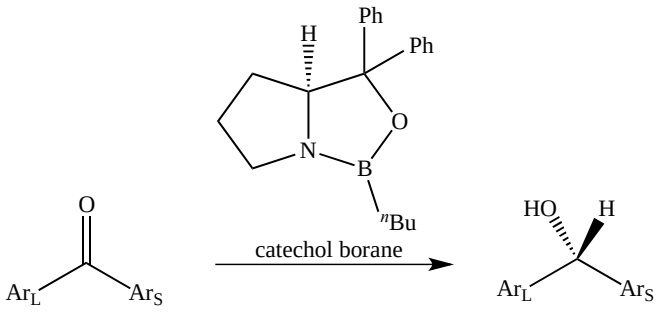
X	yield (%)	ee (%)
o-Me	99	93
o-MeO	100	99
o-F	99	97
o-Cl	99	97
o-Br	99	96
m-Me	98	33
p-Me	98	8
p-MeO	95	35
p-Cl	97	9

Chen extended this approach to aromatic/heteroaromatic ketone reductions in 2003, but steric hindrance exerted by an *o*-substituent (or very bulky *m*-substituents) was still required for high enantioselectivity.[72] Furthermore, high catalyst cost and the limited scope have limited the utility of this reduction pathway.

The Corey group developed the CBS-catalyzed enantioselective hydroboration, which uses an oxazaborolidine-derived from an amino acid and borane. A number of benzophenone derivatives were reduced to give diarylmethanols in excellent yields and enantioselectivities (***Scheme 2.2.6***).[73] The transition state for the hydride transfer is shown in ***Figure 2.2.1***. The enantioselectivity arises from the selective coordination of the borane to the carbonyl oxygen. Consider the example of *p*-methoxy-*p'*-nitrobenzophenone. When the boron atom coordinates to either lone pair of the carbonyl oxygen, rotating the electron-rich aryl substituent out of plane disrupts conjugation with the carbonyl and reduces steric interactions of that substituent. The

more favorable rotation out-of-plane is the electron deficient *p*-nitro group, which keeps the electron rich *p*-methoxy group in conjugation. The substituent of the ketone that is rotated out of the plane has less steric interactions, and thus, would occupy the R_S position.

Scheme 2.2.6. CBS reduction of diarylketones



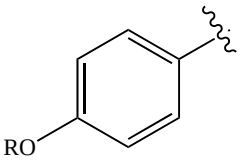
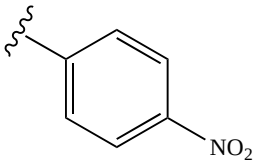
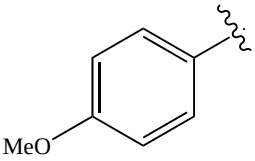
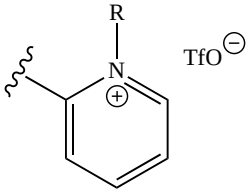
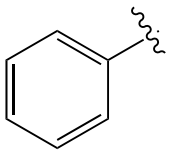
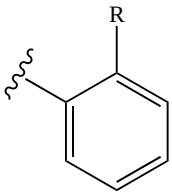
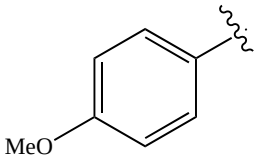
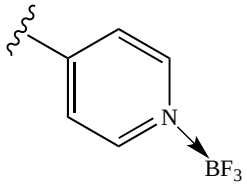
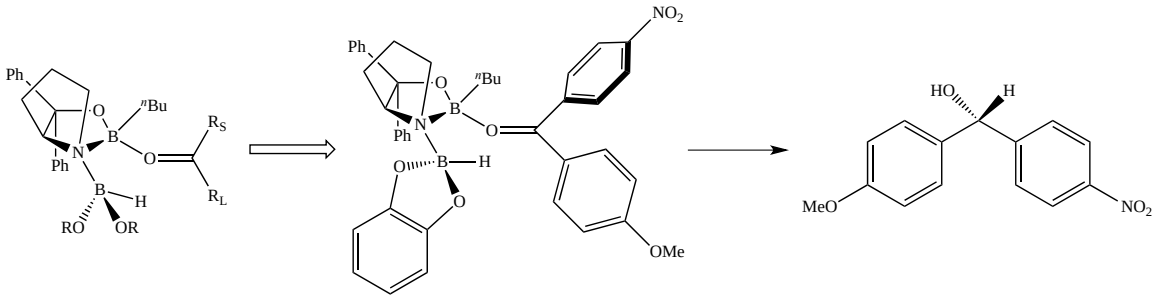
Ar_L	**Ar_S**	**yield (%)**	**ee (%)**
		R = Me, 88 R = TIPS, 88	R = Me, 81 R = TIPS, 95
		R = Me, 95 R = allyl, 65	R = Me, >90 R = allyl, 99
		R = Me, 99 R = Br, 90 Ar_S = naphthyl, 99	R = Me, 97 R = Br, 97 Ar_S = naphthyl, 97
		83	93

Figure 2.2.1. Transition state of CBS hydroboration



The same rationale explains the enantioselectivity of *o*-substituted benzophenones but from a different chemical bias.[74] The steric interaction between an *o*-substituent and the carbonyl oxygen rotates that benzene ring out of plane, thus the *o*-substituted benzene would occupy the R_S position in the transition state.

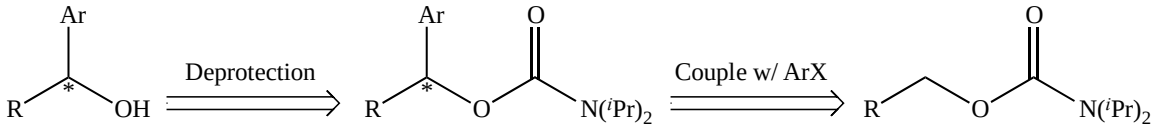
2.3 Statement of the problem

The direct asymmetric arylation of benzyl-type carbamates would allow convenient, one-step access to carbamoyl-protected, chiral diarylmethanols. This methodology could expand the limited scope of diarylmethanol syntheses discussed above by the transition metal-catalyzed cross-coupling of the appropriate benzyl carbamate with the appropriate, corresponding aryl halide. The direct arylation of alkyl carbamates has also never been reported. The proposed cross-coupling reaction will provide novel access to carbamoyl-protected, monoaryl alcohols and their derivatives.

2.4 Results/Discussion

Stereoselective cross-coupling of arylcarbamates and aryl halides, followed by facile reduction of the carbamate should yield highly enantiopure arylmethanols (***Scheme 2.3.1***).

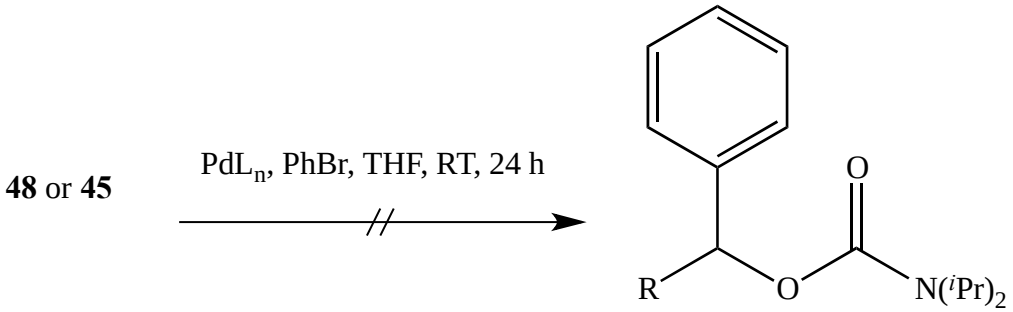
Scheme 2.3.1. Retrosynthesis of arylmethanols *via* arylation of carbamates



R = aryl or alkyl

The stannyl alkylcarbamate, **48**, was the first substrate subjected to a transition metal-catalyzed cross-coupling arylation. Under the standard Stille cross-coupling conditions (***Scheme 2.3.2***), the organostannane did not transmetallate and no evidence of protodestannalation was observed. The results were the same in the case of the stannyl benzylcarbamate, **45**, which should be more reactive due to its benzylic nature.

Scheme 2.3.2. Standard Stille cross-coupling conditions



R = C_5H_{11} or Ph

Manipulation of these standard conditions included several different Pd complexes, solvents, and reaction temperatures (***Table 2.2***). The Pd complex was obtained from commercial sources and added directly, or it was formed *in situ* from $PdCl_2$ or $Pd(OAc)_2$ plus the appropriate ligand. The Liebeskind promotor, CuTc, did not afford the desired cross-coupling product either. Changing the solvent from THF to hexanes, toluene, or diethyl ether did not result in successful cross-coupling products. Increasing the reaction temperature up to refluxing toluene (111 °C) also had no effect.

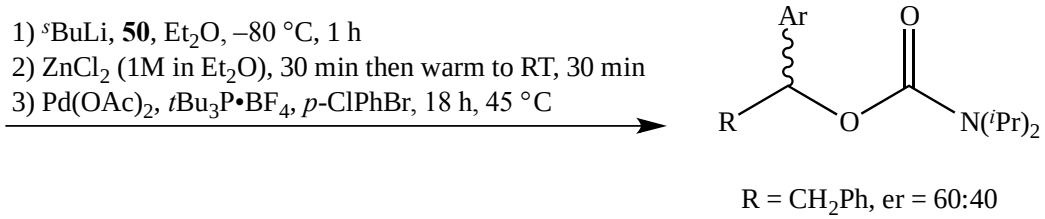
Table 2.2. Stille cross-coupling parameters

Entry	Carbamate	Solvent	Catalyst	Temp (°C)	ArX	CsF
1	Hexyl	Et_2O	$Pd(dppe)Cl_2$	20	PhI	No
2	Hexyl	hexanes	$Pd(dppe)Cl_2$	20	PhI	No
3	Hexyl	toluene	$Pd(dppe)Cl_2$	60	PhI	No
4	Hexyl	toluene	$Pd(dppe)Cl_2$	60	PhI	Yes
5	Hexyl	toluene	$Pd(dppe)Cl_2$	80	PhI	Yes
6	Hexyl	toluene	$Pd(dppe)Cl_2$	111	PhI	Yes
7	Hexyl	THF	$Pd(dppe)Cl_2$	20	PhI	No
8	Hexyl	THF	$Pd(dppe)Cl_2$	66	PhI	No
9	Hexyl	THF	$Pd(dppe)Cl_2$	66	PhI	Yes
10	Hexyl	THF	$Pd(dppe)Cl_2$	66	PhBr	Yes
11	Hexyl	THF	$Pd(dppf)Cl_2$	66	PhI	Yes
12	Hexyl	THF	$Pd_2(dba)_3$, $^tBu_3P$	66	PhI	Yes
13	Hexyl	THF	$PdCl_2(Ph_3P)_2$	66	PhI	Yes
14	Hexyl	THF	$Pd(Ph_3P)_4$	66	PhI	Yes
15	Hexyl	THF	$Pd(OAc)_2$, $^tBu_3P$	66	PhI	Yes
16	Hexyl	THF	CuTc	20	PhI	No
17	Benzyl	toluene	$Pd(dppe)Cl_2$	60	PhI	No
18	Benzyl	toluene	$Pd(dppe)Cl_2$	60	PhI	Yes
19	Benzyl	toluene	$Pd(dppe)Cl_2$	80	PhI	Yes
20	Benzyl	toluene	$Pd(dppe)Cl_2$	111	PhI	Yes
21	Benzyl	THF	$Pd(dppe)Cl_2$	66	PhI	No
22	Benzyl	THF	$Pd(dppe)Cl_2$	66	PhI	No
23	Benzyl	THF	$Pd(dppe)Cl_2$	66	PhI	Yes
24	Benzyl	THF	$Pd(dppe)Cl_2$	66	PhBr	Yes
25	Benzyl	THF	$Pd(dppf)Cl_2$	66	PhI	Yes
26	Benzyl	THF	$Pd_2(dba)_3$, $^tBu_3P$	66	PhI	Yes
27	Benzyl	THF	$PdCl_2(Ph_3P)_2$	66	PhI	Yes
28	Benzyl	THF	$Pd(Ph_3P)_4$	66	PhI	Yes
29	Benzyl	THF	$Pd(OAc)_2$, $^tBu_3P$	66	PhI	Yes
30	Benzyl	THF	CuTc	20	PhI	No

The non-reactivity problem of the Stille-coupling was overcome by utilizing a Negishi-type coupling of an organozinc that was used in the piperidine chemistry.[34] Racemic arylation of CbHx and CbBn proceeded in good to excellent yields with a number of aryl electrophiles. Deprotonative lithiation using *s*-BuLi and TMEDA at –80 °C, followed by addition of $ZnCl_2$ gave the desired organozinc species. The cross-coupling reaction was accomplished by using $Pd(OAc)_2$ and *t*-BuP•BF_4. The highest yielding reactions were performed with aryl bromides.

The asymmetric version of the Negishi-type cross-coupling (***Scheme 2.3.3***) was attempted using **43**, **50** (instead of TMEDA), and *p*-chloro-bromobenzene to give the desired product with an er of 60:40. When the organolithium produced in Step 1 of ***Scheme 2.3.3*** was quenched with $(CH_3)_3SiCl$, the product was obtained with 99:1 er. Attempts to determine if the racemization was occurring during transmetallation to zinc were unsuccessful due to the zincate not reacting with electrophiles.

Scheme 2.3.3. Asymmetric Negishi-type cross-coupling arylation



R = CH_2Ph, er = 60:40

Presumably, the racemization is occurring after transmetallation to Pd via a disassociation/association sequence.[75]

Alternatively, and perhaps a more practical route to enantioenriched products could be accessible using a chiral Pd ligand to induce selectivity from a racemic lithiation/zincation sequence. The only chiral catalyst available was *R*-BINAP, which was used in place of *t*-Bu_3P•HBF_4 and gave

racemic products. It is highly probable that a chiral Pd catalyst system would give highly enantioselective products *via* this method, but access to a large library of Pd ligands would greatly facilitate the process.

2.5 Experimental Procedures

General procedure for arylation by Stille Cross-Coupling

To an oven-dried flask, the stannyl carbamate (1 eq.), PdL_2, aryl electrophile, and freshly distilled THF were added and stirred at ambient temperature or up to reflux for 18 h. Then, NH_4OH was added and stirred for 30 min, followed by filtration through Celite. Then, the organic layer was washed with 1 N HCl, twice with H_2O, and dried over $MgSO_4$. Finally, solvent was removed *in vacuo*.

General procedure for arylation by Negishi Cross-Coupling

To an oven-dried flask, **carbamate** (1 eq.), *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 4 eq.), and freshly distilled Et_2O were added and stirred at –80 °C. Then, *s*-BuLi (1.2 eq.) was slowly added and stirred for 5 h. Then, $ZnCl_2$ in Et_2O (0.6 eq.) was added dropwise and stirred for 30 min. This was followed by slow warming to ambient temperature, and then stirred for another 30 min. Then, $Pd(OAc)_2$ (0.04 eq.), *t*-Bu_3P•HBF_4 (0.08 eq.), and the aryl electrophile (1.5 eq.) were added and stirred for 18 h. Then, NH_4OH was added and stirred 30 min, followed by filtration through Celite™. Then, the organic layer was washed with 1 N HCl, twice with H_2O, and dried over $MgSO_4$. Finally, the solvent was removed *in vacuo*.

Hexyl carbamates:

ArX = 3-iodobenzotrifluoride Ret. Time 8.42 min (M+1 374) ^{1}H NMR (400Mhz $CDCl_3$) δ 7.47-7.59 (4H) 5.73-5.76 (1H) 1.95 (2H) 0.80-1.85 (5 CH_3 4 CH_2)

ArX = 1-bromo-4-chlorobenzene Ret. Time 10.10 min (M+1 340) ^{1}H NMR (400Mhz $CDCl_3$) δ 7.25-7.35 (4H) 5.65 (1H) 1.70-2.00 (2H) 0.80-1.6 (5 CH_3 4 CH_2)

ArX = 1—fluroro-3-iodobenzene Ret. Time 9.18 min (M+1 324) ^{1}H NMR (400Mhz $CDCl_3$) δ 7.49, 8.22 (4H) 5.74 (1H) 1.76-1.94 (2H) 0.88-1.65 (5 CH_3 4 CH_2)

ArX = 1-bromo-3,5-(bis)trifluoromethylbenzene Ret. Time 8.24 min (M+1 442) ^{1}H NMR (400Mhz $CDCl_3$) δ 7.78 (4H) 5.78 (1H) 1.77-1.94 (2H) 0.80-1.60 (5 CH_3 4 CH_2)

ArX = 1-bromo-4-nitrobenzene Ret. Time 11.42 min (M+1 351) ^{1}H NMR (400Mhz $CDCl_3$) δ 7.49, 8.22 (4H) 5.74 (1H) 1.94 (2H) 0.88-1.81 (5 CH_3 4 CH_2)

ArX = 4-bromotoluene Ret. Time 9.68 min (M-1 318) ^{1}H NMR (400Mhz $CDCl_3$) δ 7.78 (4H) 5.79 (1H) 1.39-1.42 (2H) 0.89-1.60 (5 CH_3 4 CH_2)

Benzyl Carbamates:

ArX = 3-iodobenzotrifluoride Ret. Time 9.75 min (M+1 360) ^{1}H NMR (400Mhz $CDCl_3$) δ 7.46-7.60 (9H) 5.75 (1H) 1.75 (2H) 0.88-1.63 (4 CH_3)

ArX = 1-bromo-4-chlorobenzene Ret. Time 10.58 min (MAI 181) ^{1}H NMR (400Mhz $CDCl_3$) δ 7.28-7.50 (9H) 6.80 (1H) 1.66 (2H) 0.90-1.40 (4 CH_3)

ArX = 1-fluroro3-iodobenzene Ret. Time 10.06 min (M+1 310) ^{1}H NMR (400Mhz $CDCl_3$) δ 7.28-7.38 (9H) 5.16 (1H) 1.66 (2H) 0.82-1.46 (4 CH_3)

ArX = 1-bromo-3,5-(bis)trifluoromethylbenzene Ret. Time 8.99 min (M+1 448) ^{1}H NMR (400Mhz $CDCl_3$) δ 7.10-7.39 (8H) 5.16 (1H) 1.73 (2H) 1.08-1.40 (4 CH_3)

ArX = 1-bromo-4-nitrobenzene Ret. Time 11.16 min (M+1 207) ^{1}H NMR (400Mhz $CDCl_3$) δ 7.12-7.52 (9H) 5.03 (1H) 1.60 (2H) 0.87-1.50 (4 CH_3)

ArX = 4-bromotoluene Ret. Time 10.58 min (M-1 209)

ArX = 1-bromothiophene Ret. Time 10.22 min (MAI 213) ^{1}H NMR (400Mhz $CDCl_3$) δ 6.95-7.40 (8H) 5.16 (1H) 1.91 (2H) 0.87-1.53 (4 CH_3)

ArX = 2-bromonaphthalene Ret. Time 12.49 min (M+1 362) ^{1}H NMR (400Mhz $CDCl_3$) δ 7.31-7.88 (12H) 5.16 (1H) 1.73 (2H) 0.82-1.52 (4 CH_3)

2.6. References

53. Echavarren, A. M. a. C.; Diego, J., Mechanistic aspects of metal-catalyzed C,C- and C,X-bond-forming reactions., In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Edition, de Meijere, A. a. D.; Francois, Ed. Wiley-VCH: **2004**; Vol. 1. Pp 1-31.

54. Azarian, D.; Dua, S. S.; Eaborn, C.; Walton, D. R. M., Reactions of organic halides with R3 MMR3 compounds (M = Si, Ge, Sn) in the presence of tetrakis(triarylphosphine)palladium. *J. Organomet. Chem.*, **1976**, *117* (3), C55-C57.

55. Milstein, D.; Stille, J. K., A general, selective, and facile method for ketone synthesis from acid chlorides and organotin compounds catalyzed by palladium. *J. Am. Chem. Soc.*, **1978**, *100* (11), 3636-3638.

56. Tang, H. F.; Menzel, K.; Fu, G. C., Ligands for palladium-catalyzed cross-couplings of alkyl halides: Use of an alkyldiaminophosphane expands the scope of the stille reaction. *Angew. Chem. Int. Edit.*, **2003**, *42* (41), 5079-5082.

57. Kalkofen, R.; Hoppe, D., First example of an enantiospecific sp3-sp2 Stille coupling of a chiral allylstannane with aryl halides. *Synlett*, **2006**, *2006* (12), 1959-1961.

58. Falck, J. R.; Ratel, P. K.; Bandyopadhyay, A., Stereospecific cross-coupling of alpha-(thiocarbamoyl)organostannanes with alkenyl, aryl, and heteroaryl iodides. *J. Am Chem. Soc*., **2007**, *13* (2), 344-346.

59. Goli, M.; He, A.; Falck, J. R., Pd-catalyzed cross-coupling of α-(acyloxy)-tri-n-butylstannanes with alkenyl, aryl, and heteroaryl electrophiles. *Org. Lett*., **2010**, *13* (2), 344-346.

60. Li, L.; Wang, C. Y.; Huang, R. C.; Biscoe, M. R., Stereoretentive Pd-catalyzed Stille cross-coupling reactions of secondary alkyl azastannatranes and aryl halides. *Nat. Chem.*, **2013**, *5* (7), 607-612.

61. Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K., Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II): an effective catalyst fro cross-coupling of secondary and primary alkyl Grignard and alkylzinc reagents with organic halides. *J. Am. Chem. Soc*., **1984**, *106* (1), 158-163.

62. Han, C.; Buchwald, S. L., Negishi coupling of secondary alkylzinc halides with aryl bromides and chlorides. *J. Am. Chem. Soc.*, **2009**, *131* (22), 7532-7533.

63. Calimsiz, S.; Organ, M. G., Negishi cross-coupling of secondary alkylzinc halides with aryl/heteroaryl halides using Pd-PEPPSI-IPent. *Chem. Commun.*, **2011**, *47* (18), 5181-5183.

64. Barker, G; McGrath, J. L.; Klapars, A.; Stead, D.; Zhou, G.; Campos, K. R.; O'Brien, P., Enantioselective, palladium-catalyzed α-arylation of N-Boc pyrrolidine: in situ react IR spectroscopic monitoring, scope, and synthetic applications. *J. Org. Chem.*, **2011**, *76* (15), 5936-5953.

65. Dosa, P. I.; Ruble, J. C.; Fu, G. C., Planar-chiral heterocycles as ligands in metal-catalyzed processes: enantioselective addition of organozinc reagents to aldehydes. *J. Org. Chem.*, **1997**, *62* (3), 444-445.

66. Huang, W. S.; Pu, L., The first highly enantioselective catalytic diphenylzinc additions to aldehydes: synthesis of chiral diarylcarbinols by asymmetric catalysis. *J. Org. Chem*., **1999**, *64* (12), 4222-4223.

67. Huang, W. S.; Pu, L., New and improved ligands for highly enantioselective catalytic diphenylzinc additions to aryl aldehydes. *Tetrahedron Lett.*, **2000**, *41* (2), 145-149.

68. Fontes, M.; Verdaguer, X.; Solà, L.; Periàs, M. A.; Riera, A., 2-Piperidino-1,1,2-triphenylethanol: a highly effective catalyst for the enantioselective arylation of aldehydes. *J. Org. Chem.*, **2004**, *69* (7), 2532-2543.

69. Bolm, C.; Rudolph, J., Catalyzed asymmetric aryl transfer reactions to aldehydes with boronic acids as aryl source. *J. Am. Chem. Soc.*, **2002**, *124* (50), 14850-14851.

70. Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C., Catalytic asymmetric approaches towards enantiomerically enriched diarylmethanols and diarylmethylamines. *Chem. Soc. Rev.*, **2006**, *35* (5), 454- 470.

71. Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R., Selective hydrogenation of benzophenones to benzhydrols. *Org. Lett.*, **2000**, *2* (5), 659-662.

72. Chen, C. Y.; Reamer, R. A.; Chilenski, J. R.; McWilliams, C. J., Highly enantioselective hydrogenation of aromatic-heteroaromatic ketones. *Org. Lett.*, **2003**, *5* (26), 5039-5042.

73. Corey, E. J.; Helal, C. J., Novel electronic effects of remote substituents on the oxazaborolidine-catalyzed enantioselective reduction of ketones. *Tetrahedron Lett.*, **1995**, *36* (50), 9153-9156.

74. (a) Trost, B. M.; Van Vranken, D. L., Asymmetric transition metal-catalyzed allylic alkylations. *Chem. Rev.*, **1996**, *96* (1), 395-422; (b) Trost, B. M.; Crawley, M. L., Asymmetric transition-metal-catalyzed allylic alkylations: application in total synthesis. *Chem. Rev.*, **2003**, *103* (8), 2921-2944.