Published in final edited form as:
J Am Chem Soc. 2013 July 31; 135(30): 10946–10949. doi:10.1021/ja4054114.

Enantioconvergent Cross-Couplings of Racemic Alkylmetal Reagents with Unactivated Secondary Alkyl Electrophiles: Catalytic Asymmetric Negishi α-Alkylations of *N*-Boc-pyrrolidine

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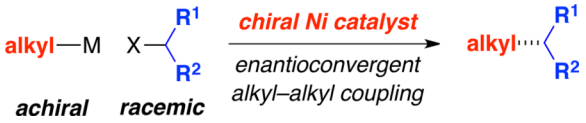
Abstract

Although enantioconvergent alkyl-alkyl couplings of racemic electrophiles have been developed, there have been no reports of the corresponding reactions of racemic nucleophiles. Herein, we describe Negishi cross-couplings of racemic α-zincated *N*-Boc-pyrrolidine with unactivated secondary halides, thus providing a one-pot, catalytic asymmetric method for the synthesis of a range of 2-alkylpyrrolidines (an important family of target molecules) from *N*-Boc-pyrrolidine, a commercially available precursor. Preliminary mechanistic studies indicate that two of the most straightforward mechanisms for enantioconvergence (a dynamic kinetic resolution of the organometallic coupling partner and a simple β-hydride elimination/β-migratory insertion pathway) are unlikely to be operative.

Recently, we have been pursuing the development of an array of metal-catalyzed alkyl-alkyl cross-coupling processes.[1,2,3] As part of this program, we have described several nickel-catalyzed methods for the enantioconvergent coupling of achiral alkylmetal reagents with racemic secondary alkyl electrophiles (eq 1).[4,5]



(1)

The reversed-polarity process, wherein a racemic alkyl *nu-cleophile* is coupled with an alkyl electrophile, has remained an unsolved challenge (eq 2). However, Kumada has described a nickel-catalyzed enantioconvergent coupling of a racemic benzylic Grignard reagent (PhCHMeMgCl) with an alkenyl halide (bromoethylene) to generate an enantioenriched allylbenzene.[6,7]

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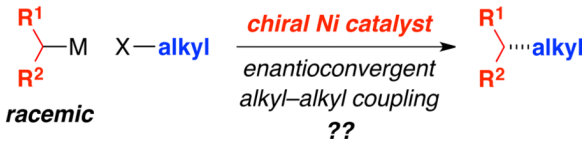
ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

Notes

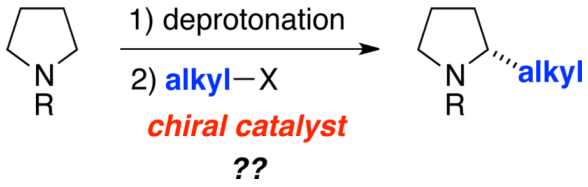
The authors declare no competing financial interest.



(2)

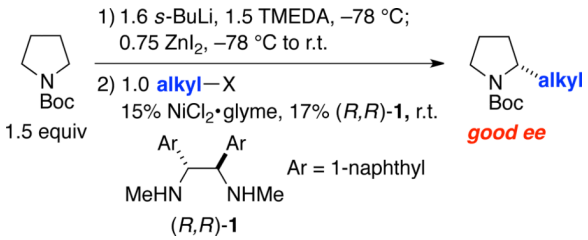
Pyrrolidines that bear an alkyl substituent in the 2 position are important across many areas of chemistry and biology. For example, they are present as subunits in bioactive natural[8] and non-natural[9] products, function as versatile intermediates in the synthesis of other useful classes of compounds,[10] and serve as effective chiral organocatalysts and ligands in asymmetric catalysis.[11] Because of this wide-ranging significance, the development of efficient methods for the enantioselective synthesis of 2-alkylpyrrolidines has been the target of substantial effort, and a broad array of approaches have been described, ranging from chiral-pool strategies to asymmetric synthesis.[12,13]

The catalytic enantioselective 2-alkylation of pyrrolidine (or a readily available protected derivative) via deprotonation/electrophile-trapping represents an attractive, direct approach to the asymmetric synthesis of 2-alkylpyrrolidines (eq 3); to the best of our knowledge, such a process has not yet been reported. On the other hand, pioneering studies by Beak have established that deprotonation of *N*-Boc-pyrrolidine in the presence of a stoichiometric quantity of (−)-sparteine,[14] followed by trapping with any of a wide range of electrophiles (e.g., *n*-Bu_3SnCl, Me_3SiCl, benzophenone, and carbon dioxide), can furnish 2-substituted pyrrolidines with high enantioselectivity; among unactivated alkyl electrophiles, only dimethyl sulfate and methyl iodide have been shown to serve as suitable coupling partners.[15] O'Brien built upon these key observations and developed a method that employs a substoichiometric quantity (20 mol%) of a chiral amine, providing 2-functionalized (although not 2-alkyl) *N*-Boc-pyrrolidines in up to 88% ee.[16]



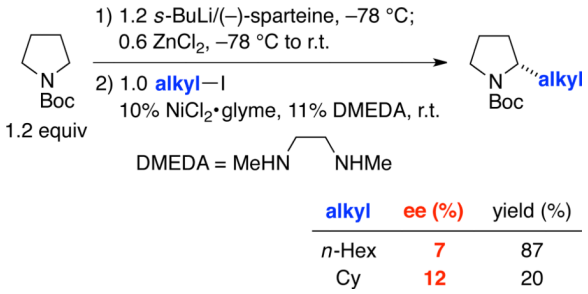
(3)

In view of the potential utility of the transformation outlined in eq 3, we have pursued the development of the first enantioconvergent alkyl-alkyl cross-coupling wherein a racemic alkyl nucleophile is employed as a reaction partner. In particular, we have determined that, in the presence of a chiral nickel catalyst, racemic α-zincated *N*-Boc-pyrrolidine (prepared in situ from commercially available *N*-Boc-pyrrolidine) can be coupled with unactivated alkyl electrophiles to generate 2-alkylpyrrolidines in good ee (eq 4).[17]



(4)

Initially, in view of recent reports by Campos of stoichiometric asymmetric α-lithiation/transmetalation/palladium-catalyzed Negishi arylation of *N*-Boc-pyrrolidine,[18] we examined the cross-coupling of enantioenriched α-zincated *N*-Boc-pyrrolidine (>90% ee)[19] with *n*-hexyl iodide and cyclohexyl iodide in the presence of an achiral nickel/1,2-diamine catalyst (eq 5). In both cases, the alkyl-alkyl coupling product formed in low ee (<15% ee).[20] Because the organozinc reagent is configurationally stable at room temperature, these observations suggest that stereochemical scrambling occurs during the nickel-catalyzed cross-coupling process.



alkyl	ee (%)	yield (%)
n-Hex	7	87
Cy	12	20

(5)

Given that the use of an achiral catalyst for the cross-coupling of a highly enantioenriched nucleophile had provided almost racemic product, we decided to examine a stereochemically converse transformation: the use of a chiral catalyst for the cross-coupling of a racemic nucleophile to generate enantioenriched product. In view of the paucity of asymmetric metal-catalyzed alkyl-alkyl couplings of secondary nucleophiles with secondary electrophiles,[21] we chose to employ cyclohexyl iodide as the electrophilic coupling partner.

Upon investigating a range of parameters, we determined that the desired enantioconvergent coupling of racemic α-zincated *N*-Boc-pyrrolidine with cyclohexyl iodide can be achieved by a combination of $NiCl_2$ glyme and chiral 1,2-diamine ligand **1**[22] in high ee and in good yield at room temperature (93% ee, 86% yield; entry 1 of Table 1). In the absence of either $NiCl_2$-glyme or ligand **1**, essentially no alkyl-alkyl cross-coupling product was observed (entries 2 and 3); similarly, α-lithiated *N*-Boc-pyrrolidine was not a suitable coupling partner (entry 4). Under the same conditions, related C_2-symmetric 1,2-diamines furnished somewhat lower enantioselectivity and yield (entries 5 and 6). Use of less catalyst (entry 7) or of other nickel sources (entries 8 and 9) led to comparable ee but reduced yield. *Our observation that 2-cyclohexyl-N-Boc-pyrrolidine formed in 90% ee and 74% yield in the presence of 0.5 equivalents of the diorganozinc reagent provides strong evidence that the cross-coupling is an enantioconvergent process, not a simple kinetic resolution (entry 10).*

The catalytic asymmetric synthesis of an array of 2-alkylpyrrolidines can be achieved via the coupling of a single precursor (*N*-Boc-pyrrolidine) with a variety of readily available, unactivated alkyl iodides (Table 2).[23] Thus, three parent cycloalkyl iodides undergo enantioconvergent alkyl-alkyl cross-coupling with racemic α-zincated *N*-Boc-pyrrolidine with good enantioselectivity (entries 1–3); the process can be conducted on a gram scale with comparable efficiency (when entry 1 was carried out on a 6.0 mmol scale: 94% ee and 74% yield; 1.12 g of product). Heterocyclic electrophiles couple in high ee (entries 4–6), as does an acyclic secondary alkyl iodide (entry 7). In contrast, moderate ee is observed for the asymmetric Negishi reaction of a primary alkyl iodide (entry 8).

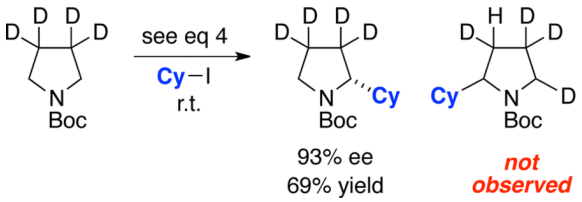
This method thus complements other catalytic enantiose-lective approaches to the synthesis of 2-alkylpyrrolidines, which are typically only effective for the incorporation of a primary alkyl group.[24] Pyrrolidines that bear a secondary alkyl substituent in the 2 position are found in a wide variety of compounds, including an array of pyrrolizidine (simplest example: heliotridane), indolizidine (simple example: ta-shiromine; also: grandisine A[25]), and crambescidin[26] alkaloids.

Not only alkyl iodides, but also alkyl bromides, can be employed as electrophiles in these nickel-catalyzed enantioconvergent cross-couplings of a racemic nucleophile (Table 3).[27] Under the same conditions as for iodides (except for the temperature, in a few cases), alkyl-alkyl bond formation between α-zincated *N*-Boc-pyrrolidine and a range of cyclic and acyclic unactivated secondary alkyl bromides proceeds in good ee, although generally modest yield (entries 1–4). As in the case of a primary alkyl iodide, a primary bromide cross-couples with lower enantioselectivity (entry 5).

We next focused our attention on gaining insight into the origin of the stereoconvergence in these asymmetric Negishi eactions of α-zincated *N*-Boc-pyrrolidine.[28] In Kumadas earlier study of the enantioselective cross-coupling of racemic PhCHMeMgCl with bromoethylene to form an allylbenzene, it was postulated that stereoconvergence arose from a dynamic kinetic resolution of a rapidly racemizing benzylic nucleophile y the cbhiral nickel catalyst.[6] In contrast, our nucleophile,α-zincated *N*-Boc-pyrrolidine, is configurationally stable under our reaction conditions in the absence of nickel. Thus, enantioenriched organozinc reagent was prepared from the corresponding stannane through Sn-Li exchange followed by transmetalation to zinc (Figure 1).[29] When this nucleophile was cross-coupled with bromobenzene under the Campos conditions,[18] (*R*)-2-phenyl-*N*-Boc-pyrrolidine was generated in 90% ee and 95% yield, thereby establishing the stereochemical integrity of the organozinc reagent. When this enantioenriched nucleophile was reacted with cyclohexyl iodide under our standard conditions using either *(R,R)* or *(S,S)* 1,2-diamine ligand **1**, the stereochemistry of the cross-coupling product was dependent primarily on the stereochemistry of the ligand, rather than of the organozinc nucleophile.

One of the possible mechanisms for enantioconvergence in the nickel-catalyzed asymmetric Negishi reactions described herein is a series of β-hydride eliminations/β-migratory insertions of an organonickel intermediate, without dissociation of the olefin from nickel (Figure 2). We have in fact observed such an isomerization process in an enantioselective Negishi cross-coupling of a racemic electrophile with an achiral cyclopentylzinc reagent.[21]

To assess the viability of the pathway outlined in Figure 2, we investigated the Negishi reaction of a deuteriumlabeled *N*-Boc-pyrrolidine (eq 6). Essentially no (<5%) deuterium incorporation is observed α to nitrogen in the cross-coupling product, which indicates that the β-hydride elimination/β-migratory insertion pathway for stereomutation that is depicted in Figure 2 is not the mechanism by which stereoconvergence is achieved.[30]



(6)

In summary, we have developed the first enantioconvergent alkyl-alkyl cross-couplings of a racemic *nucleophile*, specifically, the asymmetric Negishi reaction of α-zincated *N*-Boc-pyrrolidine with unactivated secondary iodides and bromides, providing a one-pot route to an array of 2-alkylpyrrolidines from a single, readily available precursor (*N*-Boc-pyrrolidine). Because the highest enantioselectivity is obtained for the incorporation of secondary alkyl substituents, this method complements existing catalytic asymmetric approaches to the synthesis of 2-alkylpyrrolidines, which are generally most effective for primary alkyl groups. The pathway for stereoconvergence for the present method does not involve a dynamic kinetic resolution of the organometallic coupling partner, in contrast to a previous report of an enantioconvergent alkyl–*alkenyl* cross-coupling. Furthermore, a deuteriumlabeling study rules out stereomutation via a simple β-hydride elimination/β-migratory insertion pathway that we had observed in another nickel-catalyzed alkyl-alkyl coupling. Additional investigations are underway to continue to elucidate the mechanism of this unusual enantioconvergent cross-coupling, as well as to expand the range of racemic nucleophiles that can be employed in such alkyl-alkyl coupling processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences: R01- GM62871). We thank Dr. Scott C. Virgil (Caltech Center for Catalysis and Chemical Synthesis) and Dr. David G. VanderVelde (Caltech NMR facility) for assistance.

REFERENCES

1. (a) For a recent report of a nickel-catalyzed process, see: Wilsily A, Tramutola F, Owston NA, Fu GC. J. Am. Chem. Soc. 2012; 134:5794–5797. [PubMed: 22443409] (b) For an overview of palladium-catalyzed couplings, see: Netherton MR, Fu GC. Top. Organomet. Chem. 2005; 14:85–108.
2. For leading references, see: Glasspoole BW, Crudden CM. Nature Chem. 2011; 3:912–913. [PubMed: 22109267] Glorius F. Angew. Chem. Int. Ed. 2008; 47:8347–8349. Rudolph A, Lautens M. Angew. Chem. Int. Ed. 2009; 48:2656–2670. Jana R, Pathak TP, Sigman MS. Chem. Rev. 2011; 111:1417–1492. [PubMed: 21319862]
3. For examples of applications of palladium-catalyzed alkyl-alkyl cross-couplings in the total synthesis of natural products, see: Griggs ND, Phillips AJ. Org. Lett. 2008; 10:4955–4957. [PubMed: 18844364] Keaton KA, Phillips AJ. Org. Lett. 9:2007. 2717–2719. [PubMed: 17447778]
4. (a) For a recent report of a Suzuki reaction, see Reference 1a. (b) For an example of a Negishi reaction, see: Son S, Fu GC. J. Am. Chem. Soc. 2008; 130:2756–2757. [PubMed: 18257579]
5. For a recent application in the total synthesis of a natural product, see: Schmidt T, Kirschning A. Angew. Chem. Int. Ed. 2012; 51:1063–1066.

6. Hayashi T, Tajika M, Tamao K, Kumada M. J. Am. Chem. Soc. 1976; 98:3718–3719. Hayashi T, Konishi M, Fukushima M, Mise M, Kagotani T, Tajika M, Kumada M. J. Am. Chem. Soc. 1982; 104:1180–186.
7. Other examples of the asymmetric cross-coupling of a racemic nucleophile with an alkenyl electrophile have been described. However, the conversion of *both* enantiomers of the racemic nucleophile into the enantioenriched coupling product has generally not been clearly demonstrated, i.e., the ee of the product could in principle be the result of a simple kinetic resolution in which one enantiomer of the nucleophile has been selectively cross-coupled.
8. For examples and leading references, see: Rizk AFM. Naturally Occurring Pyrrolizidine Alkaloids. 1991Boca RatonCRC Press Mattocks AR. Chemistry and Toxicology of Pyrrolizidine Alkaloids. 1986LondonAcademic Press Bronner SM, Im GYJ, Garg NK. Majumdar KC, Chattopadhyay SK. Heterocycles in Natural Product Synthesis. 2011WeinheimWiley-VCH:221–265. Michael JP. Nat. Prod. Rep. 2008; 25:139–165. [PubMed: 18250900] Michael JP. Alkaloids. 2001; 55 91–258.
9. For reviews that include examples, see: (a) Table 6 in: Roughley SD, Jordan AM. J. Med. Chem. 2011; 54:3451–3479. [PubMed: 21504168] Li X, Li J. Mini-Reviews in Med. Chem. 2010; 10:794–805. Cheng X-C, Wang Q, Fang H, Xu WF. Curr. Med. Chem. 2008; 15:374–385. [PubMed: 18288992] Karoyan P, Sagan S, Lequin O, Quancard J, Lavielle S, Chassaing G. Targets in Heterocyclic Systems. 2004; 8:216–273.
10. For example, see: Blum A, Diederich WE. Curr. Org. Synth. 2009; 6:38–53.
11. For example, see: Zhang S, Wang W. Zhou QL. Privileged Chiral Ligands and Catalysts. 2011WeinheimWiley-VCHChapter 11
12. For a review and leading references, see: Companyo X, Alba A-N, Rios R. Targets in Heterocyclic Systems. 2009; 13:147–174.
13. For examples of recent reports of methods for the catalytic asymmetric synthesis of 2-alkylpyrrolidines, see: Brown AR, Uyeda C, Brotherton CA, Jacobsen EN. J. Am. Chem. Soc. 2013; 135:6747–6749. [PubMed: 23597402] Trost BM, Lam TM, Herbage MA. J. Am. Chem. Soc. 2013; 135:2459–2461. [PubMed: 23363050]
14. Only the (−) enantiomer of sparteine is naturally occurring, and this compound is no longer available from suppliers such as Sig-ma-Aldrich. A surrogate of (+)-sparteineDearden MJ, Firkin CR, Hermet JPR, O'Brien P. P.J.Am. Chem. Soc. 2002; 124:111870–11871.is commercially available
15. For reviews and leading references on enantioselective lithiations, see: Beak P, Johnson TA, Kim DD, Lim SH. Top. Organomet. Chem. 2003; 5:139–176. Hoppe D, Christoph G. Rappoport Z, Marek I. Chemistry of Organolithium Compounds. 2004; ChichesterJohn Wiley & SonsVol. 2:1055–1164. Gawley RE. Top. Stereochem. 2010; 26:93–133. [PubMed: 21804654] Mitchell EA, Peschiulli A, Lefevre N, Meerpoel L, Maes BUW. Chem. Eur. J. 2012; 18:10092–10142. [PubMed: 22829434]
16. McGrath MJ, O'Brien P. J Am. Chem. Soc. 2005; 127:16378–16379. [PubMed: 16305208]
17. For examples of recent reports of methods for the synthesis of 2-alkylpyrrolidines, see: (a) Racemic products: Hennessy ET, Betley TA. Jurberg ID, Peng B, Wöstefeld E, Wasserloos M, Maulide N. Science. Angew. Chem. Int. Ed. 2012; 2012; 34051:591–595. 1950–1953. [PubMed: 23641113] (b) Enantioenriched 2-benzyl- and 2-methylpyrrolidines: Reference 13a.
18. Campos KR, Klapars A, Waldman JH, Dormer PG, Chen Cy. J. Am. Chem. Soc. 2006; 128:3538–3539. [PubMed: 16536525] Barker G, McGrath JL, Klapars A, Stead D, Zhou G, Campos KR, O'Brien P. J. Org. Chem. 2011; 76:5936–5953. [PubMed: 21714542]
19. A portion of the enantioenriched organozinc reagent (eq 5) was subjected to the Campos arylation procedure (coupling partner: bromobenzene), which afforded *N*-Boc-2-phenylpyrrolidine in 92% ee and 97% yield.
20. Our attempts to apply the Campos procedure (which employs a Pd/P(*t*-Bu)$_3$ catalyst) to cross-couplings of alkyl electrophiles were not successful.
21. For exceptions (couplings of achiral secondary nucleophiles with racemic secondary electrophiles), see: Binder JT, Cordier CJ, Fu GC. J. Am. Chem. Soc. 2012; 134:17003–17006. [PubMed: 23039358] Zultanski SL, Fu GC. J. Am. Chem. Soc. 2011; 133:15362–15364. [PubMed: 21913638]

22. All previous reports of enantioselective alkyl-alkyl Negishi cross-couplings (which had employed racemic electrophiles rather than racemic nucleophiles) had utilized nickel in combination with a pyridine-oxazoline-type ligand, never with a chiral diamine ligand. However, when such pyridine-oxazolines were applied to the coupling of α-zincated *N*-Boc-pyrrolidine with cyclohexyl iodide, the desired product was generated in <10% yield. For leading references, see References 1a, 4b, and 21a.

23. Notes: (a) The ee of the product is essentially constant during the course of the reaction. (b) Under the standard cross-coupling conditions, 3-iodopentane and *t*-butyl iodide react very slowly (<20% yield after 2.5 days) and the use of $ZnCl_2$ rather than ZnI_2 leads to inferior results.

24. For example, the hydroamination of olefins: Reznichenko AL, Hultzsch KC. Nugent TC. Chiral Amine Synthesis. 2011WeinheimWiley-VCH:341–375.

25. For example, see: Maloney DJ, Danishefsky SJ. Angew. Chem. Int. Ed. 2007; 46:7789–7792.

26. For pioneering studies, see: Coffey DS, McDonald AI, Overman LE, Rabinowitz MH, Renhowe PA. J Am. Chem. Soc. 2000; 122:4893–4903.

27. Under the standard cross-coupling conditions, cyclohexyl chloride reacts very slowly (<10% yield after 2.5 days).

28. For examples of and leading references to diastereoconvergent palladium-catalyzed Negishi reactions of cyclic organozinc reagents, see: Seel S, Thaler T, Takatsu K, Zhang C, Zipse H, Straub BF, Mayer P, Knochel P. J Am. Chem. Soc. 2011; 133:4774–4777. [PubMed: 21388211]

29. Gross KMB, Beak P. J. Am. Chem. Soc. 2001; 123:315–321. [PubMed: 11456518] Notes: (a) Sn-Li exchange was employed, rather than (−)-sparteinemediated lithiation, in order to avoid any complications in the nickel-catalyzed cross-coupling due to the presence of (−)-sparteine. (b) The absolute configuration of the stannane has been determined by X-ray crystallography: Gawley RE, Narayan S, Vicic DA. J. Org. Chem. 2005; 70:328–329. [PubMed: 15624941]

30. In a preliminary study, when 2,2-d_2 *N*-Boc-pyrrolidine was subjected to the standard asymmetric cross-coupling conditions, no evidence of deuterium scrambling was observed.

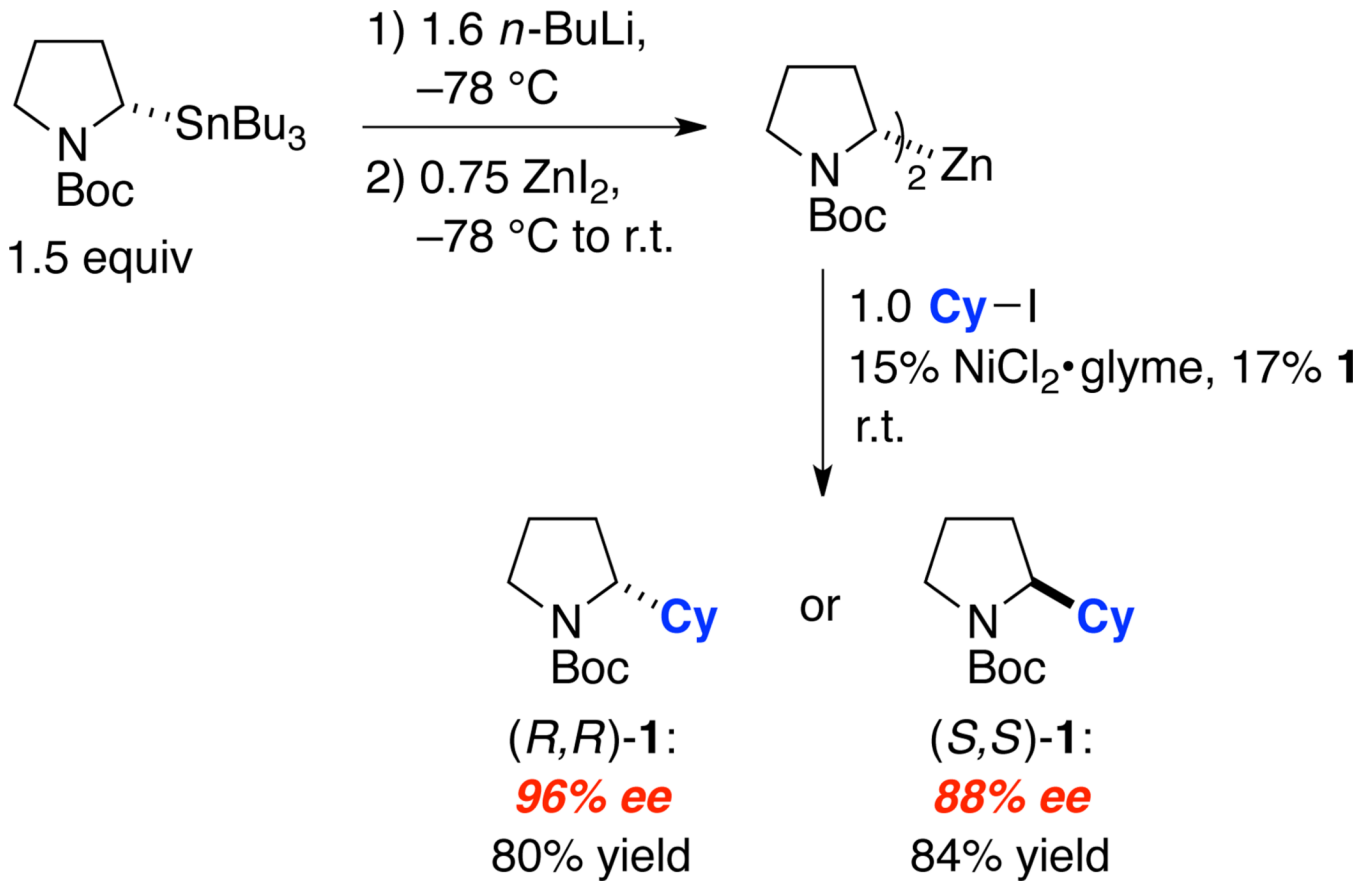


Figure 1.
The stereochemistry of the alkyl-alkyl cross-coupling product is controlled predominantly by the stereo chemistry of the chiral nickel catalyst, not of the nucleophile, in a Negishi reaction of α-zincated *N*-Boc-pyrrolidine.

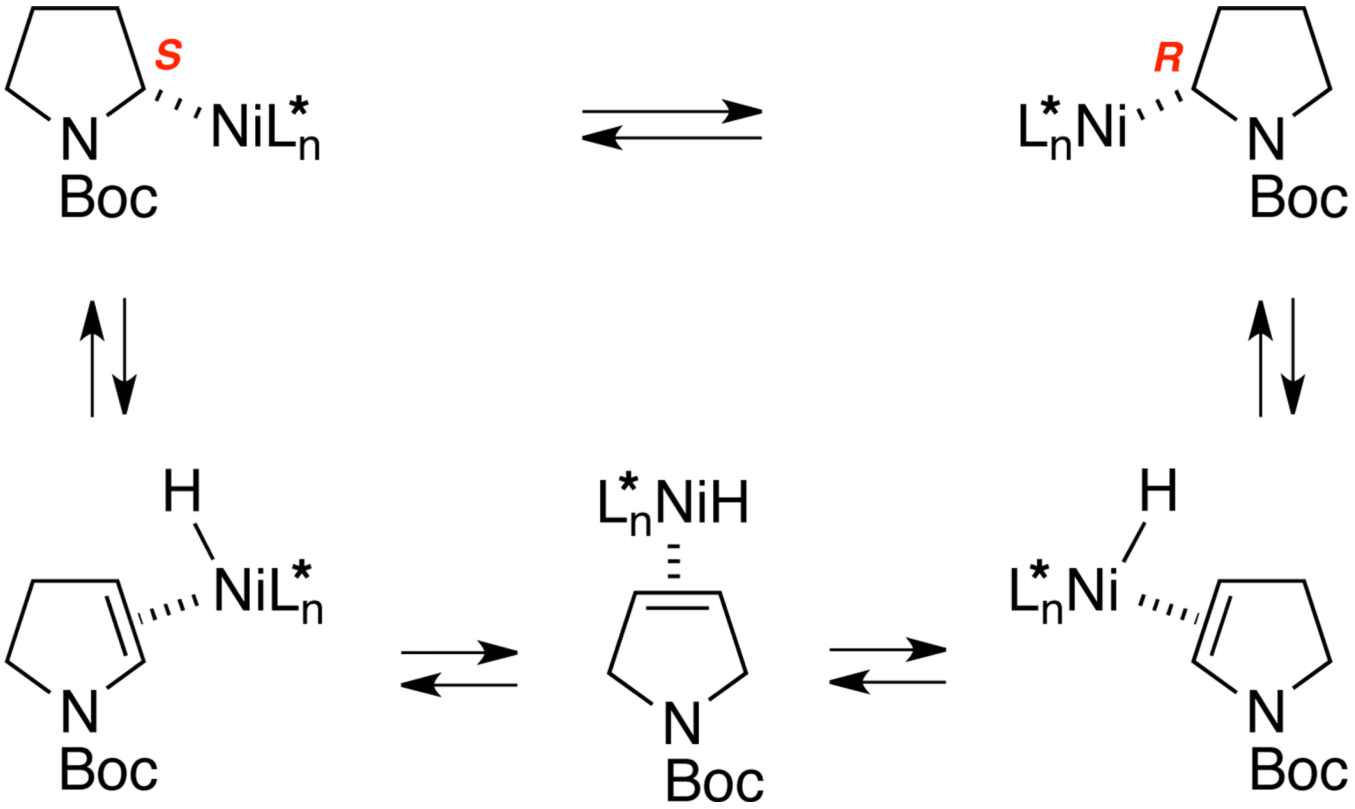
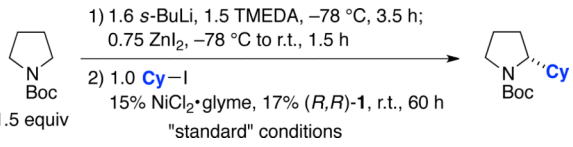


Figure 2.
A hypothetical pathway for stereomutation of an α-metalated *N*-Boc-pyrrolidine: β-hydride elimination and β-migratory insertion without olefin dissociation.

Table 1

Enantioconvergent Cross-Coupling of a Racemic Nucleophile: Effect of Reaction Parameters[a]



entry	variation from the “standard” conditions	ee (%)	yield (%)[b]
1	none	**93**	**86**
2	no $NiCl_2$·glyme	–	<2
3	no **1**	–	2
4	no ZnI_2	–	<2
5	**2**, instead of **1**	82	80
6	**3**, instead of **1**	75	76
7	10% $NiCl_2$·glyme, 12% **1**	92	53
8	$Ni(cod)_2$, instead of $NiCl_2$·glyme	93	61
9	$NiBr_2$·glyme, instead of $NiCl_2$·glyme	92	38
10	0.5, instead of 0.75, ZnR_2 (R = *N*-Boc-pyrrolidinyl)	**90**	**74**

[a]All data are the average of two experiments.

[b]Yield determined by GC analysis versus a calibrated internal standard.

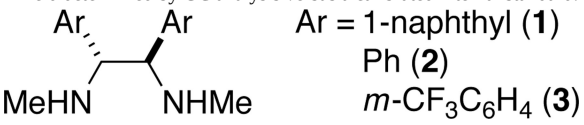
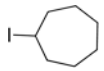
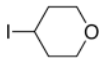
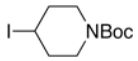
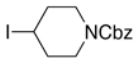
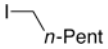


Table 2

Enantioconvergent Negishi Reactions of Racemicα-Zincated*N*Boc-pyrrolidine with Unactivated Alkyl Iodides (reaction conditions: eq 4)[a]

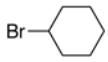
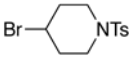
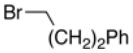
entry	electrophile	ee, yield (%)[b]	entry	electrophile	ee, yield (%)[b]
1		**93**, 80	5		**94**, 96
2		**82**, 91	6		**91**, 94
3		**84**, 50	7		**90**, 85
4		**92**, 96	8		**58**, 85

[a] All data are the average of two experiments.

[b] Yield of purified product (scale of the reaction: 1.0 mmol of the electrophile).

Table 3

Enantioconvergent Negishi Reactions of Racemic α-Zincated*N*Boc-pyrrolidine with Unactiva-ted Alkyl Bromides (reaction conditions: eq 4)[a]

entry	electrophile	ee(%)	yield (%)[b]
1[c]		**92**	41
2		**88**	80
3[c]		**88**	44
4[c]		**90**	51
5		**58**	61

[a]All data are the average of two experiments.

[b]Yield of purified product.

[c]Reaction temperature: 35 °C.