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

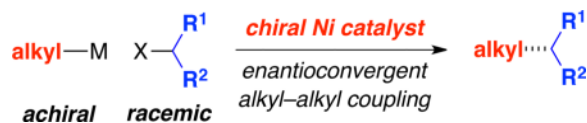
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Abstract

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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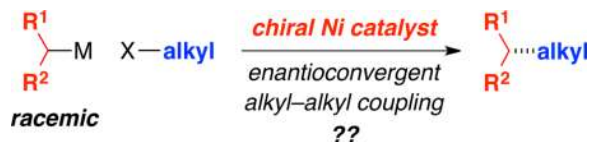
ASSOCIATED CONTENT

Supporting Information

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

Notes

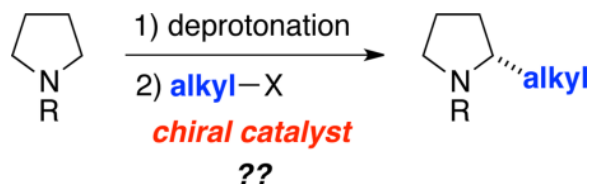
The authors declare no competing financial interest.



(2)

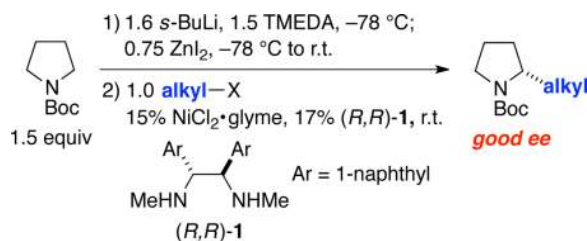
Pyrrolidines that bear an alkyl substituent in the 2 position are important across many areas of chemistry and biology. For example, they are present as subunits in bioactive natural⁸ and non-natural⁹ products, function as versatile intermediates in the synthesis of other useful classes of compounds,¹⁰ 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*-Bu₃SnCl, Me₃SiCl, 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



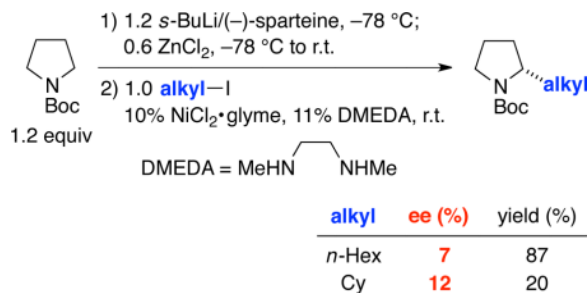
(3)

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 \square -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.



(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 NiCl₂ 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 NiCl₂-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 Δ -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).

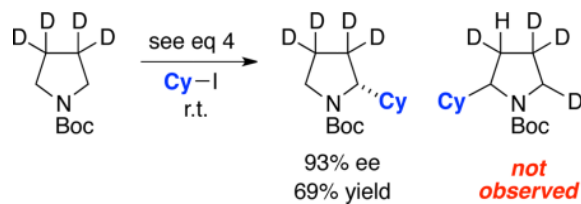
This method thus complements other catalytic enantioselective approaches to the synthesis of 2-alkylpyrrolidines, which are typically only effective for the incorporation of a primary alkyl group.²⁴ Pyrrolidines that bear a secondary alkyl substituent in the 2 position are found in a wide variety of compounds, including an array of pyrrolizidine (simplest example: heliotridane), indolizidine (simple example: ta-shiromine; also: grandisine A²⁵), and crambescidin²⁶ 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 Δ -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 reactions of Δ -zincated *N*-Boc-pyrrolidine.²⁸ In Kumada's 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 by the chiral nickel catalyst.⁶ In contrast, our nucleophile, Δ -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 β 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 δ -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 deuterium labeling study rules out stereomutation via a simple δ -hydride elimination/ δ -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

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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.
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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 ZnCl₂ rather than ZnI₂ leads to inferior results.
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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.

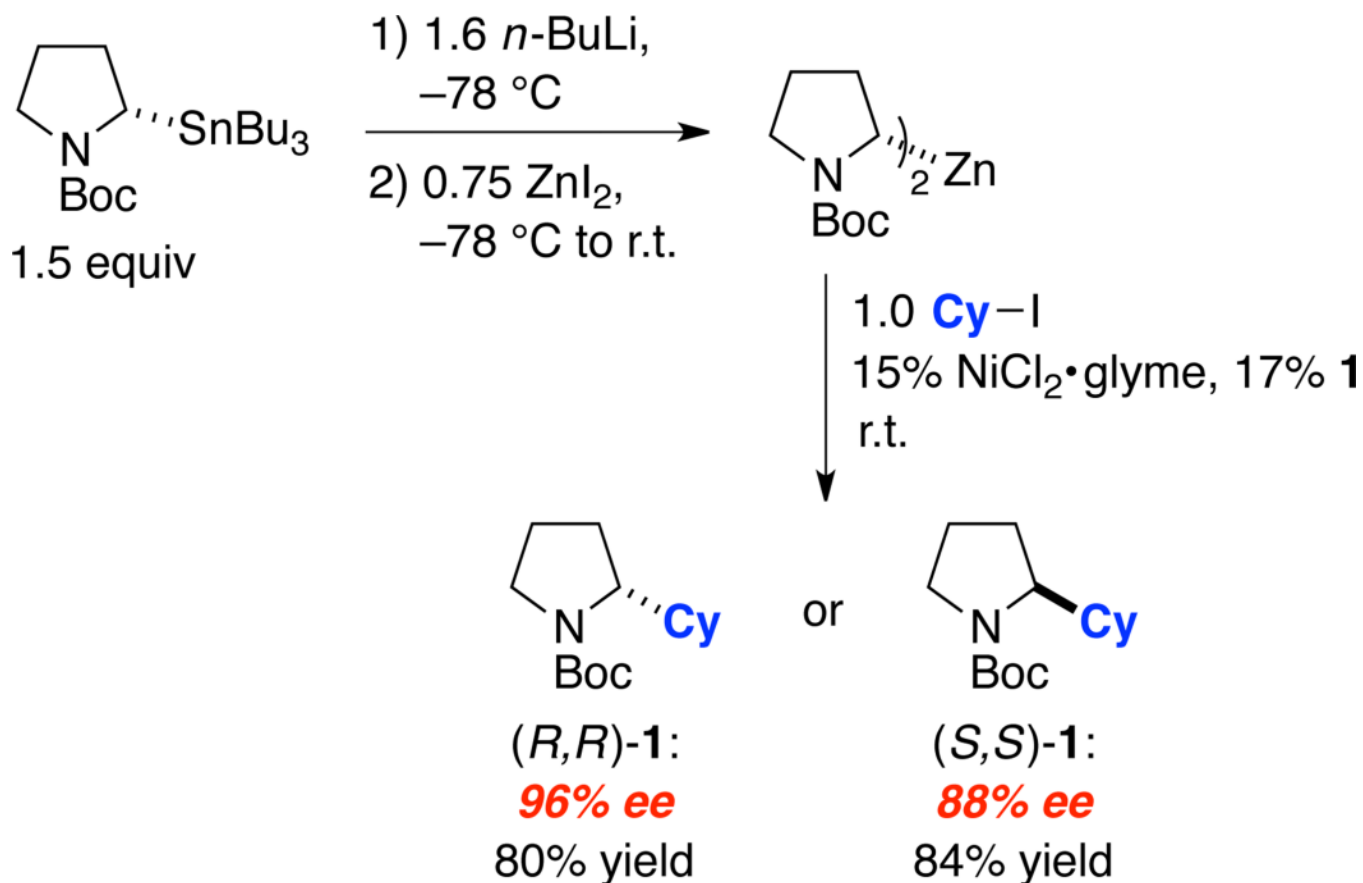


Figure 1. The stereochemistry of the alkyl-alkyl cross-coupling product is controlled predominantly by the stereochemistry of the chiral nickel catalyst, not of the nucleophile, in a Negishi reaction of π -zincated *N*-Boc-pyrrolidine.

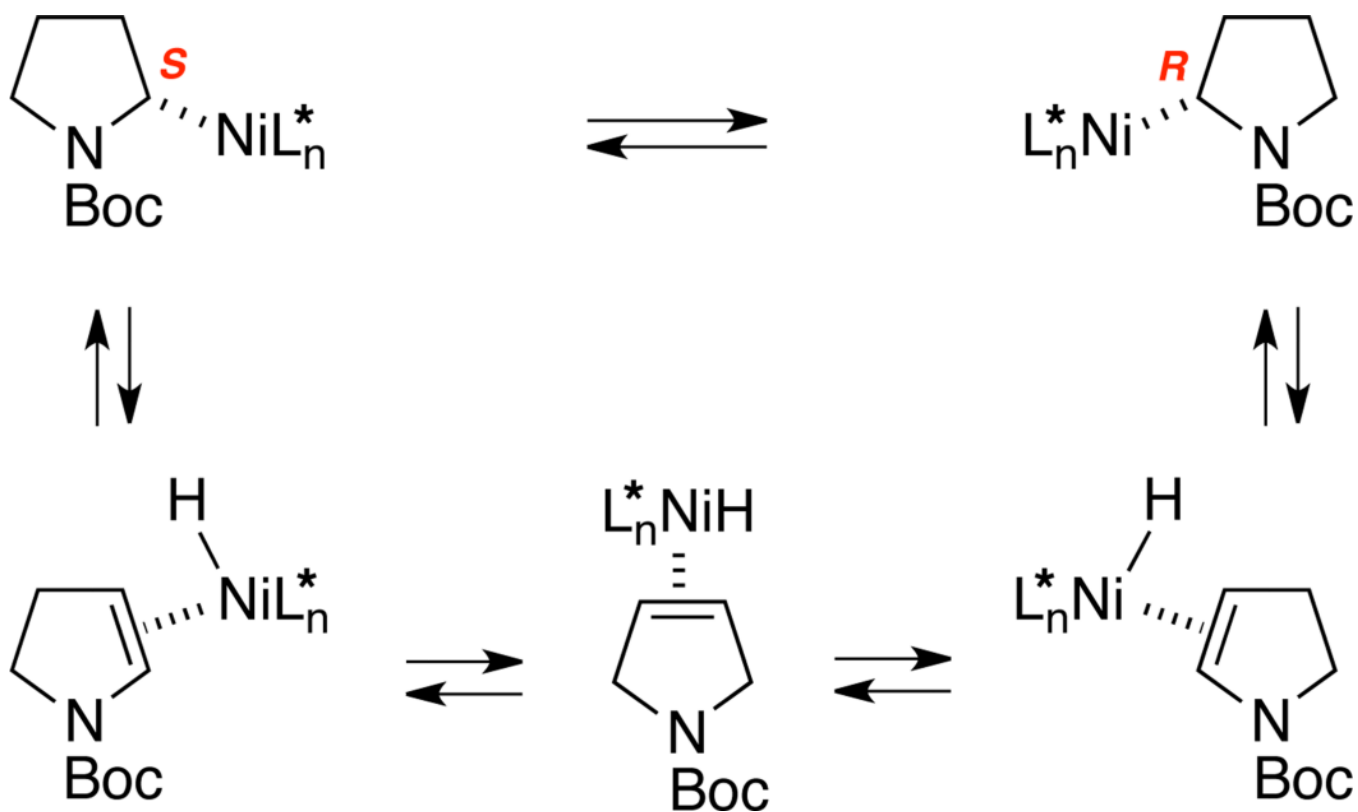
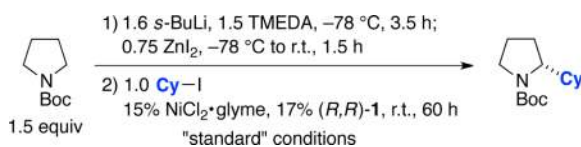
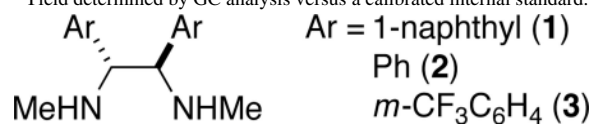


Figure 2.
A hypothetical pathway for stereomutation of an η -metalated *N*-Boc-pyrrolidine: η -hydride elimination and η -migratory insertion without olefin dissociation.





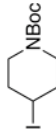
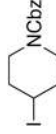

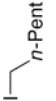
Table 1Enantioconvergent Cross-Coupling of a Racemic Nucleophile: Effect of Reaction Parameters^a

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 = <i>N</i> -Boc-pyrrolidinyl)	90	74

^aAll data are the average of two experiments.^bYield determined by GC analysis versus a calibrated internal standard.

Enantioconvergent Negishi Reactions of Racemic \square Zincated MBoc-pyrrolidine with Unactivated Alkyl Iodides (reaction conditions: eq 4)^a

Table 2



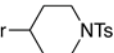

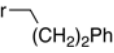
entry	electrophile	ee, yield (%) ^b	entry	electrophile	ee, yield (%) ^b
1		93, 80	5		94, 96
2		82, 91	6		91, 94
3		84, 50	7		90, 85
4		92, 96	8		58, 85

^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 Δ -Zincated *N*Boc-pyrrolidine with Unactivated 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

^aAll data are the average of two experiments.

^bYield of purified product.

^cReaction temperature: 35 °C.