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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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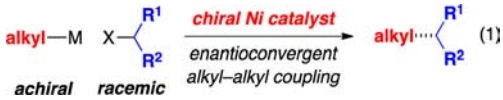
Supporting Information

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 indicated that two of the most straightforward mechanisms for enantioconvergence (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.[1−3] As part of this program, we have described several Ni-catalyzed methods for the enantioconvergent coupling of achiral alkylmetal reagents with racemic secondary alkyl electrophiles (eq 1).[4,5]



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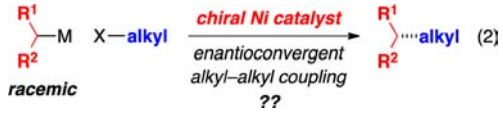
The reversed-polarity process, wherein a racemic alkyl *nucleophile* is coupled with an alkyl electrophile (eq 2), has

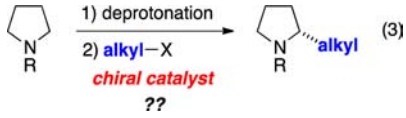


(2)

remained an unsolved challenge. However, Kumada has described a Ni-catalyzed enantioconvergent coupling of a racemic benzylic Grignard reagent (PhCHMeMgCl) with an alkenyl halide (bromoethylene) to generate an enantioenriched allylbenzene.[6,7]

Pyrrolidines bearing an alkyl substituent at 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



(3)

our knowledge, such a process has not been reported to date. On the other hand, pioneering studies by Beak 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, CO_2) 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] Building on these key observations, O'Brien developed a method that employs a substoichiometric quantity (20 mol %) of a chiral amine and provides 2-functionalized (although not 2-alkyl) *N*-Boc-pyrrolidines with up to 88% ee.[16]

In view of the potential utility of the transformation outlined in eq 3, we 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 found that, in the presence of a chiral Ni 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 with good ee (eq 4).[17]

Initially, in view of recent reports by Campos of stoichiometric asymmetric α-lithiation/transmetalation/Pd-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 Ni–1,2-diamine catalyst (eq 5). In both

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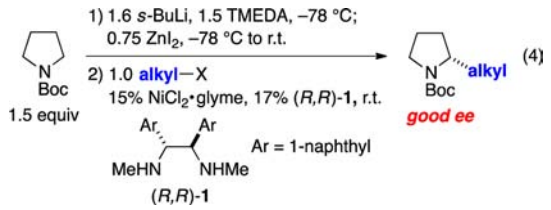
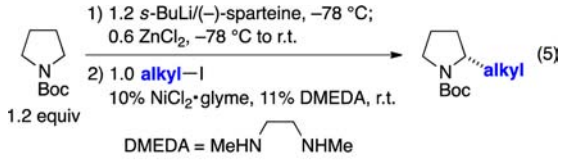




alkyl	ee (%)	yield (%)
n-Hex	7	87
Cy	12	20

cases, the alkyl–alkyl coupling product was formed with low ee (<15% ee).[20] Because the organozinc reagent is configurationally stable at room temperature, these observations suggest that stereochemical scrambling occurs during the Ni-catalyzed cross-coupling process.

Because the use of an achiral catalyst for the cross-coupling of a highly enantioenriched nucleophile provided almost racemic product, we decided to examine the 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. Investigation of a range of parameters showed that the desired enantioconvergent coupling of racemic α-zincated *N*-Boc-pyrrolidine with cyclohexyl iodide can be achieved using a combination of $NiCl_2$·glyme and chiral 1,2-diamine ligand **1**[22] in good yield (86%) with high ee (93% ee) at room temperature (Table 1, entry 1). In the absence of either $NiCl_2$·glyme or **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 ee and yield (entries 5 and 6). Using less catalyst (entry 7) or another Ni source (entries 8 and 9) led to comparable ee but reduced yield. *Our observation that 2-cyclohexyl-N-Boc-pyrrolidine formed in 74% yield with 90% ee in the presence of 0.5 equiv of the diorganozinc reagent (entry 10) provides strong evidence that the cross-coupling is an enantioconvergent process, not a simple kinetic resolution.*

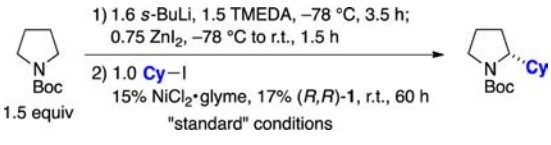
The catalytic asymmetric synthesis of an array of 2-alkylpyrrolidines can be achieved via the coupling of a single precursor (*N*-Boc-pyrrolidine) with a variety of readily available, unactivated alkyl iodides (Table 2).[23] Three parent cycloalkyl iodides underwent enantioconvergent alkyl–alkyl cross-coupling with racemic α-zincated *N*-Boc-pyrrolidine with good enantioselectivity (entries 1–3); the process could be conducted on a gram scale with comparable efficiency [performing entry 1 on a 6.0 mmol scale gave 1.12 g of product (74% yield) with 94% ee]. Heterocyclic electrophiles coupled with high ee (entries 4–6), as did an acyclic secondary alkyl iodide (entry 7). In contrast, moderate ee was 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 bearing a secondary alkyl substituent at the 2-position are found in a wide variety of compounds, including an array of pyrrolizidine (e.g., heliotridane), indolizidine (e.g., tashiromine, grandisine A[25]), and crambescidin[26] alkaloids.

Alkyl *bromides* can also be employed as electrophiles in these Ni-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 proceeded with good ee's but generally modest yields (entries 1–4). As in the case of a primary alkyl iodide, a primary bromide cross-coupled with lower ee (entry 5).

We next focused on gaining insight into the origin of the stereoconvergence in these asymmetric Negishi reactions of α-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

Table 1. Enantioconvergent Cross-Coupling of a Racemic Nucleophile: Effect of the 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 averages of two experiments. [b]Determined by GC analysis vs a calibrated internal standard.

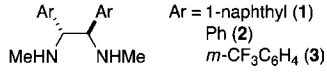
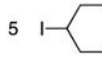
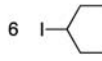
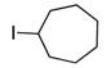
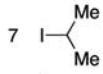
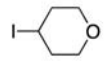
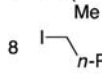


Table 2. Enantioconvergent Negishi Reactions of Racemic α-Zincated *N*-Boc-pyrrolidine with Unactivated Alkyl Iodides[a]

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]For the reaction conditions, see eq 4. All data are averages of two experiments. [b]Yields of purified products (reaction scale: 1.0 mmol of the electrophile).

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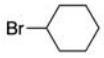
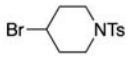
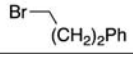
Table 3. Enantioconvergent Negishi Reactions of Racemic α-Zincated *N*-Boc-pyrrolidine with Unactivated Alkyl Bromides[a]

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

[a]For the reaction conditions, see eq 4. All data are averages of two experiments. [b]Yields of purified products. [c]Reaction temperature: 35 °C.

rapidly racemizing benzylic nucleophile by the chiral Ni catalyst.[6] In contrast, our nucleophile, α-zincated *N*-Boc-pyrrolidine, is configurationally stable under our reaction conditions in the absence of Ni. Thus, an enantioenriched organozinc reagent was prepared from the corresponding stannane through Sn−Li exchange followed by transmetalation to zinc (Figure 1).[29] When

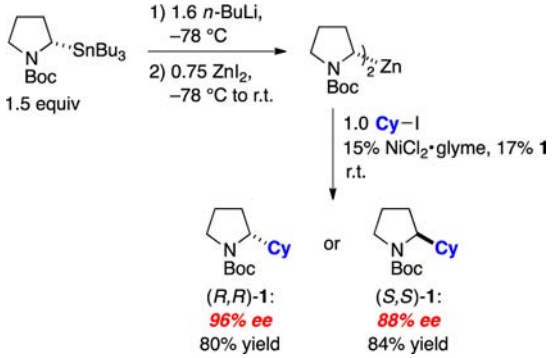


Figure 1. The product stereochemistry is controlled predominantly by the stereochemistry of the chiral Ni catalyst, not that of the nucleophile, in a Negishi reaction of α-zincated *N*-Boc-pyrrolidine.

this nucleophile was cross-coupled with bromobenzene under the Campos conditions,[18] (*R*)-2-phenyl-*N*-Boc-pyrrolidine was generated in 95% yield with 90% ee, 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**, the stereochemistry of the cross-coupling product was dependent primarily on the stereochemistry of the ligand rather than of the organozinc nucleophile.

A possible mechanism for enantioconvergence in the Ni-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 Ni (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 deuterium-labeled *N*-Boc-

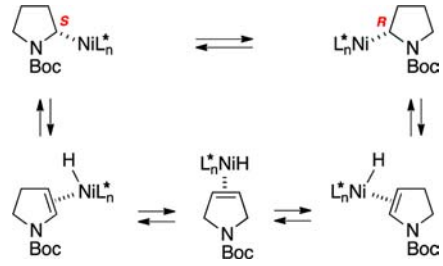
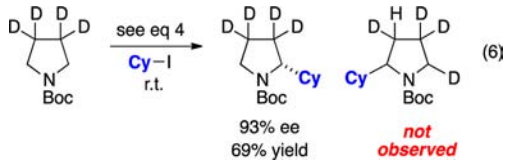


Figure 2. A hypothetical pathway for stereomutation of an α-metalated *N*-Boc-pyrrolidine: β-hydride elimination and β-migratory insertion without olefin dissociation.

pyrrolidine (eq 6). Essentially no deuterium incorporation (<5%) α to nitrogen in the cross-coupling product was observed,



indicating that the β-hydride elimination/β-migratory insertion pathway for stereomutation depicted in Figure 2 is not the mechanism by which stereoconvergence is achieved.[30]

In summary, we have developed the first enantioconvergent alkyl−alkyl cross-coupling 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 was 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 in 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 ruled out stereomutation via a simple β-hydride elimination/β-migratory insertion pathway that we had observed in another Ni-catalyzed alkyl−alkyl coupling. Additional investigations to elucidate the mechanism of this unusual enantioconvergent cross-coupling and to expand the range of racemic nucleophiles that can be employed in such alkyl−alkyl coupling processes are underway.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(7) Other examples of the asymmetric cross-coupling of racemic nucleophiles with alkenyl electrophiles have been described, but 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 result from a simple kinetic resolution in which one enantiomer of the nucleophile is selectively cross-coupled).

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(17) For recent reports of methods for the synthesis of racemic 2-alkylpyrrolidines, see: (a) Hennessy, E. T.; Betley, T. A. *Science* **2013**, *340*, 591. (b) Jurberg, I. D.; Peng, B.; Wöstefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 1950. For enantioenriched 2-benzyl- and 2-methylpyrrolidines, see ref 13a.

(18) (a) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc.* **2006**, *128*, 3538. (b) Barker, G.; McGrath, J. L.; Klapars, A.; Stead, D.; Zhou, G.; Campos, K. R.; O'Brien, P. *J. Org. Chem.* **2011**, *76*, 5936.

(19) A portion of the enantioenriched organozinc reagent (eq 5) was subjected to the Campos arylation procedure using bromobenzene as the electrophile, which afforded *N*-Boc-2-phenylpyrrolidine in 97% yield with 92% ee.

(20) Our attempts to apply the Campos procedure [which employs a $Pd/P(t\text{-}Bu)_3$ catalyst] to cross-couplings of alkyl electrophiles were not successful.

(21) For exceptions (couplings of achiral secondary nucleophiles with racemic secondary electrophiles), see: (a) Binder, J. T.; Cordier, C. J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 17003. (b) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362.

(22) All previous reports of enantioselective alkyl−alkyl Negishi cross-couplings (which employed racemic electrophiles rather than racemic nucleophiles) utilized Ni 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 refs 1a, 4b, and 21a.

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

(24) For example, for the hydroamination of olefins, see: Reznichenko, A. L.; Hultzsch, K. C. In *Chiral Amine Synthesis*; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, Germany, 2011; pp 341−375.

(25) For example, see: Maloney, D. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7789.

(26) For pioneering studies, see: Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 4893.

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

(28) For examples of and leading references to diastereoconvergent Pd-catalyzed Negishi reactions of cyclic organozinc reagents, see: Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2011**, *133*, 4774.

(29) Gross, K. M. B.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315. Notes: (a) Sn−Li exchange, rather than (−)-sparteine-mediated lithiation, was employed to avoid any complications in the Ni-catalyzed cross-coupling due to the presence of (−)-sparteine. (b) The absolute configuration of the stannane has been determined by X-ray crystallography. See: Gawley, R. E.; Narayan, S.; Vicic, D. A. *J. Org. Chem.* **2005**, *70*, 328.

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