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## Catalytic Asymmetric Synthesis of Secondary Nitriles via Stereoconvergent Negishi Arylations and Alkenylations of Racemic $\alpha$ -Bromonitriles

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### Abstract

The first method for the stereoconvergent cross-coupling of racemic  $\alpha$ -halonitriles is described, specifically, nickel-catalyzed Negishi arylations and alkenylations that furnish an array of enantioenriched  $\alpha$ -arylnitriles and allylic nitriles, respectively. Noteworthy features of this investigation include: the highly enantioselective synthesis of  $\alpha$ -alkyl- $\alpha$ -aryl nitriles that bear *secondary*  $\alpha$ -alkyl substituents; the first examples of the use of *alkeny/zinc* reagents in stereoconvergent Negishi reactions of alkyl electrophiles; demonstration of the utility of a new family of ligands for asymmetric Negishi cross-couplings (a bidentate bis(oxazoline), rather than a tridentate pybox); in the case of arylzinc reagents, carbon–carbon bond formation at a remarkably low temperature ( $-78$  °C), the lowest reported to date for an enantioselective cross-coupling of an alkyl electrophile; a mechanistic dichotomy between Negishi reactions of an unactivated versus an activated secondary alkyl bromide.

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Many bioactive compounds bear a cyano group attached to a stereogenic carbon.<sup>1</sup> Furthermore, nitriles serve as versatile precursors to a diverse array of molecules, including heterocycles, aldehydes, ketones, amides, carboxylic acids, and amines.<sup>2</sup> Enantioenriched  $\alpha$ -alkyl- $\alpha$ -arylnitriles are particularly noteworthy targets, since they can be transformed into  $\alpha$ -aryl carboxylic acids such as  $\alpha$ -arylpropionic acids, which are widely used as non-steroidal anti-inflammatory drugs (e.g., naproxen).<sup>3</sup>

A variety of methods have been described for the catalytic asymmetric synthesis of  $\alpha$ -alkyl- $\alpha$ -arylnitriles.<sup>4,5,6</sup> For example, nickel-catalyzed hydrocyanation of vinylarenes can generate  $\alpha$ -methyl- $\alpha$ -arylnitriles with excellent ee; however, there have been no reports of corresponding highly enantioselective hydrocyanations of substituted styrenes to produce nitriles that bear  $\alpha$ -alkyl substituents larger than methyl. The conjugate addition of H–CN to  $\beta$ -aryl- $\alpha,\beta$ -unsaturated carbonyl compounds provides an alternate route to  $\alpha$ -alkyl- $\alpha$ -arylnitriles, although current methods generally only furnish products with  $\alpha$ -alkyl groups that are primary.

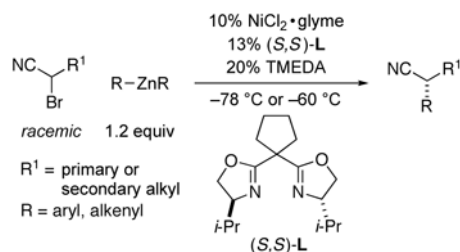
We have been interested in exploring the catalytic asymmetric synthesis of secondary  $\alpha$ -arylnitriles through the reaction of an aryl nucleophile with a nitrile that bears a leaving group geminal to the cyano substituent; to the best of our knowledge, there is no precedent for this transformation using a chiral catalyst.<sup>7</sup> However, while our study was underway, Falck reported an important investigation of Suzuki arylations of  $\alpha$ -(sulfonyl)nitriles in the

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

presence of an achiral palladium catalyst.<sup>7c</sup> In the case of two enantioenriched electrophiles (one unhindered and one doubly activated), he established that carbon–carbon bond formation proceeds with inversion of stereochemistry with little or no erosion in ee; on the other hand, Falck did not describe the stereochemical outcome for Suzuki couplings of electrophiles that bear a *secondary* alkyl substituent. In this report, we provide a complementary approach wherein a *chiral* catalyst achieves stereoconvergent Negishi cross-couplings of *racemic* electrophiles with aryl, as well as with alkenyl, nucleophiles (eq 1).

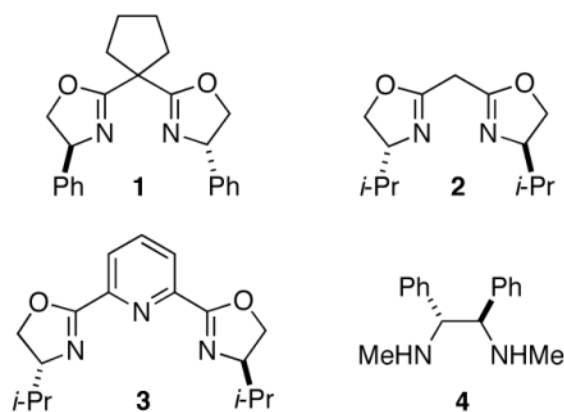


(1)

Negishi reactions are an especially attractive family of cross-coupling processes, due to the compatibility of organozinc reagents with a wide range of functional groups and the typical lack of a need for a stoichiometric quantity of a Brønsted-basic additive.<sup>8</sup> In previous studies, we determined that several classes of activated electrophiles are suitable coupling partners in asymmetric Negishi alkylations or arylations; in every instance, nickel with a pybox ligand proved to be the catalyst of choice.<sup>9,10</sup> Unfortunately, however, when we applied any of the arylation methods to the phenylation of an  $\alpha$ -bromonitrile, we obtained disappointing results (<40% ee).

We decided to look beyond tridentate pybox ligands, and after substantial effort we determined that the Negishi phenylation of an  $\alpha$ -bromonitrile can be achieved in good ee and yield in the presence of NiCl<sub>2</sub>·glyme and a new, readily available *bis(oxazoline)* ligand<sup>11</sup> (94% ee, 98% yield; Table 1, entry 1).<sup>12</sup> The reaction proceeds at  $-78$  °C, which is, to the best of our knowledge, the lowest temperature that has been employed for a cross-coupling of an alkyl electrophile.<sup>13</sup>

As illustrated in Table 1, essentially no cross-coupling of the  $\alpha$ -bromonitrile is observed in the absence of NiCl<sub>2</sub>·glyme (entry 2) or of bis(oxazoline) **L** (entry 3), as well as when an arylzinc halide is employed as the nucleophilic reaction partner (entry 4). The reaction proceeds in poor ee and yield when conducted at room temperature (entry 5), and ligands other than **L** provide modestly (bis(oxazoline) **1**; entry 6) or substantially (bis(oxazoline) **2**, pybox **3**, and 1,2-diamine **4** (entries 7–9)) inferior results. Use of less Ph<sub>2</sub>Zn (entry 10) or less catalyst (entry 11) leads to a decrease in yield, but no loss in enantioselectivity.

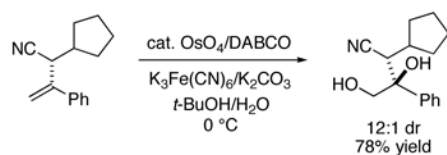


With our optimized method, asymmetric Negishi cross-couplings of  $\text{Ph}_2\text{Zn}$  with a range of racemic  $\alpha$ -bromonitriles proceed efficiently, furnishing  $\alpha$ -phenylnitriles in good ee and yield (Table 2).<sup>14</sup> A wide variety of functional groups are compatible with the reaction conditions, including an ether (entry 5), a carbamate (entry 6), an amide and a heterocycle (entry 7), a sulfonamide (entries 8 and 9), an unactivated alkyl chloride (entry 9), and an alkene (entries 11 and 12). In view of the limitations of other methods for generating highly enantioenriched  $\alpha$ -alkyl- $\alpha$ -arylnitriles in the case of *branched* alkyl groups (e.g., via asymmetric hydrocyanation; *vide supra*), our high ee's for Negishi cross-couplings of hindered electrophiles (entries 1–9) are particularly noteworthy.

This process for the Negishi arylation of  $\alpha$ -bromonitriles is not limited to *phenylation* reactions. Thus, we can cross-couple with a range of nucleophiles in uniformly high ee and yield (Table 3), regardless of whether the aryl group is electron-rich (entries 1–3) or electron-poor (entry 4).<sup>15</sup>

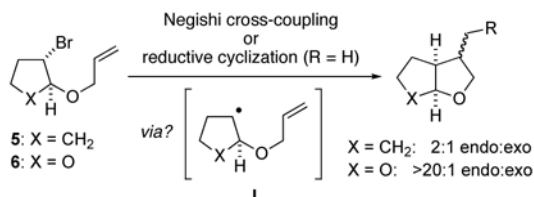
Although we have previously described examples of stereoconvergent Negishi reactions of activated electrophiles with *alkyl*- and *aryl*zinc reagents, we have never been able to achieve corresponding cross-couplings with *alkenyl*zinc reagents.<sup>9</sup> We were therefore pleased to determine that we can apply the conditions (except reaction temperature<sup>16</sup>) that we developed for enantioselective Negishi arylations (Table 3) of  $\alpha$ -bromonitriles to alkenylations (Table 4).<sup>17</sup> Thus, as depicted in Table 4, we can accomplish an array of asymmetric alkenylations with good ee, thereby providing ready access to enantioenriched allylic nitriles.<sup>18</sup> No racemization or isomerization (to the conjugated nitrile) of the allylic nitrile is observed under these mild conditions.

The enantioenriched allylic nitriles are suitable substrates for stereoselective functionalizations. For example, osmium-catalyzed dihydroxylation proceeds with good diastereoselectivity (eq 2).



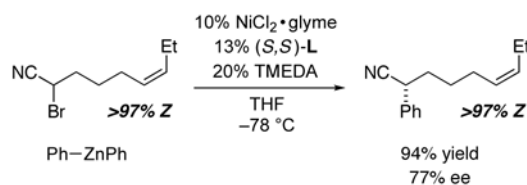
(2)

We have previously proposed that a radical intermediate may be involved in the oxidative-addition step of certain nickel-catalyzed cross-couplings of unactivated secondary alkyl halides.<sup>19</sup> One observation consistent with this hypothesis is the stereochemistry of cyclization/cross-couplings of electrophiles that bear pendant olefins. We have now determined that, as for Hiyama and Suzuki reactions,<sup>20</sup> Negishi reactions of secondary bromides **5** and **6** proceed with the same diastereoselectivities as observed for reductive cyclizations of these substrates by Bu<sub>3</sub>SnH, which is consistent with a common intermediate (**I**) in the cyclization step for all of these processes (eq 3).



(3)

In this regard, it is interesting to note that the substrates depicted in entries 11 and 12 of Table 2, which have the potential to cyclize/cross-couple to furnish five-membered rings, afford only acyclic coupling products. To gain insight into whether cyclization of a radical intermediate might be occurring, but reversibly, in enantioselective cross-couplings of  $\alpha$ -bromonitriles that bear pendant olefins, we examined the Negishi reaction of the electrophile illustrated in eq 4. If radical cyclization is occurring, but the *acyclic* radical preferentially proceeds to the cross-coupling product (Curtin–Hammett scenario), then the *Z* stereochemistry of the starting material would not be preserved in the acyclic product. However, we observe only the *Z* isomer, which suggests that radical cyclization is not occurring in this Negishi reaction of an  $\alpha$ -bromonitrile, in contrast to our previous studies of cross-couplings of unactivated secondary alkyl bromides.<sup>21</sup>



(4)

In summary, we have developed the first method for the stereoconvergent cross-coupling of racemic  $\alpha$ -halonitriles, specifically, nickel-catalyzed Negishi arylations and alkenylations that generate a variety of useful enantioenriched secondary  $\alpha$ -arylnitriles and allylic nitriles, respectively. With regard to accessing secondary  $\alpha$ -alkyl- $\alpha$ -arylnitriles, this work complements other prominent approaches, which are most effective for the synthesis of products in which the alkyl group is methyl (hydrocyanation of olefins) or a primary alkyl substituent (conjugate addition of HCN). For the first time for studies of asymmetric Negishi cross-couplings, an *alkenylzinc* reagent can serve as an effective nucleophilic partner, and a ligand other than a tridentate pybox is the ligand of choice; this latter observation is significant for future explorations of enantioselective Negishi reactions. Couplings with arylzinc reagents occur at a remarkably low temperature ( $-78$  °C), the lowest temperature reported to date for such asymmetric carbon–carbon bond-forming processes. Finally, a

mechanistic study provides a contrast between nickel-catalyzed Negishi reactions of unactivated vs. activated secondary alkyl bromides. An array of additional investigations of enantioselective cross-couplings of alkyl electrophiles are underway.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

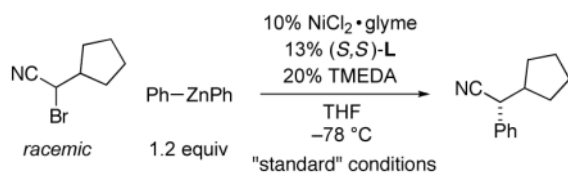
Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, grant R01-GM62871) and the Kwanjeong Educational Foundation (fellowship to J.C.). We thank Ashraf Wilsily for assistance in the preparation of substrates

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10. For a very recent application of our asymmetric allylation method in the total synthesis of a natural product (carolacton), see: Schmidt T, Kischning A. *Angew Chem, Int Ed.* 2012; 51:1063–1066.
11. Bis(oxazoline) L can be prepared in one step from commercially available 1,1-cyclopentanedicarbonitrile and valinol.

12. All of the diorganozinc compounds are generated from Grignard reagents and  $\text{Zn(OMe)}_2$  (for a report of the use of  $\text{Zn(OMe)}_2$  to generate organozinc reagents, see: Côté A, Charette AB. *J Am Chem Soc.* 2008; 130:2771–2773. [PubMed: 18266374] When  $\text{ZnX}_2$  (X=Cl, Br, or I) is employed instead of  $\text{Zn(OMe)}_2$ , somewhat lower ee and/or yield are observed.
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14. Notes: Under our standard conditions: on a gram-scale, the asymmetric Negishi reaction illustrated in entry 8 of Table 2 proceeds in 90% ee and 93% yield; if  $\text{PhMgBr}$  is employed as the nucleophile (Table 2, entry 2), Kumada coupling occurs in 88% ee and 6% yield; there is no erosion in the enantiomeric excess of the product during the course of a cross-coupling; an  $\alpha$ -chloronitrile and an  $\alpha$ -iodonitrile cross-couple in significantly lower ee (chloride) and/or yield (chloride and iodide); diethylzinc and alkylzinc halides are not suitable cross-coupling partners.
15. Under our standard reaction conditions, essentially no cross-coupling is observed when (*o*-tol) $_2\text{Zn}$  is employed as the nucleophile.
16. The cross-coupling proceeds in high ee, but somewhat slowly, at  $-78^\circ\text{C}$ .
17. Under our standard reaction conditions, divinylzinc cross-couples in 55% ee and 80% yield.
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21. It is possible that, in the case of certain activated electrophiles, oxidative addition may not proceed via an initial  $\text{S}_{\text{H}}2$ -like abstraction of the halide by nickel to generate an alkyl radical.

Table 1











Stereoconvergent Negishi Phenylation of a Racemic  $\alpha$ -Bromonitrile: Effect of Reaction Parameters<sup>a</sup>

entry	variation from the "standard" conditions	ee (%)	yield (%) <sup>b</sup>
1	none	94	98
2	no $\text{NiCl}_2 \cdot \text{glyme}$	–	<2
3	no <b>L</b>	<2	3
4	$\text{PhZnX}$ , instead of $\text{Ph}_2\text{Zn}$	90	6
5	r.t., instead of $-78$ °C	4	16
6	<b>1</b> , instead of <b>L</b>	84	89
7	<b>2</b> , instead of <b>L</b>	8	88
8	<b>3</b> , instead of <b>L</b>	8	32
9	<b>4</b> , instead of <b>L</b>	32	25
10	0.6 equiv $\text{Ph}_2\text{Zn}$	93	48
11	5% $\text{NiCl}_2 \cdot \text{glyme}$ , 6.5% $(S,S)\text{-L}$	93	68

<sup>a</sup>All data are the average of two experiments.<sup>b</sup>Yield determined by GC analysis versus a calibrated internal standard.

Table 2

Stereoconvergent Negishi Phenylations of Racemic  $\alpha$ -Bromonitriles<sup>a</sup>

entry	R <sup>1</sup>	ee (%)	yield (%) <sup>b</sup>
1	<i>i</i> -Pr	92	77
2		92	98
3		92	92
4 <sup>c</sup>		92	92
5		92	94
6		90	96
7		85	95
8		91	94
9		90	94
10	Me	82	67 (83) <sup>d</sup>
11		78	88
12		76	94

<sup>a</sup>All data are the average of two experiments.<sup>b</sup>Yield of purified product.<sup>c</sup>Reaction temperature: -60 °C.<sup>d</sup>Yield determined by GC analysis versus a calibrated internal standard.

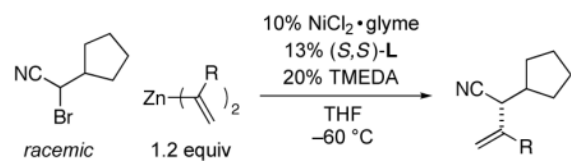


**Table 3**Stereoconvergent Negishi Arylations of Racemic Bromonitriles<sup>a</sup>

entry	Ar	ee (%)	yield (%) <sup>b</sup>
1		94	94
2		94	92
3		94	81
4 <sup>c</sup>		93	99

<sup>a</sup> All data are the average of two experiments.<sup>b</sup> Yield of purified product.<sup>c</sup> Reaction temperature: -60 °C.

Table 4

Stereoconvergent Negishi Alkenylations of Racemic  $\alpha$ -Bromonitriles<sup>a</sup>

entry	R	ee (%)	yield (%) <sup>b</sup>
1	(CH <sub>2</sub> ) <sub>3</sub> Ph	80	64
2		86	59
3		89	78
4	Ph	91	94
5		92	92

<sup>a</sup>All data are the average of two experiments.<sup>b</sup>Yield of purified product.