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Asymmetric Suzuki Cross-Couplings of Activated Secondary Alkyl Electrophiles: Arylations of Racemic α-Chloroamides

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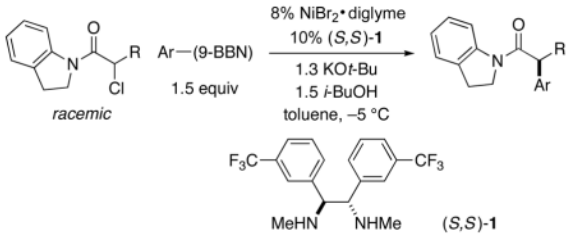
Abstract



A nickel-catalyzed stereoconvergent method for the enantioselective Suzuki arylation of racemic α-chloroamides has been developed. This process represents the first example of an asymmetric arylation of an α-haloamide, of an enantioselective arylation of an α-chlorocarbonyl compound, and of an asymmetric Suzuki reaction with an activated alkyl electrophile or an arylboron reagent. The method is also applicable to the corresponding enantioselective cross-coupling of α-bromoamides. The coupling products can be transformed without racemization into useful enantioenriched α-arylcarboxylic acids and primary alcohols. An unprecedented (and modest) kinetic resolution of the α-chloroamide has been observed; a mechanistic study indicates that the selectivity likely reflects the discrimination by the chiral catalyst of the two enantiomeric α-chloroamides in an irreversible oxidative-addition process.

Enantioenriched α-arylcarboxylic acids that bear a tertiary α stereocenter, including arylpropionic acids such as naproxen, serve as important therapeutics as well as useful intermediates in organic synthesis.[1,2] Although the cross-coupling of enolates with aryl electrophiles has not yet proved to be a viable route to the generation of such compounds,[3] a few reports have described the umpolung approach, i.e., the coupling of an α-halocarbonyl compound with an aryl nucleophile. Whereas organozinc,[4] organosilicon,[5] and organomagnesium[6] reagents have been employed in such processes (with α-bromoketones and α-bromoesters), organoboron compounds have not.[7,8,9,10] In this report, we establish that a chiral nickel catalyst can achieve asymmetric cross-couplings of arylboron reagents with racemic α-haloamides to generate tertiary α-arylcarbonyl compounds in good ee (eq 1).

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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.

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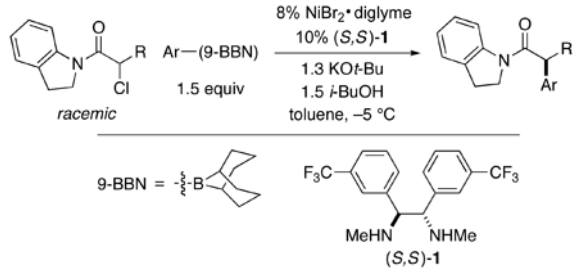
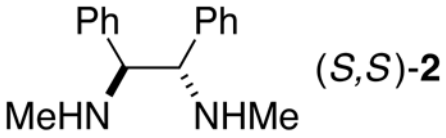


(1)

After surveying an array of reaction parameters, we determined that $NiBr_2 \cdot$ diglyme/**1** can catalyze the cross-coupling of an α-chlorobutyramide with Ph-(9-BBN) in good ee and yield (entry 1 of Table 1). The cross-coupling illustrated in entry 1 is noteworthy in part because there are no previous examples of enantioselective arylations of α-haloamides, of asymmetric Suzuki reactions of activated alkyl electrophiles or arylboron[11] reagents, or of enantioselective arylations of α-chlorocarbonyl compounds.[12] Both $NiBr_2 \cdot$ diglyme and ligand **1** are commercially available.

In the absence of $NiBr_2 \cdot$ diglyme, essentially no carbon–carbon bond formation is observed (entry 2 of Table 1), and, in the absence of ligand **1**, the cross-coupling proceeds very slowly (entry 3). If *i*-BuOH is omitted, the reaction is also sluggish (entry 4), and, if water is used in place of *i*-BuOH, the product is generated with good enantioselectivity, but modest yield (entry 5). The cross-coupling occurs with somewhat lower ee if ligand **2** is employed rather than ligand **1** (entry 6) or if it is conducted at room temperature (entry 7). Use of less catalyst leads to a slightly diminished yield (entry 8). A variety of other α-chloroamides (both tertiary and secondary), as well as an α-chloroester, are less suitable cross-coupling partners than the indolinylamide (entries 9–13).



Cross-couplings that illustrate the scope of this new stereoconvergent method for the synthesis of α-arylcarboxylic acid derivatives are provided in Table 2.[13] Functional groups such as an olefin and a silyl ether (entries 3 and 4), as well as β branching (entry 5), are tolerated in the alkyl side chain of the electrophile. For the nucleophile, a meta (entries 6 and 7) or a para (entries 8 and 9) substituent can be present, and it can be electron-withdrawing (entry 6) or electron-donating (entries 7 and 8). This asymmetric Suzuki cross-coupling proceeds with comparable efficiency on a gram scale, and the product amide can be recrystallized to >99% ee (entry 2 of Table 2: 92% ee and 88% yield before recrystallization; >99% ee and 70% yield after recrystallization).

This method for catalytic enantioselective carbon–carbon bond formation was developed and optimized for Suzuki arylations of α-chloroamides. Nevertheless, it can be applied without modification to a racemic α-bromoamide, providing comparable results (eq 2).

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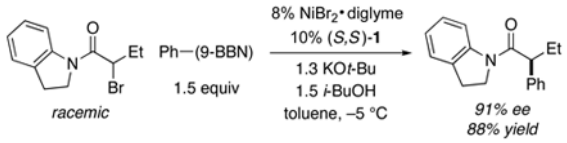
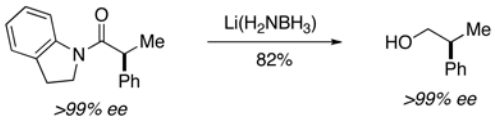
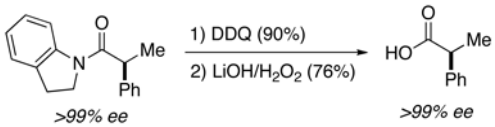


(2)

The products of these asymmetric cross-coupling reactions can be reduced to a primary alcohol (83%; eq 3) or converted into an α-arylcarboxylic acid (e.g., an arylpropionic acid; eq 4). No racemization is observed.

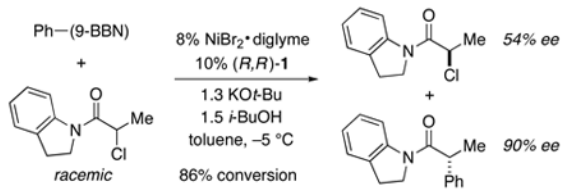


(3)



(4)

As for the other nickel-catalyzed enantioselective cross-couplings of alkyl electrophiles that have been described to date,[4–6,8a,14] this new asymmetric Suzuki reaction is also stereoconvergent: both enantiomers of the racemic starting material are converted preferentially into the same enantiomer of the product. However, in contrast to all of the other processes, in these Suzuki arylations the unreacted electrophile is kinetically resolved[15] with a significant ee (eq 5).[16]



(5)

Our observation that the recovered α-chloroamide is not racemic indicates that the enantiopure catalyst has the ability to differentiate between the two enantiomers of the starting material. The moderate ee of the unreacted electrophile even at high conversion could be due to modest differentiation of the enantiomers by the chiral catalyst, or it could result from excellent discrimination, but some reversibility, in the oxidative addition to nickel.[17]

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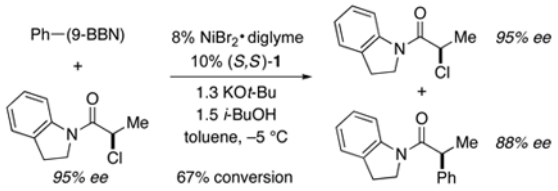
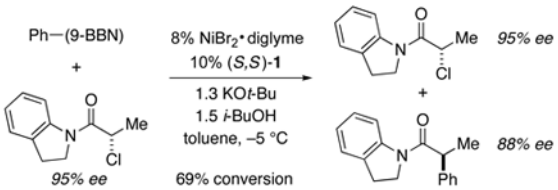
In order to gain insight into this issue, we examined the Suzuki arylation of the individual enantiomers of the α-chloroamide (eq 6 and eq 7). For both cross-couplings, the ee of the unreacted electrophile at partial conversion is essentially unchanged, consistent with irreversible oxidative addition under the reaction conditions. Consequently, the ee observed in eq 5 for the recovered α-chloroamide likely reflects the inherent selectivity of the chiral catalyst toward the two enantiomers of the electrophile in the oxidative-addition step of the catalytic cycle (selectivity factor ~1.8).

The data in eq 6 and eq 7 illustrate that $NiBr_2$· diglyme/(*S*,*S*)-**1** transforms each enantiomer of the α-chloroamide into the same enantiomer of the product with essentially identical ee. This confirms the dominant role played by the chirality of the catalyst, rather than the substrate, in determining the ee of the product.



(6)



(7)

In conclusion, we have developed a nickel-catalyzed stereoconvergent method for the enantioselective Suzuki arylation of racemic α-chloroamides that employs commercially available catalyst components ($NiBr_2$· diglyme and ligand **1**). This process represents the first example of an asymmetric arylation of an α-haloamide, of an enantioselective arylation of an α-chlorocarbonyl compound, and of an asymmetric Suzuki reaction with an activated alkyl electrophile or an arylboron reagent. The method is also applicable to the corresponding enantioselective cross-coupling of α-bromoamides. The coupling products can be transformed without racemization into useful enantioenriched α-arylcarboxylic acids and primary alcohols. An unprecedented (and modest) kinetic resolution of the α-chloroamide has been observed; a mechanistic study indicates that the selectivity likely reflects the discrimination by the chiral catalyst of the two enantiomeric α-chloroamides in an irreversible oxidative-addition process. Further efforts to develop catalytic asymmetric methods for cross-coupling alkyl electrophiles, as well as additional mechanistic studies, are underway.

Supplementary Material

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11. Although asymmetric Suzuki reactions of arylboron reagents with *alkyl* electrophiles have not previously been reported, enantioselective cross-couplings with *aryl* electrophiles have been described. For leading references, see Reference 8b.
12. For examples of reports that α-chlorocarbonyl compounds are not suitable cross-coupling partners in other enantioselective arylation processes, see footnote 16a of Reference 4 and footnote 16c of Reference 6.
13. Notes: (a) The ee of the product is essentially constant throughout the course of the reaction. (b) In preliminary studies under our standard conditions, the following compounds were not effective cross-coupling partners: an alkyl-(9-BBN), an alkenyl-(9-BBN), and an ortho-substituted aryl-(9-BBN); $PhB(OH)_2$ and $PhB(OR)_2$; the α-chloroamide with an α-*i*-Pr substituent.
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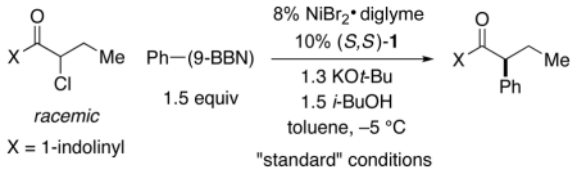
Table 1

Effect of Some Reaction Parameters on the Asymmetric Suzuki Arylation of a Racemic α-Chloroamide.



entry	variation from the “standard” conditions	ee (%)	yield (%)[a]
1	none	92	89
2	no $NiBr_2$·glyme	–	<2
3	no (*S*,*S*)-**1**	–	8
4	no *i*-BuOH	–	8
5	water, instead of *i*-BuOH	91	25
6	(*S*,*S*)-**2**, instead of (*S*,*S*)-**1**	85	74
7	r.t.	82	84
8	4% $NiBr_2$· glyme, 5% (*S*,*S*)-**1**	91	78
9	X = NBnPh	–	6
10	X = NPh_2	–	4
11	X = NEt_2	76	19
12	X = NMe(OMe)	<5	84
13	X = NHMe	26	82
14	X = OEt	50	74

All data are the average of two experiments.

[a]The yield was determined by GC or ^{1}H NMR analysis versus an internal standard.

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Table 2

Asymmetric Suzuki Arylations of α-Chloroamides (see eq 1).

entry	R	Ar	ee (%)	yield (%)[a]
1	Et	Ph	92	78
2	Me	Ph	87	88
3	$CH_2CH=CH_2$	Ph	90	80
4	CH_2CH_2OTBS	Ph	84	80
5	*i*-Bu	Ph	85	84
6[b]	Et	3-ClC_6H_4	92	76
7	Et	3-MeC_6H_4	92	84
8	Et	4-$OMeC_6H_4$	90	80
9	Et	4-FC_6H_4	94	70

All data are the average of two experiments.

[a] Yield of purified product.

[b] 10% $NiBr_2$ · diglyme and 12.5% (*S*,*S*)-**1** were used.