Enantioconvergent Cross–Couplings of Alkyl Electrophiles: The Catalytic Asymmetric Synthesis of Organosilanes

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Abstract

Metal-catalyzed enantioconvergent cross-coupling reactions of alkyl electrophiles are emerging as a powerful tool in asymmetric synthesis. To date, high enantioselectivity has been limited to couplings of electrophiles that bear a directing group or a proximal p/π orbital. In this report, we demonstrate for the first time that enantioconvergent cross-couplings can be achieved with electrophiles that lack such features; specifically, we establish that a chiral nickel catalyst can accomplish Negishi reactions of racemic α-halosilanes with alkylzinc reagents with good enantioselectivity under simple and mild conditions, thereby providing access to enantioenriched organosilanes, an important class of target molecules.

Graphical Abstract
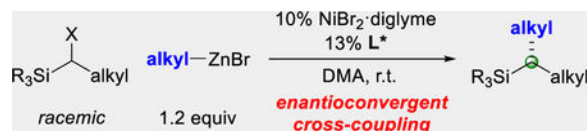
For the first time, enantioconvergent cross-couplings can be achieved with electrophiles that lack a directing group or a proximal p/π orbital. Specifically, a chiral nickel catalyst can accomplish Negishi reactions of racemic α-halosilanes with alkylzinc reagents with good enantioselectivity under simple and mild conditions, thereby providing access to enantioenriched organosilanes, an important class of target molecules.

Keywords

alkylation; asymmetric catalysis; cross-coupling; nickel; silicon

Significant progress has been described in the development of methods for the synthesis of carbon–carbon bonds through enantioconvergent substitution reactions of racemic alkyl electrophiles with carbon nucleophiles.[1–3] To date, high enantioselectivity has only been
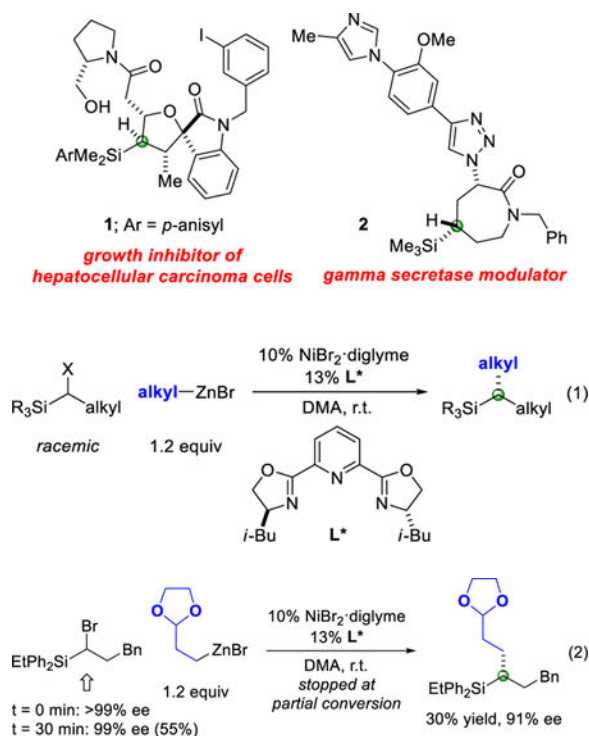
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observed in cross-couplings wherein the electrophile bears either a directing group (**A**) or a p/π orbital proximal to the leaving group (**B**) (Figure 1).[4]

We have been interested in expanding the scope of enantioconvergent cross-couplings to include electrophiles that lack either of the features illustrated in **A** and **B** (Figure 1). An example of such an electrophile is α-halosilane **C**,[5,6] enantioconvergent cross-coupling of which would provide chiral organosilanes. Chiral organosilanes (e.g., **1**[7] and **2**[8]) are of interest in fields such as medicinal chemistry, since replacement of carbon with silicon can lead to improved pharmacological properties (e.g., enhanced lipophilicity and potency) without element-specific toxicity due to the presence of silicon;[9] to date, there are limited methods for the direct catalytic asymmetric synthesis of such organosilanes.[10,11] In this report, we establish that a chiral nickel catalyst can achieve the asymmetric synthesis of organosilanes via the cross-coupling of racemic α-halosilanes with alkylzinc reagents under simple and mild conditions [Eq. (1)], thereby demonstrating that enantioconvergent cross-couplings are possible with electrophiles that lack both a directing group and a proximal p/π orbital (Figure 1).

1; Ar = *p*-anisyl

growth inhibitor of hepatocellular carcinoma cells

2

gamma secretase modulator

Upon examining a range of reaction parameters, we determined that NiBr$_2$·diglyme and a chiral pybox ligand (**L***) can accomplish the enantioconvergent Negishi cross-coupling illustrated in Table 1 in good yield and high *ee* (78% yield, 92% *ee*; entry 1). In the absence of NiBr$_2$·diglyme, virtually no carbon–carbon bond formation is observed (entry 2), whereas in the absence of ligand **L***, the coupling proceeds in low yield (entry 3). When the reaction is run under an atmosphere of air or in the presence of water, formation of product is inefficient, although the *ee* is good (entries 4 and 5). Other ligands, including representative examples of classes of ligands that have been useful in other nickel-catalyzed
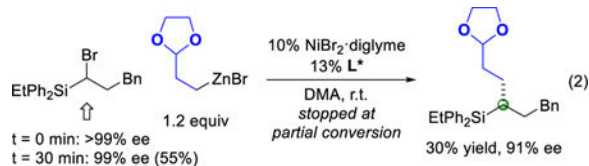
enantioconvergent cross-couplings,[1] are less effective than ligand **L*** (entries 6–9). Although the corresponding alkyl iodide cross-couples with fairly good yield and *ee* under these conditions (entry 10), use of the alkyl chloride leads to essentially no carbon–carbon bond formation (entry 11). A lower catalyst loading can be employed with only a small loss in yield and no loss in enantioselectivity (entry 12).

α-Bromosilanes that bear a variety of functional groups serve as suitable electrophiles in these nickel-catalyzed enantioconvergent cross-couplings (Table 2). Thus, an alkene, ether, or an aryl chloride, as well as a saturated or an unsaturated oxygen or nitrogen heterocycle, can be present, with little impact on *ee*. Although branching in the α position of the alkyl group of the electrophile inhibits cross-coupling, branching in the β position is tolerated (entries 7–9). The enantioconvergent coupling proceeds with an array of substituents on silicon, with lower yields observed as the steric demand of the electrophile increases (entries 11–14).[12]

Organozinc reagents that include various functional groups, such as an alkyl fluoride, an ether, a nitrile, and an ester, can be employed as nucleophiles in these nickel-catalyzed enantioconvergent cross-couplings (entries 1–5 of Table 3). The cross-coupling is sensitive to steric effects–while branching at the γ position is tolerated (entry 6), little carbon–carbon bond formation occurs if there is branching at the α or the β position. On a gram scale, the coupling illustrated in entry 2 proceeds in 88% *ee* and 89% yield (1.66 g of product).[13]

Our working hypothesis is that this process may be following a pathway analogous to that elucidated for nickel/pybox-catalyzed enantioconvergent Negishi arylations of propargylic halides, wherein nickel complex **C** is the predominant resting state of nickel during catalysis, and complexes **A**, **B**, and **D** do not accumulate (Figure 2).[14] Consistent with this suggestion, ESI–MS analysis of a cross-coupling (the model reaction in Table 1) at partial conversion reveals a strong signal at m/z = 488.2, consistent with the presence of [L*Ni–R^1]$^+$ (**C** in Figure 2; R^1 = 2-(1,3-dioxolan-2-yl)ethyl; exact mass: 488.2). Similarly, the EPR spectrum of a reaction at partial conversion indicates that odd-electron nickel intermediates such as **A** or **D** do not accumulate to a significant (>2%) extent.

An enantioenriched α-bromosilane does not racemize under the standard conditions [Eq. (2)],[15,16] indicating that C–Br bond cleavage is irreversible and that the chiral catalyst is processing both enantiomers of the electrophile in the stereoconvergent coupling of a racemic electrophile (no dynamic kinetic resolution). When an enantioconvergent cross-coupling of a racemic electrophile is stopped at partial conversion, the unreacted electrophile is still racemic, indicating that the chiral catalyst is not discriminating between the enantiomeric electrophiles (no kinetic resolution).[17]

Thus, we have expanded the scope of enantioconvergent cross-couplings beyond electrophiles that bear a directing group or a p/π orbital proximal to the leaving group. Specifically, we have determined that a chiral nickel/pybox catalyst can achieve stereoconvergent cross-couplings of racemic α-bromosilanes with alkylzinc reagents under simple and mild conditions to afford enantioenriched organosilanes, a useful family of target compounds. Our mechanistic observations indicate that the chiral catalyst reacts with both enantiomers of the electrophile, without kinetic resolution, to provide the enantioenriched product via irreversible C–Br bond cleavage. This work sets the stage for substantial enlargement of the range of racemic electrophiles that can be employed in enantioconvergent cross-couplings, free of the need for a directing group or p/π conjugation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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[10]. For examples of early studies of the catalytic asymmetric synthesis of related chiral silanes (two alkyl substituents on the stereogenic carbon that bears silicon), see: a) 1,4-addition to α,β-unsaturated carbonyl compounds: Hayashi T, Matsumoto Y, Ito Y, J. Am. Chem. Soc 1988, 110, 5579–5581b) hydrosilylation of olefins: Uozumi Y, Hayashi T, J. Am. Chem. Soc 1991, 113, 9887–9888.

[11]. For recent examples of (and leading references to) the catalytic asymmetric synthesis of related chiral silanes (two alkyl substituents on the stereogenic carbon that bears silicon), see: a) hydrosilylation of olefins: Cheng B, Liu W, Lu Z, J. Am. Chem. Soc 2018, 140, 5014–5017 [PubMed: 29589919] b) hydrogenation of vinylsilanes: Wang A, Bernasconi M, Pfaltz A, Adv. Synth. Catal 2017, 359, 2523–2529.

[12]. Notes: (a) For the electrophile illustrated in entry 12 of Table 2, when Si is replaced with C, essentially no cross-coupling is observed under our standard conditions.

[13]. When PhZnBr in THF is employed as the nucleophile, under otherwise identical conditions, essentially no cross-coupling is observed.

[14]. Schley ND, Fu GC, J. Am. Chem. Soc 2014, 136, 16588–16593. [PubMed: 25402209]

[15]. Consistent with the hypothesis that an organic radical is an intermediate in these nickel-catalyzed cross-couplings, the model reaction (Table 1) does not proceed (<1% yield) in the presence of TEMPO (0.4 equiv).

[16]. For an example of isomerization of the electrophile in a nickel-catalyzed enantioconvergent cross-coupling of an alkyl halide, see: Mu X, Shibata Y, Makida Y, Fu GC, Angew. Chem. Int. Ed 2017, 56, 5821–5824; Angew. Chem. 2017, 129, 5915–5918.

[17]. For an example of kinetic resolution of the electrophile in a nickel-catalyzed enantioconvergent cross-coupling of a racemic alkyl halide, see: Lundin PM, Fu GC, J. Am. Chem. Soc 2010, 132, 11027–11029. [PubMed: 20698665]

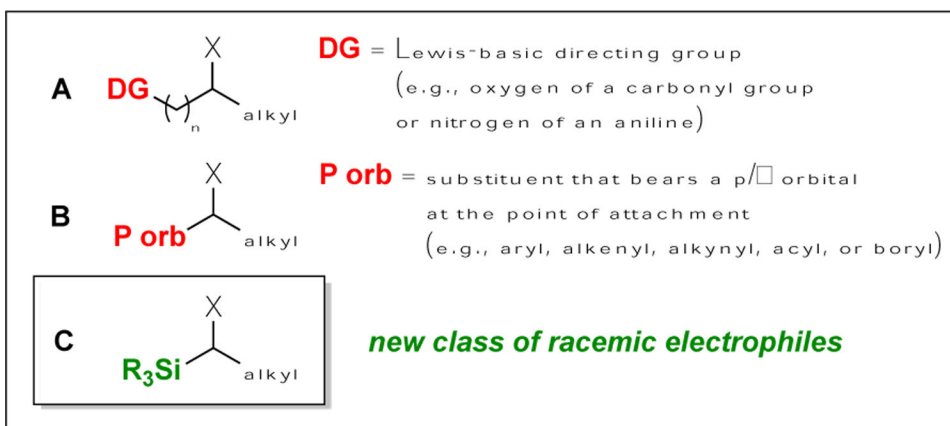**Figure 1.**
Background: Racemic electrophiles used in enantioconvergent cross-couplings. **A** and **B**:
Prior work. **C**: This study.

L*XNi^I

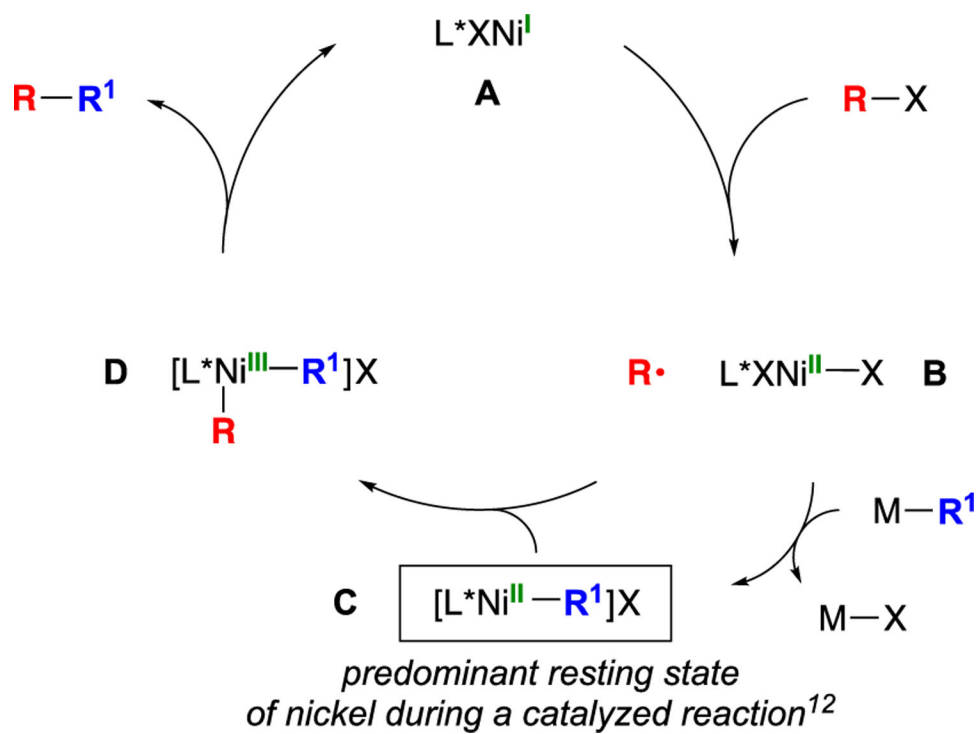**A**

R—R^1

R—X

D [L*Ni^{III}—R^1]X

R

R·   L*XNi^{II}—X   **B**

M—R^1

C   [L*Ni^{II}—R^1]X

M—X

predominant resting state
of nickel during a catalyzed reaction[12]

Figure 2.
Outline of a possible mechanism.

Table 1.

Effect of Reaction Parameters.

entry	variation from the "standard" conditions	yield (%)^a	ee (%)
1	none	78	92
2	no NiBr$_2$·diglyme	<1	–
3	no L*	16	–
4	under air (capped vial)	12	88
5	H$_2$O (0.05 equiv) added	38	90
6	L1, instead of L*	55	74
7	L2, instead of L*	30	<5
8	L3, instead of L*	8	<5
9	L4, instead of L*	<1	–
10	alkyl–I, instead of alkyl –Br	61	88
11	alkyl–Cl, instead of alkyl–Br	<1	–
12	5% NiBr$_2$·diglyme, 6.5% L*	62	92

^{a} The yield was determined via GC analysis versus an internal standard (average of two experiments).
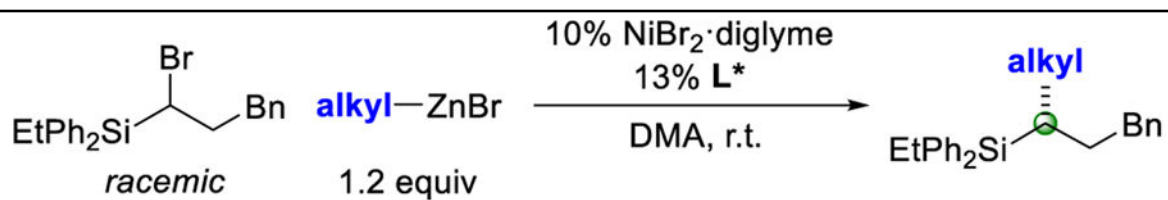
Table 2.

Scope with Respect to the Electrophile.

entry	electrophile		ee (%)	yield (%)[a]
1	EtPh₂Si, Br, n-pentyl		90	64
2	EtPh₂Si, Br, (benzyl)		94	65
3	EtPh₂Si, Br, (allyl)		91	54
4	EtPh₂Si, Br, (p-X-phenyl)	X = H	93	74
5		OMe	92	86
6		Cl	91	55
7	EtPh₂Si, Br, (4-X-cyclohexyl)	X = CH₂	90	59
8		O	91	68
9		NBoc	90	68
10	EtPh₂Si, Br, (5-Me-furyl)		90	72
11	R₃Si, Br, (phenethyl)	R₃Si = SiMePh₂	85	80
12		SiMe₃	85	80
13		SiEt₃	90	50
14		Si(t-Bu)Me₂	84	25

[a] Yield of purified product (average of two experiments).

Table 3.

Scope with Respect to the Nucleophile.

entry	alkyl—ZnBr	ee (%)	yield (%)[a]
1	F⌒⌒⌒⌒ZnBr	87	56
2	PhO⌒⌒⌒ZnBr	88	80
3	TBSO⌒⌒⌒ZnBr	88	69
4	NC⌒⌒⌒ZnBr	87	50
5	EtO₂C⌒⌒⌒⌒⌒ZnBr	87	59
6	Me₂CH⌒⌒ZnBr (Me / Me)	91	66

[a] Yield of purified product (average of two experiments).