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Retention or Inversion in Stereospecific Nickel-Catalyzed Cross-Coupling of Benzylic Carbamates with Arylboronic Esters: Control of Absolute Stereochemistry with an Achiral Catalyst

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Abstract

Stereospecific coupling of benzylic carbamates and pivalates with aryl- and heteroarylboronic esters has been developed. The reaction proceeds with selective inversion or retention at the electrophilic carbon depending on the nature of the ligand. Tricyclohexylphosphine ligand provides product with retention, while an NHC ligand provides product with inversion.

The mechanisms of alkyl cross-coupling reactions are hardwired with implications for the stereochemical outcome at the reactive centers.[1] Simple changes to the reaction conditions do not typically perturb the inherent bias for racemization, retention, or inversion at the reactive centers. For example, palladium-catalyzed reactions of alkyl electrophiles are typically stereospecific and proceed with inversion at the stereogenic center,[2,3] while nickel-catalyzed reactions of alkyl halides proceed with racemization at the electrophilic carbon[4] and judicious use of chiral catalyst permits stereoconvergent reactions.[5] Overcoming the intrinsic preference, such that a reaction that typically proceeds with inversion at the stereogenic center can proceed with retention is quite unusual, and requires a significant change to the mechanism of the transformation. For stereospecific reactions, special cases using α-chiral *transmetallating agents* have been reported where modification of reaction conditions or substrate structure can affect a switch in the sense of absolute stereochemistry.[6] Transmetallation typically occurs with retention at the stereogenic center;[7,8] select examples that proceed with inversion have been reported.[9] In seminal contributions, Hiyama demonstrated that palladium-catalyzed couplings of alkylsilanes could proceed with retention or inversion, depending on the reaction conditions.[10] Recently, the Suginome group has developed stereodivergent reactions of α-(acetylamino)benzylboronic esters that are controlled by choice of additive to afford, selectively, either retention or inversion (Scheme 1a).[11,12]

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ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data, including X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

No competing financial interests have been declared.

[‡]Contributing author solved X-ray structure of compound **(S)-Table 2, entry 19**.

In this communication, we demonstrate catalyst control of the stereochemical course with respect to the *electrophilic* partner in a cross-coupling reaction. Stereospecific nickel-catalyzed cross-coupling reactions of benzylic alcohol derivatives typically proceed with inversion at the electrophilic carbon.[13,14] In this manuscript we report nickel-catalyzed cross-coupling of benzylic esters where the achiral ligand structure dictates whether the reaction proceeds with retention or inversion (Scheme 1b). Use of SIMes, an N-heterocyclic carbene (NHC) ligand, affords inversion, while PCy_3 gives retention. To the best of our knowledge, these results constitute the first cross-coupling reactions of alkyl electrophiles that undergo two distinct stereospecific mechanistic pathways to provide either retention or inversion at the electrophilic carbon.

In previous work, we established synthesis of enantioenriched triarylmethanes by stereospecific nickel-catalyzed cross-coupling of ethers with aryl Grignard reagents.[13b] The triarylmethane moiety is present in medicinal chemistry targets, natural products, and synthetic materials.[15,16] Despite recent advances in the preparation of racemic triarylmethanes,[17] there are few methods for their enantioselective synthesis.[18] As part of our ongoing interest in developing nickel-catalyzed stereospecific reactions of alkyl electrophiles, we chose to examine cross-coupling reactions of arylboronic esters for triarylmethane synthesis. The functional group tolerance and ready availability of a wide range of boronic esters makes them attractive coupling partners.

We began by examining a range of benzylic alcohol derivatives (Table 1). Our initial reaction conditions resulted in a modest conversion of carbonate **(S)-3** and low enantiospecificity (es; entry 1).[19] To our surprise, in contrast to the Kumada coupling, the product, **(R)-2**, results from *retention* at the electrophilic carbon. An improvement to 43% es was observed when the solvent was changed from toluene to THF (entry 2). Alcohol additives further improved the yield and stereo-chemical fidelity of the reaction, with *n*-BuOH providing the highest es, 87% (entry 4). More sterically encumbered alcohols provided more modest improvements, while water and the electron-deficient alcohol trifluoroethanol proved detrimental to the reaction (entries 3, 5, and 7). The enantiospecificity of the reaction showed a marked dependence on the identity of the leaving group. While the use of pivalate **(S)-4** in the cross-coupling reaction resulted in lower enantiomeric excess of the product (entry 8), the benzoate and carbamate derivatives **(S)-5** and **(S)-1** showed a significant increase in product ee, providing 91 and 95% es, respectively (Table 1, entries 8, 10, and 12). An additional small improvement in yield and es resulted from using a 1:1 mixture of THF:toluene as the solvent (c.f. entries 12 and 15).

We examined other ligands[20] under the reaction conditions and found that the NHC ligand SIMes[21] afforded comparable yields and enantiospecificity of **2**, however, the major product was the (*S*)-enantiomer, resulting from *inversion* at the electrophilic carbon.[22] Catalyst-control of the stereochemical outcome of the reaction was consistent across the range of esters and carbamates that we examined: PCy_3 and SIMes reliably afforded opposite enantiomers of product (entries 8–11, 15 and 16).[23] Under the optimal reaction conditions conditions, addition of *n*-BuOH was found to improve stereochemical fidelity when using either ligand (c.f. entries 13–16).

Having optimized reaction conditions for stereospecfic synthesis of either enantiomer of product, we turned our attention to the scope of the reaction with respect to the boronic ester (Table 2). Electron donating and withdrawing substituents on the arylboronic ester are well tolerated under the reaction conditions (entries 1–8), which are mild and allow for broad functional group tolerance. Boronic esters containing ketone, free alcohol and carbamate functional groups all couple in good yield and es (entries 9–14). Heterocyclic boronic esters including pyrimidine, furan, and indole underwent smooth cross-coupling (entries 15–20).

The reaction conditions developed for the formation of either enantiomer of **2** are general across the range of boronic esters that we examined: of 20 examples, 18 provide high es. Therefore, by choosing the appropriate ligand, PCy_3 or SIMes, either enantiomer of a given product can be obtained from the same enantiomer of starting material.

We set as our goal the cross-coupling of oxidative additon partners that do not include a naphthylene moiety. These electrophiles are typically less reactive in cross-coupling reactions,[13c] and were not competent for triarylmethane synthesis via Kumada coupling.[13b] Indeed, neither the corresponding carbamates nor the use of PCy3 as ligand provide acceptable yields of product. However, benzhydril pivalates undergo smooth cross-coupling under our optimized reaction conditions when SIMes is utilized as the ligand (Table 3). Efficient cross-coupling is achieved for pivalates with a range of arylboronic esters (entries 1–4). Functionality is also tolerated on the electrophile: furan and benzodioxane substituted pivalates couple in good yield and excellent es (entries 5 and 6).

In summary, we have developed a nickel-catalyzed Suzuki-Miyaura cross-coupling reaction for the synthesis of enantioenriched triarylmethanes. Reactions proceed with high stereochemical fidelity. Achiral ligand identity controls whether the reaction proceeds with inversion or retention at the electrophilic carbon, therefore either enantiomer of product can be formed from a single enantiomer of starting material. This method expands the range of triarylmethanes that may be prepared in enantioenriched form, as simple benhydril pivalates and a variety of functionalized arylboronic esters, including heterocyclic compounds can be used in the reaction. Efforts to further expand the scope of the reaction and elucidate the mechanistic details are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Funding Sources

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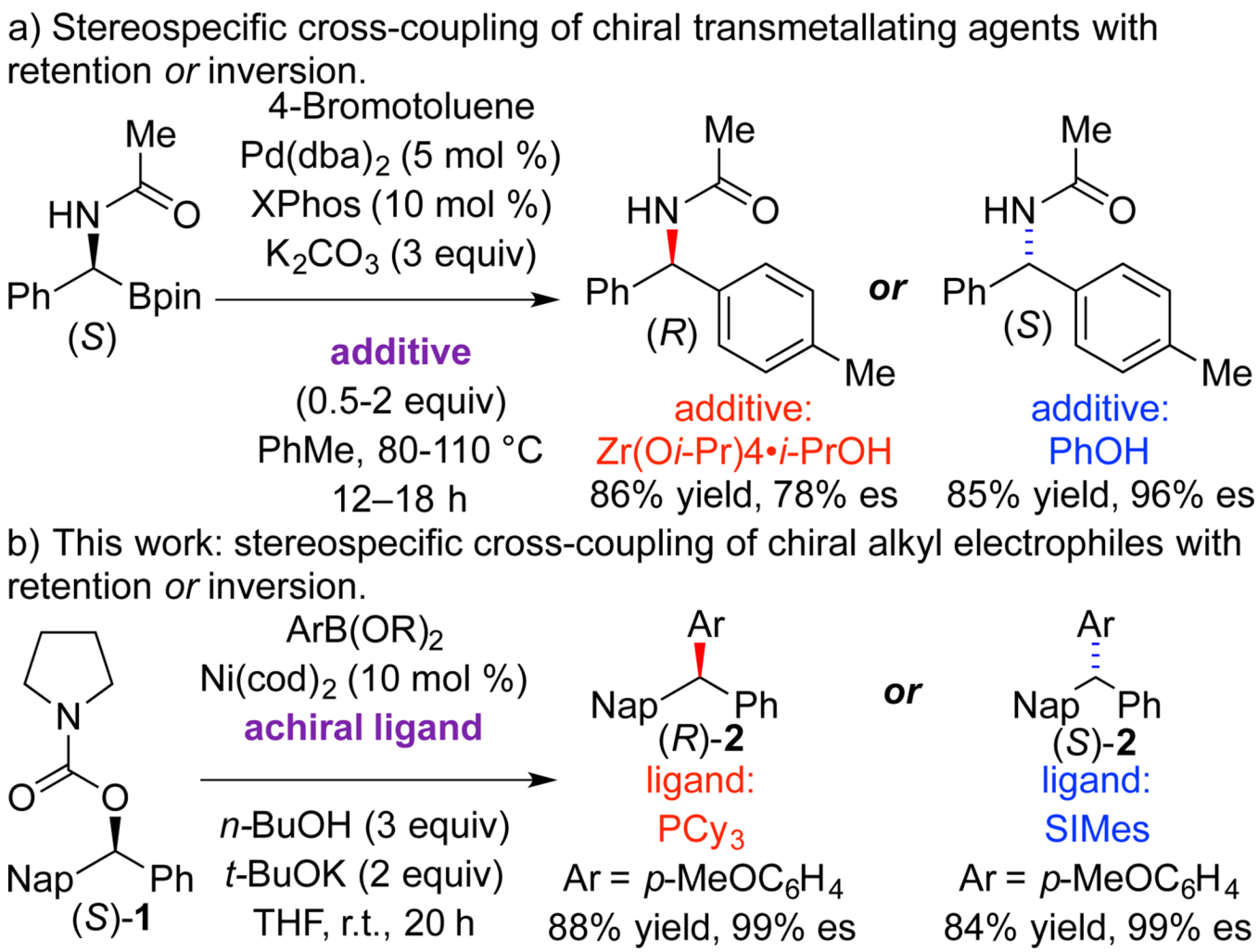
19. Es: Denmark SE, Vogler T. Chem.–Eur. J. 2009; 15:11737. [PubMed: 19760721]
20. For results with other ligands, see the SI.
21. SIMes = (1,3-Bis(2,6-diisopropylphenyl)-4,5-di-hydroimidazoliumtetrafluoroborate

22. We hypothesize ligation of the carbamate to the nickel complex directs oxidative addition when PCy3 is employed; see SI Scheme SI4. Comparison of NHC to PR_3: Clavier H, Nolan SP. Chem. Commun. 2010; 46:841.

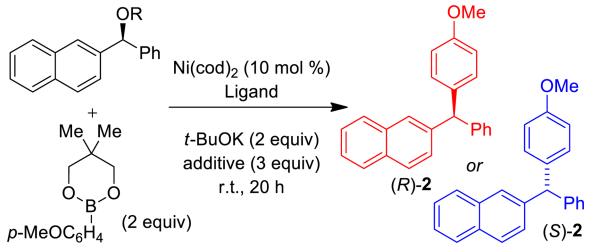
23. Changing PCy_3 loading from 20 mol % to 11 mol % does not affect the stereochemical outcome; see SI.

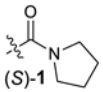


Scheme 1.
Control of product stereochemistry in stereospecific reactions

Table 1

Optimization of reaction conditions.



Entry	R	ligand[a]	solvent	additive	%yield[b]	es[c]	retention/ inverson
1	 (*S*)-**3**	PCy_3	PhMe	none	46	7	retention
2		PCy_3	THF	none	53	43	retention
3		PCy_3	THF	H_2O	74	10	retention
4		PCy_3	THF	*n*-BuOH	76	87	retention
5		PCy_3	THF	*i*-ProH	46	78	retention
6		PCy_3	THF	*t*-BuOH	55	43	retention
7		PCy_3	THF	F_3CCH_2OH	<5	na	retention
8	 (*S*)-**4**	PCy_3	THF	*n*-BuOH	53	76	retention
9		SIMes	THF	*n*-BuOH	60	77	inversion
10	 (*S*)-**5**	PCy_3	THF	*n*-BuOH	57	91	retention
11		SIMes	THF	*n*-BuOH	83	>99	inversion
12	 (*S*)-**1**	PCy_3	THF	*n*-BuOH	62	95	retention
13		PCy_3	THF/PhMe	none	67	35	retention
14		SIMes	THF/PhMe	none	82	92	inversion
15		**PCy_3**	**THF/PhMe**	***n*-BuOH**	**88**	**99**	**retention**
16		**SIMes**	**THF/PhMe**	***n*-BuOH**	**84**	**99**	**inversion**

[a] PCy_3 (20 mol %), SIMes (11 mol %).

[b] Isolated yield after column chromatography.

[c] Enantiospecificity (es) = $ee_{product}/ee_{starting\ material} \times 100\%$.

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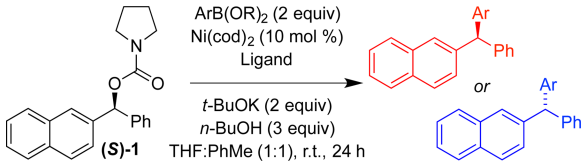
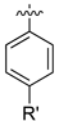
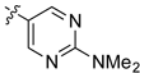
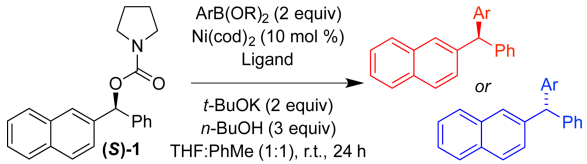
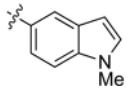
Table 2

Scope with respect to arylboronic ester.[a]



Entry	Ar	ligand[b]	yield (%)[c]	SM ee (%)[d]	product ee (%)[d]	es (%)	retention/ inversion
1	R' = OMe	PCy_3	88	93	92	98	retention
2	 OMe	SIMes	84	93	93	>99	inversion
3	NMe_2	PCy_3	86	93	92	99	retention
4	NMe_2	SIMes	71	93	92	98	inversion
5	F	PCy_3	82	93	90	97	retention
6	F	SIMes	80	97	88	91	inversion
7	CF_3	PCy3	88	97	57	59	retention
8	CF_3	SIMes	70	93	91	98	inversion
9	COMe	PCy_3	76	93	89	96	retention
10	COMe	SIMes	98	98	97	99	inversion
11	CH_2OH	PCy_3	67	93	82	88	retention
12	CH_2OH	SIMes	0	97	ND	ND	ND
13	CH_2NHBoc	PCy_3	84	93	91	98	retention
14	CH_2NHBoc	SIMes	94	98	97	97	inversion
15		PCy_3	86	93	89	96	retention
16[e]		SIMes	75	98	92	94	inversion
17		PCy_3	79	93	94	>99	retention
18		SIMes	65	98	83	85	inversion



Entry	Ar	ligand[b]	yield (%)[c]	SM ee (%)[d]	product ee (%)[d]	es (%)	retention/ inversion
19		PCy_3	90	93	93	99	retention
20		SIMes	71	93	92	98	inversion

[a] All data are average of two experiments unless other-wise indicated.

[b] PCy_3 (20 mol %), SIMes (11 mol %).

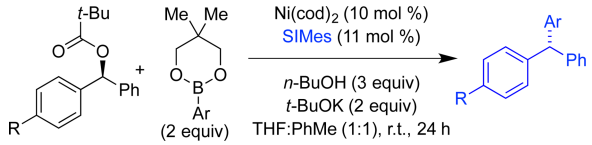
[c] Isolated yield after column chromatography.

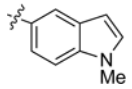
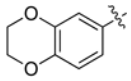
[d] Determined by chiral SFC chromatography.

[e] Data obtained from a single experiment.

Table 3

Scope of oxidative addition partner.[a]



Entry	R	Ar	yield (%)[b]	SM ee (%)[c]	product ee (%)[c]	es (%)
1	Ph	*p*-$MeOC_6H_4$	85	96	84	88
2	Ph	*p*-$(Me_2N)C_6H_4$	75	82	79	96
3	Ph	*p*-$(BocNHCH_2)C_6H_4$	54	98	92	94
4	Ph		66	96	96	>99
5			80	93	87	94
6			60	93	93	99

[a] All data are average of two experiments.

[b] Isolatedyield after column chromatography.

[c] Determined by chiral SFC chromatography.