

A General Approach to Stereospecific Cross-Coupling Reactions of Nitrogen-Containing Stereocenters

Xinghua Ma, Haoran Zhao, Meruyert Binayeva, Glenn Ralph, Mohamed Diane, Shibin Zhao, Chao-Yuan Wang, and Mark R. Biscoe*

Department of Chemistry & Biochemistry, The City College of New York, 160 Convent Ave., New York, NY 10031

Ph.D. Program in Chemistry, the Graduate Center of The City University of New York, 365 Fifth Ave., New York, NY 10016

Supporting Information Placeholder

ABSTRACT: A novel strategy employing cyclohexyl spectator ligands in Stille cross-coupling reactions has been developed as a general, unified approach to the long-standing challenge of conducting stereospecific cross-coupling reactions at nitrogen-containing stereocenters. This method enables direct access to enantioenriched products that are difficult (or impossible) to obtain via alternative preparative methods. Using reaction conditions that have been tuned to promote alkyl transmetalation from tin, and that exploit subtle electronic differences between activated and unactivated alkyl units, selective and predictable transfer of a single secondary alkyl unit can be achieved. Through this approach, enantioenriched α -stannylated nitrogen-containing stereocenters undergo Pd-catalyzed arylation and acylation reactions with exceptionally high stereofidelity in all instances investigated. We demonstrate this process using α -stannylated pyrrolidine and azetidine nucleophiles, as well as α -stannylated open-chain (benzylic and non-benzylic) nucleophiles in stereospecific arylation and acylation reactions. This process will facilitate rapid and reliable access to enantioenriched compounds possessing nitrogen-substituted stereocenters, which constitute ubiquitous structural motifs in biologically active compounds emerging from the drug discovery process. We further demonstrate the synthetic application of this method in the preparation of inhibitors of CDK8, which is proposed to act as an oncogene in the development of colorectal cancers. Our studies suggest that stereospecific cross-coupling reactions will likewise be achievable using other enantioenriched R_3Sn nucleophiles that bear an electronically differentiated alkyl unit. In addition to enabling highly selective and stereospecific alkyl transfer from tin, R_3Sn compounds offer the added practical benefits of lower toxicity and significantly higher crystallinity than their commonly used $\text{R}_3\text{Sn}^n\text{Bu}_3$ counterparts.

The biological properties of organic molecules are greatly influenced by the presence of nitrogen atoms within their molecular architectures.¹ Nitrogen-containing stereocenters are particularly common structural motifs within biologically active molecules that emerge from the drug discovery process. Indeed, four of the top five most commonly encoun-

tered nitrogen-containing heterocycles in FDA-approved drugs contain saturated rings, and therefore the possibility of stereoisomers.² When preparing such molecules, control of the absolute and relative stereochemistry of the nitrogen-containing stereocenter is a vital concern. Thus, the development of general synthetic strategies that enable precise stereochemical control of nitrogen-containing stereocenters constitutes an essential goal in organic chemistry.

Over the past decade, stereospecific cross-coupling strategies have emerged as viable synthetic options to achieve precise stereocontrol of carbon-carbon bonds.³⁻⁹ We, and others, have demonstrated that configurationally stable, enantioenriched organotin¹⁰⁻²² and organoboron²³⁻³⁷ may be employed in Pd-catalyzed cross-coupling reactions where transmetalation proceeds primarily through a stereoretentive or stereoinvertive mechanism, leading to predictable stereochemical outcomes (Figure 1a). Commonly, use of alkyl nucleophiles that bear specific modes of activation such as α - $\text{C}(\text{sp}^2)$ groups, α -heteroatoms, ring strain, and/or strongly coordinating substituents³⁸ are required to facilitate transmetalation of the intrinsically hindered, secondary alkyl centers (Figure 1b). Use of a highly electron-deficient electrophilic coupling partner (e.g., acyl electrophiles) can also be employed to render the palladium catalyst more electrophilic, thereby accelerating transmetalation.^{10,21} These activation effects are additive, with nucleophiles bearing multiple activation modes undergoing more rapid transmetalation than singly activated comparative systems. Commonly, specific combinations of these activation modes are required to facilitate transfer of secondary alkyl groups from alkyltin or alkylboron reagents to palladium.³ As a result, viable substrates are limited to those that possess the requisite structural features necessary for transmetalation in each specific system. Importantly, the stereochemical outcome of transmetalation (retentive vs. invertive) may also vary unpredictably between differently activated systems, resulting in eroded stereochemical transfer. In Suzuki cross-coupling reactions, minor electronic or structural perturbations of alkylboron nucleophiles have particularly unpredictable effects on stereochemical transfer.⁴ In contrast, studies of analogous alkylstannane reactions have revealed more consistently predictable stereochemical outcomes and broader substrate scopes, which suggests that use of

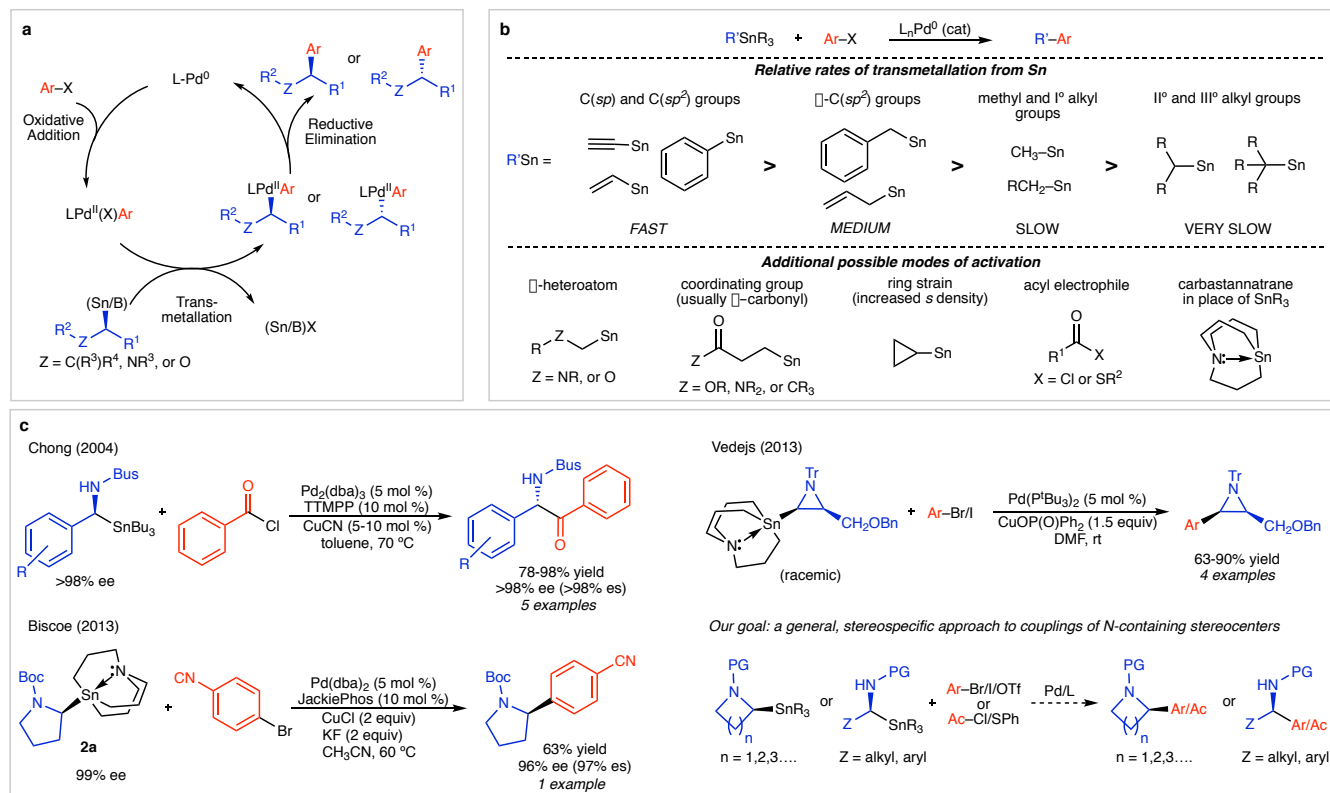


Figure 1. Stereospecific cross-coupling reactions of enantioenriched α -stannylated amines. **a**, Catalytic cycle for stereospecific Pd-catalyzed cross-coupling reactions involving enantioenriched alkyltin and alkylboron nucleophiles. **b**, Relative rates of group transfer from organotin compounds, and activation strategies. **c**, Prior examples of Pd-catalyzed Stille cross-coupling reactions involving the stereospecific transfer of a nitrogen-containing stereocenter.

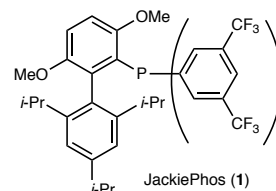
alkyltin nucleophiles may be more conducive to development of a broadly general method for the stereospecific cross coupling of nitrogen-containing stereocenters.³ Here, we report a new approach to stereospecific cross-coupling reactions involving only marginally activated alkyl nucleophiles. Using cyclohexyl spectator ligands in place of *n*-butyl spectator ligands on alkylstannane nucleophiles (e.g., $R'SnCy_3$ instead of $R'Sn^tBu_3$), we have developed conditions that promote the stereospecific transfer and cross coupling of nitrogen-containing carbon stereocenters. We demonstrate this process using α -stannylated pyrrolidine and azetidine heterocyclic nucleophiles, as well using α -stannylated open-chain (benzylic and non-benzylic) nucleophiles in Pd-catalyzed cross-coupling reactions. In these reactions, the electronic properties of the nitrogen-protecting group greatly influence the selectivity of alkyl transfer from the organostannane nucleophile. Using our conditions, nitrogen-containing carbon stereocenters undergo stereospecific arylation and acylation reactions with net stereoretention of absolute configuration. This process enables the first cross-coupling reaction using an azetidine nucleophile, and constitutes the first general cross-coupling method to enable stereospecific transfer of nitrogen-containing stereocenters in a highly reliable and predictable manner. These results also suggest that use of cyclohexyl spectator ligands will be broadly applicable in stereospecific coupling reactions where the *n*-butyl groups of

an analogous $R'Sn^tBu_3$ nucleophile undergo competitive alkyl transfer to palladium.

Results and discussion

Development of a general cross-coupling reaction employing α -stannyl pyrrolidine derivatives.

Whereas inclusion of an α -oxygen substituent on a secondary alkyltin nucleophile is an effective strategy to promote selective alkyl transmetalation,^{3,39,40} far fewer examples of activation via an α -nitrogen substituent have been demonstrated.^{13,18,19,41} This possibly arises from the lower electronegativity of nitrogen, which results in a muted propensity to promote alkyl transfer. Cross-coupling reactions involving the transmetalation of nitrogen-substituted alkyltin nucleophiles reported by Chong,¹³ Vedejs,¹⁹ and ourselves¹⁸



have been limited to cases that utilize multiple modes of activation, and thereby offered limited potential scope (Figure 1b,c). In an attempt to overcome the dependence of transmetalation on remote activating groups, we introduced

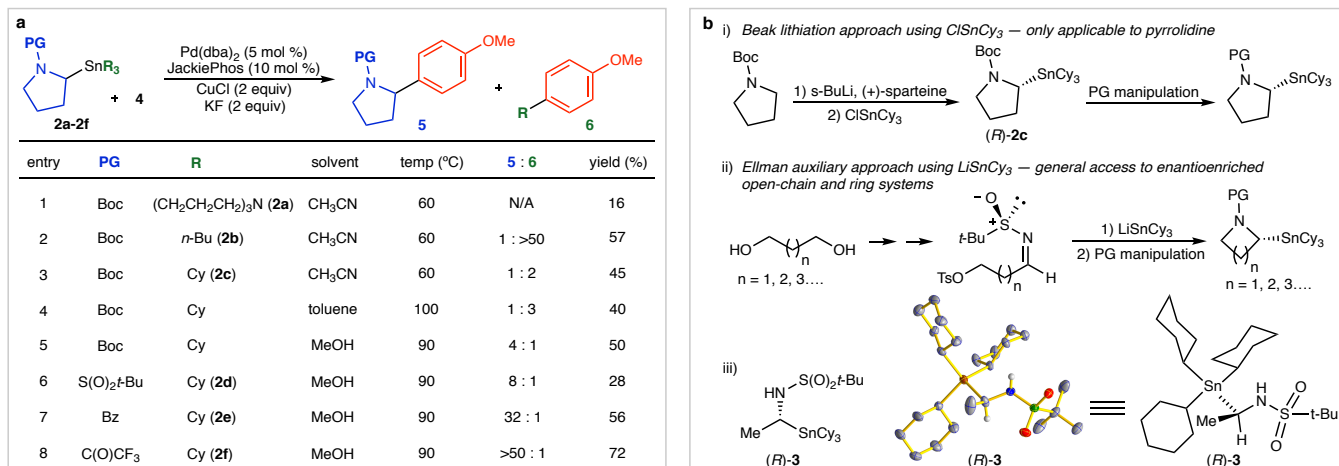


Figure 2. Selective transfer of nitrogen-containing stereocenters from alkyltin nucleophiles. **a**, Influence of tin spectator ligands and nitrogen protecting groups on selectivity of α -pyrrolidine transfer. **b**, Synthetic strategies employed in the preparation of enantioenriched alkyltin nucleophiles bearing an α -nitrogen group. X-ray crystal structure used to confirm stereochemistry of LiSnCy₃ addition to imine bearing Ellman auxiliary (thermal ellipsoids at 50% probability).

the use of enantioenriched carbastannatrane^{42,43} nucleophiles in stereospecific cross-coupling reactions.¹⁸ The use of carbastannatrane enabled, for the first time, stereospecific cross-coupling reactions of completely unactivated secondary alkyl nucleophiles when the electron-deficient biarylphosphine JackiePhos⁴⁴ (**1**) was employed as a supporting ligand. Unfortunately, ensuing studies on the generality of this process revealed that α -stannatranlyl pyrrolidine **2a** (Figure 2a) performs poorly in cross-coupling reactions. Combined activation from the α -nitrogen *and* use of the carbastannatrane unit renders **2a** over-activated, leading to competitive decomposition through protodestannylation when all but the most reactive aryl electrophiles are employed. Indeed, use of 4-bromoanisole in this reaction resulted in only a 16% yield of arylation product (Figure 2a, entry 1). Attempting to dampen the reactivity and increase the stability of the α -stannyl pyrrolidine nucleophile, we investigated use of compound **2b**, which contains *n*-butyl units as spectator groups in place of the carbastannatrane. Unfortunately, use of **2b** resulted exclusively in *n*-butyl coupling product, with no evidence of selective pyrrolidine transfer (Figure 2a, entry 2). Because secondary alkyl groups undergo significantly slower transmetallation from tin compared to primary alkyl groups (Figure 1b), we exchanged the *n*-butyl groups of compound **2c** for cyclohexyl groups.⁴⁵ Using **2c** in methanol, with CuCl as a co-transmetallating agent,⁴⁶ pyrrolidine transfer predominated, though ca. 20% cyclohexyl transfer was still observed (Figure 2a, entry 5). The ability of JackiePhos to support the transmetallation of unactivated cyclohexyl units was surprising, and underscores its unique activity in cross-coupling reactions of alkyltin species. At this point, we reasoned that installation of a more electron-deficient nitrogen-protecting group might address this problem by enhancing the activating effect of the nitrogen atom. Installation of a *t*-butylsulfonyl (Bus) (**2d**) or benzoyl protecting group (**2e**) resulted in improved selectivity. However, a trifluoroacetyl protecting group (**2f**) was found to promote the optimal se-

lectivity and yield for the pyrrolidine coupling product (Figure 2b, entry 8), with only trace evidence of cyclohexyl transfer.

Preparation of enantioenriched alkylstannanes bearing nitrogen-containing stereocenters.

Few methods for the preparation of enantioenriched alkyltin nucleophiles exist. This is unsurprising as enantioenriched alkyltin nucleophiles lack significant utility without methods to promote selective alkyl transfer. Though the sparteine-mediated asymmetric lithiation chemistry devised by Beak⁴⁷ works extremely well for the preparation of α -stannylated *N*-Boc-protected pyrrolidine compounds, it is not applicable to other nitrogen-containing heterocycles or open-chain amines. As a more general alternative to the Beak protocol, we devised a cyclization strategy using Ellman's auxiliary,⁴⁸ starting from terminal diols (Figure 2b). Using this strategy, we prepared enantioenriched α -stannylated pyrrolidines and azetidines. Though we have focused on the pyrrolidine and azetidine ring systems for this initial study, larger rings should be readily accessible using an analogous strategy alongside the appropriate diol precursors. As previously demonstrated by Chong,⁴⁹ this route also enables the preparation of enantioenriched, α -stannylated derivatives of open-chain secondary amines. Thus, in principle, use of the Ellman auxiliary approach should provide universal access to α -stannylated, enantioenriched amine derivatives. Protection group manipulation can be readily accomplished following installation of the tin unit for these products (see Supporting Information). In contrast to RSnⁿBu₃ compounds, RSnCy₃ compounds generally exhibit high crystallinity and have no odor (ClSnCy₃ is also odorless and crystalline). Additionally, toxicity of RSnCy₃ compounds has been reported to be lower than that of the corresponding RSnBu₃ compounds.⁵⁰⁻⁵² Such practical benefits should facilitate the broad implementation of our method, as well as the general use of RSnCy₃ compounds in organic synthesis.

Table 1. Stereospecific cross-coupling reactions of enantioenriched *N*-trifluoroacetyl-2-tricyclohexylstannyl pyrrolidine (2f**).**

Entry	X	Product	Yield* (%)	es (%)	Entry	X	Product	Yield* (%)	es (%)
1	Br		70	96	8	I		52	99
2	Br		65	98	9	Br		50	94
3	Br		80	95	10	Cl		66	98
4	Br		70	93	11 [§]	SPh		72	>40:1 dr
5	Br		54	96	12 [†]	SPh		92	>40:1 dr
6	OTf		57	100	13 [§]	SPh		70	>40:1 dr
7	Br		62	95	14 [†]	SPh		88	>40:1 dr

Reaction conditions: aryl or acyl electrophile (0.25 mmol), (*R*)-**2f** (0.32 mmol), CuCl (0.5 mmol), KF (0.5 mmol), Pd(dba)₂ (5 mol %), **1** (15 mol %), MeOH (1 mL) at 90 °C.

*Average isolated yield of two runs. [§] Using (*S*)-**2c** in 1,4-dioxane at 110 °C. [†] Using (*R*)-**2c** in 1,4-dioxane at 110 °C. % es = 100 x (% ee of product)/(% ee of starting material).

Scope of stereospecific cross-coupling reactions using enantioenriched α -stannyl pyrrolidine derivatives.

Using the reaction conditions shown in entry 8 of Figure 2a, enantioenriched **2f** was employed in cross-coupling reactions with different aryl electrophiles (Table 1). No observable transfer of the cyclohexyl group occurred in these reactions. For all reactions, transmetalation proceeded primarily through a stereoretentive pathway, which enabled isolation of α -arylated pyrrolidine derivatives in high % e.e. and with predictable stereochemistry. Electron-rich, electron-neutral, electron-deficient, and *ortho*-substituted aryl electrophiles all underwent cross-coupling reaction with high enantiospecificity (% e.s.). Heteroaryl electrophiles and aryl electrophiles bearing protic functional groups were also well tolerated in

these reactions. Aryl bromides, iodides, and triflates all proved to be viable substrates for this method. These examples showcase the breadth of substrate scope compatible with this process. Additionally, use of benzoyl chloride as the electrophilic component enabled a stereospecific acylation reaction under standard conditions in the absence of the fluoride additive. Highlighting the operational simplicity of this process, all reactions were conducted on the benchtop using disposable test tubes and screw-top septum caps without need for an inert atmosphere glovebox.

Thioesters are valuable synthons for use in diastereoselective processes as enantioenriched thioesters can be readily prepared from α -stereogenic carboxylic acids. Stereospecific cross-coupling reactions of α -stereogenic thioesters and

enantioenriched nucleophiles would enable the preparation of individual diastereomers through a completely reagent-controlled process. To expand the scope of our cross-coupling process, we employed thioesters as acyl electrophiles (Table 1, entries 11-14). Though reactions of **2f** with thioesters did provide the desired cross-coupling product

with excellent diastereoselectivity, we found that higher yields could be more consistently achieved using Boc-protected pyrrolidine analogue **2c**. In these reactions, the presence of an acyl ligand on palladium accelerates transmetalation, which enables use of a less electron

Table 2. Stereospecific cross-coupling reactions of enantioenriched *N*-Boc-2-tricyclohexylstannyl azetidine (9**).**

Entry	X	Product	Yield* (%)	es (%)
1	Br		76	98
2	Br		66	98
3	Br		69	93
4	Br		75	99
5	Br		72	99
6	Br		46	90

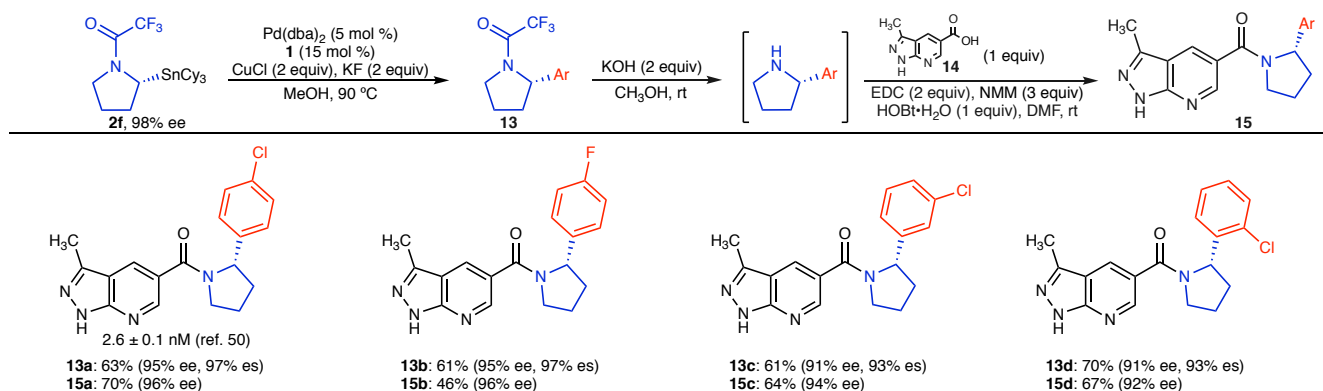
Reaction conditions: aryl bromide (0.1 mmol), (*R*)-**9** (0.11 mmol), CuCl (0.05 mmol), KF (0.2 mmol), Pd(dba)₃ (5 mol %), **1** (10 mol %), toluene (1 mL) at 110 °C.
 *Average isolated yield of two runs. % es = 100 x (% ee of product)/(% ee of starting material).

Table 3. Stereospecific cross-coupling reactions of enantioenriched open-chain α -amino tricyclohexylstannanes (11**).**

Entry	X	Product	Yield* (%)	es (%)
1	Br		80	100
2	Br		61	97
3	Br		65	82
4	Br		65	100
5	Br		46	100
6	Br		81	99

Reaction conditions: aryl bromide (0.1 mmol), (*R*)-**11** (0.11 mmol), CuCl (0.2 mmol), KF (0.2 mmol), Pd(dba)₃ (5 mol %), **1** (10 mol %), toluene (1 mL) at 110 °C.
 *Average isolated yield of two runs. % es = 100 x (% ee of product)/(% ee of starting material).

Table 4. Preparation of new CDK8 inhibitor derivatives (15) using a stereospecific cross-coupling strategy.



deficient protecting group on the pyrrolidine nucleophile, though the SnCy₃ group is still essential. Using the thioesters derived from L-proline and (*S*)-naproxen, we demonstrated that exceptionally high diastereoselectivity could be achieved for both enantiomers of **2c**. Thus, selective incorporation of new stereocenters could be readily achieved in a highly rational and predictable manner without influence from existing stereocenters on a chiral substrate. This shows that our approach is not limited to enantioselective processes, but can also be employed as a general strategy to achieve diastereocontrol in cross-coupling reactions.

Extension to stereospecific cross-coupling reactions using enantioenriched α -stannyl azetidines and open-chain derivatives.

Use of the Ellman auxiliary approach to the preparation of enantioenriched α -stannylated amines enables access to numerous potential enantioenriched scaffolds. The cyclization strategy shown in Figure 2b was employed to prepare α -stannylated azetidine **9** in high enantiopurity. Though the *t*-butylsulfonyl (Bus) protecting group did not enable selective pyrrolidine transfer from **2d**, we found that the additional ring strain of the 4-member azetidine ring facilitates selective azetidine transfer from RSnCy₃ in the presence of the *t*-butylsulfonyl protecting group, which is readily formed via oxidation of the Ellman auxiliary. Using the conditions of Table 1 with only nominal modification, arylation reactions of **9** proceeded with high enantiofidelity for electron-deficient and electron-neutral aryl bromides (Table 2). Ketone, aldehyde, ester, and ortho substituents were well tolerated in this reaction. This constitutes the first example of a Pd-catalyzed cross-coupling reaction involving α -metallated azetidine nucleophiles (racemic or stereospecific), and provides a simple route to access enantioenriched α -aryl azetidine derivatives for potential applications in drug discovery. The unprecedented success of this approach using azetidine and pyrrolidine ring systems suggests that other ring systems (e.g., piperidine, piperazine, azepane) will also be viable nucleophilic components in stereospecific cross-coupling reactions.

To further demonstrate the generality of this system, we prepared enantioenriched open-chain α -stannylated amine derivatives using the Ellman auxiliary approach. We found that α -stannylated nucleophiles of secondary amines (**11**) underwent more facile transmetalation than unactivated tertiary amine nucleophiles such as pyrrolidine derivatives. As observed for the azetidine nucleophiles, activation imparted by the *t*-butylsulfonyl protecting group was sufficient to enable selective transfer of the open-chain alkylamine unit from RSnCy₃, enabling the first stereospecific cross-coupling reactions of non-benzylic α -stannylated secondary amines. The protecting group, however, can be easily varied if desired.⁴⁹ For the open-chain nucleophiles, use of *n*-butyl groups as spectator ligands resulted in ca. 20% *n*-butyl transfer during the transmetalation step. Excellent enantiospecificity was observed using non-benzyl and benzylamine derivatives under analogous conditions to those in Tables 1 and 2. These results are particularly noteworthy as they suggest that additional modes of activation such as inclusion of an α -C(sp²) substituent do not affect the mechanism of transmetalation in these cross-coupling reactions, which highlights the truly general scope of this transformation. Inclusion of a branched alkyl substituent (**12c**) was also tolerated in this reaction though slightly decreased enantiospecificity was obtained in the cross-coupling product.

Preparation of CDK8 inhibitors through stereospecific cross-coupling reactions.

Cyclin dependent kinase CDK8 has been proposed to act as an oncogene in the development of colorectal cancers.⁵³⁻⁵⁵ Additionally, increased CDK8 expression has been linked to breast and ovarian cancers.⁵¹ High-throughput screening alongside systematic structural modification has recently been employed in the development of compound **15a**, a potent inhibitor of CDK8.⁵⁶ These studies suggested that derivatives of **15a** with pyrrolidine units that bear a monohalogenated aryl group at the stereogenic α position display particularly favorable potency, selectivity, bioavailability, and safety profiles in preclinical *in vivo* studies. To demonstrate the application of stereospecific cross-coupling reactions to the preparation of enantioenriched drug candidates, we prepared analogues of compound **15a** through the stereospecific

ic variation of its mono-halogenated aryl substituent (Table 4). Stereospecific cross-coupling reactions using the method shown in Table 1 enabled the direct preparation of highly enantioenriched **13**, which could then be elaborated to **15** through simple deprotection and amidation reactions. Through this strategy, we prepared **15a** as well as previously unreported analogues **15b-d**. Therefore, the use of stereospecific cross-coupling reactions enables a more streamlined synthetic approach to the preparation of potential CDK8 inhibitors, in contrast to previously applied strategies that required resolution of the desired enantiomer from the corresponding racemic mixtures.⁵⁶

In summary, we have found that the synergistic use of cyclohexyl spectator ligands on tin (selectively slows transmetallation of undesired units) and the bi-phenylphosphine ligand JackiePhos (general acceleration of transmetallation) enables the selective transfer of an enantioenriched alkyl unit from tin when a minor structural perturbation electronically differentiates that unit. Thus, competitive transfer of *n*-Bu ligands from RSnⁿBu₃ reagents can be circumvented in stereospecific Stille reactions of enantioen-

Methods

General procedure for cross-coupling reactions using enantioenriched α -stannylated amines. Pd(dba)₂ (5 mol %), JackiePhos (10-15 mol %), RSnCy₃ nucleophile (1.1-1.3 equiv), CuCl (0.5-2 equiv), and KF (for aryl electrophiles, 2 equiv) were weighed out on the benchtop, and transferred to an oven-dried 8 mL screw-top test tube with stir bar. The test tube was sealed with a septum screw cap and electrical tape. Using a needle attached to a Schlenk line, the reaction tube was evacuated (100 mTorr) and backfilled with argon. This process was repeated three times. The liquid aryl or acyl electrophile (1 equiv) was then added to the reaction tube via microsyringe, followed by degassed methanol, dioxane, or toluene (0.5-1.0 mL). If the aryl or acyl electrophile were a solid, it was weighed on the benchtop alongside the other solids. The reaction tube was sealed with additional electrical tape and heated to 90 or 110 °C for 12 h (unoptimized reaction time) using a heating block. The cooled reaction mixture was transferred to a separatory funnel, diluted with water, and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and then dried over Na₂SO₄. The dried organic layer was filtered, concentrated, and purified by column chromatography on silica gel.

X-ray crystallography data. CCDC 1903639 contains the crystallographic data for compound **3**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

References

- Lipinski, C. A., Lombardo, F., Dominy, B. W. and Feeney, P. J. (2001). Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Adv. Drug Deliv. Rev.* **46**, 3-26.

riched alkylstannanes. Using this strategy, we have developed a general, unified approach to stereospecific Pd-catalyzed cross-coupling reactions of nitrogen-containing stereocenters. This process was demonstrated using α -stannylated pyrrolidine and azetidine nucleophiles, as well as α -stannylated open-chain (benzylic and non-benzylic) nucleophiles in stereospecific arylation and acylation reactions. The uniformity of reaction conditions employed, the predictability of stereochemical outcomes achieved, and the breadth of α -stannylated amines tolerated in these reactions will facilitate the broad use of this method in organic synthesis. These results suggest that use of carbastannatrane nucleophiles will only be necessary when transmetallation of completely unactivated nucleophiles is desired, and that high stereofidelity could likewise be achievable in cross-coupling reactions using other enantioenriched RSnCy₃ nucleophiles bearing an electronically differentiated alkyl unit. Additionally, RSnCy₃ compounds offer the practical benefits of lower toxicity and significantly higher crystallinity than their commonly used RSnⁿBu₃ counterparts, which should enhance the general attractiveness of this protocol.

- Vitaku, E., Smith, D. T. and Njardarson, J. T. (2014). Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **57**, 10257-10274.
- Wang, C.-Y., Derosa, J. and Biscoe, M. R. (2015). The use of stable, optically active organometallic nucleophiles in cross-coupling reactions. *Chem. Sci.* **6**, 5105-5113.
- Leonori, D. and Aggarwal, V. K. (2015). Stereospecific Couplings of Secondary and Tertiary Boronic Esters. *Angew. Chem. Int. Ed.* **54**, 1082-1096.
- Rygus, J. P. G. and Crudden, C. M. (2017). Enantiospecific and iterative Suzuki-Miyaura cross-couplings. *J. Am. Chem. Soc.* **139**, 18124-18137.
- Cherney, A. H., Kadunce, N. T. and Reisman, S. E. (2015). Enantioselective and enantiospecific transition-metal-catalyzed cross-coupling reactions of organometallic reagents to construct C-C bonds. *Chem. Rev.* **115**, 9587-9652.
- Swift, E. C. and Jarvo, E. R. (2013). Asymmetric transition metal-catalyzed cross-coupling reactions for the construction of tertiary stereocenters. *Tetrahedron* **69**, 5799-5817.
- Pound, S. M. and Watson, M. P. (2018). Asymmetric synthesis via stereospecific C-N and C-O bond activation of alkyl amine and alcohol derivatives. *Chem. Commun.* **54**, 12286-12301.
- Campos, K. R., Klapars, A., Waldman, J. H., Dormer, P. G. and Chen, C.-Y. (2006). Enantioselective, palladium-catalyzed α -arylation of *N*-*boc*-pyrrolidine. *J. Am. Chem. Soc.* **128**, 3538-3539.
- Ye, J., Bhatt, R. K. and Falck, J. R. (1994). Stereospecific palladium/copper cocatalyzed cross-coupling of α -alkoxy- and α -aminostannanes with acyl chlorides. *J. Am. Chem. Soc.* **116**, 1-5.
- Falck, J. R.; Bhatt, R. K. and Ye, J. (1995). Tin-copper transmetalation: Cross-coupling of α -heteroatom-substituted alkyltributylstannanes with organohalides. *J. Am. Chem. Soc.* **117**, 5973-5982.
- Mohapatra, S.; Bandyopadhyay, A.; Barma, D. K.; Capdevila, J. H. and Falck, J. R. (2003). Chiral α , β -dialkoxy- and α -alkoxy- β -aminostannanes: Preparation and copper-mediated cross-coupling. *Org. Lett.* **5**, 4759-4762.
- Kells, K. W. and Chong, J. M. (2004). Stille coupling of stereochemically defined α -sulfonamidoorganostannanes. *J. Am. Chem. Soc.* **126**, 15666-15667.
- Kalkofen, R. and Hoppe, D. (2006). First example of an enantiospecific sp³-sp² Stille coupling of a chiral allylstannane with aryl halides. *Synlett* 1959-1961.

15. Lange, H., Fröhlich, R. and Hoppe, D. (2008). Cu(I)-catalyzed stereospecific coupling reactions of enantioenriched α -stannylated benzyl carbamates and their application. *Tetrahedron* **64**, 9123-9135.
16. Falck, J. R., Patel, P. K. and Bandyopadhyay, A. (2007). Stereospecific cross-coupling of α -(thiocarbamoyl)organostannanes with alkenyl, aryl, and heteroaryl iodides. *J. Am. Chem. Soc.* **129**, 790-793.
17. Li, H., He, A., Falck, J. R. and Liebeskind, L. S. (2011). Stereocontrolled synthesis of α -amino- α' -alkoxy ketones by a copper-catalyzed cross-coupling of peptidic thiol esters and α -alkoxyalkylstannanes. *Org. Lett.* **13**, 3682-3685.
18. Li, L., Wang, C.-Y., Huang, R. and Biscoe, M. R. (2013). Stereoretentive Pd-catalyzed Stille cross-coupling reactions of secondary alkyl azastannatranes and aryl electrophiles. *Nature Chem.* **5**, 607-612.
19. Theddu, N. and Vedejs, E. (2013). Stille coupling of an aziridinyll stannatranes. *J. Org. Chem.* **78**, 5061-5066.
20. Jia, T., Cao, P., Wang, D., Lou, Y. and Liao, J. (2015). Copper-catalyzed asymmetric three-component borylstannation: enantioselective formation of C-Sn bond. *Chem. Eur. J.* **21**, 4918-4923.
21. Wang, C.-Y., Ralph, G., Derosa, J. and Biscoe, M. R. (2017). Stereospecific Pd-catalyzed acylation of alkylcarbostannatranes reagents. *Angew. Chem. Int. Ed.* **56**, 856-860.
22. Ma, X., Diane, M., Ralph, G., Chen, C. and Biscoe, M. R. (2017). Stereospecific electrophilic fluorination of alkylcarbostannatranes reagents. *Angew. Chem. Int. Ed.* **56**, 12663-12667.
23. Imao, D., Glasspoole, B. W., Laberge, V. S. and Crudden, C. M. (2009). Cross coupling reactions of chiral secondary organoboronic esters with retention of configuration. *J. Am. Chem. Soc.* **131**, 5024-5025.
24. Sandrock, D. L., Jean-Gerard, L., Chen, C.-Y., Dreher, S. D. and Molander, G. A. (2010). Stereospecific cross-coupling of secondary alkyl β -trifluoroboroamides. *J. Am. Chem. Soc.* **132**, 17108-17110.
25. Ohmura, T., Awano, T. and Suginome, M. (2010). Stereospecific Suzuki-Miyaura coupling of chiral α -(acylamino)benzylboronic esters with inversion of configuration. *J. Am. Chem. Soc.* **132**, 13191-13193.
26. Awano, T., Ohmura, T. and Suginome, M. (2011). Inversion or retention? Effects of acidic additives on the stereochemical course in enantiospecific Suzuki-Miyaura coupling of α -(acetyl amino)benzylboronic esters. *J. Am. Chem. Soc.* **133**, 20738-20741.
27. Lee, J. C. H., McDonald, R. and Hall, D. G. (2011). Enantioselective preparation and chemoselective cross-coupling of 1,1-diboron compounds. *Nature Chem.* **3**, 894-899.
28. Partridge, B. M., Chausset-Boissarie, L., Burns, M., Pulis, A. P. and Aggarwal, V. K. (2012). Enantioselective synthesis and cross-coupling of tertiary propargylic boronic esters using lithiation-borylation of propargylic carbamates. *Angew. Chem. Int. Ed.* **51**, 11795-11799.
29. Molander, G. A. and Wisniewski, S. R. (2012). Stereospecific cross-coupling of secondary organotrifluoroborates: Potassium 1-(benzyloxy)alkyltrifluoroborates. *J. Am. Chem. Soc.* **134**, 16856-16868.
30. Li, L., Zhao, S., Joshi-Pangu, A., Diane, M. and Biscoe, M. R. (2014). Stereospecific Pd-catalyzed cross-coupling reactions of secondary alkylboron nucleophiles and aryl chlorides. *J. Am. Chem. Soc.* **136**, 14027-14030.
31. Sun, C., Potter, B. and Morken, J. P. (2014). A catalytic enantiotopic-group-selective Suzuki reaction for the construction of chiral organoboronates. *J. Am. Chem. Soc.* **136**, 6534-6537.
32. Matthew, S. C., Glasspoole, B. W., Eisenberger, P. and Crudden, C. M. (2014). Synthesis of enantiomerically enriched triarylmethanes by enantiospecific Suzuki-Miyaura cross-coupling reactions. *J. Am. Chem. Soc.* **136**, 528-5831.
33. Lou, Y., Cao, P., Jia, T., Zhang, Y., Wang, M. and Liao, J. (2015). Copper-catalyzed enantioselective 1,6-boration of *para*-quinone methides and efficient transformation of *gem*-diarylmethine boronates to triarylmethanes. *Angew. Chem. Int. Ed.* **54**, 12134-12138.
34. Hoang, G. L. and Takacs, J. M. (2017). Enantioselective γ -borylation of unsaturated amides and stereoretentive Suzuki-Miyaura cross-coupling. *Chem. Sci.* **8**, 4511-4516.
35. Ohmura, T., Miwa, K., Awano, T. and Suginome, M. (2018). Enantiospecific Suzuki-Miyaura coupling of nonbenzylic α -(acylamino)alkylboronic acid derivatives. *Chem. Asian J.* **13**, 2414-2417.
36. Zhao, S., Gensch, T., Murray, B., Niemeyer, Z. L., Sigman, M. S. and Biscoe, M. R. (2018). Enantiodivergent Pd-catalyzed C-C bond formation enabled through ligand parameterization. *Science* **362**, 670-674.
37. Lehman, J. W., Crouch, I. T., Blair, D. J., Trobe, M., Wang, P., Li, J. and Burke, M. D. (2019) Axial shielding of Pd(II) complexes enables perfects stereoretention in Suzuki-Miyaura cross-coupling of Csp³ boronic acids. *Nat. Comm.* **10**, 1263.
38. Itami, K., Kamei, T. and Yoshida, J. (2001). Unusually accelerated silylmethyl transfer from tin in Stille coupling: Implication of coordination-driven transmetalation. *J. Am. Chem. Soc.* **123**, 8773-8779.
39. Zhu, F., Rourke, M. J., Yang, T., Rodriguez, J. and Walczak, M. A. (2016). Highly stereospecific cross-coupling reactions of anomeric stannanes for the synthesis of C-aryl glycosides. *J. Am. Chem. Soc.* **138**, 12049-12052.
40. Dakarapu, R. and Falck, J. R. (2018). Stereospecific Stille cross-couplings using Mn(II)Cl₂. *J. Org. Chem.* **83**, 1241-1251.
41. Krizkova, P. M. and Hammerschmidt, F. (2013). On the configurational stability of chiral heteroatom-substituted [D₁]methylpalladium complexes as intermediates of Stille and Suzuki-Miyaura cross-coupling reactions. *Eur. J. Org. Chem.* **5143**-5148.
42. Jurkschat, K., Tzschach, A. and Meunier-Piret, J. (1986). Crystal and molecular structure of 1-aza-5-stannamethyltricyclo[3.3.3.0^{1,5}]undecane. Evidence for a transannular donor-acceptor interaction in a tetraorganotin compound. *J. Organomet. Chem.* **315**, 45-49.
43. Vedejs, E., Haight, A. R. and Moss, W. O. (1992). Internal coordination at tin promotes selective alkyl transfer in the Stille coupling reaction. *J. Am. Chem. Soc.* **114**, 6556-6558.
44. Hicks, J. D., Hyde, A. M., Cuezva, A. M. and Buchwald, S. L. (2009). Pd-catalyzed *N*-arylation of secondary acyclic amides: Catalyst development, scope, and computational study. *J. Am. Chem. Soc.* **131**, 16720-16734.
45. Labadie, J. W. and Stille, J. K. (1983). Mechanisms of the palladium-catalyzed couplings of acid chlorides with organotin reagents. *J. Am. Chem. Soc.* **105**, 6129-6137.
46. Mee, S. P. H., Lee, V. and Baldwin, J. E. (2004) Stille coupling made easier – the synergic effect of copper(I) salts and the fluoride ion. *Angew. Chem. Int. Ed.* **43**, 1132-1136.
47. Beak, P., Kerrick, S. T., Wu, S. and Chu, J. (1994). Complex induced proximity effects: Enantioselective syntheses based on asymmetric deprotonations of *N*-boc-pyrrolidines. *J. Am. Chem. Soc.* **116**, 3231-3239.
48. Robak, M. T., Herbage, M. A. and Ellman, J. A. (2010). Synthesis and applications of *tert*-butanesulfinamide. *Chem. Rev.* **110**, 3600-3740.
49. Kells, K. W. and Chong, J. M. (2003). Addition of Bu₃SnLi to *tert*-butanesulfinimines as an efficient route to chiral, nonracemic α -aminoorganostannanes. *Org. Lett.* **5**, 4215-4218.
50. Egorova, K. S. and Ananikov, V. P. (2017). Toxicity of metal compounds: knowledge and myths. *Organometallics* **36**, 4071-4090.
51. Kimbrough, R. D. (1976) Toxicity and health effects of selected organotin compounds: a review. *Environ.* **14**, 51-56.
52. Sunday, A. O., Alafara, B. A. and Oladele, O. G. (2012) Toxicity and speciation analysis of organotin compounds. *Chem. Spec. Bioavailab.* **24**, 216-226.

53. Adler, A. S., et al. (2012). CDK8 maintains tumor dedifferentiation and embryonic stem cell pluripotency. *Cancer Res.* 72, 2129-2139.
54. Firestein, R., et al. (2008). CDK8 is a colorectal cancer oncogene that regulates β -catenin activity. *Nature* 455, 547-551.
55. Firestein, R., et al. (2010). CDK8 expression in 470 colorectal cancers in relation to β -catenin activation, other molecular alterations and patient survival. *Int. J. Cancer* 126, 2863-2873.
56. Czodrowski, P., et al. (2016). Structure-based optimization of potent, selective, and orally bioavailable CDK8 inhibitors discovered by high-throughput screening. *J. Med. Chem.* 59, 9337-9349.

Acknowledgements

We thank the City College of New York, the National Institutes of Health (R01GM131079) and the National Science Foundation (CHE-1665189) for support of this work. The authors are grateful to Chunhua Hu for assistance with the X-

ray analysis, and acknowledge the Molecular Design Institute of NYU for purchase of the single crystal diffractometer.

Author contributions

M. R. B. directed the project and wrote the manuscript. M.R.B and X. M. conceived of the research strategies for the project. X. M., H. Z., M. B., G. R., S. Z., and C.-Y. W. conducted all experiments and isolated all products. M. D. conducted initial exploratory studies on the use of $R\text{SnCy}_3$ nucleophiles in cross-coupling reactions.

Additional information

The authors declare no competing financial interests.

