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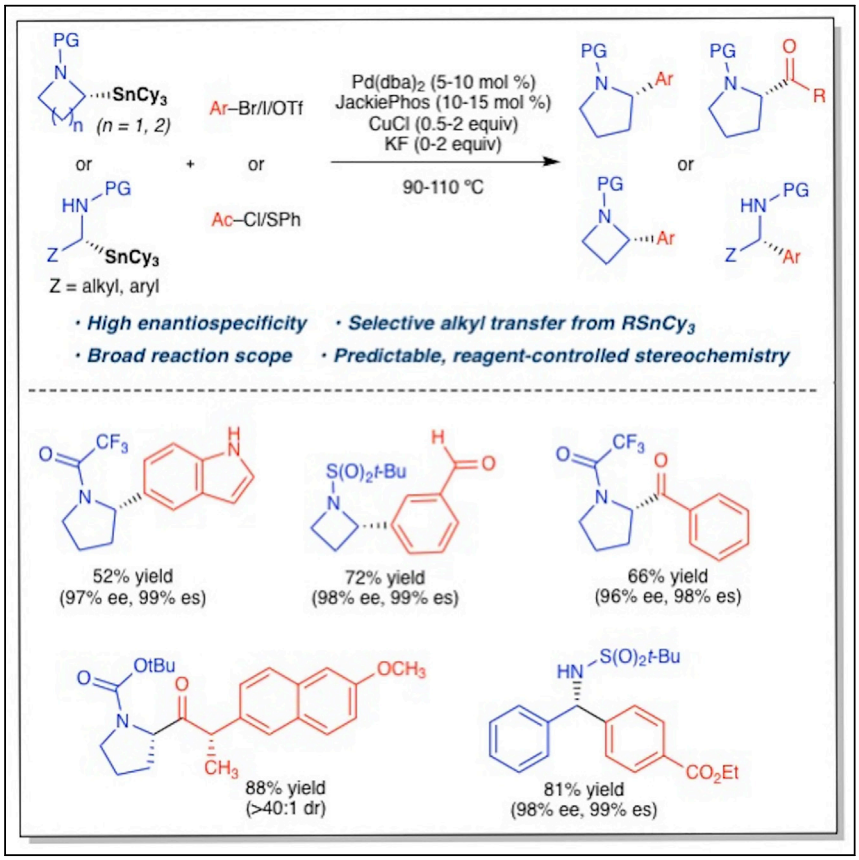
A General Approach to Stereospecific Cross-Coupling Reactions of Nitrogen-Containing Stereocenters



A general approach to the stereospecific cross-coupling of enantioenriched nitrogen-containing stereocenters has been developed. With cyclohexyl spectator ligands on organotin nucleophiles, selective and stereospecific transfer of a nitrogen-containing alkyl unit can be readily achieved in palladium-catalyzed cross-coupling reactions. This new reaction will enable the rapid generation of stereochemically defined nitrogen-containing carbon centers, which are common components of biologically active molecules emerging from the drug-discovery process.

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

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HIGHLIGHTS

N-Substituted alkyl groups undergo selective transfer from cyclohexyl-substituted tin

Enantioenriched N-substituted alkyl groups transfer from tin with high stereofidelity

Stereospecific couplings work broadly for heterocyclic and open-chain nucleophiles

Stereospecific couplings can be used to prepare a library of CDK8 inhibitors

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

Xinghua Ma,[1,2] Haoran Zhao,[1,2] Meruyert Binayeva,[1,2] Glenn Ralph,[1,2] Mohamed Diane,[1,2] Shibin Zhao,[1,2] Chao-Yuan Wang,[1,2] and Mark R. Biscoe[1,2,3,*]

SUMMARY

A novel strategy employing cyclohexyl spectator ligands in Stille cross-coupling reactions has been developed as a general solution 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. Selective and predictable transfer of a single secondary alkyl unit can be achieved under reaction conditions that exploit subtle electronic differences between activated and unactivated alkyl units. 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 by using α-stannylated pyrrolidine, azetidine, and open-chain (benzylic and non-benzylic) nucleophiles in stereospecific 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.

INTRODUCTION

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 encountered 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 organotin[10–22] and organoboron[23–37] may be employed in Pd-catalyzed cross-coupling reactions where transmetallation proceeds primarily through a stereoretentive or stereoinvertive mechanism, leading to predictable stereochemical outcomes (Figure 1A). Commonly, the use of alkyl nucleophiles that bear specific modes of activation, such as α-C(sp^2) groups, α-heteroatoms, ring strain, and/or

The Bigger Picture

Two molecules that have the same structure and composition but are mirror images of each other can produce very different biological responses. Therefore, control of the 3D atomic arrangement in molecules is critical in the drug-discovery process. Because biologically active molecules tend to contain C–N bonds, a general method to control the 3D structure of nitrogen-substituted carbon atoms would be particularly useful toward facilitating the discovery and development of new medicines. In this report, we detail a general method to modify the 3D structure of nitrogen-containing carbon centers. We employ palladium-catalyzed cross-coupling reactions in C–C bond-forming reactions where the initial 3D structure of the reactant is predictably transferred to the final product. With this new method, scientists will now be able to use cross-coupling reactions to rapidly generate libraries of new compounds while controlling the 3D architecture of the compounds.

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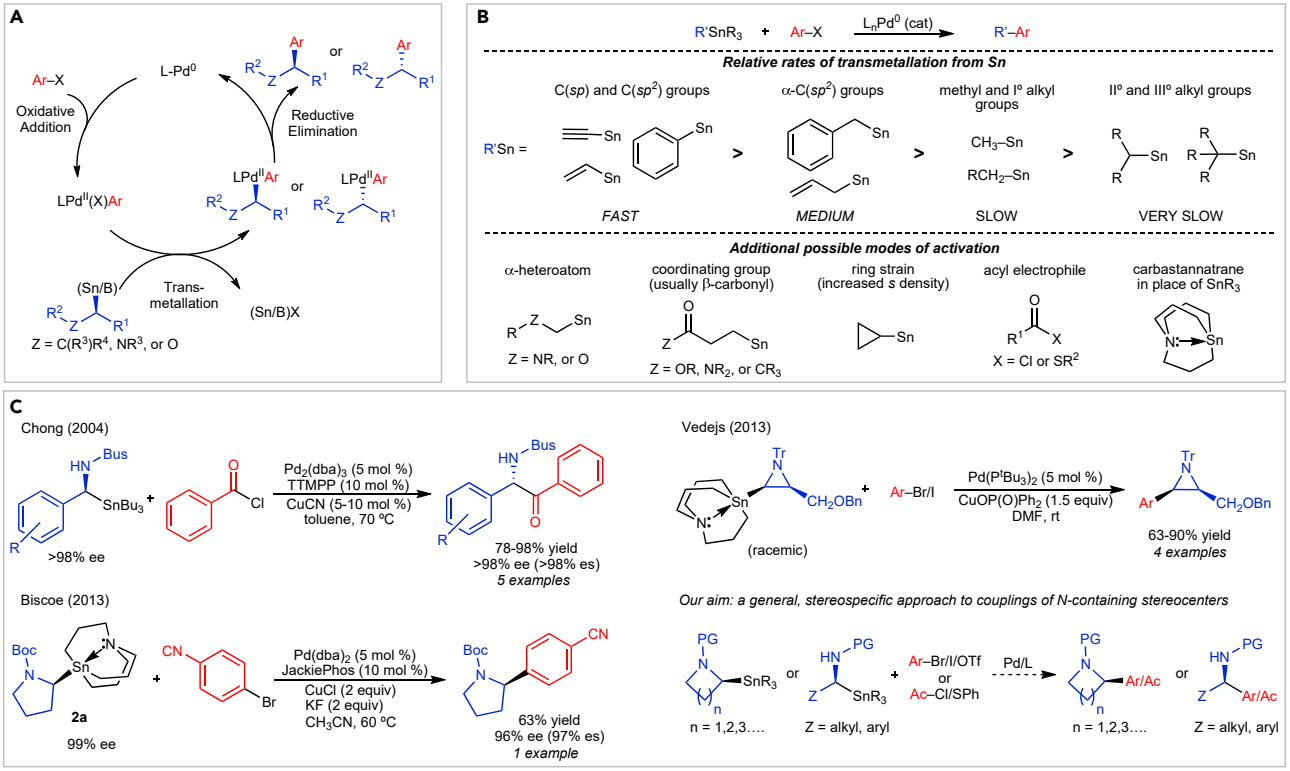

Figure 1. Stereospecific Cross-Coupling Reactions of Enantioenriched α-Stannylated Amines

(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, as well as activation strategies.

(C) Prior examples of Pd-catalyzed Stille cross-coupling reactions involving the stereospecific transfer of a nitrogen-containing stereocenter.

strongly coordinating substituents,[38] are required to facilitate transmetallation of the intrinsically hindered, secondary alkyl centers (Figure 1B). The use of a highly electron-deficient electrophilic coupling partner (e.g., acyl electrophiles) can also be employed to render the palladium (Pd) catalyst more electrophilic, thereby accelerating transmetallation.[10,21] These activation effects are additive such that nucleophiles bearing multiple activation modes undergo more rapid transmetallation 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 Pd.[3] As a result, viable substrates are limited to those that possess the requisite structural features necessary for transmetallation in each specific system. Importantly, the stereochemical outcome of transmetallation (retentive versus 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 the use of 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., $RSnCy_3$ instead of RSn^nBu_3), we have developed conditions that promote the

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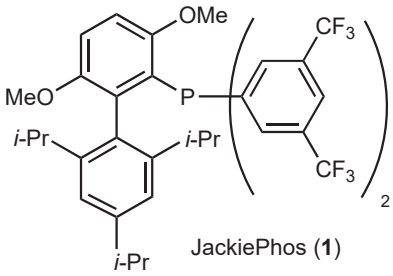


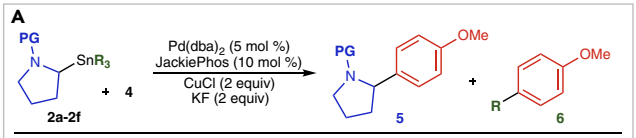
Figure 2. Molecular Structure of JackiePhos (1)

stereospecific transfer and cross coupling of nitrogen-containing carbon stereocenters. We demonstrate this process by 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. Under 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 the use of cylclohexyl spectator ligands will be broadly applicable in stereospecific coupling reactions where the *n*-butyl groups of an analogous RSn^nBu_3 nucleophile undergo competitive alkyl transfer to Pd.

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 for promoting selective alkyl transmetallation,[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 transmetallation of nitrogen-substituted alkyltin nucleophiles reported by Kells and Chong,[13] Theddu and Vedejs,[19] and Li et al.[18] have been limited to cases that utilize multiple modes of activation and thereby offered limited potential scope (Figures 1B and 1C). In an attempt to overcome the dependence of transmetallation on remote activating groups, we introduced the use of enantioenriched carbastannatrane[42,43] nucleophiles in stereospecific cross-coupling reactions.[18] The use of carbastannatranes enabled, for the first time, stereospecific cross-coupling reactions of completely unactivated secondary alkyl nucleophiles when the electron-deficient biarylphosphine JackiePhos[44] (**1**) (Figure 2) was employed as a supporting ligand. Unfortunately, ensuing studies on the generality of this process revealed that α-carbastannatranyl pyrrolidine **2a** (Figure 3A) performs poorly in cross-coupling reactions. Combined activation from the α-nitrogen *and* use of the carbastannatrane unit render **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 3A, entry 1). Attempting to dampen the reactivity and increase the stability of the α-stannyl pyrrolidine nucleophile, we investigated the use of compound **2b**, which contains *n*-butyl units as spectator groups in place of the carbastannatrane. Unfortunately, the use of **2b** resulted exclusively in *n*-butyl coupling product



entry	PG	R	solvent	temp (°C)	5 : 6	yield (%)
1	Boc	$(CH_2CH_2CH_2)_3N$ (**2a**)	CH_3CN	60	N/A	16
2	Boc	*n*-Bu (**2b**)	CH_3CN	60	1 : >50	57
3	Boc	Cy (**2c**)	CH_3CN	60	1 : 2	45
4	Boc	Cy	toluene	100	1 : 3	40
5	Boc	Cy	MeOH	90	4 : 1	50
6	$S(O)_2t$-Bu	Cy (**2d**)	MeOH	90	8 : 1	28
7	Bz	Cy (**2e**)	MeOH	90	32 : 1	56
8	$C(O)CF_3$	Cy (**2f**)	MeOH	90	>50 : 1	72

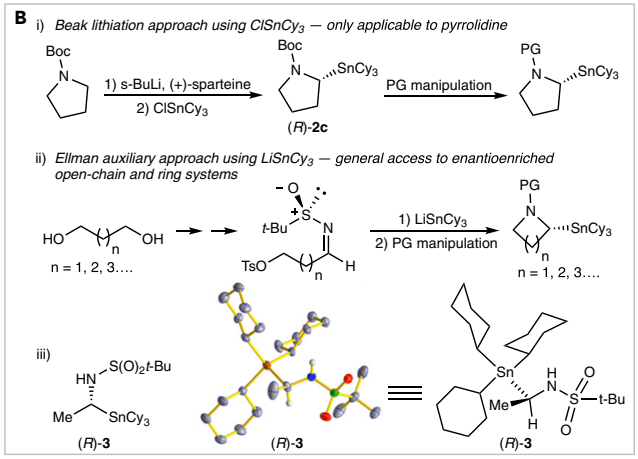


Figure 3. Selective Transfer of Nitrogen-Containing Stereocenters from Alkyltin Nucleophiles

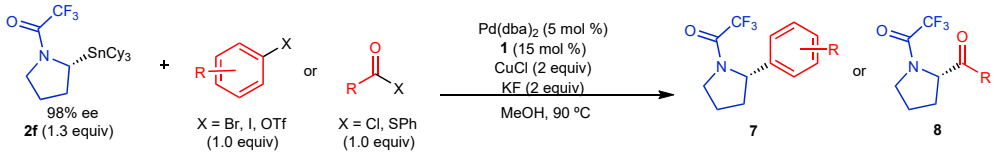
(A) Influence of tin spectator ligands and nitrogen protecting groups on selectivity of α-pyrrolidine transfer in cross-coupling reactions with 4-bromoanisole (**4**).

(B) Synthetic strategies employed in the preparation of enantioenriched alkyltin nucleophiles bearing an α-nitrogen group. X-ray crystal structure (*R*)-**3** was used to confirm stereochemistry of $LiSnCy_3$ addition to imine bearing Ellman auxiliary (thermal ellipsoids at 50% probability).

without any evidence of selective pyrrolidine transfer (Figure 3A, entry 2). Because secondary alkyl groups undergo significantly slower transmetallation from tin than 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 3A, 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 selectivity and yield for the pyrrolidine coupling product (Figure 3B, 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 Beak et al.[47] 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 3B). 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 Kells and 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. Protecting-group manipulation can be



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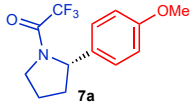
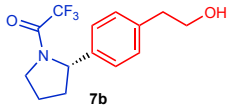
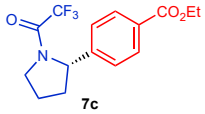
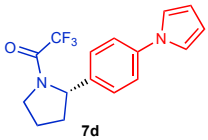
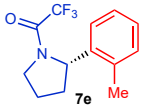
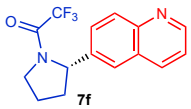
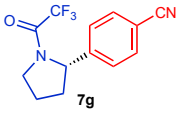
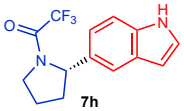
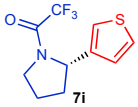
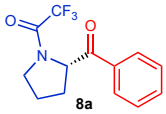
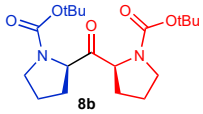
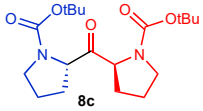
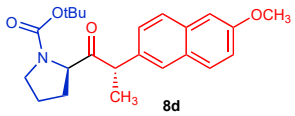
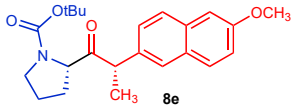
1	Br	 7a	70	96
2	Br	 7b	65	98
3	Br	 7c	80	95
4	Br	 7d	70	93
5	Br	 7e	54	96
6	OTf	 7f	57	100
7	Br	 7g	62	95
8	I	 7h	52	99
9	Br	 7i	50	94
10	Cl	 8a	66	98
11§	SPh	 8b	72	>40:1 dr
12†	SPh	 8c	92	>40:1 dr
13§	SPh	 8d	70	>40:1 dr
14†	SPh	 8e	88	>40:1 dr

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).

Figure 4. Stereospecific Cross-Coupling Reactions of Enantioenriched *N*-Trifluoroacetyl-2-tricyclohexylstannyl Pyrrolidine (2f)

readily accomplished following installation of the tin unit for these products (see Supplemental Information). In contrast to RSn^nBu_3 compounds, $RSnCy_3$ compounds generally exhibit high crystallinity and have no odor ($ClSnCy_3$ is also odorless and crystalline). Additionally, toxicity of $RSnCy_3$ compounds has been reported to be lower than that of the corresponding $RSnBu_3$ compounds.[50–52] Such practical benefits should facilitate the broad implementation of our method, as well as the general use of $RSnCy_3$ compounds in organic synthesis.

Scope of Stereospecific Cross-Coupling Reactions Using Enantioenriched α-Stannyl Pyrrolidine Derivatives

Using the reaction conditions shown in entry 8 of Figure 3A, we employed enantioenriched **2f** in cross-coupling reactions with different aryl electrophiles (Figure 4).

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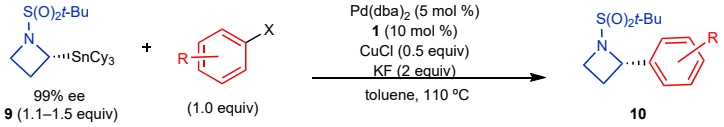
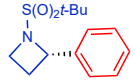
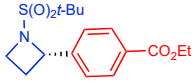
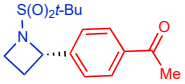
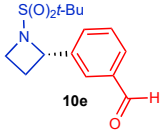
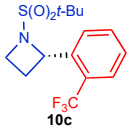
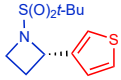


Entry	X	Product	Yield* (%)	es (%)	Entry	X	Product	Yield* (%)	es (%)
1	Br	 10a	76	98	4	Br	 10d	75	99
2	Br	 10b	66	98	5	Br	 10e	72	99
3	Br	 10c	69	93	6	Br	 10f	46	90

Reaction conditions: aryl bromide (0.1 mmol), (*R*)-**9** (0.11 mmol), CuCl (0.05 mmol), KF (0.2 mmol), $Pd(dba)_2$ (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).

Figure 5. Stereospecific Cross-Coupling Reactions of Enantioenriched *N*-Bus-2-tricyclohexylstannyl Azetidine (9)

No observable transfer of the cyclohexyl group occurred in these reactions. For all reactions, transmetallation 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, the 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 with disposable test tubes and screw-top septum caps without the need for an inert atmosphere glovebox.

Thioesters are valuable synthons for use in diastereoselective processes because 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 (Figure 4, entries 11–14). Although 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 with Boc-protected pyrrolidine analog **2c**. In these reactions, the presence of an acyl ligand on Pd accelerates transmetallation, which enables use of a less electron-deficient protecting group on the pyrrolidine nucleophile, though the $SnCy_3$ 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

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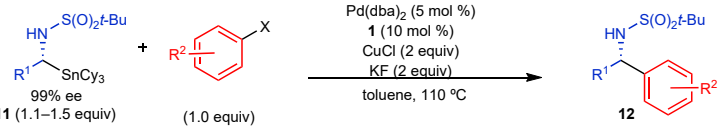
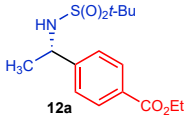
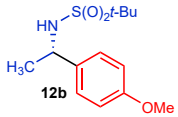
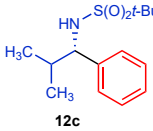
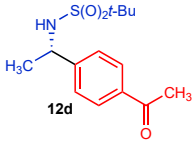
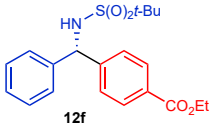


Entry	X	Product	Yield* (%)	es (%)
1	Br	 12a	80	100
2	Br	 12b	61	97
3	Br	 12c	65	82
4	Br	 12d	65	100
5	Br	 12e	46	100
6	Br	 12f	81	99

Reaction conditions: aryl bromide (0.1 mmol), (*R*)-**11** (0.11 mmol), CuCl (0.2 mmol), KF (0.2 mmol), $Pd(dba)_2$ (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).

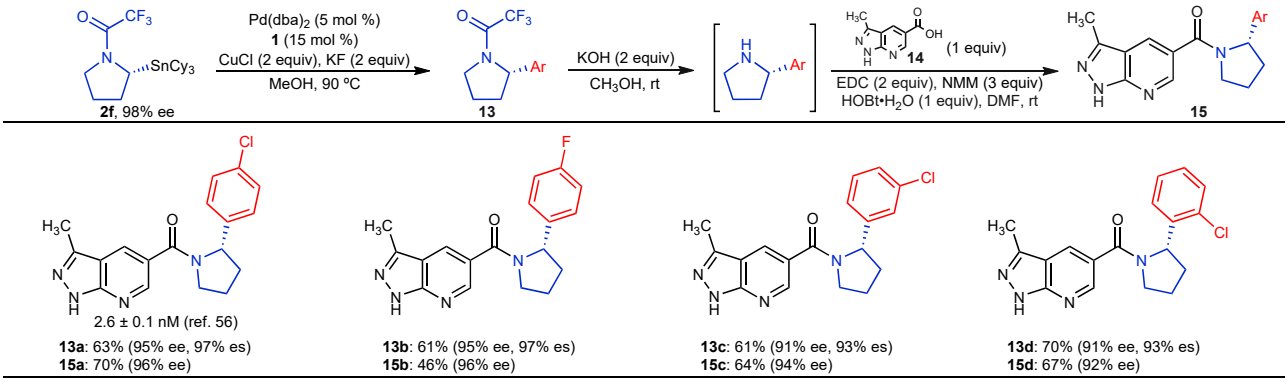
Figure 6. Stereospecific Cross-Coupling Reactions of Enantioenriched Open-Chain α-Amino Tricyclohexylstannanes (11)

and predictable manner without influence from existing stereocenters on a chiral substrate. This shows that our approach is not limited to enantioselective processes and can also be employed as a general strategy for achieving 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. We employed the cyclization strategy shown in Figure 3B to prepare α-stannylated azetidine **9** in high enantiopurity. Although 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 facilitated selective azetidine transfer from $RSnCy_3$ in the presence of the *t*-butylsulfonyl protecting group, which was readily formed via oxidation of the Ellman auxiliary. Under the conditions in Figure 4 with only nominal modification, arylation reactions of **9** proceeded with high enantiofidelity for electron-deficient and electron-neutral aryl bromides (Figure 5). 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 accessing 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, and 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 by using the Ellman auxiliary approach. We found that α-stannylated nucleophiles of secondary amines (**11**) underwent more



Reaction conditions: a) *cross-coupling reaction:* aryl bromide (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 ºC; b) *deprotection*: **13** (0.1 mmol), KOH (0.2 mmol), MeOH (0.3 mL) at rt; c) *amide coupling*: **14** (0.1 mmol), EDC (0.2 mmol), *N*-methylmorpholine (0.3 mmol), HOBt hydrate (0.1 mmol), DMF (0.4 mL) at rt. % es = 100 x (% ee of product)/(% ee of starting material).

Figure 7. Preparation of New CDK8 Inhibitor Derivatives (15) via a Stereospecific Cross-Coupling Strategy

facile transmetallation 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 $RSnCy_3$, enabling the first stereospecific cross-coupling reactions of non-benzylic α-stannylated secondary amines (Figure 6). The protecting group, however, can be easily varied if desired.[49] For the open-chain nucleophiles, the use of *n*-butyl groups as spectator ligands resulted in ca. 20% *n*-butyl transfer during the transmetallation step. Excellent enantiospecificity was observed with non-benzyl and benzylamine derivatives under conditions analogous to those in Figures 4 and 5. These results are particularly noteworthy because they suggest that additional modes of activation, such as the inclusion of an α-C(sp^2) substituent, do not affect the mechanism of transmetallation in these cross-coupling reactions, which highlights the truly general scope of this transformation. The inclusion of a branched alkyl substituent (**12c**) was also tolerated in this reaction, although 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 mono-halogenated 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 analogs of compound **15a** through the stereospecific variation of its mono-halogenated aryl substituent (Figure 7). Stereospecific cross-coupling reactions using the method shown in Figure 4 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 analogs **15b–15d**. Therefore, the use of stereospecific cross-coupling reactions enables a more streamlined synthetic approach to the preparation of potential CDK8 inhibitors than previously applied

strategies that require 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 biphenylphosphine 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 RSn^nBu_3 reagents can be circumvented in stereospecific Stille reactions of enantioenriched alkylstannanes. Using this strategy, we have developed a general approach to stereospecific Pd-catalyzed cross-coupling reactions of nitrogen-containing stereocenters. This process was demonstrated with 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 the use of carbastannatrane nucleophiles will be necessary only when transmetallation of completely unactivated nucleophiles is desired and that high stereofidelity could likewise be achievable in cross-coupling reactions using other enantioenriched $RSnCy_3$ nucleophiles bearing an electronically differentiated alkyl unit. Additionally, $RSnCy_3$ compounds offer the practical benefits of lower toxicity and significantly higher crystallinity than their commonly used RSn^nBu_3 counterparts, which should enhance the general attractiveness of this protocol.

EXPERIMENTAL PROCEDURES

General Procedure for Cross-Coupling Reactions Using Enantioenriched α-Stannylated Amines

$Pd(dba)_2$ (5 mol %), JackiePhos (10–15 mol %), $RSnCy_3$ 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), followed by degassed methanol, dioxane, or toluene (0.5–1.0 mL), was then added to the reaction tube via microsyringe. If the aryl or acyl electrophile was 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°C or 110°C for 12 h (unoptimized reaction time) with a heating block. The cooled reaction mixture was transferred to a separatory funnel, diluted with water, and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and then dried over Na_2SO_4. The dried organic layer was filtered, concentrated, and purified by column chromatography on silica gel.

DATA AND CODE AVAILABILITY

The crystallographic data for compound **3** are available under accession number CCDC: 1903639 and can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.2020.02.002.

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AUTHOR CONTRIBUTIONS

M.R.B. directed the project and wrote the manuscript. M.R.B. and X.M. conceived 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 $RSnCy_3$ nucleophiles in cross-coupling reactions.

DECLARATION OF INTERESTS

M.R.B. has filed provisional patent US 62/876,293 for the use of $RSnCy_3$ in cross-coupling reactions.

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