Asymmetric Catalysis

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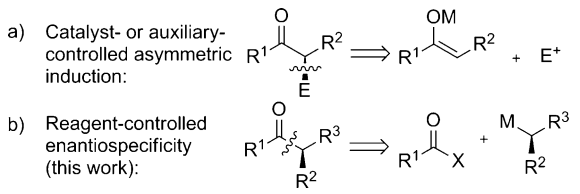
Stereospecific Palladium-Catalyzed Acylation of Enantioenriched Alkylcarbastannatranes: A General Alternative to Asymmetric Enolate Reactions

*Chao-Yuan Wang, Glenn Ralph, Joseph Derosa, and Mark R. Biscoe**

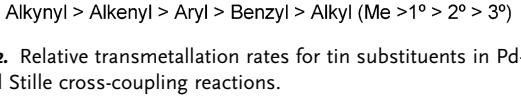
Abstract: *We report the development of a Pd-catalyzed process for the cross coupling of unactivated primary, secondary, and tertiary alkylcarbastannatrane nucleophiles with acyl electrophiles. Reactions involving optically active alkylcarbastannatranes occur with exceptional stereofidelity and with net retention of absolute configuration. Because the stereochemistry of the resulting products is entirely reagent-controlled, this process may be viewed as a general, alternative approach to the preparation of products typically accessed via asymmetric enolate methodologies. Additionally, we report a new method for the preparation of optically active alkylcarbastannatranes, which should facilitate their future use in stereospecific reactions.*

Catalyst- and auxiliary-controlled asymmetric enolate reactions have an extensive history of application in the construction of complex organic molecules (Scheme 1 a).[1] However, the development of a general approach to employ enolates and enolate equivalents in asymmetric reactions has been hindered by multiple complicating factors. First, a catalyst or auxiliary must broadly control facial attack on the enolate independent of the enolate carbon skeleton or the functional groups present. Second, reaction conditions must not be conducive to racemization of the newly formed stereogenic center (this is particularly challenging in arylation reactions).[2] Third, when ketones possess two enolizable carbon atoms, the chemoselectivity of the enolization process must be efficiently controlled. In principle, a stereospecific coupling reaction between a stable, optically active organometallic nucleophile and an acyl electrophile (Scheme 1 b) would circumvent these constraints. Because such cross-coupling reactions would feature completely reagent-controlled enantiospecificity, the transfer of stereochemical information should be both general and predictable.

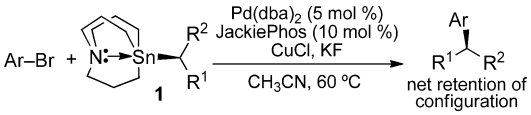


Scheme 1. Retrosynthetic approaches to the asymmetric construction of α-substituted carbonyl compounds.

Over the past few decades, transition-metal-catalyzed cross-coupling reactions have emerged as invaluable tools for the construction of organic molecules.[3] Although classical studies of cross-coupling reactions have largely focused on the formation of $C(sp^2)$–$C(sp^2)$ bonds, and thus the construction of planar molecular topologies, recent studies have suggested that three-dimensional molecular structure may be manipulated through the strategic use of $C(sp^3)$ nucleophiles and electrophiles.[4,5] Thus, alternative retrosynthetic disconnections can be envisioned during a planned synthesis, and new approaches to C–C bond construction may be pursued using $C(sp^3)$ coupling partners.[6] In Stille cross-coupling reactions, alkyl groups typically serve as inert ligands for tin, the presence of which enables selective transfer of more labile alkynyl, alkenyl, and aryl groups (Scheme 2). Achieving facile transfer of secondary and tertiary alkyl groups from tin to palladium is the greatest challenge to the development of stereospecific alkyl variants of the Stille cross-coupling reaction. Building upon the pioneering work of Jurkschat[7] and Vedejs,[8] we recently showed that secondary alkylcarbastannatranes (**1**) can be employed in stereospecific Pd-catalyzed cross-coupling reactions with aryl electrophiles (Scheme 3).[6e,9] The carbastannatrane backbone selectively activates its apical substituent, which facilitates the transmetallation of alkyl groups that are otherwise unactivated (i.e., without a $C(sp^2)$ α-carbon, heteroatomic α-substituent,



Scheme 2. Relative transmetallation rates for tin substituents in Pd-catalyzed Stille cross-coupling reactions.



Scheme 3. Use of enantioenriched alkylcarbastannatranes in stereospecific Pd-catalyzed arylation reactions.

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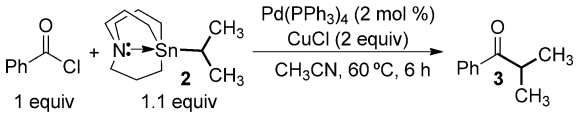
or coordinating β-carbonyl group).[10] This initial work suggested that alkylcarbastannatrane reagents have tremendous potential for broad application as isolable sources of stereodefined alkyl nucleophiles in transition metal-catalyzed reactions. Herein, we demonstrate that carbastannatranes facilitate the transmetallation of unactivated primary, secondary, and tertiary alkyl units in Pd-catalyzed coupling reactions with acyl electrophiles. Using an array of isolable, optically active, secondary alkylcarbastannatranes, we have developed a stereospecific process to access enantioenriched α-substituted ketones from acyl electrophiles. This process represents the first stereospecific cross-coupling reactions of unactivated alkyltin nucleophiles and acyl electrophiles,[11,12] and constitutes a synthetic alternative to asymmetric enolate methodologies.[13]

In our initial exploratory studies, we used the Pd-catalyzed coupling of benzoyl chloride and isopropylcarbastannatrane (**2**) as a model system. We found that the desired cross-coupling product (**3**) could be generated in good yield using 2 mol% $Pd(PPh_3)_4$ alongside two equivalents of CuCl in acetonitrile at 60 °C (Table 1). No evidence of isomerization

Table 1: Optimization of the Pd-catalyzed cross-coupling reaction of benzoyl chloride and **2**.

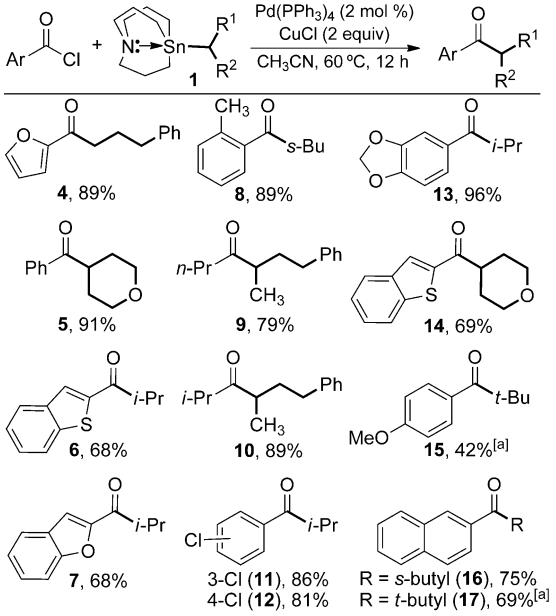


Entry	Variations from above	Yield [%][a]
1	none	80
2	0.1 mmol scale instead of 0.02 mmol	90
3	*i*-Pr_4Sn instead of carbastannatrane **2**	0
4	RT instead of 60 °C	52
5	2 equiv KF added	15
6	CuBr instead of CuCl	40
7	CuCN instead of CuCl	12
8	0.5 equiv CuCl	38
9	Toluene instead of CH_3CN	50

[a] Yields and selectivities determined by GC analysis.

of the secondary alkyl component from β-hydride elimination/reinsertion sequences was observed in this reaction. When *i*-Pr_4Sn was used in place of carbastannatrane **2**, no product was formed. This highlights the unique ability of the carbastannatrane backbone to selectively labilize bulky, unactivated alkyl groups that are typically inert towards transmetallation. The use of CuCl as a co-transmetallating agent is essential to the success of this reaction.[14]

Using the optimized conditions of Table 1, we investigated the scope of acyl chlorides tolerated in this cross-coupling reaction using achiral and racemic alkylcarbastannatranes (Scheme 4). We found that acyl chlorides bearing heteroaryl groups could be efficiently employed as electrophiles. Inclusion of an *ortho*-methyl substituent on benzoyl chloride had little impact on the reaction. Acyl chlorides bearing alkyl groups underwent coupling (products **9** and **10**) without evidence of alkyl isomerization via decarbonylation/β-hydride elimination/reinsertion/re-carbonylation sequences.[15]

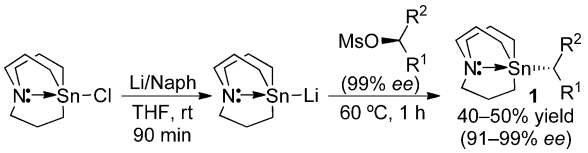


Scheme 4. Pd-catalyzed cross-coupling reactions of alkylcarbastannatranes and acyl chlorides. [a] $Pd(dba)_2$ (5 mol%), JackiePhos (10 mol%).

Chloro-substituted arenes were also well tolerated under these reaction conditions, which should enable cross-coupling products such as **11** and **12** to be further modified using existing cross-coupling technologies. In regards to the nucleophilic component, use of unactivated primary and unactivated secondary alkylcarbastannatranes was tolerated under the standard reaction conditions. No isomerization of the secondary alkyl nucleophiles was observed in these reactions. In contrast, when *t*-butyl carbastannatrane was employed under the standard conditions, significant isomerization of *t*-butyl to *i*-butyl was observed. Use of bulky biarylphosphine ligand JackiePhos[16] completely suppressed isomerization and enabled isolation of *t*-butyl aryl ketones **15** and **17** in decent yields. This constitutes the first example of *t*-butyl transfer from an alkylstannane in a cross-coupling reaction, and again underscores the remarkable ability of the carbastannatrane backbone to activate alkyl groups that are typically inert towards transmetallation.

When we initially disclosed the use of optically active alkylcarbastannatrane reagents (**1**) in stereospecific arylation reactions, enantioenrichment of **1** was achieved only via asymmetric lithiation/stannylation or via preparative HPLC separation of racemates. This limitation impeded our ability to employ derivatives of **1** extensively in stereospecific reactions. To address this deficiency, we have developed a method to prepare highly enantioenriched alkylcarbastannatranes via the S_N2 reaction of lithium carbastannatrane[17] and enantioenriched secondary alkyl mesylates (Scheme 5). This process should significantly expand the accessibility of unactivated, enantioenriched alkylcarbastannatranes for potential use in stereospecific reactions.

When unactivated, enantioenriched, secondary alkylcarbastannatranes **18** and **19** were employed in cross-coupling reactions with acyl chlorides, the corresponding

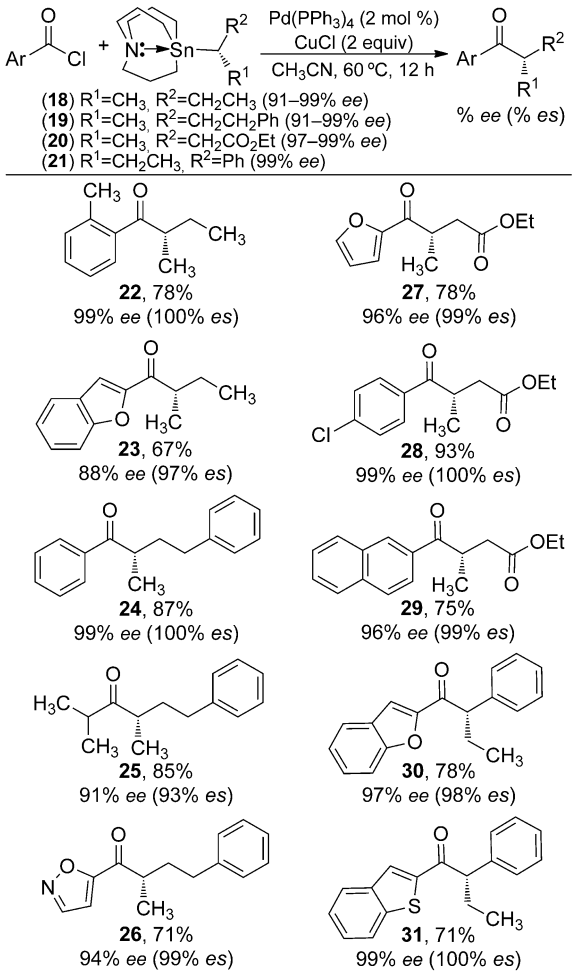


Scheme 5. Preparation of enantioenriched carbastannatranes from optically active alkyl mesylates.

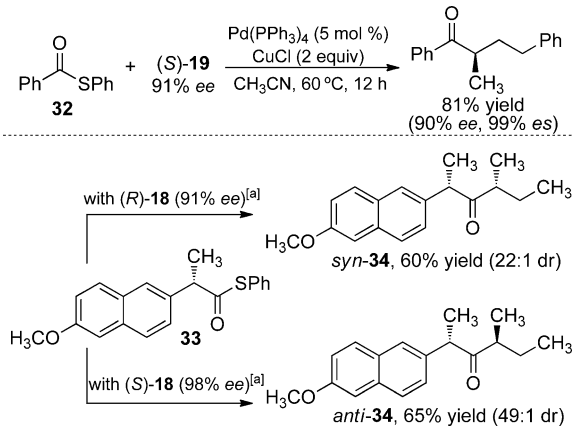
products were obtained with near perfect enantiospecificity (% *es*)[18] for most substrates (Scheme 6). This constitutes the first demonstration of a stereospecific, metal-catalyzed acylation reaction using a stable, unactivated, enantioenriched nucleophile. Consistent with our previously reported arylation reactions,[6e] this process proceeds with net retention of absolute configuration (see Supporting Information for details). In seminal studies conducted by Falck and others, stereospecific couplings of enantioenriched alkytin nucleophiles and acid chlorides were limited to use of specific classes of activated alkyltin nucleophiles.[12] To evaluate stereoelectronic influences of the nucleophile on stereospecificity in the present system, we also studied the use of electronically activated enantioenriched carbastannatranes (**20** and **21**) in these cross-coupling reactions. **20** and **21** both underwent cross-coupling reactions with exceptionally high stereofidelity. Therefore, electronic perturbations of the nucleophile (i.e., inclusion of a C(sp^2) α-carbon or strongly coordinating β-carbonyl group) do not appear to influence stereospecificity in this process. Retrosynthetically, products **22**–**29** constitute formal asymmetric *alkylation* reactions of enolates, whereas **30** and **31** constitute formal asymmetric *arylation* reactions of enolates. It is noteworthy that the mild conditions employed in this process are not conducive to racemization of the enantioenriched product, even with an α-aryl substituent present.

The combined results of Schemes 4 and 6 suggest that the nucleophilic scope of this reaction is quite broad. Primary, secondary, *and* tertiary alkylcarbastannatranes may be successfully employed in acylation reactions. Activated and unactivated secondary alkylcarbastannatranes all undergo highly efficient stereospecific cross-coupling reactions using identical conditions. Oxygen-containing nucleophiles could also be readily employed. Unfortunately, carbastannatranes bearing nitrogen-containing groups (e.g., piperidine and pyrrolidine derivatives) were largely unsuccessful in these reactions. This appears to be the major limitation of the present system.

Because thioesters are more stable and more easily handled than their corresponding acid chlorides, we explored the possibility of using thioesters as acyl electrophiles in stereospecific cross-coupling reactions.[13,19] Using the standard conditions with 5 mol% $Pd(PPh_3)_4$, we successfully effected the cross-coupling reaction of (*S*)-**19** and thioester **32** in high yield and with high stereofidelity (Scheme 7). Since non-racemic thioesters can be readily prepared from enantioenriched α-chiral carboxylic acids, we felt that such thioesters might be effective substrates for diastereospecific reactions, forming optically active α,α′-disubstituted ketones with complete reagent control of stereochemistry. Using the thioester of (*S*)-Naproxen (**33**), we successfully generated *syn*-**34** and *anti*-**34** from stereospecific reactions with (*R*)-**18** and (*S*)-**18**, respectively. The products of these reactions com-



Scheme 6. Stereospecific Pd-catalyzed couplings of enantioenriched alkylcarbastannatranes and acyl chlorides.



Scheme 7. Stereospecific coupling reactions of enantioenriched alkylcarba-stannatranes and thioesters. [a] $Pd(dba)_2$ (5 mol%), JackiePhos (10 mol%).

pletely retained the stereochemistry of their original coupling partners.

In summary, we have developed a general Pd-catalyzed process for the stereospecific cross coupling of enantioenriched alkylcarbastannatranes and acyl electrophiles. These reactions occur with outstanding stereofidelity and with retention of absolute configuration. Because the stereochemistry of the resulting products is entirely reagent controlled, this method offers an alternate, general strategy for the preparation of compounds typically generated via asymmetric reactions of enolates or enolate equivalents. We have additionally shown that the carbastannatrane backbone facilitates the transfer of *t*-butyl groups in Pd-catalyzed cross-coupling reactions. This represents the first example of the selective transfer of an unactivated tertiary alkyl group from tin, and suggests the potential for stereospecific quaternary center formation from enantioenriched tertiary alkylcarbastannatranes.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbastannatrane · cross coupling · enolate · palladium catalysis · stereospecific catalysis

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Communications

Asymmetric Catalysis

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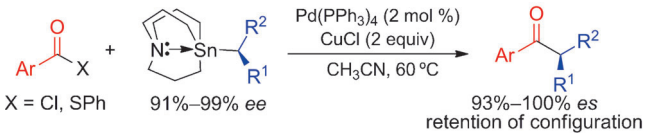

Stereospecific Palladium-Catalyzed Acylation of Enantioenriched Alkylcarbastannatranes: A General Alternative to Asymmetric Enolate Reactions

Finding new ways: A Pd-catalyzed process for the cross-coupling of unactivated primary, secondary, and tertiary alkylcarbastannatrane nucleophiles with acyl electrophiles was developed. This reaction provides as a general, alternative approach to the preparation of products typically accessed via asymmetric enolate methodologies.