Stereospecific Acylative Suzuki-Miyaura Cross-Coupling: A General Access to Optically Active α-Aryl Carbonyl Compounds

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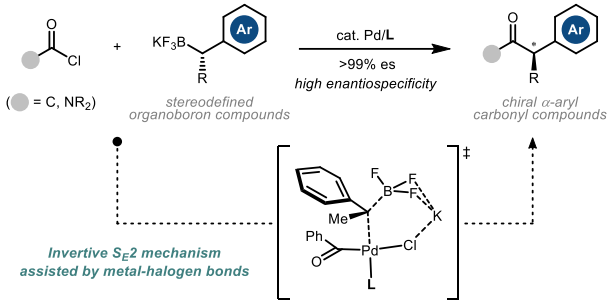
ABSTRACT: A novel strategy for the stereospecific Pd-catalyzed acylative cross-coupling of enantiomerically enriched alkylboron compounds has been developed. The protocol features an extremely high level of enantiospecificity to allow facile access to synthetically challenging and valuable chiral ketones and carboxylic acid derivatives. The use of a sterically encumbered and electron-rich phosphine ligand proved to be crucial for the success of the reaction. Furthermore, based on experimental and computational studies, a unique mechanism for the transmetalation of the C(sp^3)-based organoboron reagent has been identified.



Stereochemically enriched α-aryl carbonyl groups are an important class of structural motifs that are ubiquitously found in bioactive compounds, including natural products and pharmaceuticals (**Figure 1A**).[1] The biomedical significance of these moieties has prompted the synthetic community to devise numerous strategies to access the structural target with special focus on (a) the efficient installation of the aryl group and (b) the introduction/preservation of the stereochemical integrity at the reaction center.[2] Over time, the synthetic approaches that are based on either enolates (**Figure 1B**, **a**) or α-halo carbonyl compounds (**Figure 1B**, **b**) have played a pivotal role in the advancement of the discipline with the help of transition metal-based asymmetric catalysis.[3,4] More recently, orthogonal approaches that exploit the elevated reactivity of an activated acyl donor have successfully furnished the target structure via stereoselective introduction of a benzylic moiety (**Figure 1B**, **c**).[5] These methods, in combination with other types of catalytic approaches, have significantly contributed to providing the valuable α-aryl carbonyl compounds in an enantiopure form.[6]

Among the established approaches, acyl donor-based strategies have several crucial synthetic advantages, such as convenient access to precursors, convergence of the synthetic design, and mild reaction conditions. However, the stereo-induction process of this category presents synthetic challenges arising from the fundamental limitations of enantioselective catalysis. The performance of chiral catalysts can often be perturbed by numerous reaction parameters, for instance, the existing stereochemical information of the reaction partners and/or functional groups that can influence stereoselectivity. Therefore, an ideal alternative to the existing method is the stereospecific cross-coupling reaction.[7] The utilization of an optically active, preformed organometallic reagent could, in principle, enable highly efficient transfer of stereochemical information, independent of other complicating factors. Indeed, this possibility was recognized, and the preparation of optically active ketones from chiral alkyl stannanes was demonstrated.[8] However, the inherent restraints embedded in the preparation and utilization of organotin reagents has stymied a wider application of the strategy, both in terms of safety and practicality. In addition, the

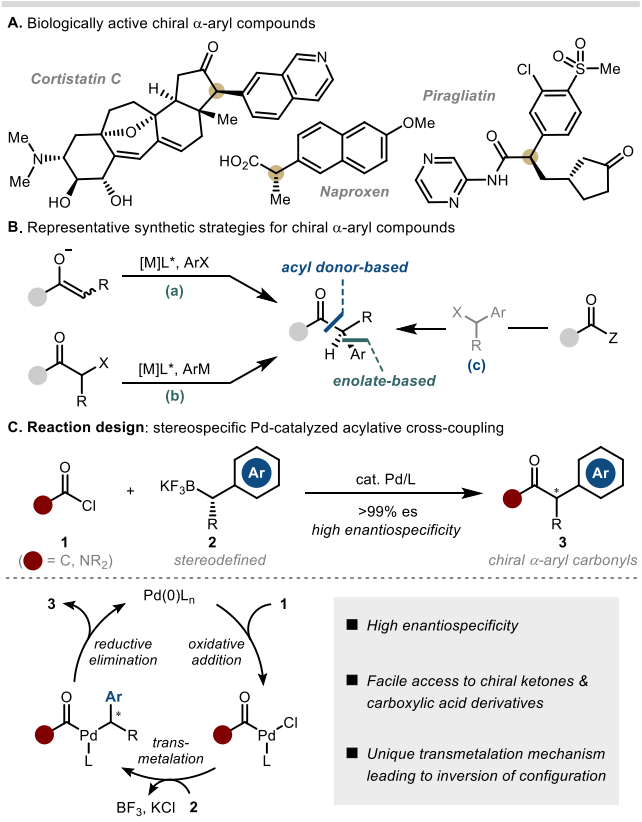


Figure 1. Synthetic strategies for chiral α-aryl carbonyl compounds

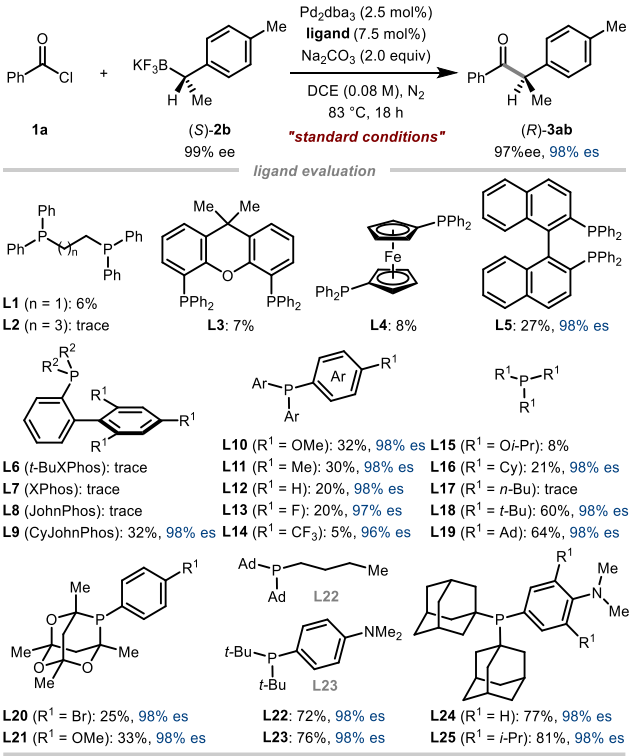
limited reactivity of organometallic reagents is not sufficient for the comprehensive preparation of chiral carbonyl compounds, particularly carboxylic acid derivatives. We envisioned that stereospecific employment of enantioenriched organoboron reagents in a Pd-catalyzed reaction system could resolve these integral synthetic problems (**Figure 1C**). Specifically, the rapidly advancing borylation techniques can widen the synthetic applicability of the system.[9] In addition, the synthetically versatile nature of organoboron reagents should resolve the problems of applicability, and allow access to a more diverse set of carbonyl compounds.[10]

Herein, we report an unprecedented stereospecific Pd-catalyzed acylative Suzuki-Miyaura cross coupling of chiral organoboron reagents to deliver a multitude of chiral α-aryl carbonyl compounds, including aryl/alkyl ketones and, carboxylic acid derivatives.[11–13] The approach generally exhibits an extremely high level of stereospecificity through a novel process that enables the transfer of stereochemical information from the organoboron reagent to the reaction center of the catalytic system.

Our initial investigation commenced with the cross-coupling reaction between benzoyl chloride (**1a**) and an enantioenriched benzylic trifluoroborate (**2b**) as model substrates (**Table 1**).[9b, 14] Based on multidimensional evaluation of reaction parameters, the use of Pd_2dba_3 as the Pd(0) source and Na_2CO_3 as the base was demonstrated to be optimal (*See SI for details*). Interestingly, the system exhibited the best performance in rigorously anhydrous 1,2-dichloroethane (DCE) solvent.[15] Conventional catalytic systems of organoboron reagents usually utilize aqueous solvent systems that can effectively hydrolyze the organoboron compounds.[16] Therefore, the result suggests the unique participation of trifluoroborate in its native form (*vide infra*). Another important element for successful transformation is the identity of the supporting ligand. Most bidentate (**L1**–**L4**) and dialkylbiarylphosphine ligands (**L6**–**L8**) were shown to be ineffective. Only BINAP (**L5**) and CyJohnPhos (**L9**) exhibited moderate reactivity in terms of product formation. In contrast, monodentate triaryl (**L10**–**L14**) and trialkyl phosphines (**L16**–**L19**) exhibited a noticeable level of reactivity. In general, more efficient product formation was observed as the phosphine ligand became bulkier and more electron-rich (**L18** and **L19**). Further optimization of the ligand structure revealed that the placement of two bulky alkyl groups and one arene ring effectively promoted the transformation (**L20**–**L24**). Eventually, diadamantyl phosphine with a highly electron-rich arene was identified as the optimal ligand (**L25**).[17] Interestingly, the stereochemical outcome was minimally affected by the variations in the ligand structure. Generally, a high level of enantiospecificity was obtained throughout the study, and the stereochemical information of the nucleophile was delivered with a net inversion at the reaction center.

After establishing the optimal conditions, we explored the applicability of the protocol with respect to both enantioenriched alkylboron reagents and acyl donors, by forming optically pure α-aryl ketones (**Table 2**). First, a variety of arene substituents, with different electronic and steric properties, were tolerated, affording the desired products in good yields with excellent enantiospecificity (**3aa**–**3ag**). Trifluoroborates with an electron-rich arene (**3aa**–**3ac**) or an electron-deficient arene (**3ad**–**3ae**) participated equally in the reaction with high efficiency. In addition, systems containing an extended π system or a bicyclic unit are also competent reaction partners (**3af** and **3ag**). Furthermore, borates with longer alkyl chains could be used as nucleophilic counterparts (**3ah**–**3aj**), although reduced reaction efficiency was observed for substrates with a bulkier substituent adjacent to the reaction center (**3ak**–**3am**). Importantly, straightforward control of the stereochemical outcome was achieved simply by utilizing a reaction partner with alternative stereochemistry at the reaction center ((*S*)-**3ab** and (*S*)-**3ah**).

Table 1. Optimization of the reaction conditions[a]

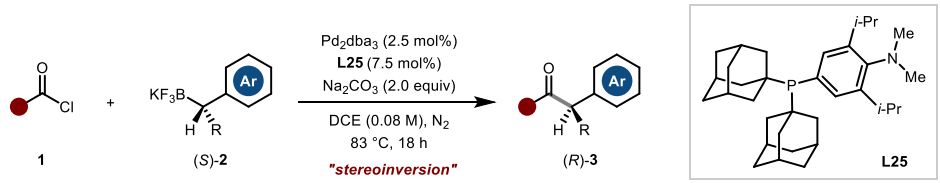


[a]Unless otherwise noted, the reactions were conducted with **1a** (2.0 equiv), (*S*)-**2b** (0.1 mmol), Pd_2dba_3 (2.5 mol%), **ligand** (7.5 mol%), and Na_2CO_3 (2.0 equiv) in DCE (1.2 mL) at 83 °C for 18 h under nitrogen atmosphere. The yields indicate ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard. The enantiomeric excess was determined by HPLC analysis

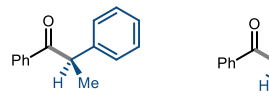
Next, the range of reactivity of the acyl donor was evaluated using either a commercially available acid chloride or a reagent generated *in situ* from the corresponding carboxylic acid. Placement of a variety of substituents with different electronic properties on the arene ring of the acyl donor was well tolerated (**3bb**–**3ib**). The substrate derived from chloroarene was also found to be suitable for product formation, demonstrating the mildness of the reaction conditions (**3gb**). Sterically encumbered substrates could be conveniently subjected to this protocol to afford the corresponding products in synthetically useful yields (**3fb** and **3ib**).

Notably, medicinally important heterocycles, such as furan (**3jb**), thiophene (**3kb** and **3lb**), pyrrole (**3mb**) and indole (**3nb**) could be successfully incorporated into the product. Therefore, pharmaceutically relevant structural motifs, including a natural product analogue (**3jb**), could be constructed in an enantiopure form.[18] Furthermore, aliphatic acid chlorides also exhibited the desired reactivity (**3ob**–**3qb**). Interestingly, sterically demanding acid chlorides exhibited even greater efficiency in terms of product formation (**3pb**) than substrates containing a smaller aliphatic alkyl group (**3qb**–**3sb**). Finally, to further demonstrate the synthetic robustness of this strategy, we attempted the direct functionalization of complex commercial pharmaceuticals

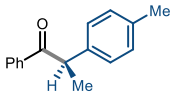
Table 2. Stereospecific Pd-catalyzed acylative cross-coupling reaction for the synthesis of chiral ketones[a]



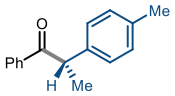
applicability of trifluoroborates with 1a (benzoyl chloride)



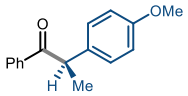
3aa, 68% yield
96% ee, 99% es



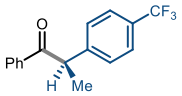
3ab, 75% yield
97% ee, 98% es



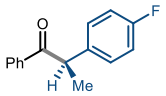
(*S*)-**3ab**, 73% yield
97% ee, 98% es
(from 97% ee (*R*)-**2b**)



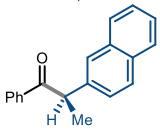
3ac, 85% yield
94% ee, >99% es



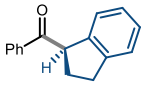
3ad, 83% yield
97% ee, >99% es



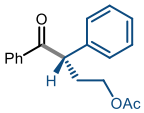
3ae, 88% yield
99% ee, >99% es



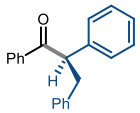
3af, 60% yield
92% ee, 95% es



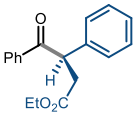
3ag, 70% yield
90% ee, 91% es



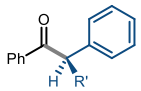
(*S*)-**3ah**, 61% yield
93% ee, 94% es
(from 99% ee (*R*)-**2h**)



3ai, 30% yield
96% ee, 98% es

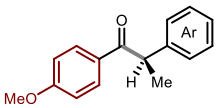


3aj, 25% yield
82% ee, 96% es

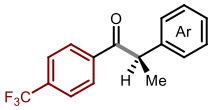


3ak, R' = Et, <5% yield
3al, R' = *iso*-Pr, trace
3am, R' = *tert*-Bu, N.R

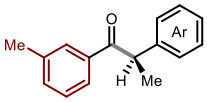
applicability of (hetero)aryl carbonyl chlorides with 2b (Ar = p-tol)



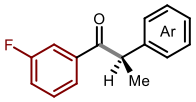
3bb, 68% yield
99% ee, >99% es



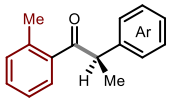
3cb, 58% yield
96% ee, 97% es



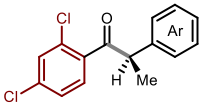
3db, 72% yield
97% ee, 98% es



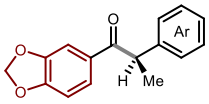
3eb, 62% yield
94% ee, 95% es



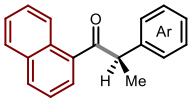
3fb, 43% yield
96% ee, 97% es



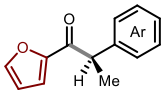
3gb, 47% yield
94% ee, 95% es



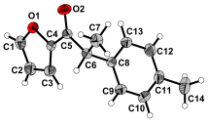
3hb, 83% yield
97% ee, 98% es



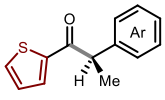
3ib, 68% yield
93% ee, 94% es



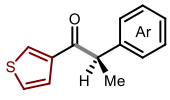
3jb, 80% yield
99% ee, >99% es



X-ray of **3jb**

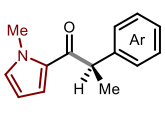


3kb, 83% yield
98% ee, 99% es

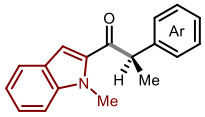


3lb, 65% yield
98% ee, 99% es

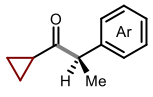
applicability of alkyl carbonyl chlorides with 2b (Ar = p-tol)



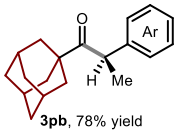
3mb, 78% yield
98% ee, 99% es



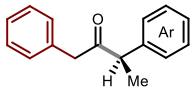
3nb, 60% yield
98% ee, 99% es



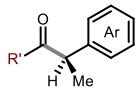
3ob, 25% yield
70% ee, 71% es



3pb, 78% yield
90% ee, 91% es

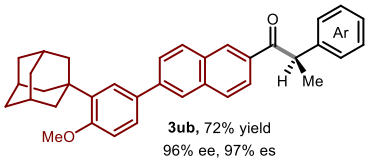


3qb, 10% yield
92% ee, 93% es

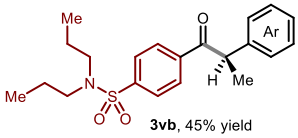


3rb, R' = CH_2CH_2Ph, <5%
3sb, R' = isopropyl, N.R

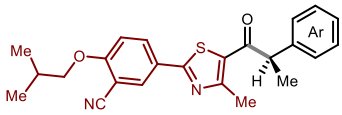
applicability of carbonyl chlorides derived from pharmaceuticals with 2b (Ar = p-tol)



3ub, 72% yield
96% ee, 97% es
from adapalene



3vb, 45% yield
96% ee, 97% es
from probenecid



3wb, 63% yield
94% ee, 95% es
from febuxostat

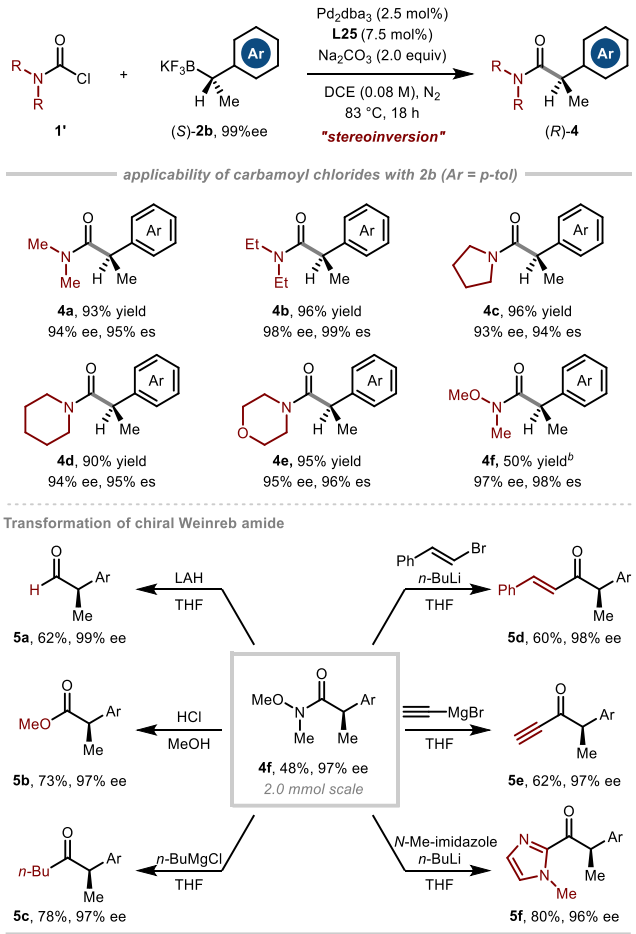
[a]Unless otherwise noted, the reactions were conducted with **1** (2.0 equiv), (*S*)-**2** (0.2 mmol), Pd_2dba_3 (2.5 mol%), **L25** (7.5 mol%), and Na_2CO_3 (2.0 equiv) in DCE (2.4 mL) at 83 °C for 18 h under nitrogen atmosphere. All yields are of purified products. The enantiomeric excess was determined by HPLC analysis.

(**3ub**–**3wb**). Acid chlorides originating from adapalene, probenecid, and febuxostat were successfully employed to afford the corresponding ketone products in synthetically useful yields with excellent stereochemical integrity. The complex architecture of these bioactive molecules remained intact throughout the transformation.

Thereafter, we applied the developed synthetic strategy to the preparation of carboxylic acid derivatives (**Table 3**). Readily available carbamoyl chlorides could be successfully incorporated into the catalytic carbamoylation process to furnish chiral α-aryl amides. Both acyclic and cyclic carbamoyl chlorides were competent reaction partners for this transformation, affording the desired chiral amides (**4a**–**4e**). Importantly, *N*-methoxy-*N*-methylcarbamoyl chloride could be used efficiently as the carbamoyl donor under slightly modified conditions to yield the corresponding Weinreb amide (**4f**).[19] Moreover, the protocol has been demonstrated to be amenable to a scale-up reaction. No significant loss of reactivity was observed with a 10-fold increase in reaction scale. Accordingly, using the Weinreb amide as the key intermediate, the developed strategy could be advanced to a general synthetic protocol for the preparation of val-

uable chiral α-aryl carbonyl compounds. Simple hydride addition or Fisher esterification could be used to construct the corresponding aldehyde or methyl ester with complete preservation of stereochemical integrity (**5a** and **5b**). We also found that

Table 3. Stereospecific synthesis of carboxylic acid derivatives[a]



[a]Unless otherwise noted, the reactions were conducted with **1** (2.0 equiv), (*S*)-**2b** (0.1 mmol), Pd_2dba_3 (2.5 mol%), **L25** (7.5 mol%), and Na_2CO_3 (2.0 equiv) in DCE (1.2 mL) at 83 °C for 18 h under nitrogen atmosphere. [b]PAd_3 (7.5 mol%) was used instead of **L25**. All yields are of purified products. The enantiomeric excess was determined by HPLC analysis.

nucleophilic substitution with a carbon-based organometallic reagent can provide a range of synthetically challenging chiral ketones. For instance, the addition of a primary alkyl nucleophile resulted in the formation of an alkyl ketone (**5c**), which is difficult to access using the direct addition of a trifluoroborate to an acid chloride (**Table 2**, **3rb** and **3sb**). Furthermore, the addition of C(sp^2)- or C(sp)-based carbon nucleophiles was demonstrated to be viable, affording delicate α,β-unsaturated ketones (**5d** and **5e**). Finally, a direct installation of a heterocycle was performed to furnish a pharmaceutically relevant carbonyl compound (**5f**). In all these cases, the stereospecificity was consistently high.

We then explored the origin of the high stereospecificity of the catalytic system based on detailed mechanistic investigations. In a stereospecific cross-coupling reaction of chiral organoboron reagents, the stereochemical outcome is governed by the mechanism over the course of transmetalation, which usually follows an S_E2-type mechanism.[7] A stereoretentive pathway is commonly observed, although several factors, including internal coordination by the substrate,[20] supporting ligand,[21] steric nature of nucleophile[22] or additives[23] are known to influence the process. To shed light on the robust stereoinvertive transmetalation of our system, we used density functional theory computations using Gaussian 16 with PBE-D3BJ/6-31G(d) and LANL2DZ. A solvent model based on density was employed for DCE at 83 °C (**Figure 2**, **A**). Metal coordination to the transition structures as well as various intermediates were investigated to capture the thermodynamically most likely coordination environment (*see SI for details*).

The overall process commences with the oxidative addition of palladium(0) species (**I**), doubly ligated with the catalytically relevant ligand APhos (**L23**), to carbonyl chloride **1a** to form the corresponding oxidative addition complex (**II**) (**Figure 2**, **A**). The dissociation of one phosphine ligand leads to the formation of the reactive acylpalladium(II) species (**III**) to set the stage for the subsequent transmetalation.[24] The ligand dissociation process from an analogous complex with a smaller ligand (**II'** to **III'**, L = PPh_3) was disfavored by at least 10.8 kcal/mol owing to the low energy of the bisligated palladium species **II'**. These energy profiles are consistent with the experimental observation that the reaction with a smaller ligand results in diminished reactivity over a bulky ligand (**Table 1**). The potential formation of a cationic palladium species (**III** to **III''**) through liberation of the chloride ligand was demonstrated to be energetically unfavorable. Presumably, the nonpolar nature of the reaction medium disfavors the commonly postulated prerequisite step for a facile transmetalation.[16f]

Eventually, by comparing the two transition states for transmetalation, the origin of the observed selectivity could be explained (**Figure 2**, **B**).[25] The transition state leading to inversion of the stereochemistry (**TS^{inv}-IV**) was calculated to be lower in energy than that of retention (**TS^{ret}-IV**) by 2.3 kcal/mol, a number fully consistent with the observed level of selectivity. Interestingly, the **TS^{inv}-IV** exhibits a cyclic array of reaction partners interlocked by the coordination of the potassium ion.[26] The involvement of the cyclic transition state forces the Pd–C–B angle to deviate from the conventionally proposed 180° arrangement (135.6°), allowing efficient transmetalation. The unprecedented interplay of multiple metal-halogen interactions in the transition state is made possible by the direct participation of the unhydrolyzed trifluoroborate ion, underscoring the importance of the anhydrous reaction medium.[16a-c,f] Importantly, the related transition states without the potassium ion were demonstrated to be significantly higher in energy for both inversion and retention (*See SI for details*).[27] Finally, reductive elimination from complex **V** completes the stereoselective cross-coupling process (**TS-VI**).

In conclusion, we have developed a new Pd-catalyzed method for the preparation of valuable chiral α-aryl carbonyl compounds. The method exploits a direct use of activated acyl and carbamoyl donors that react with stereochemically enriched benzylic trifluoroborates in a highly stereospecific fashion. By utilizing the strategy, a wide range of α-arylated ketones and carboxylic acid derivatives were prepared with high stereochemical integrity. The process was successfully mediated by a catalyst system supported by a bulky and electron-rich monodentate dialkylaryl phosphine ligand. In addition, a unique metal-halogen interaction in the transition state was identified

to facilitate a novel invertive transmetalation process at the sp^3-hybridized reaction center. It is expected that the mechanistic insights attained from this study should extend the applicability of the C(sp^3)-based organometallic compounds to a more general setting.

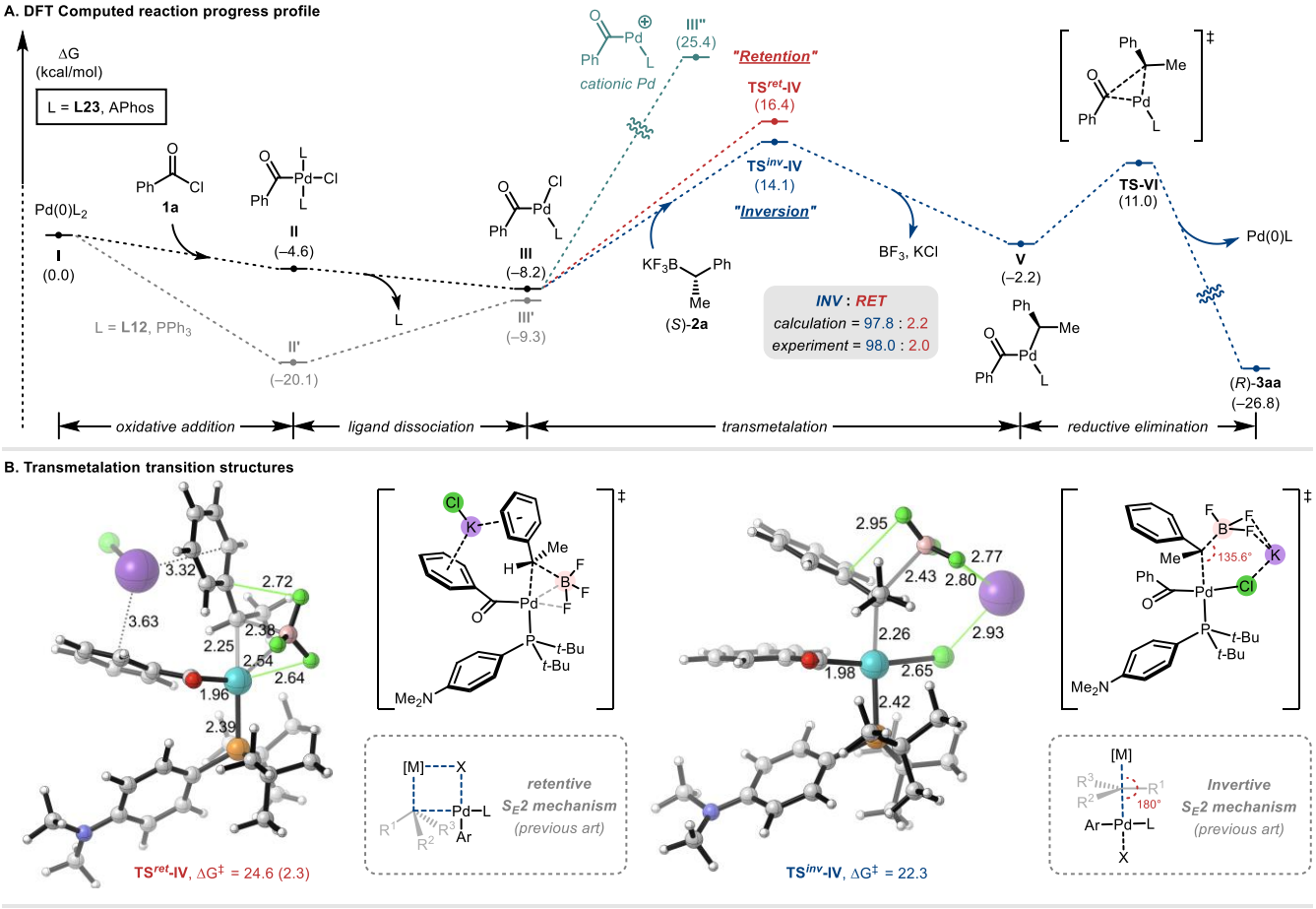


Figure 2. DFT computed reaction progress profile (Top, A); Transmetalation transition structures, energies in kcal/mol, distances in Å (Bottom, B).

ASSOCIATED CONTENT

General information, method for synthesis of substrates, optimization in details, general experimental procedures, compounds characterization, density functional theory (DFT), details of HPLC and NMR spectra.

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REFERENCES

(1) (a) Sarabu, R.; Bizzarro, F. T.; Corbett, W. L.; Dvorozniak, M. T.; Geng, W.; Grippo, J. F.; Haynes, N.-E.; Hutchings, S.; Garofalo, L.; Guertin, K. R.; Hilliard, D. W.; Kabat, M.; Kester, R. F.; Ka, W.; Liang, Z.; Mahaney, P. E.; Marcus, L.; Matschinsky, F. M.; Moore, D.; Racha,

J.; Radinov, R.; Ren, Y.; Qi, L.; Pignatello, M.; Spence, C. L.; Steele, T.; Tengi, J.; Grimsby, J. Discovery of Piragliatin−First Glucokinase Activator Studied in Type 2 Diabetic Patients. *J. Med. Chem.* **2012**, *55*, 7021−7036. (b) Harrington, P. J.; Lodewijk, E. Twenty Years of Naproxen Technology. *Org. Process Res. Dev.* **1997**, *1*, 72−76. (c) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. Cortistatins A, B, C, and D, Anti-angiogenic Steroidal Alkaloids, from the Marine Sponge Corticium simplex. *J. Am. Chem. Soc.* **2006**, *128*, 3148−3149.

(2) For representative reviews on enantioselective α-arylation, see: (a) Hao, Y.-J.; Hu, X.-S.; Zhou, Y.; Zhou, J.; Yu, J.-S. Catalytic Enantioselective α-Arylation of Carbonyl Enolates and Related Compounds. *ACS Catal.* **2020**, *10*, 955−993. (b) Orlandi, M.; Escudero-Casao, M.; Licini, G. Transition-Metal-Catalyzed Enantioselective α-Arylation of Carbonyl Compounds to Give Tertiary Stereocenters. *Synthesis* **2021**, *53*, 4559–4566.

(3) For selected recent advances, see: (a) Yin, H; Fu, G. C. Mechanistic Investigation of Enantioconvergent Kumada Reactions of Racemic α-Bromoketones Catalyzed by a Nickel/Bis(oxazoline) Complex. *J. Am. Chem. Soc.* **2019**, *141*, 15433–15440. (b) Escudero-Casao, M.; Licini, G.; Orlandi, M. Enantioselective α-Arylation of Ketones via a Novel Cu(I)−Bis(phosphine) Dioxide Catalytic System. *J. Am. Chem. Soc.* **2021**, *143*, 3289−3294. (c) Kalkman, E. D.; Hartwig, J. F., Direct Observation of Diastereomeric α-C-Bound Enolates during Enantioselective α-Arylations: Synthesis, Characterization, and Reactivity of Arylpalladium Fluorooxindole Complexes. *J. Am. Chem. Soc.* **2021**, *143*, 11741–11750.

(4) For examples on reductive cross-coupling with α-halo carbonyl compounds, see: (a) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. Catalytic Asymmetric Reductive Acyl Cross-Coupling: Synthesis of Enantioenriched Acyclic α,α-Disubstituted Ketones. *J. Am. Chem. Soc.* **2013**, *135*, 7442−7445. (b) Kadunce, N. T.; Reisman, S. E. Nickel Catalyzed Asymmetric Reductive Cross-Coupling between Heteroaryl Iodides and α-Chloronitriles. *J. Am. Chem. Soc.* **2015**, *137*, 10480−10483. (c) Guan, H.; Zhang, Q.; Walsh, P. J.; Mao, J. Nickel/Photoredox-Catalyzed Asymmetric Reductive Cross-Coupling of Racemic α-Chloro Esters with Aryl Iodides. *Angew. Chem., Int. Ed.* **2020**, *59*, 5172−5177. (d) Chen, J.; Zhu, S. Nickel-Catalyzed Multicomponent Coupling: Synthesis of α-Chiral Ketones by Reductive Hydrocarbonylation of Alkenes. *J. Am. Chem. Soc.* **2021**, *143*, 14089−14096. (e) DeLano, T. J.; Dibrell, S. E.; Lacker, C. R.; Pancoast, A. R.; Poremba, K. E.; Cleary, L. B.; Sigman, M. S.; Reisman, S. E. Nickel-Catalyzed Asymmetric Reductive Cross-Coupling of α-Chloroesters with (Hetero)Aryl Iodides. *Chem. Sci.* **2021**, *12*, 7758−7762.

(5) (a) Kang, B. C.; Nam, D. G.; Hwang, G.; Ryu, D. H. Catalytic Asymmetric Formal Insertion of Aryldiazoalkanes into the C−H Bond of Aldehydes: Synthesis of Enantioenriched Acyclic α-Tertiary Aryl Ketones. *Org. Lett.* **2015**, *17*, 4810−4813. (b) Oost, R.; Misale, A.; Maulide, N. Enantioconvergent Fukuyama Cross-Coupling of Racemic Benzylic Organozinc Reagents. *Angew. Chem., Int. Ed.* **2016**, *55*, 4587−4590. (c) Bandar, J. S.; Ascic, E.; Buchwald, S. L. Enantioselective CuH-catalyzed reductive coupling of aryl alkenes and activated carboxylic acids. *J. Am. Chem. Soc.* **2016**, *138*, 5821−5824. (d) Zhou, Y.; Bandar, J. S.; Buchwald, S. L. Enantioselective CuH-catalyzed hydroacylation employing unsaturated carboxylic acids as aldehyde surrogates. *J. Am. Chem. Soc.* **2017**, *139*, 8126−8129. (e) Yang, J.; Rerat, A.; Lim, Y. J.; Gosmini, C.; Yoshikai, N. Cobalt-Catalyzed Enantio- and Diastereoselective Intramolecular Hydroacylation of Trisubstituted Alkenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 2449−2453. (f) Huang, Y.; Smith, K. B.; Brown, M. K. Copper-catalyzed Borylacylation of Activated Alkenes with Acid Chlorides. *Angew. Chem., Int. Ed.* **2017**, *56*, 13314−13318. (g) Gandolfo, E.; Tang, X.; Roy, S. R.; Melchiorre, P. Photochemical Asymmetric Nickel-Catalyzed Acyl Cross-Coupling. *Angew. Chem., Int. Ed.* **2019**, *58*, 16854−16858. (h) Huan, L.; Shu, X.; Zu, W.; Zhong, D.; Huo, H. Asymmetric Benzylic C(sp^3)−H Acylation via Dual Nickel and Photoredox Catalysis. *Nat. Commun.* **2021**, *12*, 3536. (i) Feng, S.; Dong, Y.; Buchwald, S. L. Enantioselective Hydrocarbamoylation of Alkenes. *Angew. Chem. Int. Ed.* **2022**, e202206692.

(6) (a) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. Enantioselective Protonation. *Nat. Chem.* **2009**, 1, 359−369. (b) Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L. A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. Asymmetric Photoredox Transition-Metal Catalysis Activated by Visible Light. *Nature* **2014**, *515*, 100−103. (c) Zhang, L.; Meggers, E. Steering Asymmetric Lewis Acid Catalysis Exclusively with Octahedral Metal Centered Chirality. *Acc. Chem. Res.* **2017**, *50*, 320−330. (d) Li, J.; Berger, M.; Zawodny, W.; Simaan, M.; Maulide, N. A Chemoselective α-Oxytriflation Enables the Direct Asymmetric Arylation of Amides. *Chem.* **2019**, *5*, 1883−1891. (e) Guo, L.; Yuan, M.; Zhang, Y.; Wang, F.; Zhu, S.; Gutierrez, O.; Chu, L. General Method for Enantioselective Three-Component Carboarylation of Alkenes Enabled by Visible-Light Dual Photoredox/Nickel Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 20390−20399. (f) Cao, J.; Zhu, S.-F. Catalytic Enantioselective Proton Transfer Reactions. *Bull. Chem. Soc. Jpn.* **2021**, *94*, 767−789. (g) Zhang, C.; Gao, A. Z.; Nie, X.; Ye, C.-X.; Ivlev, S. I.; Chen, S.; Meggers, E. Catalytic α-Deracemization of Ketones Enabled by Photoredox Deprotonation and Enantioselective Protonation. *J. Am. Chem. Soc.* **2021**, *143*, 13393−13400. (h) Kong, M.; Tan, Y.; Zhao, X.; Qiao, B.; Tan, C.-H.; Cao, S.; Jiang, Z. Catalytic Reductive Cross Coupling and Enantioselective Protonation of Olefins to Construct Remote Stereocenters for Azaarenes. *J. Am. Chem. Soc.* **2021**, *143*, 4024−4031. (i) Huang, M.; Zhang, L.; Pan, T.; Luo, S. Deracemization through photochemical E/Z isomerization of enamines. *Science* **2022**, *375*, 869−874.

(7) For representative reviews on stereospecific cross-coupling, see: (a) Wang, C.-Y.; Derosa, J.; Biscoe, M. R. The use of stable, optically active organometallic nucleophiles in cross-coupling reactions. *Chem. Sci.* **2015**, *6*, 5105−5113. (b) Leonori, D.; Aggarwal, V. K. Stereospecific Couplings of Secondary and Tertiary boronic esters. *Angew. Chem. Int. Ed.* **2015**, *54*, 1082−1096. (c) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents To Construct C–C bonds. *Chem. Rev.* **2015**, *115*, 9587−9652. (d) Rygus, J. P. G.; Crudden, C. M. Enantiospecific and Iterative Suzuki–Miyaura cross-couplings. *J. Am. Chem. Soc.* **2017**, *139*, 18124−19137. (e) Ma, X.; Murray, B.; Biscoe, M. R. Stereoselectivity in Pd-catalysed cross-coupling reactions of enantioenriched nucleophiles. *Nat. Rev. Chem.* **2020**, 4, 584−599.

(8) For selected examples on stereospecific Pd-catalyzed acylative Stille cross-coupling, see: (a) Ye, J.; Bhatt, R. K.; Falck, J. R. Stereospecific Palladium/Copper Cocatalyzed Cross-Coupling of α-Alkoxy- and α-Aminostannanes with Acyl chlorides. *J. Am. Chem. Soc.* **1994**, *116*, 1−5. (b) Kells, K. W.; Chong, J. M. Stille Coupling of Stereochemically Defined α-Sulfonamidoorganostannanes. *J. Am. Chem. Soc.* **2004**, *126*, 15666−15667. (c) Wang, C.-Y.; Ralph, G.; Derosa, J.; Biscoe, M. R. Stereospecific Palladium-Catalyzed Acylation of Enantioenriched Alkylcarbastannatranes: A General Alternative to Asymmetric Enolate reactions. *Angew. Chem. Int. Ed.* **2017**, *56*, 856−860. (d) Zhu, F.; Rodriguez, J.; O'Neill, S.; Walczak, M. A. Acyl Glycosides through Stereospecific Glycosyl Cross-Coupling: Rapid Access to C(sp^3)-Linked Glycomimetics. *ACS Cent. Sci.* **2018**, *4*, 1652−1662. (e) Ma, X.; Zhao, H.; Binayeva, M.; Ralph, G.; Diane, M.; Zhao, S.; Wang, C.-Y.; Biscoe, M. R. A General Approach to Stereospecific Cross-Coupling Reactions of Nitrogen-Containing Stereocenters. *Chem* **2020**, *6*, 781−791.

(9) For representative reviews on borylation, see: (a) Leonori, D.; Aggarwal, V. K. Lithiation−Borylation Methodology and Its Application in Synthesis. *Acc. Chem. Res.* **2014**, *47*, 3174−3183. (b) Collins, B. S. L.; Wilson, C. M.; Myers, E. L.; Aggarwal, V. K. Asymmetric Synthesis of Secondary and Tertiary Boronic Esters. *Angew. Chem., Int. Ed.* **2017**, *56*, 11700−11733. (c) Friese, F. W.; Studer, A. New Avenues for C−B Bond Formation via Radical Intermediates. *Chem. Sci*. **2019**, *10*, 8503. (d) Wang, M.; Shi, Z. Methodologies and Strategies for Selective Borylation of C−Het and C−C Bonds. *Chem. Rev.* **2020**, 120, 7348−7398. (e) Tian, Y.-M.; Guo, X.-N.; Braunschweig, H.; Radius, U.; Marder, T. B. Photoinduced Borylation for the Synthesis of Organoboron Compounds. *Chem. Rev.* **2021**, *121*, 3561. (f) Hu, J.; Ferger, M.; Shi, Z.; Marder, T. B. Recent Advances in Asymmetric Borylation by Transition Metal Catalysis. *Chem. Soc. Rev.* **2021**, *50*, 13129−13188.

(10) For representative reviews on applications of organoboron compounds, see: (a) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron compounds. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062−5085. (c) Maluenda, I.; Navarro, O. Recent Developments in the Suzuki-Miyaura reaction: 2010–2014. *Molecules* **2015**, *20*,

7528–7557. (d) Lennox, A.J.J.; Lloyd-Jones, G.C. Selection of boron reagents for Suzuki-Miyaura coupling. *Chem. Soc. Rev.* **2014**, *43*, 412–443. (e) Defrancesco, H.; Dudley, J.; Coca, A. Boron Chemistry: An Overview. *ACS Symp. Ser.* **2016**, *1236*, 1–25. (f) Fyfe, J. W. B.; Watson, A. J. B. Recent Developments in Organoboron Chemistry: Old Dogs, New Tricks. *Chem.* **2017**, *3*, 31−55. (g) Sandford, C.; Aggarwal, V. K. Stereospecific functionalizations and transformations of secondary and tertiary boronic esters. *Chem. Commun.* **2017**, *53*, 5481−5494. (h) Beletskaya, I. P.; Alonso, F.; Tyurin, V. The Suzuki-Miyaura reaction after the Nobel prize. *Coord. Chem. Rev.* **2019**, *385*, 137−173. (i) Buchspies, J.; Szostak, M. Recent Advances in Acyl Suzuki Cross-Coupling. *Catalysts* **2019**, *9*, 53. (j) El-Maiss, J.; Mohy El Dine, T.; Lu, C.-S.; Karame, I.; Kanj, A.; Polychronopoulou, K.; Shaya, J. Recent Advances in Metal-Catalyzed Alkyl−Boron ($C(sp^3)$−$C(sp^2)$) Suzuki-Miyaura Cross-Couplings. *Catalysts* **2020**, 10, 296.

(11) For examples of non-stereoselective acylation of alkyl organoboron reagents, see: (a) Amani, J.; Sodagar, E.; Molander, G. A. Visible Light Photoredox Cross-Coupling of Acyl Chlorides with Potassium Alkoxymethyltrifluoroborates: Synthesis of α-Alkoxyketones. *Org. Lett.* **2016**, *18*, 732−735. (b) Amani, J.; Molander, G. A. Synergistic Photoredox/Nickel Coupling of Acyl Chlorides with Secondary Alkyltrifluoroborates: Dialkyl Ketone Synthesis. *J. Org. Chem.* **2017**, *82*, 1856−1863 (c) Amani, J.; Alam, R.; Badir, S.; Molander, G. Synergistic Visible-Light Photoredox/Nickel-Catalyzed Synthesis of Aliphatic Ketones via N−C Cleavage of Imides. *Org. Lett.* **2017**, *19*, 2426–2429. (d) Amani, J.; Molander, G. A. Direct Conversion of Carboxylic Acids to Alkyl Ketones. *Org. Lett.* **2017**, *19*, 3612−3615. (e) Masson-Makdissi, J.; Vandavasi, J.; Newman, S. Switchable Selectivity in the Pd-Catalyzed Alkylative Cross-Coupling of Esters. *Org. Lett.* **2018**, *20*, 4094–4098. (f) Chatupheeraphat, A.; Liao, H.-H.; Srimontree, W.; Guo, L.; Minenkov, Y.; Poater, A.; Cavallo, L.; Rueping, M. Ligand-Controlled Chemoselective C(acyl)–O Bond vs C(aryl)–C Bond Activation of Aromatic Esters in Nickel Catalyzed $C(sp^2)$–$C(sp^3)$ Cross-Couplings. *J. Am. Chem. Soc.* **2018**, *140*, 3724–3735. (g) Liu, X.; Hsiao, C.; Guo, L.; Rueping, M. Cross-Coupling of Amides with Alkylboranes via Nickel-Catalyzed C−N Bond Cleavage. *Org. Lett.* **2018**, *20*, 2976–2979. (h) Shi, W.; Zou, G. Palladium-Catalyzed Room Temperature Acylative Cross-Coupling of Activated Amides with Trialkylboranes. *Molecules* **2018**, *23*, 2412. (i) Meng, G.; Szostak, M. Palladium/NHC (NHC = N-Heterocyclic Carbene)-Catalyzed B-Alkyl Suzuki Cross-Coupling of Amides by Selective N−C Bond Cleavage. *Org. Lett.* **2018**, *20*, 6789–6793. (j) Zheng, Y. L.; Xie, P. P.; Daneshfar, O.; Houk, K. N.; Hong, X.; Newman, S. G. Direct Synthesis of Ketones from Methyl Esters by Nickel-Catalyzed Suzuki-Miyaura Coupling. *Angew. Chem., Int. Ed.* **2021**, *60*, 13476−13483. (k) Huang, H.; Dai, Q.-S.; Leng, H.-J.; Li, Q.-Z.; Yang, S.-L.; Tao, Y.-M.; Zhang, X.; Qi, T.; Li, J.-L. Suzuki-type cross-coupling of alkyl trifluoroborates with acid fluoride enabled by NHC/photoredox dual catalysis. *Chem. Sci.* **2022**, *13*, 2584–2590.

(12) For diastereoselective acylative coupling of alkyl organoboron reagents, see: Chen, H.; Deng, M.-Z. A novel stereocontrolled synthesis of 1,2-trans cyclopropyl ketones via Suzuki-type coupling of acid chlorides with cyclopropylboronic acids. *Org. Lett.* **2000**, *2*, 1649−1651.

(13) During the preparation of this manuscript, a Cu-catalyzed stereoretentive acylation of chiral alkylboron compounds has been reported by the Morken group, see: Xu, N; Liang, H; Morken, J. P. Copper-Catalyzed Stereospecific Transformations of Alkylboronic Esters. *J. Am. Chem. Soc.* **2022**, *144*, 11546−11552.

(14) (a) Molander, G. A.; Bernardi, C. R. Suzuki−Miyaura Cross-Coupling Reactions of Potassium Alkenyltrifluoroborates. *J. Org. Chem.* **2002**, *67*, 8424−8429. (b) Molander, G. A.; Ellis, N. Organotrifluoroborates: Protected Boronic Acids That Expand the Versatility of the Suzuki Coupling Reaction. *Acc. Chem. Res.* **2007**, *40*, 275−286. (c) Molander, G. A. Organotrifluoroborates: Another Branch of the Mighty Oak. *J. Org. Chem.* **2015**, *80*, 7837−7848.

(15) Rigorously anhydrous conditions using a glovebox were required for the best result. However, a synthetically useful yield could still be obtained simply by applying the straightforward Schlenk technique ((*R*)-**3ab**, 51% yield, 97% ee).

(16) For selected examples on cross-coupling reactions of organoboron reagents under strictly non-aqueous or non-protic conditions, see: (a) Adonin, N. Y.; Babushkin, D. E.; Parmon, V. N.; Bardin, V. V.; Kostin, G. A.; Mashukov, V. I.; Frohn, H.-J. The Effect of N-Heterocyclic Carbene Ligands in The Palladium-Catalyzed Cross-Coupling Reaction of $K[C_6F_5BF_3]$ With Aryl Iodides and Aryl Bromides. *Tetrahedron* **2008**, *64*, 5920−5924. (b) Wang, B.; Sun, H.-X.; Sun, Z.-H. A general and efficient Suzuki-Miyaura cross-coupling protocol using weak base and no water: the essential role of acetate. *Eur. J. Org. Chem.* **2009**, 2009, 3688–3692. (c) Shabalin, A. Y.; Adonin, N. Y.; Bardin, V. V.; Parmon, V. N. The influence of the nature of phosphine ligand on palladium catalysts for cross-coupling of weakly nucleophilic potassium pentafluorophenyltrifluoroborate with ArHal and $PhCH_2Hal$ (Hal = Br, Cl). *Tetrahedron* **2014**, *70*, 3720−3725. (d) Delaney, C. P.; Kassel, V. M.; Denmark, S. E. Potassium Trimethylsilanolate Enables Rapid, Homogeneous Suzuki−Miyaura Cross-Coupling of Boronic Esters. *ACS Catal.* **2020**, *10*, 73−80. (e) Kassel, V. M.; Hanneman, C. P.; Delaney, C. P.; Denmark, S. E. Heteroaryl-Heteroaryl, Suzuki-Miyaura, Anhydrous Cross-coupling Reactions Enabled by Trimethyl Borate. *J. Am. Chem. Soc.* **2021**, *143*, 13845−13853. (f) Niwa, T.; Uetake, Y.; Isoda, M.; Takimoto, T.; Nakaoka, M.; Hashizume, D.; Sakurai, H.; Hosoya, T. Lewis acid-mediated Suzuki−Miyaura cross-coupling reaction. *Nat. Catal.* **2021**, *4*, 1080−1088. (g) Delaney, C. P.; Marron, D. P.; Shved, A. S.; Zar, R. N.; Waymouth, R. M.; Denmark, S. E. Potassium Trimethylsilanolate-Promoted, Anhydrous Suzuki–Miyaura Cross-Coupling Reaction Proceeds via the "Boronate Mechanism": Evidence for the Alternative Fork in the Trail. *J. Am. Chem. Soc.* **2022**, *144*, 4345-4364.

(17) Sinai, Á.; Simkó, D. C.; Szabó, F.; Paczal, A.; Gáti, T.; Bényei, A.; Novák, Z.; Kotschy, A. Aryl-Diadamantyl Phosphine Ligands in Palladium-Catalyzed Cross-Coupling Reactions: Synthesis, Structural Analysis, and Application. *Eur. J. Org. Chem.* **2020**, *2020*, 1122−1128.

(18) (a) Fraga, B. M. Natural sesquiterpenoids. *Nat. Prod. Rep.* **2013**, *30*, 1226−1264. (b) Tharra, P.; Baire, B. Mild Approach to 2-Acylfurans via Intercepted Meyer−Schuster Rearrangement of 6-Hydroxyhex-2-en-4-ynals. *J. Org. Chem.* **2015**, *80*, 8314−8328.

(19) (a) Nahm, S.; Weinreb, S. M. N-Methoxy-N-methylamides as effective acylating agents. *Tetrahedron Lett.* **1981**, 22, 3815−3818. (b) Senatore, R.; Ielo, L.; Monticelli, S.; Castoldi, L.; Pace, V. Weinreb Amides as Privileged Acylating Agents for Accessing α-Substituted Ketones. *Synthesis* **2019**, *51*, 2792−2808.

(20) (a) Ohmura, T.; Awano, T.; Suginome, M. Stereospecific Suzuki-Miyaura coupling of chiral α-(acylamino)benzylboronic Esters with Inversion of Configuration. *J. Am. Chem. Soc.* **2010**, *132*, 13191–13193. (b) Sandrock, D. L.; Jean-Gérard, L.; Chen, C.-y; Dreher, S. D.; Molander, G. A. Stereospecific cross-coupling of secondary alkyl β-trifluoroboratoamides. *J. Am. Chem. Soc.* **2010**, *132*, 17108–17110. (c) Lee, J. C. H.; McDonald, R.; Hall, D. G. Enantioselective preparation and chemoselective cross-coupling of 1,1-diboron compounds. *Nat. Chem.* **2011**, *3*, 894–899. (d) Molander, G. A.; Wisniewski, S. R. Stereospecific Cross-Coupling of Secondary Organotrifluoroborates: Potassium 1-(Benzyloxy)alkyltrifluoroborates. *J. Am. Chem. Soc.* **2012**, *134*, 16856–16868.

(21) (a) Zhao, S.; Gensch, T.; Murray, B.; Niemeyer, Z. L.; Sigman, M. S.; Biscoe, M. R. Enantiodivergent Pd-Catalyzed C–C Bond Formation Enabled through Ligand Parameterization. *Science* **2018**, 362, 670−674. (b) Lehmann, J. W.; Crouch, I. T.; Blair, D. J.; Trobe, M.; Wang, P.; Li, J.; Burke, M. D. Axial Shielding of Pd(II) Complexes Enables Perfect Stereoretention in Suzuki-Miyaura Cross-Coupling of Csp^3 Boronic Acids. *Nat. Commun.* **2019**, 10, 1263.

(22) (a) Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R. Stereospecific Pd-Catalyzed Cross-Coupling Reactions of Secondary-Alkylboron Nucleophiles and Aryl Chlorides. *J. Am. Chem. Soc.* **2014**, 136, 14027−14030. (b) Murray, B.; Zhao, S.; Aramini, J. M.; Wang, H.; Biscoe, M. R. *ACS Catal.* **2021**, *11*, 2504–2510.

(23) (a) Awano, T.; Ohmura, T.; Suginome, M. Inversion or retention? Effects of Acidic Additives on the Stereochemical Course in Enantiospecific Suzuki-Miyaura Coupling of α-(acetylamino)benzylboronic Esters. *J. Am. Chem. Soc.* **2011**, *133*, 20738–20741. (b) Lou, Y.; Cao, P.; Jia, T.; Zhang, Y.; Wang, M.; Liao, J. Copper-Catalyzed Enantioselective 1,6-Boration of *para*-Quinone Methides and Efficient Transformation of *gem*-Diarylmethine Boronates to Triarylmethanes. *Angew. Chem., Int. Ed.* **2015**, *54*, 12134−12138. (c) Ohmura, T.; Miwa, K.; Awano, T.; Suginome, M. Enantiospecific Suzuki–Miyaura Coupling

of Nonbenzylic α-(Acylamino)alkylboronic Acid Derivatives. *Chem. Asian J.* **2018**, *13*, 2414–2417.

(24) For selected examples on the involvement of monoligated Pd-complexes in transmetalation, see: (a) Barrios-Landeros, F.; Hartwig, J. F. Distinct Mechanisms for the Oxidative Addition of Chloro-, Bromo-, and Iodoarenes to a Bisphosphine Palladium(0) Complex with Hindered Ligands. *J. Am. Chem. Soc.* **2005**, *127*, 6944−6945. (b) Ariafard, A.; Yates, B. F. Subtle Balance of Ligand Steric Effects in Stille Transmetalation. *J. Am. Chem. Soc*. **2009**, *131*, 13981−13991. (c) McMullin, C. L.; Fey, N.; Harvey, J. N. Computed Ligand Effects on the Oxidative Addition of Phenyl Halides to Phosphine Supported Palladium(0) Catalysts. *Dalt. Trans.* **2014**, *43*, 13545−13556. (d) Zheng, Q.; Liu, Y.; Chen, Q.; Hu, M.; Helmy, R.; Sherer, E. C.; Welch, C. J.; Chen, H. Capture of Reactive Monophosphine-Ligated Palladium(0) Intermediates by Mass Spectrometry. *J. Am. Chem. Soc.* **2015**, *137*, 14035−14038. (e) Lyngvi, E.; Sanhueza, I. A.; Schoenebeck, F. Dispersion Makes the Difference: Bisligated Transition States Found for the Oxidative Addition of $Pd(PtBu_3)_2$ to Ar-OSO_2R and Dispersion-Controlled Chemoselectivity in Reactions with $Pd[P(iPr)(tBu_2)]_2$. *Organometallics* **2015**, *34*, 805−812. (f) Quesnel, J. S.; Moncho, S.; Ylijoki, K. E. O.; Torres, G. M.; Brothers, E. N.; Bengali, A. A.; Arndtsen, B. A. Computational Study of the Palladium-Catalyzed Carbonylative Synthesis of Aromatic Acid Chlorides: The Synergistic Effect of $PtBu_3$ and CO on Reductive Elimination. *Chem. Eur. J.* **2016**, *22*, 15107−15118. (g) Niemeyer, Z. L.; Milo, A.; Hickey, D. P.; Sigman, M. S. Parameterization of Phosphine Ligands Reveals Mechanistic Pathways and Predicts Reaction Outcomes. *Nat. Chem.* **2016**, *8*, 610−617. (h) Sperger, T.; Fisher, H. C.; Schoenebeck, F. Computationally Deciphering Palladium-Catalyzed Reaction Mechanisms. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2016**, *6*, 226−242.

(25) The formation of the transmetalation transition state is initiated by the approach of the nucleophile (*S*)-**2a** to the oxidative addition complex **III**. While the transition state for inversion could be accessed directly from **III** and (*S*)-**2a**, the generation of the transition state for retention required the rearrangement of the chloride (*See SI for details*).

(26) A related interaction has been reported for a ground state Pd complex, see: Wolfe, M. M. W.; Shanahan, J. P.; Kampf, J. W.; Szymczak, N. K. Defluorinative Functionalization of Pd(II) Fluoroalkyl Complexes. *J. Am. Chem. Soc.* **2020**, *142*, 18698−18705.

(27) To further substantiate the involvement of potassium ion for the cyclic transition state, a series of control experiments were carried out in the presence of 18-crown-6 to perturb the proposed metal-halogen interactions. As anticipated, the incorporation of 18-crown-6 proportionally impeded product formation, suggesting the importance of the potassium ion for product formation. During the course, the stereospecificity remained unchanged (*see SI for details*).