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Catalytic Conjunctive Cross-Coupling Enabled by Metal-Induced Metallate Rearrangement

Liang Zhang, Gabriel J. Lovinger, Emma K. Edelstein, Adam A. Szymaniak, Matteo P. Chierchia, and James P. Morken

Department of Chemistry, Boston College, Chestnut Hill, MA 02467

Abstract

Transition metal catalysis plays a central role in contemporary organic synthesis. Considering the tremendously broad array of transition-metal-catalyzed transformations, it is remarkable that the underlying elementary reaction steps are relatively few in number. Here we describe an alternative to the organometallic transmetallation step that is common in many metal-catalyzed reactions such as Suzuki-Miyaura coupling. Specifically, we demonstrate that vinyl boronic ester ate complexes, prepared by combining organoboronates and organolithium reagents, engage in Pd-induced metallate rearrangement wherein 1,2-migration of an alkyl or aryl group from boron to the vinyl α -carbon occurs concomitantly with C-Pd σ -bond formation. This elementary reaction enables a powerful cross-coupling reaction in which a chiral palladium catalyst merges three simple starting materials – an organolithium, an organoboronic ester, and an organotriflate – into chiral organoboronic esters with high enantioselectivity.

Organoboronic acids and their derivatives are widely available and broadly useful starting materials for organic synthesis (1). In addition to being environmentally benign and generally inexpensive, these reagents exhibit a near ideal balance of stability and reactivity. Although chemically and configurationally stable, organoboronic esters engage in a broad array of carbon-carbon and carbon-heteroatom bond-forming processes upon activation. The most commonly practiced such reaction is the transition metal-catalyzed Suzuki-Miyaura cross-coupling reaction between organic electrophiles and organoboron compounds (2). In broad strokes, the mechanism of the Suzuki-Miyaura reaction involves a sequence of (i) oxidative addition between a metal catalyst and the electrophile, (ii) transmetallation with the organoboron reagent, and (iii) reductive elimination of the C-C bonded product (3). Here we present an alternative pathway to the organoboron transmetallation step. The overall putative catalytic cycle enables a class of organoboron cross-coupling that we term “conjunctive cross-coupling” (Fig. 1a) as it merges two nucleophilic reagents into one during the course of the reaction. Overall, the conjunctive cross-coupling constructs chiral products by merging three simple starting materials: an organolithium reagent, an organoboronic ester, and an organic electrophile. The reaction, which adds to recent catalytic alkene carboboration reactions (4,5), establishes two new carbon-carbon bonds and forms a stereogenic center bearing a useful organoboronic ester with high enantioselectivity.

Organoboronic esters are known to participate in a wide range of reactions that occur by stereospecific 1,2-metallate rearrangements (6,7). The preponderance of these reactions occur with a four-coordinate anionic boron centered “ate” complex (Fig. 1b) that rearranges

by a 1,2 carbon shift from boron to an adjacent sp^3 -hybridized electrophilic center (designated “A”) bearing an attached leaving group (X). The stereoelectronic requirements of the metallate shift dictate an antiperiplanar arrangement of the migrating carbon atom (R) and the leaving group such that the overall process is stereoretentive at R, but stereoinvertive at A (8). These processes are common (9) for transformations where the “A” group is a carbon, nitrogen, or oxygen atom, and less common but still established for sulfur and phosphorus (10,11). Because of the stereospecific nature of the above-described processes, stereoselectivity in metallate shifts is generally subject to substrate control (12) though Jadhav and Man reported an example with selectivity dictated by a chiral catalyst (13). 1,2-Metallate rearrangements from boron to sp (14) and sp^2 (15) hybridized carbons often require the addition of an external electrophilic activator (Fig. 1c) and generally the 1,2-metallate shift is followed by elimination to reestablish unsaturation (17). In this context we considered that in place of stoichiometric electrophilic activating agents, π -acidic late transition metals might similarly promote the 1,2-metallate shift of alkenyl boronates (Fig. 1d) and that the resulting organometallic intermediate might be employed in subsequent bond-forming processes.

In one embodiment of catalysis based on metal-induced 1,2-metallate rearrangements, we considered that an electrophilic palladium complex (**II**, Fig. 1e), generated by oxidative addition of **I** with an organic electrophile, might induce 1,2-migration in a vinyl boronate-derived “ate” complex (**III**→**IV**) and establish a new C-C bond and a boron-substituted stereogenic center. Subsequent reductive elimination (**IV**→**I**) would serve to establish a second C-C bond, release the product, and concomitantly furnish a reduced Pd complex that might continue a catalytic cycle. Although π -acidic late transition metal complexes are well known to activate alkenes for nucleophilic attack, nucleopalladation with Pd(II) complexes generated by oxidative addition reactions are less common (18,19). For the envisioned process to be successful, several key questions emerged: Would the Pd(II) aryl complexes be sufficiently π -acidic to facilitate metallate rearrangement (**III**→**IV**)? Would common direct transmetallation (**III**→**V**) dominate the reaction and furnish Suzuki-Miyaura products? Could facial selectivity in olefin binding obtain and render the migration (**III**→**IV**) enantioselective? Finally, would β -hydrogen elimination in intermediates such as **IV** compete with reductive elimination?

To begin our studies of the conjunctive cross-coupling reaction, we selected phenyl triflate as the electrophile, anticipating that the outer-sphere triflate anion would leave open a coordination site on Pd for alkene binding (Fig. 1e, **III**). In an effort to minimize steric penalties that might inhibit metallate shift, we opted for an unsubstituted vinyl group in construction of the boron “ate” complex. Similarly, on the basis of recent studies from Mayr and Aggarwal (20,21), we selected a neopentylglycolato ligand for boron as the “ate” complexes derived from this ligand (vs. others readily available) were determined to be the most nucleophilic. Lastly, in an effort to favor reductive elimination relative to β -hydrogen elimination in putative intermediate **IV**, we selected ligands with large bite angles for the palladium complex. Initial experiments with achiral bidentate ferrocenyl 1,1'-diphosphines were promising and suggested that the conjunctive cross-coupling could indeed operate. A survey of a number of chiral diphosphine structures revealed that Josiphos (22) and

MandyPhos (23) are particularly effective ligand classes, with the MandyPhos ligand **L1** providing an outstanding level of enantioselectivity and very good catalyst efficiency in the reaction.

In optimizing the reaction conditions, we found tetrahydrofuran to be the most effective solvent. Therefore, when the migratory R group was appended to boron by addition of hydrocarbon solutions of organolithium reagents to vinylB(neo) (Fig. 2), the resulting “ate” complexes were evaporated to dryness and redissolved in THF prior to reaction. The efficiency of the reaction was also greatly diminished by chloride, bromide or iodide ions, an obstacle easily overcome by the continued use of aryl and alkenyl triflates as the electrophile. For coupling of alkenyl triflate electrophiles, the reaction selectivity was markedly enhanced with boron “ate” complexes derived from pinacolato ligands in place of the *neo*-pentylglycol derivative (eg. product **15** is formed in 53% yield and 82:18 er when using the *neo*-pentylglycol ligand) while for aryltriflates the *neo*-pentylglycol ligand furnished higher selectivity (**1** formed in 94% yield, 93:7 er using B(pin) group). With these features optimized, the scope of the conjunctive coupling was explored with an array of ate complexes and electrophiles. During these experiments it was most convenient to oxidize the product organoboron ester to the derived alcohol by treatment with NaOH and H₂O₂; however, isolation of the organoboron product itself is also possible (the organoboron precursor to alcohol **7** was isolated in 71% yield by silica gel chromatography). As shown in Fig. 2, both aryl and alkyl groups proved competent migrating elements in conjunctive coupling reactions. In cases where the yield of product is low, analysis of the reaction mixture prior to oxidation showed that by-products generally consist of recovered organoboron ester (likely generated during workup by protonolysis of one carbon ligand from the ate complex) and direct Suzuki-Miyaura products. Primary and secondary alkyl groups migrate as do functionalized alkyl appendages [eg, (trimethylsilyl)methyl]. Conjunctive couplings were also effective for both electron-rich and electron-poor electrophiles. Moderately encumbered electrophiles such as *ortho* substituted arenes can engage in the reaction although the more highly substituted 2,6-dimethylphenyl derivative suffered from lower selectivity. With respect to preparation of chiral hydrocarbon frameworks, a range of substituted alkenyl triflates participate and the configuration of the product alkene directly reflects that of the precursor electrophile.

The “ate” complex could be generated either by addition of an organolithium reagent to vinylB(neo) (Fig. 2) or by addition of vinylolithium to organoboron esters (Fig. 3). Considering the broad array of organoboron esters that are already available for use in common cross-coupling processes, the latter strategy is particularly enabling. In this context, we found that the presence of lithium halide salts, even at 1–2 mol% loading, significantly erodes conjunctive coupling efficiency. Thus, to perform the reaction with highest efficiency with 2 mol % catalyst loading, it is critical that halide-free vinylolithium be employed. To prepare this reagent, we developed a procedure that involved lithium-halogen exchange with *n*-BuLi in ether/hexane, followed by low-temperature recrystallization of pure vinylolithium. When these precautions are taken, conducting the reaction as in Fig. 4 allowed the scope of the migrating group to be surveyed more completely and revealed that while reactions requiring migration of very electron deficient groups are still a challenge, electron-neutral

and electron-rich arenes can engage in the migration as can those that are more highly substituted (i.e. 2,6-disubstituted arenes). We also found that with 5 mol% catalyst loading, vinylolithium prepared as above but without recrystallization was effective (eg., **3** formed in 69% yield, 98:2 er), and that vinylolithium prepared by lithium tin-exchange (**24**) could be used directly (2 mol% catalyst, **1** formed in 83% yield, 97:3 er).

To probe the utility of conjunctive cross-coupling to practical organic synthesis, we were attracted to the natural product (–)-combretastatin (**25**), a member of a family of cytotoxic stilbene-derived natural products that bind β -tubulin (Fig. 4a). Though many synthetic methods have facilitated the construction of combretastatins (**26**), alternative processes may engage different starting materials and thereby provide access to distinct analogs. In the case of conjunctive cross-coupling, the requisite boronic ester and electrophile are readily available, and as depicted in Figure 4a, are readily converted to the coupled product in an efficient and highly selective fashion. Removal of the silicon protecting group furnished the target structure, spectra of which were fully consistent with the natural isolate.

The mechanism of the conjunctive coupling reaction is the subject of ongoing investigations, though the substrate scope (Figures 2 and 3) gives clues about the process. The observation that electron-deficient arenes are less prone to migration is consistent with the mechanistic hypothesis put forward in Fig. 1e. According to this hypothesis, formation of **IV** would likely be stereochemistry determining and, in line with this prediction, the selectivity of the reaction depends not only on the ligand framework, but also on the organoboronic ester ligand (pinacol versus neopentyl glycol), the migrating group, and the electrophile. In addition to these observations, one preliminary experiment sheds significant light on the nature of the metal-induced metallate rearrangement that appears to underlie the conjunctive coupling process. As depicted in Fig. 4b, when the reacting “ate” complex was constructed from stereochemically-defined deuterium-labeled vinylolithium (**27**) and phenylB(pin), the (1*R*,2*R*) stereoisomer of the conjunctive coupling product was formed in >20:1 diastereoselection (82:18 er). Although other interpretations are possible, should the mechanism be in line with that proposed in Fig. 1e and reductive elimination occur with retention of configuration at carbon (a reasonable assumption), the observed stereochemical outcome in Fig. 4b is consistent with *anti* migration of the arene group to a Pd-olefin complex (Fig. 1d). Such an outcome is reminiscent of nucleometallation reactions that do not involve preassociation of the migrating group and the metal center (**28**).

We anticipate that many other transition metal catalyzed reactions might also be reengineered to incorporate metal-induced metallate rearrangements thereby providing distinct strategies for catalytic enantioselective synthesis.

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Fig. 1. Metal-induced metallate shift as a strategy for catalytic reaction design

(A) The catalytic conjunctive cross-coupling process. (B) Common metallate shift to saturated carbon centers requires a leaving group. (C) Metallate shift to unsaturated carbons often is activated by addition of an external electrophile. (D) A metallate shift promoted by a metal complex can serve as an alternative to a transmetallation process. (E) Proposed catalytic cycle for conjunctive cross-coupling.

Fig. 2. Scope of the catalytic conjunctive cross-coupling reaction starting from vinyl boronic esters

Yields represent isolated yield of purified material and are an average of two experiments. The absolute configuration was determined by anomalous dispersion x-ray and by chromatographic comparison to known compounds. *VinylB(neo) was replaced with vinylB(pin); †Reaction conducted at 80 °C. er (enantiomeric ratio) was determined by chiral supercritical fluid chromatography.

Fig. 3. Scope of the catalytic conjunctive cross-coupling reaction starting from alkyl or aryl boronic esters

Yields represent isolated yield of purified material and are an average of two experiments.

Fig. 4. Synthesis and mechanistic studies

(**A**) Synthesis of combretastatin by conjunctive cross-coupling. (**B**) The stereochemical course of metal-induced metallate rearrangement.