One-Pot Alkene Hydroboration/Palladium-Catalyzed Migratory Suzuki–Miyaura Cross-Coupling

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ABSTRACT: Chain-walking is a powerful approach toward the functionalization of C–H bonds remote to a functional group. Whereas various Pd-catalyzed migratory cross-couplings have been developed in the past years, the design of an efficient migratory version of the popular Suzuki–Miyaura cross-coupling has remained elusive. The current article reports a one-pot procedure consisting of alkene hydroboration and migratory Suzuki–Miyaura coupling of the resulting alkylboronic acid intermediate. A high regioselectivity for the benzylic position of the initial alkene was achieved by using $P(t\text{-Bu})_2\text{Me}$ as the ligand and an ortho-substituted aryl electrophile. Regioconvergence from alkene positional and geometrical isomers and long-range migration were demonstrated. Mechanistic investigations indicated that the migration occurs through a partially reversible, nondissociative mechanism.

KEYWORDS: C–C coupling, chain-walking, palladium, regioconvergence, remote functionalization

■ INTRODUCTION

Transition-metal-catalyzed cross-coupling reactions have been extensively developed and are now an essential tool for advanced organic synthesis.¹ Yet, these methodologies rely on the direct transformation at prefunctionalized and/or acidic positions of the reaction partners. In this context, the replacement of an unactivated C–H bond with a functional group, termed C–H bond functionalization, is a desirable yet challenging step-economical approach to functionalized organic intermediates and has been under intense investigations in the last two decades.² While $C(sp^2)\text{--}H$ functionalization has grown into a mature tool, the extension to alkyl C–H bonds has proven to be more difficult owing to the lesser reactivity of these bonds toward organometallic bond cleavage.³ These issues have mainly been addressed by using “innate” reactivity (based on electronic, steric, or stereo-electronic factors), the use of a leaving or directing group, and ligand design.

More recently, a different approach enabling bond construction at a remote unfunctionalized $C(sp^3)\text{--}H$ site has received increasing attention. This process, termed “chain-walking”, operates via dynamic displacement of a transition-metal catalyst along an alkyl chain, often associated with the translocation of a double bond, to a terminal position, presumably due to steric effects or due to a resonance-stabilized position such as the one adjacent to an aromatic group or heteroatom.⁴ Significant progress in remote C–H functionalization through chain-walking has already been achieved with different transition metals such as Zr,⁵ Co,⁶ Ni,⁷ Ru,⁸ or Pd.^{9–11} Previous reports from our research group on palladium(0)-catalyzed migratory cross-couplings relied on

ligand-controlled chain-walk with enolates as nucleophiles¹⁰ or organozinc compounds obtained by directed lithiation and Li–Zn transmetalation or under Barbier conditions (Figure 1a).^{11,12} To further expand and demonstrate the power of the remote C–H functionalization toolbox, we designed a benzylic-selective migratory Suzuki–Miyaura cross-coupling reaction (Figure 1b).¹³ Undesired migration products were previously observed in B-alkyl Suzuki–Miyaura cross-couplings,¹⁴ but these migratory cross-couplings have not been synthetically exploited.

Ideally, the organoboron reagent would be synthesized upon simple hydroboration of an alkene with borane and subsequent quenching with water, generating an inconsequential regioisomeric mixture of alkylboronic acids owing to the low regioselectivity of the hydroboration step. The crude reaction mixture would then be engaged in a one-pot manner into the palladium-catalyzed migratory cross-coupling, hence avoiding the occasionally difficult purification and isolation of alkylborane intermediates. The different boronic regioisomers would be convergently transformed to a single cross-coupling product with an aryl halide coupling partner,^{11c} generating 1,1-diaryllalkanes, which are structural motifs present in natural or synthetic bioactive molecules (Figure 1c).¹⁵ The selectivity would be achieved by careful selection of the ancillary ligand

Figure 1. (a) Initial report and terminal-selective functionalization of alkyl chains by our group. (b) This work on the one-pot hydroboration/benzylic-selective Suzuki–Miyaura coupling. (c) Selected examples of biologically active 1,1-diaryllkanes. DavePhos = 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl.

on the palladium as well as steric and electronic properties of the electrophilic coupling partner, directly impacting the properties of the organopalladium intermediates.^{10,11} Accordingly, it should be possible to enhance the kinetics of the β -hydride elimination against the direct reductive elimination until palladium reaches a thermodynamically favored benzylic position, from which reductive elimination becomes more favorable, hence furnishing the desired benzylic functionalized products. Besides recent reports on nickel-catalyzed benzylic-selective migratory arylations employing arylboronic acids^{7l,m} and on a migratory allylic arylation reaction,^{9m} this work represents to the best of our knowledge the first example of a palladium-catalyzed benzylic-selective migratory Suzuki–Miyaura cross-coupling of B-alkyl boronic acids and aryl halides.

RESULTS AND DISCUSSION

We initiated our studies with the modification of a one-pot procedure for the generation and Suzuki–Miyaura cross-coupling of linear trialkylboranes with aryl halides from Li, Zhong, and co-workers.^{14b} Interestingly, the authors observed some migration along the alkyl chain when the reaction was performed from tri(*sec*-butyl)borane with (*n*Bu)₂PAd (cataCXium A) as the ligand, resulting in a 4:1 mixture of direct and migratory coupling products (Scheme 1a). We first tested our hypothesis with different alkene substrates (Scheme 1b). With alkene **1a**, the migration was favored using $\text{P}(\text{tBu})_2\text{Me}$ as the ligand (*vide infra*), but the competition for the site of reductive elimination between the benzylic and terminal position was significant. Increasing the steric bulk of the terminal position

Scheme 1. Initial Results; (a) Observation of a Migratory Coupling with Tri(*sec*-butyl)borane; (b) Preliminary Investigations on Regioselectivity^a

^aReaction conditions: alkene (1.0 equiv), $\text{BH}_3\cdot\text{DMS}$ (0.4 equiv), toluene, 50 °C, 1 h, then quench with H_2O , then add ArBr (1.1 equiv), Pd_2dba_3 (2.5 mol %), $\text{P}(\text{tBu})_2\text{Me}$ (10 mol %), Cs_2CO_3 (2.0 equiv), toluene/ H_2O [0.42 M], 100 °C, 18 h. Regioisomeric ratios were determined by GCMS analysis of the crude reaction mixture.

with an isopropyl group (alkene **1b**) gave, as expected, a better selectivity in favor of the benzylic position. However, to reach excellent levels of regioselectivity, a blocking group such as *tert*-butyl was required to completely exclude the migration of the catalyst to the terminal position (alkene **1c**). Indeed, and to our delight, we observed exclusive benzylic selectivity when using $\text{P}(\text{tBu})_2\text{Me}$ as the ligand and an *o*-chloro-substituted aryl bromide, the two key factors which favor the migration of the palladium complex along the alkyl chain.^{10–12}

With these preliminary results in hand, we moved on with the optimization of the reaction conditions for the benzylic-selective migratory cross-coupling of (*Z*)-(5,5-dimethylhex-3-en-1-yl)benzene (**1c**) and bromobenzene (**2b**) (Table 1). As the selectivity of the hydroboration step does not affect the general outcome of the reaction, we retained the borane dimethyl sulfide complex as a cheap and easy-to-handle hydroboration reagent.^{11b} ^{11}B NMR of the hydroboration crude mixture indicated quantitative conversion to the secondary alkylboronic acid (Figure S3). When comparing different ligands, we only obtained a 7:93 ratio of the benzylic product/other regioisomers using cataCXium A and a 78:22 ratio with RuPhos.¹⁴ PCy_3 , which favored the migratory product in enolate arylations,^{10a} furnished a 49:51 ratio, and cataCXium PiPr, which provided optimal selectivities in migratory Negishi couplings,¹¹ gave only a 21:79 ratio, thus highlighting the differences between the previous and current migratory cross-coupling reactions (entry 1–4). Gratifyingly, we obtained an excellent yield and regioselectivity when using the small and

Table 1. Optimization of the Reaction Conditions

1c: n = 0 (Z/E >99:1)
1d: n = 1 (Z/E 3:1)
1.2 equiv

entry	variation from std. conditions	ArBr	alkene	yield (%) ^a	rr ^b
1	ligand: cataCXium A	2b	1c	9	7:93
2	ligand: RuPhos	2b	1c	27	78:22
3	ligand: PCy ₃	2b	1c	18	49:51
4	ligand: cataCXium PiPr	2b	1c	10	21:79
5		2b	1c	96	96:4
6		2b	1d	77	84:16
7		2c	1d	70	>99:1
8		2c	1c	quant.	>99:1
9	reaction time: 18 h	2c	1c	65	>99:1
10	temperature: 100 °C	2c	1c	59	>99:1
11	base: K ₂ CO ₃	2c	1c	69	>99:1
12	base: K ₃ PO ₄	2c	1c	50	>99:1
13	base: NaOH	2c	1c	33	>99:1
14	Pd source: Pd(OAc) ₂	2c	1c	50	>99:1
15	Pd source: PdCl ₂	2c	1c	37	>99:1
16	Pd source: Pd ₂ (dba) ₃ ·CHCl ₃	2c	1c	29	>99:1
17	0.45 equiv of BH ₃ ·DMS	2c	1c	75 ^c	>99:1
18	2d instead of 2c	2d	1c	91	>99:1
19	2e instead of 2c	2e	1c	74	>99:1
20	2f instead of 2c	2f	1c	37	>99:1

^aYield determined by ¹H NMR using CH₂Br₂ as the internal standard.
^bRegioisomeric ratio of benzylic/sum of other regioisomers determined by GCMS analysis. ^cYield of the isolated product.

electron-rich ligand P(*t*Bu)₂Me (entry 5).¹⁶ Indeed, such ligands are known to facilitate β-H elimination and Pd migration over direct reductive elimination.^{10,11,17} However, the regioselectivity decreased significantly when the chain was elongated on both sides of the alkene by just one methylene unit (entry 6). Presumably, the steric bulk of the *tert*-butyl group on the substrate with a shorter chain (1c) is sufficient to favor the chain-walk, but this effect weakens with a longer chain (1d). The loss in regioselectivity could be recovered when 1-bromo-2-chlorobenzene (2c) was used as electrophile to furnish the benzylic product in high yield and perfect regioselectivity (entries 7–8), as it has been demonstrated that ortho-substituents disfavor the direct reductive elimination and favor the migration pathway.^{10a,11c} The rather high temperature and long reaction time were required for good results (entries 9–10), and other bases which are typically used in Suzuki–Miyaura couplings led to significant drops in yield without affecting the selectivity of the chain-walk (entries 11–13). Different Pd sources were also screened (entries 14–16), and intriguingly, when using Pd₂(dba)₃·CHCl₃ the yields were significantly lower (entry 16). Furthermore, diminishing the amount of borane, and favoring the formation of the tri(sec-

alkyl)borane intermediate, led to a slight decrease in yield, presumably because of the lower transmetalation rate of the latter compared to the corresponding alkylboronic acid (entry 17).¹⁸ Nevertheless, it is noteworthy that the developed system is able to react with the three secondary alkyl moieties of this trialkylborane, which is to date, unmet in a general protocol.^{14b,19} Finally, other *o*-dihalobenzenes were tested (entries 18–20). Although *o*-dichlorobenzene 2d also furnished good results (entry 18), they were all less efficient than *o*-chlorobromobenzene 2c (entry 8).

Using the optimized conditions described in Table 1, entry 8, we then investigated the generality of the benzylic-selective migratory Suzuki–Miyaura cross-coupling reaction (Figure 2). We first evaluated the scope of the alkenes with 1-bromo-2-chlorobenzene (2c) as the electrophile (Figure 2a). A range of alkenes, bearing electron-rich or electron-withdrawing substituents in ortho- (3d, 3e), meta- (3f, 3g), and para-position (3h, 3i) of the initial aryl moiety and a disubstituted 1,2-methylenedioxybenzene (3j) were all well-tolerated. Importantly, pure (*Z*)- (3c, 3d, 3o, 3p), (*E*)-alkenes (3n, 3q–3ae), as well as *E/Z* mixtures (3e–3m) underwent hydroboration and migratory Suzuki–Miyaura cross-coupling without noticeable impact on the efficiency and selectivity. Remarkably, excellent results were obtained with a longer-chain alkene as the starting material, yielding product 3k in high yield and excellent regioselectivity with a migratory distance of 10 positions with respect to the initial alkene. Besides a *tert*-butyl moiety to block the terminal position, the reaction was also found to be compatible with a *tert*-butyl ether (3n, 3q–3ae) or a cyclohexyl group (3m), with the former enabling further functional group transformation at this end of the alkyl chain. The practicability of this reaction was further demonstrated by conducting the reaction on a 10-fold larger scale (5.0 mmol) and without the use of a glove box for the synthesis of the model product 3c. The latter was obtained in 91% yield and excellent selectivity, with the slightly lower yield mainly arising from a difficult purification. In addition, as discussed previously, very good regioselectivities were obtained without an ortho-substituent on the aryl bromide, provided that the terminal position was blocked and the migration distance was short (3o, 3p).

We then investigated the scope of the electrophiles with (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (1e) as the alkene (Figure 2b). We first evaluated 1-bromo-2-chlorobenzene containing additional substituents. Electrophiles with both electron-rich and electron-withdrawing substituents in para- (3q–3t) and both meta-positions (3u–3x) with respect to the formed bond reacted in moderate to good yields and high regioselectivities. Disubstitution and a heteroaromatic electrophile were also tolerated as shown with a dioxolane (3ab), an indole (3ac), and a pyridine (3ad), although the reaction was less selective with the latter. Moreover, the reaction was more sluggish with a 2,6-disubstituted aryl bromide bearing an electron-rich substituent (3ae). Importantly, the chloride ortho-substituent could be replaced with a methyl (3y), a methoxy (3z), or a trifluoromethyl group (3aa) to obtain ortho-substituted products in good yields and excellent regioselectivities, hence showing that the ortho substituent mainly exerts a steric effect on the selectivity (*vide infra*).

The obtained products were then further transformed to demonstrate the versatility of products accessible through this reaction (Scheme 2). The chloride, which was used to amplify the selectivity, could efficiently be removed by Pd-catalyzed

Figure 2. Scope of the migratory Suzuki–Miyaura cross-coupling. The geometry of the initial alkene is indicated in parenthesis, and the initial position of the alkene is highlighted in dark blue. Scale of the reactions: 0.50 mmol unless otherwise noted. Yields refer to the isolated product. Regioisomeric ratios (rr) of benzylic/sum of other regioisomers were determined by gas chromatography–mass spectrometry (GCMS) analysis of the crude reaction mixture. ^aPerformed on a 5.0 mmol scale. ^bIsolated as the C–H arylation products (**8g**, **8i**), yield over two steps, see also Scheme 2. (a) Scope of alkenes. (b) Scope of electrophiles.

dehalogenation to give compound **5**,²⁰ thus serving as a removable directing group (Scheme 2a). In addition, the *tert*-butyl ether on the end of the alkyl chain (compound **3n**) was cleaved under classic conditions to give the primary alcohol **6** quantitatively. The aryl chloride could also be employed to

perform further chemistry as shown by the coupling with *p*-anisylboronic acid under classical Suzuki–Miyaura conditions (product **7**, 92% yield) or by the intramolecular C(sp²)–H arylation to obtain alkylfluorene **8c**.²¹ Two other fluorenes (**8g**,

Scheme 2. Removal of the *o*-Cl and ^tBu Groups, Postfunctionalization and Example of Regioconvergent Coupling; (a) Removal of Directing and Protecting Group; (b) Postfunctionalization; (c) Regioisomeric Mixture of Alkenes^a

^aStandard reaction conditions: **1c** (0.6 equiv), **1f** (0.6 equiv), BH₃·DMS (1.4 equiv), toluene, 25→60 °C, 1 h, then quench with H₂O (11 equiv), 60 °C, 1 h, then add *o*-chlorobromobenzene (1.0 equiv), Pd(TFA)₂ (5 mol %), P(^tBu₂)Me·HBF₄ (15 mol %), Cs₂CO₃ (3.0 equiv), toluene/H₂O [0.42 M], 120 °C, 48 h.

8i) were also synthesized from the corresponding migratory Suzuki–Miyaura products (see Figure 2a).

Arguably, one of the most powerful features of migratory cross-couplings is their ability to transform regio- and stereoisomers into a single product. To demonstrate this, besides the convergence from (*Z*)- and (*E*)-alkenes shown above (see Figure 2a), we engaged a 1:1 mixture of two positional isomers (**1c**, **1f**), which indeed furnished a single coupling product (**3c**) in quantitative yield and perfect regioselectivity (Scheme 2c).

To gain insights into the mechanism and the factors influencing the chain-walk process, we then performed some additional test reactions. The reaction was first carried out with *para*-trifluoromethylbromobenzene and *para*-bromoanisole to further investigate the influence of the electronic properties of

the electrophile (Figure 3a). An electron-withdrawing substituent (**3af**) provided a slightly better selectivity compared to an electron-donating one (**3ag**). On the other

Figure 3. Mechanistic studies. Yields refer to the isolated product; rr of benzylic/sum of other regioisomers were determined by GCMS analysis of the crude reaction mixture. ^aStandard reaction conditions: alkene (1.2 equiv), BH₃·DMS (1.4 equiv), toluene, 25→60 °C, 1 h, then quench with H₂O (11 equiv), 60 °C, 1 h, then add ArBr (1.0 equiv), Pd(TFA)₂ (5 mol %), P(^tBu₂)Me·HBF₄ (15 mol %), Cs₂CO₃ (3.0 equiv), toluene/H₂O [0.42 M], 120 °C, 48 h. ^bYield determined by ¹H NMR using CH₂Br₂ as the internal standard. ^cDeuterium contents determined by ²H NMR analysis. (a) Influence of the substituents on both partners on the regioselectivity. (b) Crossover experiment. (c) Isotopic labeling experiment.

hand, we already showed that electronically diverse ortho-substituents such as methyl (3y), methoxy (3z), or trifluoromethyl (3aa) provided excellent regioselectivities (see Figure 2b). These results combined indicate that steric factors on the aryl electrophile have a more pronounced influence than electronic effects, similar to the migratory Negishi coupling.^{11c} In contrast, a 1:1 ratio of products 3ah and 3ai was observed with an alkyl chain containing an electron-rich and an electron-poor arene on each end, hence showing that the aryl group on the alkylboronic acid partner has no influence on the selectivity. Next, a crossover experiment was carried out to further assess whether the palladium hydride intermediate dissociates during the chain-walk process (Figure 3b). This crossover experiment was performed by adding an alkene bearing a substituent on the aryl group (1g) to the reaction mixture after the hydroboration of 1c. The lack of product containing the methoxy substituent (3h) is indicative of a nondissociative chain-walk process,^{4d} similar to other migratory cross-couplings investigated by our group.^{10–12}

Furthermore, we performed an experiment from deuterated alkene 1h to determine if deuterium scrambling occurs and to what positions (Figure 3c). Remarkably, no deuterium was observed in any of the two benzylic positions (a, d), indicating that the Pd migration to the benzylic position is irreversible. This observation is in agreement with the fact that the electronic properties of the benzylic position do not influence the selectivity (Figure 3a, bottom). Interestingly, only little incorporation of deuterium was measured in both homo-benzylic positions (~5%), whereas all the remaining methylene groups bear deuterium atoms, which also indicates that β -hydride elimination to reach the benzylic position is favored over the back-migration. Altogether, these results indicate that the benzylpalladium intermediate acts as a thermodynamic sink within the migration pathway.

To summarize, the following catalytic cycle is proposed for the current migratory Suzuki–Miyaura coupling (Scheme 3). The oxidative addition of the electrophile to the in situ-generated Pd^0 catalyst I gives intermediate II. Then, the hydroxypalladium species III, obtained after ligand exchange, undergoes transmetalation with the alkylboronic acid obtained by alkene hydroboration, yielding intermediate IV.^{18b,22} At this point, reductive elimination would furnish the direct coupling product, but using a small and electron-rich ligand and an ortho-substituted Ar^1 group significantly increases its activation barrier as proposed by density functional theory calculations for related cross-couplings.^{10a,b} Instead, the alkylpalladium species IV goes through a series of β -hydride elimination/ π -bond rotation/insertion steps, also referred to as chain-walking, until the palladium species reaches a benzylic position. The reductive elimination barrier is lower at the benzylic position, and therefore, reductive elimination of the palladium intermediate VII furnishes the benzylic cross-coupling product 3 at the expense of other regioisomers, while regenerating the Pd^0 catalyst.

CONCLUSIONS

In conclusion, we have developed a highly selective and efficient palladium-catalyzed benzylic-selective migratory Suzuki–Miyaura cross-coupling for the synthesis of 1,1-diarylalkanes from cheap and readily available chemicals, that is, alkenes, borane, and bromoarenes. The designed one-pot procedure for the synthesis of B-alkyl boronic acids and their

Scheme 3. Proposed Catalytic Cycle^a

^aGeneration of the active Pd^0 catalyst has been omitted for clarity.

subsequent cross-coupling avoided the difficult purification and isolation of these intermediates. Employing an *ortho*-chloro substituent on the electrophile as a removable directing group allowed for a broad diversity of substitution patterns and postfunctionalization reactions. The regioconvergent nature and the long-range migration of this transformation further demonstrated its practical value. Additionally, mechanistic experiments indicated a partially reversible nondissociative Pd-migration along the alkyl chain until the stabilized benzylic position, where reductive elimination is facile.

ASSOCIATED CONTENT

Full experimental and characterization data, including copies of ^1H , ^{13}C , and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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