

Pd-Catalyzed Cross-Coupling of Potassium Alkenyltrifluoroborates with 2-Chloroacetates and 2-Chloroacetamides

Gary A. Molander,* Thiago Barcellos, and Kaitlin M. Traister

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States.

gmolandr@sas.upenn.edu

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ABSTRACT



A protocol for the stereocontrolled synthesis of (*E*)- and (*Z*)-β,γ-unsaturated esters and amides is reported. 2-Chloroacetates as well as secondary and tertiary 2-chloroacetamides were successfully employed as electrophiles in the Suzuki–Miyaura cross-coupling reaction with potassium (*E*)- and (*Z*)-alkenyltrifluoroborates, affording the corresponding products in high yield.

(*E*)- and (*Z*)-β,γ-unsaturated esters and amides are encountered in many natural products that exhibit biological activity,¹ and they are also important precursors for the synthesis of biologically active compounds.²

The stereocontrolled synthesis of this significant class of compounds has been considered quite difficult. The most general method involves the palladium- or ruthenium-catalyzed carbonylation of allylic substrates.³ Another common method is the deprotonation/reprotonation of α,β-unsaturated carbonyl compounds. Alternative approaches include the reaction of alkenyl-9-BBN compounds with α-halo carbanions generated from ethyl bromoacetate⁴ or ethyl (dimethylsulfuranylidene) acetate,⁵

cross-metathesis of allyl halides with olefins bearing amides,⁶ or a sequential elimination–reduction process of α-halo-β-hydroxy-γ,δ-unsaturated esters promoted by SmI₂.⁷ Radical addition of alkenylindiums to α-halo carbonyl compounds⁸ and Ni-catalyzed enantioselective addition of alkenylzirconium reagents to α-bromo esters and ketones⁹ have emerged as more recent advances in the synthesis of β,γ-unsaturated carbonyl moieties.

Although numerous pathways toward accessing the β,γ-unsaturated carbonyl motif have been studied, all suffer from specific limitations. Carbonylation reactions require the use of toxic CO gas, which is sometimes required under high pressures.^{3a} Isomerization reactions afford a mixture of (*E*)- and (*Z*)-isomers.¹⁰ Both the cross-metathesis reaction and the SmI₂-catalyzed reactions mentioned above require complex starting materials that are not readily available. Reactions involving other organometallic species, such as alkenylindiums and alkenyl-9-BBN compounds, have proven effective in the formation of β,γ-unsaturated carbonyl esters, but these require

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Table 2. Cross-Coupling of *N*-Benzyl-2-chloroacetamide with (*E*)- and (*Z*)-Alkenyltrifluoroborates^a

| entry | product | yield (%) |
|-------|---------|-----------------|
| 1 | | 95 |
| 2 | | 88 |
| 3 | | 93 |
| 4 | | 90 |
| 5 | | 72 |
| 6 | | 89 ^b |

^a Reaction conditions: *N*-benzyl-2-chloroacetamide (0.5 mmol), potassium alkenyltrifluoroborate (0.525 mmol, 1.05 equiv), K₂CO₃ (1.5 mmol, 3 equiv), XPhos-Pd-G2 (5 μmol, 1 mol %), solvent (2 mL), 80 °C. ^b Product contains > 5% trans isomer.

Suzuki–Miyaura cross-coupling of 2-chloroesters or amides with potassium (*E*)- and (*Z*)-alkenyltrifluoroborates. Initially, a limited screening of Pd/ligand systems was carried out with benzyl chloroacetate **1a** and potassium (*E*)-styryltrifluoroborate as model substrates. Palladium(II) sources such as Pd(OAc)₂ and (η³-C₃H₅)Pd₂Cl₂ were evaluated with a variety of electron-rich ligands. XPhos (Figure 1) in combination with both Pd sources afforded good conversion to the desired product. However, an increased amount of homocoupling was detected in the presence of Pd(OAc)₂. The combination of K₂CO₃ and THF/H₂O (4:1) proved to be the most effective reaction system, leading to high conversions to the β,γ-unsaturated ester.

Subsequently, the second generation Buchwald precatalyst, XPhos-Pd-G2 (Figure 1)¹⁶ was evaluated in comparison to the (η³-C₃H₅)Pd₂Cl₂/XPhos system. An increased reaction rate was observed, and the catalyst loading could be reduced to 0.5 mol % on a 0.5 mmol reaction scale. Additionally, 1.05 equiv of potassium trifluoroborate was sufficient to obtain **3a** in 96% yield after 8 h (Table 1, entry 1).

Once the optimal conditions were determined, various potassium (*E*)- and (*Z*)-alkenyltrifluoroborates were evaluated in the cross-coupling reaction with benzyl 2-chloroacetate **1a** as shown in Table 1. Unstabilized (*E*)- and (*Z*)-alkenyltrifluoroborates were illustrated to be

Table 3. Expanded 2-Chloroacetamide Scope for Cross-Coupling with (*E*)-Alkenyltrifluoroborates^a

| entry | product | yield (%) |
|-------|---------|-----------|
| 1 | | 89 |
| 2 | | 91 |
| 3 | | 78 |
| 4 | | 71 |
| 5 | | 87 |
| 6 | | 94 |
| 7 | | 58 |
| 8 | | 68 |
| 9 | | 79 |

^a Reaction conditions: 2-chloroacetamide (0.5 mmol), potassium alkenyltrifluoroborate (0.525 mmol, 1.05 equiv), K₂CO₃ (1.5 mmol, 3 equiv), XPhos-Pd-G2 (5 μmol, 1 mol %), solvent (2 mL), 80 °C.

suitable substrates, leading to stereocontrolled β,γ-unsaturated ester products in high yield. The crude ¹H NMR spectra of the reactions reveal that none of the α,β-unsaturated regioisomers of the desired products are formed under the optimized conditions, and the (*Z*)-1-decenyltrifluoroborate (entry 3) was transformed with complete stereospecificity. However, some *E/Z* isomerization was observed with *cis*-propenyl and *cis*-styrenyl substrates (Table 1, entries 16 and 17, and Table 2, entry 6). Thus, although the commercially obtained starting materials for these two contained ~5% of the corresponding (*E*) isomers, the cross-coupled products contained about 10–12% of the diastereomer. The levels of the trans isomers that appeared in the final product could not be accounted for solely by preferential reaction of the (*E*) isomeric starting material, and thus an isomerization event

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occurred either during the cross-coupling event or upon formation of the final product.¹⁷

The reaction conditions were shown to be compatible with a potassium alkenyltrifluoroborate containing a nitrile group, which afforded the desired product in high yield (Table 1, entry 7). A cyclic substrate was also shown to be a viable nucleophilic partner in the employed reaction conditions (Table 1, entry 6). The scalable nature of the reaction conditions was illustrated by the ability to reduce the Pd loading to 0.25 mol % on a 5.0 mmol scale without a significant decrease in reaction yield (Table 1, entry 2).

Isopropyl and *tert*-butyl 2-chloroacetates (**1c**, **1b**) were also evaluated as electrophilic coupling partners in the optimized reaction conditions. Both esters showed good selectivity. However, only moderate yields of the desired products were achieved (Table 1, entries 9–11). To illustrate the advantageous nature of these reaction conditions in terms of functional group compatibility, benzyl chloroacetate was cross-coupled with substrates bearing an alkyl chloride (Table 1, entry 12), a tertiary amine (Table 1, entry 13), and benzyl and THP-protected alcohols (Table 1, entries 14–15).

The reactivity of 2-chloroacetamides in the cross-coupling with potassium alkenyltrifluoroborates was subsequently investigated. Longer reaction times were necessary to allow the reaction to proceed to completion, and

moderate yields were observed under the initial reaction conditions. Increasing the catalyst loading of XPhos-Pd-G2 to 1 mol % was sufficient for the cross-coupling of *N*-benzyl-2-chloroacetamide **4a** with various alkenyltrifluoroborates as shown in Table 2. An allylic amide that has been demonstrated to be an important substrate in domino hydrocarbonylation reactions¹⁸ and ring-closing metathesis¹⁹ was obtained in good yields (Table 2, entry 4).

In addition to *N*-benzyl-2-chloroacetamide **3a**, several other α -chloroacetamides were successfully employed as the electrophilic coupling partners (Table 3). Primary, secondary, and tertiary amides were successfully cross-coupled under the same reaction conditions. A cyclic, fluorinated alkenyltrifluoroborate was shown to react in good yield under the employed conditions (Table 3, entry 9).

In summary, a simple, scalable, and general protocol to obtain stereoselective, functionalized (*E*)- and (*Z*)- β,γ -unsaturated esters as well as primary, secondary, and tertiary amides through mild cross-coupling conditions with low catalyst loading is disclosed. All reaction components are air-stable and are easily prepared or obtained from commercial sources.

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Supporting Information Available. Complete experimental procedures and characterization data (¹H and ¹³C NMR, IR, and HRMS). This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

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