

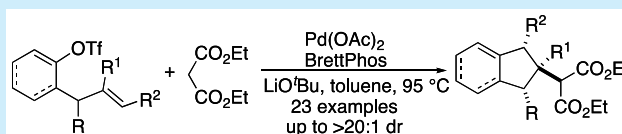
Pd-Catalyzed Alkene Difunctionalization Reactions of Malonate Nucleophiles: Synthesis of Substituted Cyclopentanes via Alkene Aryl-Alkylation and Akenyl-Alkylation

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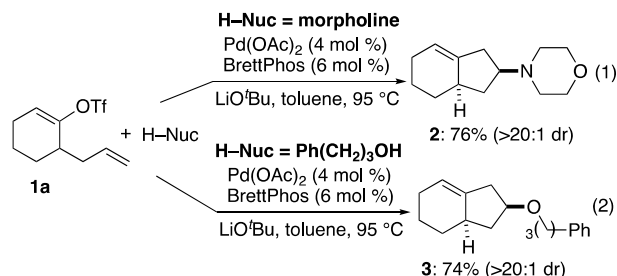
S Supporting Information

ABSTRACT: The Pd-catalyzed coupling of malonate nucleophiles with alkenes bearing tethered aryl or alkenyl triflates is described. These alkene difunctionalization reactions afford malonate-substituted cyclopentanes that contain fused aryl or cycloalkenyl rings. The transformations generate a five-membered ring, two C–C bonds, and provide products bearing up to three stereocenters with good chemical yield and generally high diastereoselectivity.



In recent years, transition metal-catalyzed alkene difunctionalization reactions that form two carbon–carbon bonds have emerged as powerful tools for the construction of substituted alkanes, heterocycles, and carbocycles.¹ Our group has described a new series of Pd-catalyzed alkene difunctionalization reactions that involve the coupling of amine,² alcohol/phenol,³ or indole¹¹ nucleophiles with alkenes tethered to aryl or alkenyl triflates (Scheme 1). The transformations

Scheme 1. Prior Studies

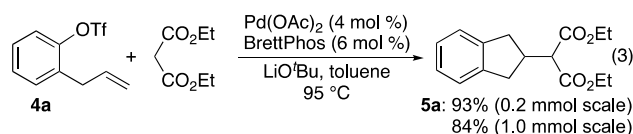


generate functionalized cyclopentane derivatives in good yield with high diastereoselectivity. For example, treatment of **1a** with morpholine in the presence of Pd(OAc)₂, BrettPhos, and LiOtBu afforded **2** in 76% yield with >20:1 dr (Scheme 1, eq 1), and similar conditions affected the coupling of **1a** with 3-phenylpropanol to provide **3** in 74% yield and >20:1 dr (Scheme 1, eq 2).

We sought to explore the use of malonates as carbon centered nucleophiles in alkene aryl-alkylation or alkenyl-alkylation variants of these transformations. Malonate anions are good nucleophiles with basicity that is comparable to that of phenoxides, so the feasibility of the transformation seemed high. Importantly, the resulting malonate-substituted cyclopentane products could be further elaborated through manipulation of the malonate or functionalization of the double bond in alkenyl-triflate derived products. Moreover,

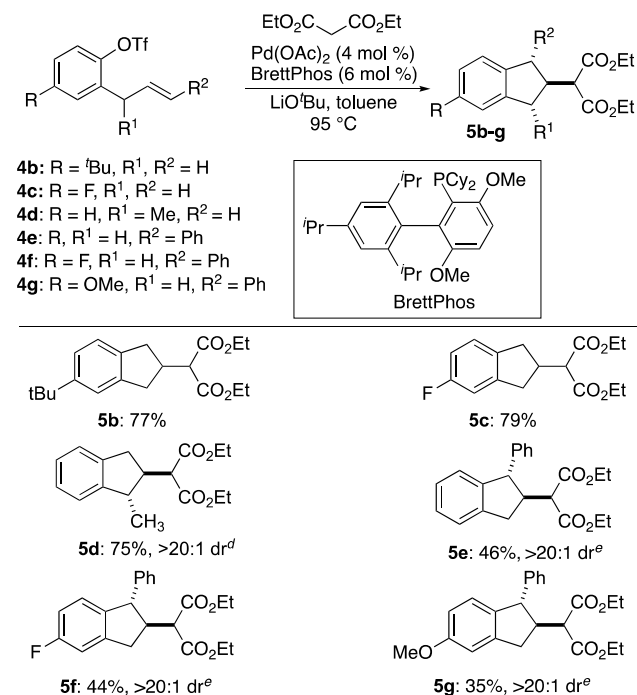
malonate substituted cyclopentanes have found prior utility as synthetic intermediates.^{4,5} The results of our preliminary studies are described in this manuscript.

In initial experiments, we examined the coupling of 2-allylphenyltriflate **4a** with diethyl malonate using conditions that previously were effective in analogous reactions of amines or alcohol nucleophiles.^{2b,3} We were gratified to find those conditions, which employed a Pd(OAc)₂/BrettPhos catalyst, LiOtBu as base, toluene solvent, and a temperature of 95 °C also performed well with malonates. The desired product **5a** was obtained in 93% isolated yield on a 0.2 mmol scale, and upon scale up to 1 mmol, the product was obtained in comparable but slightly lower (84%) isolated yield (eq 3).



Given this initial success, we briefly surveyed the reactivity of several different aryl triflate substrates. As shown in Scheme 2, transformations of terminal alkene substrates **4b–d** proceeded smoothly to afford **5b–d** in good chemical yield. Substrate **4d** that contains an allylic methyl group was converted to *trans* disubstituted product **5d** with high (>20:1) diastereoselectivity. However, reactions of substrates **4e–g** that contain 1,2-disubstituted alkenes were much more challenging.⁶ The binding of the more sterically hindered alkene to the Pd-center is less favorable, and these substrates are also prone to base-mediated isomerization of the alkene. In addition, the sluggish reactivity of these substrates led to other competing side reactions such as base-mediated cleavage of the triflate to yield the corresponding phenoxide. After some experimentation, we found that decreasing the reaction temperature to 65 °C

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Scheme 2. Reactions of Aryl Triflates^{a,b,c}

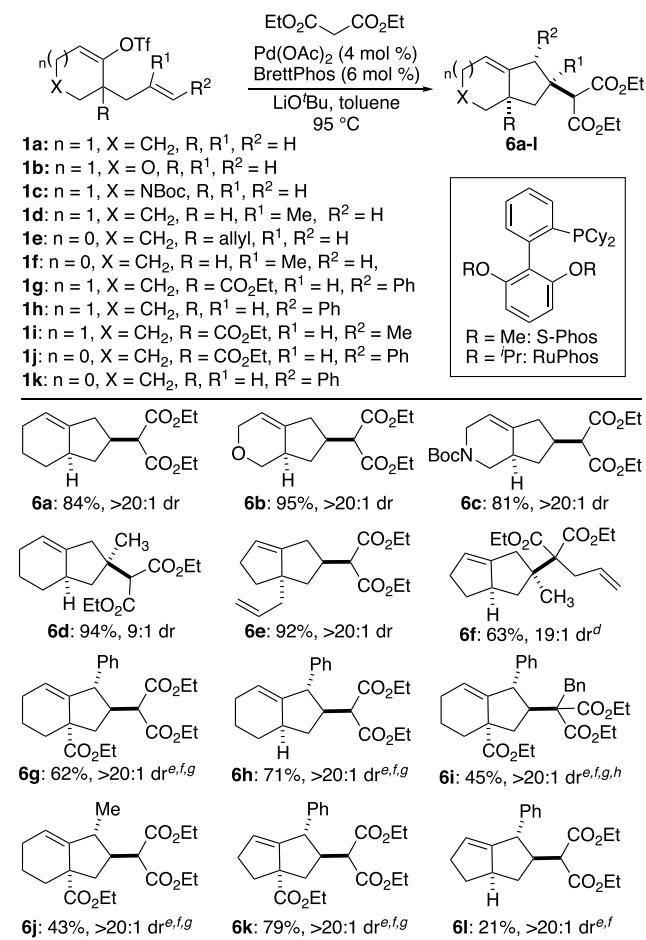
^aConditions: 1.0 equiv **4**, 1.2 equiv diethyl malonate, 1.4 equiv LiOtBu, 4 mol % Pd(OAc)₂, 6 mol % BrettPhos, toluene (0.1 M), 95 °C, 16 h. Reactions were conducted on a 0.1–0.25 mmol scale.

^bDiastereomeric ratios were determined by ¹H NMR analysis. Diastereomeric ratios were identical for crude reaction mixtures and isolated compounds unless otherwise noted. ^cYields are average isolated yields of two or more experiments. ^dReaction was conducted using (BrettPhos)Pd(allyl)(Cl) in place of Pd(OAc)₂. ^eReaction was conducted using 2.2 equiv of LiOtBu and 3.6 equiv of diethyl malonate, a substrate concentration of 0.8 M, and a reaction temperature of 65 °C.

diminished the amount of alkene isomerization, and when the amounts of diethyl malonate and base were increased to 3.6 and 2.2 equiv, respectively, products **5e–g** were obtained in modest yield and excellent (>20:1) diastereoselectivity.

As shown in Scheme 3, the reactions are also effective using alkenyl triflate substrates **1a–k**. The substrates can easily be prepared from the corresponding cyclic ketones via allylation followed by enol triflate formation.⁷ Transformations of terminal alkene substrates **1a–f** proceeded smoothly under our standard conditions to afford **6a–f** in good yield and generally high diastereoselectivity. The presence of heteroatoms in the starting material is well tolerated (**6b–c**), as was the presence of a methyl group at the internal position of the alkene (**6d** and **6f**). In addition, malonates bearing an allyl (**6f**) or benzyl substituent (**6i**) were also effective coupling partners, although use of smaller ligands (RuPhos or S-Phos) was required.

Reactions of alkenyl triflate substrates bearing tethered internal alkenes proved to be even more challenging than the corresponding reactions of aryl triflates. Efforts to employ either the standard conditions, or the conditions that were effective with aryl triflates, led to very low yields of desired products (<5%), along with significant amounts of a side product resulting from reduction of the triflate group. We reasoned that a smaller phosphine ligand might lead to improved results, as complexation of the more sterically

Scheme 3. Reactions of Alkenyl Triflates^{a,b,c}

^aConditions: 1.0 equiv **1**, 1.2 equiv diethyl malonate, 1.4 equiv LiOtBu, 4 mol % Pd(OAc)₂, 6 mol % BrettPhos, toluene (0.1 M), 95 °C, 16 h. Reactions were conducted on a 0.1–0.25 mmol scale.

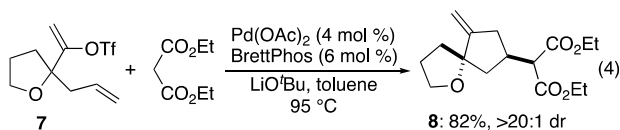
^bDiastereomeric ratios were determined by ¹H NMR analysis. Diastereomeric ratios were identical for crude reaction mixtures and isolated compounds unless otherwise noted. ^cYields are average isolated yields of two or more experiments. ^dReaction was conducted using RuPhos as ligand. ^eReaction was conducted using 2.2 equiv of LiOtBu and 3.6 equiv of diethyl malonate, a substrate concentration of 0.8 M. ^fReaction was conducted using S-Phos as ligand. ^gReaction was conducted using Pd(acac)₂ in place of Pd(OAc)₂. ^hReaction was conducted in xylenes solvent at 110 °C.

hindered 1,2-disubstituted alkenes to the metal center is more difficult. As such, we explored the use of different phosphine ligand palladium sources⁷ and after some experimentation found that the combination of Pd(acac)₂ and either S-Phos or RuPhos provided the best results for most internal alkene substrates (**1g–k**). In all cases, products bearing three stereocenters were generated with >20:1 diastereoselectivity, with products resulting from *anti*-addition of the alkenyl group and the malonate to the double bond. Not surprisingly, the coupling of a substituted malonate with a disubstituted alkene proceeded in lower yield. However, the transformation of substrate **1i** bearing an alkenyl methyl group proceeded in considerably lower yield than the analogous reaction of **1g**, which contained an alkenyl phenyl substituent.

Substrates **1g** and **1h**, which differ in the nature of their R substituent (H vs CO₂Et), were transformed to **6g** and **6h**, respectively, in comparable yield. However, the outcome of

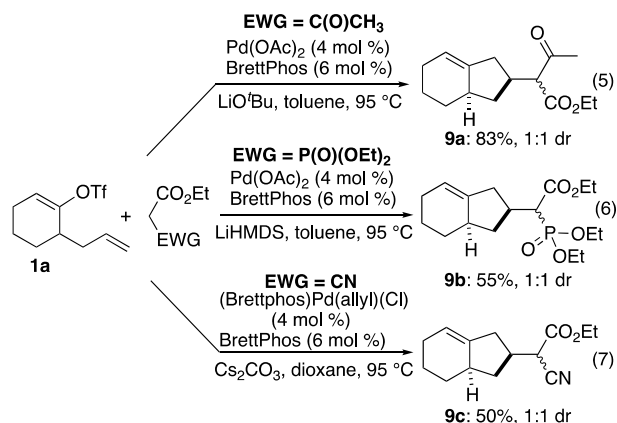
related cyclopentane-derived substrates **1j** and **1k** was much different, as **1j** was converted to **6k** in 79% yield, but the coupling of **1k** with diethyl malonate afforded **6l** in only 21% yield. The difference in the reactivity of **1j** and **1k** is likely due to a Thorpe-type effect,⁸ but the difference in reactivity of cyclohexene substrate **1h** and cyclopentane substrate **1k** is presumably a result of ring strain in the transition state for the formation of bicyclo[3.3.0]octane product **6l**.

We also briefly examined the reactivity of acyclic alkenyl triflate substrate **7**. As shown in eq 4, this transformation afforded spirocyclic compound **8** in 82% yield with >20:1 dr. However, preliminary efforts to employ other acyclic alkenyl triflates led to complex mixtures of products; future efforts will be directed toward improving the desired reactivity of these substrates.



Although we have focused the bulk of our preliminary studies on reactions of diethyl malonate as a nucleophile, other activated methylene nucleophiles can be employed in these transformations. As shown in Scheme 4, the coupling of **1a**

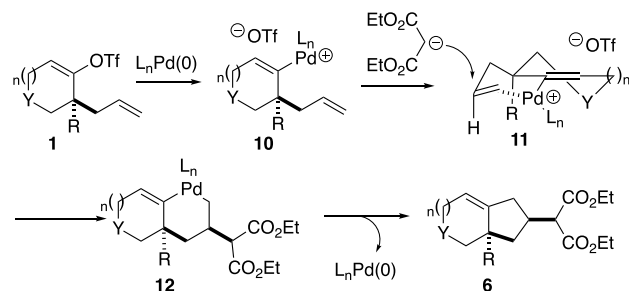
Scheme 4. Reactions of Other Activated Methylene Nucleophiles



with ethyl acetoacetate proceeded under standard conditions to afford **9a** in 83% yield as a 1:1 mixture of diastereomers epimeric at the stereocenter adjacent to the carbonyl groups (Scheme 4, eq 5). Use of triethyl phosphonoacetate provided **9b** in 55% yield and 1:1 dr,⁹ although use of LiHMDS as base was needed to obtain optimal results (Scheme 4, eq 6). The reactivity of ethyl cyanoacetate proved to be more challenging, but after some optimization we found that use of (BrettPhos)-Pd(allyl)(Cl) as the precatalyst,¹⁰ combined with Cs₂CO₃ as base and dioxane as solvent, provided **9c** in 50% yield (Scheme 4, eq 7). Although the coupling reactions of **1a** with other malonate derivatives provided moderate amounts of the desired products, efforts to combine internal alkene substrates (e.g., **1g**) with these nucleophiles were unsuccessful.

The mechanism of these reactions is likely similar to that of related transformations of amine or alcohol nucleophiles.^{2b,3} As shown in Scheme 5, oxidative addition of the alkenyl (or aryl) triflate to Pd(0) generates intermediate **10**, which then undergoes coordination of the alkene to Pd followed by anti-

Scheme 5. Proposed Mechanism



carbopalladation of the alkene through chairlike conformation **11**. The resulting intermediate **12** then affords the product **6** via reductive elimination, which also regenerates the active Pd(0) catalyst. The stereochemical outcome of these reactions is consistent with prior models involving minimization of nonbonding interactions in chairlike transition states similar to **11**.^{2,3}

In conclusion, we have developed a new Pd-catalyzed alkene difunctionalization reaction between malonate nucleophiles and alkenes bearing tethered alkenyl or aryl triflate electrophiles. The transformations generate two carbon–carbon bonds and provide products that contain up to three stereocenters with good to excellent diastereoselectivity. We have also demonstrated that use of smaller phosphine ligands allows for transformations of substrates bearing 1,2-disubstituted alkenes. Future studies will be directed toward expanding the scope of these transformations to other types of carbanion nucleophiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01258.

Experimental procedures, characterization data, copies of ¹H and ¹³C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(7) See the [Supporting Information](#) for complete experimental details.

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