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Fluorination Enables a Ligand-Controlled Regiodivergent Palladium-Catalyzed Decarboxylative Allylation Reaction to Access α,α -Difluoroketones

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Abstract

α,α -Difluoroketones possess unique physicochemical properties that are useful for developing therapeutics and probes for chemical biology. In order to access the α -allyl- α,α -difluoroketone substructure, complementary Pd-catalyzed decarboxylative allylation reactions were developed to provide linear and branched α -allyl- α,α -difluoroketones. For these orthogonal processes, the regioselectivity was uniquely controlled by fluorination of the substrate and the structure of ligand.

Keywords

allylation; regioselectivity; synthetic methods; P ligands; palladium

Decarboxylative coupling is a powerful method for the construction of C—C bonds that generates reactive organometallic intermediates under mild conditions and releases CO₂ as the only byproduct.^[1] Moreover, this strategy enables the formation of reactive intermediates and regioselective coupling to provide products that might be difficult to access otherwise.^[2] While Pd-catalyzed decarboxylative allylation reactions of soft C-based (e.g. malonates, β -diketones, β -ketoesters) and heteroatom-based nucleophiles can provide both branched^[3] and linear^[4] products, Pd-catalyzed allylation reactions of hard enolate-nucleophiles with monosubstituted allylic substrates almost exclusively provide linear products.^[1b,5] In a rare example, a Pd-catalyzed allylation of a ketone enolate employed stoichiometric Li additives to provide this uncommon branched product.^[6, 7] However, the ability of a ligand to control the regioselectivity for Pd-catalyzed allylation reactions of ketone enolates has not been demonstrated. Herein, we report complementary Pd-catalyzed decarboxylative allylation reactions of hard α,α -difluoroketones that generate both linear and branched products. Notably in these reactions, the fluorination pattern of the substrate enables the ligands to dictate the regioselectivity of the transformations.

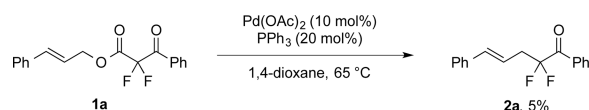
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Dedicated to Prof. Stephen L. Buchwald in honor of his 60's birthday.

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α,α -Difluoroketones represent a unique substructure in medicinal chemistry that inhibits serine and aspartyl proteases via interaction with the nucleophilic residue of a protease or a water molecule in the active site of the protease to form stable tetrahedral adducts.^[8,9] In addition, this substructure can enhance bioactivities for alternate therapeutic targets,^[10] and can serve as an intermediate for further functionalization (Figure 1).^[11] Thus, strategies for accessing α,α -difluoroketones should be useful for the development of biological probes.

Based on our ongoing studies aimed at accessing privileged fluorinated functional groups using decarboxylative strategies,^[12] we envisioned that a decarboxylative strategy should afford α -allyl- α,α -difluoroketones from allylic alcohols. Decarboxylative allylation reactions of F-containing nucleophiles are restricted to α -fluoroketones,^[13] and decarboxylative reactions of α,α -difluoroketones have not been realized. Additionally, even simple allylation reactions of α,α -difluoroketone enolates remain restricted to a single reaction that uses stoichiometric Cu,^[14] and no catalytic allylation reactions generate this substructure.



(1)

Initial attempts to develop a catalytic decarboxylative allylation reaction to generate α -allyl- α,α -difluoroketones revealed that a Pd-based catalyst could promote the desired transformation (eq. 1). A broad screen of P-based ligands identified biarylmonophosphines^[15] as privileged ligands for the present reaction, and in fact, these ligands enabled access to both linear and branched products with high regioselectivity (Table 1, entry 1). Specifically, *t*-BuBrettPhos,^[16] an electron-rich and bulky ligand generated linear product **2a** in good yield and regioselectivity, and PhXPhos,^[17] a smaller and more electron-deficient ligand, provided an uncommon branched product (**3a**) in excellent selectivity and yield (entry 1).^[18] In the present reaction, the ligand-controlled regioselectivity was only observed for the α,α -difluorinated substrate, and the analogous mono- and non-fluorinated substrates did not provide branched products in good yield and regioselectivity (entries 2–3). Thus, the physicochemical perturbation resulting from fluorination of the substrate facilitated formation of the branched product.

Based on classical reactivity patterns, the ability of α,α -difluoroacetophenone to provide both branched and linear products is unexpected. Traditionally for Pd-catalyzed allylation reactions, “hard” and “soft” nucleophiles have been identified by pK_a , with hard nucleophiles ($pK_a > 25$) being less acidic than soft nucleophiles ($pK_a < 25$).^[19] However for most pronucleophiles, the presence of a resonance-stabilizing group lowers the pK_a and increases polarizability of molecular orbitals (e.g. ketone vs. β -ketoester or β -diketone).^[1b, 20] In contrast for α,α -difluoroketones ($pK_a = 20.2$),^[21] the lower pK_a results from an inductive effect that makes anions harder (negative fluorine effect).^[22] Thus for the present allylation reaction, the α,α -difluoroketone enolates should be harder than acetophenone ($pK_a = 24.7$),^[21] which typically provides linear products.^[1b, 5] Thus based on

classic hard/soft reactivity trends, the α,α -difluoroketones would not provide the uniquely observed branched product.

Utilizing the optimized conditions, a variety of substrates bearing electron-donating and -withdrawing functional groups on the cinnamyl component underwent regioselective coupling to provide both linear and branched products (Table 2). Notably, with catalyst system A [$\text{Pd}(\text{OAc})_2/t\text{-BuBrettPhos}/1,4\text{-dioxane}/60\text{ }^\circ\text{C}$], electron-deficient allylic moieties (**5a–c**) provided better selectivity than neutral (**5d–e**) and electron-rich (**5f–g**) substrates. In addition, an *ortho*-substituted cinnamyl substrate provided linear product (**5h**) in excellent yield and selectivity. In contrast, catalyst system B [$\text{Pd}(\text{OAc})_2/\text{PhXPhos}/1,4\text{-dioxane}/90\text{ }^\circ\text{C}$] showed excellent selectivity for branched products (generally $> 49 : 1$), regardless of electronic properties of the cinnamyl fragment (**6a–h**). Both catalyst systems tolerated substitution at the C-2 position of the allyl fragment (**5i** and **6i**). However, the reaction of *t*-butyl-derived substrate (**4j**) provided low-to-modest yields of both linear and branched products (**5j** and **6j**). Moreover, substrates bearing β -hydrogens on the allyl fragment underwent elimination to generate dienes instead of coupling products.

Both catalyst systems also transformed substrates bearing distinct aryl and alkyl α,α -difluoroketone moieties (Table 3). Reactions of electron-rich and neutral aryl α,α -difluoroketone substrates afforded good selectivities and yields for linear (**8a–8c**) and branched (**9a–9c**) products under both conditions. Even heteroaryl α,α -difluoroketone substrates (**7d–7e**) generated linear (**8d–8e**) and branched (**9d–9e**) products in good selectivities and yields. Using the standard reaction conditions, an aliphatic α,α -difluoroketone was less reactive; however, improved yields and high selectivities were obtained by increasing the catalyst loading [5 mol% $\text{Pd}(\text{OAc})_2$, 10 mol% ligands] and reaction time (**8f** and **9f**). Thus, both catalyst systems enabled access to a variety of unique α,α -difluoroketone products that would be challenging to prepare otherwise.

The complementary products may derive from a common $\text{L}_n\text{-Pd}(\pi\text{-allyl})(\text{enolate})$ intermediate (**11**) *via* distinct ligand-controlled regioselective C–C bond-forming events (Figure 2A). To establish the intermediacy of a π -allyl complex, secondary ester **15** was subjected to both conditions A and B (Figure 2B), and the results were compared to reactions of the corresponding linear substrates (Table 2). System A transformed both linear and branched substrates (**4a**, **15**) into linear product **5a** in comparable selectivity (br/lin = 1 : 23 vs. 1 : 21), while system B transformed both linear and branched substrates (**4a**, **15**) into branched product **6a** in high selectivity (br/lin = 99 : 1). Combined, these data: 1) implicate the existence of π -allyl **11** in both reaction pathways; 2) discount memory effects controlling the regioselectivity for either system; 3) confirm that ligands ultimately control the regiochemical fate of the reaction.

Evaluation of the relationship between the electronic structures of cinnamyl-derived substrates and regioselectivities of catalytic reactions suggests that the branched and linear products derive from distinct pathways. For outer-sphere processes, the electronic structure of cinnamyl-derived substrates can perturb the regiochemical outcome of the reaction. Specifically, electron-rich substrates provide linear products in lower selectivity than electron-deficient substrates,^[3a, 23] because $\text{S}_{\text{N}}1$ -like attack at the stabilized 2° position of

the π -allyl intermediates (path ii) competes with S_N2 -like the attack at the unhindered 1° position (path i). For system A, a similar trend was observed, as confirmed by a linear free-energy correlation (Figure 3). Thus, system A may proceed predominantly via an analogous outer-sphere mechanism (path i).

In contrast, system B notably generates branched products that are less commonly observed in Pd-catalyzed allylation reactions of hard ketone enolates.^[1b,5] If S_N1 -like attack of intermediate **10** would predominantly occur at the 2° position (path ii), the electronic properties of cinnamyl-derived substrates (**1a**, **4a–4c**, **4e** and **4g**) would likely allow path i to compete and influence the regioselectivity of the reactions.^[3a,23] However for system B, substrates bearing electron-rich, -neutral, and -deficient cinnamyl moieties all underwent coupling to afford branched products in high selectivities (**3a**, **6a–6c**, **6e** and **6g**). This lack of a correlation between the electronic properties of cinnamyl-derived substrates and regioselectivity may discount outer-sphere path ii.

An alternate explanation for the unique regioselectivity involves the sigmatropic rearrangement of an η^1 -allyl intermediate (path iii).^[24,25] Although this mechanism has been computationally predicted, experimental evidence for palladacyclic transition state **12** has not been established. In support of this rearrangement mechanism, non-metal-catalyzed 3,3-sigmatropic rearrangements of allyl α,α -difluoroenoleters similarly react more rapidly than the non-fluorinated counterparts.^[26] Thus in the present case, the fluorine atoms might also provide unique physical properties that facilitate an analogous Pd-catalyzed rearrangement to provide the branched product.

In conclusion, both fluorination of a substrate and the selection of appropriate ligands facilitated a pair of orthogonal Pd-catalyzed regioselective decarboxylative allylation reactions to afford α,α -difluoroketone products. Computational studies should provide insight into the physicochemical basis by which fluorination enables formation of the branched product, and the relationship between structures of the ligands and regioselectivities of the transformations. Ongoing work aims to exploit this reaction pathway to generate other unique fluorinated substructures, including enantioenriched products. We envision that these strategies should be useful for accessing α,α -difluoroketone-based probes that would otherwise be challenging to prepare.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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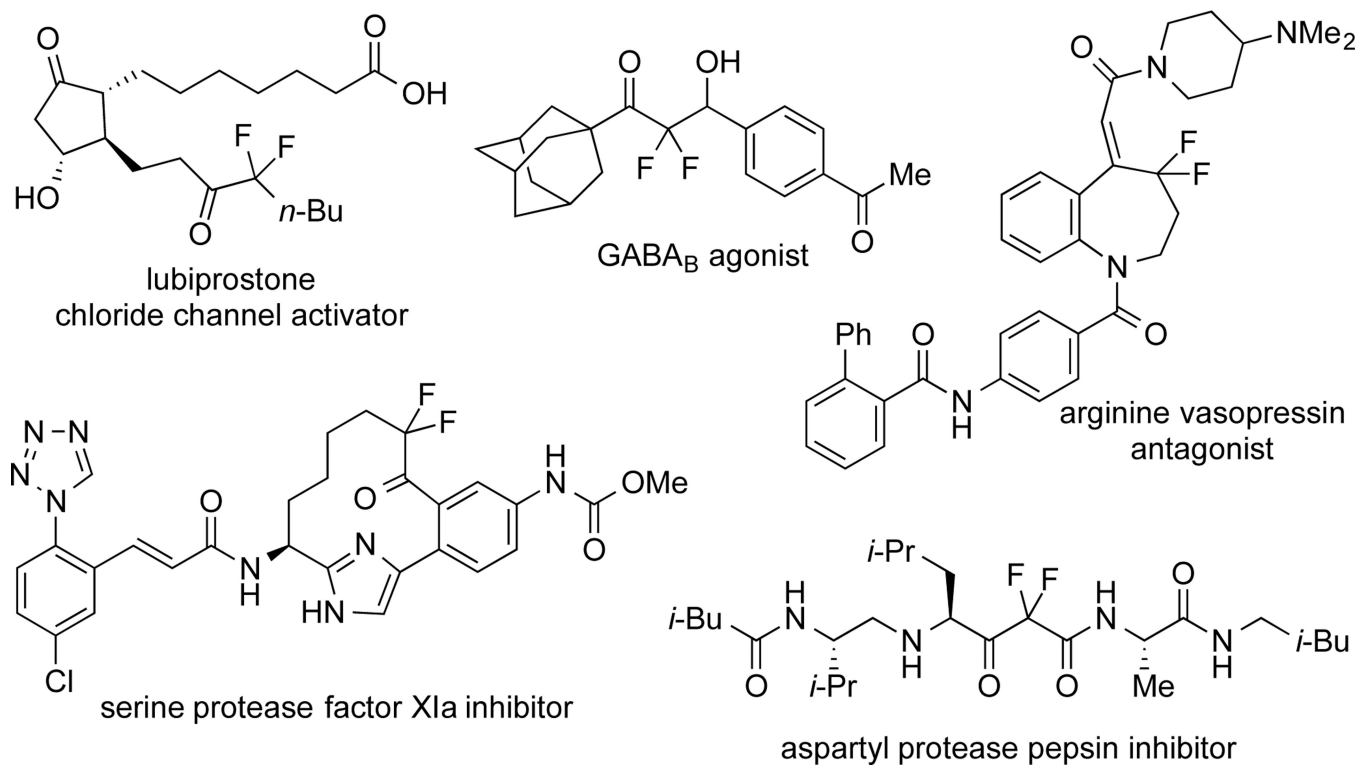
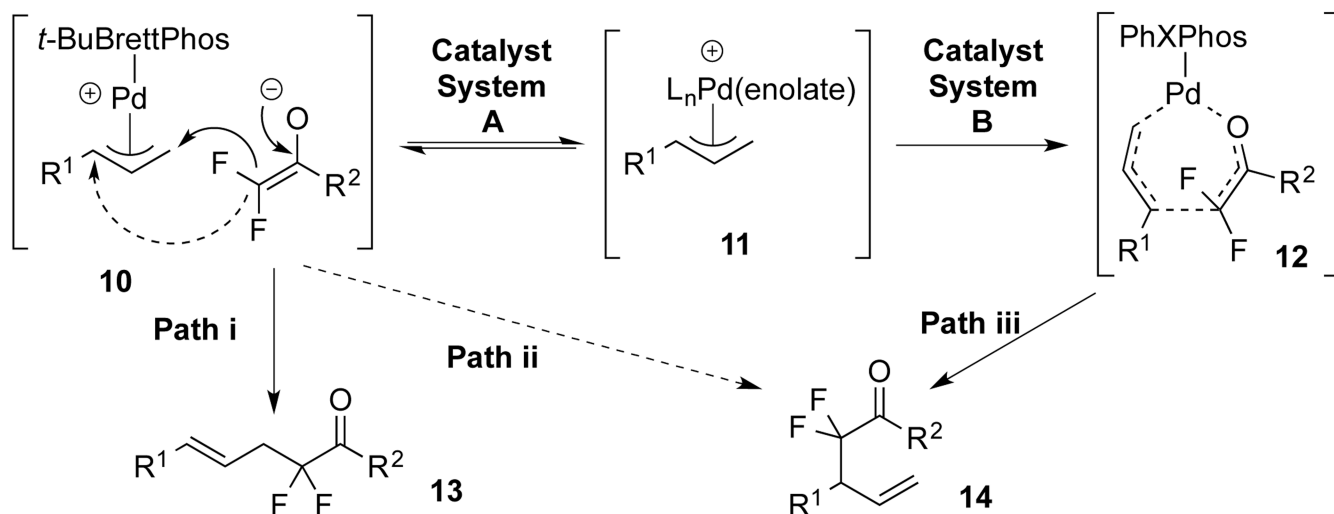


Figure 1.
 α,α -Difluoroketones serve as drugs, biological probes, and synthetic intermediates.

A) Proposed Pathways Involve π -Allyl Intermediates



B) Branched Substrate Provides Linear and Branched Products

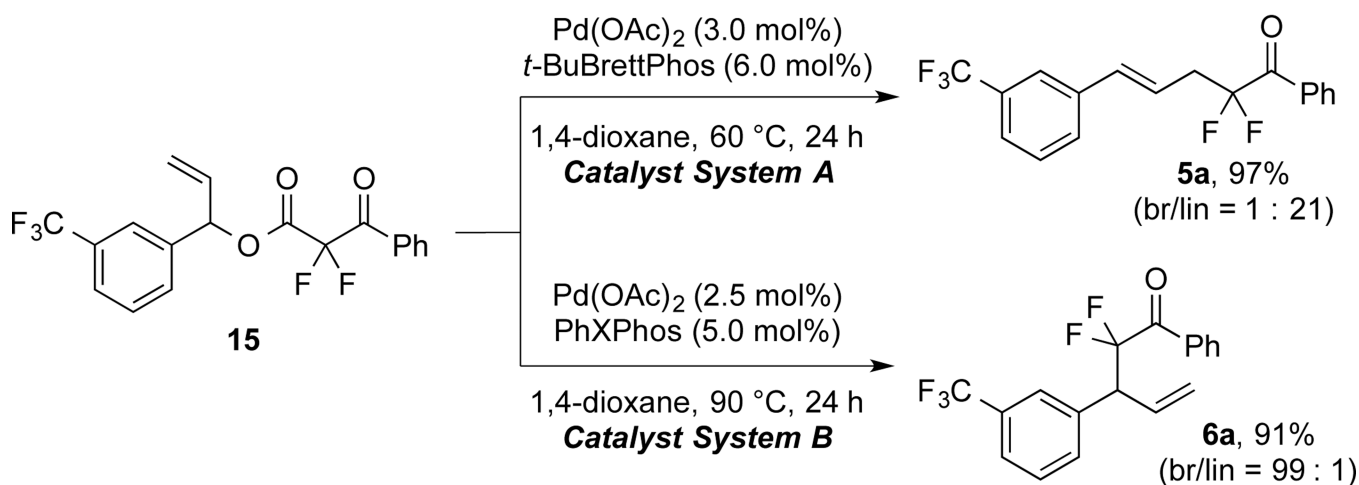


Figure 2. Formation of Linear and Branched Products May Involve a Common π -Allyl Intermediate.

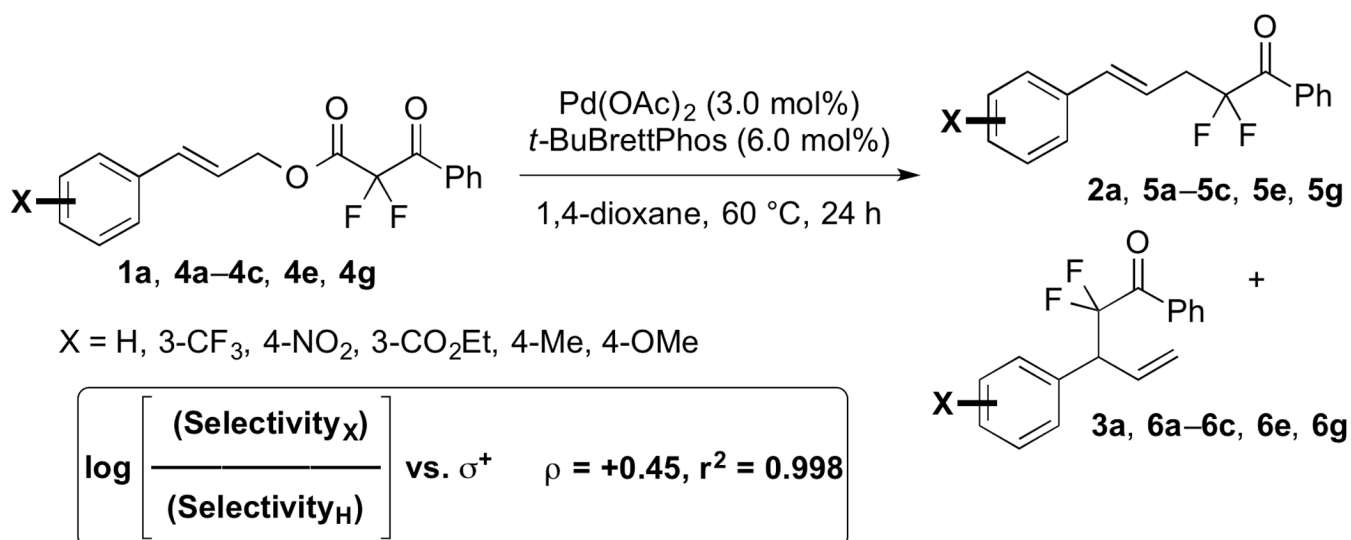


Figure 3.
 Catalyst System A: Improved Linear Selectivity for Electron-deficient Substrates.

Table 1

Fluorination and Ligands Enable Regioselective Allylation Reactions.^[a]

Entry	Substrate	Catalyst System A	Catalyst System B
<p style="text-align: center;"> </p>			
1	<p style="text-align: center;">1a</p>	<p style="text-align: center;">2a, 89% (br/lin = 1 : 18)</p>	<p style="text-align: center;">3a, 94% (br/lin = 99 : 1)</p>
2	<p style="text-align: center;">1b</p>	<p style="text-align: center;">2b, 24% (br/lin < 1 : 24)</p>	<p style="text-align: center;">3b, 36% (br/lin = 2.1 : 1) (br dr = 2 : 1)</p>
3	<p style="text-align: center;">1c</p>	<p style="text-align: center;">2c, 85% (br/lin < 1 : 50)</p>	<p style="text-align: center;">3c, 5% (br/lin = 1 : 2)</p>

^[a] Catalyst System A: substrate (1.0 equiv), Pd(OAc)₂ (3.0 mol%), *t*-BuBrettPhos (6.0 mol%), 1,4-dioxane (0.50 M), 60 °C, 20 h; Catalyst System B: substrate (1.0 equiv), Pd(OAc)₂ (2.5 mol%), PhXPhos (5.0 mol%), 1,4-dioxane (0.10 M), 90 °C, 20 h. For fluorinated products, yields and

selectivities were determined by ^{19}F NMR using PhCF_3 or PhF as an internal standard, respectively. For non-fluorinated products, yields and selectivities were determined by ^1H NMR using CH_2Br_2 as an internal standard.

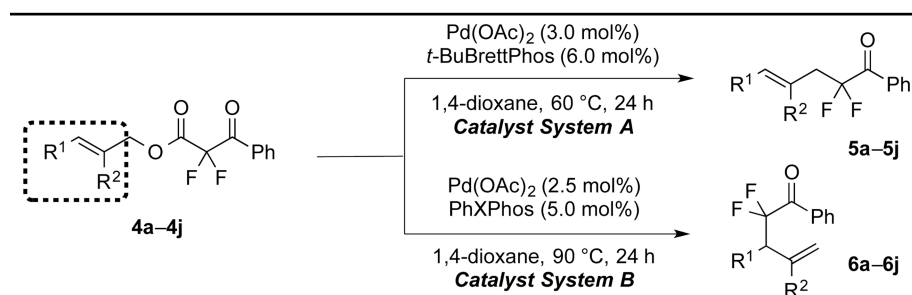
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Table 2

Reactions of Substrates Bearing Distinct Allyl Moieties.^[a]

Catalyst System A		Catalyst System B	
 5a , 92% (87%) br/lin = 1 : 23	 5b , 70% (43%) ^[b] br/lin = 1 : 30	 6a , 93% (83%) br/lin = 99 : 1	 6b , 92% (78%) br/lin = 49 : 1
 5c , 89% (82%) br/lin = 1 : 21	 5d , 84% (84%) ^[c] br/lin = 1 : 14	 6c , 94% (80%) br/lin = 99 : 1	 6d , 94% (76%) br/lin = 49 : 1
 5e , 85% (86%) br/lin = 1 : 10	 5f , 77% (68%) br/lin = 1 : 7	 6e , 96% (89%) br/lin = 99 : 1	 6f , 92% (80%) br/lin = 99 : 1
 5g , 64% (55%) br/lin = 1 : 6	 5h , 90% (81%) br/lin = 1 : 75	 6g , 81% (70%) br/lin = 99 : 1	 6h , 70% (52%) br/lin = 99 : 1
 5i , 73% (77%) ^[c] br/lin = 1 : 10	 5j , 22% (19%) ^[c,d] br/lin = 1 : 9	 6i , 91% (82%) br/lin = 28 : 1	 6j , 51% (38%) ^[e] br/lin = 10 : 1

^[a] Catalyst System A: **4a–j** (1.0 equiv), Pd(OAc)₂ (3.0 mol%), *t*-BuBrettPhos (6.0 mol%), 1,4-dioxane (0.50 M), 60 °C, 24 h; Catalyst System B: **4a–j** (1.0 equiv), Pd(OAc)₂ (2.5 mol%), PhXPhos (5.0 mol%), 1,4-dioxane (0.10 M), 90 °C, 24 h. ¹⁹F NMR yields for the major isomers were

determined using PhCF₃ as an internal standard (average of two runs). The values in parentheses represent the yields of the major products. The regioselectivities were determined by ¹H NMR analysis of the crude reaction mixtures.

[b]_{70 °C}.

[c]_{Pd(OAc)₂ (5 mol%), *t*-BuBrettPhos (10 mol%)}.

[d]_{100 °C}.

[e]_{130 °C, *o*-Xylene}, the regioselectivities were determined by GC and ¹⁹F NMR of the crude reaction mixtures.

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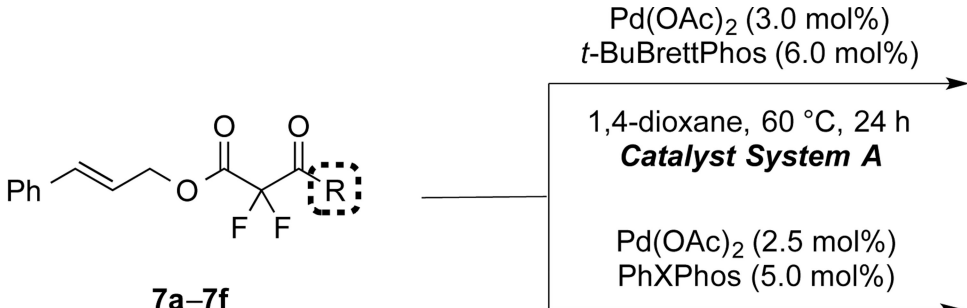
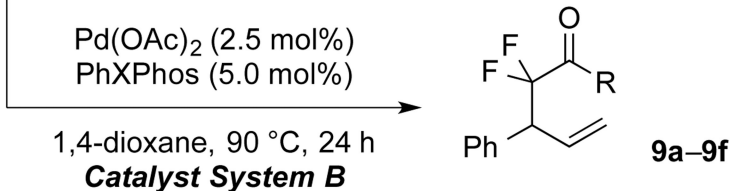
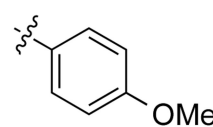
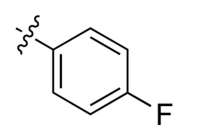
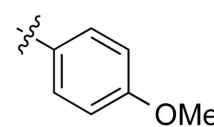
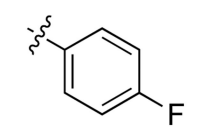
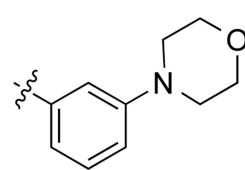
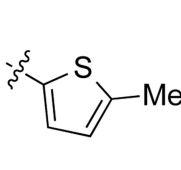
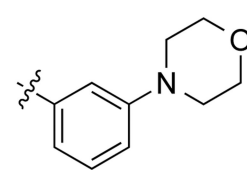
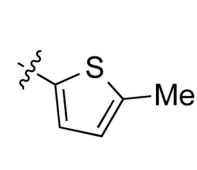
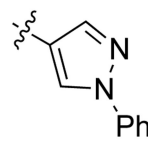
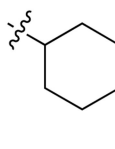
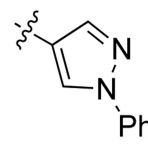
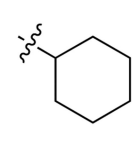
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Table 3

Reactions of Substrates Bearing Distinct Ketone Moieties.^[a]

			
		Catalyst System A	
Catalyst System A		Catalyst System B	
 8a , 87% (78%) ^[b] br/lin = 1 : 25	 8b , 87% (86%) br/lin = 1 : 13	 9a , 93% (83%) ^[d] br/lin = 49 : 1	 9b , 94% (83%) br/lin = 99 : 1
 8c , 86% (80%) br/lin = 1 : 27	 8d , 92% (86%) br/lin = 1 : 15	 9c , 88% (85%) ^[f] br/lin = 99 : 1	 9d , 94% (86%) ^[e] br/lin = 49 : 1
 8e , 79% (63%) ^[b] br/lin = 1 : 13	 8f , 62% (60) ^[b,c] br/lin = 1 : 20	 9e , 94% (71%) ^[f] br/lin = 99 : 1	 9f , 83% (71%) ^[f,g] br/lin = 63 : 1

^[a]Catalyst System A: **7a–f** (1.0 equiv), Pd(OAc)₂ (3.0 mol%), *t*-BuBrettPhos (6.0 mol%), 1,4-dioxane (0.50 M), 60 °C, 24 h; Catalyst System B: **7a–f** (1.0 equiv), Pd(OAc)₂ (2.5 mol%), PhXPhos (5.0 mol%), 1,4-dioxane (0.10 M), 90 °C, 24 h. ¹⁹F NMR yields for the major isomers were

determined by using PhCF₃ as an internal standard (average of two runs). The values in parentheses represent the yields of the major products. The regioselectivities were determined by ¹H NMR analysis of the crude reaction mixtures.

[b] Pd(OAc)₂ (5.0 mol%), *t*-BuBrettPhos (10 mol%).

[c] 70 °C, 36 h.

[d] Pd(OAc)₂ (3.5 mol%), PhXPhos (7.0 mol%).

[e] 18 h.

[f] Pd(OAc)₂ (5.0 mol%), PhXPhos (10 mol%).

[g] 90 °C, 36 h.

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