Fluorine

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Ligand-Controlled Regiodivergent Palladium-Catalyzed Decarboxylative Allylation Reaction to Access α,α-Difluoroketones**

*Ming-Hsiu Yang, Douglas L. Orsi, and Ryan A. Altman**

Dedicated to Professor Stephen L. Buchwald on the occasion of his 60th birthday

Abstract: *α,α-Difluoroketones possess unique physicochemical properties that are useful for developing therapeutics and probes for chemical biology. To access the α-allyl-α,α-difluoroketone substructure, complementary palladium-catalyzed decarboxylative allylation reactions were developed to provide linear and branched α-allyl-α,α-difluoroketones. For these orthogonal processes, the fluorination pattern of the substrate enabled the ligands to dictate the regioselectivity of the transformations.*

Decarboxylative coupling is a powerful method for the construction of C–C bonds that generates reactive organometallic intermediates under mild conditions and releases CO_2 as the only byproduct.[1] Moreover, this strategy enables the formation of reactive intermediates and regioselective couplings to provide products that might be difficult to access otherwise.[2] Whereas Pd-catalyzed decarboxylative allylation reactions of soft carbon-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, the use of stoichiometric Li additives facilitated a Pd-catalyzed allylation of a ketone enolate to provide this uncommon branched product.[6,7] However, the ability of a ligand to control the regioselectivity of Pd-catalyzed allylation reactions of ketone enolates has not been demonstrated. Herein, we report complementary Pd-catalyzed decarboxylative allylation reactions of hard fluorinated enolate nucleophiles 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.

α,α-Difluoroketones are a unique substructure in medicinal chemistry that inhibits serine and aspartyl proteases through interactions 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] Furthermore, this substructure can also enhance bioactivities for non-protease targets,[10] and it can serve as an intermediate for further functionalization (Figure 1).[11] Therefore, strategies for accessing α,α-difluoroketones should be useful for the development of biological probes.

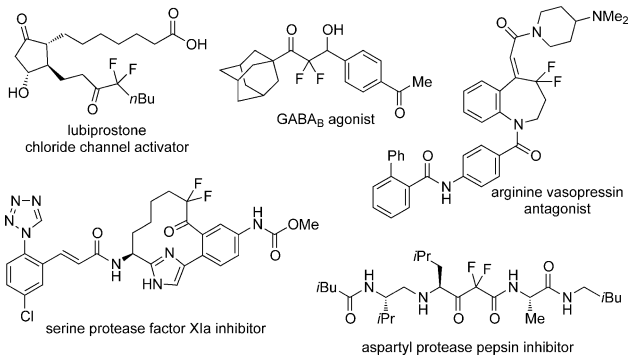

Figure 1. α,α-Difluoroketones serve as drugs, biological probes, and synthetic intermediates.

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

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 biaryl monophosphines[15] as privileged ligands for the present reaction, and in fact, these ligands enabled access to both the linear and branched products with high regioselectivity (Table 1, entry 1). Specifically, *t*BuBrettPhos,[16] an

[*] M.-H. Yang, D. L. Orsi, Prof. Dr. R. A. Altman
Department of Medicinal Chemistry, University of Kansas
1251 Wescoe Hall Drive, Lawrence, KS 66045 (USA)
E-mail: raaltman@ku.edu

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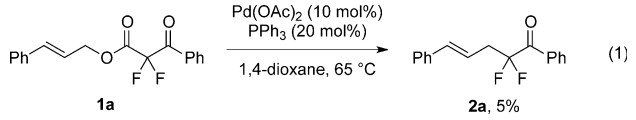
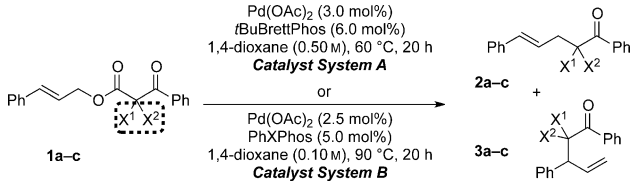
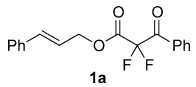
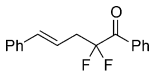
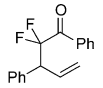
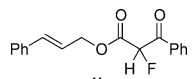
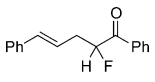
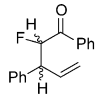
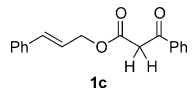
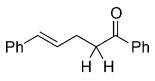
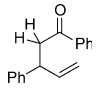


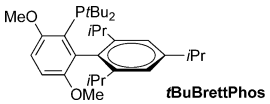
(1)

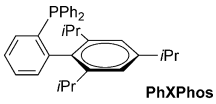
Table 1: Ligand-controlled regioselective allylation reactions of fluorinated substrates.[a]



Entry	Substrate	Catalyst system A	Catalyst system B
1	 **1a**	 **2a**, 89% (br/lin = 1:18)	 **3a**, 94% (br/lin = 99:1)
2	 **1b**	 **2b**, 24% (br/lin < 1:24)	 **3b**, 36% (br/lin = 2.1:1; br: 2:1 d.r.)
3	 **1c**	 **2c**, 85% (br/lin < 1:50)	 **3c**, 5% (br/lin = 1:2)

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

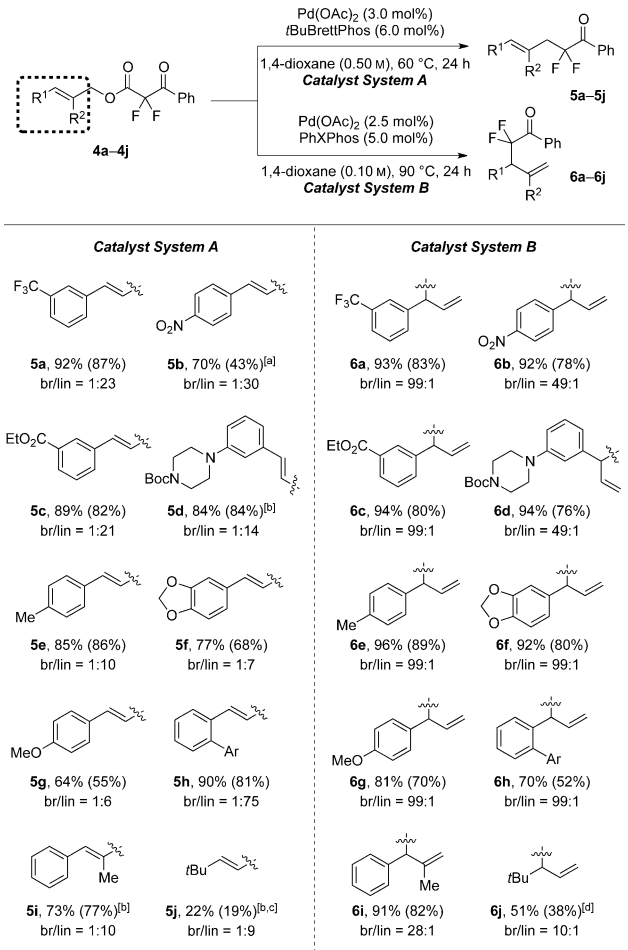




electron-rich and bulky ligand, generated linear product **2a** in good yield and regioselectivity, and PhXPhos,[17] a smaller and more electron-deficient ligand, provided an uncommon branched product (**3a**) in excellent selectivity and yield (entry 1).[18] In the present reaction, the ligand-controlled 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). Therefore, 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 their pK_a values, 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 value and increases the polarizability of the 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 value results from an inductive effect that makes the 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] Therefore, based on classic hard/soft reactivity trends, the α,α-difluoroketones would not provide the uniquely observed branched product.

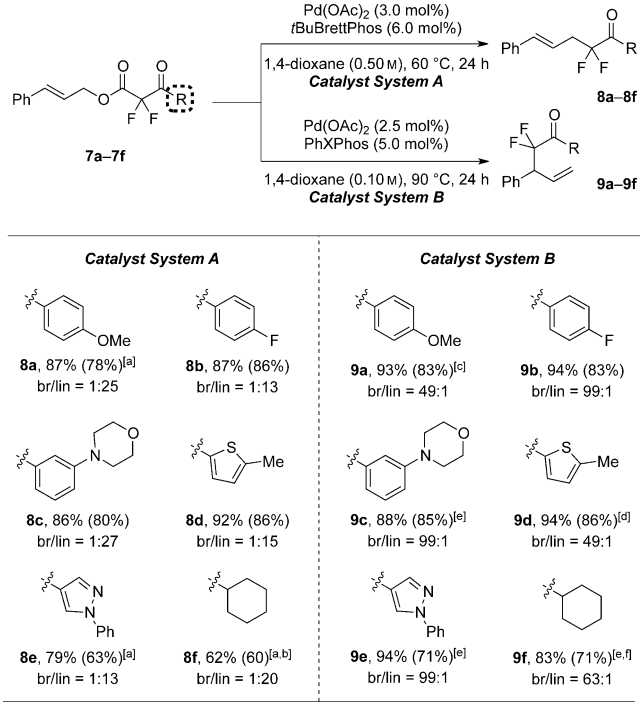
Utilizing the optimized conditions, a variety of substrates bearing electron-donating and -withdrawing functional groups on the cinnamyl component underwent regioselective coupling to provide both the linear and branched products (Scheme 1). Notably, with catalyst system A [$Pd(OAc)_2$/*t*BuBrettPhos/1,4-dioxane/60 °C], substrates bearing electron-deficient allylic moieties (**5a–c**) provided better selectivities than neutral (**5d–e**) and electron-rich (**5f–g**) substrates. Furthermore, an *ortho*-substituted cinnamyl substrate



Scheme 1. Reactions of substrates bearing distinct allyl moieties. Yields for the major isomers were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard (average of 2 runs). Yields of isolated products (major isomer) given in parentheses. Regioselectivities were determined by ^{1}H NMR analysis of the crude reaction mixtures. Ar = *para*-cyanophenyl. [a] 70 °C. [b] $Pd(OAc)_2$ (5 mol%), *t*BuBrettPhos (10 mol%). [c] 100 °C. [d] 130 °C, *ortho*-xylene; the regioselectivities were determined by GC and ^{19}F NMR analysis of the crude reaction mixtures.

provided the linear product (**5h**) in excellent yield and selectivity. In contrast, catalyst system B [$Pd(OAc)_2$/PhXPhos/1,4-dioxane/90 °C] showed excellent selectivity for the branched products (generally > 49:1), regardless of the electronic properties of the cinnamyl moiety (**6a–h**). Both catalyst systems tolerated substitution at the C2 position of the allyl fragment (**5i** and **6i**). However, the reactions of *tert*-butyl-derived substrate **4j** provided low-to-modest yields of both the linear and branched products (**5j** and **6j**). Moreover, substrates bearing β-hydrogen atoms on the allyl fragment underwent elimination to generate dienes instead of the coupling products.

Both catalyst systems also transformed substrates bearing distinct aryl and alkyl α,α-difluoroketone moieties (Scheme 2). Reactions of electron-rich and -neutral aryl



Scheme 2. Reactions of substrates bearing distinct ketone moieties. Yields for the major isomers were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard (average of 2 runs). Yields of isolated products (major isomer) given in parentheses. The regioselectivities were determined by ^1H NMR analysis of the crude reaction mixtures. [a] $Pd(OAc)_2$ (5.0 mol%), *t*BuBrettPhos (10 mol%). [b] 70 °C, 36 h. [c] $Pd(OAc)_2$ (3.5 mol%), PhXPhos (7.0 mol%). [d] 18 h. [e] $Pd(OAc)_2$ (5.0 mol%), PhXPhos (10 mol%). [f] 90 °C, 36 h.

α,α-difluoroketone substrates afforded good selectivities and yields for the linear (**8a–8c**) and branched (**9a–9c**) products under the respective conditions. Even heteroaryl α,α-difluoroketone substrates (**7d–7e**) generated linear (**8d–8e**) and branched (**9d–9e**) products in good selectivities and yields. Under 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% $Pd(OAc)_2$, 10 mol% ligand] and reaction time (**8f** and **9f**). Thus, both catalyst systems enabled access to a variety of unique α,α-difluoroketone products, which would be challenging to prepare otherwise.

The complementary products may derive from a common L_n–Pd(π-allyl)(enolate) intermediate (**11**) through distinct ligand-controlled regioselective C–C bond-forming events (Figure 2A). To establish the intermediacy of a π-allyl

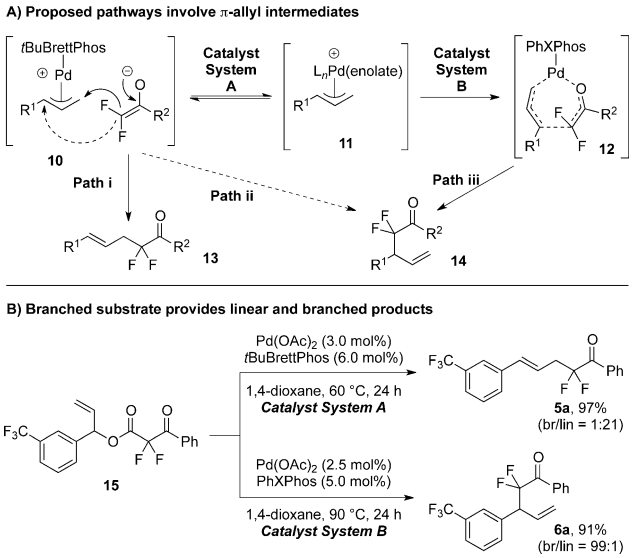


Figure 2. The formation of linear and branched products may involve a common π-allyl intermediate.

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 (Scheme 1). System A transformed both linear and branched substrates (**4a**, **15**) into linear product **5a** with comparable selectivity (br/lin = 1:23 vs. 1:21), whereas system B transformed both linear and branched substrates (**4a**, **15**) into branched product **6a** with high selectivity (br/lin = 99:1). Combined, these data 1) implicate the intermediacy of π-allyl species **11** in both reaction pathways, 2) discount the hypothesis that memory effects control the regioselectivity for either system, and 3) confirm that the ligands ultimately control the regiochemical fate of the reaction.

An evaluation of the relationship between the electronic structures of the cinnamyl-derived substrates and the regioselectivities of the 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 with lower selectivity than electron-deficient substrates,[3a,23] because S_N1-like attack at the stabilized secondary position of the π-allyl intermediates (path ii) competes with S_N2-like attack at the unhindered primary position (path i). For system A, a similar trend was observed, as confirmed by a linear free energy correlation (Figure 3). Thus, under conditions A, the reaction may proceed predominantly through an analogous outer-sphere mechanism (path i).

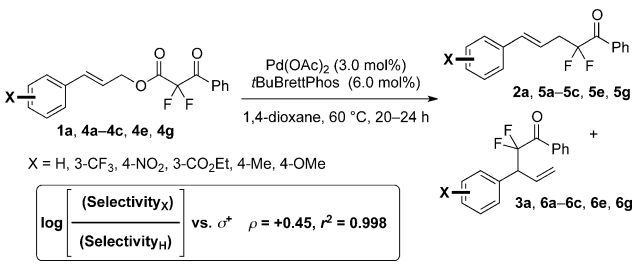


Figure 3. Catalyst system A: improved linear selectivity for electron-deficient substrates.

In contrast, system B notably generates branched products, which are less commonly observed in Pd-catalyzed allylation reactions of hard ketone enolates.[1b,5] If S_N1-like attack of intermediate **10** predominantly occurred at the secondary position (path ii), the electronic properties of the 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 the branched products with high selectivities (**3a**, **6a**–**6c**, **6e**, and **6g**). This lack of a correlation between the electronic properties of the cinnamyl-derived substrates and the 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-difluoroenol ethers similarly proceed more rapidly than those of 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, the fluorine substituents of the substrate and the selection of appropriate ligands together facilitated a pair of orthogonal palladium-catalyzed regioselective decarboxylative allylation reactions to afford α,α-difluoroketone products. Computational studies should provide insight into the physicochemical basis on which fluorination enables formation of the branched product and into the relationship between the ligand structure and the regioselectivity of the transformation. Ongoing work aims at exploiting 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.

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[1] a) O. Baudoin, *Angew. Chem. Int. Ed.* **2007**, *46*, 1373; *Angew. Chem.* **2007**, *119*, 1395; b) J. D. Weaver, A. Recio III, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846; c) D. C. Behenna, B. M. Stoltz, *Top. Organomet. Chem.* **2013**, *44*, 281; d) S. Arseniyadis, J. Fournier, S. Thangavelu, O. Lozano, S. Prevost, A. Archambeau, C. Menozzi, J. Cossy, *Synlett* **2013**, 2350.

[2] a) A. Recio III, J. A. Tunge, *Org. Lett.* **2009**, *11*, 5630; b) R. Jana, J. J. Partridge, J. A. Tunge, *Angew. Chem. Int. Ed.* **2011**, *50*, 5157; *Angew. Chem.* **2011**, *123*, 5263.

[3] a) R. Prétôt, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 323; *Angew. Chem.* **1998**, *110*, 337; b) S.-L. You, X.-Z. Zhu, Y.-M. Luo, X.-L. Hou, L.-X. Dai, *J. Am. Chem. Soc.* **2001**, *123*, 7471; c) W.-H. Zheng, N. Sun, X.-L. Hou, *Org. Lett.* **2005**, *7*, 5151; d) X.-F. Yang, W.-H. Yu, C.-H. Ding, Q.-P. Ding, S.-L. Wan, X.-L. Hou, L.-X. Dai, P.-J. Wang, *J. Org. Chem.* **2013**, *78*, 6503; e) T. Hayashi, K. Kishi, *Tetrahedron Lett.* **1990**, *31*, 1743; f) A. M. Johns, Z. Liu, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2007**, *46*, 7259; *Angew. Chem.* **2007**, *119*, 7397; g) I. Dubovyk, I. D. G. Watson, A. K. Yudin, *J. Org. Chem.* **2013**, *78*, 1559; h) B.-H. Zheng, C.-H. Ding, X.-L. Hou, *Synlett* **2011**, 2262; i) P. Fang, C.-H. Ding, X.-L. Hou, L.-X. Dai, *Tetrahedron: Asymmetry* **2010**, *21*, 1176.

[4] a) B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton, T. J. Dietsche, *J. Am. Chem. Soc.* **1978**, *100*, 3416; b) M. Kawatsura, Y. Uozumi, T. Hayashi, *Chem. Commun.* **1998**, 217; c) M. D. K. Boele, P. C. J. Kamer, M. Lutz, A. L. Spek, J. G. de Vries, P. W. N. M. Van Leeuwen, G. P. F. Van Strijdonck, *Chem. Eur. J.* **2004**, *10*, 6232; d) J. D. Weaver, B. J. Ka, D. K. Morris, W. Thompson, J. A. Tunge, *J. Am. Chem. Soc.* **2010**, *132*, 12179.

[5] a) S. Oliver, P. A. Evans, *Synthesis* **2013**, 3179; b) J. Tsuji, T. Yamada, I. Minami, M. Yuhara, M. Nisar, I. Shimizu, *J. Org. Chem.* **1987**, *52*, 2988.

[6] W.-H. Zheng, B.-H. Zheng, Y. Zhang, X.-L. Hou, *J. Am. Chem. Soc.* **2007**, *129*, 7718.

[7] P.-P. Chen, Q. Peng, B.-L. Lei, X.-L. Hou, Y.-D. Wu, *J. Am. Chem. Soc.* **2011**, *133*, 14180.

[8] "Inhibition of Enzymes by Fluorinated Compounds": J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, **2008**, chap. 7, pp. 246–256.

[9] a) M. H. Gelb, J. P. Svaren, R. H. Abeles, *Biochemistry* **1985**, *24*, 1813; b) J. R. Corte, T. Fang, C. P. Decicco, D. J. P. Pinto, K. A. Rossi, Z. Hu, Y. Jeon, M. L. Quan, J. M. Smallheer, Y. Wang, W. Yang (Bristol-Myers Squibb), WO 2011/100401A1, **2011**.

[10] a) R. Ginzburg, E. M. Ambizas, *Expert Opin. Drug Metab. Toxicol.* **2008**, *4*, 1091; b) C. Han, A. E. Salyer, E. H. Kim, X. Jiang, R. E. Jarrard, M. S. Powers, A. M. Kirchhoff, T. K. Salvador, J. A. Chester, G. H. Hockerman, D. A. Colby, *J. Med. Chem.* **2013**, *56*, 2456.

[11] Y. Shimada, N. Taniguchi, A. Matsuhisa, K. Sakamoto, T. Yatsu, A. Tanaka, *Chem. Pharm. Bull.* **2000**, *48*, 1644.

[12] a) B. R. Ambler, R. A. Altman, *Org. Lett.* **2013**, *15*, 5578; b) B. R. Ambler, S. Peddi, R. A. Altman, *Synlett* **2014**, 1938; c) Y. Qiao, T. Si, M.-H. Yang, R. A. Altman, *J. Org. Chem.* **2014**, *79*, 7122.

[13] a) I. Shimizu, H. Ishii, *Tetrahedron* **1994**, *50*, 487; b) I. Shimizu, H. Ishii, A. Tasaka, *Chem. Lett.* **1989**, *18*, 1127; c) M. Nakamura, A. Hajra, K. Endo, E. Nakamira, *Angew. Chem. Int. Ed.* **2005**, *44*, 7248; *Angew. Chem.* **2005**, *117*, 7414; d) E. C. Burger, B. R. Barron, J. A. Tunge, *Synlett* **2006**, 2824.

[14] S. Kobayashi, H. Tanaka, H. Amii, K. Uneyama, *Tetrahedron* **2003**, *59*, 1547.

[15] a) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871; *Angew. Chem.* **2004**, *116*, 1907; b) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27.

[16] a) T. Ikawa, T. E. Barder, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 13001; b) B. P. Fors, K. Dooleweerdt, Q. Zeng, S. L. Buchwald, *Tetrahedron* **2009**, *65*, 6576.
[17] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685.
[18] For additional data on the selectivity imparted by the use of alternate biaryl monophosphine ligands, see the Supporting Information.
[19] a) B. M. Trost, *Chem. Rev.* **1996**, *96*, 395; b) B. M. Trost, D. A. Thaisrivongs, *J. Am. Chem. Soc.* **2008**, *130*, 14092.
[20] S. Norsikian, C.-W. Chang, *Adv. Org. Synth.* **2013**, *3*, 81.
[21] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456.
[22] a) C. Ni, L. Zhang, J. Hu, *J. Org. Chem.* **2008**, *73*, 5699; b) W. Zhang, C. Ni, J. Hu, *Top. Curr. Chem.* **2012**, *308*, 25.
[23] T. Hayashi, M. Kawatsura, Y. Uozumi, *Chem. Commun.* **1997**, 561.
[24] a) J. A. Keith, D. C. Behenna, J. T. Mohr, S. Ma, S. C. Marinescu, J. Oxgaard, B. M. Stoltz, W. A. Goddard III, *J. Am. Chem. Soc.* **2007**, *129*, 11876; b) J. A. Keith, D. C. Behenna, N. Sherden, J. T. Mohr, S. Ma, S. C. Marinescu, R. J. Nielsen, J. Oxgaard, B. M. Stoltz, *J. Am. Chem. Soc.* **2012**, *134*, 19050.
[25] M. Méndez, J. M. Cuerva, E. Gómez-Bengoa, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2002**, *8*, 3620.
[26] a) P. Cresson, *Bull. Soc. Chim. Fr.* **1964**, 2618; b) B. W. Metcalf, E. T. Jarvi, J. P. Burkhart, *Tetrahedron Lett.* **1985**, *26*, 2861.

