JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Rhodium-Catalyzed Asymmetric Arylation/Defluorination of 1-(Trifluoromethyl)alkenes Forming Enantioenriched 1,1-Difluoroalkenes

Yinhua Huang and Tamio Hayashi*

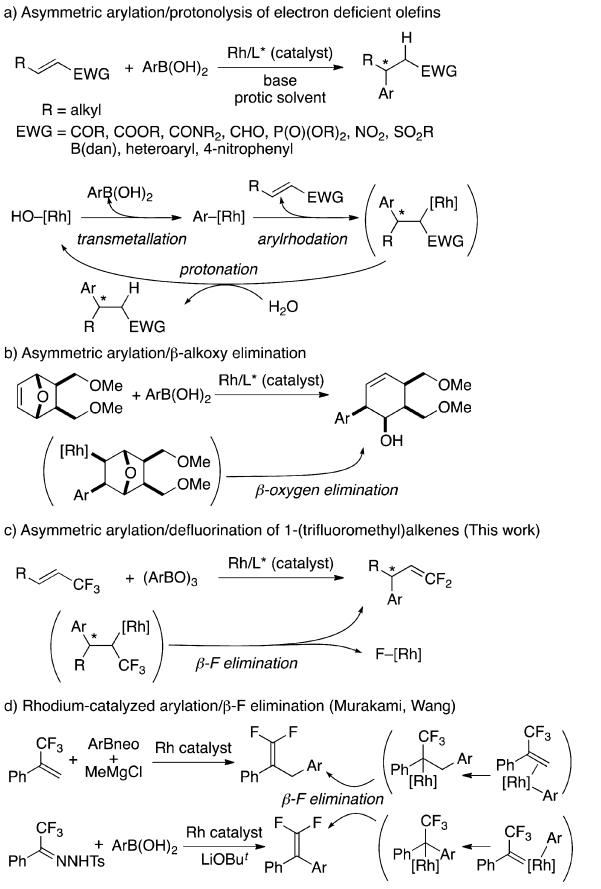
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371, Singapore

Supporting Information

ABSTRACT: The reaction of 1-(trifluoromethyl)alkenes ($CF_3CH=CHR$) with arylboroxines $(ArBO)_3$ in the presence of a chiral diene-rhodium catalyst gave high yields of chiral 1,1-difluoroalkenes ($CF_2=CHC^*HArR$) with high enantioselectivity (≥95% ee). The reaction is assumed to proceed through β-fluoride elimination of a β,β,β-trifluoroalkylrhodium intermediate that is generated by arylrhodation of the 1-(trifluoromethyl)alkene.

The rhodium-catalyzed asymmetric arylation of alkenes with arylboronic acids is well recognized to be one of the most convenient and reliable methods of creating benzylic stereocenters with high enantioselectivity.[1] In most cases, the reaction has been conducted in the presence of proton sources, typically water, to lead to hydroarylation products. The catalytic cycle of the hydroarylation reaction consists of (1) transmetalation of aryl group from boron to rhodium to generate aryl-rhodium species, (2) addition of the aryl-rhodium to alkene to form alkyl-rhodium species, and (3) protonation of the alkyl-rhodium intermediate to release the hydroarylation product[2] (Scheme 1a). As another type of rhodium-catalyzed asymmetric arylation, there have been some reports[3] on asymmetric arylation where the final step is not protonation but β-oxygen elimination leading to the olefin formation. They have been reported by Murakami[3] and Lautens[4] in the reactions of oxabicyclo[2.2.1]heptenes (Scheme 1b) and but-2-ene-1,4-diol. Herein we report 1-(trifluoromethyl)alkenes as a new entry of the alkene substrates for the rhodium-catalyzed asymmetric arylation, where the β-fluoride elimination from a β,β,β-trifluoroalkylrhodium intermediate produces chiral 1,1-difluoroalkenes with high enantioselectivity (Scheme 1c). The enantiomerically enriched organofluorine compounds are known to be of great importance in medicinal chemistry[5] and they are attracting increasing attention as synthetic intermediates.[6] The β-fluoride elimination has been extensively studied by Ichikawa[7] and others[8−10] as a key step in transition metal-catalyzed or -mediated reactions. As a reaction closely related to the present study, Murakami reported a rhodium-catalyzed reaction of α-(trifluoromethyl)styrenes with arylborates producing achiral β,β-difluorostyrene derivatives where the β-fluoride elimination is involved in the catalytic cycle.[9] The rhodium-β-fluoride elimination is also reported[10] by Wang to be involved in the reaction of a (trifluoromethyl)carbene with an arylboronic acid (Scheme 1d).

Scheme 1. Rhodium-Catalyzed Asymmetric Arylation of Alkenes



The 1-(trifluoromethyl)alkene substrates for the present study should have a substituent at 2-position to generate a new stereogenic center at 2-position by the asymmetric arylation reactions. This type of linear 1-(trifluoromethyl)alkenes have not been studied for their reactivity or selectivity in the rhodium-catalyzed addition reactions, to the best of our knowledge. As a substrate for the first set of reactions, we chose benzyl ether of γ-(trifluoromethyl)allyl alcohol **1a**, because **1a** is readily prepared from a commercial source.[11] Before asymmetric reactions, **1a** was

Received: July 29, 2016
Published: September 14, 2016

DOI: 10.1021/jacs.6b07844
J. Am. Chem. Soc. 2016, 138, 12340−12343

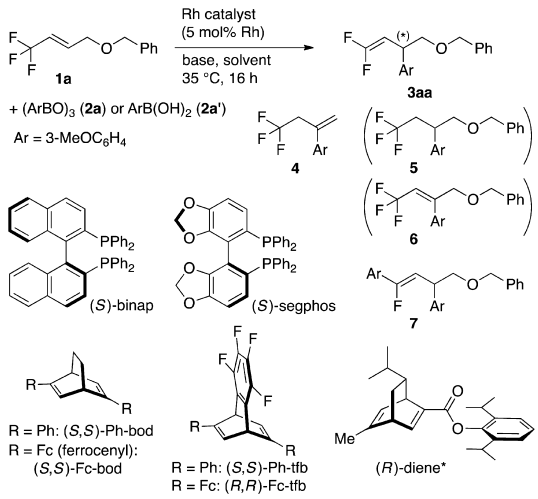
examined for its reactivity and chemoselectivity in the presence of a rhodium/cod (cod = 1,5-cyclooctadiene) catalyst. Under base free conditions using $[RhCl(cod)]_2$ in toluene/H_2O[12] or $[RhOH(cod)]_2$ in dioxane/H_2O,[13] which are effective for the arylation of α,β-unsaturated carbonyl compounds, the reaction of **1a** with arylboroxine $(3\text{-}MeOC_6H_4BO)_3$ (**2a**) was very slow, most of the substrate **1a** being recovered unreacted at the reaction temperature of 80 °C (Table 1, entries 1 and 2). Addition of KOH greatly accelerated the arylation reaction,[14] and the conversion of **1a** is generally higher with a more amount of KOH (entries 3−5). The highest yield of the arylation/defluorination product **3aa** was obtained with 2.2 equiv of KOH (entry 5). Thus, the reaction of **1a** with boroxine **2a** in the presence of $[RhCl(cod)]_2$ (5 mol % of Rh) and KOH (2.2 equiv) in dioxane/H_2O (10/1) at 35 °C for 16 h gave 85% yield of **3aa** together with 8% of terminal alkene **4** and 6% of unreacted **1a**. The yield of **3aa** was slightly lower (79%) with the corresponding boronic acid **2a′** in place of boroxine **2a** (entry 6). The conversion of **1a** and the selectivity in giving **3aa** or **4** are dependent on the solvent and base employed (entries 7−9).

A catalytic cycle producing **3aa** and **4** is illustrated in Scheme 2, which is based on the catalytic cycles proposed for rhodium-catalyzed hydroarylation of electron deficient alkenes[2] and for the reactions involving β-oxygen and β-fluoride elimination[3,4,9] as a key step. Addition of an aryl−Rh species **A** to the double bond of **1a**, which may be activated by the trifluoromethyl group, generates alkyl−Rh intermediate **B**. The pathway giving the defluorination product **3aa** is simple. β-Fluoride elimination produces **3aa** leaving an F−Rh complex **C**. Formation of alkene **4** requires a multistep pathway; β-H elimination forming alkene complex **D**, addition of H−Rh to the double bond with the other regiochemistry to give another alkyl−Rh intermediate **E** where the rhodium is at the benzylic carbon, and β-alkoxy elimination finally leads to the alkene product **4**. Interestingly, hydroarylation product **5**, which would be a standard product in the reactions performed in protic solvents, or β-hydrogen elimination product **6**, which would be formed by dissociation from **D**, was not detected under the conditions in entries 1−9. It follows that protonation of the alkyl-Rh bond on intermediate **B** is very slow, which is different from the alkyl intermediates shown in Scheme 1a, and that the intermediate **D** does not undergo the dissociation of alkene but it quickly undergoes the hydrorhodation.

Chiral diene[15] and phosphine ligands were examined for the asymmetric synthesis of **3aa** under the conditions of entry 5. It is remarkable that the catalytic activity and selectivity in giving **3aa** or **4** is strongly dependent on the ligand used (entries 10−16 in Table 1). The best result giving 92% yield of **3aa** with 99% ee (*R*) was obtained with (*R*,*R*)-Fc-tfb ligand, where the side products are 6% of **4** and 2% of diarylation product **7** (entry 10). The formation of **7** is discussed at the derivatization of defluorination products **3** (Scheme 4). The high performance of Fc-tfb ligand has been reported in several other rhodium-catalyzed asymmetric reactions.[16] The tfb skeleton is important for the high selectivity giving **3aa** (entries 10 and 11). The selectivity is reversed with bod ligands, Ph-bod[17] and Fc-bod,[18] the main product being alkene **4** (entries 12 and 13). With (*R*)-diene*[19] and bisphosphine ligands,[20] the selectivity was low (entries 14−16). In the reaction of **1a**, the β-F elimination and β-H elimination on alkyl intermediate **B** (Scheme 2) are competing processes and the selectivity is very sensitive to the reaction conditions, ligand on Rh as well as bases and solvents.

The reaction of other 1-(trifluoromethyl) alkenes that do not have the alkoxy functionality was much easier to perform, because the reaction produces the corresponding arylation/defluorination

Table 1. Rhodium-Catalyzed Asymmetric Arylation/Defluorination of 1-(Trifluoromethyl)alkene 1a[a]

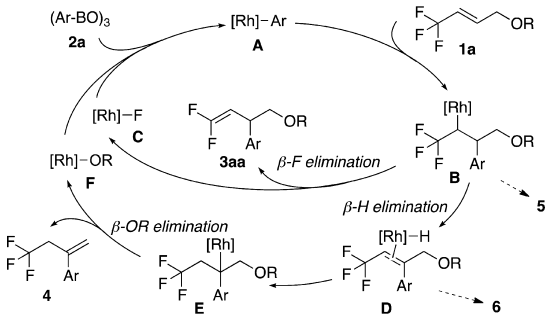


entry	ligand on Rh	base (eq)	solvent[b]	recvd (%)[c] 1a	yield (%)[c] 3aa	% ee[d] 3aa	yield (%)[c] 4
1[e]	cod[f]		Tol/H_2O	84	0		4
2[e]	cod[g]		Diox/H_2O	85	2		5
3	cod[f]	KOH (0.4)	Diox/H_2O	58	40		1
4	cod[f]	KOH (1.2)	Diox/H_2O	19	77		4
5	cod[f]	KOH (2.2)	Diox/H_2O	6	85		8
6[h]	cod[f]	KOH (2.2)	Diox/H_2O	10	79		7
7	cod[f]	KOH (2.2)	Diox	0	66		28
8	cod[f]	K_3PO_4 (2.2)	Diox/H_2O	4	64		25
9	cod[f]	Cs_2CO_3 (2.2)	Diox/H_2O	65	21		11
10	(*R*,*R*)-Fc-tfb[i]	KOH (2.2)	Diox/H_2O	0	92	99[j]	6[k]
11	(*S*,*S*)-Ph-tfb[l]	KOH (2.2)	Diox/H_2O	17	72	90	4
12	(*S*,*S*)-Ph-bod[m]	KOH (2.2)	Diox/H_2O	0	19	85	69
13	(*S*,*S*)-Fc-bod[n]	KOH (2.2)	Diox/H_2O	35	14	94	45
14	(*R*)-diene*[o]	KOH (2.2)	Diox/H_2O	45	19	−81	5
15	(*S*)-binap[p]	KOH (2.2)	Diox/H_2O	0	25	75	53
16	(*S*)-segphos[q]	KOH (2.2)	Diox/H_2O	3	21	89	57

[a]Reaction conditions: **1a** (0.12 mmol), $(3\text{-}MeOC_6H_4BO)_3$ (**2a**) (0.12 mmol (0.36 mmol of B)), Rh catalyst (5 mol % of Rh), at 35 °C for 15 h. [b]Diox and Tol stand for 1,4-dioxane and toluene, respectively. Diox/H_2O (1.0/0.1 mL). Diox (1.0 mL). Tol/H_2O (1.0/0.5 mL). [c]The yields are obtained by ^{19}F NMR analysis of the crude reaction mixture. [d]The % ee was determined by HPLC on a chiral stationary phase column. [e]At 80 °C. [f]$[RhCl(cod)]_2$. [g]$[RhOH(cod)]_2$. [h]3-$MeOC_6H_4B(OH)_2$ (**2a′**, 0.36 mmol) in place of boroxine **2a**. [i]$[RhCl((R,R)\text{-Fc-tfb})]_2$. [j]The absolute configuration (*R*) was determined by X-ray crystal structure analysis of the related compound **3be**. [k]Compound **7** was formed in 2% yield. [l]$[RhCl((S,S)\text{-Ph-tfb})]_2$. [m]$[RhCl((S,S)\text{-Ph-bod})]_2$. [n]$[RhCl((S,S)\text{-Fc-bod})]_2$. [o]$[RhCl((R)\text{-diene*})]_2$. [p]$[RhCl((S)\text{-binap})]_2$. [q]$[RhCl((S)\text{-segphos})]_2$.

DOI: 10.1021/jacs.6b07844
J. Am. Chem. Soc. 2016, 138, 12340−12343

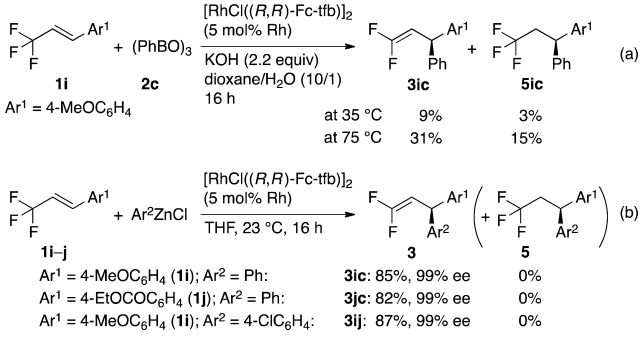
Scheme 2. Catalytic Cycle for the Rhodium-Catalyzed Arylation of 1-(Trifluoromethyl)alkene 1a with Arylboroxine 2a



products selectively without serious side reactions. With (*R*,*R*)-Fc-tfb ligand under the conditions of entry 10 in Table 1, trifluoromethylalkene substrates containing phthalimino (**1b**), secondary and tertiary amino (**1c** and **1d**), ester group(s) (**1e** and **1f**), and hydroxyl group (**1g**), all gave the target compounds **3** in high yields with high enantioselectivity (95−99% ee) (Table 2). For the arylboroxine counterparts, those substituted with alkoxy, methyl, bromo, and trifluoromethyl at 3 or 4 position of phenyl were introduced successfully in high yields (entries 2−8). The yield was slightly lower with a bulky aryl group (entry 10). It is notable that present reaction is applicable to the synthesis of chiral allylsilane **3ha** bearing a stereogenic center at the α-position with high % ee (entry 19).

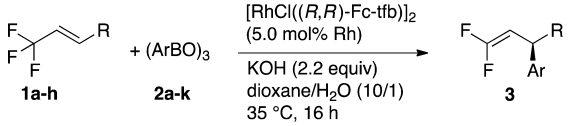
The reactivity and selectivity of an aryl-substituted trifluoromethylalkene are different from those of alkyl-substituted ones **1a−g**, as shown in Scheme 3. The reaction of 1-(trifluoromethyl)-2-(4-methoxyphenyl)ethene (**1i**) with phenylboroxine (**2c**) under the conditions of Table 2 gave low yields of a mixture of the arylation/defluorination product **3ic** (9%) and hydroarylation product **5ic** (3%) (Scheme 3a). At higher temperature (75 °C), their yields were improved to some extent, but the selectivity giving **3ic** or **5ic** was low. Selective formation of defluorination product **3ic** was realized by use of a phenylzinc reagent in aprotic solvent in place of $(PhBO)_3$ in dioxane/H_2O. Thus, the reaction of **1i** with PhZnCl catalyzed by [RhCl((*R*,*R*)-Fc-tfb)]$_2$ in THF at room temperature gave 85% yield of **3ic** with 99% ee.[21] The reaction with zinc reagent is applicable to the synthesis of diary-substituted difluoroalkenes **3jc** and **3ij** (Scheme 3b).

Scheme 3. Reaction of 1-(Trifluoromethyl)-2-arylethenes



Taking advantages of the difluoroethenyl functionality in the arylation/defluorination products **3**, they were derivatized into other chiral compounds without loss of enantiomeric purity (Scheme 4). Cross-coupling of (*R*)-**3dc** with excess Grignard reagents RMgBr (R = Me, Ph) proceeded in the presence of a Ni/dppp catalyst in refluxing benzene to give the corresponding disubstitution products **8a** and **8b** in high yields.[22,23] Selective monophenylation of (*R*)-**3dc** producing **9** was found to be catalyzed well by a rhodium/Ph-bod complex in the presence of excess Ph-bod ligand in toluene/H_2O solvent system.[24] The

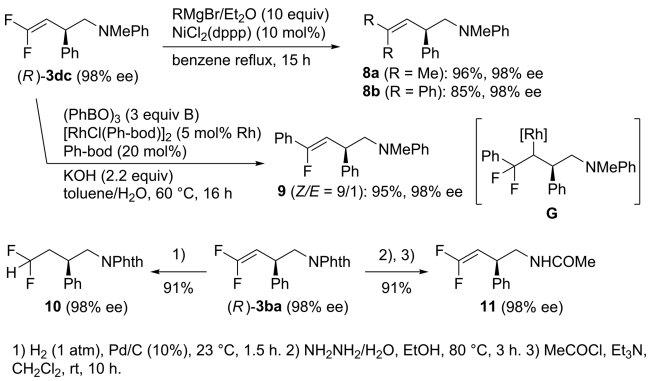
Table 2. Rhodium-Catalyzed Asymmetric Arylation/Defluorination of 1-(Trifluoromethyl)alkenes 1[a]



entry	1: R	2: Ar	3: yield (%)[b]	ee (%)[c]
1	**1a**: CH_2OCH_2Ph	**2a**: 3-$MeOC_6H_4$	**3aa**: 90	99
2	**1b**: CH_2NPhth[d]	**2a**: 3-$MeOC_6H_4$	**3ba**: 95	99
3	**1b**: CH_2NPhth[d]	**2b**: 4-$MeOC_6H_4$	**3bb**: 95	99
4	**1b**: CH_2NPhth[d]	**2c**: Ph	**3bc**: 95	98
5	**1b**: CH_2NPhth[d]	**2d**: 4-MeC_6H_4	**3bd**: 95	99
6	**1b**: CH_2NPhth[d]	**2e**: 4-BrC_6H_4	**3be**: 94	99[e]
7	**1b**: CH_2NPhth[d]	**2f**: 4-$CF_3C_6H_4$	**3bf**: 94	99
8	**1b**: CH_2NPhth[d]	**2g**: 3,4-$OCH_2OC_6H_3$	**3bg**: 93	99
9	**1b**: CH_2NPhth[d]	**2h**: 2-naphthyl	**3bh**: 93	99
10	**1b**: CH_2NPhth[d]	**2i**: 2-MeC_6H_4	**3bi**: 80	99
11[f]	**1c**: CH_2NHPh	**2c**: Ph	**3cc**: 93	97
12[f]	**1d**: CH_2NMePh	**2c**: Ph	**3dc**: 94	98
13	**1e**: $CH_2CH_2CO_2Me$	**2a**: 3-$MeOC_6H_4$	**3ea**: 88	95
14	**1e**: $CH_2CH_2CO_2Me$	**2c**: Ph	**3ec**: 85	96
15	**1e**: $CH_2CH_2CO_2Me$	**2f**: 4-$CF_3C_6H_4$	**3ef**: 82	98
16	**1e**: $CH_2CH_2CO_2Me$	**2j**: 4-ClC_6H_4	**3ej**: 92	96
17	**1f**: $CH_2CH(CO_2Me)_2$	**2c**: Ph	**3 fc**: 85	96
18	**1g**: $CH_2CH_2CH_2OH$	**2a**: 3-$MeOC_6H_4$	**3ga**: 87	98
19[f]	**1h**: $SiMe_3$	**2a**: 3-$MeOC_6H_4$	**3ha**: 78	96

[a]Reaction conditions: **1** (0.12 mmol), $(ArBO)_3$ **2** (0.12 mmol (0.36 mmol of B)), KOH (0.26 mmol), and Rh catalyst (5 mol % of Rh) in dioxane/H_2O (1.0/0.1 mL) at 35 °C for 16 h. [b]Isolated yield. [c]The % ee was determined by HPLC using chiral stationary phase columns. [d]NPhth stands for phthalimino group. [e]The absolute configuration of **3be** was determined to be (R) by X-ray crystal structure analysis (CCDC 1496404). Other products are estimated to have the same configuration (R) where R is italic, by stereochemical similarity of the reactions. [f]At 60 °C.

Scheme 4. Derivatization of the Arylation/Defluorination Products



DOI: 10.1021/jacs.6b07844
J. Am. Chem. Soc. 2016, 138, 12340−12343

monophenylation is assumed to proceed through phenylrhodation/β-F elimination mechanism[25] with **G** as an intermediate. Interestingly, the phenylation did not take place at all with cod or phosphorus ligands (PPh_3, dppp), whereas it was promoted by Ph-bod and Fc-tfb ligands. Scheme 4 also shows hydrogenation of the difluoroethenyl group into difluoroethyl group and deprotection of phthalimino group in (*R*)-**3ba** into amino group without loss of % ee.

In summary, we have developed a new type of catalytic asymmetric reaction where 1-(trifluoromethyl)alkenes (CF_3CH=CHR) are converted into chiral 1,1-difluoroalkenes (CF_2=CHC*HArR) with high enantioselectivity (≥95% ee) by the reaction with arylboroxines $(ArBO)_3$ in the presence of a chiral diene-rhodium catalyst. The CF_3 group plays key roles in activating the alkene substrates toward arylrhodation and in carrying the catalytic cycle by β-fluoride elimination of a β,β,β-trifluoroalkylrhodium intermediate as a key step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07844.

Crystallographic data for $C_{18}H_{12}BrF_2NO_2$ (CIF)
Experimental procedures (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*hayashi@ntu.edu.sg

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Nanyang Technological University for supporting this research.

■ REFERENCES

(1) For pertinent reviews, see: (a) Heravi, M. M.; Dehghani, M.; Zadsirjan, V. *Tetrahedron: Asymmetry* **2016**, *27*, 513. (b) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95. (c) Berthon, G.; Hayashi, T. In *Catalytic Asymmetric Conjugate Reactions*; Córdova, A., Ed.; Wiley-VCH: Weinheim, Germany, 2010; Chapter 1, p 1. (d) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093. (e) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840. (f) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, *2003*, 4313. (g) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (h) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

(2) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(3) (a) Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390. (b) Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 595. See also for related reactions: (c) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094. (d) Shimada, M.; Harumashi, T.; Miura, T.; Murakami, M. *Chem. - Asian J.* **2008**, *3*, 1035. (e) Miura, T.; Shimada, M.; Murakami, M. *Chem. - Asian J.* **2006**, *1*, 868.

(4) (a) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311. (b) Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695. (c) Panteleev, J.; Menard, F.; Lautens, M. *Adv. Synth. Catal.* **2008**, *350*, 2893. (d) Tsui, G. C.; Tsoung, J.; Dougan, P.; Lautens, M. *Org. Lett.* **2012**, *14*, 5542.

(5) For selected reviews on fluorine in medicinal chemistry, see: (a) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. And references cited therein. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (e) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013.

(6) For recent reviews, see: (a) Unzner, T. A.; Magauer, T. *Tetrahedron Lett.* **2015**, *56*, 877. (b) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. *Chem. Rev.* **2015**, *115*, 931. (c) Chelucci, G. *Chem. Rev.* **2012**, *112*, 1344. (d) Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J. F. *Chem. Soc. Rev.* **2011**, *40*, 2867. (e) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119. (f) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

(7) (a) Sakoda, K.; Mihara, J.; Ichikawa, J. *Chem. Commun.* **2005**, 4684. (b) Ichikawa, J.; Nadano, R.; Ito, N. *Chem. Commun.* **2006**, 4425. (c) Ichitsuka, T.; Fujita, T.; Arita, T.; Ichikawa, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 7564. (d) Fujita, T.; Arita, T.; Ichitsuka, T.; Ichikawa, J. *Dalton Trans.* **2015**, *44*, 19460. (e) Ichitsuka, T.; Fujita, T.; Ichikawa, J. *ACS Catal.* **2015**, *5*, 5947.

(8) (a) Kraft, B. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 8681. (b) Braun, T.; Wehmeier, F.; Altenhöner, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5321. (c) Kühnel, M. F.; Lentz, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 2933. (d) Hu, M.; He, Z.; Gao, B.; Li, L.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 17302. (e) Zhang, H.; Lin, J.-H.; Xiao, J.-C.; Gu, Y.-C. *Org. Biomol. Chem.* **2014**, *12*, 581.

(9) Miura, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2008**, *37*, 1006.

(10) Zhang, Z.; Zhou, Q.; Yu, W.; Li, T.; Wu, G.; Zhang, Y.; Wang, J. *Org. Lett.* **2015**, *17*, 2474.

(11) Wang, B.-L.; Yu, F.; Qiu, X.-L.; Jiang, Z.-X.; Qing, F.-L. *J. Fluorine Chem.* **2006**, *127*, 580.

(12) Dou, X.; Lu, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 6739.

(13) Kina, A.; Yasuhara, Y.; Nishimura, T.; Iwamura, H.; Hayashi, T. *Chem. - Asian J.* **2006**, *1*, 707.

(14) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.

(15) For reviews on chiral diene ligands, see: (a) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482. (b) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31. (c) Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *Synlett* **2011**, *2011*, 1345. (d) Feng, X.; Du, H. *Asian J. Org. Chem.* **2012**, *1*, 204.

(16) (a) Nishimura, T.; Kumamoto, H.; Nagaosa, M.; Hayashi, T. *Chem. Commun.* **2009**, 5713. (b) Lim, K. M.-H.; Hayashi, T. *J. Am. Chem. Soc.* **2015**, *137*, 3201. (c) Huang, Y.; Hayashi, T. *J. Am. Chem. Soc.* **2015**, *137*, 7556 and references cited..

(17) (a) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503. (b) Abele, S.; Inauen, R.; Spielvogel, D.; Moessner, C. *J. Org. Chem.* **2012**, *77*, 4765.

(18) Dou, X.; Huang, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 1133.

(19) (a) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, 4815. (b) Ref 12, and references cited.

(20) binap: (a) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629. (b) segphos: Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(21) Use of arylzinc reagents for rhodium-catalyzed asymmetric conjugate arylation has been reported: See ref 1 and Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240.

(22) 1,1-Dibromo- and 1,1-dichloroolefins are known to be good substrates for cross-coupling reactions (ref 6c). One example of Pd-catalyzed cross-coupling of $ArCH=CF_2$ with Ar'ZnCl has been reported: Saeki, T.; Takashima, Y.; Tamao, K. *Synlett* **2005**, 1771.

(23) The cross-coupling did not take place with Pd catalysts. For the Ni-catalyzed cross-coupling in benzene reflux, see: (a) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246. (b) Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 3915.

(24) The high Ph-bod/Rh ratio (5/1) is necessary for the high conversion. The reaction stops at a low conversion with the ratio of 1/1.

(25) The addition/elimination mechanism has been proposed for the Pd-catalyzed monoarylation of 1-aryl-2,2-difluoroalkenes: (a) Thornbury, R. T.; Toste, F. D. *Angew. Chem., Int. Ed.* **2016**, *55*, 11629. See also: (b) Matsuda, T.; Suzuki, K.; Miura, N. *Adv. Synth. Catal.* **2013**, *355*, 3396.

DOI: 10.1021/jacs.6b07844
J. Am. Chem. Soc. 2016, 138, 12340−12343