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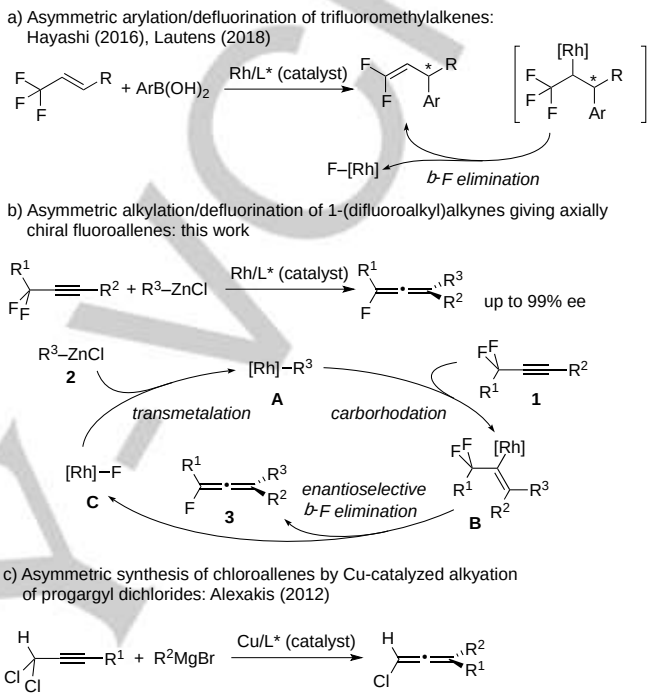
Asymmetric Synthesis of Fluorinated Allenes by Rhodium-Catalyzed Enantioselective Alkylation/Defluorination of Propargyl Difluorides with Alkylzincs

Jia Sheng Ng[b] and Tamio Hayashi*[a,b]

Abstract: The reaction of propargyl difluorides $R^1CF_2C{\equiv}CR^2$ with alkylzincs R^3ZnCl giving axially chiral fluorinated allenes $R^1FC{=}C{=}CR^2R^3$ with high enantioselectivity (up to 99% ee) was found to be catalyzed by a chiral diene/rhodium complex. A key step in the catalytic cycle is selective elimination of one of the enantiotopic fluorides at β-position of an alkenyl–Rh intermediate which is generated by regioselective addition of R^3–Rh onto the triple bond of the starting difluorides.

Axially chiral allenes have attracted increasing attention owing to their synthetic utility based on their unique structure and reactivity.[1] While a variety of catalytic asymmetric reactions have been reported for obtaining axially chiral allenes,[1,2] it is still important and challenging to develop a new efficient method of synthesizing this class of chiral molecules with high enantioselectivity. Here we report rhodium-catalyzed asymmetric synthesis of tetra-substituted chiral allenes[3] where one of the four substituents is fluoride.[4,5]

We have previously reported that the reaction of 1-trifluoromethylalkenes with arylboronic acids in the presence of a chiral diene/Rh catalyst gives enantioenriched 1,1-difluoroalkenes[6] (Scheme 1a). This reaction is different from other Rh-catalyzed asymmetric arylation reactions[7] in that its catalytic cycle involves β-fluoride elimination[8,9,10] from an alkyl–Rh intermediate generated by the arylrhodation of a 1-trifluoromethylalkene. More recently this type of asymmetric reactions that produce 1,1-difluoroalkenes bearing a chiral carbon center at the allylic position have been developed for the synthesis of enantioenriched allyl-boranes and -silanes.[11] Here we report asymmetric synthesis of fluoride-substituted chiral allenes (Scheme 1b), where the stereochemical outcome is decided at β-elimination of one of the two enantiotopic fluorides from the alkenyl-Rh intermediate **B**. As a catalytic asymmetric reaction related to ours in terms of reaction pathway, Alexakis has previously reported copper-catalyzed asymmetric reaction of propargyl dichlorides with alkyl Grignard reagents giving chloride-substituted allenes[12] (Scheme 1c). There have been two reports on the asymmetric synthesis of chiral fluoroallenes. One is asymmetric reduction of trifluoroallene with a chiral zirconocene hydride giving 1,3-difluoroallene reported by Lentz[4a] and the other is Rh(III)-catalyzed C-H activation reported by Wang during his studies on asymmetric synthesis of isoindolinones.[4b]



Scheme 1. Catalytic asymmetric synthesis of axially chiral allenes by rhodium-catalyzed alkylation/defluorination.

Scheme 2 shows some of the results obtained for our preliminary experiments using a rhodium/1,5-cyclooctadiene (cod) catalyst to find the conditions where the target product, fluoride-substituted allene, is formed in a high yield with high chemoselectivity. The reaction of propargyl difluoride **1a** with $PhB(OH)_2$ (**2a**) under the conditions used for the reaction of trifluoromethylalkenes[6] (Scheme 1a), that is, with KOH (20 mol%) in dioxane/H_2O (10/1) at 50 °C, gave 22% yield of the fluoroallene **3aa**, together with 15% of hydrophenylation product **4** and 37% of ortho-disubstituted benzene **5**. The side products **4** and **5** are most likely formed through the intermediate **D** which is generated from intermediate **B** by 1,4-shift of rhodium from alkenyl carbon to ortho-position of the phenyl ring.[13] Although the formation of **5** with this good selectivity is interesting in its reaction pathway as well as in the synthetic utility of **5**, we focus our present study on the synthesis of fluoroallenes in a high yield. Use of zinc reagent PhZnCl (**2a'**)[14,15] instead of $PhB(OH)_2$ (**2a**) improved the yield of allene **3aa** (66%), but the reaction was still accompanied by the formation of **5** albeit in a lower yield (31%). It turned out that organozinc nucleophiles which do not undergo the 1,4-shift produce the corresponding fluoroallenes in high yields. Thus, 3,5-dichlorophenylzinc chloride (**2b**), where the Cl-substituents at meta-positions prohibit the rhodium from shifting to the ortho-positions, gave high yield (90%) of the fluoroallene **3ab** with high selectivity. Interestingly, benzylzinc chloride (**2c**), which has been rarely used for rhodium-catalyzed

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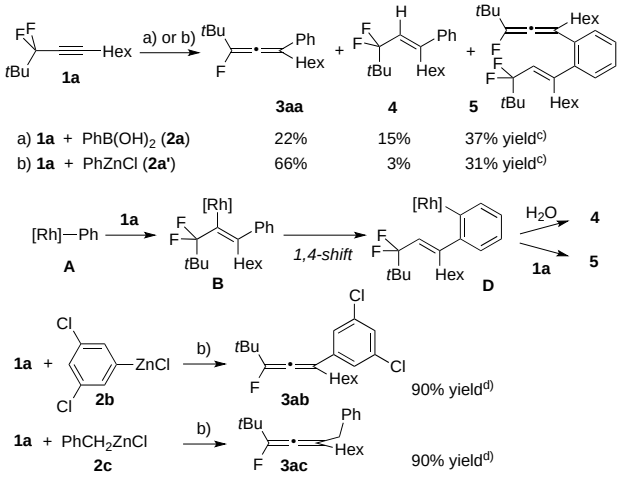
addition reactions onto either alkynes or alkenes,[7] was found to be an active reagent for the present reaction to give the corresponding allene **3ac** in 90% yield.

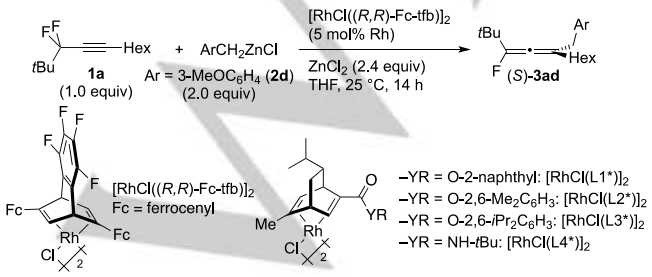


a) $PhB(OH)_2$ (2 equiv), $[RhCl(cod)]_2$ (5 mol% Rh), KOH (20 mol%), dioxane/H_2O (10/1) at 50 °C for 14 h. b) RZnCl (2 equiv), $[RhCl(cod)]_2$ (5 mol% Rh), THF at 25 °C for 14 h, and then H_2O. c) Yields by NMR analysis. d) Isolated yields.

Scheme 2. Rhodium-catalyzed reaction of propargyl difluoride **1a** with organoboron and zinc reagents producing fluorinated allenes **3**.

The reaction of propargyl difluoride **1a** with 3-methoxybenzylzinc chloride (**2d**) (2.0 equiv)[16] was examined using several chiral diene ligands[17] for the high chemo- and enantio-selectivity in giving chiral allene **3ad** (Table 1). The best result was obtained with a rhodium/Fc-tfb catalyst[18] (5 mol% Rh) in the presence of 2.4 equiv of $ZnCl_2$ in THF at 25 °C for 14 h, which gave 75% yield of (*S*)-**3ad** with 98% ee (entry 1). Other chiral diene/rhodium complexes[19] also catalyzed the reaction to give 60–74% yields of **3ad**, while the enantioselectivity was lower to some extent (entries 2–5). Bisphosphine/rhodium complexes are not catalytically active for the present reaction, leaving the propargyl difluoride **1a** unreacted (entries 6 and 7). The reaction was very slow at 0 °C and the enantioselectivity was lower at 50 °C (entries 8 and 9). The effects of the zinc salts on the present asymmetric reaction were studied in the reaction with amide ligand L4* (entries 5 vs 10–12). The use of $ZnBr_2$ instead of $ZnCl_2$ gave the product **3ad** with essentially the same enantioselectivity (90% ee) albeit in a lower yield. The amount of $ZnCl_2$ did not affect the enantioselectivity, the % ee being kept between 90% and 91% with 3 and 5 equiv of $ZnCl_2$.[20]

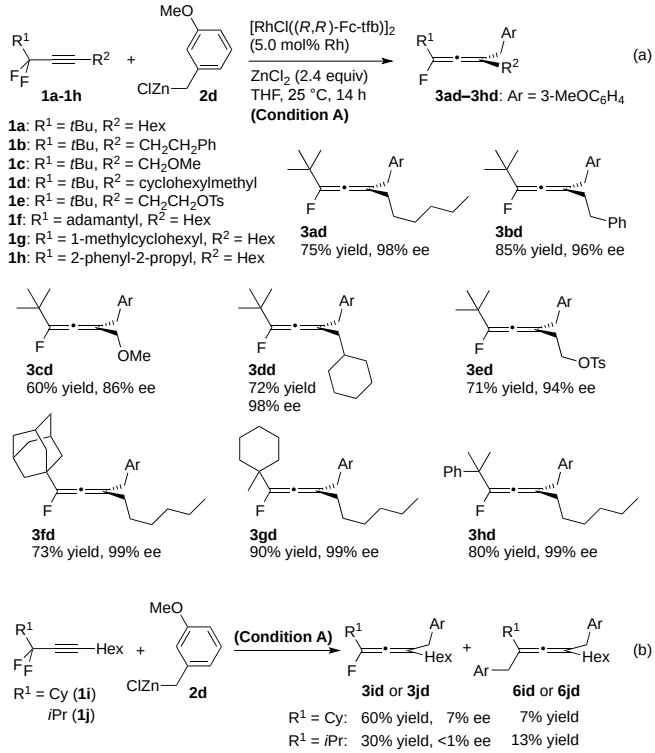
Table 1. Catalytic asymmetric reaction of alkyne **1a** with 3-methoxybenzylzinc chloride (**2d**).[a]



Entry	Variations from standard conditions (shown above)	Conv (%)[b] of **1a**	Yield (%)[c] of **3ad**	% ee[d] of **3ad**
1	none	96	75	98 (*S*)
2	$[RhCl(L1^*)]_2$	98	74	92 (*R*)
3	$[RhCl(L2^*)]_2$	94	61	96 (*R*)
4	$[RhCl(L3^*)]_2$	92	60	97 (*R*)
5	$[RhCl(L4^*)]_2$	72	69	91 (*R*)
6	$[RhCl(coe)_2]_2$ + (*R*)-binap[e]	0	0	—
7	$[RhCl(coe)_2]_2$ + (*R*)-segphos[f]	0	0	—
8	0 °C instead of 25 °C	25	21	98 (*S*)
9	50 °C instead of 25 °C	97	78	96 (*S*)
10	$[RhCl(L4^*)]_2$ and $ZnBr_2$ (2.4 equiv)	71	55	90 (*R*)
11	$[RhCl(L4^*)]_2$ and $ZnCl_2$ (3.0 equiv)	60	47	90 (*R*)
12	$[RhCl(L4^*)]_2$ and $ZnCl_2$ (5.0 equiv)	43	24	91 (*R*)

[a] Reaction conditions: Alkyne **1a** (0.15 mmol), $ArCH_2ZnCl$ **2d** (0.30 mmol), $ZnCl_2$ (0.36 mmol), and Rh catalyst (5 mol% of Rh) in THF (0.8 mL) at 25 °C for 14 h. The zinc reagent $ArCH_2ZnCl$ was generated by the reaction of $ArCH_2MgBr$ (1.0 equiv) with $ZnCl_2$ (2.2 equiv) in THF. For the details, see Supporting Information. [b] Determined by 19F NMR of the crude reaction mixture. [c] Isolated yield. [d] The % ee was determined by HPLC on a chiral stationary phase column. [e] binap = 2.2'-bis(diphenylphosphino)-1,1'-binaphthyl. [f] segphos = 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole.

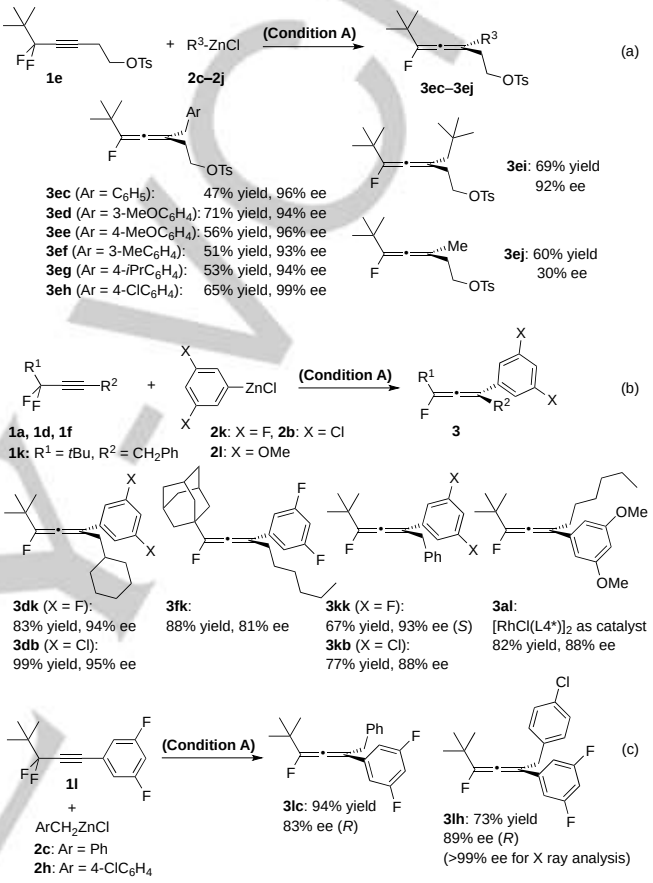
The best reaction condition (Condition A, entry 1 in Table 1) was applied to the reaction of 3-methoxybenzylzinc chloride (**2d**) with propargyl difluorides bearing various types of substituents at α (R^1) and γ (R^2) positions (Scheme 3). The high selectivity giving allene **3** was observed for the reaction of those substituted with tertiary alkyl groups at α position (Scheme 3(a)). Thus, the reaction of propargyl difluorides **1a–1e**, which have a *t*Bu group at α position, all gave the corresponding fluoroallenes **3ad–3ed** in high yields. The substituents R^2 at γ position are primary alkyl groups including functionalized ones, CH_2OMe (**3cd**) and CH_2CH_2OTs (**3ed**). An aromatic group at γ position is also a good substituent giving the fluoroallene in high yield (**1l** in Scheme 4(c)). The enantioselectivity was generally high, higher than 90% ee in most cases. Other tertiary alkyl groups, 1-adamantyl (**1f**), 1-methylcyclohexyl (**1g**), and 2-phenyl-2-propyl (**1h**), which are sterically more demanding than *t*Bu, gave the corresponding fluoroallenes, **3fd**, **3gd**, and **3hd**, with higher (99%) enantioselectivity. The advantage of tertiary alkyl groups at α position was observed for both high chemoselectivity and enantioselectivity. The reaction of propargyl difluoride **1i**, where the R^1 group at α position is a secondary alkyl (cyclohexyl), gave a low yield (60%) of the fluoroallene **3id** together with 7% of dibenzylation product **6id** (Scheme 3(b)), the latter being formed by the Rh-catalyzed reaction[21] of **3id** with benzylzinc **2d**. The selectivity giving fluoroallene is even lower (30%) with a smaller secondary alkyl at α position, which is shown by the reaction of propargyl difluoride **1j** (R^1 = *i*Pr). Interestingly, the enantiomeric purity of the fluoroallene products **3id** and **3jd** obtained was very low, which may be related to the stereochemical pathway to decide the enantioselectivity of the present reaction (vide infra).



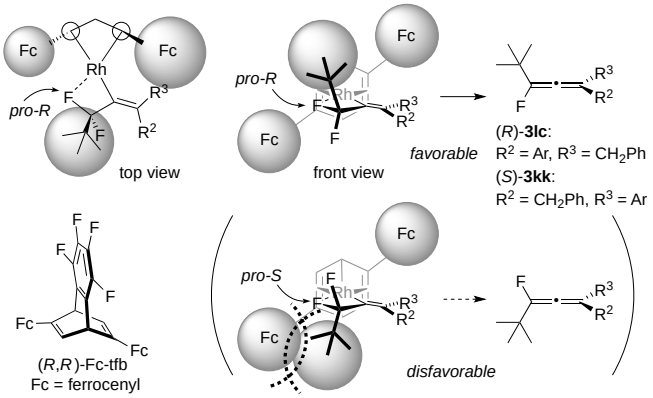
Scheme 3. Asymmetric synthesis of fluorinated allenes catalyzed by [RhCl((*R*,*R*)-Fc-tfb)]$_2$. Scope of propargyl difluorides.[a]

Benzylic zinc reagents with some other substituents on the benzene ring **2c**–**2h** gave the corresponding fluoroallenes **3ec**–**3eh** with high enantioselectivity (93%–99% ee) in the reaction with propargyl difluoride **1e** (Scheme 4(a)). The OTs functionality is installed into the side chain of **1e** for easier separation of allene enantiomers at their HPLC analysis as well as for further transformation of the allene products. Neopentylzinc chloride (**2i**) was used successfully for the present reaction, which gave the corresponding fluoroallene **3ei** in 69% yield with 92% ee. MeZnCl[22] also gave the fluoroallene **3ej** although the enantioselectivity was not as high (30% ee). A complex mixture was formed in the reaction with EtZnCl, which is probably due to the β-hydrogen elimination from ethyl-Rh intermediate. The arylzinc reagents, **2k** and **2b**, which are disubstituted with F and Cl, respectively, at meta,meta-positions, can be also used for the present reaction to give the corresponding arylated fluoroallenes with high enantioselectivity (Scheme 4(b). see also Scheme 2).

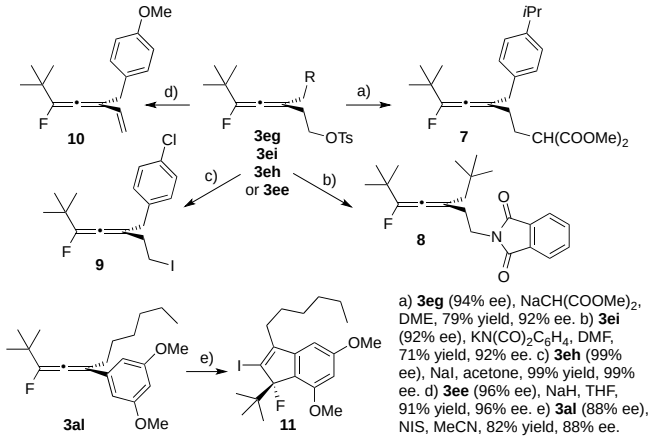
The absolute configuration of fluoroallene product **3lh**, which was obtained by the reaction of propargyl difluoride **1l** (R^2 = 3,5-$F_2C_6H_3$) with benzylic zinc **2h**, was determined to be *R* by X-ray crystal analysis (CCDC 2063773) (Scheme 4(c)). It is remarkable that the allenes **3kk** and **3lc**, which were produced by the reactions shown in Scheme 4(b) and Scheme 4(c), respectively, are a pair of enantiomers. The *R* configuration for **3lc** and *S* configuration for **3kk** are rationalized by the stereochemical pathway shown in Scheme 5, where *pro-R* fluoride participates in the β-F elimination from the alkenyl–Rh intermediate. The participation of *pro-S* fluoride would suffer from a steric repulsion between one of the ferrocenyl groups on the chiral diene ligand and *t*Bu group on the difluoride substrate. Because the ferrocenyl and R^1 groups are not very close each other, the substituent R^1 must be large enough for this repulsion to work well. This mechanism of stereocontrol is consistent with the low enantioselectivity observed for the reaction of difluorides **1i** (R^1 = Cy) and **1j** (R^1 = *i*Pr) shown in Scheme 3(b), where the R^1 is not a tertiary alkyl group.



Scheme 4. Asymmetric synthesis of fluorinated allenes catalyzed by [RhCl((*R*,*R*)-Fc-tfb)]$_2$. Scope of organozinc reagents.[a]



Scheme 5. Stereochemical pathway in the asymmetric synthesis of fluorinated allenes catalyzed by [RhCl((*R*,*R*)-Fc-tfb)]$_2$.



a) **3eg** (94% ee), $NaCH(COOMe)_2$, DME, 79% yield, 92% ee. b) **3ei** (92% ee), $KN(CO)_2C_6H_4$, DMF, 71% yield, 92% ee. c) **3eh** (99% ee), NaI, acetone, 99% yield, 99% ee. d) **3ee** (96% ee), NaH, THF, 91% yield, 96% ee. e) **3al** (88% ee), NIS, MeCN, 82% yield, 88% ee.

Scheme 6. Derivatization of the fluoroallene products **3**.

Taking advantages of the tosylate as a leaving group, those fluoroallenes bearing a tosylate were readily converted into malonate **7**, phthalimide **8**, iodide **9**, and conjugated alkene **10** without serious loss of their enantiomeric purity (Scheme 6). The iodonium-induced cyclization giving indene[23] was successfully applied to the chiral arylallene **3al** to give the chiral indene **11** with a quaternary carbon center with 88% ee.

In summary, we have developed a new type of catalytic asymmetric reaction producing axially chiral fluorinated allenes with high % ee, where the enantioposition-selective β-F elimination from an alkenyl-Rh intermediate[24] is a key step in the catalytic cycle.

Acknowledgements

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Keywords: axially chiral allene • asymmetric defluorination • chiral diene ligand • rhodium catalyst

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[20] The small effects of the amount of $ZnCl_2$ on the % ee may indicate that the transmetalation between alkenyl-Rh intermediate **B** and $ZnCl_2$ generating alkenylzinc, which would produce racemic product **3ad** through β-F elimination, is not taking place in the present reaction.

[21] An addition/elimination mechanism has been proposed for this type of coupling reactions (ref 8). See also: a) R. T. Thornbury, F. D. Toste, *Angew. Chem. Int. Ed.* **2016**, *55*, 11629; *Angew. Chem.* **2016**, *128*, 11801; b) T. Matsuda, K. Suzuki, N. Miura, *Adv. Synth. Catal.* **2013**, *355*, 3396.

[22] The use of Me_2Zn instead of MeZnCl (MeMgBr + $ZnCl_2$ (2.2 eq)) gave 80% yield of **3ej** with 15% ee, and Me_2Zn + $MgCl_2$ (1.0 eq) gave 82% yield of **3ej** with 22% ee.

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[24] The β-elimination to form a Rh–F intermediate was observed by ^{19}F NMR in a stoichiometric reaction of propargyl difluoride (**1a**, 1 equiv) with 3,5-$Cl_2C_6H_3B(OH)_2$ (0.5 equiv) and $[Rh(OH)(cod)]_2$ (1 equiv of Rh). For details, see Supporting Information. For NMR studies on F–Rh complexes see, J. Vincente, J. Gil-Rubio, D. Bautista, A. Sironi, N. Masciocchi. *Inorg. Chem.* **2004**, *43*, 5665.

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Asymmetric Synthesis of Fluorinated Allenes by Rhodium-Catalyzed Enantioselective Alkylation/Defluorination of Propargyl Difluorides with Alkylzincs

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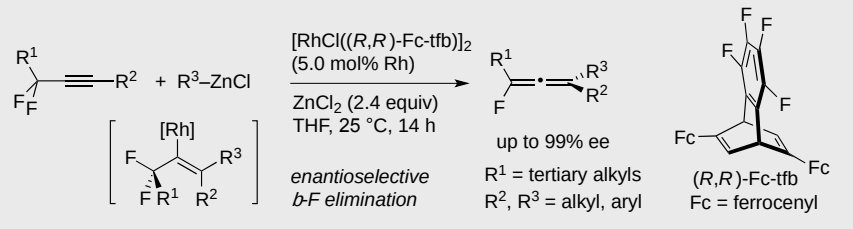

The reaction of propargyl difluorides $R^1CF_2C{\equiv}CR^2$ with alkylzincs R^3ZnCl giving axially chiral fluorinated allenes $R^1FC{=}C{=}CR^2R^3$ with high enantioselectivity (up to 99% ee) was found to be catalyzed by a chiral diene/rhodium complex. A key step in the catalytic cycle is selective elimination of one of the enantiotopic fluorides at β-position of an alkenyl–Rh intermediate which is generated by regioselective addition of R^3–Rh onto the triple bond of the starting difluorides.

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