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Highly enantioselective amination of η^3-(2-fluorocycloheptenyl)palladium complexes bearing chiral P,P- and P,N-ligands

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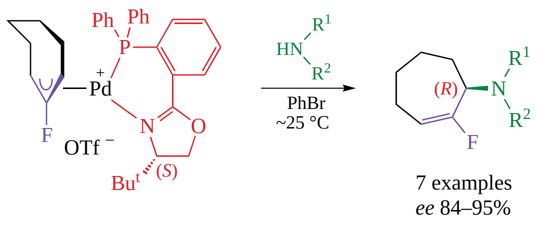
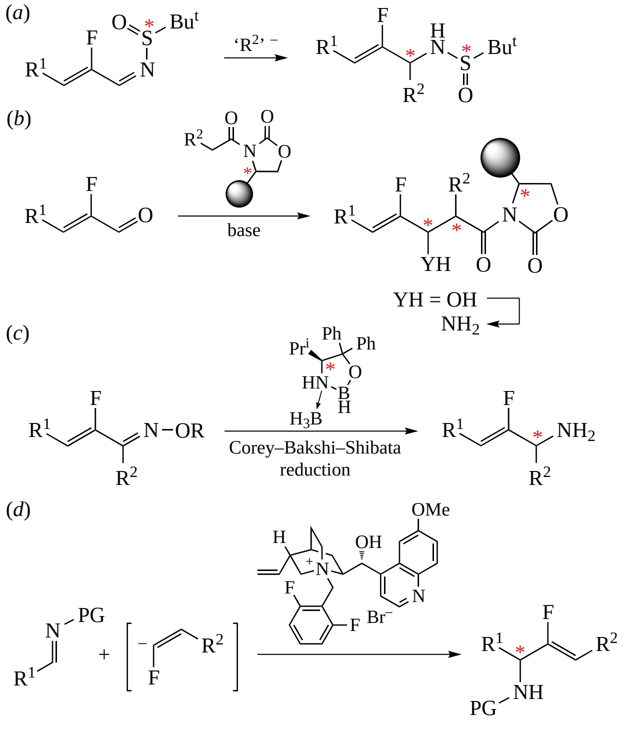
The key enantioselectivity-determining step in Pd-catalyzed asymmetric amination of 2-fluoroallylic substrates was optimized using model reaction of η^3-(2-fluorocycloheptenyl)-palladium complexes bearing chiral P,P- and P,N-ligands with various amines. (*S*)-Bu^{t}PHOX was found to be the most effective ligand allowing the formation of 2-fluoroallyl amines and anilines with high enantioselectivity.



Keywords: fluoroalkenes, 2-fluoroallyl amines, enantioselective catalysis, chiral palladium complexes, allylic amination.

The high impact of 2-fluoroallyl amines in drug design makes the development of effective and straightforward enantioselective strategies to these compounds an important task.[1–7] The most commonly used strategy toward chiral 2-fluoroallyl amines utilizes *tert*-butyl sulfinyl imine as a chiral directing group in nucleophilic additions of organometallics, enolates or in reduction[8–10] (Scheme 1, part *a*). Otherwise, α,β-unsaturated imines or carbonyl compounds can be reacted with chiral nucleophiles such as Evans enolates[11,12] or oxaazaborolidines[13] (the Corey–Bakshi–Shibata reduction, see Scheme 1, parts *b* and *c*). Additionally, organocatalyzed monofluoroalkenylation of imines should be mentioned[14] (part *d*).



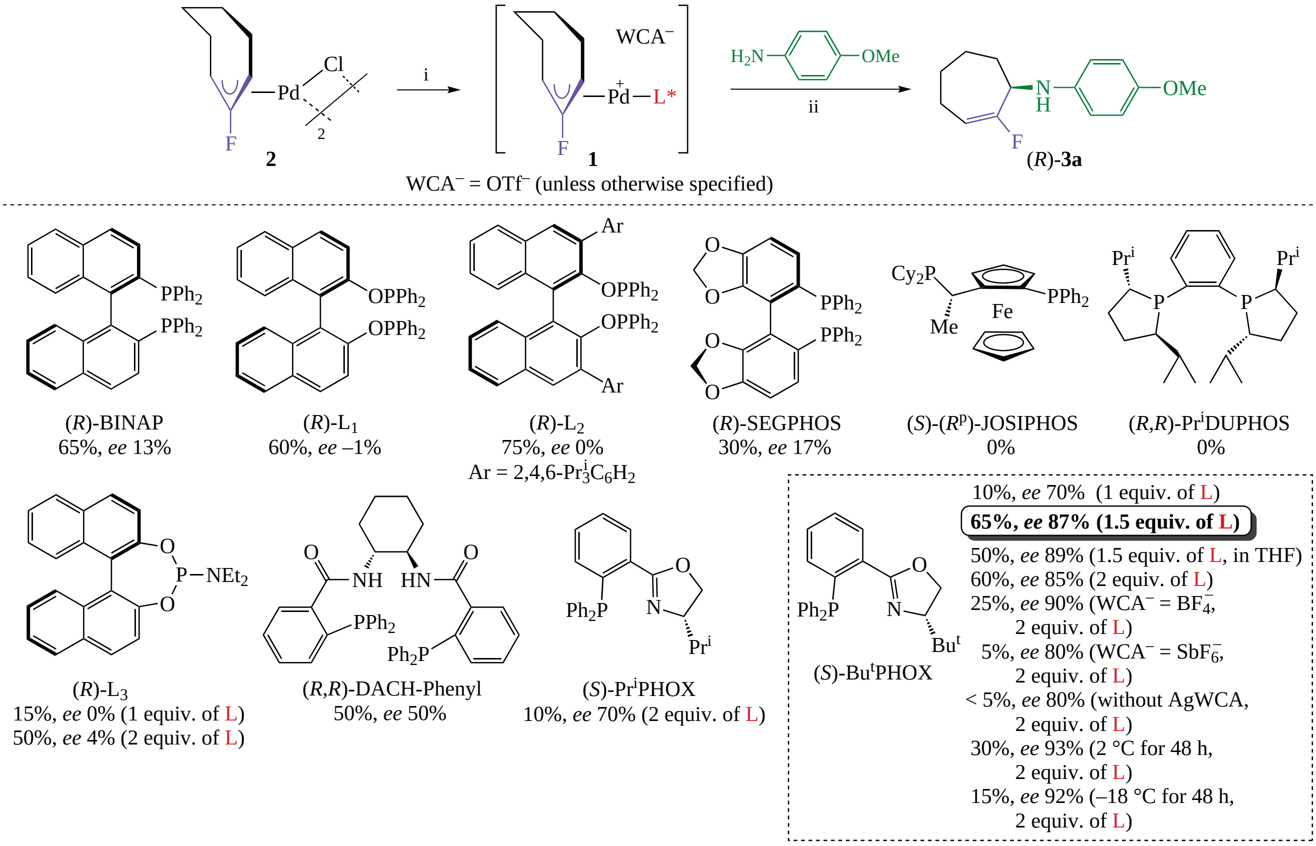
Scheme 1

Asymmetric Pd-catalyzed Tsuji–Trost amination of appropriate 2-fluoroallylic electrophiles could be an attractive route to chiral 2-fluoroallyl amines. However, examples of enantioselective Pd-catalyzed allylic substitutions in fluorinated substrates are limited mostly to unsubstituted 2-fluoroallyl[15,16] and α,α-difluoroalkenyl[17,18] derivatives while no example of applying N-centered nucleophiles in such reactions has been reported yet.

The key enantioselectivity-determining step in these processes is the nucleophile addition to intermediate chiral η^3-allyl palladium complex.[19,20] Therefore, in the current work we have optimized this key step for the enantioselective preparation of (2-fluoroallyl)amines using model reaction of η^3-(2-fluorocycloheptenyl)palladium complexes **1** bearing chiral P,P- and P,N-ligands with various amines.

Complexes **1** were prepared *in situ* using our previous strategy[21] that includes the reaction of (2-fluoroallyl)palladium chloride dimer **2** with the appropriate ligand using AgOTf as the chloride scavenger (Scheme 2). Complexes generated by this procedure were then reacted with *p*-anisidine as the model nucleophile. The reactions were carried out in the presence of PhBr used for interception of active Pd^0-species formed after aniline addition and thus suppressing the reverse process and racemization.

The obtained results (see Scheme 2) indicate that various BINOL-based ligands (BINAP, **L$_1$**, **L$_2$**, **L$_3$**) provide high yields of the target aniline **3a**, however, with negligible enantioselectivity. More electron-reach SEGPHOS lowered the yield and only slightly improved the *ee* value. More complex JOSIPHOS and Pr^{i}DUPHOS ligands completely inhibit the



Scheme 2 *Reagents and conditions*: i, AgWCA, ligand L*, 2-methyltetrahydrofuran, room temperature, 1 h; ii, *p*-anisidine, PhBr, room temperature, 5 h.

reaction and no traces of **3a** were detected. The Trost's cyclohexanediamine-based ligand DACH-Phenyl was found to be more effective affording **3a** with moderate *ee*. Switching next to PHOX P,N-ligand family allowed to dramatically improve the enantioselectivity to *ee* of almost 90% with Bu^{t}PHOX. The absolute configuration of amine **3a** was estimated by X-Ray crystallography of its' hydrobromide salt (Figure 1).[†]

Subsequent variation of Pd/Ligand ratio revealed that the highest yield and enantioselectivity are achieved using 1.5 equiv. of Bu^{t}PHOX. Minor differences were noted between the reaction solvents THF and 2-methyltetrahydrofuran when the latter gave higher yield of **3a** while in THF *ee* was somewhat higher. Lowering of the reaction temperature improved enantioselectivity only slightly but seriously dropped the yields. Interestingly, the effect of the counter-ion nature on the reaction outcome was strong. Changing it from OTf$^-$ to BF_4^- led only to slightly higher *ee* but with much lower yield. Use of SbF_6^- afforded only traces of **3a**. Similarly only traces of **3a** were obtained in the absence of AgWCA. Such differences point to the possibly high importance of weak interactions between WCA and the reactive palladium species on the reaction progress, and more detailed mechanistic insights into this phenomenon are obviously required.

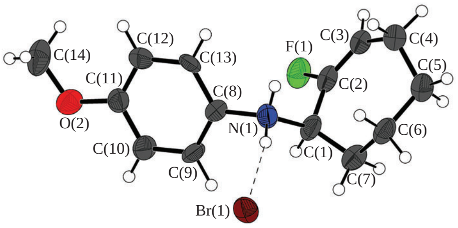


Figure 1 Crystal structure of (*R*)-**3a**·HBr.

Next, we have varied amines and anilines in order to determine the scope and limitations for Bu^{t}PHOX ligand (Scheme 3). First, we found that the reaction strongly depended both on electronic and steric properties of used aniline. Thus, only electron-rich

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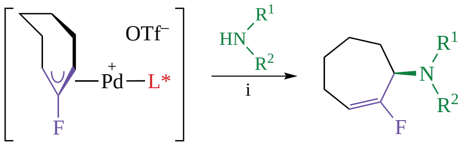
[†] *Crystal data for (R)*-**3a**·HBr. Crystals of $C_{14}H_{19}BrFNO$ (M = 316.21) are monoclinic, space group $P2_1$, at 120 K, a = 7.9220(16), b = 10.062(2) and c = 17.568(4) Å, β = 91.68(3)°, V = 1399.8(5) Å^3, Z = 4, d_{calc} = 1.500 g cm^{-3}, μ(synchrotron) = 3.304 mm^{-1}, F(000) = 648. 20834 reflections were measured, and 7680 independent reflections (R_{int} = 0.0542) were used in a further refinement. The refinement converged to wR_2 = 0.2217 and GOF = 1.037 for all independent reflections [R_1 = 0.0915 was calculated against F for 6297 observed reflections with $I > 2\sigma(I)$]. X-ray diffraction datasets for (*R*)-**3a**·HBr were collected at the 'Belok/XSA' beamline (λ = 0.745 Å) of the Kurchatov Synchrotron Radiation Source (National Research Center 'Kurchatov Institute', Moscow, Russian Federation) using a Rayonix SX165 CCD detector.

Crystal data for **1**·BARF. Crystals of $C_{64}H_{48}BF_{25}NOPPd$ (M = 1469.85) are tetragonal, space group $P4_22_12$, at 100 K, a = 25.184(3), b = 25.184(3) and c = 59.525(10) Å, V = 37753(11) Å^3, Z = 24, d_{calc} = 1.552 g cm^{-3}, μ(MoKα) = 0.437 mm^{-1}, F(000) = 17708. 213169 reflections were measured, and 37353 independent reflections (R_{int} = 0.1798) were used in a further refinement. The refinement converged to wR_2 = 0.3579 and GOF = 1.089 for all independent reflections [R_1 = 0.1268 was calculated against F for 20518 observed reflections with $I > 2\sigma(I)$]. X-ray diffraction datasets for **1**·BARF were collected on an in-lab Bruker QUEST diffractometer [graphite monochromator, φ and ω scan mode, λ = 0.71083 Å (MoKα)].

Both structures were solved by direct method and refined in anisotropic approximation for non-hydrogen atoms with the ShelXL program. Hydrogens atoms of methyl, methylene and aromatic fragments were calculated according to those idealized geometry and refined with constraints applied to C–H and N–H bond lengths and equivalent displacement parameters [U_{eq}(H) = 1.2U_{eq}(X), X – cental atom of XH_2 group; U_{eq}(H) = 1.5U_{eq}(Y), Y – central atom of YH_3 group]. All structures were solved with the ShelXT program and refined with the ShelXL program.

CCDC 2169028 and 2172095 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

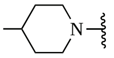


1*

L* = (*S*)-Bu^{t}PHOX

(*R*)-**3a–g**

* Prepared *in situ* using [Pd]/Bu^{t}PHOX in 1 : 1.5 ratio

a R^1 = 4-MeOC$_6$H$_4$, R^2 = H (65%, *ee* 87%)
b R^1 = 4-FC$_6$H$_4$, R^2 = H (60%, *ee* 84%)
c R^1 = 2-BuOC$_6$H$_4$, R^2 = H (15%, *ee* 78%)
d R^1 = Cy, R^2 = H (90%, *ee* 95%)
e R^1 = Bn, R^2 = H (> 95%, *ee* 94%)
f R^1 = (2-furyl)methyl, R^2 = H (> 95%, *ee* 91%)
g R^1 + R^2 = EtO$_2$C  (> 95%, *ee* 93%)

No reactions for:
R^1 = 4-EtO$_2$CC$_6$H$_4$, R^2 = H
R^1 = 4-O$_2$NC$_6$H$_4$, R^2 = H
R^1 = R^2 = Bn
R^1 = Cy, R^2 = 4-MeOC$_6$H$_4$CH$_2$

Scheme 3 *Reagents and conditions*: i, PhBr, 2-methyltetrahydrofuran, room temperature, 5 h (for **3a**,**d**–**g**) or 24 h (for **3b**,**c** and inactive amines).

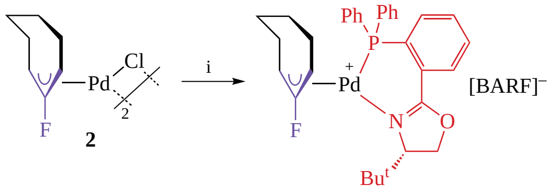
structures react successfully to give products **3a**,**b** while in the cases of electron-poor ones no product could be detected. Additionally, increase in steric hindrance by *ortho*-substituent lowered the yield dramatically (product **3c**). Similarly, secondary acyclic amines also were unsuitable nucleophiles that gave no even traces of the target products.

But surprisingly, aliphatic primary amines such as cyclohexylamine, benzylamine and furfurylamine were found to be valuable nucleophiles in amination of complex **1** to afford the corresponding products **3d–f** with excellent enantioselectivities with *ee* values of 91–95%. Similarly high enantioselectivity was observed also for piperidine derivative **3g** (see Scheme 3).

For structural characterization, complex **1** was prepared and isolated in pure form using [BARF]$^-$ as the counterion to facilitate single-crystals growing (Scheme 4 and Figure 2).[†]

The high value of the developed complex as a promising catalytic system for the enantioselective amination of 2-fluoroallylic electrophiles was also demonstrated. Pyridinium-derived electrophiles are the substrates of choice due to their high reactivity and availability as tetrafluoroborate salts *via* CuX-catalyzed ring-opening of *gem*-fluorohalocyclopropanes.[22] Thus, 2-fluoroallyl pyridinium tetrafluoroborate **4** effectively reacted with *p*-anisidine in the presence of 5 mol% of complex **1** generated *in situ* affording target amine (*R*)-**3a** in high yield with excellent enantioselectivity (Scheme 5).

In summary, we have disclosed that (*S*)-Bu^{t}PHOX is a powerful ligand for amination of η^3-2-fluoroallyl palladium complexes with primary amines, cyclic secondary amine and electron-rich anilines. The developed catalytic version of this process using 2-fluorocycloheptenyl pyridinium salt demonstrates high potential of this Pd-catalyzed strategy for enantioselective preparation of biologically-valuable 2-fluoroallyl amines. Further researches in this field are currently performed in our laboratory.



2

[BARF] = [3,5-(F$_3$C)$_2$C$_6$H$_3$]$_4$B

1·BARF, 97%

Scheme 4 *Reagents and conditions*: i, (*S*)-Bu^{t}PHOX, Na[BARF], MeCN, room temperature, 1 h.

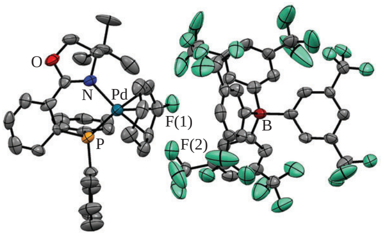
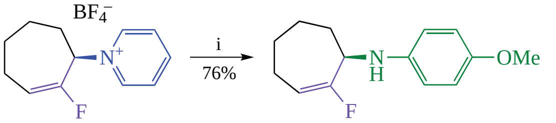


Figure 2 Crystal structure of **1**·BARF.



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(*R*)-**3a**, *ee* 88%

Scheme 5 *Reagents and conditions:* i, *p*-anisidine (3 equiv.), complex **1** (prepared *in situ* in 1 : 0.9 [Pd]/Bu^{t}PHOX ratio, 5 mol%), Na$_3$PO$_3$ (3 equiv.), 2-methyltetrahydrofuran, room temperature, 7 days.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.016.

References

1 N. A. Meanwell, *J. Med. Chem.*, 2018, **61**, 5822.
2 B. M. Johnson, Y.-Z. Shu, X. Zhuo and N. A. Meanwell, *J. Med. Chem.*, 2020, **63**, 6315.
3 S. D. Edmondson, L. Wei, J. Xu, J. Shang, S. Xu, J. Pang, A. Chaudhary, D. C. Dean, H. He, B. Leiting, K. A. Lyons, R. A. Patel, S. B. Patel, G. Scapin, J. K. Wu, M. G. Beconi, N. A. Thornberry and A. E. Weber, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2409.
4 M. Drouin, J. Laxio Arenas and J.-F. Paquin, *ChemBioChem*, 2019, **20**, 1817.
5 M. Drouin, P. Wadhwani, S. L. Grage, J. Bürck, J. Reichert, S. Tremblay, M. S. Mayer, C. Diel, A. Staub, J.-F. Paquin and A. S. Ulrich, *Chem. – Eur. J.*, 2020, **26**, 1511.
6 O. I. Afanasyev, I. Cherkashchenko, A. Kuznetsov, F. Kliuev, S. Semenov, O. Chusova, G. Denisov and D. Chusov, *Mendeleev Commun.*, 2020, **30**, 112.
7 S. Runikhina and D. Chusov, *Mendeleev Commun.*, 2021, **31**, 781.
8 M. Drouin and J.-F. Paquin, *Beilstein J. Org. Chem.*, 2017, **13**, 2637.
9 B. Zhang, J. Liu, D. Gao, X. Yu, J. Wang and X. Lei, *Eur. J. Med. Chem.*, 2019, **182**, 111672.
10 B. Zhang, G. Shan, Y. Zheng, X. Yu, Z.-W. Ruan, Y. Li and X. Lei, *Marine Drugs*, 2019, **17**, 333.
11 B. Wei, J. Gunzner-Toste, H. Yao, T. Wang, J. Wang, Z. Xu, J. Chen, J. Wai, J. Nonomiya, S. P. Tsai, J. Chuh, K. R. Kozak, Y. Liu, S.-F. Yu, J. Lau, G. Li, G. D. Phillips, D. Leipold, A. Kamath, D. Su, K. Xu, C. Eigenbrot, S. Steinbacher, R. Ohri, H. Raab, L. R. Staben, G. Zhao, J. A. Flygare, T. H. Pillow, V. Verma, L. A. Masterson, P. W. Howard and B. Safina, *J. Med. Chem.*, 2018, **61**, 989.
12 C. Lamy, J. Hofmann, H. Parrot-Lopez and P. Goekjian, *Tetrahedron Lett.*, 2007, **48**, 6177.
13 G. Dutheuil, L. Bailly, S. Couve-Bonnaire and X. Pannecoucke, *J. Fluorine Chem.*, 2007, **128**, 34.
14 C. B. Jacobsen, M. Nielsen, D. Worgull, T. Zweifel, E. Fisker and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2011, **133**, 7398.
15 Y. Lu, E. L. Goldstein and B. M. Stoltz, *Org. Lett.*, 2018, **20**, 5657.
16 K. J. Schwarz, C. M. Pearson, G. A. Cintron-Rosado, P. Liu and T. N. Snaddon, *Angew. Chem., Int. Ed.*, 2018, **130**, 7926.
17 X.-J. Zhang, Y.-M. Cheng, X.-W. Zhao, Z.-Y. Cao, X. Xiao and Y. Xu, *Org. Chem. Front.*, 2021, **8**, 2315.
18 M. Drouin and J.-F. Paquin, *Tetrahedron*, 2018, **74**, 6023.
19 O. Pàmies, J. Margalef, S. Cañellas, J. James, E. Judge, P. J. Guiry, C. Moberg, J.-E. Bäckvall, A. Pfaltz, M. A. Pericàs and M. Diéguez, *Chem. Rev.*, 2021, **121**, 4373.
20 R. Grange, E. Clizbe and P. Evans, *Synthesis*, 2016, **48**, 2911.
21 A. Yu. Bobrova, M. A. Novikov, I. A. Mezentsev and Yu. V. Tomilov, *J. Fluorine Chem.*, 2020, **236**, 109553.
22 A. Yu. Bobrova, M. A. Novikov and Yu. V. Tomilov, *Org. Biomol. Chem.*, 2021, **19**, 4678.

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