C-F Bond Construction From Fancy Novelty to Useful Tool

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Table of Contents

PET imaging and ¹⁸F labeling

Aryl Fluoride

Challenges of C-F Bond Formation

Nucleophilic Arene Fluorination

- Pd⁰/Pd^{II}
- Cu^I/Cu^{III}

Electrophilic Arene Fluorination

- Ag-Mediated Fluorination
- Reductive Elimination from Pd^{IV}
- High-valent Ni^{III} and Ni^{IV}
- Biⁱⁱⁱ/Bi^v

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- Directed arene C–H fluorination
- Direct arene C–H fluorination

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¹⁸F-Labeling of Arenes: *Chem. Rev.* 2016, 116, 719.
C(sp²)-F forming: *Synthesis* 2010, 1804. *Chem. Rev.* 2015, 115, 612. *Nature*, 2011, 473, 470.
F-Containing Pharmaceuticals: *Chem. Rev.* 2016, 116, 422.
Positron Emission Tomography: *Nat. Chem.* 2017, 9, 1. *ACIE* 2008, 47, 8998.



Positron emission tomography (PET)

X射线透过不同部位的人体组织后,与人体内部的原子相互作用而导致衰减,进而被探测器上的相应位 置被接收。光电效应是主要衰减形式,与介质的原子序数的三次方成正比。 X射线在骨骼中(磷酸钙) 衰减相对较高(胃肠钡餐造影、血管碘造影)。





- **CT-**多角度X射线的投影信息的重建三维图像。(断层扫描)
- PET主要是由正电子发射核素(¹¹C、¹³N、¹⁵O、¹⁸F等)衰变后释放正电子。正电子会在1-3mm范围内与体内负电子相遇并湮灭,同时释放出一对能量相同、方向相反的光子。探测器检测到两个信号存在时间差,进而可反推出事件发生的位置。
- PET/CT: CT提供的是人体解剖结构的信息(结构成像),PET提供的主要是目标区域的功能信息(功能成像)。对于非常早期的癌组织以及癌扩散等CT上较难分辨的情况,PET都可以做出精确监测。
- 初筛乱像?(8000-15000 RMB)卫生部要求PET-CT检查阳性率不得低于70%。
 而实际上,目前全国用于的PET-CT体检中,癌症的检出比率均不超过2%。











Positron emission tomography (PET)

■ ¹⁸F-FDG (氟代脱氧葡萄糖)是目前应用最广泛的正电子放射性药物。制备¹⁸F-FDG 所使用的仪器包括 医用回旋加速器以及¹⁸F-FDG 全自动合成器系统等。【回旋加速器生产 ¹⁸F⁻ - QMA 柱捕获并测试活度 - K_{2.2.2}/K₂CO₃ 溶液洗脱干燥 - 氟化反应 - 水解反应 - 纯化 - 收集瓶 - 质量控制; 29min, 43%-65%】



- For known and new biological targets, PET can provide valuable insight on the *in vivo* behavior of drug candidates much earlier in the drug discovery pipeline.
- Challenge: rapid labeling of complex molecules with ¹⁸F (half-life 110 min)
- The radionuclide ¹⁸F is made available as an aqueous solution of [¹⁸F]F⁻ (activity: 4×10⁴ GBq/µmol) or as gaseous [¹⁸F]F₂ (activity: 0.4-2 GBq/µmol).



- S_NAr: most frequently used. (reliably and on large scales) (substrate-centred restrictions, harsh conditions)
- Electrophilic fluorination: [¹⁸F]F₂ low FG tolerance and low molar activity; Other electrophilic ¹⁸Ffluorinating reagents([¹⁸F]NFSI and [¹⁸F]Selectfluor) are prepared from [¹⁸F]F₂
- Nucleophilic fluorination: the standard method for [¹⁸F]F⁻ incorporation to previously inaccessible aromatics.

Nucleophilic aromatic substitution



15 min; (ii) [¹⁸F]fluoride, K₂₂₂/KHCO₃, DMSO, 110 °C, 15 min.

Challenges associated with C–F bond formation

A thermodynamically feasible but kinetically challenging reaction can be addressed ideally by catalysis.



- The most challenging step in C-F bond formation is reductive elimination: sufficient orbital overlap between both metal–ligand σ-bonds.
- π effect: R.E. to form the carbon–heteroatom bonds occurs more rapidly from complexes with more nucleophilic heteroatoms.



• *σ* effect: faster R.E. may be attributed to a decrease in the polarity of the metal–heteroatom bond (ionic contribution to the bond energy).



a) b) Fluorine [He] 2s²2p⁵ Halogens

) Small ionic radius (1.33 Å)

Most electronegative element

Metal-fluorine bonds are significantly polarized towards fluorine. The significant ionic contribution to the bond increases the energy barrier.

- c) Strong hydrogen bonding (only weakly nucleophilic in the presence of H-bond donors)
 hydrolysis of the metal–fluorine bond
- d) Basic (When H-bond donors are excluded) side reactions

Synthesis 2010, 1804. Nature 2011, 473, 470.

Fluoro palladium complex

The first X-ray structural characterization of a molecular fluoro palladium complex. JACS 1997, 119, 4769.



Aryl-Fluoride Reductive Elimination from Pd^{II}

- Three-coordinate T-shaped geometry was shown to offer kinetics and thermodynamics of Ar-F elimination largely compatible with synthetic applications.
- Strong fourth ligands to Pd or association of hydrogen bond donors with F each caused pronounced stabilization of Pd(II) reactant and increased activation barrier beyond the practical range.
- Stability of the fluoride-bridged dimer forms of the requisite Pd^{II}Ar-(F)L as the key remaining obstacle to Ar-F reductive elimination in practice.
- Interligand steric repulsion with P(t-Bu)₃ served to destabilize dimer 18 by 20 kcal/mol, estimated with DFT relative to PMe₃, yet was insufficient to enable formation of greater than trace quantities of Ar-F.



Figure 2. Computed effects of coordination of an additional strong donor ligand on Ph–F reductive elimination from a three-coordinate PdPh(F)L.



Computed structure of syn-18 and reactivity profiles of $[Pd(C_6H_4-4-NO_2)(L)(\mu-F)]_2$ (L = $P(t-Bu)_3$, $[PtBu_310_{NO_2}]_2$; L = PMe_3 , $[10_{NO_2}]_2$, in blue).

Pd⁰/Pd^{II}-Catalyzed Aromatic Fluorination



Pd⁰/Pd^{II}-Catalyzed Aromatic Fluorination



In Situ Catalyst Modification



- The ability of ligands to undergo arylation may play a role in their success (or failure) in previously reported transformations (more complicated)
- The relief of unfavorable steric interactions between the alkyl groups on phosphorus and the aryl substituent is a powerful factor in promoting the rearrangement.





JACS 2011, 133, 18106. JACS 2012, 134, 19922. Acc. Chem. Res. 2016, 49, 2146.

Formation of Regioisomer



Improved Catalyst System



- Room-Temperature and Regioselective JACS 2015, 137, 13433.
- Modification at C3' with an electron-withdrawing group would diminish the donation of electron density from C1' to the Pd(II) metal center, providing an intermediate with more three-coordinate character.
- The lack of an intramolecular CH…F interaction in F results in ground-state destabilization



- Forms shorter bonds than Pd
- Harder Lewis acidity than Pd
- Higher affinity for O, N ligands
- Smaller coordination shell can not accommodate large ancillary ligands



d⁸, metal cation isoelectronic with Pd(II)

- Highly electrophilic and unstable
- Potent oxidizer
- Unstable towards the reverse R.E.
- Requires the Nu to be in the coordination sphere prior to O.A.

PORTA DE LA 2012 VOL 31-155UE 22 ORGANOMETALLICS



The radical approach to the copper O.A. problem: Science 2019, 364, eaav9713.

Palladium based Buchwald–Hartwig reaction



Ligand development and precatalyst design led to significant advances!!

Broad substrate scopes: CI, Br, I, OTf Mild conditions: many reactions work well at r.t Catalyst loadings: some reactions need 0.1-0.001 mol% of catalyst

Review: Chem. Sci., 2011, 2, 27. ACS Catal. 2015, 5, 1386.

The use of bidentate ligands for copper.



Broad substrate scopes: CI, Br, I Mild conditions: 80-100°C for many reactions Catalyst loadings: 5-20 mol% in most cases

Review: Chem. Soc. Rev. 2014, 43, 3525. ACIE. 2017, 56, 16136.

■ The first observation of aryl halide O.A. to Cu^I resulting in formation of an aryl-Cu^{III}-X species





Aryl radicals can be captured by Cu(II) species at a rate approaching diffusion



Macmillan et al. Science 2018, 360, 1010. JACS 2019, 141, 6853.

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Silver-Mediated Fluorination



High-valent Palladium Complexes

Reviews: Chem. Soc. Rev. 2010, 39, 712. Nature 2012, 484, 177.



t-Bu	F nitroben 1 h, 90	XeF ₂ zene X (3a-c)	F + X-		t-Bu	
entry	Х	complex	% 3	% 4	Pd ^{IV}	
1	F	2a	57	7		
2	CF ₃	2 b	60	3	, H	
3	OMe	2c	45	6	F	

Stoichiometric Reactivities at the Pd^{IV} center

Reductive elimination at the Pd(IV) center occurs predominantly. After the reductive elimination, highly reactive Pd(IV) species transformed to the thermodynamically more stable Pd^{II} complexes.



Single-Electron Transfer Pathway via Pd^{III}



Fluoride-Derived Electrophilic Reagent

■ A two-step "fluoride capture/transfer" sequence

Ritter et al. Science 2011, 334, 639. Chem. Sci., 2014, 5, 169.



High-valent Ni^{III} and Ni^{IV} Species

- Ni⁰/Ni^{II} catalytic cycles are widespread, but the easy accessibility of Ni^I and Ni^{III} oxidation states allows different modes of reactivity and radical mechanisms (Ni^I/Ni^{II}/Ni^{III}, Ni⁰/Ni^{II}/Ni^{III}/Ni^{II}) Review of nickel catalysis: *Nature* 2014, 509, 299. with photocatalysis, *Nat. Rev. Chem.* 2017, 1, 0052.
- Nickel-catalyzed reactions where alkyl/arylnickel(III) species are proposed as reactive intermediates and oxidative transformations of organonickel(II) complexes via nickel(III) are commonly accepted.
- First isolated organometallic Ni^{III} species that can form C-C or C-X bond. Mirica *et al. JACS* **2014**, 136, 6499.



Oxidatively induced aryl-F coupling from Nickel(III) intermediate



Ritter *et al. JASC* **2012,** 134, 17456. *ACIE* **2017**, 56, 6966.

High-valent Ni^{III} and Ni^{IV} Species

Reviews: ACIE. 2015, 54, 7488. Refs in ACIE 2017, 56, 6966. Molecules 2020, 25, 1141.

(8)

A cutting-edge discovery: the isolation and complete characterization of Ni^{IV} compounds able to promote cross-coupling events. Sanford et al. Science 2015, 347, 1218. JACS 2015, 137, 8034 ⊖ OTf Ð S⊕ Θ OTf CF₃ =н. CH₃CN, rt N3 (92%) (5) (Py₃CH) (6)Ni C18 ⊕[⊖]OTf (a) (**b**) C25 C1 1.2 equiv NMe₄OAc CD₃CN, 95 °C, 7 h >Ni^{II} - [Ni^{II}] CH₃CN, 25 °C, 1.5 h N (7) (3) (quantitative) (78% isolated) (6) C(sp³)–O bond formation C(sp²)–C(sp³) bond formation 10. Oxidative transformations of organonickel(II) complexes via nickel(IV) is rapid established. Sanford et al. JACS 2019, 141, 13261. These results demonstrate the viability of C-F reductive elimination from Ni^{IV} complexes. They stand in interesting contrast to Ni^{III}-mediated fluorination reactions demonstrated by Ritter. ⊝ K[⊕] HB HB HB Selectfluor MeCN Ni^{IV} Nill THF, 50 °C 25 °C, 30 min N_2H_4 12 h (48%) — [Ni] (9) (60% yield) (10)

(11)

Catalytic Bi^{III}/Bi^V fluorination

- The synthetic utility of arylbismuth(V) compounds has been well established, and tetraphenylbismuth carboxylates(Ph₄BiX)(X=OCOR) and sulfonates(X=OSO₂R) are often employed for phenylation.
- Tetraphenylbismuth(V) compounds with a strongly coordinating (highly nucleophilic) anion (Ph₄BiX)(X=Cl, Br) are known to decompose rapidly to yield Ph₃Bi and the corresponding PhX.



Planas et al., Science 2020, 367, 313.

Catalytic Bi^{III}/Bi^v fluorination



Catalytic Electrophilic Fluorination?



Directed Electrophilic C-H Fluorination

■ The first Pd^{II}/Pd^{IV} aryl C-H fluorination: a major breakthrough in the field of C-F bond formation, and the beginning of the field of Pd-catalyzed C-H fluorination. Sanford *et al. JACS* **2006**, 128, 7134.



Non-directed Aromatic C-H Fluorination

The proof-of-concept for direct electrophilic fluorination. Subramanian *et al. Science* **2002**, 297, 1665.



Selective C-H Fluorination of Pyridines, quinolines and diazines. Hartwig et al. Science 2013, 342, 956.



Non-directed Aromatic C-H Fluorination

Pd-catalysed electrophilic aromatic C–H fluorination. Ritter *et al. Nature* **2018**, 554, 511.



Fluoride(F⁻) as Fluorine Source





■ C–H fluorination with ¹⁸F⁻ via organic photoredox catalysis. Nicewicz *et al. Science* **2019**, 364, 1170.



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- Cu^I/Cu^{III}

Electrophilic Arene Fluorination

- Agⁱ/Agⁱⁱ-Agⁱⁱ
- Pd^{III} and Pd^{IV}

F-

- Ni^{III} and Ni^{IV}
- Bi^{III}/Bi[∨]