Literature Report 8

A Fluoride-Derived Electrophilic Late-Stage Fluorination Reagent for PET Imaging

Reporter: Ran-Ning Guo
Checker： Zhang-Pei Chen
Date: 2013/06/18

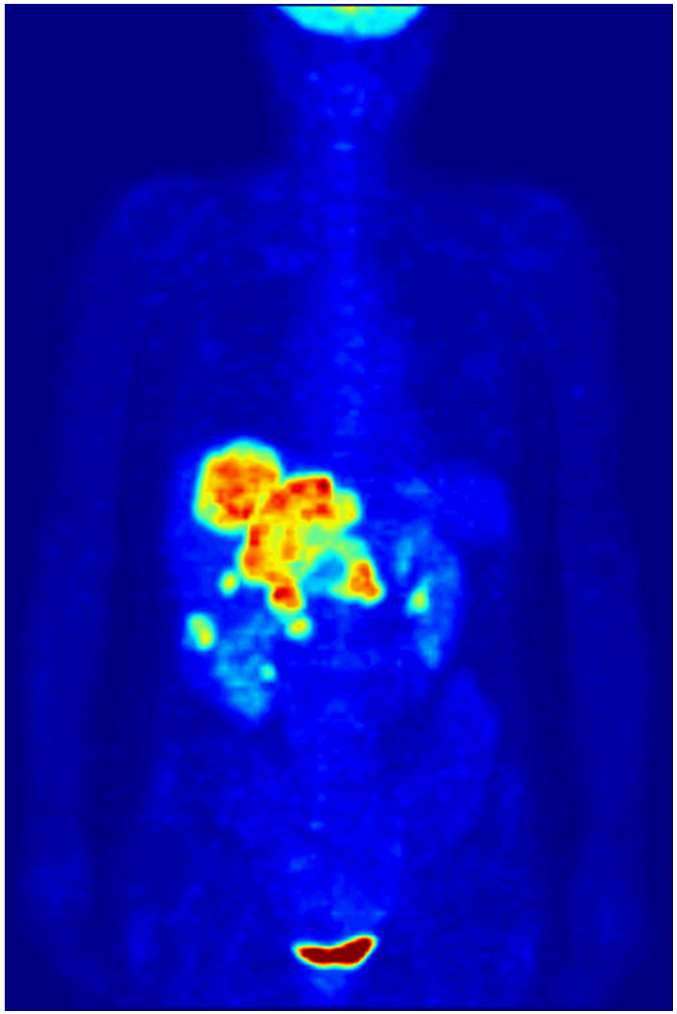
T. Ritter. *Science* **2011**, *334*, 639.

目录

背景知识

正电子发射计算机断层扫描（PET)：Positron emission tomography， 是一种核医学成像技术，它为全身提供三维的和功能运作的图像。正电子发射计算机断层扫描既是医学也是研究的工具。PET技术是目前唯一的用解剖形态方式进行功能、代谢和受体显像的技术，具有无创伤性的特点，在肿瘤学临床医学影像和癌扩散方面的研究方面有着大量的应用，是核医学领域最先进的临床检查影像技术。

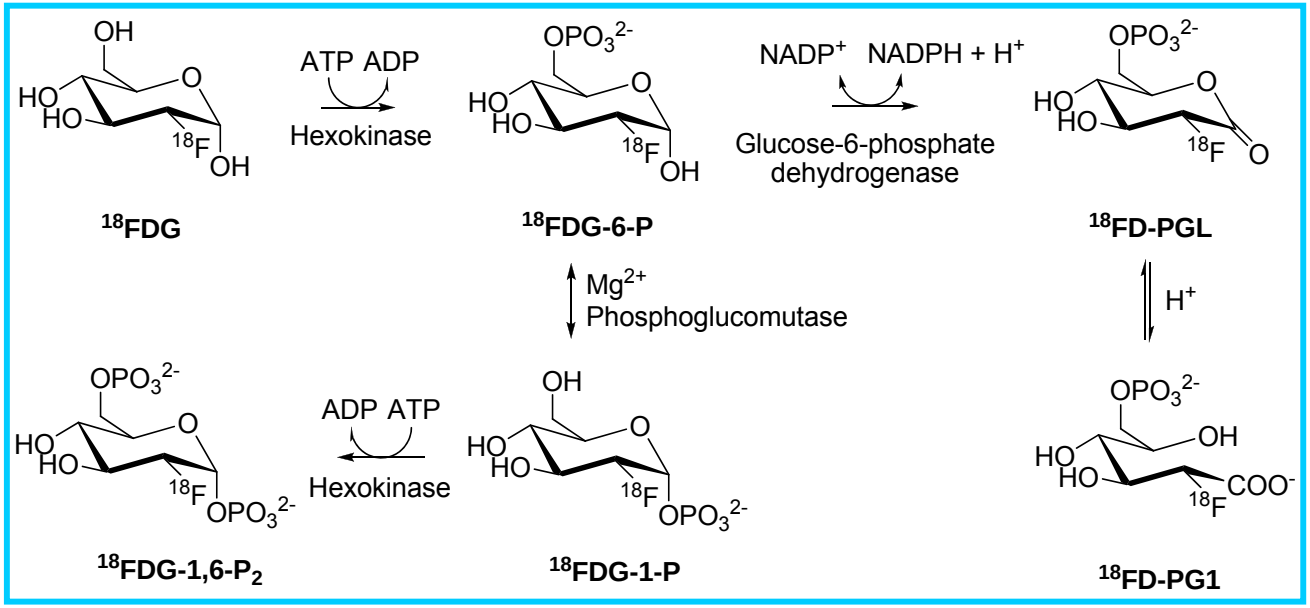
正电子发射计算机断层扫描（PET）设备



典型的最大强度投影(MIP)
^{18}F-FDG 全身PET影像撷取

背景知识

氟代脱氧葡萄糖(^{18}F-FDG): 即2-氟-2-脱氧-D-葡萄糖， 最常用于正电子发射断层扫描(PET)类的医学成像设备。^{18}F-FDG可用于评估心脏、肺脏以及脑部的葡萄糖代谢状况。同时，^{18}F-FDG还在肿瘤学方面用于肿瘤成像。在被细胞摄取之后，^{18}F-FDG将由己糖激酶（在快速生长型恶性肿瘤之中，线粒体型己糖激酶显著升高）加以磷酸化，并为代谢活跃的组织所滞留，如大多数类型的恶性肿瘤。因此，FDG-PET可用于癌症的诊断、分期和治疗监测，尤其是对于霍奇金氏病、非霍奇金氏淋巴瘤、结直肠癌、乳腺癌、黑色素瘤以及肺癌。另外，FDG-PET还已经用于阿耳茨海默氏病的诊断。



① 背景知识

③ **^{18}F的来源**：医用回旋加速器(medical cyclotron)之中用于产生 ^{18}F的高能粒子轰击条件会破坏像脱氧葡萄糖或葡萄糖之类的有机物分子，因此必须首先在回旋加速器之中制备出氟化物形式的放射性^{18}F。这可以通过采用氘核轰击氖-20来完成；但在通常情况下，^{18}F的制备是这样完成的：采用质子轰击富^{18}O水（^{18}O-enriched water，重氧水），导致^{18}O之中发生(p,n)核反应(中子脱出，或者说散裂（spallation）)，从而产生出具有放射性核素标记的氢氟酸（hydrofluoric acid，HF）形式的^{18}F。接着，将这种不断快速衰变的$^{18}F^-$（18-氟化物，18-fluoride）收集起来，并立即在“热室(hot cel)（放射性同位素化学制备室）”之中，借助于一系列自动的化学反应（亲核取代反应或亲电取代反应），将其连接到脱氧葡萄糖之上。

④ **放射性比度**：即specific activity , 将一个化合物或元素中的放射性同位素的浓度称为“放射性比度”，也用以表示单位数量的物质的放射性强度。单位：居里（Curie简写*Ci*）

Late-Stage Fluorination?

② 作者简介

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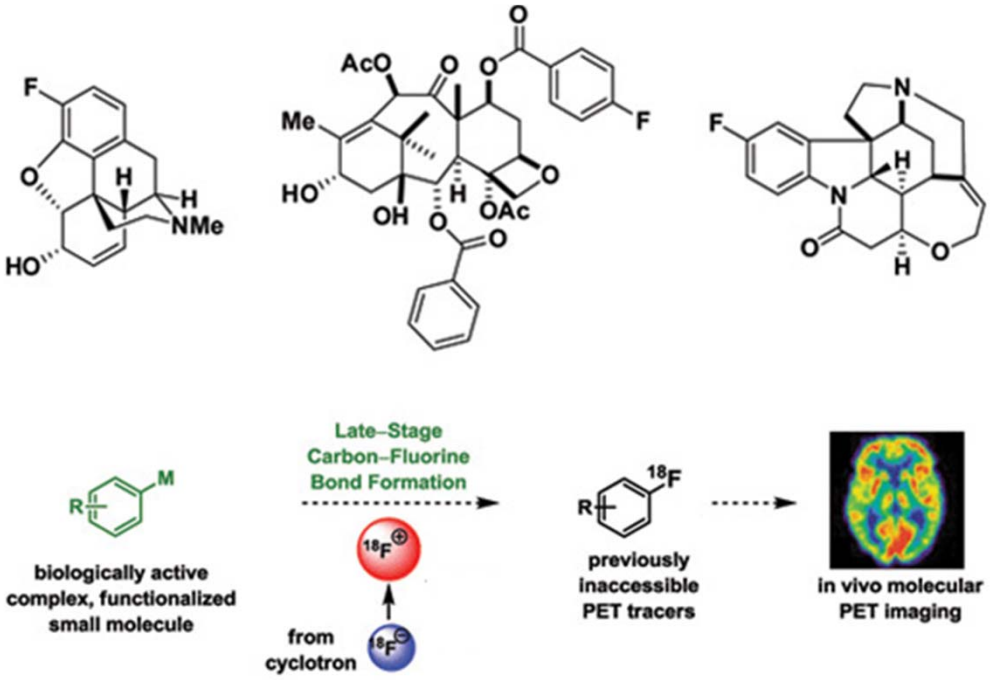
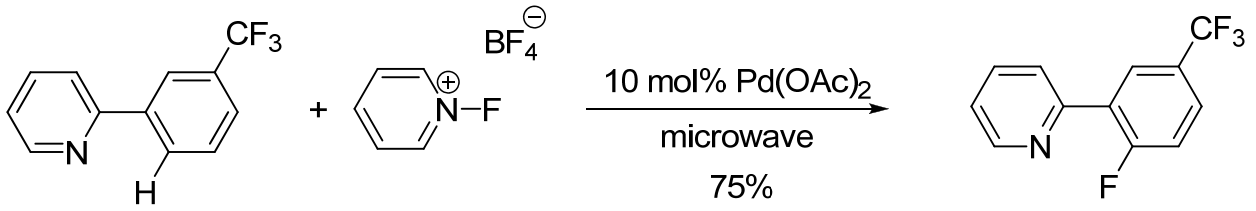
Harvard University,
Department of Chemistry
and Chemical Biology

currently focuses:
fluorination chemistry for late-stage functionalization of complex natural and unnatural products;
bimetallic transition metal redox catalysis.

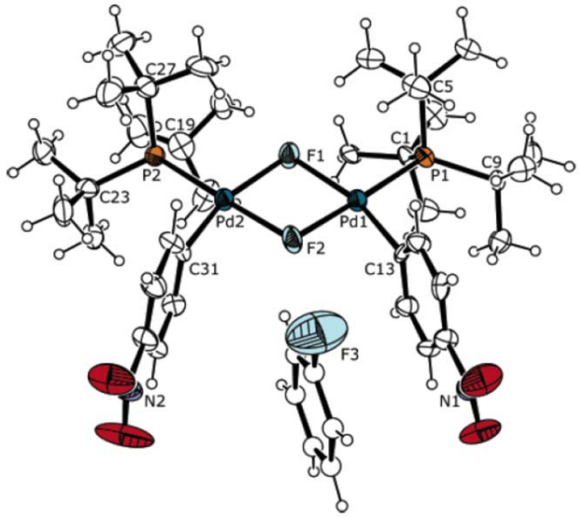
Born in **1975** in Lübeck, Germany;
Received his undergraduate education in Braunschweig, Germany, Bordeaux, France, Lausanne, Switzerland, and Stanford, US, and received a master of science from Braunschweig University in **1999**;
undergraduate research with Prof. Barry M. Trost at Stanford;
PhD working with Prof. Erick M. Carreira at ETH Zurich in **2004**;
Postdoc with Prof. Robert H. Grubbs at Caltech;
Assistant Professor in the Department of Chemistry and Chemical Biology at Harvard In **2006**;
Promoted to Associate Professor in **2010**;

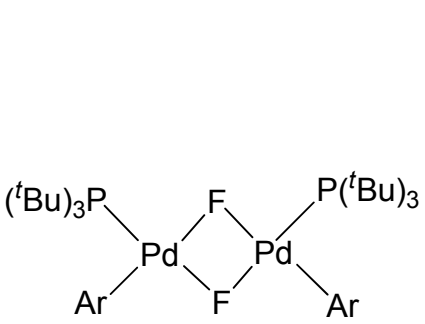


钯催化的芳基硼酸氟化反应-课题基础

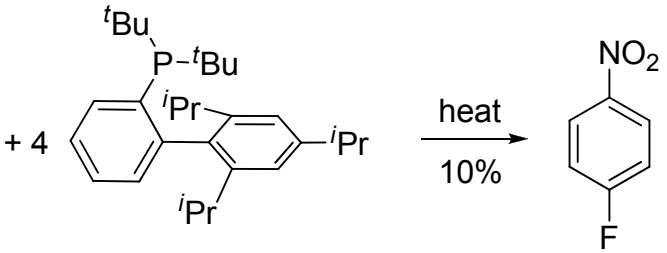


M. S. Sanford, *J. Am. Chem. Soc*. **2006**, *128*, 7134.



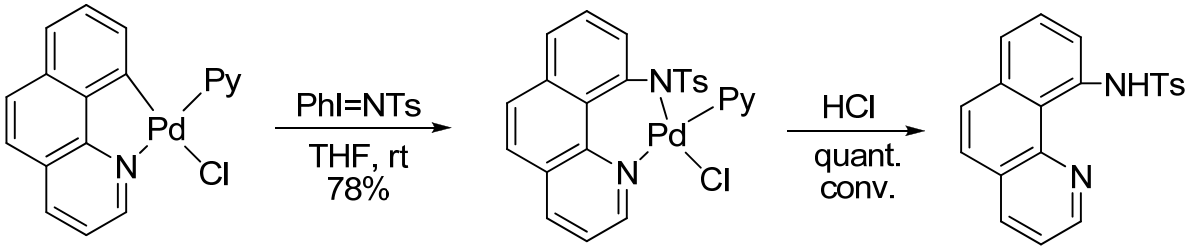


Ar = *p*-NO_2Ph-

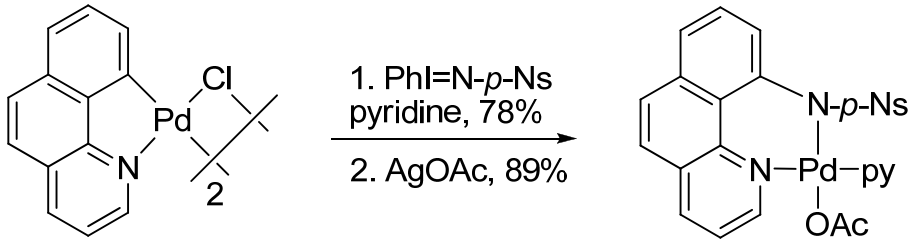


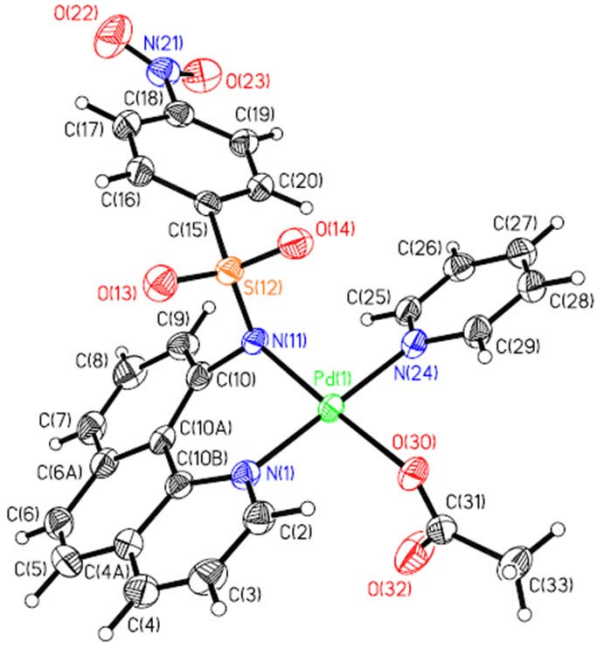
D. V. Yandulov, *J. Am. Chem. Soc*. **2007**, *129*, 1342.

钯催化的芳基硼酸氟化反应-课题思路

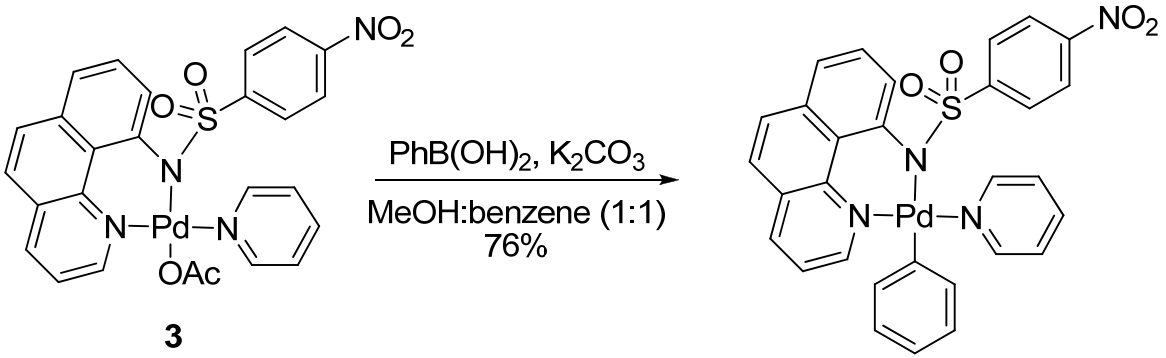


M. S. Sanford, *Organometallics* **2007**, *26*, 1365.





钯催化的芳基硼酸氟化反应



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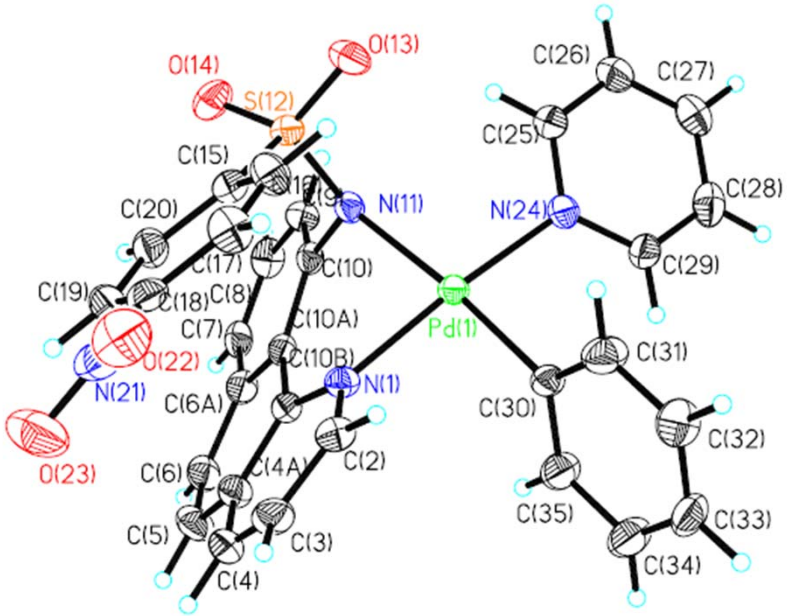
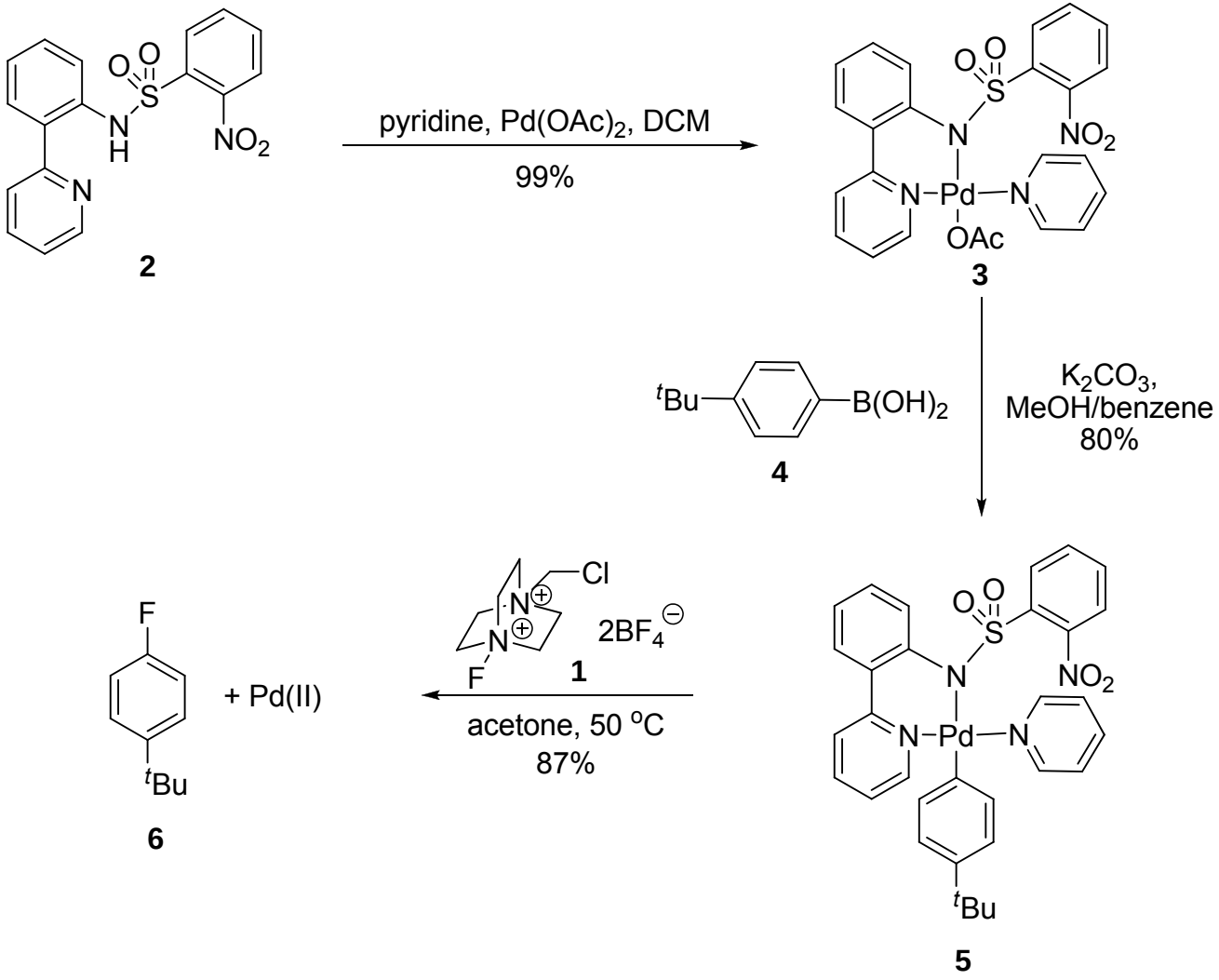


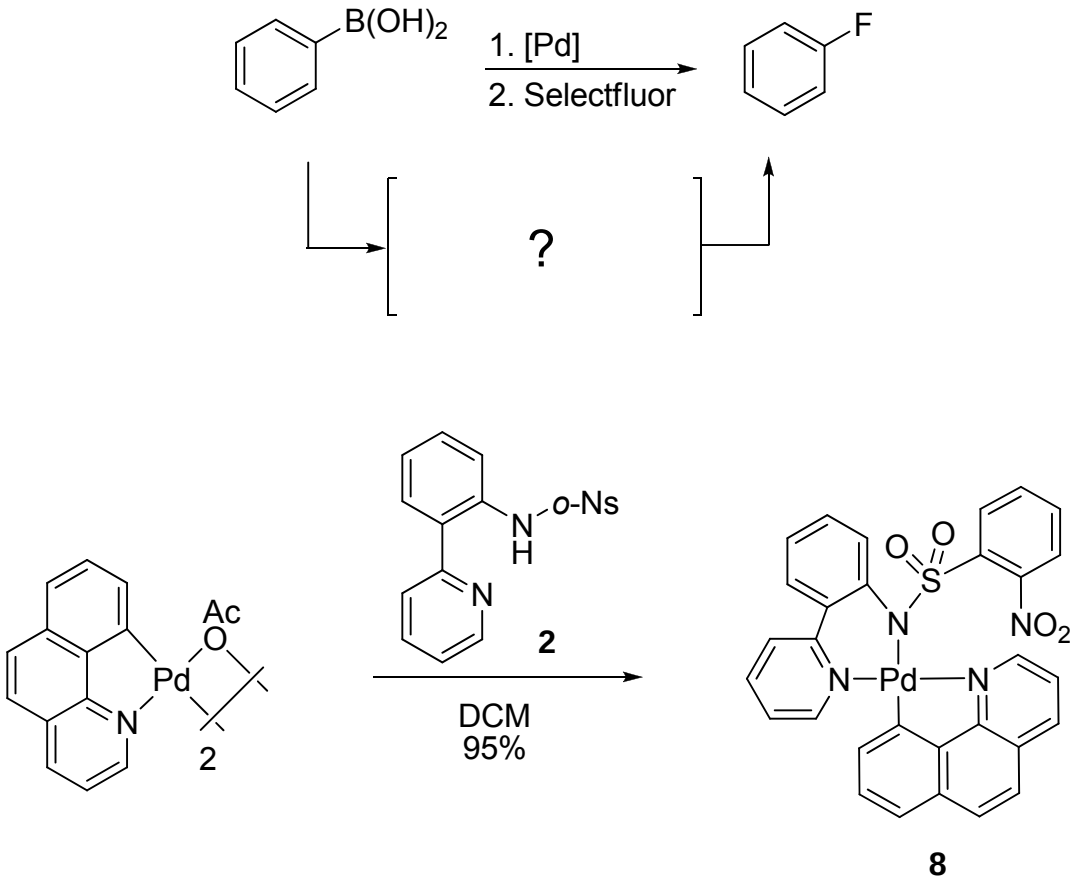
T. Ritter. *Angew. Chem. Int. Ed.* **2008**, *47*, 5993

钯催化的芳基硼酸氟化反应



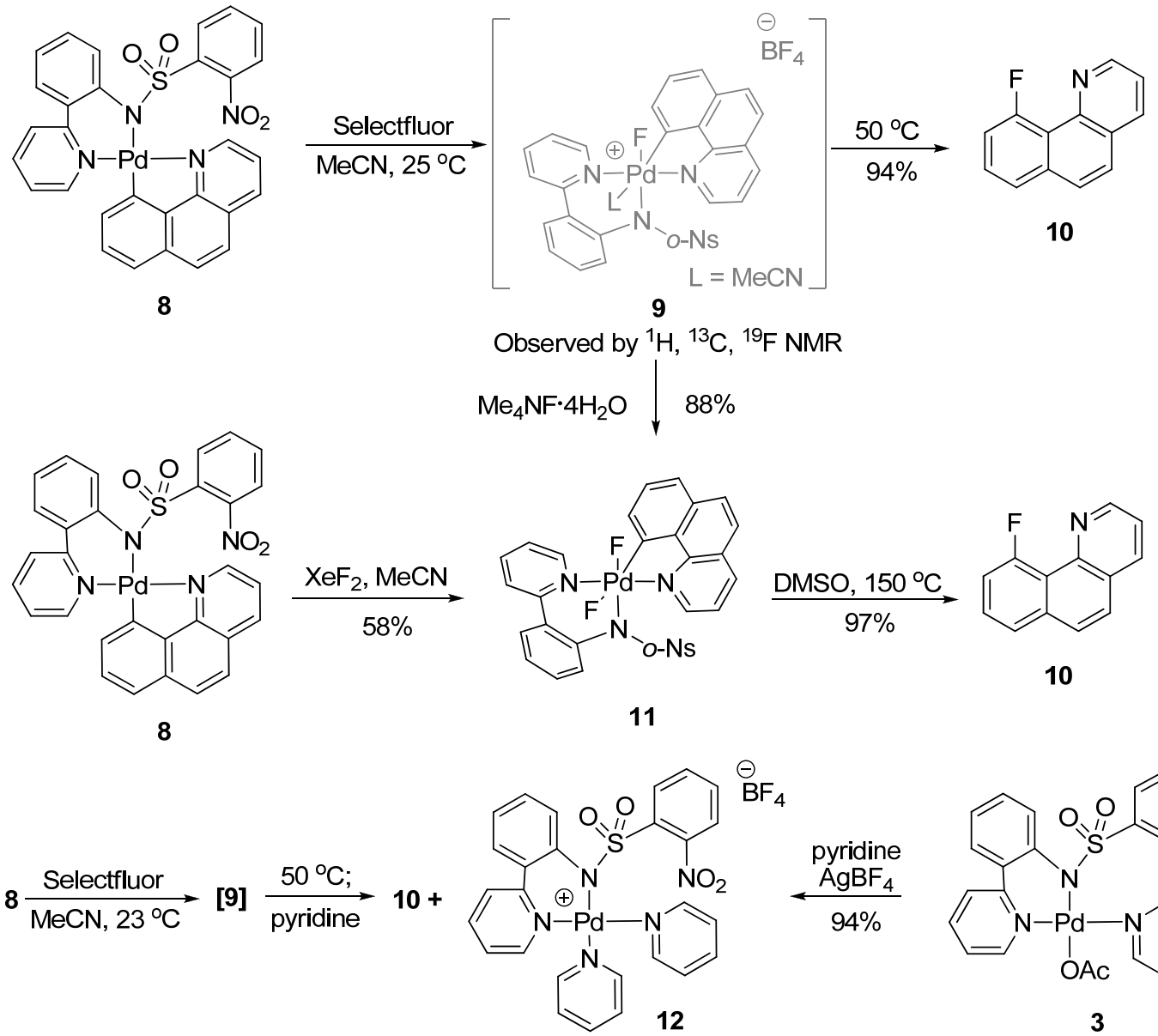
T. Ritter. *Angew. Chem. Int. Ed.* **2008**, *47*, 5993.

钯催化芳基硼酸氟化反应的机理研究



T. Ritter. *J. Am. Chem. Soc.* **2008**, *130, 10060.*

钯催化芳基硼酸氟化反应的机理研究



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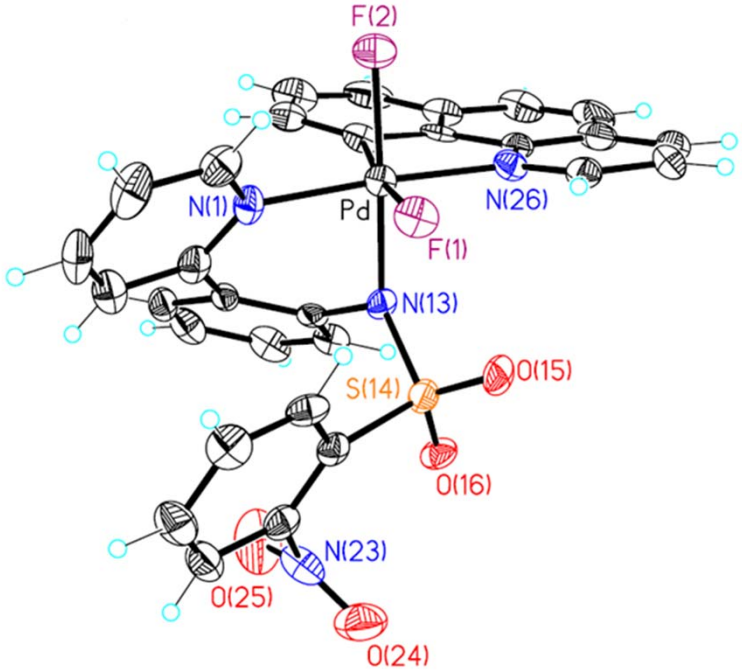

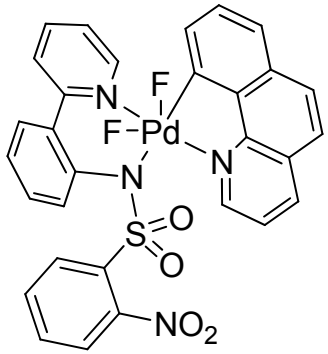

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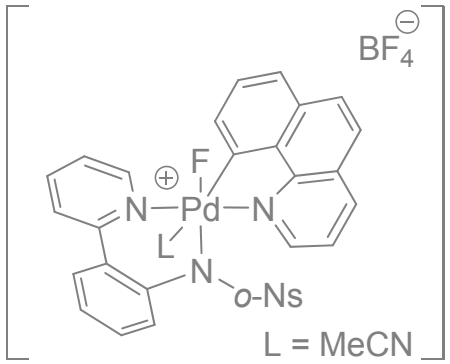
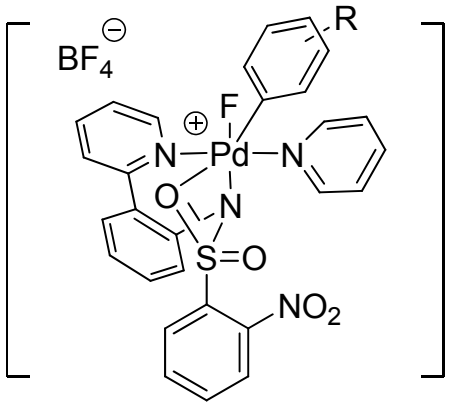
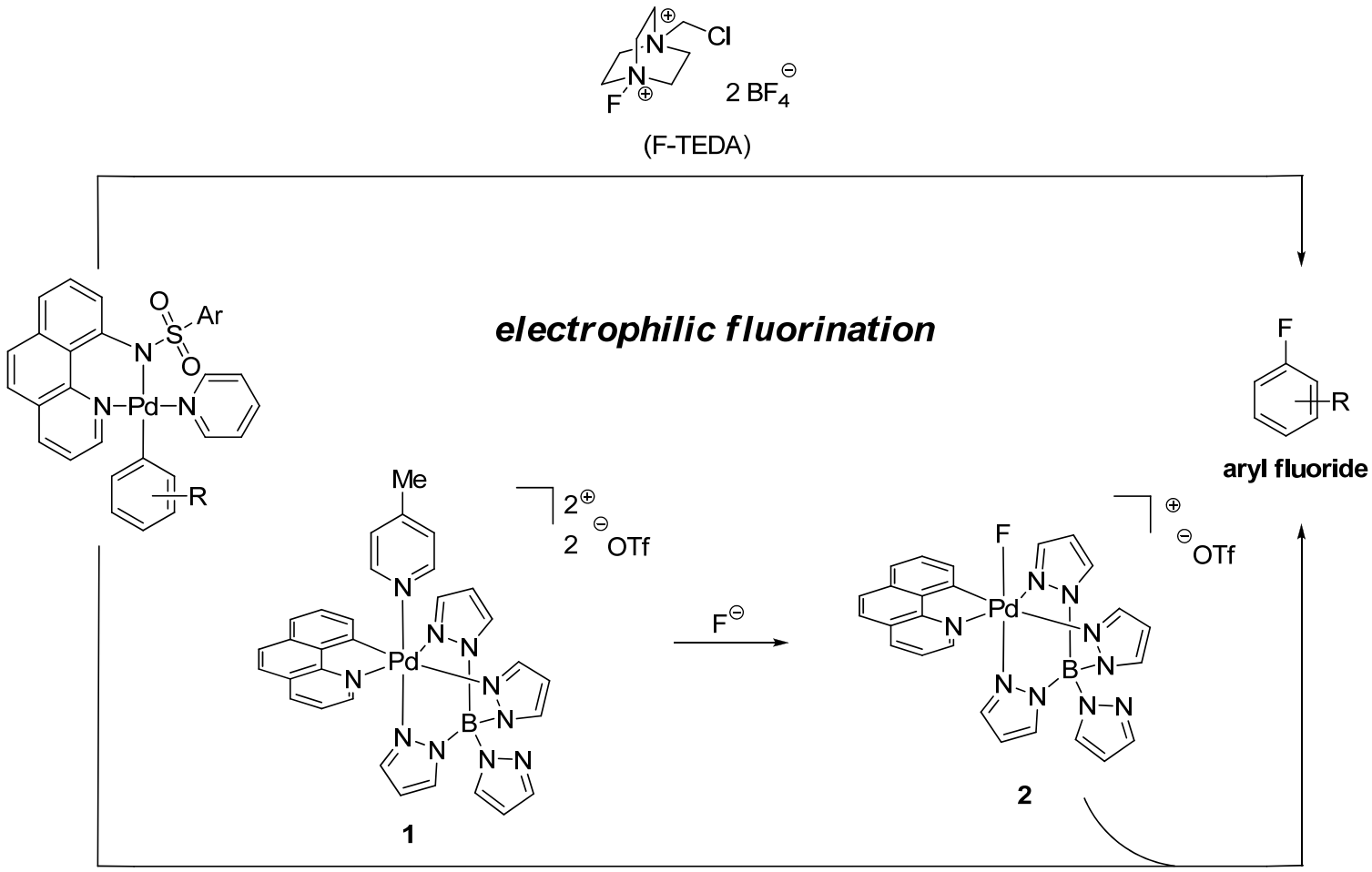
^{19}F NMR: -169 ppm, -278 ppm;
$^{2}J_{F\text{-}F}$ = 113 Hz;
$^{2}J_{C\text{-}F}$ = 63 Hz.





T. Ritter. *J. Am. Chem. Soc*. **2010**, *132, 3793*

“后期氟化”反应设计


(F-TEDA)
2 BF4
electrophilic fluorination
aryl fluoride
OTf
F⊖
1
2

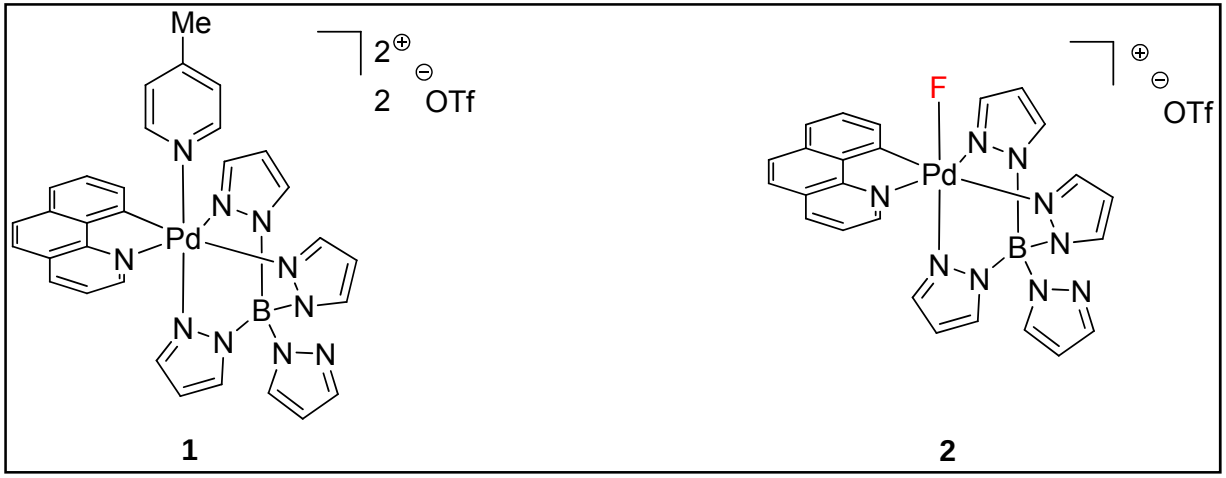
“后期氟化”氟化试剂的设计原理

钯配合物**2**在反应中作为一种S_N2反应的亲电体，亲核进攻发生在氟取代基上。对于配合物**1**和**2**的设计基于以下原理：

■ **1**中钯中心带有三个形式正电荷（有2个 $^-$OTf抗衡离子和1个负一价的B配体），能够捕捉溶液中的F^-，由于氟在溶液中的低浓度（10^{-4} M），高的氟相分配系数才能保证**1**在放射化学中的应用；

■ 配合物**1**和**2**的金属中心都是Pd（Ⅳ），对于钯是很高的氧化态。高氧化态的后过渡金属**1**能够作为一种氧化剂，转移一个配体到亲核体上，同时本身被还原；**2**中的钯金属能作为一种电子受体，从而在接下来的反应中充当氧化剂；

■ 辅助配体苯并喹啉和四吡唑硼酸（Tp）作为多齿配体，能够稳定金属中心，促进**1**和**2**进行还原消除；**2**经过还原消除会解离一个配体，形成一个五配位的配合物。多齿配体很难解离，因此能够降低其潜在的解离速率；



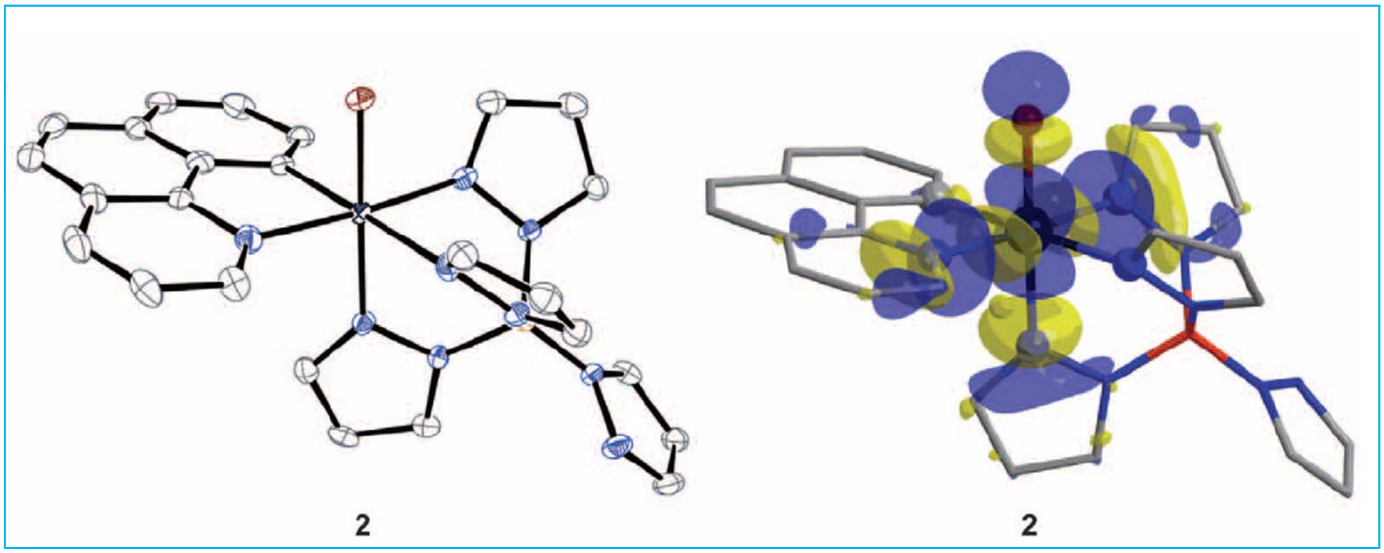
1 **2**

“后期氟化”氟化试剂的设计原理

■ 正八面体的Pd（Ⅳ）能够抑制金属上的亲核进攻: Pd-F键中部分负电荷分配到F，正电荷分配到Pd。单纯考虑库仑力的相互作用，亲核进攻会发生在Pd上。然而，正八面体的$(t_{2g})^6(e_g)^0$ Pd（Ⅳ）中，可能发生亲核进攻的轨道$d_{x^2-y^2}$和d_{z^2}能量很高，在高轨道上亲核进攻是不利的；

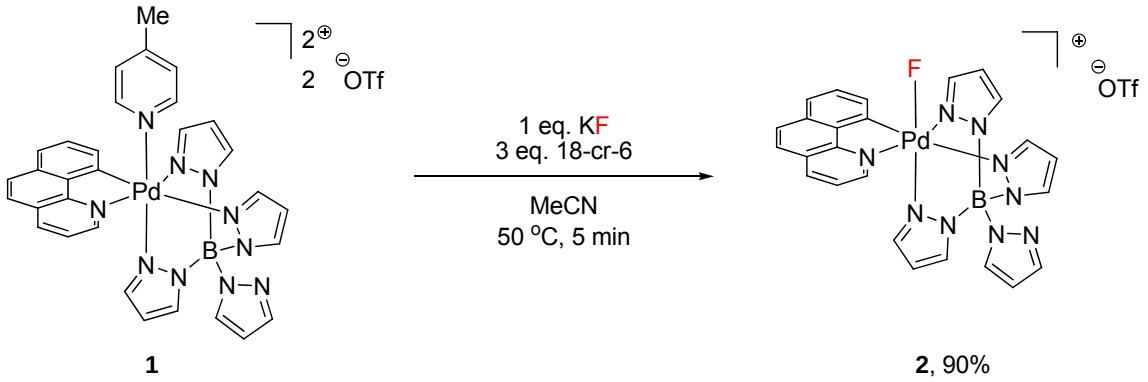
■ 带有芳环基团的辅助多齿配体能抑制发生在配位于金属中心的碳和氮上的亲核进攻。

钯配合物**2**被设计成一种亲电氟化试剂，亲核进攻发生在σ^*_{Pd-F}反键轨道上，在这种S_N2反应中，钯是离去集团，价态从Pd（Ⅳ）变为Pd（Ⅱ）。经过计算，亲核进攻只能发生在**2**的最低未占用轨道(LUMO)，其中只有氟原子的波瓣（lobe）指向未占据空间，其他的都被芳环配体阻挡了轨道。

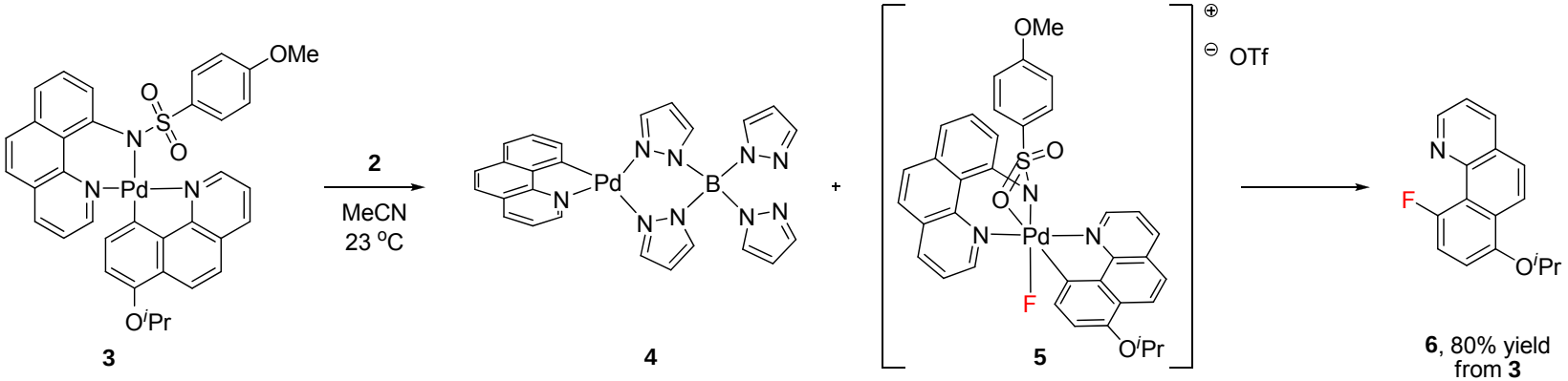


X-ray structure and calculated lowest unoccupied molecular orbital (LUMO) of **2**.

“后期氟化”反应路线设计



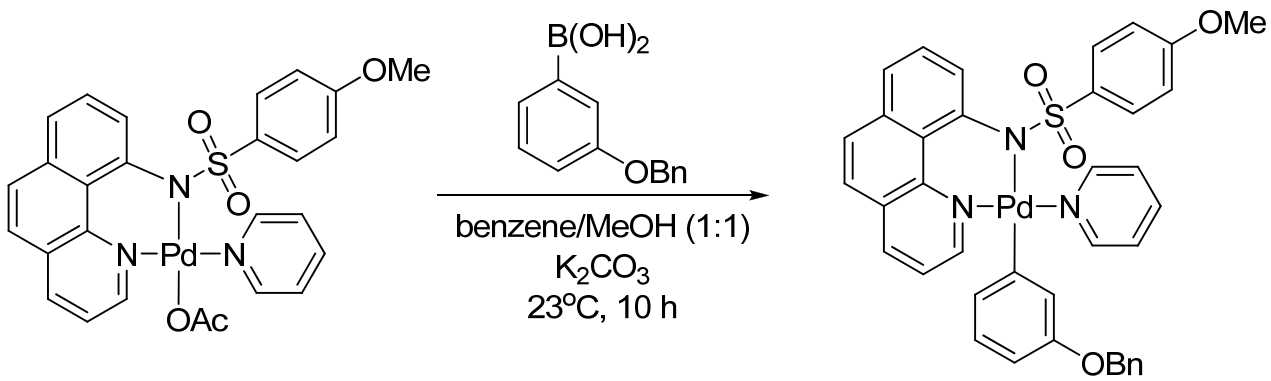
1 **2**, 90%



3 **4** **5**

6, 80% yield from **3**

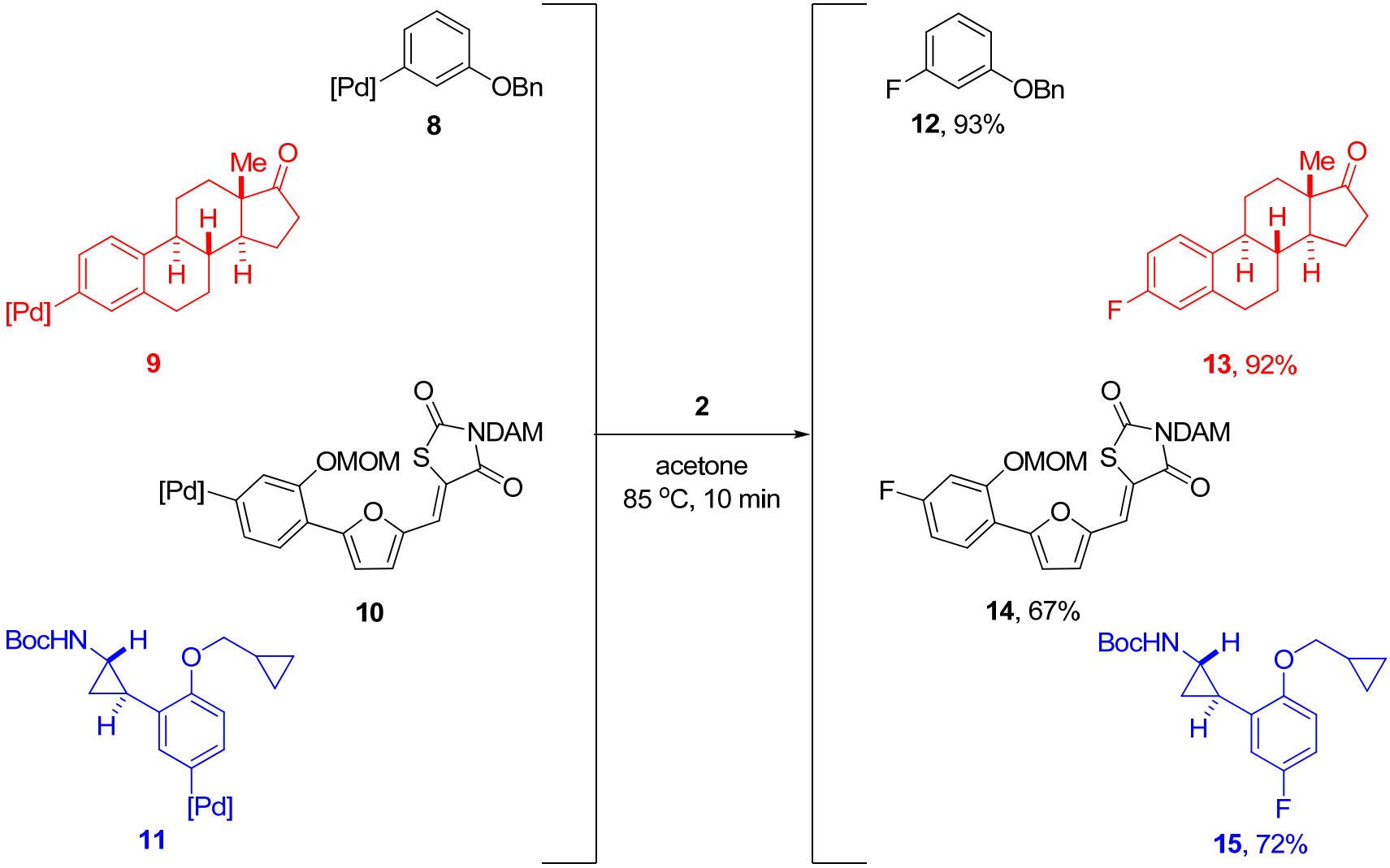
“后期氟化”反应的应用



7

8, 94%

“后期氟化”反应的应用


[Pd]
OBn
8
Me
O
H
H
H
[Pd]
9
O
NDAM
OMOM
S
[Pd]
O
O
10
BocHN
H
O
H
[Pd]
11
2
acetone
85 °C, 10 min
F
OBn
12, 93%
Me
O
H
H
H
F
13, 92%
O
NDAM
OMOM
S
F
O
O
14, 67%
BocHN
H
O
H
F
15, 72%

“后期氟化”反应的优势

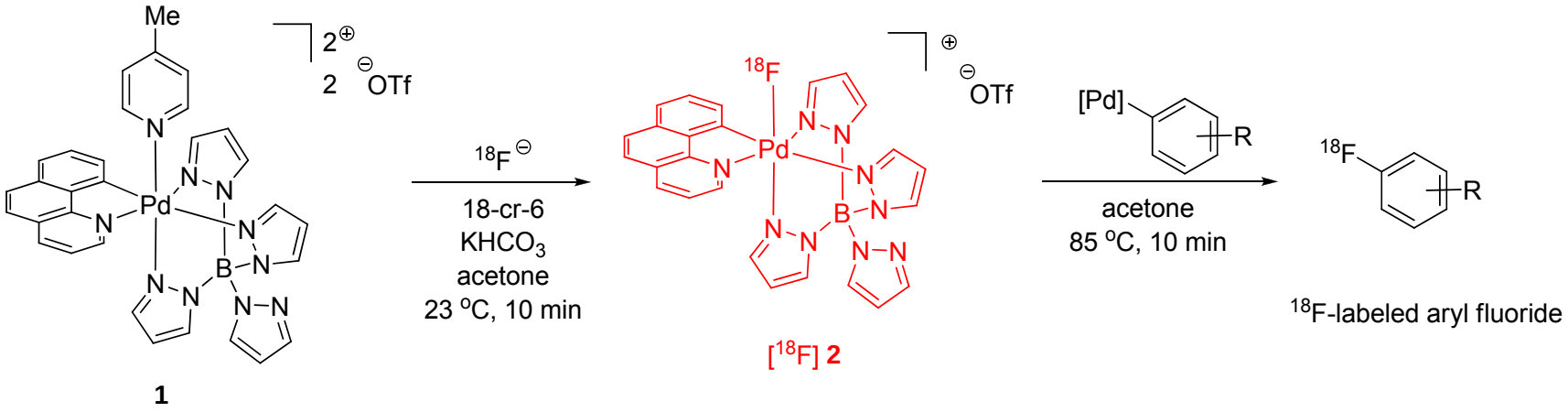
^{19}F向^{18}F的转化是很有挑战性的：

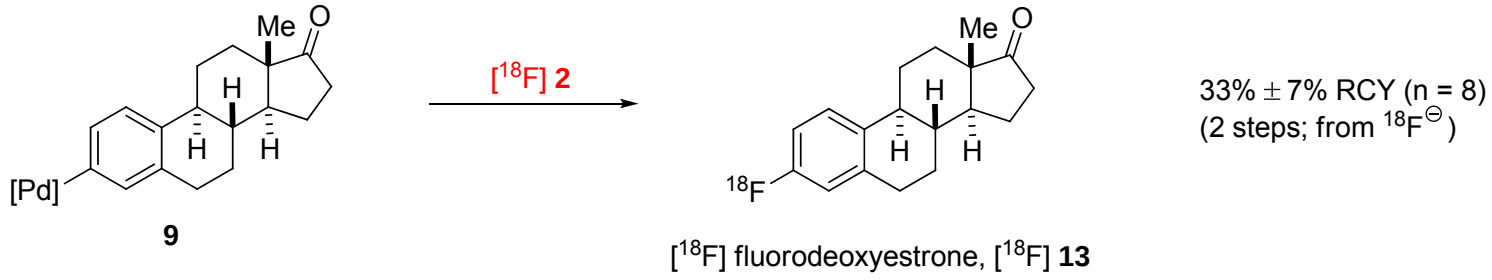
■氟源的浓度由mmol/L变为μmol/L;
■反应在电离辐射下进行；
■受^{18}F半衰期为110 min的时间所限制；
■金属有机合成在医疗设备条件下无法实施……

“后期氟化”的优势：

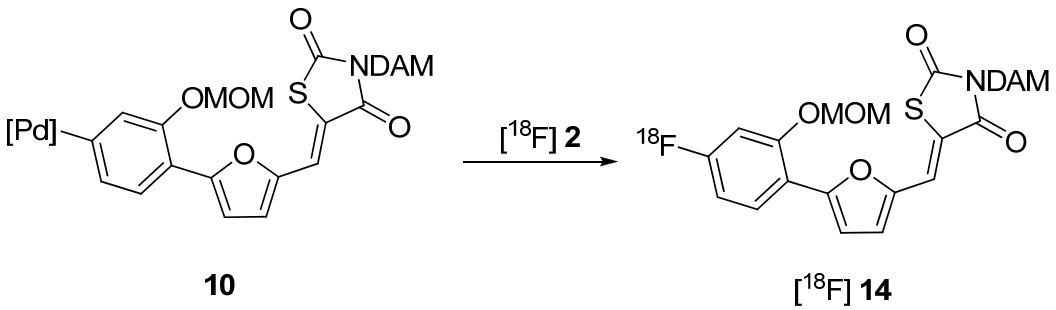
■配合物**1**在室温与空气下稳定；
■配合物**2**甚至在高温和水中保持稳定（100 ℃下24 h未分解，10% 乙腈水溶液室温下3 h未分解）；
■芳基钯配合物能够进行柱层析纯化，并在空气中进行储存和远距离输送。

^{18}F标记的氟化物的后期合成



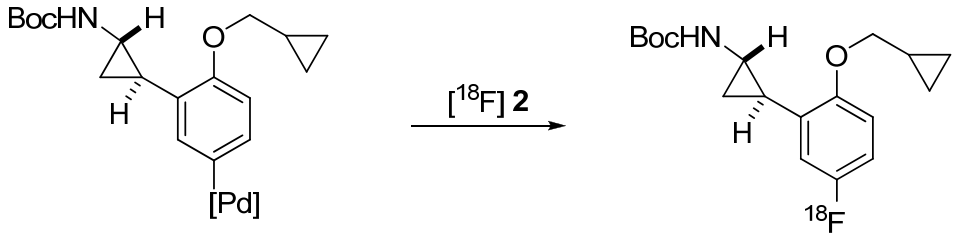


^{18}F标记的氟化物的后期合成



10 **[^{18}F] 14**

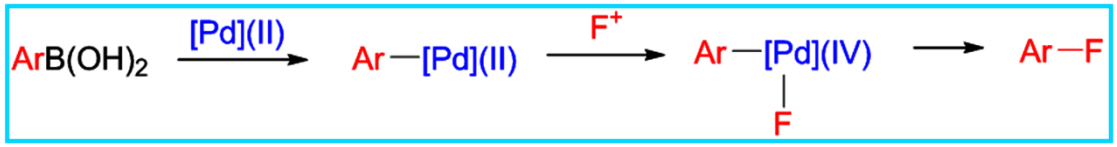
10% ± 2% RCY (n = 7)
(2 steps; from $^{18}F^{\ominus}$)



11 **[^{18}F] 15**

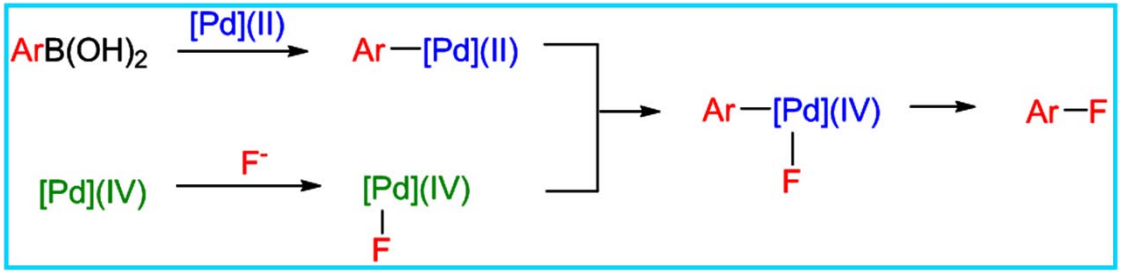
18% ± 5% RCY (n = 8)
(2 steps; from $^{18}F^{\ominus}$)

Late-stage fluorination



亮点：
钯配合物的设计从催化量到当量！

T. Ritter *et al*. *Angew. Chem. Int. Ed.* **2008**, *47*, 5993；
J. Am. Chem. Soc. **2008**, *130,* 10060；
J. Am. Chem. Soc. **2010**, *132,* 3793.



亮点：
将钯氟配合物作为氧化剂和亲电氟试剂！

T. Ritter *et al*. *Science* **2011**, *334*, 639.

Positron emission tomography (PET) is a noninvasive imaging technology used to observe and probe biological processes in vivo. Although several positron-emitting isotopes can be used for PET imaging, fluorine-18 (^{18}F) is the most clinically relevant radioisotope. For example, the radiotracer [^{18}F] fluorodeoxyglucose ([^{18}F]-FDG) has revolutionized clinical diagnosis in oncology. Despite the success of PET and decades of research, there remains a major deficiency in the ability to synthesize complex PET tracers; in fact, no general method is available to radiolabel structurally complex molecules with ^{18}F. In organic molecules, fluorine atoms are typically attached by carbon-fluorine bonds, yet carbon-fluorine bond formation is challenging, especially in the presence of the variety of functional groups commonly found in structurally complex molecules. For PET applications, chemical challenges are exacerbated by the short half-life of ^{18}F (110 min), which dictates that carbon-fluorine bond formation occur at a late stage in the synthesis to avoid unproductive radioactive decay before injection in vivo.

We have shown that a late-stage fluorination reaction can access ^{18}F-labeled functionalized molecules, which would be particularly difficult to prepare with conventional fluorination reactions. The availability of a fluorination reagent with high specific activity that functions as an electrophile may find applications in ^{18}F fluorination of pharmaceutical candidates for evaluation of their biodistribution to accelerate drug development, as well as in the development of previously unavailable ^{18}F-PET tracers for clinical care.

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