Late-stage C-H functionalization for drug development
1. Introduction of late-stage C-H functionalization (LSF)
2. Strategies for obtaining regioselectivity in LSF
3. Application of LSF: Drug discovery
4. Summary
1. Introduction of late-stage C-H functionalization (LSF)
The concept of late-stage C-H functionalization (LSF)

Use of LSF

Direct and fast development of derivatives

Conventional method

cumbersome protection/deprotection lengthen the synthetic route
Application of LSF in various fields

Late-stage diversification via C–H bond activation/functionalization sequence

Yu 2011 (ref. 14)
Itami & Wünsch 2012 (ref. 19)
Doucet & Guerchais 2012 (ref. 20)
Kim, Shinokubo & Osuka 2009 (ref. 22)
Glorius 2011 (ref. 26)
Hartwig & Hillmyer 2002 (ref. 29)
Bae 2009 (ref. 34)

LSF can modify natural products


LSF enables direct functionalization of natural complex products.
LSF enables the use of radioactive materials

Conventional method

\[ {^{18}\text{F}} \rightarrow \text{FG}_1 \rightarrow \text{FG}_2 \rightarrow \text{FG}_3 \quad \text{(TM)} \]

Low radiochemical yields

\[ ^{18}\text{F} \text{ decays under long synthetic process. (} t_{1/2} = 110 \text{ min) } \]

Method using LSF

\[ \rightarrow \text{FG}_1 \rightarrow \text{H} \rightarrow \text{LSF} \rightarrow \text{FG}_1 \rightarrow \text{FG}_2 \rightarrow \text{FG}_3 \quad \text{(TM)} \]

High radiochemical yields

\[ \downarrow \]

LSF can contribute to making materials containing radioactive isotopes.
Application of LSF for ADC


LSF can contribute to the synthesis of antibody-drug conjugates.
Late-stage C-H functionalization
= Conversion of C-H bonds to various functional groups at the end of synthetic process

LSF has potential applications in various fields.

Modification of complex products such as natural products and functional molecules.
2. Strategies for obtaining regioselectivity in LSF
The difficulties of LSF

conventional conditions (non-suitable for LSF)

Many C-H bonds
Regioselectivity

Many reactive functional groups
Functional group tolerance, chemoselectivity
Strategies for obtaining regioselectivity in LSF

1. Functionalize innately reactive C-H bonds

2. Use of bulky reagents sensitive to steric factor

3. Use of directing groups (DG)

4. Use of other convertible functional groups which can be introduced regioselectively
Innate reactivity depends on the structures of substrates. For example, electron density and acidity.

**Merit**
No extra conversion is required.

**Problem**
Regioselectivity mainly depends on substrates.
Strategy ①-2: LSF by innate C-H functionalizations

Mn(TMP)Cl (12 mol%)  
AgF (3 eq)  
TBAF (0.3 eq)  
PhIO (10 eq)

sclareolide

42%  
α/β = 3.1

16%  
α/β = 7.8

Strategy ①-3: LSF by innate C-H functionalizations

Proposed catalytic cycle
Strategy ①-4: LSF by innate C-H functionalizations

**A**

- **Mn**\(^{4+}\)(Por) → **Mn**\(^{3+}\)(Por) + X

- **X** = OH
- **X** = F

**B**

- Geometry optimizations and zero-point vibrational energy
- Mn: B3LYP/LACVP**
- Other atoms: B3LYP/6-31G**

- Single-point energy calculations
- Mn: B3LYP/LANL2TZ(f)
- Other atoms: B3LYP/6-311++G**
Carbon radical was involved

➤ Innately reactive C-H bonds were electron rich C-H bonds
   For example
   (A) distant from electron withdrawing groups
   (B) tertiary or secondary C-H bonds
Strategy ②-1: LSF by bulky reagents

Sterically less hindered C-H bond

Sterically hindered C-H bond

Use of bulky reagents

Sterically accessible C-H bonds are likely to be functionalized.

Merit
It is possible to functionalize innately less reactive C-H bonds.

Problem
It is necessary to strengthen the activity of the reagent because the active site is hindered.
Strategy ②-2: LSF by bulky reagents


Approach trajectories cone became narrow.

⇒ Fe(CF₃-PDP) is more bulky than Fe(PDP).
Strategy②-3: LSF by bulky reagents

\[ (S,S)-\text{Fe}(\text{PDP}) \quad (5\times3 \text{ mol\%}) \]
\[ \text{AcOH} \quad (0.5\times3 \text{ eq}) \]
\[ \text{H}_2\text{O}_2 \quad (1.2\times3 \text{ eq}) \]

\[ \text{MeCN, air} \rightarrow \]

\[ \text{product A major} \]

\[ \text{yields A:54\%, B:22\%} \]
\[ \text{(C9:C10=1:2)} \]

\[ \text{Substrate control} \]

\[ (+)-\text{artemisinin} \]

\[ (S,S)-\text{Fe}(\text{CF}_3\text{-PDP}) \quad (5\times3 \text{ mol\%}) \]
\[ \text{AcOH} \quad (0.5\times3 \text{ eq}) \]
\[ \text{H}_2\text{O}_2 \quad (1.2\times3 \text{ eq}) \]

\[ \text{MeCN, air} \rightarrow \]

\[ \text{product B major} \]

\[ \text{yields A:<5\%, B:52\%} \]
\[ \text{(C9:C10=11:1)} \]

\[ \text{Catalyst control} \]
Strategy ③-1: Guided by directing groups (DG)

Yu, J.-Q. et al., JACS. 2011, 133, 7222.

Use of DG ➞ Regioselectivity was obtained.
Strategy 3-2: Guided by directing groups (DG)

\[
\text{Pd(OAc)}_2 \text{ (10 mol\%)} + \text{Fromyl-Gly-OH (20 mol\%)} \quad \text{KH}_2\text{PO}_4 \text{ (50 mol\%)} + \text{AgOAc (3 eq)} \quad \text{HFIP, 90 °C, 24 h}
\]

16 examples


Other locations (for example, meta and para) selective reaction is limited.
Strategy ③-3: Guided by directing groups (DG)

1. Stepwise procedure
2. Usage of stoichiometric amount of DG

Usage of ubiquitous FG as DG is desirable.
Strategy ④-1: Use of other FG regioselectivity

**Merit**
It is not necessary to transform regioselectively from other FGs to target FG. Strategies of the introduction of target FGs increase.

**Problem**
Synthetic steps increase because of stepwise synthesis.
Strategy 4-2: Use of other FG regioselectivity

<table>
<thead>
<tr>
<th>Aromatic Fluorination</th>
<th>Transition Metal</th>
<th>F Source</th>
<th>Aliphatic Fluorination</th>
<th>Transition Metal</th>
<th>F Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=CHR'</td>
<td>Au cat.</td>
<td>Et₂N+HCl</td>
<td>X = H, Cl, R</td>
<td>Co(Co)cat. or Lewis base cat.</td>
<td>F-TEDA[16]</td>
</tr>
<tr>
<td></td>
<td>Pt cat.</td>
<td>Ag(F)[16]</td>
<td>X = H, Cl, Br, OR</td>
<td>Pd cat.</td>
<td>F-TEDA[16]</td>
</tr>
<tr>
<td></td>
<td>Ag med.</td>
<td>F-TEDA[16]</td>
<td>R = COOH</td>
<td>Fe cat.</td>
<td>F-TEDA[16]</td>
</tr>
<tr>
<td></td>
<td>KF[16]</td>
<td></td>
<td>R = F</td>
<td>Pd cat.</td>
<td>F-TEDA[16]</td>
</tr>
</tbody>
</table>


To introduce F at the late stages, other FGs are often used.
Strategy 3: C-H $\rightarrow$ C-Bpin $\rightarrow$ C-F


Some regioselective borylation reactions can use in LSF.
**Strategy 4-4: C-H → C-Bpin → C-F**

\[
\begin{align*}
R\text{B(OH)}_2 & \xrightarrow{\text{K}_2\text{CO}_3, \text{MeOH}:\text{C}_6\text{H}_6=1:1} \xrightarrow{23 \degree \text{C}, 2\sim 18 \text{ h}} N-p-\text{Ns} \\
& \xrightarrow{\text{MeCN}, 50 \degree \text{C}, 30 \text{ min}} R\text{F} \\
12 \text{ examples} & \text{ yields } 65\sim 91 \%
\end{align*}
\]


\[
\begin{align*}
\text{Bpin} & \xrightarrow{(\text{tBuCN})_2\text{CuOTf} (2 \text{ eq}), \text{AgF} (2 \text{ eq}), \text{THF}, 50 \degree \text{C}, 18 \text{ h}} \text{F} \\
& \xrightarrow{67 \%}
\end{align*}
\]

Summary of section 2

1. Functionalize innately reactive C-H bonds
2. Use of bulky reagents

Merit: Functionalization is mainly one step.
Demerit: Regioselectivity highly depends on substrates and reagents.

3. Use of directing groups (DG)
4. Use of other functional groups

Merit: Regioselectivity can be reliably obtained.
Demerit: Synthesis efficacy decreases because of stepwise process.
3. Application of LSF: Drug discovery
1. Development of positron emission tomography (PET) tracer

2. Lead optimization
   structure-activity relationship (SAR) and structure-property relationship (SPR)
LSF is used in the development of PET tracer (1)

Image of PET inspection

Radiopharmaceuticals

Gamma ray

Detector

molecular imaging

$^{11}\text{C}$, $^{13}\text{N}$, $^{15}\text{O}$ and $^{18}\text{F}$ are used for PET
LSF is used in the development of PET tracer (2)

**Generation of $^{18}$F source**

- Deuteron irradiation using cyclotron: $^{20}\text{Ne} \rightarrow 18\text{F}_2$
- Proton irradiation using cyclotron: $\text{H}_2^{18}\text{O} \rightarrow 18\text{F}^-$

$^{18}$F$_2$ and $^{18}$F$^-$ can be obtained.

**Synthesis of $^{18}$F-FDG**

1) $^{18}$F$^-$

2) hydrolysis

![Chemical structure of 18F-FDG](image)
LSF is used in the development of PET tracer (3)

\[
\begin{align*}
\text{R \text{B(OH)}_2} & \xrightarrow{\text{K}_2\text{CO}_3} \text{MeOH:C}_6\text{H}_6=1:1, 23 \degree \text{C, some hours}} \xrightarrow{\text{[^{18}F]A}} \text{acetone, 80 \degree \text{C, 10 min}} \\
\text{N-Pd} & \xrightarrow{\text{[^{18}F]A}} \text{acetone, 23 \degree \text{C, 10 min}} \xrightarrow{\text{18-crown-6, KHCO}_3, \text{acetone, 23 \degree \text{C, 10 min}}} \text{[^{18}F]A}
\end{align*}
\]

LSF is used in the development of PET tracer (4)

radiochemical yields (2 steps): 33% ± 7%
2 steps: Generation of [18F]A + this step

Challenges still remain.

New PET tracers may be developed using LSF. Information obtained from PET is used for drug development.

- the selection of potential drug candidates at an earlier stage of development
- an understanding of a drug's mechanism of action
- aid in guiding dose selection

For the success of lead optimization

The construction of structure-activity relationship (SAR) and structure-property relationship (SPR) are essential

LSF contributes to rapid development of derivatives, SAR and SPR.
LSF is used in the lead optimization (2)

Table 1. Enzymatic and Cellular Activities and Pharmaceutical Properties of Monofluorinated Compounds

<table>
<thead>
<tr>
<th>compd</th>
<th>X₁</th>
<th>X₂</th>
<th>X₃</th>
<th>X₄</th>
<th>X₅</th>
<th>X₆</th>
<th>R₂</th>
<th>HCT116</th>
<th>MEK1</th>
<th>C-Raf</th>
<th>solubility (μg/mL)</th>
<th>CL human (μL/min/mg)</th>
<th>PAMPA (10⁻⁶ cm/s)</th>
<th>AUCₚ₀ (μM-h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
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<td>530</td>
<td>32</td>
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<td>104</td>
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<tr>
<td>1b</td>
<td>F</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
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<td>H</td>
<td>950</td>
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<td>830</td>
<td>9</td>
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<td>5</td>
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<td>F</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>610</td>
<td>44</td>
<td>1100</td>
<td>37</td>
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<td>ND</td>
<td>ND</td>
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<tr>
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<td>H</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>18</td>
<td>53</td>
<td>13</td>
<td>273</td>
<td>6</td>
<td>6</td>
<td>40¹&lt;sup&gt;⁵&lt;/sup&gt;</td>
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<tr>
<td>1e</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>H</td>
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<td>87</td>
<td>110</td>
<td>180</td>
<td>114</td>
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<td>5</td>
<td>61&lt;sup&gt;⁶&lt;/sup&gt;</td>
</tr>
<tr>
<td>1f</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
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<tr>
<td>8a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>24</td>
<td>110</td>
<td>300</td>
<td>32</td>
<td>20</td>
<td>6</td>
<td>78&lt;sup&gt;⁶&lt;/sup&gt;</td>
</tr>
<tr>
<td>8b</td>
<td>F</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>550</td>
<td>2900</td>
<td>2400</td>
<td>51</td>
<td>22</td>
<td>5</td>
<td>75</td>
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<td>H</td>
<td>F</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>9</td>
<td>38</td>
<td>8</td>
<td>81</td>
<td>13</td>
<td>5</td>
<td>70&lt;sup&gt;⁶&lt;/sup&gt;</td>
</tr>
<tr>
<td>8e</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>Me</td>
<td>22</td>
<td>64</td>
<td>ND</td>
<td>55</td>
<td>13</td>
<td>5</td>
<td>99</td>
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</tr>
<tr>
<td>8g</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>F</td>
<td>Me</td>
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<td>66</td>
<td>120</td>
<td>72</td>
<td>22</td>
<td>4</td>
<td>86</td>
<td></td>
</tr>
</tbody>
</table>

<sup>¹</sup>Compounds were evaluated in 24 h exposure studies in mice at 100 mg/kg and formulated as solutions of 5% DMSO, 5% Cremophor EL, 15% PEG400, 15% HPCD, and 60% water. <sup>⁵</sup>At 50 mg/kg. <sup>⁶</sup>Sodium salt was used.

LSF is used in the lead optimization (3)

Table 3  $\sigma_1$ and $\sigma_2$ receptor affinities of the synthesized spirocyclic thiophenes and reference compounds

<table>
<thead>
<tr>
<th>Compd.</th>
<th>X</th>
<th>Aryl</th>
<th>$K_1 \pm \text{SEM} \ [\text{nM}] \ (n = 3)$</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>OCH$_3$</td>
<td>CH$_3$</td>
<td>21 ± 2.3</td>
<td>&gt; 1 $\mu$M</td>
</tr>
<tr>
<td>1b</td>
<td>OCH$_3$</td>
<td>C$_6$H$_5$</td>
<td>1.5 ± 0.08</td>
<td>&gt; 1 $\mu$M</td>
</tr>
<tr>
<td>2</td>
<td>OCH$_3$</td>
<td>H</td>
<td>0.32 ± 0.10</td>
<td>&gt; 1 $\mu$M</td>
</tr>
<tr>
<td>3a</td>
<td>H</td>
<td>C$_6$H$_5$</td>
<td>4.5 ± 2.9</td>
<td>&gt; 1 $\mu$M</td>
</tr>
<tr>
<td>3b</td>
<td>H</td>
<td>p-MeO$_2$C$_6$H$_4$</td>
<td>1.7 ± 0.54</td>
<td>617</td>
</tr>
<tr>
<td>3c</td>
<td>H</td>
<td>p-MeC$_6$H$_4$</td>
<td>1.7 ± 0.79</td>
<td>444</td>
</tr>
<tr>
<td>3d</td>
<td>H</td>
<td>p-NOC$_6$H$_4$</td>
<td>3.4 ± 0.90</td>
<td>588</td>
</tr>
<tr>
<td>3e</td>
<td>H</td>
<td>p-CN$_6$H$_4$</td>
<td>4.0 ± 1.9</td>
<td>294</td>
</tr>
<tr>
<td>3f</td>
<td>H</td>
<td>1-naphthyl</td>
<td>1.0 ± 0.40</td>
<td>13</td>
</tr>
<tr>
<td>4a</td>
<td>OCH$_3$</td>
<td>C$_6$H$_5$</td>
<td>2.2 ± 0.13</td>
<td>341</td>
</tr>
<tr>
<td>4b</td>
<td>OCH$_3$</td>
<td>p-MeO$_2$C$_6$H$_4$</td>
<td>2.0 ± 0.81</td>
<td>500</td>
</tr>
<tr>
<td>4c</td>
<td>OCH$_3$</td>
<td>p-MeC$_6$H$_4$</td>
<td>1.6 ± 0.16</td>
<td>1000</td>
</tr>
<tr>
<td>4d</td>
<td>OCH$_3$</td>
<td>p-NOC$_6$H$_4$</td>
<td>0.25 ± 0.14</td>
<td>625</td>
</tr>
<tr>
<td>4e</td>
<td>OCH$_3$</td>
<td>p-CN$_6$H$_4$</td>
<td>5.7 ± 2.3</td>
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<tr>
<td>4f</td>
<td>OCH$_3$</td>
<td>p-CF$_3$C$_6$H$_4$</td>
<td>5.0 ± 0.50</td>
<td>420</td>
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<td>4i</td>
<td>OCH$_3$</td>
<td>3-pyridyl</td>
<td>2.2 ± 0.42</td>
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<td>4j</td>
<td>OCH$_3$</td>
<td>p-biphenyl</td>
<td>30 ± 18</td>
<td>&gt; 1 $\mu$M</td>
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<tr>
<td>5</td>
<td>H</td>
<td>H</td>
<td>0.35 ± 0.06</td>
<td>657</td>
</tr>
<tr>
<td>6</td>
<td>OCH$_3$</td>
<td>H</td>
<td>0.22 ± 0.06</td>
<td>3664</td>
</tr>
<tr>
<td>13</td>
<td>OCH$_3$</td>
<td>H</td>
<td>3.2 ± 0.41</td>
<td>83</td>
</tr>
<tr>
<td>14</td>
<td>HC$_3$=CH</td>
<td>H</td>
<td>1.9 ± 0.66</td>
<td>45</td>
</tr>
<tr>
<td>haloperidol</td>
<td></td>
<td>H</td>
<td>3.9 ± 1.5</td>
<td>20</td>
</tr>
<tr>
<td>di-β-tolylguanidine</td>
<td></td>
<td>H</td>
<td>61 ± 8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

LSF is used in the lead optimization (4)

Table 1: Relative solubility enhancement of the oxidized compounds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R^1</th>
<th>Relative Solubility Enhancement: Assay 1 (FaSSIF)^a</th>
<th>Relative Solubility Enhancement: Assay 2 (FeSSIF)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH_2OH</td>
<td>3</td>
<td>274x</td>
<td>no change</td>
</tr>
<tr>
<td>2</td>
<td>CH_2OH</td>
<td>4</td>
<td>8.00x</td>
<td>0.077x</td>
</tr>
<tr>
<td>3</td>
<td>CH_2OH</td>
<td>7</td>
<td>121x</td>
<td>0.357x</td>
</tr>
<tr>
<td>4</td>
<td>CH_2OH</td>
<td>6</td>
<td>no change</td>
<td>0.077x</td>
</tr>
<tr>
<td>5</td>
<td>CO_2H</td>
<td>5</td>
<td>0.056x^k^</td>
<td>0.115x^k^</td>
</tr>
<tr>
<td>6</td>
<td>CO_2H</td>
<td>8</td>
<td>0.112x^k^</td>
<td>17.4x^k^</td>
</tr>
<tr>
<td>7</td>
<td>CO_2H</td>
<td>9</td>
<td>0.019x^k^</td>
<td>3.83x^k^</td>
</tr>
<tr>
<td>8</td>
<td>CO_2H</td>
<td>10</td>
<td>0.002x^k^</td>
<td>0.462x^k^</td>
</tr>
</tbody>
</table>

[a] Solubility ratio substrate/1 in the fasted state simulated intestinal fluid. [b] Solubility ratio substrate/1 in the fed state simulated intestinal fluid. [c] Solubility ratio substrate/2. R^1 refers to the position shown in the structure of Figure 5 (C17).
Summary of section 3

1. Rapid synthesis of derivatives → SAR and SPR

2. Synthesis of molecules which cannot obtained by conventional method → PET tracer

**LSF contributes to drug development.**
4. Summary
LSF contributes to various fields including drug discovery.

LSF has several challenges including regioselectivity.

The reactions used in LSF are limited and have limited substrate scopes.

It is necessary to develop new excellent reactions which can be used in LSF. They contribute not only to chemistry but also to various fields.