Ligand-Accelerated \textit{ortho}-C–H Olefination of Phenylacetic Acids

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\textit{Checked by Sandeep N. Raikar and Huw M. L. Davies}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{reaction_diagram}
\end{figure}

\textbf{Procedure}

\textbf{Caution! The reaction is run in a sealed vessel at elevated temperature under 1 atm O\textsubscript{2}. Though no incidents have been encountered in the submitters’ laboratory, it is nonetheless recommended that a blast shield be used as a precaution.}

A. \textit{(E)-2-(2-(3-Ethoxy-3-oxoprop-1-enyl)-6-fluorophenyl)acetic acid (3a)}. An oven-dried, single-necked 500-mL round-bottomed flask (Notes 1 and 2) is equipped with a magnetic stir bar (oval shaped, 40 mm length and 16 mm diameter). Palladium(II) acetate (280.6 mg, 1.25 mmol, 0.050 equiv) (Note 3), N-acetyl isoleucine (216.5 mg, 1.25 mmol, 0.050 equiv) (Note 4), 2-fluorophenylacetic acid (1a) (3.85 g, 25.0 mmol, 1.00 equiv) (Note 5), and potassium bicarbonate (5.01 g, 50.0 mmol, 2.00 equiv) (Note 6) are added to the round-bottomed flask (Note 7).
t-AmylOH (50.0 mL) (Note 8) and ethyl acrylate (2a) (2.93 mL, 27.5 mmol, 1.1 equiv) (Note 9) are added via syringe. The reaction flask is tightly fitted with a rubber septum (as shown in the image below). Into the septum is placed an 18G × 1½” needle attached to a modified 1 mL syringe. (The plunger is removed, and the end opposite from the needle juncture is cut off using scissors). The severed end of the syringe is attached to thick-walled rubber tubing (25 cm length), which is connected to a three-way valve. The second connection of the valve is attached by rubber tubing to a high vacuum line and the third to a balloon filled with O₂. The reaction flask is evacuated briefly (Note 10) under high vacuum (0.1 mmHg, 23 °C) and charged with O₂; this process is repeated three times and then the flask is charged with O₂ for a minute. The needle attached to the rubber septum is removed. The reaction mixture is stirred (Note 11) at room temperature for 5 min, during which time it is yellow to orange in color. The reaction flask is
placed in an oil bath and then heated to 90 °C and stirred for 4 h (Note 12). While heating, a blast shield is placed in front of the reaction set-up as a safety precaution. During the course of the reaction, the solution becomes green/yellow to dark brown in color. The reaction flask is removed from the oil bath and allowed to cool to room temperature and then placed in an ice bath for 5 min. The stopper is then removed, and 2.0 N aqueous HCl solution (50 mL) is added dropwise over 20 min with vigorous stirring (Note 13). The mixture is transferred to a 500 mL separatory funnel and extracted with EtOAc (3 × 100 mL) (Notes 14 and 15). The organic layers are combined in a 500 mL Erlenmeyer flask, and anhydrous sodium sulfate (Note 16) is added. The solution is allowed to stand for 5 min. Sodium sulfate is removed using a Büchner filter funnel, and the filtrate is concentrated in vacuo (30 mmHg, 40 °C) to obtain the crude product as a viscous red/brown oil (Note 17). The resulting residue is purified by silica gel flash column chromatography (Notes 18 and 19) using 66:33:1 hexanes:EtOAc:HOAc as the eluent, giving product 3a as an off-white solid (5.17 g, 82%) (Notes 20 and 21). The product is further purified by recrystallization from hexanes/EtOAc (Notes 22–26) to provide 4.91 g (78%) of a white solid.

Notes

1. In the submitters’ experiment, a 350-mL Schlenk flask is used. The reaction vessel contains a high-vacuum valve with PTFE O-ring at the tip and PTFE wiper to protect the O-ring on the shaft.
2. Prior to use, the reaction vessel and stir bar are cleaned in the following way. They are first allowed to soak in concentrated nitric acid for two or more hours to remove trace transition metal precipitates. The nitric acid is poured off, and the items are rinsed five times with distilled water, then three times with acetone, and allowed to dry in an oven for two hours.
3. Palladium acetate trimer (>99.99% trace metals basis) is purchased from Pressure Chemical Co. (product 1730) and used as received.
4. N-Acetyl-isoleucine (Ac-Ile-OH) (>99%) is purchased from Bachem (product E-1080.0005) and used as received (white crystalline solid).
5. 2-Fluorophenylacetic acid (1a) (98%) is purchased from Oakwood (product 001292 (25 g)) and used as received (white crystalline solid).
6. Potassium bicarbonate (>99.5%) is purchased from Fisher (product P235-500) and used as received (white crystalline solid).

7. The reagents are weighted out on individual pieces of weighing paper, folded diagonally, and then added to the reaction flask in the aforementioned order. To avoid spilling the solid reagents when adding them to the flask, an additional piece of weighing paper is gently rolled (corner to opposite corner) and fitted inside the neck of the flask prior to transferring in the solid reagents, then removed before addition of liquid reagents. None of the reagents are air- or moisture-sensitive, so they can be measured out without special precautions.

8. 2-Methyl-2-butanol (t-AmylOH) (99%) is purchased from Sigma Aldrich (product 152463-1L) and used as received (colorless liquid). In the submitters' experience, newly opened bottles give the most consistent results. Solvent obtained from older bottles can give inconsistent results, unless the solvent is distilled before use.

9. Ethyl acrylate (2a) (99%) containing 10–20 ppm hydroquinone monomethyl ether as an inhibitor is purchased from Sigma Aldrich (product E9706-100ML) and used as received (colorless liquid).

10. Both t-AmylOH and ethyl acrylate are volatile under reduced pressure. Thus, each evacuation should be done carefully. The three-way valve is adjusted and connected to the vacuum until gentle bubbling of the solution is observed, and the exposure to high vacuum should last no longer than 5 seconds. Slowly swirling the reaction vessel, while the solution is under vacuum helps modulate bubbling.

11. The solution was stirred at 500–600 rpm, which is the highest controlled stirring rate that could be maintained.

12. The oil bath temperature is 90 °C. Complete conversion of 1a to 3a is normally observed after 90–120 min. In this procedure, the extended reaction time is to ensure complete conversion.

13. A 2.0 N hydrochloric acid solution is prepared by adding 12.1 N “concentrated” HCl (EMD Chemicals, product HX0603-3) to deionized water (17:83, HCl,H2O, vol:vol).

14. Prior to purification, it is recommended that the conversion be assayed by collecting a 1H NMR spectrum of the crude reaction mixture. To do this, a small aliquot of the organic phase (the top layer in the separatory funnel after quenching with HCl and adding EtOAc), is concentrated in vacuo and dissolved in CDCl3. The resulting solution is added to an NMR tube and analyzed. The conversion is determined by integration of the benzylic methylene protons, which appear as singlets.
(approximately 3.72 ppm for 1a and 3.87 ppm for 3a, as referenced from the residual chloroform peak at 7.26 ppm).

15. All bulk organic solvents are purchased from Fisher Scientific and used as received.

16. Anhydrous sodium sulfate was purchased from Fischer Scientific (product S421-10) and used as received.

17. 1H NMR analysis of the crude material after extraction reveals only the desired product, trace quantities of Ac-Ile-OH, and residual 1-amyIOL. The pure product is a white crystalline solid. Thus, the yellow/orange/red color of the crude material is possibly due to unidentifiable oligomeric/polymeric byproducts or organometallic species. The purification procedures outlined herein are designed to remove these byproducts.

18. Silica gel (32–63 µm, 60 Å) was purchased from Dynamic Adsorbents, Inc. (product 02826-25) and used as received.

19. The column is 60 mm wide in diameter, and the height of the silica is 20 cm inside the column. The eluent was collected in 100 mL fractions.

20. Column chromatography gives the product as an off-white solid. Though it appears >95% pure by 1H NMR analysis, the pale yellow color is evidence of trace impurities, which are challenging to remove.

21. A reaction on half-scale provided 2.61 g (83%) of an off-white solid before recrystallization.

22. The column-purified product is dissolved in 4 mL of hot EtOAc (70 °C), then allowed to cool to room temperature and diluted with 1 mL of hexanes. The solution is cooled to –5 °C and kept overnight. The resulting crystals are collected by vacuum filtration on a Büchner funnel and washed with 2 mL of ice-cold hexanes. The mother liquor is concentrated in vacuo (30 mmHg, 40 °C), and the crystallization procedure is repeated with 1 mL EtOAc and 1 mL hexanes. The combined crystals were transferred to a 50-mL, round-bottomed flask and dried overnight at 0.37 mmHg to provide 4.91 g (78%) of a white solid.

23. Analytically pure material suitable for elemental analysis is obtained by taking the column-purified product and recrystallizing it from EtOAc/hexanes twice using the procedure in Note 22.

24. The product is indefinitely stable to air and moisture.

25. Single crystals suitable for X-ray diffraction are obtained by preparing a concentrated solution of 3a in EtO in a 2 mL vial, placing this smaller vial in a 20 mL scintillation vial containing 5 mL of hexanes, sealing the
larger vial, and allowing the system to stand unperturbed overnight (approximately 8 hours).

26. Analytical data for product 3a: TLC (hexanes:EtOAc:HOAc, 66:33:1) Rf = 0.29; M.p = 97–99 °C; 'H NMR (600 MHz, CDCl3) δ: 1.33 (t, J = 7.2 Hz, 3 H), 3.87 (d, J = 1.8 Hz, 2 H), 4.27 (q, J = 6.6 Hz, 2 H), 6.38 (d, J = 15.6 Hz, 1 H), 7.10 (t, J = 9.6 Hz, 1 H), 7.29 (td, J1 = 8.4, J2 = 6.0 Hz, 1 H), 7.38 (d, J = 7.8 Hz, 1 H), 7.84 (d, J = 15.6 Hz, 1 H); 13C NMR (150 MHz, CDCl3) δ: 14.2, 30.5 (d, J_{C–F} = 5.1 Hz), 60.9, 116.5 (d, J_{C–F} = 22.7 Hz), 120.5 (d, J_{C–F} = 16.1 Hz), 122.1, 122.5 (d, J_{C–F} = 3.2 Hz), 129.1 (d, J_{C–F} = 9.0 Hz), 136.3 (d, J_{C–F} = 3.5 Hz), 140.3 (d, J_{C–F} = 3.4 Hz), 161.4 (d, J_{C–F} = 245.6 Hz), 166.5, 175.9; Decoupled 19F NMR (375 MHz, CDCl3) δ: –115.11 (s, 1 F); IR (film): 2984, 1735, 1705, 1638, 1574, 1462, 1369, 1318, 1264, 1241, 1183, 1156, 1001, 971, 866, 802 cm⁻¹; HRMS (ESI-TOF) m/z calcd for C\textsubscript{13}H\textsubscript{14}FO\textsubscript{4} [M+H]⁺: 253.0876, found: 253.0871; Anal. calcd. for C\textsubscript{13}H\textsubscript{13}FO\textsubscript{4}: C 61.90, H 5.20, F 7.53, found: C 62.07, H 5.36, F 7.42.

Working with Hazardous Chemicals

The procedures in Organic Syntheses are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in Organic Syntheses, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment...
Discussion

Transition metal–catalyzed reactions that form C(sp²)–C(sp²) linkages are an invaluable component of modern organic synthesis. Prominent among this family of synthetic transformations is the Pd(0)-catalyzed Mizoroki–Heck reaction, which couples aryl halides and olefins. The first step in the catalytic cycle for the Mizoroki–Heck reaction is the oxidative addition of [Pd(0)Lₙ] to the aryl halide (ArX) to form a [Pd(II)(Ar)(X)Lₙ] species, which goes on to react via olefin coordination, 1,2-migratory insertion, and β-hydride elimination. Reductive elimination from the resulting [Pd(II)(H)(X)] species then regenerates the active [Pd(0)Lₙ] species. From the vantage point of synthetic efficiency, an attractive alternative would be to take advantage of a Pd(II)-mediated C(aryl)–H cleavage event (which, mechanistically, is redox neutral with concomitant loss of HX), to generate an analogous [Pd(II)(Ar)Lₙ] species, which could then proceed through the above sequence of elementary steps. Reoxidation of Pd(0) at the end of the catalytic cycle with an external oxidant would regenerate the active catalyst. This approach is potentially advantageous because it obviates the need for the regioselective installation of a halide onto the arene, which can take several steps or be infeasible altogether in intricately functionalized or sensitive organic molecules.

Since the seminal discoveries of Fujiwara and Moritani in the late 1960s, Pd(II)-mediated C(aryl)–H olefination has steadily progressed to improved levels of catalytic efficiency and broadened substrate scope. However, the practical utility of these reactions in organic synthesis has remained limited for a several reasons. Firstly, there is a lack of positional selectivity with substituted arenes (e.g., toluene). Secondly, large stoichiometric excess of the arene must typically be used to overcome the
low affinity between the arene and the metal center. Thirdly, reactivity with electron-poor arenes is typically low because the mechanism of C–H cleavage is thought to involve a Friedel–Crafts-type electrophilic palladation event. Solutions to these problems include the use of electron-rich heteroarenes and/or substrates containing a coordinating functional group which can direct ortho-C–H cleavage.Indeed, with electron-rich nitrogen heterocycles, the power of Pd(II)-mediated C(aryl)–H olefination for the expedient synthesis of complex carbon skeletons has been demonstrated in the total synthesis of several alkaloid natural products.

During the past 10 years, our research group has worked extensively to develop synthetically enabling C–H functionalization reactions. As part of this effort, we have focused on the design, discovery, and optimization of ligand scaffolds to control and accelerate C–H activation with Pd(II) catalysts. In 2010, we found that mono-N-protected amino acid (MPAA) ligands, which we originally used to achieve chiral induction in enantioselective C–H activation, also enhanced kinetic reactivity in Pd(II)-catalyzed C–H olefination of phenylacetic acid substrates. Mechanistic studies were consistent with the observed rate increases stemming from acceleration of the C–H cleavage step. Since this series of initial reports, MPAA ligands have found use in promoting a broad range Pd(II)-catalyzed C–H functionalization reactions.

As previously demonstrated, the MPAA-accelerated ortho-C–H olefination reaction tolerates a range of electron-donating and -withdrawing substituents on the aryl group of the phenylacetic acid (Table 1). Additionally, hydrocinnamic acids are also competent substrates. Substrates bearing mono-substitution at the α-position are compatible with the MPAA-accelerated conditions, including commercial non-steroidal anti-inflammatory drugs, such as ketoprofen and naproxen. A similar acceleration effect using MPAAs with α,α-disubstituted substrates has not been observed in our studies. In the absence of a blocking group at the ortho or meta position, formation of the corresponding 2,6-diolefinated product is observed, and a separate procedure has been optimized to facilitate that transformation (Scheme 1). Various functionalized olefin coupling partners are tolerated; acrylates, vinyl ketones, and styrenes are all reactive (Table 2). Simple terminal alkenes also participate in the reaction but give the formal C–H allylation product.
Table 1. Pd(II)-catalyzed ortho-C–H olefination with representative phenylacetic acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenylacetic Acid</th>
<th>Olefin</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[R2][R1]CO2H</td>
<td>[R2][R3]CO2Et</td>
<td>[R2][R1]CO2Et</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>Me[CO2H]</td>
<td>[R2][R3]CO2Et</td>
<td>[R2][R1]CO2Et</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>F3C[CO2H]</td>
<td>[R2][R3]CO2Et</td>
<td>[R2][R1]CO2Et</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>Me[CO2H]</td>
<td>[R2][R3]CO2Et</td>
<td>[R2][R1]CO2Et</td>
<td>83[c]</td>
</tr>
<tr>
<td>5</td>
<td>MeO[CO2H]</td>
<td>[R2][R3]CO2Et</td>
<td>[R2][R1]CO2Et</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>NO2[CO2H]</td>
<td>[R2][R3]CO2Et</td>
<td>[R2][R1]CO2Et</td>
<td>70[c]</td>
</tr>
<tr>
<td>7</td>
<td>Ph[CO2H]</td>
<td>[R2][R3]CO2Et</td>
<td>[R2][R1]CO2Et</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>MeO[CO2H]</td>
<td>[R2][R3]CO2Et</td>
<td>[R2][R1]CO2Et</td>
<td>94</td>
</tr>
</tbody>
</table>

*a Isolated yields. b An additional 11% of the 2,6-diolefinated product was formed. c An additional 6% of the decarboxylated product was formed.
Table 2. Pd(II)-catalyzed ortho-C–H olefination with representative olefin coupling partners\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenylacetic Acid</th>
<th>Olefin</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO\textsubscript{2}H</td>
<td>CO\textsubscript{2}t-Bu</td>
<td>CO\textsubscript{2}t-Bu</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>CO\textsubscript{2}H</td>
<td>CO\textsubscript{2}Bn</td>
<td>CO\textsubscript{2}Bn</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>CO\textsubscript{2}H</td>
<td>(n)-Bu</td>
<td>CO\textsubscript{2}n-Pr</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>CO\textsubscript{2}H</td>
<td>(n)-Bu</td>
<td>CO\textsubscript{2}n-Pr</td>
<td>65\textsuperscript{c}</td>
</tr>
<tr>
<td>5</td>
<td>CO\textsubscript{2}H</td>
<td>(n)-Bu</td>
<td>CO\textsubscript{2}n-Pr</td>
<td>62\textsuperscript{c}</td>
</tr>
<tr>
<td>6</td>
<td>CO\textsubscript{2}H</td>
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<td>94</td>
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<tr>
<td>7</td>
<td>CO\textsubscript{2}H</td>
<td>Et</td>
<td>CO\textsubscript{2}Et</td>
<td>97\textsuperscript{c}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The reaction conditions are identical to those in Table 1. \textsuperscript{b} Isolated yields. \textsuperscript{c} 10 h.
Overall, the method is high-yielding, operationally simple, and tolerant towards a variety of functional groups (see Table 1). The reaction is atom-economical in the sense that every atom from both starting materials (discounting the formal loss of “H₂”) is incorporated into the product, and the only byproduct that is produced is H₂O (or H₂O₂). The synthetic utility of this C–H olefination reaction has recently been demonstrated in the total synthesis of (+)-lithospermic acid and related analogs.

In this manuscript, we describe an optimized version of our MPAA-accelerated ortho-C–H olefination reaction that is more amenable to scale-up. Specifically, compared to our earlier report, we have reduced the olefin and MPAA ligand equivalents. Furthermore, we demonstrate that with a representative phenylacetic acid substrate, the reaction can be run at a higher concentration (0.5 M) and can be performed on over a 5-gram scale. The connectivity of the product and the olefin stereochemistry have been confirmed via single-crystal X-ray diffraction (Figure 1). This work demonstrates the essential role that the ligand plays in developing practical Pd(II)-catalyzed C–H functionalization reactions that are reliable in preparative-scale synthesis.

Figure 1. X-ray crystal structure of 3a
References

1. Department of Chemistry, The Scripps Research Institute (TSRI), 10550 N. Torrey Pines Road, La Jolla, CA 92037 (USA). E-mail: yu200@scripps.edu. This research was supported by the NIH (NIGMS, 1 R01 GM084019-02), the NSF (NSF CHE-1011898), Amgen, and Eli Lilly. Individual awards and fellowships were granted by the NSF GRFP, the NDSEG Fellowship Program, TSRI, and the Skaggs-Oxford Scholarship program (K.M.E.); the Austrian Science Fund (N.D.); the EPA STAR Graduate Fellowship Program (Agreement No. FP917296-01-0) (P.S.T.-B.); the China Scholarship Council (D.-H.W.); and the ARCS and Donald and Delia Baxter Foundations (A.C.S.). TSRI Manuscript No. 21472.


Appendix

Chemical Abstracts Nomenclature (Registry Number)

N-Acetyl isoleucine (Ac-Ile-OH); (2S,3S)-2-acetamido-3-methylpentanoic acid (3077-46-1)

Potassium bicarbonate; (298-14-6)
Palladium(II) acetate; (3375-31-3)

2-Fluorophenylacetic acid; 2-(2-fluorophenyl)acetic acid (451-82-1)

tert-Amyl alcohol (t-AmylOH); 2-methyl-2-butanol (75-85-4)

Ethyl acrylate; Ethyl propenoate (140-88-5)

Keary Mark Engle graduated Phi Beta Kappa and summa cum laude from the University of Michigan, where he worked with Prof. Adam Matzger studying self-assembled monolayers. A Fulbright Scholar, he spent the 2007–2008 academic year studying under the tutelage of Prof. Manfred Reetz at the Max-Planck-Institut für Kohlenforschung (Germany). He completed his graduate work jointly at The Scripps Research Institute and the University of Oxford, under the supervision of Prof. Jin-Quan Yu and Prof. Véronique Gouverneur, respectively, earning a Ph.D. in Chemistry and a DPhil in Biochemistry. During graduate school, his honors included NSF and NDSEG Predoctoral Fellowships. Presently, Keary is an NIH Postdoctoral Fellow with Prof. Robert H. Grubbs at Caltech.
Navid Dastbaravardeh studied chemistry at the Ludwig Maximilian University of Munich (LMU, Germany) and received his diploma in 2008. He then moved to the Vienna University of Technology (VUT, Austria), where he completed his Ph.D. in Organic Chemistry under the supervision of Profs. Michael Schnürch and Marko D. Mihovilovic. Supported by an Erwin-Schrödinger Research Fellowship, he is currently pursuing postdoctoral research with Prof. Jin-Quan Yu at The Scripps Research Institute, focusing on palladium-catalyzed C–H bond-functionalization reactions.

Peter S. Thuy-Boun carried out undergraduate research with Prof. Lijuan Li and Prof. Paula Diaconescu, graduating with a BS in Chemistry from UCLA. Since 2010, he has been a graduate student at The Scripps Research Institute working on Pd-catalyzed C–H alkylation methodology under the supervision of Prof. Jin-Quan Yu and on proteomic characterization of the human gut microbiome under the guidance of Prof. Dennis W. Wolan. His graduate work is supported by an EPA STAR Predoctoral Fellowship.

Dong-Hui Wang completed his BSc at Lanzhou University in 2000 then carried out research at the Shanghai Institute of Organic Chemistry under Prof. Zhaoguo Zhang. In 2004, he began graduate studies under Prof. Jin-Quan Yu. He earned his MSc from Brandeis University before relocating to The Scripps Research Institute, where he completed his Ph.D. in 2010. His thesis research was recognized with the Chinese Government Award for Outstanding Self-Financed Students Abroad. Dong-Hui worked as a postdoctoral research fellow in the laboratory of Prof. Stephen Buchwald at MIT (2010–2012), and as a medicinal chemist at Abide Therapeutics (2012–2014). Presently, he is an Assistant Professor at the Shanghai Institute of Organic Chemistry (China).
Aaron C. Sather earned his BSc at the University of Oregon, working with Prof. Darren W. Johnson on arsenic remediation and anion recognition. He graduated *cum laude* with the distinction of departmental honors. He then moved to The Scripps Research Institute to study molecular recognition under the guidance of Prof. Julius Rebek, Jr., where he was both a Baxter Fellow and an ARCS Fellow. Presently, Aaron is a NIH Postdoctoral Fellow at MIT in the research laboratory of Prof. Stephen Buchwald.

Jin-Quan Yu received his BSc in Chemistry from East China Normal University and his MSc from the Guangzhou Institute of Chemistry. In 2000, he obtained his PhD at the University of Cambridge with Prof. J. B. Spencer. Following time as a junior research fellow at Cambridge, he joined the laboratory of Prof. E. J. Corey at Harvard University as a postdoctoral fellow. He then began his independent career at Cambridge (2003–2004), before moving to Brandeis University (2004–2007), and finally to The Scripps Research Institute, where he is currently Frank and Bertha Hupp Professor of Chemistry. His group studies transition metal–catalyzed C–H activation.

Dr. Sandeep N. Raikar did his BSc and MSc from Sri Satya Sai Institute of Higher Learning-India. He then moved to University of Kansas where he worked with Prof. Helena C. Malinakova and obtained his Ph.D. degree in 2013. Currently he is a postdoctoral associate in Prof. Huw M. L. Davies laboratory at Emory University.
$^{13}$C NMR, 150 MHz, CDCl$_3$
$^{19}$F NMR, 375 MHz, CDCl$_3$