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Pd-Catalyzed Aerobic Oxidative Heck Cross-Coupling for the Straightforward Construction of Indole δ-Lactams

HIGHLIGHTS

Construction of indole δ-lactams enabled by a Pd-catalyzed oxidative Heck coupling

The phosphinamide L₅ was crucial as a co-ligand for prompting the reaction

A Pd(II)/Pd(0) catalytic cycle is proposed to be responsible

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Pd-Catalyzed Aerobic Oxidative Heck Cross-Coupling for the Straightforward Construction of Indole δ-Lactams

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SUMMARY

The [6.5.6]-tricyclic indole δ-lactam represents a common key intermediate for the synthesis of a broad variety of structurally intriguing indole alkaloids. The development of a method for the versatile and straightforward construction of such structural motif is of great importance for potential synthetic applications. Herein, we present a co-ligand-prompted Pd-catalyzed 6-exo-trig intramolecular cyclization of indolyl amides via the aerobic oxidative Heck cross-coupling. The method provided a general and efficient way for the construction of [6.5.6]-tricyclic indole δ-lactams. A mechanistic study suggests that a Pd(I)/Pd(III) catalytic cycle should be responsible for effective coupling, which represents a mechanistically alternative pathway when compared with the Pd(0)/Pd(II) cycle proposed for other related coupling reactions.

INTRODUCTION

The leuconoxine subfamily of aspidosperma-derived monoterpene indole alkaloids (e.g., 1–8 in Figure 1) was isolated from the plants of the genus Leuconotis (Apocynaceae) (Paffenbich and Gaich, 2016; Geng et al., 2016; Tokuyama, 2015). These natural products possess a unique diaza-[5.5.6.6]-fenestrane structural motif that is extremely rare in indole natural products. The latex of the plants was used traditionally to treat worm infections and yaws diseases. Owing to their high structural complexity and interesting biological properties, these and the related natural products have attracted much attention in the synthetic community. The efficient construction of the δ-lactam-containing (Figure 1, highlighted in red) ring-fused system has been the key issue of intensive synthetic efforts. The reported methods include free radical-induced cyclization (Magolan and Kerr, 2006; Magolan et al., 2008; Biechy and Zard, 2009; Zhu et al., 2015; Yu et al., 2016a, 2016b), Heck cross-coupling (Umehara et al., 2014; Iwama et al., 2013), and Friedel-Crafts reactions (Feng et al., 2015; Lv et al., 2014; Zhong et al., 2012, 2014, 2015; Liang et al., 2016; Zheng et al., 2013, 2015; Nakajima et al., 2010; Higuchi et al., 2015; Li et al., 2015) or oxidative amidation of alcohol (Paffenbich and Gaich, 2013) at C20−C21; the amidation of ester (Xu et al., 2013, 2015; Nakajima et al., 2010; Higuchi et al., 2015; Li et al., 2015) or oxidative amidation of alcohol (Paffenbich and Gaich, 2013) at N1−C2; and the transannular cyclization (Yang et al., 2014a, 2014b; Dagoneau et al., 2016) of an aryl amide with ketone functionality via N1−C21.

Having experienced the synthetic studies on tronoharine (Zhong et al., 2015) and mersicarpine indole alkaloids (Zhong et al., 2012, 2014), we recently became interested in the leuconoxine subfamily, a class of structurally more intriguing and synthetically more challenging indole alkaloids. As mentioned, the key issue toward the efficient synthesis of this class of natural products and potential analogs with structural diversity is the establishment of a straightforward method for effective construction of the common intermediate [6.5.6]-tricyclic indole δ-lactam. To this end, we conceived of a transition-metal-catalyzed oxidative Heck coupling (i.e., dual dehydrogenative coupling) protocol, which, conceptually and strategically, would provide an ideal platform for accessing such structural skeletons as witnessed by the recent great advance in transition-metal-catalyzed oxidative C–C bonding formation (Shi et al., 2011; Liu et al., 2011, 2015). In fact, there has been rapidly growing interest in oxidative Heck-type coupling of indole and other classes of substrates (Abbiati et al., 2003; Ferreira and Stoltz, 2003; Ferreira et al., 2008; Schiﬀner et al., 2010; Pintori and Greaney, 2011; Kandukuri et al., 2012; Kandukuri and Oestreicher, 2012; Broggini et al., 2012; Yang et al., 2014a, 2014b; Ikemoto et al., 2014; Gao et al., 2016; Meng et al., 2013, 2014), and the great advantage of the related reaction in natural product synthesis has been demonstrated early by the synthesis of a few indole-type natural products (Baran et al., 2003; Meng et al., 2015; Lu et al., 2014).

However, surprisingly, a literature survey showed that among the related reports, methods for the construction of six-membered cycles through oxidative Heck coupling at indole N1 and C2 have been rarely...
reported. Of the very few relevant examples investigated so far, the attempted oxidative Heck coupling of \(9\) \((n = 2)\) afforded the 6-exo-trig product \(11\) only in poor yield under a variety of conditions (Schiffner et al., 2010) (Figure 2A). More interestingly, it was found that the substrate \(10\) \((n = 1)\) with one carbon less than \(9\) produced exclusively the 5-exo-trig product \(12\) in moderate to good yields without, however, the observation of the sterically more favored six-membered 6-endo-trig isomers \(12a\) and \(12b\) (Ferreira et al., 2008; Schiffner et al., 2010). Apparently, these unsuccessful precedents imply that the construction of six-membered cycles at indole \(N_1\) and \(C_2\) by means of oxidative Heck coupling is exceptionally challenging.

Nevertheless, we decided to investigate this challenging reaction because of the great potential utility in versatile synthesis of various indole natural products such as shown in Figure 1. In our study, a directing group-oriented oxidative coupling of indole derivatives \(13\) was devised (Figure 2B). Conceptually, we envisaged that the presence of a heteroatom-containing side chain tethered to indole \(C_3\) may serve to act as a directing group to prompt the \(C/\text{C}0\)H activation through a geometrically favored intermediate \(14\), and ultimately, driving the coupling reaction with the olefin functionality to afford the \(\delta\)-lactam \(15\). On the other hand, the side chain in the cross-coupled products, without the need to remove, can be further manipulated at the late stage as a latent functionality toward the synthesis of various indole natural products and their analogs. Taking together these advantages, the protocol proposed herein would provide not only a strategically distinctive but also a methodologically much more efficient tool for the construction of indole \(\delta\)-lactams. The successful demonstration of the devised oxidative Heck cross-coupling protocol and mechanistic study will be presented herein.

### RESULTS AND DISCUSSION

#### The Development of Method for Oxidative Heck Coupling

Optimization of the reaction parameters was carried out using indole derivative \(13a\) as a model compound (Table 1). Based on the conditions reported by Stoltz (Ferreira and Stoltz, 2003; Ferreira et al., 2008) and Oestreich (Schiffner et al., 2010; Kandukuri et al., 2012), a broad array of pyridine ligands was examined with the presence of different palladium catalysts in our initial screening because it was suggested that the basicity of pyridine nitrogen was critical to the catalytic activity of metal catalysts owing to their different coordination properties. Disappointingly, an exhaustive optimization of the reaction conditions by means of a free combination of various reaction parameters including ligands, catalysts, oxidants, additives, temperature, and solvents showed that the coupling reaction was almost ineffective in most cases (data not shown). Only a few sets of conditions could afford the desired product \(15a\) in low to moderate yields with 43% as the best outcome in the presence of \(L_1\) ligand (Table 1, entry 1). In addition, \(L_2\) afforded \(15a\) at any yield similar to \(L_1\) (entry 2). In contrast, only a trace amount of product was detected for bidentate \(L_3\) (entry 3).
The dramatic effect of the structural nature of ligands on this reaction prompted us to turn our attention to search an alternative catalyst system or ligand. Accordingly, we shifted our focus to a phosphinamide-based palladacycle catalyst, which was developed previously by our group (Du et al., 2015; Guan et al., 2014). A supportive clue, albeit not tightly related with the proposed Heck-type reaction, that encouraged us to inspect this catalyst herein is that exhibited extremely high catalytic activity for mild Suzuki coupling of a broad range of arene (pseudo)halides (Wu et al., 2015, 2018; Cao et al., 2018). To our delight, the use of as catalyst did improve substantially the yield of to 72% (entry 4). In addition, it was found that the presence of O₂ was essential because the yield was markedly decreased under air atmosphere (entries 4 versus 5). A brief screening of solvents showed that mesitylene was superior to others (entries 4 versus 6–10). Interestingly, a further comparison revealed that the direct addition of Pd(OAc)₂ and phosphinamide ligand to the reaction system gave the product in identical yield to that of utilizing the pre-formed palladium complex (entries 4 versus 11). Finally, an orthogonal evaluation on pyridine and phosphinamide ligands (entries 11–16) demonstrated that an appropriate combination of a catalytic amount of L₁ and L₅ (molar ratio = 4:1) was optimal, affording in 76% yield (entry 14). Notably, the reaction could be reliably performed on gram scale in 70% yield (entry 14). Of note is that when the ligands L₁ and L₅ were used independently, the reaction efficiency was dramatically diminished (entries 1 and 17). Our further control experiments showed that when the pre-formed palladacycle was used, L₄ was dissociated from palladacycle to recover the ligand in quantitative yield after the reaction was completed. On the other hand, a comparison study demonstrated that palladacycle did not form in situ from Pd(OAc)₂ and L₄ either in the presence or absence of substrate 13a. These results coupled with the detection of free L₄ by HRMS (see Figure S5) in the reaction system imply that L₄ may serve to act as a co-ligand rather than the formation of palladacycle with Pd(OAc)₂ in the reaction system. In the case of using palladacycle, the protonolysis of C–Pd bond may occur to release the phosphinamide ligand. Thus the effective coupling by using mixed ligands is presumably due to the well-balanced basicity of the two ligands (Ferreira et al., 2008; Kandukuri et al., 2012).

Figure 2. Oxidative Heck coupling at indole N₁ and C₂
Reported (A) and our proposed (B) oxidative Heck coupling.
With the optimized conditions established, we then examined the substrate scope (Table 2). Various substrates modified by electron-neutral (15a), electron-donating (15b), and electron-withdrawing (15c–15e) substituents at different positions in indole ring were well tolerated. In addition, different substituents such as Me (15f), Et (15g–15n), and ester (15g) at olefin terminal were also competent. Importantly, a broad compatibility was also observed for the functional groups at the indole C3 side chain, including a range of amino functionalities protected by MeOC(O) (15a–15g, 15i), Cbz (15h), Ts (15i), Tf (15j), hydroxy group (15l), and ester groups (15m and 15n). This would be an important advantage for a late-stage flexible manipulation when synthesis of indole alkaloids and potential analogs with structural diversity is under consideration. Of note is that substrates having a simple Me or H at indole C3 were intact.

Table 1. Optimization of the Reaction Conditions

| Entry | Catalyst (10 mol %) | Ligand (mol %) | Solvent | Yield (%) |
|-------|---------------------|----------------|---------|-----------|
| 1     | Pd(OAc)2            | L1 (40)        | Mesitylene | 43        |
| 2     | Pd(OAc)2            | L2 (40)        | Mesitylene | 40        |
| 3     | Pd(OAc)2            | L3 (40)        | Mesitylene | Trace     |
| 4     | 16                  | L1 (40)        | Mesitylene | 72        |
| 5     | 16                  | L1 (40)        | Mesitylene | 30        |
| 6     | 16                  | L1 (40)        | tBuO₂H | 54        |
| 7     | 16                  | L1 (40)        | DMF     | 45        |
| 8     | 16                  | L1 (40)        | DMSO    | 30        |
| 9     | 16                  | L1 (40)        | p-Cyrene | 23        |
| 10    | 16                  | L1 (40)        | PhCl    | Trace     |
| 11    | Pd(OAc)₂            | L₅/L₄ (40/10)  | Mesitylene | 72        |
| 12    | Pd(OAc)₂            | L₅/L₄ (40/10)  | Mesitylene | 74        |
| 13    | Pd(OAc)₂            | L₅/L₄ (40/10)  | Mesitylene | Trace     |
| 14    | Pd(OAc)₂            | L₅/L₄ (40/10)  | Mesitylene | 76 (70)   |
| 15    | Pd(OAc)₂            | L₅/L₄ (40/10)  | Mesitylene | 74        |
| 16    | Pd(OAc)₂            | L₅/L₆ (40/10)  | Mesitylene | 42        |
| 17    | Pd(OAc)₂            | L₆ (10)        | Mesitylene | 20        |

With the optimized conditions established, we then examined the substrate scope (Table 2). Various substrates modified by electron-neutral (15a), electron-donating (15b), and electron-withdrawing (15c–15e) substituents at different positions in indole ring were well tolerated. In addition, different substituents such as Me (15f), Et (15a–15e, 15h–15n), and ester (15g) at olefin terminal were also competent. Importantly, a broad compatibility was also observed for the functional groups at the indole C3 side chain, including a range of amino functionalities protected by MeOC(O) (15a–15g, 15k), Cbz (15h), Ts (15i), Tf (15j), hydroxy group (15l), and ester groups (15m and 15n). This would be an important advantage for a late-stage flexible manipulation when synthesis of indole alkaloids and potential analogs with structural diversity is under consideration. Of note is that substrates having a simple Me or H at indole C3 were intact.
These results are in good agreement with our hypothesis that the presence of a heteroatom-containing directing group at C3 is essential for effective coupling (vide supra). Here, an interesting observation was that except for 15g whose β-hydride elimination took place at the tertiary carbon, the β-hydride elimination for other reactions proceeded exclusively at the secondary or primary carbon to produce the thermodynamically less stable products with non-conjugated double bonds. The outcomes could be rationally explained based on the C‒H activation mechanism and coordination effect at C3 side chain (see mechanistic study vide infra).

Next, we expanded the methodology to the construction of quaternary carbon center and bridged cycle. Gratifyingly, the reaction proceeded smoothly to give both types of products in high yields under the standard conditions (Table 3). As for the construction of quaternary carbon center, the substrates decorated by various substituents in indole ring as well as at the C3 side chain and olefinic positions displayed good viability (15q–15x). Notably, the reaction could be uneventfully performed on gram scale as exemplified by the synthesis of 15w bearing an Et group at the quaternary carbon center, which appears as a common group in a number of related natural products (Figure 1, 1–8). Concerning the construction of aza[3.3.1]-bridged cycle, the substrates tethered with an aminoethyl group at C3 position were less effective under the standard conditions. For instance, a Tf-protected substrate afforded the product 15y in 21% yield containing a minor amount of inseparable by-products. However, substrates bearing a hydroxyethyl group reacted facilely. The electron-neutral (15z and 15aa), electron-donating (15ab), and electron-withdrawing (15ac) groups in indole cycle had little effect on the reactivity. The reaction could also be reliably performed on large scale (15b). As the aza[3.3.1]-bridged skeleton exists in a range of cipriani-type indole natural products (Kam et al., 1992, 1993, 2000, 2004), the method would also be potentially useful in the synthesis of these natural products.

Table 2. Substrate Scope for the Construction of Tertiary Carbon Center

| 15b, R = OMe, 16 h, 130°C, 62% | 15c, R = CI, 16 h, 130°C, 70% | 15d, R = F, 16 h, 130°C, 71% | 15e, R = F, 16 h, 130°C, 69% |
| 15f, 130°C, 16 h, 66% | 15g, R = H, 130°C, 25 h, 56% | 15h, R = Cbz, 16 h, 130°C, 57% | 15i, R = Ts, 24 h, 130°C, 47% | 15j, R = Tf, 4 h, 130°C, 78% |
| 15k, R = NHCO2Me, 16 h, 130°C, 79% | 15l, R = CH2OH, 9 h, 100°C, 72% | 15m, R = CO2Me, 16 h, 130°C, 80% | 15n, R = CO2Me, 16 h, 160°C, 64% | 15o, R = Me, 0% | 15p, R = H, 0% |
of related natural products. The structures of both types of compounds were confirmed by NMR and HRMS, and were further clarified by the single X-ray crystallography of 15q (CCDC 1866425) and 15ac (CCDC 1866424).

**Mechanistic Study of Oxidative Heck Coupling**

Having verified the broad generality of the methodology, we investigated the reaction mechanism. First, three control experiments by using 13a, deuterated 13a-D (ca. 92% D, see Figure S2), and a 1:1 mixture of 13a and 13a-D as substrates were carried out to confirm whether the C–H bond or alkene activation is involved in the catalytic cycle. Surprisingly, almost identical yields were obtained for the three reactions under standard conditions, indicating no isotopic effect. However, a further analysis on the recovered starting materials revealed that the undeuterated 13a was the major component for the reaction.

**Table 3. Substrate Scope for the Construction of Quaternary Carbon and Aza[3.3.1]-Bridged Cycle**

| Conditions: 13 (100 mg), Pd(OAc)$_2$ (10 mol %), L$_1$ (40 mol %), L$_2$ (10 mol %), O$_2$ (balloon), and tBuCO$_2$H (30.0 equiv.) in mesitylene (0.1 mol/L); isolated yield. |
|---|
| 15q, R = H, 7.5 h, 130ºC, 69% |
| 15s, R = F, 5 h, 130ºC, 66% |
| 15v, 7 h, 95ºC, 70% |
| 15w, 7 h, 95ºC, 88%, (1.27 g) |
| 15x, 12 h, 95ºC, 73% |
| 15y, R = H, X = NHTf, 16 h, 130ºC, 21% |
| 15z, R = H, X = OH, 10 h, 95ºC, 72% (0.74 g) |
| 15aa, R = Me, X = OH, 10 h, 95ºC, 71% |
| 15ab, R = OMe, X = OH, 10 h, 95ºC, 68% |
| 15ac, R = F, X = OH, 10 h, 95ºC, 68% |

15q (X-ray)  CCDC 1866425
15ac (X-ray)  CCDC 1866424
using 13a-D as substrate. The serendipitous result indicates that H/D exchange at indole C2 may take place during the reaction, which should interrupt the actual observation of isotopic effect. To clarify this point, further detailed control experiments were performed. Accordingly, treatment of the deuterated substrate 13a-D (Scheme 1, Equation 1) under the standard conditions followed by the quantitative NMR and HRMS analyses of the recovered starting material revealed that H/D interchange took place at indole C2 position (see Figure S3). Moreover, the ratio of H/D interchange increases with the elongation of reaction time (i.e., H/D = ca. 1:1 for 1 h, and ca. 7:3 for 3 h). Alternatively, treatment of undeuterated 13a under conditions identical to that of Equation 1 but just replacing tBuCO2H with tBuCO2D (ca. 90% D) resulted in an H/D = ca. 7:3 and 6:4 of the recovered 13a (Scheme 1, Equation 2) after 1 h and 3 h, respectively (See Figure S4). The orthogonal experiments clearly exemplified that significant H/D exchange between the indole C2–H of the substrate and tBuCO2H takes place.

Thus, to avoid the interruption of proton scrambling between the substrate and tBuCO2H in the study of kinetic isotopic effect (KIE), we designed two experiments. One was performed using 13a as substrate under standard conditions and the other one was carried out using deuterated 13a-D as substrate but replacing tBuCO2H with tBuCO2D (Scheme 1, Equation 3). As slow decomposition of product 15a was detected (Ferreira et al., 2008), the time-dependent conversion of substrates rather than the formation of product was monitored by high-performance liquid chromatography (Figure 3, left and see also Table S1). The KIE was deduced based on the conversion of substrates versus the reaction time (Figure 3, right). The observation of a large primary KIE with $k_{H}/k_{D} = \text{ca. 5.5:1}$ (average value of two experiments) indicates that C–H activation should be the rate-determining step of the oxidative Heck coupling.

Next, we investigated the redox cycle of palladium catalyst. Although a Pd(0)/Pd(II) cycle was tentatively proposed in the literature (Ferreira et al., 2008; Kandukuri et al., 2012) for the five-membered cyclization reaction, we envisioned that our 6-exo-trig annulation should undergo an alternative pathway based on the experimental phenomena, such as color change of the reaction system (vide infra). We used HRMS to detect any possible Pd-containing species. Four strong peaks and several weak ones related with palladium complexes were captured for the reaction under oxygen atmosphere (see Figure S5). The strong peaks at $m/z = 365.9951$ and 385.0353 can be assigned to a Pd(III) species with a formula of

\[ \text{Scheme 1. The Control Experiments of H/D Exchange (Equations 1 and 2) and Kinetic Isotopic Effect (Equation 3)} \]
Pd(III) (MeCO₂⁻)₂(tBuCO₂⁻)(H₂O)Na⁺ (calculated for C₉H₁₇NaO₇Pd⁺: m/z 365.9901) and a Pd (II) complex [Pd(II) (tBuCO₂⁻)L₁(MeCN)] (calculated for C₁₄H₁₉N₂O₄Pd⁺: m/z 385.0374), respectively. In addition, all the weak peaks can also be well assigned. However, the other two strong peaks at m/z = 468.0598 and 481.0558 cannot be rationally assigned because either the Pd (III) complexes [Pd (III) (MeCO₂⁻)₂(tBuCO₂⁻)(tBuCO₂H)(H₂O)Na⁺] (calculated for C₁₄H₂₇NaO₉Pd⁺: m/z 468.0582) and [Pd (III) (MeCO₂⁻)₂(tBuCO₂⁻)(H₂O)L₁] (calculated for C₁₄H₂₅NO₉Pd⁺: m/z 481.0559) or the Pd (II) complexes [Pd (II) (tBuCO₂⁻)₂L₁Na⁺] (calculated for C₁₇H₂₅NNaO₆Pd⁺: m/z 468.0609) and [Pd (II) (tBuCO₂⁻)(L₁)₂] (calculated for C₁₉H₂₃N₂O₆Pd⁺: m/z 481.0586) are possible. For a further clarification, we inspected the reaction under argon atmosphere. Three signals were detected involving a strong signal of Pd (II) complex at m/z = 385.0362. In addition, the two peaks at m/z = 468.0609 and 481.0589 as those that appeared under oxygen atmosphere were also observed. However, they were remarkably much weaker than those under oxygen atmosphere. Thus, a comparison of the HRMS analysis under different conditions implies that most probably the two signals should belong to Pd (III) complexes. The detection of these signals under argon atmosphere may be resulted from the oxidation of some minor oxidants involved in the reaction system. All the above experiments displayed good reproducibility.

Further support for the generation of Pd(III) complexes is the apparent color change of the reaction solution. Namely, the color changed from pale yellow to deep red-brown for the solution under oxygen atmosphere (see Figures S24 and S25), which indicates typically the generation of Pd(III) ion according to the literature (Powers and Ritter, 2009; Powers et al., 2009). In comparison, the Pd black that was precipitated out with the pale yellow solution almost remained unchanged for the reaction under argon atmosphere. Moreover, it was found that when the reaction was performed under argon atmosphere in the presence of stoichiometric amount Pd(OAc)₂ and the corresponding ratio of ligands, 15a was obtained only in lower than 20% yield. These results clearly suggest that a Pd(0)/Pd(II) cycle cannot be entirely ruled out as a minor catalytic process.

Thus, through an extensive mechanistic study, we could propose a catalytic cycle for the 6-exo-trig annulation. Namely, oxidation of Pd(II) by oxygen generates the Pd(III) complexes, which then form an infant transition state I with substrate 13 under the direction of the heteroatom-containing C₃ side chain (Figure 4). Subsequently, C–H bond activation proceeds to produce the intermediate II. Migratory syn insertion followed by syn β-hydride elimination via III delivered the product 15. The sensitive Pd(II) was reoxidized to Pd(III) via the more stable Pd(II) to bring the reaction into the next cycle. Based on the proposed mechanism, the syn insertion results in an anti-orientated R¹ group and Pd(III) ion. Subsequently, the Pd(III) coordinates with the heteroatom at the C₃ side chain to form a closed intermediate III, which prevents the elimination of anti-β-hydride at the tertiary carbon (for R¹ = H). As a result, the products with non-conjugated double bonds as shown in Table 2 are formed exclusively. As an exceptional example, the production of 15g (Table 2) should undergo epimerization via an oxa-π-allylpalladium intermediate IV to form V, and ultimately, allowing for anti-β-hydride elimination at the tertiary carbon (Kandukuri et al., 2012).
Limitations of the Study
A brief examination showed that the present method is not compatible for the construction of seven-membered indole lactams from the corresponding indolyl 5-enamide.

Conclusion
Targeted toward the efficient and collective synthesis of an array of structurally intriguing indole alkaloids as well as their potential analogs, we have designed and developed a Pd-catalyzed aerobic oxidative Heck coupling reaction that could achieve the previously challenging 6-exo-trig annulation using indolyl amides as substrates. The method provides a straightforward pathway for accessing [6.5.6]-tricyclic indole lactams, which may serve as a common intermediate for the synthesis of various indole alkaloids and their analogs. The method also displays a broad generality and could be reliably performed over gram scale as demonstrated by several different types of substrates. The keys for the successful realization of the coupling reaction are highlighted by a mechanism-based design of incorporating a heteroatom-containing directing group at indole C3 and the utilization of phosphinamide compounds as novel co-ligands. Extensive experimental results revealed that C–H activation should be the rate-determining step and that Pd(III) complexes may be responsible for effective reaction. This catalytic cycle differs from the previously proposed Pd(II)/Pd(IV) cycle for the construction of five-membered rings and would be important for the mechanism-based de novo design of relevant reactions. We believe that the method could find extensive applications for the flexible synthesis of various indole alkaloids. The investigations into the enantioselective version of the cross-coupling reaction, as well as its application in the collective synthesis of relevant natural products, are the focus of our future work.

METHODS
All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION
Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2019.06.037.

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AUTHOR CONTRIBUTIONS
F.-S.H. conceived the synthetic strategy, directed the project, and wrote the manuscript. F.-S.H. and J.Z. discussed the experimental results and commented on the manuscript. J.Z. conducted the experimental works.

DECLARATION OF INTERESTS
The authors declare no competing interests.

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Supplemental Information

Pd-Catalyzed Aerobic Oxidative Heck Cross-Coupling for the Straightforward Construction of Indole $\delta$-Lactams

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Transparent Methods

General procedure for the synthesis of reaction substrates 13 (Figure S1) and oxidative coupling (Figure S23), the theoretical and experimental isotopic distribution of Pd complexes as detected by high resolution mass spectrometer (Figures S6-22), and copies of NMR spectra of reaction substrates and products (Figures S26-81)

1. General Information
2. General procedure for the synthesis of indolyl amides
3. General procedure for oxidative C–H Heck cross-coupling
4. Characterization data of substrates and products
5. Mechanistic study
   5.1 Isotopic effect
   5.2 HRMS analysis of the reaction mixture
   5.3 The color changes under oxygen and argon atmosphere
6. X-Ray data of 15q and 15ac
7. Copies of NMR spectra of substrates and coupling products
8. Supplemental references
1. General information:

Unless otherwise noted, all commercial reagents were used without further purification. Anhydrous solvents were distilled according to standard methods. Analytical thin layer chromatography (TLC) was performed on 0.2 mm thick silica gel 60-F254 plates (Merck). Chromatographic purification of products was accomplished using forced-flow chromatography on 230-400 mesh silica gel. The $^1$H NMR spectra were recorded at 300 MHz or 400 MHz (Bruker AV) and the $^{13}$C NMR spectra were recorded at 75, 101, or 126 MHz with TMS as internal standard. All chemical shifts are given in ppm. All coupling constants ($J$ values) were reported in Hertz (Hz). High resolution mass spectra (HRMS) were obtained on an IonSpec Ultima 7.0 T FT-ICR-MS (IonSpec, USA) with a Waters Z-spray source. X-ray crystallographic analysis was performed on a Bruker D8 ADVANCE diffractometer with MoKα radiation ($\lambda = 0.71073$).

2. General procedure for the synthesis of indolyl amides (Hartung et al., 2003)

![Figure S1. Synthesis of substrates 13, related to Table 1-3](image)

To a solution of A1 and NaH in DMF was added A2 (1.5 equiv) dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 10 min. To this mixture was added aqueous NH₄Cl. The reaction mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed successively with H₂O (4 × 50 mL) and brine (50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude reaction mixture was purified by silica-gel column chromatography.

3. General procedure for oxidative C–H Heck cross-coupling

To a dried Schlenck tube equipped with a magnetic bar was charged with 13, Pd(OAc)$_2$ (10 mol%), methyl nicotinate (L₁, 40 mol%), phosphinamide L₅ (10 mol %), and tBuCO₂H (30 equiv.). The reaction tube was evacuated and back-filled with O₂ for three times. Then mesitylene was added (0.1mol/L) and the reaction mixture was stirred at the optimized temperature until the substrates 13 had disappeared as monitored by TLC. Purification of the reaction mixture by column chromatography on silica gel provided the desired product 15.
4. Characterization data of substrates and products

**13a** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 7/1) to give a white solid in 80% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.44 (d, $J = 8.1$ Hz, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.40–7.23 (m, 3H), 5.64–5.43 (m, 2H), 5.05 (s, 1H), 3.67 (s, 3H), 3.52 (q, $J = 6.8$ Hz, 2H), 2.89 (m, 4H), 2.46 (q, $J = 7.1$ Hz, 2H), 2.03–1.93 (m, 2H), 0.97 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 170.79, 157.16, 136.06, 133.85, 130.30, 126.79, 125.40, 123.54, 122.11, 119.41, 118.79, 116.84, 52.16, 40.51, 35.97, 27.50, 25.80, 25.60, 13.79. HRMS Calcd for C$_{19}$H$_{24}$N$_2$O$_3$ ([M+Na]$^+$): 351.1679; Found: 351.1676.

**13a-D** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 7/1) to give a white solid in 80% yield. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 8.34 (dd, $J = 7.4$, 1.6 Hz, 1H), 7.74 (s, 0.15H), 7.65–7.56 (m, 1H), 7.43–7.23 (m, 3H), 5.63–5.44 (m, 2H), 3.53 (s, 3H), 3.30 (d, $J = 6.8$ Hz, 2H), 3.05 (t, $J = 7.4$ Hz, 2H), 2.80 (t, $J = 7.2$ Hz, 2H), 2.38 (q, $J = 6.8$ Hz, 2H), 2.03–1.91 (m, 2H), 0.91 (t, $J = 7.4$ Hz, 3H). HRMS Calcd for C$_{19}$H$_{23}$DN$_2$O$_3$ ([M+Na]$^+$): 352.1742; Found: 352.1739.

**13b** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 7/1) to give a white solid in 60% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.34 (d, $J = 8.9$ Hz, 1H), 7.27 (s, 1H), 6.97 (s, 2H), 5.63–5.44 (m, 2H), 4.84 (s, 1H), 3.86 (s, 3H), 3.68 (s, 3H), 3.52 (q, $J = 6.8$ Hz, 2H), 2.89 (q, $J = 7.0$, 6.4 Hz, 4H), 2.50 (t, $J = 7.1$ Hz, 2H), 2.09–1.95 (m, 2H), 1.02–0.89 (m, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.46, 157.16, 156.50, 133.89, 131.36, 130.80, 126.86, 122.79, 119.24, 117.71, 113.56, 101.83, 55.80, 52.26, 40.51, 35.79, 27.64, 25.87, 25.6, 13.84. HRMS Calcd for C$_{21}$H$_{27}$N$_2$O$_4$ ([M+H]$^+$): 359.1965; Found: 359.1968.
13c was purified by column chromatography on silica gel (petroleum ether/EtOAc = 6/1) to give a yellow solid in 65% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.38 (d, $J = 8.8$ Hz, 1H), 7.48 (s, 1H), 7.33–7.23 (m, 2H), 5.66–5.42 (m, 2H), 4.82 (s, 1H), 3.68 (s, 3H), 3.51 (d, $J = 6.3$ Hz, 2H), 2.90 (dt, $J = 12.5$, 7.1 Hz, 4H), 2.49 (q, $J = 6.8$ Hz, 2H), 2.06–1.96 (m, 2H), 0.96 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.73, 157.17, 134.40, 134.07, 129.14, 126.62, 125.53, 123.36, 118.85, 118.55, 117.93, 52.3, 40.49, 35.89, 27.48, 25.64 (2C), 13.81. HRMS Calcd for C$_{19}$H$_{24}$ClN$_2$O$_3$ ([M+H]$^+$): 363.1470; Found: 363.1472.

13d was purified by column chromatography on silica gel (petroleum ether/EtOAc = 6/1) to give a yellow solid in 65% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.42 (dd, $J = 9.1$, 4.7 Hz, 1H), 7.35 (s, 1H), 7.18 (d, $J = 8.8$ Hz, 1H), 7.08 (t, $J = 9.2$ Hz, 1H), 5.66–5.44 (m, 2H), 4.80 (s, 1H), 3.68 (s, 3H), 3.52 (q, $J = 6.8$ Hz, 2H), 2.99–2.84 (m, 4H), 2.52 (t, $J = 7.1$ Hz, 2H), 2.12–1.95 (m, 2H), 0.97 (t, $J = 7.5$, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.62, 159.66 (d, $J = 240.6$ Hz), 157.21, 134.00, 132.41, 131.45 (d, $J = 10.4$ Hz), 126.66, 123.59, 119.14 (d, $J = 3.4$ Hz), 117.96 (d, $J = 8.9$ Hz), 113.00 (d, $J = 24.5$ Hz), 104.56 (d, $J = 23.9$ Hz), 52.25, 40.42, 35.76, 27.52, 25.76, 25.61, 13.79. HRMS Calcd for C$_{19}$H$_{23}$FN$_2$NaO$_3$ ([M+Na]$^+$): 369.1585; Found: 369.1586.

13e was purified by column chromatography on silica gel (petroleum ether/EtOAc = 4/1) to give a yellow solid in 70% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.45 (s, 1H), 7.33 (d, $J = 7.5$ Hz, 1H), 7.26–7.17 (m, 1H), 7.17–7.03 (m, 1H), 5.67–5.41 (m, 2H), 4.82 (s, 1H), 3.68 (s, 3H), 3.51 (q, $J = 6.4$ Hz, 2H), 2.96 (dt, $J = 31.9$, 7.1 Hz, 2H), 2.51 (q, $J = 7.0$ Hz, 2H), 2.06–1.96 (m, 2H), 0.96 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.60, 157.17, 150.29 (d, $J = 252.7$ Hz), 134.84 (d, $J = 3.6$ Hz), 133.58, 126.69, 124.37, 124.27, 122.28 (d, $J = 10.6$ Hz), 118.98, 114.79 (d, $J = 3.5$ Hz), 112.33 (d, $J = 22.6$ Hz), 52.14, 40.39, 36.36, 27.89, 25.69, 25.56, 13.75. HRMS Calcd for C$_{19}$H$_{23}$FN$_2$NaO$_3$ ([M+Na]$^+$): 369.1585; Found: 369.1587.
**13f** was purified by column chromatography on silica gel (petroleum ether/acetone = 17/1) to give a yellow solid in 40% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.45 (d, $J = 8.2$ Hz, 1H), 7.54 (d, $J = 7.6$ Hz, 1H), 7.41–7.27 (m, 3H), 5.54 (t, $J = 5.2$ Hz, 2H), 4.85 (s, 1H), 3.68 (s, 3H), 3.54 (q, $J = 6.7$ Hz, 2H), 2.98–2.88 (m, 4H), 2.53–2.46 (m, 2H), 1.68 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.79, 157.24, 136.04, 130.31, 129.07, 126.71, 125.51, 122.10, 119.44, 118.80, 116.83, 52.18, 40.50, 35.87, 27.47, 25.79, 18.00. HRMS Calcd for C$_{18}$H$_{23}$N$_2$O$_3$ ([M+H]$^+$): 315.1703; Found: 315.1705.

**13g** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 4/1) to give a white solid in 70% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.44 (d, $J = 8.1$ Hz, 1H), 7.53 (d, $J = 7.6$ Hz, 1H), 7.44–7.23 (m, 3H), 6.42 (dt, $J = 11.5$, 7.2 Hz, 1H), 5.88 (dt, $J = 11.3$, 1.3 Hz, 1H), 5.05 (s, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.66 (s, 3H), 3.55 (q, $J = 6.5$ Hz, 2H), 3.20–3.00 (m, 4H), 2.93 (t, $J = 6.8$ Hz, 2H), 1.28 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.21, 166.27, 157.17, 147.56, 136.01, 130.38, 125.45, 123.63, 122.04, 121.35, 119.82, 118.81, 116.79, 60.16, 52.13, 40.31, 35.27, 25.71, 24.23, 14.28. HRMS Calcd for C$_{20}$H$_{24}$N$_2$NaO$_5$ ([M+Na]$^+$): 395.1577; Found: 395.1570.

**13h** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 15/1) to give a white solid in 70% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.45 (d, $J = 8.2$ Hz, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.43–7.27 (m, 8H), 5.68–5.40 (m, 2H), 5.11 (s, 2H), 4.96 (s, 1H), 3.55 (q, $J = 6.7$ Hz, 2H), 3.00–2.85 (m, 4H), 2.48 (q, $J = 7.0$ Hz, 2H), 2.06–1.94 (m, 2H), 0.96 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.74, 156.43, 136.53, 136.01, 133.80, 130.23, 128.55 (2C), 128.17, 128.08 (2C), 126.76, 125.38, 123.50, 122.09, 119.28, 118.75, 116.81, 66.69, 40.47, 35.90, 27.44, 25.71, 25.57, 13.77. HRMS Calcd for C$_{25}$H$_{28}$N$_2$NaO$_3$ ([M+Na]$^+$): 427.1992; Found: 427.1989.
13i was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1) to give a white solid in 77% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.43 (d, $J = 8.2$ Hz, 1H), 7.65 (d, $J = 7.8$ Hz, 2H), 7.35 (t, $J = 8.5$ Hz, 2H), 7.24–7.18 (m, 4H), 5.66–5.44 (m, 2H), 4.66 (d, $J = 6.7$ Hz, 1H), 3.31 (q, $J = 6.6$ Hz, 2H), 2.89 (t, $J = 7.1$ Hz, 4H), 2.45 (q, $J = 7.2$ Hz, 2H), 2.39 (s, 3H), 2.07–1.95 (m, $J = 7.1$ Hz, 2H), 1.02–0.93 (m, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.88, 143.48, 136.81, 136.01, 133.83, 129.87, 129.66 (2C), 126.94 (2C), 126.79, 125.37, 123.49, 122.73, 118.55, 118.28, 116.87, 42.40, 35.83, 27.42, 25.62, 25.56, 21.60, 13.81. HRMS Calcd for C$_{24}$H$_{29}$N$_2$O$_3$S ([M+H]$^+$): 425.1893; Found: 425.1896.

13k was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a pink solid in 60% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.46 (d, $J = 8.2$ Hz, 1H), 7.57 (d, $J = 7.7$ Hz, 1H), 7.45–7.28 (m, 3H), 5.66–5.50 (m, 2H), 5.46–5.35 (m, 1H), 3.68 (q, $J = 6.4$ Hz, 2H), 3.03 (t, $J = 6.5$ Hz, 2H), 2.71 (dd, $J = 8.1$, 6.9 Hz, 2H), 2.32 (q, $J = 7.1$ Hz, 2H), 2.07–1.93 (m, 2H), 0.96 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.95, 157.12, 136.21, 133.99, 129.10, 126.71, 125.67, 123.76, 122.80, 119.61, 118.99, 116.91, 52.43, 36.46, 35.96, 27.47, 25.64, 13.82. HRMS Calcd for C$_{18}$H$_{23}$N$_2$O$_3$ ([M+H]$^+$): 315.1703; Found: 315.1709.
13l was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a white solid in 90% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.47 (d, $J = 8.2$ Hz, 1H), 7.55 (dd, $J = 8.0$, 1.3 Hz, 1H), 7.42–7.27 (m, 3H), 5.54–5.45 (m, 2H), 3.96 (t, $J = 6.3$ Hz, 2H), 3.02–2.91 (m, 4H), 2.51 (q, $J = 7.1$ Hz, 2H), 2.08–1.96 (m, 2H), 0.97 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.89, 136.06, 133.89, 130.49, 126.81, 125.43, 123.55, 119.20, 118.91, 116.88, 61.87, 35.96, 28.59, 27.50, 25.64, 13.83. HRMS Calcd for C$_{17}$H$_{22}$NO$_2$ ([M+H]$^+$): 272.1645; Found: 272.1642.

13m was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to give a yellow solid in 75% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.49 (d, $J = 8.2$ Hz, 1H), 7.55 (d, $J = 9.2$ Hz, 2H), 7.45–7.30 (m, 2H), 5.45–5.64 (m, 2H), 3.76 (s, 5H), 2.99 (t, $J = 7.5$ Hz, 2H), 2.14–1.94 (m, 2H), 0.99 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.03, 170.49, 135.44, 133.39, 129.69, 126.61, 125.04, 123.23, 123.07, 118.53, 116.41, 114.38, 51.84, 35.46, 30.34, 27.09, 25.32, 13.51. HRMS Calcd for C$_{18}$H$_{22}$NO$_3$ ([M+H]$^+$): 300.1594; Found: 300.1591.

13n was purified by column chromatography on silica gel (petroleum ether/EtOAc = 8/1) to give a white solid in 80% yield. $^1$H NMR (300 MHz, CDCl$_3$) 8.49–8.46 (m, 1H), 8.19 (s, 1H), 8.17–8.13 (m, 1H), 7.46–7.35 (m, 2H), 5.70–5.43 (m, 2H), 3.96 (s, 3H), 3.04 (t, $J = 7.4$ Hz, 2H), 2.59–2.49 (m, 2H), 2.10–1.97 (m, 2H), 0.97 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.20, 164.50, 136.03, 134.32, 130.74, 127.26, 126.32, 125.96, 124.79, 121.55, 116.60, 113.59, 51.69, 35.90, 27.36, 25.62, 13.77. HRMS Calcd for C$_{17}$H$_{20}$NO$_3$ ([M+H]$^+$): 286.1438; Found: 286.1441.
13q was purified by column chromatography on silica gel (petroleum ether/EtOAc = 8/1) to give a yellow solid in 80% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.42 (d, \(J = 8.2\) Hz, 1H), 7.51 (d, \(J = 7.6\) Hz, 1H), 7.43–7.29 (m, 3H), 5.60 (t, \(J = 6.2\) Hz, 1H), 5.26 (q, \(J = 6.8\) Hz, 1H), 3.68 (q, \(J = 6.4\) Hz, 2H), 3.04 (t, \(J = 6.5\) Hz, 2H), 2.75 (t, \(J = 7.8\) Hz, 2H), 2.33 (t, \(J = 7.8\) Hz, 2H), 1.64 (s, 3H), 1.59 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.43, 136.06, 133.53, 129.83, 125.96, 124.10, 123.17, 119.94, 119.74 (q, \(J = 320\) Hz), 118.68, 117.84, 117.05, 43.79, 34.31, 33.94, 26.92, 15.90, 13.52. HRMS Calcd for C\(_{18}\)H\(_{22}\)F\(_3\)N\(_2\)O\(_3\)S ([M+H]\(^+\)): 403.1298; Found: 403.1291.

13r was purified by column chromatography on silica gel (petroleum ether/EtOAc = 8/1) to give a yellow solid in 52% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.26 (d, \(J = 8.9\) Hz, 1H), 7.21 (s, 1H), 7.02–6.91 (m, 2H), 6.10 (s, 1H), 5.20 (q, \(J = 6.8\) Hz, 1H), 3.85 (s, 3H), 3.66 (q, \(J = 6.4\) Hz, 2H), 2.98 (t, \(J = 6.3\) Hz, 2H), 2.57 (t, \(J = 7.9\) Hz, 2H), 2.20 (t, \(J = 8.0\) Hz, 2H), 1.60 (s, 3H), 1.58 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.05, 156.78, 133.57, 130.95, 130.64, 123.76, 119.79, 119.74 (q, \(J = 319\) Hz), 117.82, 117.76, 113.76, 101.80, 55.72, 43.83, 33.99 (2C), 26.95, 15.86, 13.51. HRMS Calcd for C\(_{19}\)H\(_{24}\)F\(_3\)N\(_2\)O\(_4\)S ([M+H]\(^+\)): 433.1403; Found: 433.1409.

13s was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5/1) to give a white solid in 75% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.34 (dd, \(J = 9.0, 4.7\) Hz, 1H), 7.31 (s, 1H), 7.21–6.99 (m, 2H), 5.90 (s, 1H), 5.23 (q, \(J = 5.7, 4.7\) Hz, 1H), 3.65 (t, \(J = 6.4\) Hz, 2H), 2.98 (t, \(J = 6.5\) Hz, 2H), 2.73–2.57 (m, 2H), 2.24 (t, \(J = 7.9\) Hz, 2H), 1.62 (s, 3H), 1.57 (d, \(J = 6.7\) Hz, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.16, 159.87 (d, \(J = 242.2\) Hz), 133.39, 132.43, 130.85 (d, \(J = 9.1\) Hz), 124.54, 120.15, 119.74 (q, \(J = 319\) Hz), 118.24 (d, \(J = 9.1\) Hz), 117.42 (d, \(J = 4.0\) Hz), 113.63 (d, \(J = 24.5\) Hz), 104.47 (d, \(J = 23.9\) Hz), 43.55, 34.28, 34.02, 26.81, 15.87, 13.54. HRMS Calcd for C\(_{18}\)H\(_{20}\)F\(_4\)N\(_2\)O\(_3\)NaS ([M+Na]\(^+\)): 443.1023; Found: 443.1029.
13t was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc = 10/1) to give a white solid in 75% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.41 (d, $J = 8.1$ Hz, 1H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.30 (d, $J = 9.6$ Hz, 2H), 5.66 (s, 1H), 5.21 (q, $J = 6.5$ Hz, 1H), 3.68 (q, $J = 6.3$ Hz, 2H), 3.03 (t, $J = 6.4$ Hz, 2H), 2.75 – 2.63 (m, 2H), 2.31 (d, $J = 7.6$ Hz, 2H), 2.06 (q, $J = 7.5$ Hz, 2H), 1.59 (d, $J = 8.2$ Hz, 3H), 0.99 (t, $J = 7.6$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.38, 139.71, 136.16, 129.76, 125.97, 124.04, 123.09, 119.83 (q, $J = 321$ Hz), 119.28, 118.62, 117.66, 117.11, 43.82, 34.68, 30.97, 26.88, 23.13, 13.16, 12.92. HRMS Calcd for C$_{19}$H$_{23}$F$_3$N$_2$NaO$_3$S ([M+Na]$^+$): 439.1274; Found: 439.1281.

13u was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a white solid in 80% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.46 (d, $J = 8.1$ Hz, 1H), 7.55 (dd, $J = 8.0$, 1.3 Hz, 1H), 7.40–7.28 (m, 3H), 5.31 (q, $J = 6.7$ Hz, 1H), 3.96 (q, $J = 6.0$ Hz, 2H), 3.05–2.95 (m, 4H), 2.50 (t, $J = 7.9$ Hz, 2H), 1.69 (s, 3H), 1.63–1.58 (d, $J = 6.6$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.17, 136.11, 133.91, 130.48, 125.44, 123.55, 122.53, 119.78, 119.18, 118.89, 116.91, 61.90, 34.76, 34.20, 28.60, 16.00, 13.55. HRMS Calcd for C$_{17}$H$_{22}$NO$_2$ ([M+H]$^+$): 272.1645; Found: 272.1641.

13v was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a light-yellow solid in 79% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.46 (d, $J = 8.1$ Hz, 1H), 7.54 (d, $J = 7.6$ Hz, 1H), 7.42–7.27 (m, 3H), 5.17 (t, $J = 7.1$ Hz, 1H), 3.95 (t, $J = 6.1$ Hz, 2H), 3.00–2.93 (m, 4H), 2.56–2.43 (m, 2H), 2.13–1.98 (m, 3H), 1.64 (s, 1H), 1.01 (t, $J = 7.5$ Hz, 3H), 0.95 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.25, 138.62, 136.14, 130.48, 127.17, 125.46, 123.55, 122.58, 119.13, 118.90, 116.94, 61.94, 35.04, 31.08, 28.62, 23.44, 20.99, 14.72, 13.46. HRMS Calcd for C$_{19}$H$_{25}$NNaO$_2$ ([M+Na]$^+$): 322.1778; Found: 322.1781.
13w was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a white solid in 80% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.46 (d, $J = 8.2$ Hz, 1H), 7.55 (dd, $J = 8.1$, 1.3 Hz, 1H), 7.43–7.23 (m, 3H), 5.26 (q, $J = 6.7$ Hz, 1H), 3.96 (t, $J = 6.3$ Hz, 2H), 3.10–2.91 (m, 4H), 2.52–2.48 (m, 2H), 2.11 (q, $J = 7.6$ Hz, 2H), 1.62 (d, $J = 6.9$ Hz, 3H), 1.01 (t, $J = 7.6$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.24, 140.03, 136.17, 130.48, 125.50, 123.57, 122.55, 119.14, 118.91, 116.96, 61.96, 35.02, 31.14, 28.62, 23.19, 13.19, 12.96. HRMS Calcd for C$_{18}$H$_{24}$NO$_2$ ([M+H]$^+$): 286.1802; Found: 286.1806.

13x was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5/1) to give a yellow solid in 69% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.45 (d, $J = 8.0$ Hz, 1H), 7.54 (d, $J = 7.6$ Hz, 1H), 7.38–7.28 (m, 3H), 5.15 (t, $J = 7.1$ Hz, 1H), 3.94 (t, $J = 6.2$ Hz, 2H), 3.35–3.31 (m, 5H), 2.99–2.90 (m, 4H), 2.49 (t, $J = 8.1$ Hz, 2H), 2.13–2.04 (m, 4H), 1.93 (s, 1H), 1.67–1.54 (m, 2H), 1.01 (t, $J = 7.6$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.18, 139.80, 136.12, 130.51, 125.44, 124.65, 123.55, 122.55, 119.24, 118.90, 116.92, 72.28, 61.88, 58.61, 34.95, 31.15, 29.85, 28.62, 24.18, 23.40, 13.32. HRMS Calcd for C$_{21}$H$_{29}$NNaO$_3$ ([M+Na]$^+$): 366.2040; Found: 366.2036.

13y was purified by column chromatography on silica gel (petroleum ether/EtOAc = 7/1) to give a white solid in 78% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.49 (d, $J = 8.2$ Hz, 1H), 7.51 (d, $J = 7.7$ Hz, 1H), 7.46–7.27 (m, 3H), 5.77 (s, 2H), 5.14 (t, $J = 6.2$ Hz, 1H), 3.67 (q, $J = 6.6$ Hz, 2H), 3.19 (td, $J = 10.7$, 5.3, 2.9 Hz, 1H), 3.05 (t, $J = 6.7$ Hz, 2H), 2.54–2.37 (m, 1H), 2.35–2.17 (m, 3H), 2.04–1.76 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.84, 136.09, 129.84, 126.74, 125.79, 124.86, 123.90, 122.86, 119.75 (q, $J = 319.56$ Hz), 118.85, 117.87, 117.03, 43.68, 39.69, 28.04, 26.60, 25.60, 24.57. HRMS Calcd for C$_{18}$H$_{19}$F$_3$N$_2$NaO$_3$S ([M+Na]$^+$): 423.0961; Found: 423.0947.
13z was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a white solid in 80% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.50 (d, \(J = 8.1\) Hz, 1H), 7.54 (d, \(J = 6.6, 1H\)), 7.39–7.25 (m, 3H), 5.77 (d, \(J = 2.6\) Hz, 2H), 3.94 (t, \(J = 6.4\) Hz, 2H), 3.32–3.20 (m, 1H), 2.97 (t, \(J = 6.4\) Hz, 2H), 2.50–1.85 (m, 6H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 174.51, 136.00, 130.48, 126.62, 125.29, 125.03, 123.46, 122.25, 119.30, 118.72, 116.90, 61.65, 39.57, 28.39, 28.07, 25.67, 24.59. HRMS Calcd for C\(_{17}\)H\(_{19}\)NNaO\(_2\) ([M+Na\(^+\)]: 292.1308; Found: 292.1312.

13aa was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a white solid in 75% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.38 (d, \(J = 8.5\) Hz, 1H), 7.37 (d, \(J = 11.1\) Hz, 2H), 7.31–7.16 (m, 2H), 5.80 (d, \(J = 2.5\) Hz, 2H), 3.97 (t, \(J = 6.4\) Hz, 2H), 3.32–3.20 (m, 1H), 2.99 (t, \(J = 6.3\) Hz, 2H), 2.48 (s, 3H), 2.40–1.53 (m, 6H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 174.34, 134.41, 133.25, 130.74, 126.79, 125.28, 122.51, 119.04, 118.98, 118.81, 116.77, 61.94, 39.70, 28.61, 28.25, 25.88, 24.80, 21.56. HRMS Calcd for C\(_{18}\)H\(_{21}\)NNaO\(_2\) ([M+Na\(^+\)]: 306.1465; Found: 306.1469.

13ab was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a white solid in 60% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.39 (d, \(J = 8.8\) Hz, 1H), 7.38 (s, 1H), 6.99 (s, 1H), 6.95 (d, \(J = 3.2\) Hz, 1H), 5.77 (d, \(J = 2.5\) Hz, 2H), 3.87 (s, 5H), 3.23 (ddq, \(J = 13.5, 7.9, 2.8\) Hz, 1H), 2.95 (td, \(J = 6.3, 0.9\) Hz, 2H), 2.58–1.50 (m, 6H).\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 174.14, 156.47, 131.56, 130.84, 126.74, 125.21, 123.03, 119.08, 117.87, 113.39, 101.95, 61.81, 55.78, 39.50, 28.56, 28.26, 25.86, 24.74. HRMS Calcd for C\(_{18}\)H\(_{21}\)NNaO\(_3\) ([M+Na\(^+\)]: 322.1414; Found: 322.1419.
13ac was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a white solid in 75% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.46 (dd, $J = 9.1$, 4.7 Hz, 1H), 7.44 (s, 1H), 7.19 (dd, $J = 8.7$, 2.6 Hz, 1H), 7.07 (td, $J = 9.1$, 2.6 Hz, 1H), 5.77 (d, $J = 2.6$ Hz, 2H), 3.94 (t, $J = 6.3$ Hz, 2H), 3.29–3.10 (m, 1H), 2.93 (t, $J = 6.3$, 2H), 2.56–2.02 (m, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.34, 159.72 (d, $J = 240.7$ Hz), 132.54, 131.70 (d, $J = 9.2$ Hz), 126.79, 125.13, 123.86, 119.10 (d, $J = 4.0$ Hz), 118.21 (d, $J = 8.8$ Hz), 113.04 (d, $J = 24.6$ Hz), 104.64 (d, $J = 23.8$ Hz), 61.77, 39.59, 28.46, 28.26, 25.87, 24.72. HRMS Calcd for C$_{17}$H$_{18}$FNNaO$_2$ ([M+Na]$^+$): 310.1214; Found: 310.1201.

15a was purified by column chromatography on silica gel (petroleum ether/EtOAc = 8/1) to give a yellow solid in 76% yield with an E/Z ratio of ca. 5:1. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.51 (d, $J = 9$ Hz, 1H), 7.56–7.43 (m, 1H), 7.30 (ddd, $J = 6.3$, 3.8, 1.8 Hz, 2H), 5.63–5.53 (m, 1H), 5.37–5.24 (m, 1H), 4.81 (s, 1H), 4.22–4.08 (m, 0.17H), 3.86 (s, 0.83H), 3.66 (s, 3H), 3.49–3.34 (m, 2H), 2.94–2.62 (m, 4H), 2.29–2.12 (m, 1H), 2.09–1.97 (m, 1H), 1.80 (d, $J = 5.7$ Hz, 0.5H), 1.66 (d, $J = 6.4$ Hz, 2.5H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.13, 157.09, 137.54, 133.16, 131.53, 130.05, 129.67, 129.21 (minor isomer), 128.43, 126.27 (minor isomer), 124.72, 117.96, 117.75, 114.13, 52.22, 40.65, 34.38, 31.13 (minor isomer), 30.28 (minor isomer), 29.82, 27.83 (minor isomer), 27.06, 24.52, 17.85, 13.03 (minor isomer). HRMS Calcd for C$_{19}$H$_{22}$KN$_2$O$_3$ ([M+K]$^+$): 365.1262; Found: 365.1272.

15b was purified by column chromatography on silica gel (petroleum ether/EtOAc = 8/1) to give a yellow solid in 62% yield with an E/Z ratio of ca. 5:1. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.36 (d, $J = 8.9$ Hz, 1H), 7.01–6.86 (m, 2H), 5.57–5.29 (m, 2H), 4.76 (s, 1H), 4.22–4.08 (m, 0.17 H), 3.87 (s, 3.83H), 3.66 (s, 3H), 3.50–3.31 (m, 2H), 2.82–2.03 (m, 6H), 1.81 (d, $J = 6.0$ Hz, 0.5H), 1.67 (d, $J = 6.3$ Hz, 2.5H). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 168.87, 157.10,
15c was purified by column chromatography on silica gel (petroleum ether/EtOAc = 7/1) to give a yellow solid in 70% yield with an \( E/Z \) ratio of ca. 5:1. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.39 (dd, \( J = 8.7, 2.1 \) Hz, 1H), 7.45 (s, 1H), 7.28–7.14 (m, 1H), 5.61–5.53 (m, 1H), 5.32–5.23 (m, 1H), 4.75 (s, 1H), 4.16 (s, 0.17H), 3.86 (s, 0.83H), 3.67 (s, 3H), 3.47–3.32 (m, 2H), 2.95–2.61 (m, 4H), 2.21–2.00 (m, 2H), 1.81 (dd, \( J = 6.7, 1.5 \) Hz, 0.5H), 1.68 (d, \( J = 6.3, 2.5 \)H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 169.29, 157.10, 157.10, 136.00, 134.87, 130.37, 130.05, 129.60 (minor isomer), 128.23, 128.23, 125.89 (minor isomer), 124.73, 124.03, 118.16, 116.79, 114.61, 52.15, 40.68, 34.32, 31.23 (minor isomer), 30.38, 30.26 (minor isomer), 29.81 (minor isomer), 27.88 (minor isomer), 27.11, 24.69, 17.82, 13.02 (minor isomer). HRMS Calcd for C\(_{20}\)H\(_{24}\)N\(_2\)NaO\(_4\) ([M+Na]\(^+\)): 379.1628; Found: 379.1624.

\[ \text{15c} \]

\[ \text{15d} \]

15d was purified by column chromatography on silica gel (petroleum ether/EtOAc = 7/1) to give a yellow solid in 71% yield with an \( E/Z \) ratio of ca. 5:1. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.41 (dd, \( J = 8.9, 4.7 \) Hz, 1H), 7.17 (d, \( J = 8.8 \) Hz, 1H), 7.01 (td, \( J = 9.1, 2.6 \) Hz, 1H), 5.67–5.54 (m, 1H), 5.41–5.22 (m, 1H), 4.87 (s, 1H), 4.18–4.11 (m, 0.17H), 3.86 (s, 0.83H), 3.67 (s, 3H), 3.40–2.04 (m, 8H), 1.85 (d, \( J = 6.3 \) Hz, 0.5H), 1.68 (d, \( J = 5.7 \) Hz, 2.5H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 169.00, 160.09 (d, \( J = 240.6 \) Hz), 157.08, 138.54 (minor isomer), 137.75, 131.36 (minor isomer), 131.11, 130.08, 129.28 (minor isomer), 128.33, 126.14, 117.74 (d, \( J = 9.0 \) Hz), 114.46, 112.02 (d, \( J = 24.4 \) Hz), 104.09 (d, \( J = 24.0 \) Hz), 52.16, 40.56, 34.42, 31.06 (minor isomer), 30.36 (minor isomer), 30.20, 29.79 (minor isomer), 27.86 (minor isomer), 27.24, 27.10 (minor isomer), 24.61, 17.82, 14.30 (minor isomer), 12.99 (minor isomer). HRMS Calcd for C\(_{19}\)H\(_{21}\)F\(_2\)N\(_2\)NaO\(_3\) ([M+Na]\(^+\)): 367.1428; Found: 367.1422.
15e was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5/1) to give a yellow solid in 69% yield with an E/Z ratio of ca. 5:1. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26 (m, 2H), 7.10–6.99 (m, 1H), 5.58 (m, 1H), 5.40–5.18 (m, 1H), 4.88 (t, $J$ = 6.3 Hz, 1H), 4.20–4.09 (m, 0.17H), 3.90 (s, 0.83H), 3.67 (s, 3H), 3.45–3.34 (m, 2H), 2.89–2.06 (m, 6H), 1.83 (d, $J$ = 6.0 Hz, 0.5H), 1.68 (d, $J$ = 6.4 Hz, 2.5H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 167.09, 157.13, 150.58 (d, $J$ = 254.8 Hz), 138.13, 134.32 (d, $J$ = 4.2 Hz), 130.18, 129.43, 126.13 (minor isomer), 125.11 (d, $J$ = 7.0 Hz), 121.39 (minor isomer), 121.28 (d, $J$ = 11.7 Hz), 114.98, 113.95, 112.23 (d, $J$ = 22.9 Hz), 52.20, 40.53, 34.58, 31.38 (minor isomer), 30.62, 29.81 (minor isomer), 27.62 (minor isomer), 26.98, 24.75, 17.86, 13.03 (minor isomer). HRMS Calcd for C$_{19}$H$_{21}$FN$_2$NaO$_3$ ([M+Na]$^+$): 367.1428; Found: 367.1438.

15f was purified by column chromatography on silica gel (petroleum ether/acetone = 17/1) to give a yellow solid in 66% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.54–8.38 (m, 1H), 7.53 (d, $J$ = 6.8 Hz, 1H), 7.35–7.26 (m, 2H), 5.96 (ddd, $J$ = 17.1, 10.2, 5.4 Hz, 1H), 5.21 (d, $J$ = 10.2 Hz, 1H), 4.95–4.58 (m, 2H), 3.93 (s, 1H), 3.66 (s, 3H), 3.52–3.32 (m, 2H), 2.95–2.65 (m, 4H), 2.32–2.05 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.13, 157.15, 137.55, 134.93, 129.99, 124.86, 124.09, 118.26, 117.60 (2C), 116.83, 115.15, 52.22, 40.67, 35.21, 30.29, 26.60, 24.75. HRMS Calcd for C$_{18}$H$_{20}$N$_2$NaO$_3$ ([M+Na]$^+$): 335.1366; Found: 335.1370.

15g was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5/1) to give a white solid in 56% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.50 (d, $J$ = 8.1 Hz, 1H), 7.68 (d, $J$ = 7.7 Hz, 1H), 7.36 (ddd, $J$ = 23.4, 7.4, 1.2 Hz, 2H), 6.06 (s, 1H), 4.69 (s, 1H), 4.18 (q, $J$ = 7.2 Hz, 2H), 3.63 (s, 3H), 3.54–3.38 (m, 2H), 2.95 (t, $J$ = 6.6 Hz, 2H), 2.89 (t, $J$ = 7.2 Hz, 2H), 2.76 (t, $J$ = 6.6 Hz, 2H), 1.26 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.43, 165.41,
157.01, 141.34, 135.16, 130.42, 129.84, 126.71, 124.45, 120.77, 119.99, 118.19, 116.70, 60.79, 52.21, 39.98, 34.99, 34.64, 26.90, 14.40. HRMS Calcd for C$_{20}$H$_{22}$N$_2$NaO$_5$ ([M+Na]$^+$): 393.1426; Found: 393.1429.

![Image](15h)

**15h** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 16/1) to give a white solid in 57% yield with a $E/Z$ ratio of ca. 5:1. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.48 (d, $J = 7.8$ Hz, 1H), 7.51 (d, $J = 7.2$ Hz, 1H), 7.40–7.22 (m, 7H), 5.62–5.21 (m, 1H), 5.27 (m, 1H), 5.16–5.03 (m, 2H), 4.88 (s, 1H), 4.12–4.08 (m, 0.17), 3.83 (s, 0.83H), 3.53–3.37 (m, 2H), 2.87–1.94 (m, 6H), 1.75 (d, $J = 5.4$ Hz, 0.5H), 1.63 (d, $J = 6.5$ Hz, 2.5H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.26, 156.42, 136.67, 136.01, 134.84, 130.32, 130.04, 129.55 (minor isomer), 128.62 (2C), 128.27 (2C), 128.16, 125.87, 124.70, 124.02, 118.16, 116.78, 114.59, 66.72, 40.68, 34.30, 31.20 (minor isomer), 30.35, 29.81 (minor isomer), 27.82 (minor isomer), 27.04, 24.64, 17.81, 14.32 (minor isomer), 13.01 (minor isomer). HRMS Calcd for C$_{25}$H$_{26}$N$_2$NaO$_3$ ([M+Na]$^+$): 425.1836; Found: 425.1839.

![Image](15i)

**15i** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1) to give a yellow solid in 47% yield with a $E/Z$ ratio of ca. 5:1. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.43 (d, $J = 8.0$ Hz, 1H), 7.69–7.19 (m, 3H), 7.31–7.19 (m, 4H), 5.66–5.46 (m, 1H), 5.35–5.18 (m, 1H), 4.72–4.66 (m, 1H), 4.11 (m, 0.17H) 3.80 (s, 0.83H), 3.21 (q, $J = 6.8$ Hz, 2H), 2.91–2.60 (m, 4H), 2.38 (s, 3H), 2.18–1.93 (m, 2H), 1.78 (d, $J = 6.8$ Hz, 0.5H), 1.63 (d, $J = 6.5$ Hz, 2.5H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.27, 143.59 (minor isomer), 143.44, 136.96, 136.34, 134.79 (minor isomer), 130.35, 129.77, 129.65 (2C), 129.42 (minor isomer), 128.28, 126.97 (2C), 126.51, 126.29 (minor isomer), 124.70, 124.01, 117.90, 116.78, 113.70, 42.56, 34.31, 31.23 (minor isomer), 30.34, 30.26 (minor isomer), 29.80 (minor isomer), 27.76 (minor isomer), 27.04, 24.77, 24.65 (minor isomer), 21.60, 17.80, 14.30 (minor isomer), 13.09 (minor isomer). HRMS Calcd for C$_{28}$H$_{28}$N$_2$NaO$_3$S ([M+Na]$^+$): 445.1556; Found: 445.1564.
**15j** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 6/1) to give a yellow solid in 78% yield with a $E/Z$ ratio of ca. 5:1. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.54–8.44 (m, 1H), 7.49–7.29 (m, 3H), 5.73–5.54 (m, 1H), 5.39–5.25 (m, 1H), 5.37–5.27 (m, 1H), 4.25–4.10 (m, 0.13H), 3.88 (s, 0.87H), 3.57–2.05 (m, 8H), 1.84 (dd, $J = 6.3, 1.5$ Hz, 0.5H), 1.69 (d, $J = 6.5, 2.5$H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 169.33, 136.83, 134.91, 130.78, 129.43 (minor isomer), 129.41, 128.79, 126.83 (minor isomer), 125.41, 124.71 (minor isomer), 124.40 (minor isomer), 124.36, 119.71 (q, $J = 321$ Hz), 117.75, 117.07, 112.69, 43.77, 34.53, 31.74 (minor isomer), 31.17 (minor isomer), 30.40 (minor isomer), 30.31, 27.86 (minor isomer), 27.11, 25.60, 22.81 (minor isomer), 17.80, 14.28 (minor isomer), 13.10 (minor isomer). HRMS Calcd for C$_{18}$H$_{19}$F$_3$N$_2$NaO$_3$ ([M+Na]$^+$): 423.0961; Found: 423.0965.

**15k** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 4/1) to give a yellow solid in 79% yield with a $E/Z$ ratio of ca. 5:1. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.53–8.42 (m, 1H), 7.56 (s, 1H), 7.31 (ddd, $J = 6.5, 4.2, 1.7$ Hz, 2H), 5.71–5.49 (m, 1H), 5.39–5.20 (m, 1H), 4.80 (s, 1H), 4.51 (dd, $J = 14.7, 6.1$ Hz, 1H), 4.35 (dd, $J = 14.6, 5.1$ Hz, 1H), 4.02 (s, 1H), 3.68 (s, 3H), 2.91–2.65 (m, 2H), 2.29–2.01 (m, 2H), 1.83 (dd, $J = 6$ Hz, 0.5H), 1.67 (d, $J = 6.5$ Hz, 2.5H). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 169.36, 157.03, 157.35, 130.17, 129.17, 128.31, 125.41, 124.25, 118.33, 116.83, 114.47, 52.37, 34.95, 34.32, 31.43 (minor isomer), 30.45, 27.75 (minor isomer), 26.99, 17.88. HRMS Calcd for C$_{18}$H$_{20}$N$_2$O$_3$ ([M+Na]$^+$): 335.1366; Found: 335.1361.

**15l** was purified by column chromatography on silica gel (petroleum ether/EtOAc = 4/1) to give a yellow solid in 72% yield with a $E/Z$ ratio of ca. 5:1. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.55–8.43 (m, 1H), 7.61–7.46 (m, 1H), 7.43–7.28 (m, 2H), 5.71–5.52 (m, 1H), 5.45–5.17 (m, 1H),
4.02–3.78 (m, 3H), 2.99–2.63 (m, 4H), 2.27–1.97 (m, 2H), 1.82 (d, \( J = 6.0 \text{ Hz}, 0.5 \text{H} \)), 1.68 (d, \( J = 6.3 \text{ Hz}, 2.5 \text{H} \)).\(^1\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 169.40, 136.26, 134.86, 130.46, 130.27, 128.09, 124.71, 123.98, 118.24, 116.79, 114.24, 62.19, 34.22, 30.34, 27.68, 27.03, 17.86. HRMS Calcd for C\(_{17}\)H\(_{19}\)NNaO\(_2\) ([M+Na]\(^+\)): 292.1308; Found: 292.1308.

\[15m\] was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to give a yellow solid in 80% yield with an \( E/Z \) ratio ca. of 5:1. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.53–8.42 (m, 1H), 7.54–7.44 (m, 1H), 7.36–7.27 (m, 2H), 5.75–5.28 (m, 2H), 4.24–4.17 (m, 0.1H), 3.91 (s, 0.83H), 3.69–3.63 (m, 5H), 2.87–2.64 (m, 2H), 2.29–1.99 (m, 2H), 1.80 (dd, \( J = 6.8, 1.7 \text{ Hz}, 0.5 \text{H} \)), 1.66 (dt, \( J = 6.3, 1.5 \text{ Hz}, 2.5 \text{H} \)). \(^1\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 171.35, 169.28, 136.62, 134.69, 129.96 (minor isomer), 129.63, 129.31 (minor isomer), 128.34, 126.22, 124.80, 124.08, 118.26, 118.08 (minor isomer), 116.71, 110.93, 52.21, 34.67, 31.89 (minor isomer), 30.98 (minor isomer), 30.69, 29.95, 29.84 (minor isomer), 29.77 (minor isomer), 27.93 (minor isomer), 27.16, 17.87, 13.03 (minor isomer). HRMS Calcd for C\(_{18}\)H\(_{19}\)NNaO\(_3\) ([M+Na]\(^+\)): 320.1257; Found: 320.1260.

\[15n\] was purified by column chromatography on silica gel (petroleum ether/EtOAc = 8/1) to give a yellow solid in 64% yield with an \( E/Z \) ratio of ca. 5:1. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.51 (dd, \( J = 6.1, 3.3 \text{ Hz}, 1 \text{H} \)), 8.11 (dd, \( J = 6.1, 3.2 \text{ Hz}, 1 \text{H} \)), 7.37 (dt, \( J = 6.1, 3.7 \text{ Hz}, 2 \text{H} \)), 5.73–5.46 (m, 1H), 5.37–5.15 (m, 1H), 5.03 (s, 0.13H), 4.75 (s, 0.87H), 3.95 (s, 3H), 3.05–2.72 (m, 2H), 2.34–2.07 (m, 2H), 1.85 (dd, \( J = 6.9 \text{ Hz}, 0.5 \text{H} \)), 1.65 (dt, \( J = 6.5, 1.7 \text{ Hz}, 2.5 \text{H} \)). \(^1\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 169.75, 165.04, 147.83, 134.74, 134.74, 128.97, 127.99, 127.75 (minor isomer), 127.29, 127.17, 125.39, 125.02, 121.49, 116.52, 109.34 (minor isomer), 51.46, 34.73, 30.81 (minor isomer), 30.57 (minor isomer), 30.21, 29.83 (minor isomer), 27.38, 26.09, 18.03 (minor isomer), 13.13 (minor isomer). HRMS Calcd for C\(_{17}\)H\(_{17}\)NNaO\(_3\) ([M+Na]\(^+\)): 306.1101; Found: 306.1102.
15q was purified by column chromatography on silica gel (petroleum ether/EtOAc = 8/1) to give a yellow solid in 69% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.59–8.46 (m, 1H), 7.48 (d, $J$ = 6.5, 2.4 Hz, 1H), 7.33 (dd, $J$ = 6.9, 5.0, 1.7 Hz, 2H), 6.01 (dd, $J$ = 17.3, 10.5 Hz, 1H), 5.39 (t, $J$ = 6.1 Hz, 1H), 5.26 (d, $J$ = 10.4 Hz, 1H), 5.02 (d, $J$ = 17.4 Hz, 1H), 3.65–3.41 (m, 2H), 3.13 (t, $J$ = 7.7 Hz, 2H), 2.77 (t, $J$ = 6.5 Hz, 2H), 1.99 (qt, $J$ = 13.5, 5.6 Hz, 2H), 1.64 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 169.37, 143.70, 138.95, 134.61, 130.05, 125.44, 124.38, 119.74 (q, $J$ = 321 Hz), 117.77, 117.13, 114.94, 113.73, 43.88, 39.34, 35.52, 30.76, 26.25, 25.26. HRMS Calcd for C$_{18}$H$_{19}$F$_3$N$_2$NaO$_3$S ([M+Na]$^+$): 423.0961; Found: 423.0963.

![](image1)

15r was purified by column chromatography on silica gel (petroleum ether/EtOAc = 8/1) to give a yellow solid in 53% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.34 (d, $J$ = 8.9 Hz, 1H), 7.07–6.88 (m, 2H), 5.98 (dd, $J$ = 17.3, 10.4 Hz, 1H), 5.86 (s, 1H), 5.24 (d, $J$ = 10.4 Hz, 1H), 5.00 (d, $J$ = 17.3 Hz, 1H), 3.86 (s, 3H), 3.52 (dt, $J$ = 9.5, 4.3 Hz, 2H), 3.08 (t, $J$ = 7.8 Hz, 2H), 2.72 (t, $J$ = 6.5 Hz, 2H), 1.97 (qd, $J$ = 13.7, 12.8, 5.9 Hz, 2H), 1.60 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.32, 157.05, 143.54, 139.51, 131.33, 129.07, 119.9 (q, $J$ = 321 Hz), 117.84, 114.85, 113.94, 113.23, 101.15, 55.82, 43.73, 39.30, 35.48, 30.51, 26.39, 25.14. HRMS Calcd for C$_{19}$H$_{21}$F$_3$N$_2$NaO$_4$S ([M+Na]$^+$): 453.1066; Found: 453.1072.

![](image2)

15s was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5/1) to give a yellow solid in 66% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.47 (dd, $J$ = 9.0, 4.8 Hz, 1H), 7.18–6.97 (m, 2H), 6.00 (dd, $J$ = 17.3, 10.4 Hz, 1H), 5.27 (d, $J$ = 10.5 Hz, 1H), 5.01 (d, $J$ = 17.3 Hz, 1H), 3.52 (td, $J$ = 7.4, 2.1 Hz, 2H), 3.07 (t, $J$ = 7.8 Hz, 2H), 2.79 (t, $J$ = 6.5 Hz, 2H), 2.01 (qt, $J$ = 13.5, 6.4 Hz, 2H), 1.62 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.99, 160.19 (d, $J$ = 241.7 Hz), 143.45, 140.70, 131.30 (d, $J$ = 9.3 Hz), 130.91, 119.74 (q, $J$ = 321 Hz), 118.29 (d, $J$ = 9.0 Hz), 115.12, 113.41, 112.90 (d, $J$ = 24.3 Hz), 103.70 (d, $J$ = 24.0 Hz), 43.66, 39.43, 35.53, 30.64, 26.32, 25.17. HRMS Calcd for C$_{19}$H$_{18}$F$_3$N$_2$NaO$_3$S ([M+Na]$^+$): 441.0866; Found: 441.0872.
was purified by column chromatography on silica gel (petroleum ether/EtOAc = 15/1) to give a yellow solid in 78% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.52 (d, $J = 9.0$ Hz, 1H), 7.50 (d, $J = 8.7$ Hz, 1H), 7.35 (q, $J = 6.4$, 6.0 Hz, 2H), 6.01 (dd, $J = 17.4$, 10.5 Hz, 1H), 5.32 (t, $J = 6.0$ Hz, 1H), 5.27 (d, $J = 10.6$ Hz, 1H), 4.89 (d, $J = 17.4$ Hz, 1H), 3.56 (q, $J = 6.3$ Hz, 2H), 3.16–3.05 (m, 2H), 2.78–2.72 (m, 2H), 2.24–2.08 (m, 2H), 1.98–1.83 (m, 2H), 0.97 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.92, 142.48, 137.63, 134.74, 130.20, 125.29, 124.35, 119.77 (q, $J = 318$ Hz), 117.82, 117.02, 115.83, 114.08, 43.61, 43.49, 30.56, 30.51, 30.32, 26.77, 8.69. HRMS Calcd for C$_{19}$H$_{21}$F$_3$N$_2$NaO$_3$S ([M+Na$^+$]): 437.1117; Found: 437.1121.

was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a yellow solid in 69% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.63–8.44 (m, 1H), 7.53 (dd, $J = 7.6$, 1.5 Hz, 1H), 7.31 (qd, $J = 7.0$, 1.5 Hz, 2H), 5.99 (dd, $J = 17.3$, 10.4 Hz, 1H), 5.20 (d, $J = 6.0$ Hz, 2H), 4.98 (d, $J = 17.4$ Hz, 1H), 3.87 (td, $J = 7.4$, 1.1 Hz, 2H), 3.06 (t, $J = 7.2$ Hz, 2H), 2.77 (t, $J = 6.5$ Hz, 2H), 2.01–1.90 (m, 2H), 1.62 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.33, 143.72, 138.18, 134.51, 130.85, 124.94, 123.91, 118.27, 116.81, 115.20, 114.48, 62.22, 39.33, 35.53, 30.79, 28.06, 25.51. HRMS Calcd for C$_{17}$H$_{19}$NNaO$_2$ ([M+Na$^+$]): 292.1308; Found: 292.1316.

was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5/1) to give a yellow solid in 70% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.51 (d, $J = 7.5$ Hz, 1H), 7.54 (d, $J = 7.9$ Hz, 1H), 7.35–7.28 (m, 2H), 5.58 (d, $J = 15.6$ Hz, 1H), 5.34–5.19 (m, 1H), 3.87 (t, $J = 7.2$ Hz, 2H), 3.12–2.95 (m, 2H), 2.78–2.71 (m, 2H), 2.23–2.09 (m, 2H), 1.92–1.76 (m, 2H), 1.70–1.68 (m, 4H), 0.94 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.78, 137.70, 135.44, 134.54, 130.96, 125.85, 124.64, 123.75, 118.11, 116.66, 114.81, 61.85, 42.73, 30.98,
30.74, 30.43, 28.48, 17.85, 8.61. HRMS Calcd for C_{19}H_{23}NNaO_2 ([M+Na]^+): 320.1621; Found: 320.1626.

15w was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a yellow solid in 80% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.52 (d, J = 7.7 Hz, 1H), 7.59–7.50 (m, 1H), 7.40–7.23 (m, 2H), 5.99 (dd, J = 17.4, 10.5 Hz, 1H), 5.21 (d, J = 10.5 Hz, 1H), 4.86 (d, J = 17.4 Hz, 1H), 4.01–3.83 (m, 2H), 3.03 (dd, J = 13.8, 6.9 Hz, 2H), 2.75 (q, J = 5.2 Hz, 2H), 2.18 (tt, J = 15.2, 6.7 Hz, 2H), 2.00–1.78 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 169.54, 142.68, 136.96, 134.78, 130.95, 124.93, 123.91, 118.29, 116.87, 115.47, 115.23, 62.12, 43.74, 30.66 (2C), 30.49, 28.57, 8.72. HRMS Calcd for C_{18}H_{21}NNaO_2 ([M+Na]^+): 306.1465; Found: 306.1469.

15x was purified by column chromatography on silica gel (petroleum ether/EtOAc = 6/1) to give a yellow solid in 73% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.51 (d, J = 7.3 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.30 (t, J = 5.4 Hz, 2H), 5.68 (d, J = 15.7 Hz, 1H), 5.37–5.27 (m, 1H), 3.94–3.78 (m, 2H), 3.43 (q, J = 6.0 Hz, 2H), 3.32 (s, 3H), 3.03 (t, J = 7.3 Hz, 2H), 2.78–2.73 (m, 2H), 2.78–2.28 (m, 3H), 2.17–2.06 (m, 2H), 1.96–1.80 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 169.52, 137.51, 136.67, 134.71, 131.04, 127.63, 124.77, 123.84, 118.26, 116.82, 115.32, 72.12, 62.14, 58.59, 42.64, 33.01, 31.31, 30.48, 28.54, 8.81. HRMS Calcd for C_{21}H_{27}NNaO_3 ([M+Na]^+): 364.1883; Found: 364.1879.

15y was purified by column chromatography on silica gel (petroleum ether/EtOAc = 8/1) to give a yellow solid in 21% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.41 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.33–7.27 (m, 2H), 5.95–5.84 (m, 1H), 5.70–5.67 (m, 1H), 5.35 (t, J = 5.4 Hz, 1H), 3.66 (s, 1H), 3.59 (q, J = 6.8 Hz, 2H), 3.14 (s, 1H), 3.08–2.97 (m, 2H), 2.67–2.59 (m, 1H), 2.48–2.24 (m, 2H), 2.18–2.14 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 173.01, 139.68, 135.34,
129.60, 128.15, 126.22, 125.09, 124.37, 119.71 (q, \( J = 316.56 \) Hz), 117.98, 116.84, 110.09, 43.99, 38.05, 29.37, 28.39, 27.13, 25.97. HRMS Calcd for \( \text{C}_{18}\text{H}_{17}\text{F}_{3}\text{N}_{2}\text{NaO}_{3}\text{S} \) ([M+Na]⁺): 421.0804; Found: 421.0788.

15z was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a white solid in 72% yield. \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 8.51–8.37 (m, 1H), 7.53–7.39 (m, 1H), 7.36–7.20 (m, 2H), 6.03–5.79 (m, 1H), 5.66 (ddd, \( J = 9.8, 4.5, 2.5 \) Hz, 1H), 3.88 (q, \( J = 6.0 \) Hz, 2H), 3.69 (s, 1H), 3.19 (ddd, \( J = 6.6, 3.9, 1.9 \) Hz, 1H), 2.96 (td, \( J = 6.4, 3.0 \) Hz, 2H), 2.72–2.56 (m, 1H), 2.52–2.38 (m, 1H), 2.32 (dt, \( J = 12.8, 3.3 \) Hz, 1H), 2.16 (dt, \( J = 12.3, 3.0 \) Hz, 1H), 1.55 (t, \( J = 5.9 \) Hz, 1H). \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 172.77, 139.12, 135.29, 130.36, 128.67, 125.62, 124.66, 123.99, 118.34, 116.62, 111.50, 62.04, 38.14, 29.41, 28.45, 27.63, 27.15. HRMS Calcd for \( \text{C}_{17}\text{H}_{17}\text{NNaO}_{2} \) ([M+Na]⁺): 290.1151; Found: 290.1156.

15aa was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a yellow solid in 71% yield. \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 8.29 (d, \( J = 8.2 \) Hz, 1H), 7.24 (s, 1H), 7.11 (d, \( J = 8.4 \) Hz, 1H), 5.90 (t, \( J = 7.7 \) Hz, 1H), 5.74–5.60 (m, 1H), 3.97–3.83 (m, 2H), 3.67 (s, 1H), 2.93 (td, \( J = 6.4, 2.8 \) Hz, 2H), 2.69–2.56 (m, 1H), 2.50–2.41 (m, 4H), 2.33–2.29 (m, 1H), 2.15 (dt, \( J = 12.6, 2.7 \) Hz, 1H), 1.48 (s, 1H). \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 172.52, 139.26, 133.63, 133.46, 130.57, 128.70, 125.80, 125.63, 118.46, 116.27, 111.24, 62.09, 38.11, 29.41, 28.53, 27.66, 27.19, 21.65. HRMS Calcd for \( \text{C}_{18}\text{H}_{19}\text{NNaO}_{2} \) ([M+Na]⁺): 304.1308; Found: 304.1312.

15ab was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a yellow solid in 68% yield. \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 8.30 (d, \( J = 8.7 \) Hz, 1H), 6.96–6.85 (m, 2H), 5.89 (t, \( J = 7.8 \) Hz, 1H), 5.66–5.63 (m, 1H), 3.84–3.88 (m, 5H), 3.65 (dd, \( J = 6.7, 3.4 \) Hz, 1H), 3.14 (s, 1H), 2.91 (td, \( J = 6.5, 2.1 \) Hz, 2H), 2.66–2.38 (m, 1H), 2.49–2.34 (m, 1H), 2.29 (d, \( J = 11.3 \) Hz, 1H), 2.16 (dt, \( J = 12.6, 2.7 \) Hz, 1H), 1.82 (s, 1H). \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 172.26, 156.88, 140.00, 131.51, 129.89, 128.62, 125.69, 117.31, 111.94, 111.38,
15ac was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3/1) to give a yellow solid in 68% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.38 (dd, $J = 8.9$, 4.8 Hz, 1H), 7.11 (dd, $J = 8.9$, 2.6 Hz, 1H), 7.00 (td, $J = 9.1$, 2.6 Hz, 1H), 5.92 (t, $J = 7.8$ Hz, 1H), 5.68 (dt, $J = 9.7$, 3.9 Hz, 1H), 3.87 (d, $J = 5.2$ Hz, 2H), 3.69 (s, 1H), 3.20 (s, 1H), 2.92 (t, $J = 6.1$ Hz, 2H), 2.65 (dd, $J = 18.1$, 6.7 Hz, 1H), 2.52–2.30 (m, 2H), 2.17 (dt, $J = 12.7$, 2.7 Hz, 1H), 1.46 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.49, 160.13 (d, $J = 240.0$ Hz), 140.91, 131.84 (d, $J = 9.9$ Hz), 131.63 (d, $J = 4.0$ Hz), 128.50, 125.90, 117.60 (d, $J = 8.8$ Hz), 111.93 (d, $J = 24.3$ Hz), 111.41 (d, $J = 3.4$ Hz), 104.48 (d, $J = 23.9$ Hz), 61.96, 38.01, 29.36, 28.50, 27.57, 27.26. HRMS Calcd for C$_{17}$H$_{15}$FNaO$_2$ ([M+Na]$^+$): 308.1057; Found: 308.1061.
5. Mechanistic study

5.1 Isotopic effect

The tBuCO2D (ca. 90% D incorporation) and 2-deuterated tryptamine (ca. 92% D incorporation) for the synthesis of 13a-D were prepared according to the reported literature, respectively (Liu et al., 2013; Pan et al., 2012).

![Figure S2](image1.png)

**Figure S2.** The $^1$H NMR spectrum of 13a-D (ca. 92% D incorporation), related to Figure 4 and eq 1

![Figure S3](image2.png)

**Figure S3.** The quantitative $^1$H NMR spectra of H/D ratio for the recovered 13a-D under standard reaction conditions after 1h (upper) and 3h (lower), related to Figure 4 and eq. 1.
Figure S4. The quantitative $^1$H NMR spectra of H/D ratio for the recovered 13a by replacing tBuCO$_2$H with tBuCO$_2$D after 1h (upper) and 3h (lower), related to Figure 4 and eq. 2.

Table S1. The time-dependent conversion of substrates as monitored by HPLC, related to Figure 3.

| Entry | Time (h) | Con. (%) 13a | Con. (%) 13a-D |
|-------|----------|--------------|---------------|
| 1     | 1        | 22           | 7             |
| 2     | 2        | 31           | 14            |
| 3     | 3        | 47           | 16            |
| 4     | 4        | 54           | 16.8          |
| 5     | 5        | 61           | 17.3          |
| 6     | 6        | 70           | 21.7          |
| 7     | 7        | 75           | 22.4          |
| 8     | 8        | 76           | 25            |
| 9     | 9        | 78           | 26            |
| 10    | 10       | 79           | 31            |
5.2 HRMS analysis of the reaction mixture

LTQ-Orbitrap mass spectrometer (Thermo Fisher Scientific, USA) connected to the UHPLC instrument via ESI interface. Data acquisition and processing were carried out using Xcalibur 2.1 software (Thermo Fisher Scientific, USA). Unless otherwise noted, the operating conditions were set as follow: spray voltage 3.2 kV, heated capillary temperature 200 °C, sheath gas flow rate 35 arbitrary units, auxiliary gas flow rate 10 arbitrary units. Mobile phase is CH₃CN (100%), flow rate 0.2 mL/min.

Figure S5. HRMS spectra for the reaction mixture under oxygen atmosphere (upper) and argon atmosphere (lower) after reacted at 130 °C for 1 h, related to Figure 4
(The detailed comparison on the theoretical and experimental isotopic distribution of the peaks was showed in following).

(The values are reported for $^{106}$Pd for monomeric Pd complexes and $^{106}$Pd and $^{108}$Pd for bimetallic Pd complexes)

![Chemical Structure](image)

Chemical Formula: C$_9$H$_{17}$NaO$_7$Pd$^+$

Calcd: 365.99013

Found: 365.99512

Rel error (ppm): 13.8

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**Figure S6.** Theoretical isotopic distribution, related to **Figure 4**

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**Figure S7.** Experimental isotopic distribution, related to **Figure 4**
Figure S8. Theoretical isotopic distribution, related to Figure 4

Figure S9. Experimental isotopic distribution, related to Figure 4
Figure S10. Theoretical isotopic distribution, related to Figure 4

Figure S11. Experimental isotopic distribution, related to Figure 4
Chemical Formula: C_{14}H_{27}NaO_{9}Pd^+
Calcd: 468.05821
Found: 468.05981
Rel error (ppm): 3.4

**Figure S12.** Theoretical isotopic distribution, related to Figure 4

**Figure S13.** Experimental isotopic distribution, related to Figure 4
C16H25NO9Pd+:

Chemical Formula: C_{16}H_{25}NO_{9}Pd^{+}
Calcd: 481.05587
Found: 481.05581
Rel error (ppm): -0.1

Figure S14. Theoretical isotopic distribution, related to Figure 4

Figure S15. Experimental isotopic distribution, related to Figure 4
Figure S16. Theoretical isotopic distribution, related to Figure 4.

Chemical Formula: C_{20}H_{13}F_{5}N_{2}O_{1}P_{1}Pd_{1}
Calcd: 528.97150
Found: 528.97015
Rel Error (ppm): -2.5

Figure S17. Experimental isotopic distribution, related to Figure 4.
C13H22N4NaO5Pd2⁺: Chemical Formula: C_{13}H_{22}NaO_5Pd_{2}⁺
Calcd: 550.95562
Found: 550.95648
Rel error(ppm): 1.5

Figure S18. Theoretical isotopic distribution, related to Figure 4

ZJ_180822095522 #6 RT: 0.11 AV: 1 NL: 2.26E6
T: FTMS + p ESI Full ms [100.00-1500.00]

Figure S19. Experimental isotopic distribution, related to Figure 4
**Figure S20.** Experimental isotopic distribution, related to Figure 4

Chemical Formula: $C_{20}H_{28}F_{10}N_2O_2P_2^+$
Calcd: 767.10696
Found: 767.10364
Rel error (ppm): -4.32

Chemical Formula: $C_{20}H_{28}F_{10}N_2NaO_2P_2^+$
Calcd: 789.08890
Found: 789.08521
Rel error (ppm): -4.67
Figure S21. Theoretical isotopic distribution, related to Figure 4

Figure S22. Experimental isotopic distribution, related to Figure 4
5.3 The color changes under oxygen and argon atmosphere

As shown in Figure S24, under oxygen atmosphere, the color of the reaction mixture changed from pale yellow to deep red-brown and the solution maintained almost transparent. In contrast, palladium black precipitated out rapidly for the reaction mixture under argon atmosphere and a palladium mirror was observed after 2 h. A clearer observation on the color change could be observed from the filtrates as shown Figure S25. These results indicate the generation of Pd(III) species under oxygen atmosphere according to the reported literature (Powers et al., 2009).

Figure S23. Oxidative Heck coupling of 13a, related to Figure 4

Figure S24. The color change of the reaction mixture under O₂ and Ar atmosphere, related to Figure 4

Figure S25. The color change of the filtrates under O₂ and Ar atmosphere, related to Figure 4
6. X-Ray data of 15q and 15ac

Table S2. Crystal data and structure refinement for 15q (CCDC 1866425), related to Table 3

| Property                        | Value                  |
|---------------------------------|------------------------|
| **Formula**                     | C18 H19 F3 N2 O3 S     |
| **Formula weight**              | 400.41                 |
| **Temperature/K**              | 273(2)                 |
| **Crystal system**              | monoclinic             |
| **Space group**                 | P21/n                  |
| **Unit cell dimensions**        |                        |
| **a**                           | 9.3981(6) Å            |
| **b**                           | 18.3270(12) Å          |
| **c**                           | 11.3035(7) Å           |
| **Volume/Å³**                   | 1880.1(2)              |
| **Z**                           | 4                      |
| **Computing data collection**   | Bruker SMART           |
| **Crystal description**         | block                  |
| **Crystal colour**              | colorless              |
| **Crystal size max**            | 0.21                   |
| **Crystal size mid**            | 0.2                    |
| **Crystal size mix**            | 0.18                   |
| **ρcalc/cm³**                   | 1.415                  |
| **µ/mm¹**                       | 0.222                  |
| **F(000)**                      | 832.0                  |
| **Radiation**                   | MoKα (λ = 0.71073 Å)   |
| **2Θ range for data collection/°** | 4.344 to 52.802       |
| **Index ranges**                | h ≤ 11, k ≤ 17, l ≤ 13 |
| **Reflections collected**       | 10631                  |
| **Independent reflections**     | 3840 [Rint = 0.0277, Rsigma = 0.0352] |
| **Data/restraints/parameters**  | 3840/0/245             |
| **Goodness-of-fit on F²**       | 1.033                  |
| **Final R indexes [I>=2σ(I)]**  | R1 = 0.0825, wR2 = 0.2235 |
| **Final R indexes [all data]**  | R1 = 0.0982, wR2 = 0.2386 |
| **Largest diff. peak/hole / e Å^-3** | 1.55/-0.49           |
Table S3. Crystal data and structure refinement for 15ac (CCDC 1866424), related to Table 3

| Property                              | Value                        |
|---------------------------------------|-----------------------------|
| Formula                               | C17 H16 F N O2              |
| Formula weight                        | 316.42                      |
| Temperature/K                         | 273(2)                      |
| Crystal system                        | monoclinic                  |
| Space group                           | P21/n                       |
| Unit cell dimensions                  | a = 15.720(3) Å, alpha=90° |
|                                      | b = 8.9379(16) Å, beta=107.152(4)° |
|                                      | c = 9.8722(19) Å, gamma=90° |
| Volume/Å³                             | 1880.1(2)                   |
| Z                                     | 4                           |
| Computing data collection             | Bruker SMART                |
| Crystal description                   | block                       |
| Crystal colour                        | colorless                   |
| Crystal size max                      | 0.5                         |
| Crystal size mid                      | 0.4                         |
| Crystal size mix                      | 0.2                         |
| Radiation                             | MoKα (λ = 0.71073)          |
| 2θ range for data collection/°        | 2.72 to 49.58               |
| Index ranges                          | -17 ≤ h ≤ 18, -10 ≤ k ≤ 9, -11 ≤ l ≤ 9 |
| Reflections collected                 | 7099                        |
| Independent reflections               | 2266 [Rint = 0.0515, Rsigma = 0.0527] |
| Data/restraints/parameters            | 2266/0/191                  |
| Goodness-of-fit on F2                 | 1.079                       |
| Final R indexes [I>2σ (I)]            | R1 = 0.0442, wR2 = 0.1167   |
| Final R indexes [all data]            | R1 = 0.0580, wR2 = 0.1333   |
| Largest diff. peak/hole / e Å⁻³       | 0.21/-0.25                  |
7. Copies of NMR spectra of substrates and products

Figure S26. NOESY spectrum of 15d, related to Table 2
Figure S27. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13a, related to Table 1
Figure S28. $^1$H-NMR of compound 13a-D, related to Figure 4 and eq. 1
Figure S29. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13b, related to Table 2
Figure S30. $^1$H (upper) and $^{13}$C-NMR (lower) of compound $^{13}$c, related to Table 2
Figure S31. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13d, related to Table 2
Figure S32. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13e, related to Table 2
Figure S33. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13f, related to Table 2
Figure S34. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13g, related to Table 2
Figure S35. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13h, related to Table 2
Figure S36. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13i, related to Table 2
Figure S37. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13j, related to Table 2
Figure S38. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13k, related to Table 2.
Figure S39. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13l, related to Table 2
Figure S40. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13m, related to Table 2
Figure S41. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13n, related to Table 2
Figure S42. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13q, related to Table 3
Figure S43. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13r, related to Table 3
Figure S44. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13s, related to Table 3.
Figure S45. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13t, related to Table 3
Figure S46. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13u, related to Table 3.
Figure S47. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13v, related to Table 3
Figure S48. $^1$H (upper) and $^{13}$C-NMR (lower) of compound $^{13w}$, related to Table 3
Figure S49. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13x, related to Table 3
Figure S50. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13y, related to Table 3
Figure S51. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13z, related to Table 3
Figure S52. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13aa, related to Table 3
Figure S53. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13ab, related to Table 3
Figure S54. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 13ac, related to Table 3
Figure S55. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15a, related to Table 1
Figure S56. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15b, related to Table 2
Figure S57. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15c, related to Table 2
Figure S58. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15d, related to Table 2
Figure S59. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15e, related to Table 2
Figure S60. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15f, related to Table 2
Figure S61. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15g, related to Table 2
Figure S62. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15h, related to Table 2.
Figure S63. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15i, related to Table 2
Figure S64. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15j, related to Table 2
Figure S65. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15k, related to Table 2
Figure S66. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15l, related to Table 2
Figure S67. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15m, related to Table 2
Figure S68. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15n, related to Table 2
Figure S69. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15q, related to Table 3
Figure S70. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15r, related to Table 3
Figure S71. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15s, related to Table 3
Figure S72. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15t, related to Table 3
Figure S73. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15u, related to Table 3
Figure S74. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15v, related to Table 3
Figure S75. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15w, related to Table 3.
Figure S76. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15x, related to Table 3.
Figure S77. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15y, related to Table 3
Figure S78. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15z, related to Table 3
Figure S79. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15aa, related to Table 3
Figure S80. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15ab, related to Table 3
Figure S81. $^1$H (upper) and $^{13}$C-NMR (lower) of compound 15ac, related to Table 3
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