JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

One-Pot, Two-Step, Microwave-Assisted Palladium-Catalyzed Conversion of Aryl Alcohols to Aryl Fluorides via Aryl Nonaflates

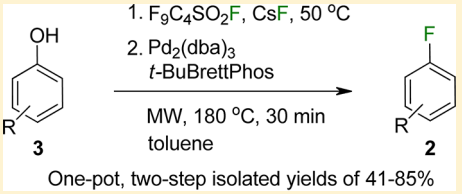
Johan Wannberg,[†,‡] Charlotta Wallinder,[‡] Meltem Ünlüsoy,[‡] Christian Sköld,[‡] and Mats Larhed*[,‡]

[†]KDev Exploratory AB, Nobels väg 3, SE-171 65 Solna, Sweden

[‡]Department of Medicinal Chemistry, Organic Pharmaceutical Chemistry, BMC, Uppsala University, P.O. Box 574, SE-751 23 Uppsala, Sweden

Supporting Information

ABSTRACT: A convenient procedure for converting aryl alcohols to aryl fluorides via aryl nonafluorobutylsulfonates (ArONf) is presented. Moderate to good one-pot, two-step yields were achieved by this nonaflation and microwave-assisted, palladium-catalyzed fluorination sequence. The reductive elimination step was investigated by DFT calculations to compare fluorination with chlorination, proving a larger thermodynamic driving force for the aryl fluoride product. Finally, a key aryl fluoride intermediate for the synthesis of a potent HCV NS3 protease inhibitor was smoothly prepared with the novel protocol.



The introduction of fluorine atoms into aromatic rings of pharmaceutically active compounds modifies their properties in various ways. Frequently, this is used as a means of blocking metabolism (aromatic oxidation), modifying the pK_a of acidic or basic groups, to increase lipophilicity or improve the affinity to a target protein.[1−3] As a consequence, fluoroaromatics are common among approved drugs as well as in biocides.[1−4] An additional area of importance for fluorochemistry is the generation of synthetic intermediates.

The classical methods for the incorporation of a fluorine atom to an aromatic scaffold (e.g., Halex− and Balz−Schiemann reaction) require severe conditions with poor functional group tolerance. However, in recent years, significant progress has been made in this field. Electrophilic fluorinations of Grignard[5,6] and other Ar-M(X)$_Y$ reagents have been presented.[7] A number of transition-metal-mediated (catalytic or stoichiometric) methods have been disclosed[7−13] including the palladium-catalyzed fluorinations of aryl triflates (Buchwald fluorination)[14] and aryl bromides.[14,15] Recently a non-metal-catalyzed method for direct deoxyfluorination of phenols was published.[16]

Our interest in fluorine as a blocker of metabolism of aromatic positions of drug compounds[17] and generation of essential building blocks in medicinal synthesis prompted us to explore the palladium-catalyzed fluorination reaction. Some issues with this reaction were identified, and solutions/improvements were examined with the aims to (1) decrease reaction times, (2) identify a one-pot, two-step protocol for synthesis of aryl fluorides (**2**) from aryl alcohols (**3**), (3) avoid the need for glovebox conditions, and (4) minimize side product formation.

Initial efforts focused on running the Buchwald fluorination protocol[14] without employing a glovebox. Aryl triflates (**1**) were used as arylating agents, CsF as the fluoride source, [(cinnamyl)PdCl]$_2$ as the palladium source, and *t*-BuBrettPhos[18,19] as the ligand in dry toluene using 140 °C controlled microwave heating.[20−22] As expected, simply trying to work fast and efficient while adding the highly hygroscopic cesium fluoride (CsF) in an open atmosphere was not enough to prevent water-induced formation of phenols (**3**) and diaryl ethers under the fluorination conditions. Thus, various methods of keeping the CsF away from the humid atmosphere was explored. In our hands, the most effective and convenient procedure of keeping the CsF dry was to weigh it in a reaction vial (2−5 mL microwave vial) and then dry the vial (with magnetic stirring bar) in a vacuum oven for at least 5 h. The vial was then capped with a septum, nitrogen flushed by syringe needles, and stored in dry atmosphere until used.

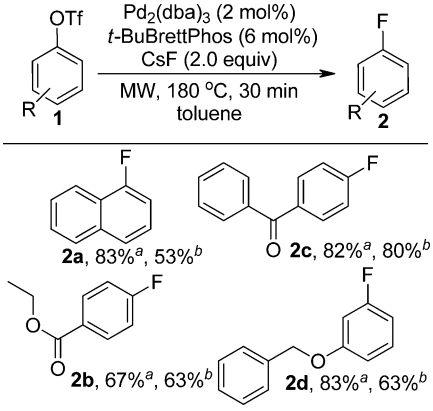
Another problem identified was the formation of small amounts of ArCl side products with the palladium salt [(cinnamyl)PdCl]$_2$ being the source of chloride. This complicated the purifications due to the similar properties of ArCl and the ArF products (**2**). Thus, a number of chloride-free palladium catalysts were screened together with *t*-BuBrettPhos as ligand, with Pd$_2$(dba)$_3$ proving to give an almost as active catalytic system as [(cinnamyl)PdCl]$_2$ but without the undesired ArCl formation. Using 1-naphthyl triflate (**1a**) as a model substrate in a 1.0 mmol reaction we were able to reach full conversion of **1a** to 1-fluoronaphthalene (**2a**) within 30 min of microwave heating in a sealed reaction vial at 140 °C. However, it was soon apparent that some less reactive substrates **1** required longer times or higher temperatures for full conversion. Since we wanted to keep the reaction times short, we found that a higher temperature of 180 °C for 30 min was suitable to provide a more robust generic reaction procedure (Table 1). Despite the poor microwave absorbing

Received: February 7, 2013
Published: March 11, 2013

dx.doi.org/10.1021/jo400255m | J. Org. Chem. 2013, 78, 4184−4189

properties of toluene,[23] a reaction temperature of 180 °C was reached within 1−2 min.

Table 1. Microwave-Heated Palladium-Catalyzed Fluorination of Aryl Triflates

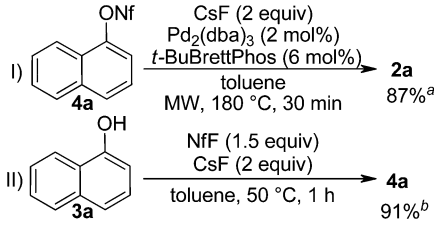


[a]GC yield. [b]Isolated yield

Product **2a** was initially isolated in surprisingly poor yield despite the relatively high GC yield,[24] while aryl fluorides **2b−d** were prepared in 63−80% isolated yields. Due to the volatility of **2a** and **2b**, great care was required to prevent significant loss of product during the purification and drying of these entries.

Aryl nonafluorobutansulfonates (aryl nonaflates, ArONf, **4**) can serve as cost-effective, convenient alternatives to aryl triflates in transition-metal-catalyzed coupling reactions.[25,26] The use of aryl nonaflates as substrates for fluorination reactions has, as far as we can tell, not been previously reported. By employing identical conditions as above (Table 1) with 1-naphthyl nonaflate (**4a**) as the arylpalladium precursor, full conversion to the corresponding fluoride (**2a**) was also achieved (Scheme 1, I). The swift and straightforward synthesis

Scheme 1. Palladium-Catalyzed Fluorination of an Aryl Nonaflate (4a) and Testing the Synthesis of 4a in Toluene with CsF Present



[a] GC yield. [b] Isolated yield.

of aryl nonaflates allowed us to envision a one-pot, two-step strategy from phenols (**3**) to aryl fluorides (**2**). Stirring 1-naphthol (**3a**) with nonafluoro-1-butansulfonylfluoride (nonaflyl fluoride, NfF) in toluene without base did not result in any reaction, even upon heating. However, after this reaction mixture was added to a vial of dry CsF, the aryl nonaflate **4a** was immediately detected. By heating at 50 °C with CsF as base, full conversion of **3a** to **4a** was reached within 1 h (Scheme 1, II).

Initial attempts of applying the one-pot, two-step strategy, whereby a slurry of $Pd_2(dba)_3$ and *t*-BuBrettPhos in toluene was added by syringe to the nonaflation reaction, were encouraging, although when using equimolar amounts or a slight excess of nonaflyl fluoride in the first step, varying amounts of diaryl ether could be observed after the fluorination step. This was attributed to subquantitative conversion of **3** to **4** and/or hydrolysis of **4** to **3** by water and subsequent palladium-catalyzed C−O coupling. Either way, increasing the excess nonaflyl fluoride to 1.5 equiv eliminated this problem by ensuring full conversion of the phenol **3** and/or by scavenging any water present. Thus, full conversion of 1-naphthol (**3a**) to 1-fluoronaphthalene (**2a**) could be achieved in a one-pot procedure with a GC yield of 83% (Table 2).

When other aryl alcohols **3** were explored, the time required to obtain full conversion into ArONf **4** varied significantly, with some very sluggish reactions. This was partly due to differences in nucleophilicity of the aryl alcohols but also due to poor solubility in toluene. The solubility could be improved by adding a small volume of dry 1,4-dioxane. Importantly, this did not seem to negatively affect the subsequent fluorination step in those instances. By applying the general fluorination conditions from the aryl triflates in Table 1 to the aryl nonaflate entries in Table 2, all showed complete consumption of **4** (and **3**) except **3b** and **3c**, which required 60 min of microwave heating to reach full conversion in the second step.

As previously observed by Buchwald,[14] 2,6-dimethyl substitution (**3d**) did not seem to affect the reaction negatively, but in this case rather the opposite. Tertiary aromatic amines (**3b**), ethers (**3c**, **3k**), nitriles (**3d**, **3h**) ketones (**3e**, **3g**) and esters (**3f**) were also well tolerated. However, electron-rich **3** or substrates containing protic functionalities proved unproductive under these conditions. The discrepancies between GC yields and isolated yields in Table 2 could mainly be explained by losses due to ArF volatility and/or other purification problems.

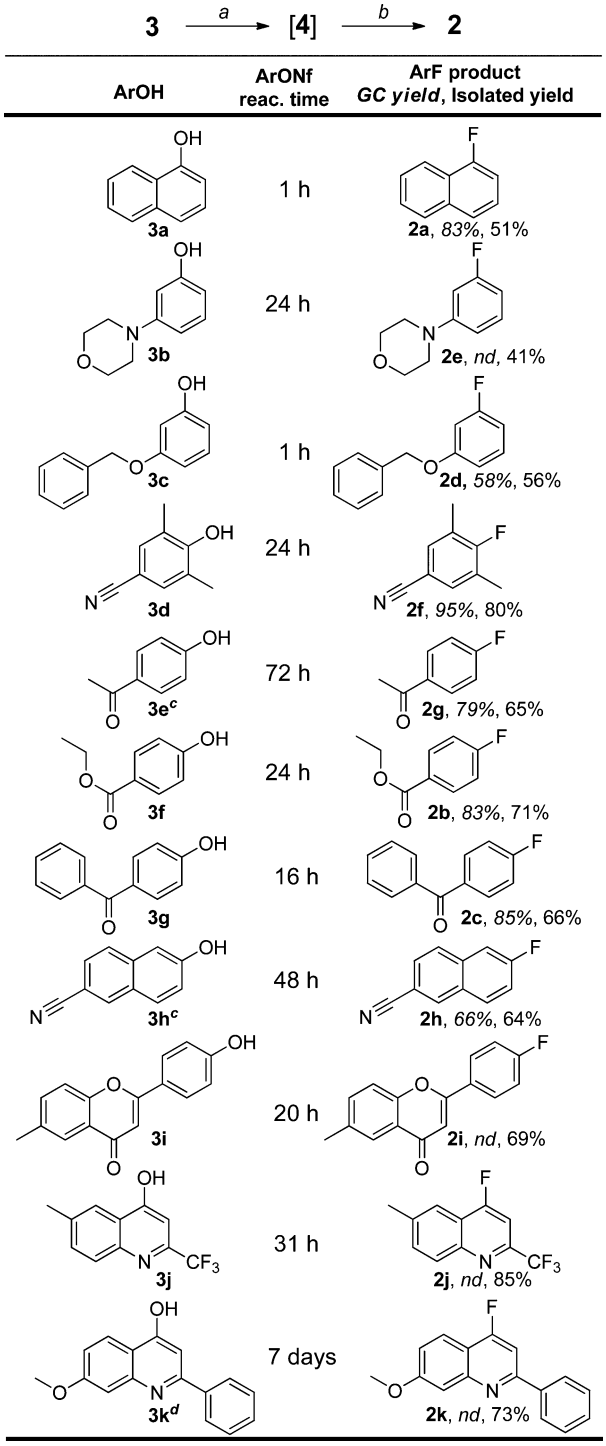
The fluoroquinoline **2k** had previously been imagined as an intermediate in the synthesis of potent hepatitis C virus (HCV) NS3 protease inhibitors, but all attempted methods to produce **2k** failed at the time.[27] Instead, the corresponding chloro derivative had to be used for the subsequent nucleophilic aromatic substitution with the 4-hydroxyphenylglycine derivative **5** resulting in a very sluggish reaction. With our new methodology, **2k** was synthesized in decent yield (Table 2), and the reaction of **2k** with **5** proceeded smoothly to furnish **6** in 6 h compared to several weeks for the chloro derivative (Scheme 2).[27]

As palladium-catalyzed chlorination and bromination of ArOTf **1a** (using KCl or KBr) has been reported using $[(cinnamyl)PdCl]_2$ and *t*-BuBrettPhos with KF as an additive,[28] we wanted to compare the reactivity of different halide salts under our conditions. A competitive experiment where 1 equiv each of CsBr, CsCl, and CsF were present showed almost exclusively the naphthyl fluoride product with <10% of ArCl **7a** and only traces of ArBr. Considering the ease of forming ArCl side product when using $[(cinnamyl)PdCl]_2$ as a Pd source, this was somewhat surprising. A suspicion that ArCl or ArBr may have formed and reacted further to ArF was disproved by follow-up experiments using CsCl or CsBr alone, which indicated practically no conversion to ArX.

In order to improve our understanding of the reaction, we decided to perform a focused computational investigation by means of density functional theory (DFT) calculations of fluorination and chlorination. Phenyl was used as model aryl moiety in the calculations. Of the parts in the proposed catalytic cycle in Figure 1 only reductive elimination was investigated because this reaction step is crucial for product formation and a

dx.doi.org/10.1021/jo400255m | J. Org. Chem. 2013, 78, 4184−4189

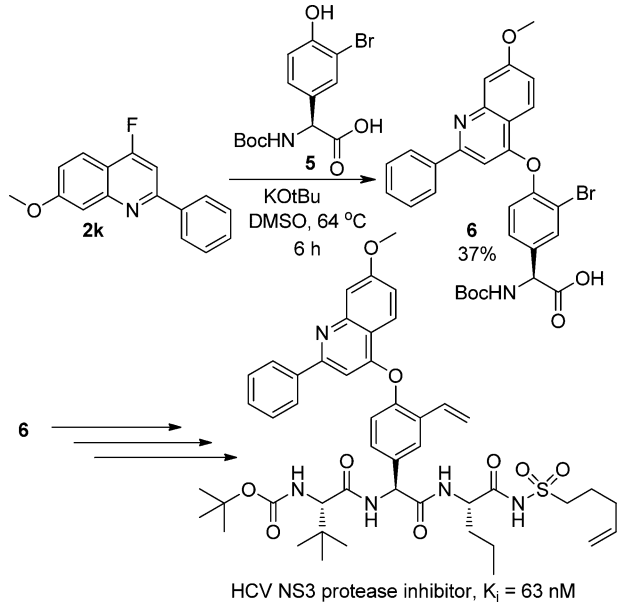
Table 2. One-Pot, Two-Step Fluorination of ArOH via ArONf



[a]NfF (1.5 equiv), CsF (2.0 equiv), toluene, 50 °C. [b]$Pd_2(dba)_3$ (2 mol %), *t*-BuBrettPhos (6 mol%), MW, 180 °C, 30 min. [c]9:1 toluene:1,4-dioxane. [d]1:1 toluene:1,4-dioxane. Isolated yields (>95% purity by ^{1}H NMR). *nd* = not determined.

successful outcome of the reaction.[29] Accordingly, the starting point for the DFT calculations was the prereductive elimination complex **I** in Figure 2, which might be generated from either a phenyl triflate (**1l**) or the corresponding phenyl nonaflate (**4l**). In this complex the phenyl moiety and halide already have the *cis* configuration that provides proximity of the moieties for

Scheme 2. Improved Synthesis of HCV NS3 Protease Inhibitor intermediate 6



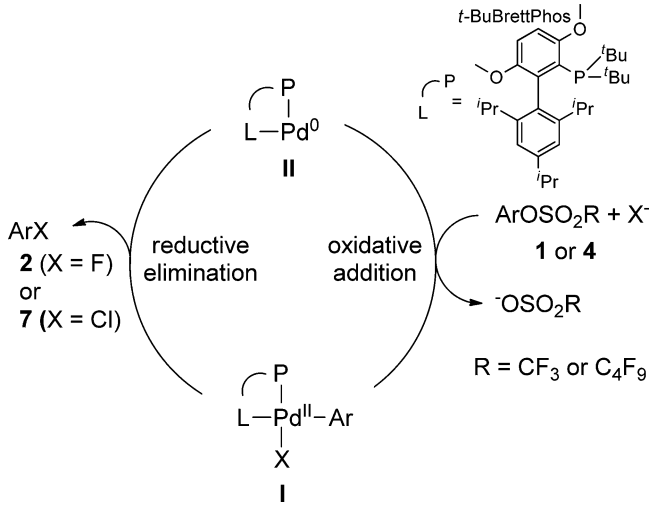


Figure 1. Proposed catalytic cycle for palladium-catalyzed aryl halogenation.

reductive elimination because the bulky *t*-BuBrettPhos ligand occupies two coordination sites, as seen in the X-ray structure of similar complexes.[30] From complex **I** reductive elimination is calculated to proceed with fairly similar energy barriers to the transition state for fluorination and chlorination, 95 and 101 kJ mol^{-1}, respectively. The structures including relevant bond lengths in the optimized geometries of **TS-a** and **TS-b** can be found in Supporting Information. Product formation giving **2l** shows that fluorination gives a significantly more thermodynamically stable product (−23 kJ mol^{-1}) compared to chlorination (+48 kJ mol^{-1}) providing **7l**. Thus, fluorination has a larger thermodynamic driving force in the reaction, and this can be rationalized by a relatively more stable Ph−X bond versus Pd−X bond for F in comparison to Cl.[31] This result is in accordance with the experimental result herein that fluorinated product is the preferred outcome of the reaction in the competitive experiments. However, the computational investigation does not explain the ease of forming the chlorinated

dx.doi.org/10.1021/jo400255m | *J. Org. Chem.* 2013, 78, 4184−4189

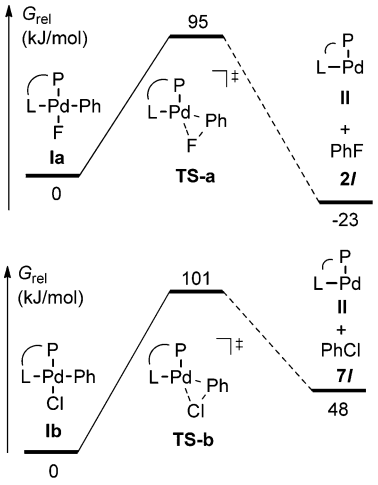


Figure 2. Free energy profile of reductive eliminations from fluoride containing **Ia** and chloride containing **Ib**.

product when using $[(cinnamyl)PdCl]_2$ as Pd source. Possibly an explanation could be revealed from a thorough investigation of the catalyst activation if chloride would enter the initial catalytic cycle.

An operationally convenient one-pot, two-step procedure for the conversion of aryl alcohols to aryl fluorides in isolated yields of 41−85% has been developed. Aryl alcohols were first in situ converted to aryl nonaflates using CsF as base. Next, $Pd_2(dba)_3$ and *t*-BuBrettPhos were added to catalyze the microwave-heated fluorination. A radiation time of 30−60 min and a reaction temperature of 180 °C furnished full conversion.

Competitive experiments showed that fluorination was favored over both chlorination and bromination under the present reaction conditions and DFT calculations showed that fluorination was preferred over the corresponding chlorination in the reductive elimination step.

EXPERIMENTAL SECTION

General Information. The microwave reactions were performed in a single-mode microwave reactor producing controlled irradiation at 2450 MHz with a power of 0−400 W. The reaction temperature was determined using the built-in online IR-sensor. GC−MS analyses were performed with a CP-SIL 8 CB Low Bleed (30 m × 0.25 mm) or a Factor Four VF 5 ms (30 m × 0.25 mm) capillary column using a 70−300 °C temperature gradient and EI ionization at 70 eV. Analytical UHPLC−MS was performed with an ion-trap mass spectrometer and UV-DAD detection using a C18 column (50 × 3 mm). Acetonitrile in 0.05% aqueous formic acid was used as mobile phase at a flow rate of 1.5 mL/min. Silica gel (Merck 60, 40−63 μm) was used for flash chromatography. Analytical thin-layer chromatography was done using aluminum sheets precoated with silica gel (Merck, F_{254}); detection was by UV (254 nm). Nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz for ^{1}H, at 100.5 MHz for ^{13}C, and at 376 MHz for ^{19}F. ^{1}H and ^{13}C NMR chemical shifts were reported as δ (ppm) and referenced using the residual solvent signal (^{1}H, $CDCl_3$ at 7.26 ppm; ^{13}C, $CDCl_3$ at 77.16 ppm). ^{19}F NMR chemical shifts were reported as δ (ppm) and verified with a reference sample containing a sealed capillary with $CFCl_3$ giving a reference signal at 0 ppm. All reagents were purchased from commercial suppliers and used without further purification. Compounds **2a**−**g**, **j** are known compounds; **2k** is a new compound. Compounds **2h** and **2i** are known, but there are no NMR data reported in the literature. All final compounds were ≥95% pure as determined by NMR.

General Procedure for Drying of CsF. CsF (320 mg, 2.0 mmol) was added as quickly as possible to a 2−5 mL microwave vial and then dried in a vacuum oven (120 °C, <10 mbar, minimum 5 h). The vial was then immediately capped with a septum and evacuated and backfilled with N_2 three times via a syringe needle. While cooling, the vial was put in a desiccator for storage until used. The highly hygroscopic CsF showed a 5% weight loss on drying at 120 °C under reduced pressure (<10 mbar) overnight. Consequently, this was compensated for when weighing in the "wet" CsF before drying.

General Procedure A: Fluorination of Aryl Triflates. Aryl triflate[32] (1.0 mmol), tris(dibenzylideneacetone)dipalladium(0) (18 mg, 0.020 mmol), and *t*-BuBrettPhos (29 mg, 0.060 mmol) (Pd:L = 1:1.5) in 4 mL of dry toluene were stirred in a dried glass vial for about 5 min at room temperature. The mixture was then added by syringe to a capped vial with CsF (2.0 mmol), and the resulting reaction mixture was microwave heated at 180 °C for 30 min. After being cooled to room temperature, the reaction mixture was purified by silica flash chromatography using the conditions indicated below.

General Procedure B: One-Pot, Two-Step Conversion of Aryl Alcohols to Aryl Fluorides. *Nonaflation Step.* Aryl alcohol (1.0 mmol) and perfluoro-1-butanesulfonyl fluoride (453 mg, 1.5 mmol) dissolved in 2 mL of dry toluene was added by syringe to a capped vial with CsF (320 mg, 2.0 mmol). (For aryl alcohols poorly soluble in toluene, the reaction vial was quickly uncapped and the alcohol added as dry material before recapping and flushing with N_2.) The reaction was stirred at 50 °C for the times indicated in Table 2.

Fluorination Step. Tris(dibenzylideneacetone)dipalladium(0) (18 mg, 0.020 mmol) and *t*-BuBrettPhos (29 mg, 0.060 mmol) (Pd:L = 1:1.5) in 2 mL of dry toluene was stirred in a dried glass vial for about 5 min at room temperature. The mixture was then added by syringe to the previous reaction mixture through the septum, and the resulting reaction mixture was microwave heated at 180 °C for 30 min. After being cooled to room temperature, the reaction mixture was purified by silica flash chromatography and isolated using the conditions indicated below.

1-Fluoronaphthalene (2a).[33] Synthesized from 1-naphthyl triflate according to general procedure A and from **3a** according to general procedure B. The reaction mixtures were purified using pentane as eluent to give **2a** as colorless oils. Procedure A: 77.2 mg, 53% yield. Procedure B: 75.1 mg, 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17−8.12 (m, 1H), 7.91−7.85 (m, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.60−7.49 (m, 2H), 7.42 (td, J = 8.0, 8.0, 5.4 Hz, 1H), 7.17 (ddd, J = 10.7, 7.7, 1.0 Hz, 1H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 158.9 (d, J_{CF} = 252 Hz), 135.0 (d, J_{CF} = 3 Hz), 127.7 (d, J_{CF} = 3 Hz), 126.9 (d, J_{CF} = 1 Hz), 126.3 (d, J_{CF} = 2 Hz), 125.7 (d, J_{CF} = 8 Hz), 123.8 (d, J_{CF} = 4 Hz), 123.9 (d, J_{CF} = 16 Hz), 120.7 (d, J_{CF} = 5 Hz), 109.5 (d, J_{CF} = 20 Hz).

Ethyl 4-Fluorobenzoate (2b).[34] Synthesized from ethyl 4-(((trifluoromethyl)sulfonyl)oxy)benzoate according to general procedure A and from **3f** according to general procedure B. The reaction mixtures were purified using 0−50% diethyl ether in pentanes to give **2b** as colorless oils. Procedure A: 107 mg, 63% yield. Procedure B: 119 mg, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 8.12−7.97 (m, 2H), 7.16−7.01 (m, 2H), 4.36 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 165.64 (d, J_{CF} = 252 Hz), 165.61, 132.01 (d, J_{CF} = 10 Hz), 126.71 (d, J_{CF} = 3 Hz), 115.39 (d, J_{CF} = 22 Hz), 61.04, 14.27.

(4-Fluorophenyl)(phenyl)methanone (2c).[35] Synthesized from 4-benzoylphenyl trifluoromethanesulfonate according to general procedure A and from **3g** according to general procedure B. The reaction mixtures were purified using 0−10% ethyl acetate in isohexane as eluent to give **2c** as colorless oils. Procedure A: 160 mg, 80% yield. Procedure B: 132 mg, 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87−7.83 (m, 2H), 7.79−7.75 (m, 2H), 7.62−7.57 (m, 1H), 7.52−7.47 (m, 2H), 7.19−7.13 (m, 2H) ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 195.40, 165.54 (d, J_{CF} = 254 Hz), 137.65, 133.96 (d, J_{CF} = 3 Hz), 132.81 (d, J_{CF} = 9 Hz), 132.61, 130.02, 128.50, 115.59 (d, J_{CF} = 22 Hz).

1-(Benzyloxy)-3-fluorobenzene (2d).[36] Synthesized from 3-(benzyloxy)phenyl trifluoromethanesulfonate according to general procedure A and from **3c** according to general procedure B. The reaction mixtures were purified using 5% dichloromethane in isohexane as eluent to give **2d** as colorless oils. Procedure A: 128

dx.doi.org/10.1021/jo400255m | J. Org. Chem. 2013, 78, 4184−4189

mg, 63% yield. Procedure B: 112 mg, 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.34 (m, 5H), 7.34−7.19 (m, 1H), 6.84−6.64 (m, 3H), 5.07 (s, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 163.66 (d, J_{CF} = 244 Hz), 160.15 (d, J_{CF} = 11 Hz), 136.51, 130.25 (d, J_{CF} = 10 Hz), 128.67, 128.15, 127.51, 110.68 (d, J_{CF} = 3 Hz), 107.77 (d, J_{CF} = 21 Hz), 102.64 (d, J_{CF} = 25 Hz), 70.25.

4-(3-Fluorophenyl)morpholine (2e).[37] Synthesized from **3b** according to general procedure B. The reaction mixture was purified using 25−50% dichloromethane in pentane as eluent to give **2e** as a colorless oil: 74.5 mg, 41% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24−7.17 (m, 1H), 6.68−6.64 (m, 1H), 6.61−6.52 (m, 2H), 3.88−3.82 (m, 4H), 3.18−3.22 (m, 4H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 164.02 (d, J_{CF} = 243 Hz), 153.12 (d, J_{CF} = 10 Hz), 130.34 (d, J_{CF} = 10 Hz), 110.94 (d, J_{CF} = 2 Hz), 106.39 (d, J_{CF} = 22 Hz), 102.58 (d, J_{CF} = 25 Hz), 66.88, 49.00.

4-Fluoro-3,5-dimethylbenzonitrile (2f).[38] Synthesized from **3d** according to general procedure B. The reaction mixture was purified using 0−50% diethyl ether in pentanes as eluent to give **2f** as a white solid: 120 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.29 (m, 2H), 2.26 (d, J = 2.3 Hz, 6H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 162.45 (d, J_{CF} = 253 Hz), 132.93 (d, J_{CF} = 6 Hz), 126.27 (d, J_{CF} = 20 Hz), 118.45, 107.44 (d, J_{CF} = 5 Hz), 14.38 (d, J_{CF} = 4 Hz).

1-(4-Fluorophenyl)ethanone (2g).[39] Synthesized from **3e** according to general procedure B, using 1,4-dioxane/toluene 1:9 as solvent. The reaction mixture was purified using a gradient of 0−20% diethyl ether in pentanes as eluent to give **2g** as a colorless oil: 89.1 mg, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01−7.87 (m, 2H), 7.16−6.99 (m, 2H), 2.54 (s, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 196.35, 165.75 (d, J_{CF} = 254 Hz), 133.54 (d, J_{CF} = 3 Hz), 130.87 (d, J_{CF} = 10 Hz), 115.55 (d, J_{CF} = 22 Hz), 26.43.

6-Fluoro-2-naphthonitrile (2h). Synthesized from **3h** according to general procedure B, using 1,4-dioxane/toluene 1:9 as solvent. The reaction mixture was purified using a gradient of 5−15% ethyl acetate in isohexane as eluent to give **2h** as a white solid: 110 mg, 64% yield, mp 125−127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23−8.20 (m, 1H), 7.95−7.85 (m, 2H), 7.66−7.62 (m, 1H), 7.50 (dd, J = 9.4, 2.5 Hz, 1H), 7.42−7.32 (m, 1H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 162.5 (d, J_{CF} = 251 Hz), 135.8 (d, J_{CF} = 10 Hz), 134.0 (d, J_{CF} = 1 Hz), 131.1 (d, J_{CF} = 9 Hz), 129.3 (d, J_{CF} = 2 Hz), 128.5 (d, J_{CF} = 6 Hz), 127.4, 118.9, 118.3, 111.5 (d, J_{CF} = 21 Hz), 108.8 (d, J_{CF} = 3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −108.8. HRMS (ESI): calcd for $C_{11}H_7FN$ $(M + H)^+$ 172.0563, found 172.0560.

2-(4-Fluorophenyl)-6-methyl-4*H*-chromen-4-one (2i). Synthesized from **3i** according to general procedure B. The reaction mixture was purified using first 0−10% ethyl acetate in isohexane, then dichloromethane as eluent to give **2i** as a white solid: 169 mg, 69% yield, mp 150−153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01−7.98 (m, 1H), 7.93−7.87 (m, 2H), 7.49 (dd, J = 8.6, 2.2 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.23−7.15 (m, 2H), 6.73 (s, 1H), 2.45 (s, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 178.5, 164.8 (d, J_{CF} = 253 Hz), 162.4, 154.6, 135.4, 135.2, 128.6 (d, J_{CF} = 9 Hz), 128.2 (d, J_{CF} = 3 Hz), 125.2, 123.6, 117.9, 116.4 (d, J_{CF} = 22 Hz), 107.3, 21.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −107.7. HRMS (ESI): calcd for $C_{16}H_{12}FO_2$ $(M + H)^+$ 255.0821, found 255.0818.

4-Fluoro-6-methyl-2-(trifluoromethyl)quinoline (2j).[14] Synthesized from **3j** according to general procedure B. The reaction mixture was purified using 0−10% ethyl acetate in isohexane as eluent to give **2j** as a white solid: 195 mg, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J = 8.8, 1.8, 1H), 7.90−7.88 (m, 1H), 7.69 (dd, J = 8.7, 2.0 Hz, 1H), 7.39 (d, J = 9.6 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 165.9 (d, J_{CF} = 270 Hz), 148.3 (dq, J_{CF} = 35, 8 Hz), 148.3 (d, J_{CF} = 6 Hz), 139.6 (d, J_{CF} = 2 Hz), 134.4, 129.7 (d, J_{CF} = 4 Hz), 121.0 (dq, J_{CF} = 275, 5 Hz), 119.9 (d, J_{CF} = 13 Hz), 119.26 (d, J_{CF} = 5 Hz), 102.3 (dq, J_{CF} = 19, 2 Hz), 22.06.

4-Fluoro-7-methoxy-2-phenylquinoline (2k). Synthesized from **3k** according to general procedure B, using 1,4-dioxane/toluene 1:1 as solvent. The reaction mixture was purified using 0−10% ethyl acetate in isohexane as eluent to give **2k** as a white solid; 186 mg, 73% yield, mp 87−89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12−8.08 (m, 2H), 7.95 (dd, J = 8.0, 0.8 Hz 1H), 7.56−7.40 (m, 5H), 7.21 (dd, J = 9.1, 2.5 Hz, 1H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 166.2 (d, J_{CF} = 265 Hz), 161.9, 159.7 (d, J_{CF} = 8 Hz), 152.5 (d, J_{CF} = 5 Hz), 139.2 (d, J_{CF} = 4 Hz), 129.8, 129.0, 127.5, 121.6 (d, J_{CF} = 5 Hz), 119.9 (d, J_{CF} = 2 Hz), 113.3 (d, J_{CF} = 13 Hz), 107.6 (d, J_{CF} = 4 Hz), 101.8 (d, J_{CF} = 17 Hz), 55.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −113.1. HRMS (ESI): calcd for $C_{16}H_{13}FNO$ $(M + H)^+$ 254.0981, found: 254.0986.

(2*S*)-2-(3-Bromo-4-((7-methoxy-2-phenylquinolin-4-yl)oxy)-phenyl)-2-((*tert*-butoxycarbonyl)amino)acetic acid (6).[27] A mixture of **5** (346 mg, 1.00 mmol) and potassium *tert*-butoxide (224 mg, 2.00 mmol) in dry DMSO (3 mL) was stirred at room temperature. After 10 min, **2k** (127 mg, 0.500 mmol) was added and the reaction stirred under nitrogen at 64 °C for 6 h. The reaction mixture was partitioned between water (60 mL) and diethyl ether (60 mL). The aqueous layer was acidified with 1 M HCl (aq) to pH 5 and extracted with dichloromethane (2 × 60 mL). The combined dichloromethane layers were dried ($MgSO_4$) and evaporated. The residue was purified by reversed-phase (C18) silica chromatography using a 10−90% gradient of acetonitrile in water with 0.05% formic acid. Product fractions were pooled and evaporated, and the product dried under vacuum overnight to give 107 mg (37%) of **6** as a light brown semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (br s, 1H), 8.20, (d, J = 9.3 Hz, 1H), 7.72−7.60 (m, 4H), 7.35 (d, J = 8.6 Hz, 1H), 7.27−7.15 (m, 4H), 7.05 (d, J = 8.6 Hz, 1H), 6.60 (s, 1H), 5.93 (br d, J = 6.9 Hz, 1H), 5.07(br d, J = 6.9 Hz, 1H), 3.87 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 173.0, 163.3, 163.3, 158.5, 155.1, 149.6, 148.1, 140.1, 135.9, 132.9, 130.8, 129.0, 128.4, 128.3, 123.5, 122.6, 120.4, 115.8, 114.5, 104.3, 101.2, 80.0, 57.9, 56.1, 28.5.

Computational Details. The DFT calculations were performed using Jaguar version 7.6[40] employing the B3LYP hybrid functional[41−43] with the LACVP*+ basis set, which uses an effective core potential[44] for Pd and 6-31+G* for all other atoms. All geometries were optimized in the gas phase with a subsequent single-point energy calculation in the solution phase, utilizing the PBF solvation model[45,46] with parameters suitable for toluene (dielectric constant, epsout = 2.38 and probe radius, radprb = 2.7620911). Vibrational analysis was performed for the optimized geometries in the gas phase, and the free energies for the geometries were calculated by adding the thermodynamic contribution, including zero-point energy, at 453.15 K to the solution-phase energy. Dispersion correction was calculated for the gas phase geometries using the DFT-D3 program[47] (version 2.0, rev 1) and was added to obtain the final energies. The TSs were verified to have exactly one negative frequency in the vibrational analysis and the ground states were verified to have no negative frequencies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}HNMR and ^{13}CNMR spectra of all isolated compounds. Structures of the optimized TS geometries. Energies and atomic coordinates for all optimized geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +46-18-4714667. Fax: +46-18-4714474. E-mail: mats.larhed@orgfarm.uu.se.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support from VINNOVA and thank Prof. Per-Ola Norrby for stimulating discussions.

■ REFERENCES

(1) Mueller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
(2) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(3) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
(4) Jeschke, P. *Pest Manage. Sci.* **2010**, *66*, 10.
(5) Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 2215.
(6) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2219.
(7) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, 1804.
(8) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470.
(9) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929.
(10) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 10795.
(11) Casitas, A.; Canta, M.; Sola, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* **2011**, *133*, 19386.
(12) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150.
(13) Tang, P.; Ritter, T. *Tetrahedron* **2011**, *67*, 4449.
(14) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661.
(15) Samant, B. S.; Bhagwat, S. S. *Appl. Catal., A* **2011**, *394*, 191.
(16) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482.
(17) Mahalingam, A. K.; Axelsson, L.; Ekegren, J. K.; Wannberg, J.; Kihlström, J.; Unge, T.; Wallberg, H.; Samuelsson, B.; Larhed, M.; Hallberg, A. *J. Med. Chem.* **2010**, *53*, 607.
(18) Fors, B. P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2009**, *65*, 6576.
(19) Hoshiya, N.; Buchwald, S. L. *Adv. Synth. Catal.* **2012**, *354*, 2031.
(20) Ersmark, K.; Larhed, M.; Wannberg, J. *Curr. Opin. Drug Discov. Dev.* **2004**, *7*, 417.
(21) Gising, J.; Odell, L. R.; Larhed, M. *Org. Biomol. Chem.* **2012**, *10*, 2713.
(22) Nilsson, P.; Gold, H.; Larhed, M.; Hallberg, A. *Synthesis* **2002**, 1611.
(23) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.
(24) GC yields were determined using dodecane as internal standard by comparing responses to three-point standard curves.
(25) Rottlander, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203.
(26) Hogermeier, J.; Reissig, H. U. *Adv. Synth. Catal.* **2009**, *351*, 2747.
(27) Lampa, A.; Ehrenberg, A. E.; Gustafsson, S. S.; Vema, A.; Åkerblom, E.; Lindeberg, G.; Karlén, A.; Danielson, U. H.; Sandström, A. *Bioorg. Med. Chem.* **2010**, *18*, 5413.
(28) Pan, J.; Wang, X.; Zhang, Y.; Buchwald, S. L. *Org. Lett.* **2011**, *13*, 4974.
(29) Grushin, V. V. *Chem.—Eur. J.* **2002**, *8*, 1006.
(30) Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 4710.
(31) Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* **2007**, *129*, 1342.
(32) Bengtson, A.; Hallberg, A.; Larhed, M. *Org. Lett.* **2002**, *4*, 1231.
(33) Yokota, M.; Fujita, D.; Ichikawa, J. *Org. Lett.* **2007**, *9*, 4639.
(34) Cai, C.; Rivera, N. R.; Balsells, J.; Sidler, R. R.; McWilliams, J. C.; Shultz, C. S.; Sun, Y. *Org. Lett.* **2006**, *8*, 5161.
(35) Xing, D.; Guan, B.; Cai, G.; Fang, Z.; Yang, L.; Shi, Z. *Org. Lett.* **2006**, *8*, 693.
(36) Kim, A.; Powers, J. D.; Toczko, J. F. *J. Org. Chem.* **2006**, *71*, 2170.
(37) Yong, F. F.; Teo, Y. C. *Tetrahedron Lett.* **2010**, *51*, 3910.
(38) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389.
(39) Murphy, J. A.; Commeureuc, A. G. J.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R. *Org. Lett.* **2005**, *7*, 1427.
(40) Jaguar, version 7.6, Schrödinger, LLC: New York, NY, 2009.
(41) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(42) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372.
(43) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(44) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.
(45) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, *100*, 11775.
(46) Tannor, D. J.; Marten, B.; Murphy, R.; Friesner, R. A.; Sitkoff, D.; Nicholls, A.; Honig, B.; Ringnalda, M.; Goddard, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 11875.
(47) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104.