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Divergent C−H Functionalizations Directed by Sulfonamide Pharmacophores: Late-Stage Diversification as a Tool for Drug Discovery

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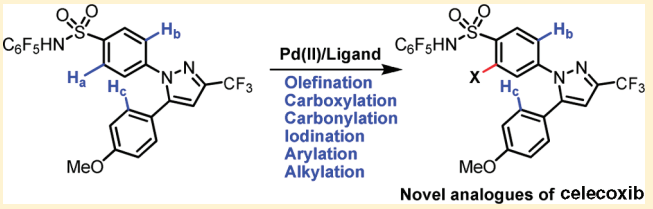
Supporting Information

ABSTRACT: Modern drug discovery is contingent on identifying lead compounds and rapidly synthesizing analogues. The use of a common pharmacophore to direct multiple and divergent C−H functionalizations of lead compounds is a particularly attractive approach. Herein, we demonstrate the viability of late-stage diversification through the divergent C−H functionalization of sulfonamides, an important class of pharmacophores found in nearly 200 drugs currently on the market, including the non-steroidal anti-inflammatory blockbuster drug celecoxib. We developed a set of six categorically different sulfonamide C−H functionalization reactions (olefination, arylation, alkylation, halogenation, carboxylation, and carbonylation), each representing a distinct handle for further diversification to reach a large number of analogues. We then performed late-stage, site-selective diversification of a sulfonamide drug candidate containing multiple potentially reactive C−H bonds to synthesize directly novel celecoxib analogues as potential cyclooxygenase-II (COX-2)-specific inhibitors. Together with other recently developed practical directing groups, such as CONHOMe and CONHC$_6$F$_5$, sulfonamide directing groups demonstrate that the auxiliary approach established in asymmetric catalysis can be equally effective in developing broadly useful C−H activation reactions.



1. INTRODUCTION

Among the many hurdles in identifying promising drug candidates, rapidly accessing molecular diversity is recognized as one of the potential bottlenecks.[1,2] Among many reported approaches,[3] site-selective replacement of inert C−H bonds of bioactive skeletons represents a unique strategy for accessing new pools of functionalized analogues.[4] To demonstrate the viability of this approach in drug discovery, we embarked on an investigation to develop a set of divergent C−H functionalization reactions directed by a privileged pharmacophore. Sulfonamide functional groups have long been acclaimed as essential structural motifs in medicinal chemistry since the early discovery of a series of sulfonamide-containing antibacterial drugs in 1932 (e.g., sulfamethoxazole).[5,6] Numerous sulfonamide-based medicines were subsequently found to be effective as diuretics (e.g., azosemide), anti-migraine agents (e.g., sumatriptan), and cyclooxygenase-II (COX-2)-specific anti-inflammatory drugs (e.g., celecoxib) (Figure 1). In the vast majority of cases, the sulfonamide moiety is thought to play a key role in the primary pharmacology and disposition characteristics of these marketed drugs. The introduction of a sulfonamide group represents an attractive tactic in medicinal chemistry for increasing pharmacologic potency and/or the absorption, distribution, metabolism, and excretion (ADME) attributes of the lead chemical matter. Therefore, late-stage, divergent C−H functionalizations directed by sulfonamides could provide a unique method for diversity-oriented synthesis (DOS) of drug candidates (Figure 1).

Herein, we report the design and discovery of six different catalytic systems to effect the efficient C−H functionalization of sulfonamides. Importantly, exclusive site-selectivity was achieved in the presence of multiple reactive C−H bonds, a traditionally challenging problem for late-stage diversification via C−H activation. In an effort to maximize access to different classes of analogues of existing aryl- and benzylsulfonamide skeletons, we developed six categorically different types of Pd(II)-catalyzed C−H functionalization reactions to install new carbon and heteroatom units. In terms of operational ease, the procedure of installation and removal of the appended directing groups is comparable to a common protection−deprotection sequence.[7] The utility of these reactions was also demonstrated by preparation of celecoxib analogues.

2. RESULTS AND DISCUSSION

2.1. Discovery of an Effective Sulfonamide Directing Group for C−H Olefination. Recently, substantial progress

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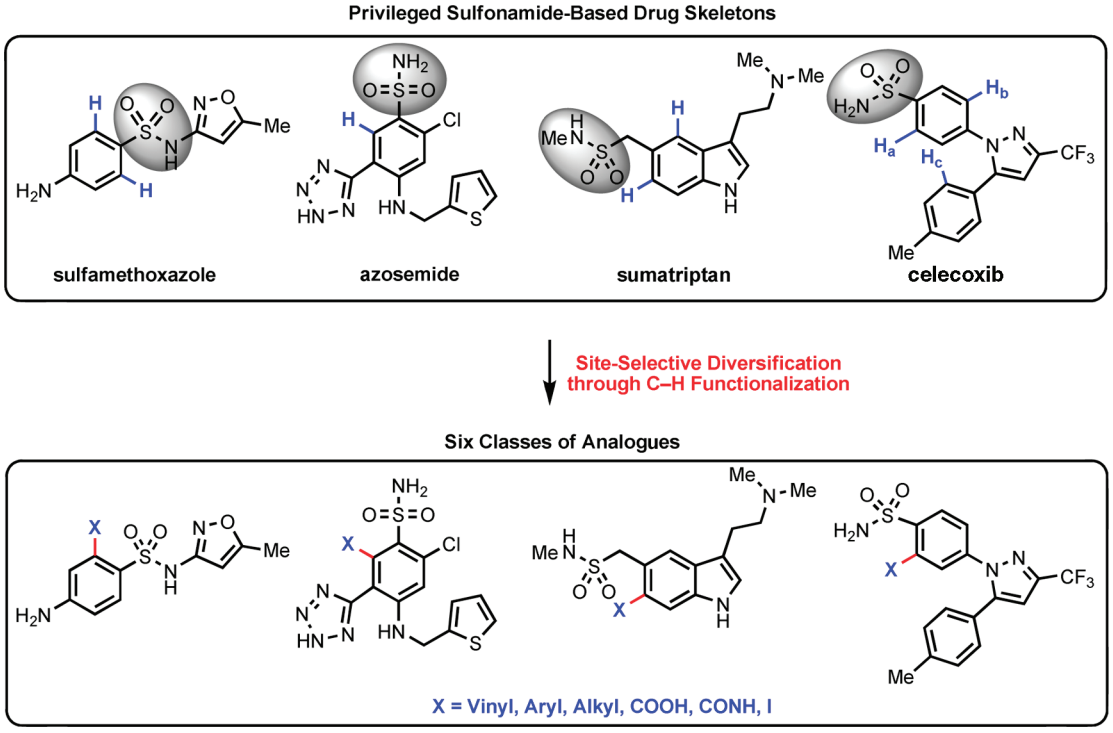
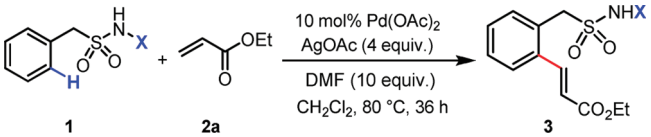
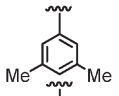
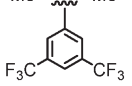
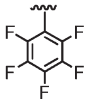


Figure 1. Site-selective diversification of sulfonamide drugs.

Table 1. Discovery of a Sulfonamide Directing Group for C−H Activation[a]

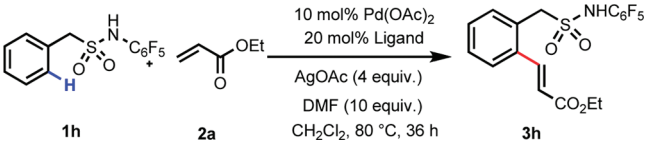


1 2a 3

entry	x	yield (%) mono	entry	x	yield (%) mono	yield (%) di
1	CH_3	N.R.	5	*i*-Pr	20	0
2		N.R.	6		< 5	
3	*t*-Bu	< 5	7		22	7
4	OMe	< 5	8		40	20

[a] Reaction conditions: **1** (0.125 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (4 equiv), **2a** (4 equiv), DMF (10 equiv), CH_2Cl_2, 80 °C, 36 h. ^1H NMR yield with CH_2Br_2 as internal standard.

Table 2. Ligand-Enabled C−H Olefination of Sulfonamides[a]



1h 2a 3h

entry	ligand	yield (%) mono	yield (%) di
1	none	40	20
2	Boc-Val-OH	35	57
3	Bz-Val-OH	48	19
4	Ac-Val-OH	15	79
5	Fmoc-Val-OH	31	65
6	(+)-menthyl(O_2C)-Leu-OH	37	59
7	**Ac-Leu-OH**	**4**	**89**
8	Boc-Leu-OH	16	78
9	Boc-Phe-OH	36	56
10	Boc-Thr(*t*-Bu)-OH	46	20
11	Boc-Tyr(*t*-Bu)-OH	33	57

[a] Reaction conditions: **1h** (0.125 mmol), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), AgOAc (4 equiv), **2a** (4 equiv), DMF (10 equiv), CH_2Cl_2, 80 °C, 36 h. ^1H NMR yield with CH_2Br_2 as internal standard.

has been made toward the development of Pd-catalyzed *ortho*-C−H functionalization reactions using simple functional groups (carboxyl,[8a,b] acidic amide,[8c−e] hydroxyl,[8f] carbonyl[8g]) to direct C−H cleavage through weak coordination. For instance, Pd(II)-catalyzed coupling of sp^3 C−H bonds with organoboronic acids has been employed to diversify bioactive natural products such as adipic acids.[4b] Pd(0)-catalyzed C−H arylation reactions have also been used to make anti-inflammatory ibuprofen analogues.[4c] To date, these reactions have not been demonstrated to be compatible with a major class of drug molecules due to lack of reactivity or selectivity. Keeping in mind that the directing group would need to be either part of the existing pharmacophore or

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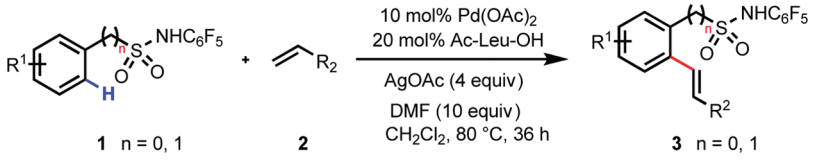
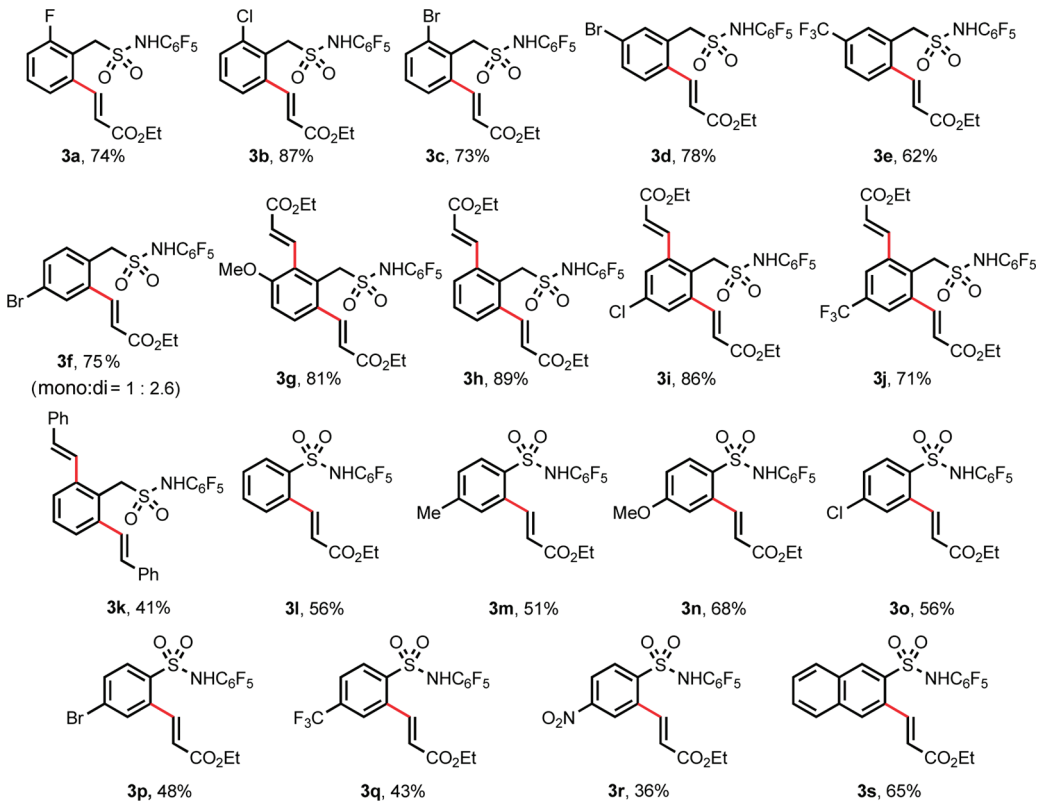
Table 3. C−H Olefination of Benzylsulfonamides and Benzenesulfonamides[a]





[a] Reaction conditions: **1** (0.125 mmol), $Pd(OAc)_2$ (10 mol %), Ac-Leu-OH (20 mol %), AgOAc (4 equiv), **2** (4 equiv), DMF (10 equiv), CH_2Cl_2, 80 °C, 36 h.

readily converted to the targeted drug molecule via simple synthetic operations, such as those that utilize a practical protecting group or Evans auxiliary,[9] we began our efforts by devising a generally applicable sulfonamide-based directing group capable of efficiently promoting divergent metal-catalyzed C−H activation reactions. Despite the pioneering Rh-catalyzed alkoxysulfonamide-directed nitrene insertion reactions,[10] sulfonamides have not been shown to direct palladation of C−H bonds. We first examined several benzylsulfonamide derivatives using a Pd(II)-catalyzed C−H olefination protocol as a screening assay for reactivity (Table 1). [Notably, a benzylsulfonamide is the key pharmacophore in sumatriptan.[5,6]] While the majority of commonly encountered sulfonamides were not sufficiently active in promoting C−H olefination, we found that the more acidic *N*-arylsulfonamide displayed encouraging reactivity, affording a mixture of mono- and di-olefinated products in 60% combined yield (entry 8).

Guided by our previous studies on ligand-accelerated C−H olefination,[11] we extensively screened mono-*N*-protected amino acid ligands (Table 2). We found that the use of Ac-Leu-OH as a ligand enhanced the reactivity drastically to produce predominantly the di-olefinated product in 89% yield (entry 7).

This olefination protocol was then applied to variety of benzylsulfonamide substrates (Table 3). C−H olefination of *ortho*- and *meta*-substituted benzylsulfonamides gave mono-olefinated products in good yields (**3a**−**3e**, Table 3). The presence of an electron-donating *meta*-OMe group enhanced the reactivity to give mainly the di-olefinated product (**3g**). Olefination of unsubstituted or *para*-substituted substrates afforded mainly the di-olefinated products accompanied by less than 5% of the mono-olefinated products, which could be readily separated by column chromatography (**3h**−**3j**). Moderate yield was obtained when styrene was used as the coupling partner (**3k**). It is noteworthy that the presence of electron-withdrawing groups (CF_3 and halides) on the aryl ring was also well-tolerated (**3a**−**3f**, **3i**, **3j**).

With this catalytic olefination protocol in hand, we then went on to test the applicability of this methodology to another important motif in drug molecules, benzenesulfonamides (Table 3). We were pleased to find that the reaction of benzenesulfonamide **1l** gave exclusively the mono-olefinated product **3l** in 56% isolated yield. The presence of an electron-donating group increased the yield to 68% (**3n**). Electron-withdrawing groups, such as halides and CF_3, decreased the yield

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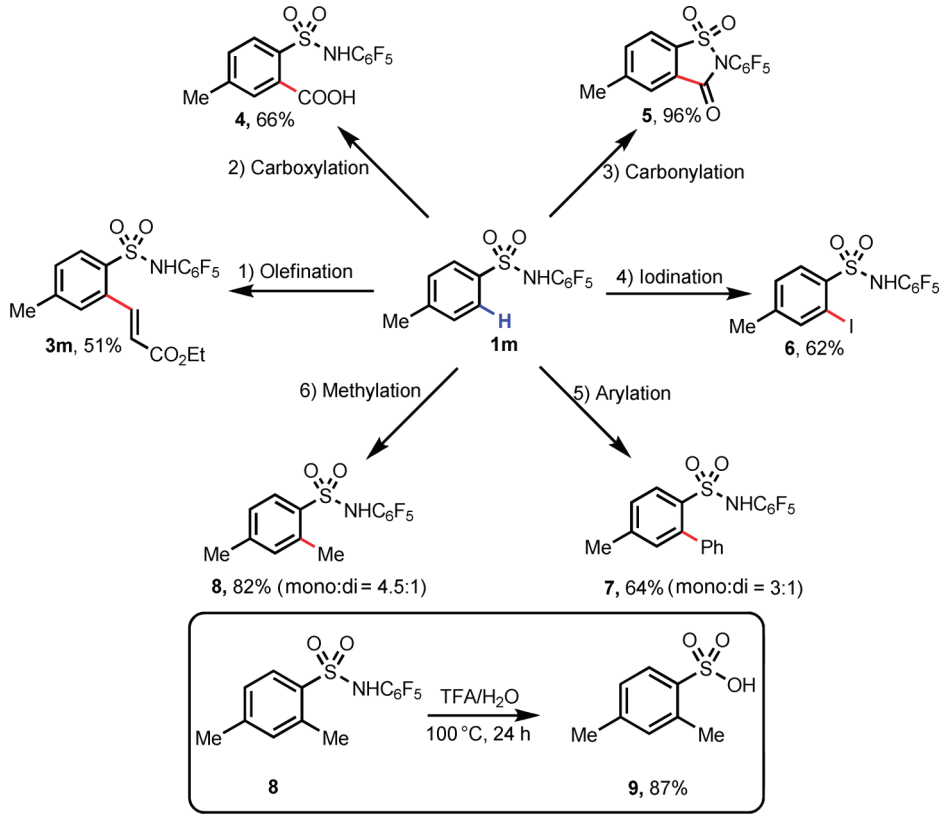
Scheme 1. Divergent C−H Functionalization Reactions of Sulfonamide 1m[a]



[a] Reaction conditions: (1) **1m** (0.125 mmol), $Pd(OAc)_2$ (10 mol %), Ac-Leu-OH (20 mol %), AgOAc (4 equiv), ethyl acrylate **2a** (4 equiv), DMF (10 equiv), CH_2Cl_2, 80 °C, 36 h; yield 51%. (2) **1m** (0.125 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (2 equiv), TEMPO (2 equiv), KH_2PO_4 (2 equiv), *n*-hexane, CO (1 atm), 130 °C, 24 h; yield 66%. (3) **1m** (0.125 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (2 equiv), KH_2PO_4 (2 equiv), *n*-hexane, CO (1 atm), 130 °C, 24 h; yield 96%. (4) **1m** (0.125 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (3 equiv), I_2 (3 equiv), DMF, 90 °C, 48 h; yield 62%. (5) **1m** (0.125 mmol), $Pd(OAc)_2$ (10 mol %), BQ (10 mol %), pinacol phenylboronate (2 equiv), K_2HPO_4 (1 equiv), Ag_2CO_3 (2 equiv), *t*-AmylOH, 110 °C, 24 h; yield 64% (mono:di = 3:1). (6) **1m** (0.125 mmol), $Pd(OAc)_2$ (10 mol %), BQ (10 mol %), $MeB(OH)_2$ (2 equiv), K_2HPO_4 (1 equiv), Ag_2CO_3 (2 equiv), *t*-AmylOH, 110 °C, 24 h; yield 82% (mono:di = 4.5:1).

(**3p**, **3q**). An extremely electron-withdrawing nitro group decreased the yield to 36% (**3r**). Interestingly, olefination of naphthalenesulfonamide proceeded with high selectivity at the 3-position to give the mono-olefinated product in 65% yield (**3s**). The relatively low reactivity of benzenesulfonamides (compared to benzylsulfonamides) is unsurprising because sulfonyl groups tend to significantly decrease the electron density of arenes. Although further improvement of this olefination can be expected through optimization of conditions and ligands, this reactivity encouraged us to move forward to develop a broad range of reactions in order to achieve diversification as described below.

2.2. Development of Divergent C−H Functionalizations Directed by Sulfonamides. To establish the sulfonamide group as a powerful handle for DOS, the next important challenge was to apply this newly uncovered C−H activation reactivity to develop a broad range of carbon−carbon and carbon−heteroatom bond-forming processes. Drawing upon our accumulated experience in developing Pd(II)-catalyzed C−H functionalization reactions,[11,12] extensive screening and optimizations were carried out to develop several new *ortho*-C−H functionalization processes. Thus far, we have successfully developed new catalytic conditions to perform a diverse range of reactions directed by the same sulfonamide functionality, including olefination,[11] carboxylation,[12a] carbonylation,[12b] iodination,[12c] arylation,[8a] and alkylation[12d] (Scheme 1). Excellent yields of the carbonylation and methylation were obtained, 96% and 82%, respectively. Notably, the majority of previously reported directing groups have only been shown to promote a limited set of C−H activation transformations. The availability of these unprecedented transformations demonstrates the power of the sulfonamide group to diversify a privileged skeleton in a manner that was previously impossible. The *N*-aryl moiety in the product can be kept as part of the pharmacophore or readily removed by hydrolysis with TFA in order to prepare other sulfonamide derivatives (Scheme 1). In terms of ease, the procedure for removing this directing group is comparable to a common deprotection step.

2.3. Preparation of Celecoxib Analogues via Late-Stage Diversifications. Finally, we performed this divergent C−H functionalization technique on celecoxib analogue **1t**, which is readily available in large quantities from the Pfizer sample bank and only differs from the blockbuster celecoxib by an OMe group in place of a Me group (Scheme 2). We chose celecoxib analogue **1t** in order to examine the viability of our late-stage diversification approach in complex settings. In this case, site-selective C−H bond functionalization must occur in the presence of multiple reactive C−H bonds that could be cleaved through competitive

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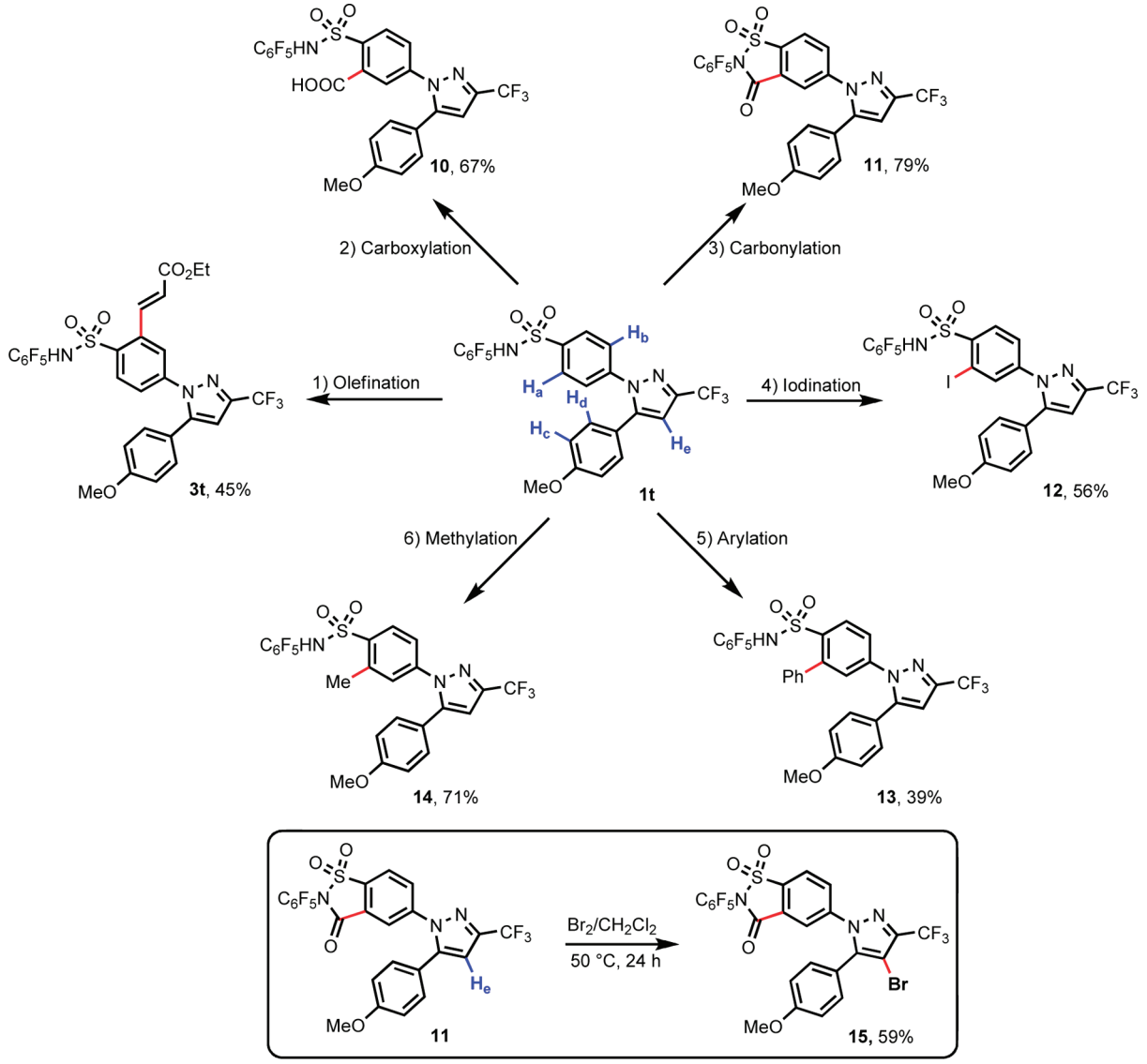
Scheme 2. Preparation of Celecoxib Analogues through Divergent C−H Functionalization[a]



[a] Reaction conditions: (1) **1t** (0.0625 mmol), $Pd(OAc)_2$ (20 mol %), Ac-Leu-OH (40 mol %), AgOAc (4 equiv), ethyl acrylate **2a** (4 equiv), DMF (10 equiv), HOAc (2 equiv), CH_2Cl_2, 100 °C, 48 h; yield 45%. (2) **1t** (0.0625 mmol), $Pd(OAc)_2$ (20 mol %), AgOAc (2 equiv), TEMPO (2 equiv), KH_2PO_4 (2 equiv), *n*-hexane, CO (1 atm), 130 °C, 24 h; yield 67%. (3) **1t** (0.0625 mmol), $Pd(OAc)_2$ (20 mol %), AgOAc (2 equiv), KH_2PO_4 (2 equiv), *n*-hexane, CO (1 atm), 130 °C, 24 h; yield 79%. (4) **1t** (0.0625 mmol), $Pd(OAc)_2$ (20 mol %), $PhI(OAc)_2$ (3 equiv), I_2 (3 equiv), DMF, 110 °C, 48 h; yield 56%. (5) **1t** (0.0625 mmol), $Pd(OAc)_2$ (20 mol %), BQ (20 mol %), pinacol phenylboronate (2 equiv), K_2HPO_4 (1 equiv), Ag_2CO_3 (2 equiv), *t*-AmylOH, 110 °C, 24 h; yield 39%. (6) **1t** (0.0625 mmol), $Pd(OAc)_2$ (20 mol %), BQ (20 mol %), $MeB(OH)_2$ (2 equiv), K_2HPO_4 (1 equiv), Ag_2CO_3 (2 equiv), *t*-AmylOH, 110 °C, 24 h; yield 71%.

reaction pathways. For instance, the $C-H_b$ bond could undergo pyrazole-directed C−H activation,[13] or alternatively, the electron-donating OMe group on the anisole ring in **1t** could render the $C-H_c$ or $C-H_d$ bonds reactive enough to undergo Fujiwara-type electrophilic palladation[14] or electrophilic bromination. Furthermore, the $C-H_e$ bond could also be brominated with $Br_2/HOAc$[15] or arylated following treatment with Pd(0)/ArBr by known procedures.[16] Thus, we were pleased to find that treatment of celecoxib analogue **1t** under our six reactions conditions (olefination, carboxylation, etc.) yielded exclusively the corresponding products (**3t** and **10**−**14**) from sulfonamide-directed functionalization of the $C-H_a$ bond; other C−H functionalization pathways were not observed. Each of these newly installed carbon or heteroatom units represents a distinct handle for further diversification to access a large number of previously unavailable celecoxib analogues for biological screening as potential COX-2-selective inhibitors.[15] For instance, C−C cross-coupling could be performed with a wide range of alkyl and aryl boron reagents. The newly installed iodide, carboxyl, and vinyl groups, on the other hand, can readily be converted to many other functional groups. It is noteworthy that selective bromination of $C-H_e$ in the functionalized products also provides a handle for further diversification (Scheme 2). It should be noted that *de novo* syntheses of these analogues would not only be laborious but could also be problematic, as the newly installed functional groups may not necessarily be compatible with a

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particular synthetic sequence. Additionally, some of the substituted sulfonamide building blocks require multiple steps to synthesize.

3. CONCLUSION

In summary, we have successfully employed key sulfonamide pharmacophores to direct a diverse range of C−H functionalization reactions. The directing power of the sulfonamide group overrides a common heterocycle directing group, affording exclusive site-selectivity in the presence of multiple potentially reactive C−H bonds. This combination of selectivity and versatility paves the way for late-stage diversifications of drug molecules. The utility of divergent C−H functionalization in drug discovery is demonstrated by the rapid preparation of six categorically distinct analogues of the blockbuster celecoxib as potential COX-2-selective inhibitors. Together with other recently developed practical directing groups, such as CONHOMe and $CONHC_6F_5$, this sulfonamide directing group further showcases the feasibility and potential of developing "Evans auxiliary equivalents" for assisting practical C−H activation reactions.

4. EXPERIMENTAL SECTION

4.1. General Information. Anhydrous solvents were obtained by purification according to standard methods,[17] and all other solvents were used as received from commercial sources without further purification. With the exception of 3-methoxylbenzylsulfonyl chloride[18] and 4-(5-(4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzene-1-sulfonyl chloride,[19,20] all the other sulfonyl chlorides, olefin coupling partners, and reagents used to prepare the sulfonamide substrates were purchased from Acros, Sigma-Aldrich, TCI, Oakwood, and Alfa-Aesar and were used as received without further purification. Palladium acetate was purchased from Sigma-Aldrich and used without further purification. The amino acid ligands were purchased from Bachem and Novabiochem. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-AV (400 and 100 MHz, respectively), Bruker DRX (500 and 125 MHz, respectively), and Bruker-DRX (600 and 150 MHz, respectively) instruments and are reported relative to the $SiMe_4$ or residual undeuterated solvent signals. High-resolution mass spectra were recorded at the Center for Mass Spectrometry, The Scripps Research Institute.

4.2. General Procedure for the C−H Olefination of Benzylsulfonamides and Benzenesulfonamides. In a 20 mL sealed tube, benzylsulfonamide **1a** (45 mg, 0.125 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol, 10 mol %), Ac-Leu-OH (4.5 mg, 0.025 mmol, 20 mol %), AgOAc (82 mg, 0.50 mmol, 4 equiv), ethyl acrylate **2a** (53 μL, 0.50 mmol, 4 equiv), and DMF (0.1 mL, 1.25 mmol, 10 equiv) were dissolved in CH_2Cl_2 (2 mL) under air. The reaction mixture was then stirred at 80 °C for 36 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a small pad of Celite. The filtrate was concentrated *in vacuo* and purified by a silica-gel-packed flash chromatography column, using ethyl acetate/hexane as the eluent. The product **3a** was obtained as a white amorphous solid (42 mg, 74% yield).

4.3. General Procedure for the C−H Carboxylation of Benzenesulfonamides. A 50 mL Schlenk-type tube (with a Teflon high-pressure valve and side arm) equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol, 10 mol %) followed by sulfonamide **1m** (42 mg, 0.125 mmol, 1.0 equiv), AgOAc (42 mg, 0.25 mmol, 2.0 equiv), KH_2PO_4 (34 mg, 0.25 mmol, 2.0 equiv), TEMPO (39 mg, 0.25 mmol, 2.0 equiv), and *n*-hexane (2 mL). The reaction tube was evacuated, back-filled with CO (five times, balloon), and heated to 130 °C for 24 h under vigorous stirring. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a small pad of Celite. The filtrate was concentrated *in vacuo* and purified by a silica-gel-packed flash chromatography column, using ethyl acetate/methanol as the eluent. The product **4** was obtained as a white amorphous solid (32 mg, 66% yield).

4.4. General Procedure for the C−H Carbonylation of Benzenesulfonamides. A 50 mL Schlenk-type tube (with a Teflon high-pressure valve and side arm) equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol, 10 mol %) followed by sulfonamide **1m** (42 mg, 0.125 mmol, 1.0 equiv), AgOAc (42 mg, 0.25 mmol, 2.0 equiv), KH_2PO_4 (34 mg, 0.25 mmol, 2.0 equiv), and *n*-hexane (2 mL). The reaction tube was evacuated, back-filled with CO (five times, balloon), and heated to 130 °C for 24 h under vigorous stirring. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a small pad of Celite. The filtrate was concentrated *in vacuo* and purified by a silica-gel-packed flash chromatography column, using ethyl acetate/hexane as the eluent. The product **5** was obtained as a white amorphous solid (43 mg, 96% yield).

4.5. General Procedure for the C−H Iodination of Benzenesulfonamides. In a 20 mL sealed tube, **1m** (42 mg, 0.125 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol, 10 mol %), $PhI(OAc)_2$ (121 mg, 0.375 mmol, 3.0 equiv), and I_2 (96 mg, 0.375 mmol, 3.0 equiv) were dissolved in DMF (2 mL) under air. The reaction mixture was then stirred at 90 °C for 48 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a small pad of Celite. The filtrate was concentrated *in vacuo* and purified by a silica-gel-packed flash chromatography column, using ethyl acetate/hexane as the eluent. The product **6** was obtained as a pale yellow amorphous solid (36 mg, 62% yield).

4.6. General Procedure for the C−H Arylation of Benzenesulfonamides. In a 20 mL sealed tube, **1m** (42 mg, 0.125 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol, 10 mol %), 1,4-benzoquinone (BQ) (1.5 mg, 0.0125 mmol, 10 mol %), Ag_2CO_3 (69 mg, 0.25 mmol, 2 equiv), pinacol phenylboronate (51 mg, 0.25 mmol, 2.0 equiv), and K_2HPO_4 (22 mg, 0.125 mmol, 1.0 equiv) were dissolved in *t*-AmylOH (2 mL) under air. The reaction mixture was then stirred at 110 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a small pad of Celite. The filtrate was concentrated *in vacuo* and purified by a silica-gel-packed flash chromatography column, using ethyl acetate/hexane as the eluent. The products **7** (25 mg, 48% yield) and **7′** (9 mg, 16% yield) were obtained as pale yellow oils.

4.7. General Procedure for the C−H Methylation of Benzenesulfonamides. In a 20 mL sealed tube, **1m** (42 mg, 0.125 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol, 10 mol %), 1,4-benzoquinone (BQ) (1.5 mg, 0.0125 mmol, 10 mol %), Ag_2CO_3 (69 mg, 0.25 mmol, 2.0 equiv), $MeB(OH)_2$ (15 mg, 0.25 mmol, 2.0 equiv), and K_2HPO_4 (22 mg, 0.125 mmol, 1.0 equiv) were dissolved in *t*-AmylOH (2 mL) under air. The reaction mixture was then stirred at 110 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a small pad of Celite. The filtrate was concentrated *in vacuo* and purified by a silica-gel-packed flash chromatography column, using ethyl acetate/hexane as the eluent. The products **8** (29 mg, 67% yield) and **8′** (7 mg, 15% yield) were obtained as pale yellow amorphous solids.

4.8. Hydrolysis of Sulfonamide 8. Sulfonamide (**8**, 22 mg, 0.0626 mmol) was dissolved in trifluoroacetic acid−H_2O (10:1, 2.2 mL), and the mixture was heated to 100 °C for 24 h before cooling to room temperature. After the solvent was removed *in vacuo*, the residue was dissolved in H_2O (5 mL) and washed with ethyl acetate (5 mL × 3). H_2O was removed *in vacuo* to obtain sulfonyl acid **9**[6] (14 mg, 87% yield) as a white amorphous solid. ^{1}H NMR (400 MHz, D_2O): δ 7.60

(d, J = 8.0 Hz, 1H), 7.09 (s, 1H), 7.03 (d, J = 7.6 Hz, 1H), 2.42 (s, 3H), 2.21 (s, 3H).

4.9. Bromination of Sulfonamide 11. To a solution of **11** (11 mg, 0.0187 mmol) in CH_2Cl_2 (1 mL) at room temperature was added a solution of 1.0 M Br_2/CH_2Cl_2 (95 μL, 0.0935 mmol) dropwise. The mixture was then stirred at 50 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and extracted with saturated $NaHCO_3$ (2 × 50 mL) followed by brine (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. The crude product was purified by a silica-gel-packed flash chromatography column, using ethyl acetate/hexane (1:4) as the eluent. The product **15** was obtained as a white amorphous solid (7.3 mg, 59% yield).

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, characterization of new compounds, and complete ref 15. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Dolle, R. E.; Bourdonnec, B. L.; Worm, K.; Morales, G. A.; Thomas, C. J.; Zhang, W. *J. Comb. Chem.* **2010**, *12*, 765. (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.

(2) (a) Schreiber, S. L. *Nature* **2009**, *457*, 153. (b) Galloway, W. R. J. D.; Spring, D. R. *Nature* **2011**, *470*, 43.

(3) (a) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem. Int. Ed.* **2008**, *48*, 104. (b) Medeiros, M. R.; Narayan, R. S.; McDougal, N. T.; Schaus, S. E.; Porco, J. A., Jr. *Org. Lett.* **2010**, *12*, 3222. (c) Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D. R.; Myers, A. G. *Science* **2005**, *308*, 395. (d) Chernyak, N.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 2743. (e) Pelish, H. E.; Westwood, N. J.; Feng, Y.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 6740.

(4) For discussion on divergent synthesis using identical advanced intermediates, see: (a) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050. (b) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (c) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. (d) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (e) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2009**, *11*, 1511. (f) Qi, X.; Rice, G. T.; Lall, M. S.; Plummer, M. S.; White, M. C. *Tetrahedron* **2010**, *66*, 4816.

(5) Kalgutkar, A.; Jones, R.; Sawant, A. In *Metabolism Pharmacokinetics and Toxicity of Functional Groups*; Smith, D. A., Ed.; RSC: Cambridge, UK, 2010; RSC Drug Discovery Series No. 1, Chapter 5.

(6) Hansch, C.; Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*; Pergamon Press: Oxford, UK, 1990; Vol. 2, Chapter 7.1.

(7) For examples of traceless directing groups, see: (a) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (b) Ihara, H.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 7502. (c) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270. (d) Dudnik, A. S.; Chernyak, N.; Huang, C.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 8729.

(8) (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (c) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (d) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (e) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. (f) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916. (g) Gandeepan, P.; Parthasarathy, K.; Cheng., C.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8569.

(9) (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 130. (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.

(10) (a) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.(b) Zalatan, D. N.; Du Bois, J. In *Topics in Current Chemistry*; Yu, J.-Q., Shi, Z., Eds.; Springer-Verlag: Berlin, Germany, 2010; Vol. 292, pp 347−378.

(11) (a) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137. (b) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315.

(12) (a) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (b) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378. (c) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 5215. (d) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78.

(13) (a) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (b) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285. (c) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466.

(14) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 6144.

(15) Penning, T. D.; et al. *J. Med. Chem.* **1997**, *40*, 1347.

(16) (a) Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042. (b) Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 8946.

(17) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, 1997.

(18) Valerie, C.; Katherine, L.; Thomas, M. S. PCT Int. Appl. WO 2007140317 A2 20071206, 2007.

(19) Gao, M.; Wang, M.; Miller, K. D.; Hutchins, G. D.; Zheng, Q.-H. *Appl. Radiat. Isot.* **2009**, *67*, 2019.

(20) Szabó, G.; Fischer, J.; Kis-Varga, Á.; Gyires, K. *J. Med. Chem.* **2008**, *51*, 142.