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Regiodivergent synthesis of sulfone-tethered lactam–lactones bearing four contiguous stereocenters†

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Sulfone-tethered lactones/amides/amines display a diverse spectrum of biological activities, including anti-psychotic and anti-hypertensive. Sulfones are also widely present in functional materials and fragrances. We therefore reasoned that a regiodivergent and stereocontrolled strategy that merges the sulfone, lactone, and lactam motifs would likely lead to the discovery of new pharmacophores and functional materials. Here, we report mild conditions for the sulfonyllactonization of γ -lactam-tethered 5-aryl-4(*E*)-pentenoic acids. The annulation is highly modular, chemoselective, and diastereoselective. With respect to regioselectivity, trisubstituted alkenoic acids display a preference for 5-*exo-trig* cyclization whereas disubstituted alkenoic acids undergo exclusive 6-*endo-trig* cyclization. The lactam-fused sulfonyllactones bear angular quaternary as well as four contiguous stereocenters. The products are post-modifiable, especially through a newly developed Co-catalyzed reductive cross-coupling protocol.

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Introduction

Biologically active and pharmaceutically-pertinent molecules are replete with the sulfone structural motif, presumably due to its overwhelmingly positive effects on metabolism, liposolubility, and stability.^{1,2} As shown in Fig. 1, ester/amide-tethered sulfones are marketed drugs for the treatment of human diseases, including anti-migraine Vioxx (A), anti-androgen Casodex (B), antipsychotic Amisulpride (C), CXCR2 antagonist Danirixin (D), r-secretase inhibitor E, and anti-hypertensive renin inhibitor Remikiren (F).³ Sulfone-bearing architectures are also widely present in functional materials where they exhibit remarkable activity.⁴ Importantly, the organic chemistry literature is saturated with examples of sulfones serving different roles in chemical synthesis.⁵ As a result, several methodologies for the construction of sulfonyl lactones have been developed.⁶ Among them, the vicinal sulfonyl functionalization of alkenes is heralded because it enables the simultaneous introduction of a sulfonyl group and other synthetically versatile functionalities such as lactones and lactams.^{6,7}

Diversity-Oriented Synthesis (DOS) is gradually transitioning from structural diversity to biological as well as functional relevance.⁷ A complementary strategy for generating biologically-relevant chemical libraries is to employ complexity-generating transformations that produce compounds with

conformationally rigid cyclic frameworks with a high ratio of sp^3 carbon atoms.⁸ Increasing the three-dimensional character of a molecule has indeed been associated with a more successful outcome in drug discovery.⁹ We therefore surmised that a diastereoselective and modular strategy that merges the pharmaceutically pertinent lactam, lactone, and sulfone motifs would likely expand the 3D-structural space for the discovery of new small molecules with medicinal value.

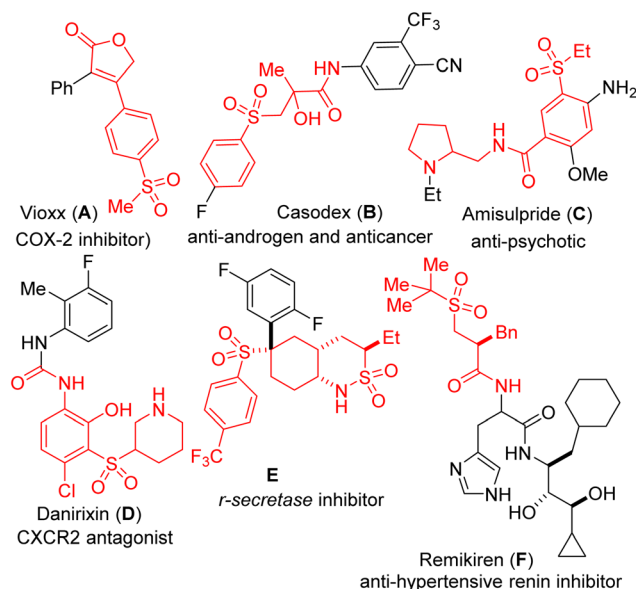


Fig. 1 Examples of bioactive ester- or amide-tethered sulfones.

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In the last decade, we have sought to popularize the 1,3-azadiene-anhydride reaction for the stereocontrolled synthesis of lactam-bearing 5-aryl-4(*E*)-pentenoic acids of type **1** (ref. 10) (Fig. 2A) and subsequent post-diversification. Recently, we developed practical and flexible methodologies toward halogen-containing, *trans*-fused lactam–lactones bearing quaternary and contiguous stereocenters (see C and D, Fig. 2A).^{10f,g} Seeking to further leverage the synthetic versatility of the aforementioned 1,3-azadiene-anhydride reaction, we decided to interrogate these sterically challenged and electronically diverse 5-aryl-4(*E*)-pentenoic acids (*i.e.*, **1**) in a sulfonyllactonization protocol (Fig. 2B). Although significant advances have been achieved in the arenas of hydrolactonization,¹¹ halolactonization,¹² aminolactonization,¹³ or trifluoromethylactonization,¹⁴ of 4-pentenoic acids, sulfonyllactonization is still at the incipient stages. Recent advances are starting to bring these once elusive building blocks into the mainstream.^{5e,6} However, most of these advances hinge on the sulfonyllactonization of electronically suitable 4-aryl-4-pentenoic acids (Fig. 2C) where the regioselectivity of the transformation can be predicted *a priori*.

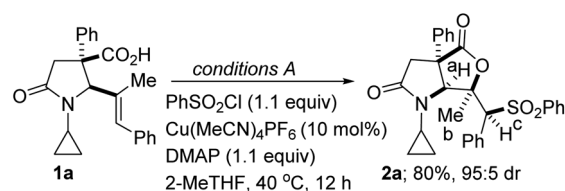
We were therefore motivated by current methodological limitations and the relevance of sulfonylated lactones to develop a regiodivergent, diastereoselective, flexible, and scalable method for the preparation of highly decorated sulfone-containing lactam–lactones bearing at least two tetrasubstituted- and four contiguous stereocenters. The successful sulfonyllactonization of trisubstituted alkenoic acids of type **1** ($R' \neq H$) would represent a significant advance given that such substrates are inherently problematic from the standpoints of

regioselectivity and diastereoselectivity. Efforts towards the manifestation of our ideals are described herein. Regarding the regioselectivity of this intramolecular vicinal difunctionalization protocol, we find that trisubstituted alkenoic acids display a preference for 5-*exo-trig* cyclization whereas 1,2-disubstituted alkenoic acids undergo exclusive 6-*endo-trig* cyclization.

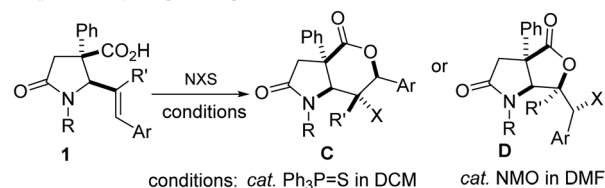
Results and discussion

We initiated studies toward the construction of sulfone-tethered fused lactam- γ -lactones by benchmarking our optimization efforts for sulfonyllactonization of alkenoic acid **1a** (see the ESI† for the preparation of the lactam-tethered alkenoic acids) with the Buchwald-inspired^{5c} reaction conditions described in Table 1. Trisubstituted alkenoic acid **1a** was chosen as the model substrate with the view of testing the power/limits of the transformation since the sulfonyllactonization of trisubstituted alkenes is quite challenging.

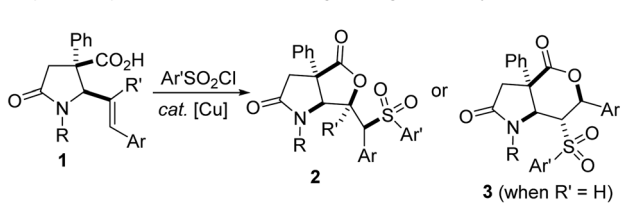
Table 1 Optimization of the sulfonyllactonization of lactam-tethered alkenoic acid **1a**^a



A (prior work): Regiodivergent halolactonization of **1**



B (this work): Stereocontrolled and regiodivergent sulfonyllactonization of **1**



C: Previously reported approaches to sulfonyllactonization of simple 4-substituted-pentenoic acids

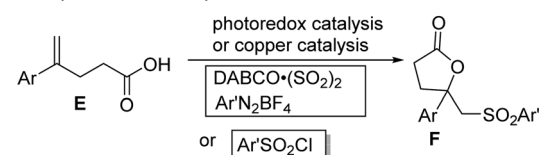


Fig. 2 (A) Our prior synthesis of fused lactam-halolactones from 5-aryl-4(*E*)-pentenoic acids **1**, (B) proposed plan for stereocontrolled sulfonyllactonization of **1**, (C) reported approaches for sulfonyllactonization of simple 4-substituted-pentenoic acids.

Entry	Deviation from conditions A	% Yield of 2a
1	EtOAc as solvent	61
2	THE as solvent	69
3	MTBE as solvent	53
4	Nitromethane as solvent	68
5	1,4-Dioxane as solvent	49
6	Dichloroethane as solvent	22
7	DMSO as solvent	48
8	PhMe	12
9	DMF	21
10	MeOH	0
11	CF ₃ CH ₂ OH	0
12	TMO	72
13	Cu(MeCN) ₄ PF ₆ omitted	0
14	CuI in place of Cu(MeCN) ₄ PF ₆	<5
15	CuBr in place of Cu(MeCN) ₄ PF ₆	22
16	CuCl in place of Cu(MeCN) ₄ PF ₆	48
17	CuOTf in place of Cu(MeCN) ₄ PF ₆	<5
18	Cu(OAc) ₂ in place of Cu(MeCN) ₄ PF ₆	0
19	Cu(NO ₃) ₂ · 3H ₂ O in place of Cu(MeCN) ₄ PF ₆	0
20	DMAP omitted	18
21	DBU in place of DMAP	73
22	KF in place of DMAP	51
23	Et ₃ N in place of DMAP	38
24	2,2'-Bipyridine in place of DMAP	15
25	After 4 h at 60 °C	53
26	After 36 h at room temperature	75

^a Relative configuration established by NOESY noe's between a and b as well as between b and c.



Reaction optimization was carried out and it was established that 2-methyltetrahydrofuran (2-MeTHF) out-performs other reaction media (*e.g.*, ethyl acetate (EtOAc), tetrahydrofuran (THF), methyl *tert*-butyl ether (MTBE), nitromethane, 1,4-dioxane, dichloroethane, dimethyl sulfoxide (DMSO), toluene, *N,N*-dimethylformamide (DMF), methanol, trifluoromethyl ethanol, and 2,2,5,5-tetramethyloxolane (TMO); entries 1–12). This is noteworthy since 2-MeTHF offers several advantages,¹⁵ including that: (a) it readily phase-separates from aqueous layers (in contrast to THF); (b) it is obtained from furfural, which originates from a renewable feedstock; (c) it is not easily oxidized; and (d) it has minimal health risks. No background reaction occurs in the absence of the copper catalyst (entry 13). Other copper(i) precatalysts that were surveyed did not perform as well as Cu(MeCN)₄PF₆ (entries 14–19). The reaction could not be catalyzed by a cationic copper(II) salt (entries 18 and 19). Of the base additives that were surveyed, DMAP emerged as the optimal base (entries 20–24). As described in Table 1, the relative configuration of 5-*exo* cyclization product **2a** was established by NOESY analysis. We are however not oblivious to the possibility of *anti*-stereoselective sulfonyllactonization followed by free rotation around the C–C sigma bond, which then places the hydrogen on the sulfone-bearing carbon (*i.e.*, H_c) on the same side as the methyl group.

The scope of the transformation with respect to the lactam-tethered alkenoic acid has been explored. Knowing that the nature of the nitrogen substituent present on a nitrogen heterocycle can have a dramatic effect on its biological activity¹⁶ and reactivity, the effect of the *N*-substituent on the sulfenolactonization was first explored. Encouragingly, *N*-alkyl-substituted allylic lactam acids are competent substrates for the annulation (see **2a/b**). *N*-arylated γ -lactam-tethered alkenoic acids underwent productive 6-*exo*-cyclization (see **2c/d**), which is noteworthy since *N*-aryl γ -lactams are embedded in several pharmacologically pertinent targets.¹⁷ Lactam-tethered alkenoic acids harboring electronically diverse *N*-benzyl substituents undergo satisfactory cyclization (see **2e–g**). The successful construction of sulfonylated lactam–lactones harboring the *N*-phenethyl group (see **2h–i**) is noteworthy given that the latter is often employed as a precursor to the indolizidine/quinolizidine scaffold.¹⁸ The transformation displays excellent chemoselectivity given that a lactam-tethered alkenoic acid bearing an *N*-allyl substituent reacts with phenylsulfonyl chloride to afford bicycle **2k**, without complications arising from sulfonyllactonization of the kinetically more accessible allyl group. We attribute this chemoselective sulfonyllactonization to conformational constraints and to the more activated nature of the styrenyl double bond. The addition process of the sulfonyl radical to the alkenoic acid is dependent on the steric hindrance of the olefin seeing as replacement of the internal methyl substituent with an unbranched hexyl group leads to a compromise in the efficiency of the annulation (**2i** vs. **2l/m**). Indeed, our luck runs out when the methyl group is replaced by a sterically imposing *tert*-butyl substituent given that no cyclization takes place (**2h** vs. **2n**). As expected, when the internal methyl group is replaced by a phenyl group, the lactam-tethered 4,5-diphenyl-4(*E*)-pentenoic acid undergoes exclusive 5-*exo*

cyclization in modest efficiency (**2h** vs. **2o**). The yield can be improved slightly when the reaction is performed at 60 °C. In these low-yielding cases, the remaining mass balance is mostly accounted for by recovered **1**. Lactam-tethered 5-aryl-4(*E*)-pentenoic acids bearing electron-rich aryl groups are as competent as their electron-deficient congeners (**2p** vs. **2q**).

In a mechanistically intuitive outcome, these studies have revealed that when disubstituted alkenoic acids are employed in place of the trisubstituted acids featured so far, a complete reversal in regioselectivity is observed and 6-*endo* cyclization predominates over 5-*exo* cyclization, leading to products of type **3** (see **3a/b**). A direct comparison between **2b** and **3a** is illuminating and clearly highlights how the internal substituent on the alkene alters the regioselectivity.

As shown in Scheme 2, the scope of the sulfonyllactonization with respect to the sulfonyl chloride has been explored, *albeit* briefly. The results indicate that both electron-deficient and electron-rich aryl sulfonyl chlorides are competent coupling partners (**2r** vs. **2t**). A sterically imposing 2-naphthyl group can be installed, but the efficiency is unsurprisingly compromised (see **2t**). *Ortho*-substituted aryl sulfonyl chlorides are tolerated as exemplified through the synthesis of sulfone **2v**. The incorporation of a fluorinated moiety into organic molecules generally increases the solubility, lipophilicity, and metabolic stability of the parent molecules, thus, explaining why about 20% of prescribed and 30% of blockbuster drugs contain at least one fluorine atom. Fluorine-functionalized materials also have applications in optical, electronic, and agrochemical technologies.¹⁹ It is therefore noteworthy that fluorinated products **2r** and **2w** are obtainable in satisfactory yields. Other halogenated precursors are well tolerated (see **2s**), which bodes well for late-stage diversification as the halogen group may be utilized as a functional handle for cross-coupling purposes. Our studies have revealed that alkyl sulfonyl chlorides undergo satisfactory vicinal sulfonyllactonization of **1**, giving rise to the alkyl sulfones depicted in Scheme 2 (see **2x** and **2y**).

Based on prior mechanistic studies performed on the sulfonyllactonization of 4-aryl-4-pentenoic acids,^{5c} and on the results obtained so far, a tentative mechanism is depicted in Fig. 3. An initial reaction between the Cu(i) catalyst and the radical source (*i.e.*, the aryl sulfonyl chloride) generates a Cu(II) species and sulfonyl radical **G**. Regioselective addition of **G** to the alkene motif resident in lactam-tethered alkenoic acid **1** affords tertiary alkyl radical intermediate **H**, which is captured intramolecularly by the pendant acid to furnish sulfone-tethered bicyclic lactam–lactone **2**, with regeneration of the Cu(i) species. As the results indicate, there is a reversal in the regioselectivity of addition of **G** to a disubstituted alkenoic acid, which instead leads to significantly more stable benzylic radical intermediate **I** (compared to the corresponding secondary nonbenzylic radical). Subsequent intramolecular capture of **I** by the tethered acid leads to 6-*endo* cyclization product **3**. The formation of **3** is not surprising since the regioselectivity of radical addition to alkenes is generally dictated by the stability of the resulting radical and the addition onto aryl-alkenes results in a stabilized benzylic radical.^{5c} The formation of 5-



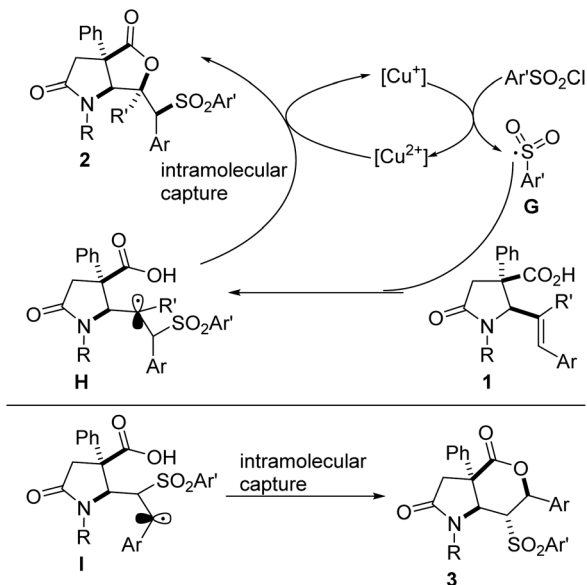
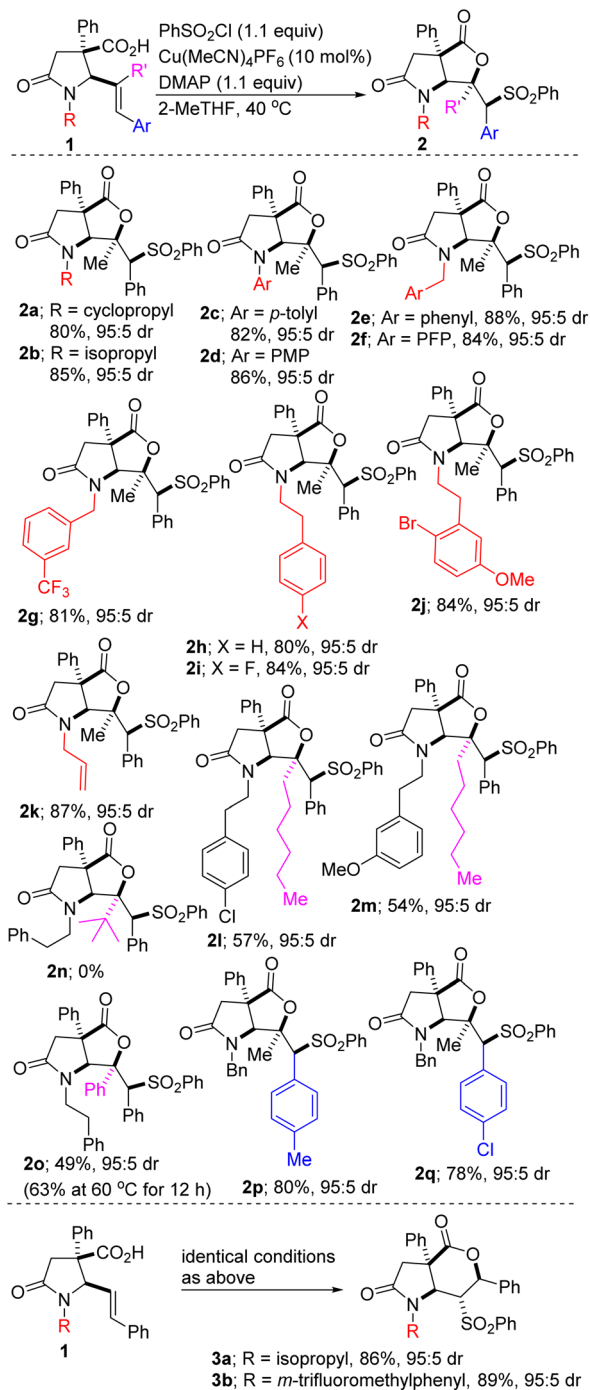


Fig. 3 Plausible mechanism for sulfonyllactonization of 1 with aryl sulfonyl chlorides.

exo cyclization products of type 2 is quite intriguing since one would expect the tertiary nonbenzylic radical (*i.e.*, **H**) to be less stable than the competing secondary benzylic radical. Although speculative, we surmise that the formation of **2** is mostly governed by sterics imposed by the bulky aryl substituents whereas the formation of **3** is almost entirely governed by the pronounced electronic effects.

In the synthesis of potential drug candidates, scalability is often a significant factor as it serves to provide sufficient amounts for clinical tests. A potentially beneficial aspect of this methodology is therefore the scalable nature of the reactions given that products such as **2a/b/h/k/p/r** have been prepared in gram scale, with little to no compromise in efficiency. This has set the stage for post-diversification studies. For example, Mg-mediated reductive hydro desulfonylation of sulfones **2b** and **2h** affords formal hydrolactonization products **4a** and **4b**, respectively (Scheme 3). When sulfones **2p** and **2r** are subjected to $B(C_6F_5)_3$ -catalyzed deoxygenation, thioether-bearing lactam–lactones **5a** and **5b** are obtained, respectively. Sulfones are often used as traceless linchpins for the construction of synthetically attractive molecular frameworks. Accordingly, several transition-metal-catalyzed and free-radical-based desulfonylative cross-couplings have emerged.^{20,21} Ni- and Co-catalyzed cross-electrophile couplings have been particularly useful in $C(sp^3)$ - $C(sp^2)$ bond-forming processes.²² In this electrophile–electrophile coupling mode, traditionally difficult functional groups (*e.g.*, ester, ketone, nitrile, or alcohol groups) are impressively tolerated and the need for pregeneration of expensive or difficult-to-handle organometallic reagents is obviated. Accordingly, we decided to explore the amenability of the alkyl sulfones prepared herein to reductive cross-coupling with bromobenzene. If successfully implemented, this would represent the discovery and development of the first Co-catalyzed reductive cross-

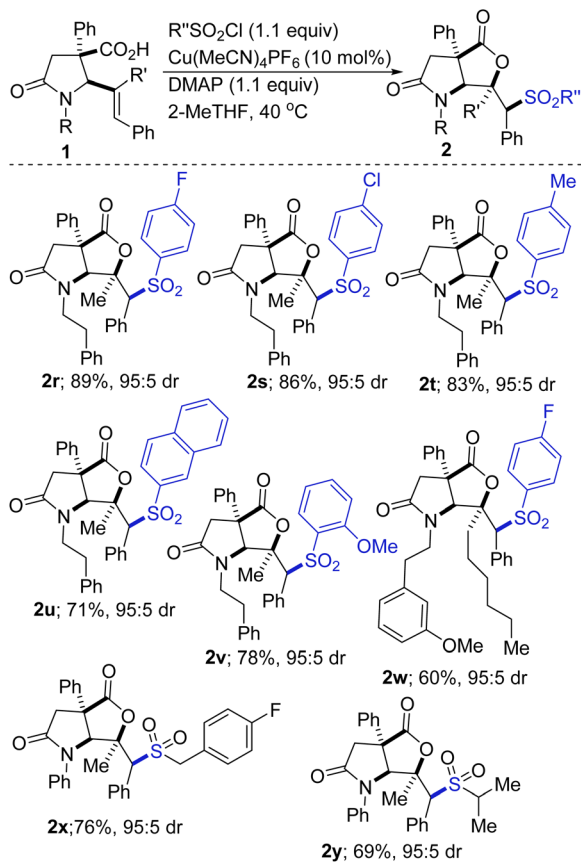


Performed on 1.0 mmol scale using 10 mL of 2-MeTHF. Isolated yields reported. Reaction times ranged from 14 to 18 h. Diastereomeric ratios were determined by GC-MS, ¹H NMR, ¹⁹F NMR (where applicable) analyses of the crude mixture. Relative configurations were established using NOESY analysis of selected compounds. The others were ascribed by analogy. PMP = *para*-methoxyphenyl, PFP = *para*-fluorophenyl.

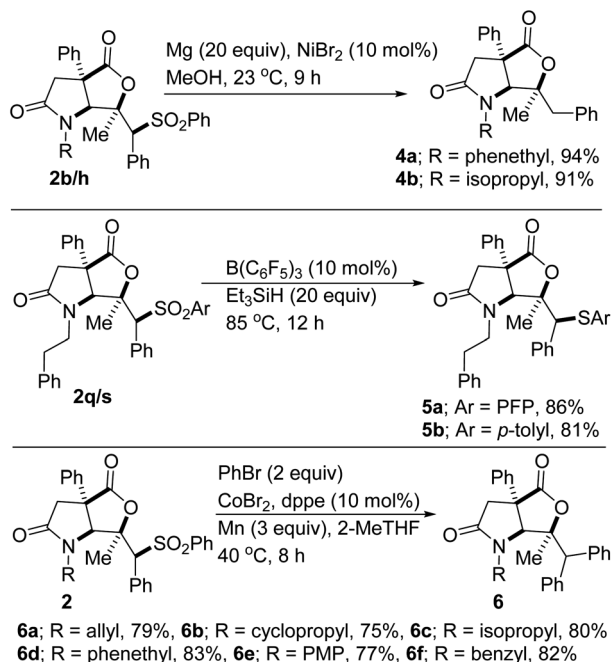
Scheme 1 Scope of lactam-tethered alkenoic acid.

electrophile coupling reaction between alkyl sulfones and an aryl bromide.²³ In the event, we were pleased to find that desulfonylative phenylation of several sulfones with





Scheme 2 Scope of sulfonyl chloride.



Scheme 3 Elaboration of the annulation products.

bromobenzene proceeds smoothly and affords formal aryl-lactonization products **6a–f**. Efforts to extend this novel mode of reactivity to other aryl bromides are underway.

Conclusions

In summary, the site-selective, diastereoselective, and scalable synthesis of sulfone-tethered lactam–lactones has been accomplished, through the deployment of γ -lactam-tethered alkenoic acids in a sulfonyllactonization protocol. With respect to regioselectivity, trisubstituted alkenoic acids display a preference for 5-*exo-trig* cyclization whereas disubstituted alkenoic acids undergo exclusive 6-*endo-trig* cyclization. These sp^3 -rich sulfonated bicycles bear medicinally relevant quaternary and contiguous stereocenters. We anticipate that this practical, cost-effective, and scalable strategy would expand the 3D-structural space for the discovery of new lactam–lactones with medicinal value. Post-modification of these versatile *N,O*-heterocycles has led to the unveiling of the first Co-catalyzed reductive cross-coupling of alkyl aryl sulfones with bromobenzene. Efforts to unambiguously determine the relative configuration of **2a** or any of the products depicted in Scheme 1 through X-ray crystallographic analysis are ongoing. So far, the crystals obtained are not of sufficient quality. We have also initiated efforts to develop an enantioselective version of the sulfonyl lactonization reaction described herein. These findings will be disclosed in due course.

Experimental

All experiments involving air and moisture-sensitive reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. 2-MeTHF was distilled from sodium benzophenone ketyl. Column chromatography was performed on silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle SiliplateTM glass backed plates (250 μ m thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or CAM, *p*-anisaldehyde, or $KMnO_4$ stain. All reported temperatures were internal to a reaction vessel. Unless otherwise indicated, 1H , ^{13}C , and DEPT-135 spectra were acquired using $CDCl_3$ as solvent, at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI⁺ data were obtained using either electrospray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx). Brine solutions are saturated solutions of aqueous sodium chloride.

General procedure A: sulfonyllactonization

An oven-dried vial equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(i) hexafluorophosphate (37 mg, 0.10 mmol, 10 mol%), the aryl sulfonyl chloride (1.1 mmol, 1.1 equiv.), DMAP (1.1 mmol, 1.1 equiv.), and alkenoic acid **1** (1.0 mmol, 1.0 equiv.). The reaction tube was sealed with a septum screw-cap and connected to a Schlenk line through a needle. The reaction tube was then briefly evacuated and backfilled with argon (for total of three times). Anhydrous 2-MeTHF (10 mL) was added to the tube *via* syringe and the argon pressure was removed. The reaction mixture was



stirred at room temperature for 12 h (TLC and GC-MS monitoring). The reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (20 mL) and ethyl acetate (20 mL). The aqueous layer was separated and extracted with ethyl acetate (20 mL \times 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was analyzed by ¹H NMR spectroscopy and GC-MS to determine the diastereomeric ratio. Purification by flash column chromatography on silica gel afforded the pure sulfone-tethered lactam-lactones.

General procedure B: desulfonation

To a well-stirred solution of sulfone **2** (0.5 mmol) in dry MeOH (10 mL) was added Mg turnings (5.0 mmol, 10 equiv.) and NiBr₂ (10 mol%) at 0 °C under Ar. The mixture was stirred at room temperature for 3 h prior to the addition of another portion of Mg turnings (5.0 mmol, 10 equiv.) and dry MeOH (10 mL). Stirring was continued for another 6 h (TLC and GC-MS monitoring). Upon completion, the reaction mixture was filtered through Celite and the residue was thoroughly washed with MeOH. The filtrate was concentrated under reduced pressure and dissolved in EtOAc. The solution was washed with a saturated solution of aqueous NH₄Cl, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the crude desulfonated product. Purification by flash column chromatography on silica gel afforded the pure lactam-lactone.

General Procedure C: reduction of sulfones to thioethers

An oven-dried 5 mL screw-capped sealed tube equipped with a magnetic stir bar was charged with B(C₆F₅)₃ (10 mol%), Et₃SiH (20 equiv.), and the sulfone-tethered lactam-lactone (0.50 mmol), under an argon atmosphere. The tube was sealed properly and transferred to an oil bath thermostatted at 85 °C. After 12 h (TLC and GC-MS monitoring), the reaction was cooled to room temperature and passed through a small plug of silica gel using EtOAc. The crude material was dried (Na₂SO₄) and filtered, and the solvent was removed under reduced pressure. The mixture was then subjected to high vacuum at 70 °C until the unreacted hydrosilane was removed from the system. The residue was purified further by flash column chromatography (silica gel, hexanes/EtOAc 90 : 10 to 50 : 50) to afford the desired thioether-tethered lactam-lactones.

General Procedure D: reductive desulfonylative cross-coupling with bromobenzene

To a solution of CoBr₂ (22 mg, 0.10 mmol, 10 mol%), *bis*-1,2-diphenylphosphinopropane (41.2 mg, 0.10 mmol, 10 mol%), and manganese powder (165 mg, 3 mmol, 3 equiv.) in 2-MeTHF (5 mL) was added bromobenzene (2 mmol, 2 equiv.) at 40 °C. A solution of the sulfone (1 mmol, 1 equiv.) in 2-MeTHF (5 mL) was added slowly (2 mL h⁻¹). After completion (as judged by TLC and GC-MS), the reaction mixture was treated with a mild acid such as 10% H₃PO₄ (aq) and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to afford the desired

coupling product as an oil. Purification was carried out by flash column chromatography on silica, eluting with Hexanes/EtOAc.

Synthesis of sulfone **2a**

Prepared in 1.0 mmol scale using General Procedure A. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50 : 50). Yellowish oil. Yield = 400.8 mg, 80%, 95 : 5 dr (*syn* : *anti*). ¹H NMR (400 MHz, CDCl₃) δ 7.54 (s, 1H), 7.28–7.19 (m, 3H), 7.23–7.12 (m, 7H), 7.00–6.97 (m, 3H), 6.25 (s, 1H), 4.73 (s, 1H), 4.03 (s, 1H), 3.00 (d, *J* = 14.8 Hz, 1H), 2.67 (d, *J* = 14.8 Hz, 1H), 2.35 (tt, *J* = 7.4, 4.1 Hz, 1H), 1.60 (s, 3H), 0.88 (dq, *J* = 9.9, 6.6 Hz, 1H), 0.63 (dtd, *J* = 10.6, 6.5, 3.9 Hz, 1H), 0.33 (dq, *J* = 9.9, 6.8 Hz, 1H), 0.00 (dq, *J* = 9.9, 6.8 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 174.3, 173.1, 139.2, 133.8, 129.7, 129.6, 129.3, 128.9, 128.8, 128.7, 128.3, 125.8, 88.2, 77.7, 71.9, 51.8, 45.1, 26.4, 21.8, 9.3, 5.1. FTIR (KBr): 2965.4, 1727.5, 1696.3, 1604.9, 1511.0, 1448.5, 1414.7, 1384.9, 1357.4, 1298.7, 1247.5, 1179.3, 1135.9, 1031.8, 905.8, 839.0. HRMS-EI⁺ (*m/z*): calc for C₂₉H₂₇NO₅S [M]⁺ 501.1610, found 501.1618.

Note: All sulfones depicted in Schemes 1 and 2 were prepared as described above. Spectroscopic data can be found in the ESI.†

Synthesis of lactam-lactone **4a**

Prepared in 0.50 mmol scale using General Procedure B. Purification: flash chromatography on silica eluting with hexane/EtOAc (75 : 25). Yellowish oil. Yield = 200 mg, 94%. ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.21 (m, 9H), 7.00–6.98 (m, 2H), 6.91–6.89 (m, 2H), 6.65 (dd, *J* = 7.7, 1.9 Hz, 2H), 4.23 (dt, *J* = 13.2, 6.0 Hz, 1H), 4.02 (s, 1H), 3.08 (d, *J* = 17.7 Hz, 1H), 2.99–2.74 (m, 5H), 2.66 (qd, *J* = 12.7, 7.0 Hz, 1H), 1.49 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 175.7, 172.3, 139.3, 137.9, 133.9, 130.9, 129.1, 128.8, 128.7, 127.8, 127.5, 126.7, 125.7, 87.4, 71.5, 53.1, 47.3, 44.5, 42.9, 33.1, 22.9. HRMS-EI⁺ (*m/z*): calc for C₂₈H₂₇NO₃ [M]⁺ 425.1991, found 425.1995.

Note: Lactam-lactone **4b** was prepared as described above. Spectroscopic data can be found in the ESI.†

Synthesis of thioether **5a**

Prepared in 0.50 mmol scale using General Procedure C. Purification: flash chromatography on silica eluting with hexane/EtOAc (50 : 50). Yellowish oil. Yield = 237.2 mg, 86%. ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.18 (m, 9H), 7.15–6.96 (m, 6H), 6.89 (t, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 7.8 Hz, 2H), 4.31 (s, 1H), 4.28 (dt, *J* = 13.8, 6.9 Hz, 1H), 4.05 (s, 1H), 3.14–3.01 (m, 2H), 2.93–2.78 (m, 2H), 2.69 (dt, *J* = 13.8, 6.7 Hz, 1H), 1.56 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 174.9, 172.3, 163.8, 161.4, 139.3, 137.6, 136.6, 134.8, 134.7, 129.9, 129.0, 128.8, 128.7, 128.3, 127.9, 126.7, 125.8, 116.4, 116.2, 89.4, 71.1, 64.6, 52.6, 44.0, 43.3, 33.0, 22.0. HRMS-EI⁺ (*m/z*): calc for C₃₄H₃₀FNO₃S [M]⁺ 551.1930, found 551.1937.

Note: Thioether **5b** was prepared as described above. Spectroscopic data can be found in the ESI.†

Synthesis of diarylmethane-tethered lactam-lactone **6a**

Prepared in 0.50 mmol scale using General Procedure D. Purification: Flash chromatography on silica eluting with hexane/



EtOAc (50 : 50). Greenish-yellow oil. Yield = 172.8 mg, 79%. ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.06 (m, 15H), 5.66–5.52 (m, 1H), 5.13–5.04 (m, 2H), 4.69–4.56 (m, 2H), 4.14 (s, 1H), 3.40 (dd, *J* = 15.0, 8.4 Hz, 1H), 3.13 (d, *J* = 18.1 Hz, 1H), 3.00 (d, *J* = 18.1 Hz, 1H), 1.43 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 174.7, 172.1, 139.6, 137.5, 134.6, 131.9, 131.0, 129.7, 129.1, 129.0, 128.6, 128.1, 128.0, 127.8, 125.7, 120.2, 89.0, 69.9, 64.3, 52.2, 45.4, 43.5, 22.5. HRMS-ESI⁺ (*m/z*): calc for C₂₉H₂₇NO₃ [M]⁺ 437.1991, found 437.1995.

Note: All desulfonylative arylation products depicted in Scheme 3 were prepared as described above. Spectroscopic data can be found in the ESI.†

Author contributions

T. K. B. – conceptualization, project administration, supervision, writing – original draft, internal funding acquisition. J. E. – investigation, data curation, validation; J. F. – investigation, methodology; K. Q. – investigation, methodology; S. S. – investigation, methodology; N. J. – investigation, methodology; M. D. – investigation, methodology.

Conflicts of interest

There are no conflicts of interest to declare.

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Notes and references

- (a) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274; (b) E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 2832; (c) M. Feng, B. Tang, H. S. Liang and X. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1200; (d) K. A. Scott and J. T. Njardarson, *Top. Curr. Chem.*, 2018, **376**, 5; (e) W.-M. Xu, F.-F. Han, M. He, D.-Y. Hu, J. He, S. Yang and B.-A. Song, *J. Agric. Food Chem.*, 2012, **60**, 1036.
- (a) S. B. Madasu, N. A. Vekariya, M. N. V. D. Hari-Kiran, B. Gupta, A. Islam, P. S. Douglas and K. R. Babu, *Beilstein J. Org. Chem.*, 2012, **8**, 1400–1405; (b) C. F. Sturino, G. O'Neill, N. Lachance, M. Boyd, C. Berthelette, M. Labelle, L. Li, B. Roy, J. Scheiget, N. Tsou, Y. Aubin, K. P. Bateman, N. Chauret, S. H. Day, J.-F. Levesque, C. Seto, J. H. Silva, L. A. Trimble, M.-C. Carriere, D. Denis, G. Greig, S. Kargman, S. Lamontagne, M.-C. Mathieu, N. Sawyer, D. Slipetz, W. M. Abraham, T. Jones, M. McAuliffe, H. Piechuta, D. A. Nicoll-Griffith, Z. Wang, R. Zamboni, R. N. Young and K. M. Metters, *J. Med. Chem.*, 2007, **50**, 794–806.
- (a) Y. I. Zhu and M. J. Stiller, *J. Am. Acad. Dermatol.*, 2001, **45**, 420–434; (b) X. Codony, J. M. Vela and M. J. Ramirez, *Curr. Opin. Pharmacol.*, 2011, **11**, 94–100; (c) G. La Regina, A. Coluccia, A. Brancale, F. Piscitelli, V. Gatti, G. Maga, A. Samuele, C. Pannecouque, D. Schols, J. Balzarini, E. Novellino and R. Silvestri, *J. Med. Chem.*, 2011, **54**, 1587–1598; (d) P. Prasit, Z. Wang, C. Brideau, C. C. Chan, S. Charleson, J. Y. Gauthier, R. Gordon, J. Guay, M. Gresser, S. Kargman, B. Kennedy, Y. Leblanc, S. Leger, J. Mancini, G. P. O'Neill, M. Ouellet, M. D. Percival, H. Perrier, D. Riendeau, I. Rodger, P. Tagari, M. Therien, P. Vickers, E. Wong, L. J. Xu, R. N. Young and R. Zamboni, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1773; (e) R. L. Lopez de Compadre, R. A. Pearlstein, A. J. Hopfinger and J. K. Seyde, *J. Med. Chem.*, 1987, **30**, 900; (f) S. Leucht, G. Pitschel-Walz, R. R. Engel and W. Kissling, *Am. J. Psychiatry*, 2002, **159**, 180; (g) W. Fischli and co-workers, *Hypertension*, 1991, **18**, 22–31; (h) S. Doswald and co-workers, *Bioorg. Med. Chem.*, 1994, **2**, 403–410; (i) M. Teall and Co-Workers, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2685–2688.
- H. Sasabe, Y. Seino, M. Kimura and J. Kido, *Chem. Mater.*, 2012, **24**, 1404.
- (a) Y.-S. Xiong, B. Zhang, Y. Yu, J. Weng and G. Lu, *J. Org. Chem.*, 2019, **84**, 13465–13472; (b) W.-H. Rao, Q. Li, F.-Y. Chen, L.-L. Jiang, P. Xu, X.-W. Deng, M. Li, G.-D. Zou and X. Cao, *J. Org. Chem.*, 2021, **86**, 11998–12007; (c) R. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2015, **137**, 8069–8077; (d) Y. Wang, L. Deng, J. Zhou, X. Wang, H. Mei, J. Han and Y. Pan, *Adv. Synth. Catal.*, 2018, **360**, 1060–1065; (e) J. Zhang, K. Zhou and J. Wu, *Org. Chem. Front.*, 2018, **5**, 813–816.
- (a) J. Zhang, Y. An and J. Wu, *Chem. – Eur. J.*, 2017, **23**, 9477–9480; (b) T. Liu, Y. Li, L. Lai, J. Cheng, J. Sun and J. Wu, *Org. Lett.*, 2018, **20**, 3605–3608; (c) X. Wang, M. Yang, W. Xie, X. Fan and J. Wu, *Chem. Commun.*, 2019, **55**, 6010–6013; (d) W.-H. Rao, L.-L. Jiang, X.-M. Liu, M.-J. Chen, F.-Y. Chen, X. Jiang, J.-X. Zhao, G.-D. Zou, Y.-Q. Zhou and L. Tang, *Org. Lett.*, 2019, **21**, 2890–2893; (e) J.-J. Wang and W. Yu, *Org. Lett.*, 2019, **21**, 9236–9240; (f) Y. Xiong, Y. Sun and G. Zhang, *Org. Lett.*, 2018, **20**, 6250–6254; (g) L.-J. Wang, J.-M. Chen, W. Dong, C.-Y. Hou, M. Pang, W.-B. Jin, F.-G. Dong, Z.-D. Xu and W. Li, *J. Org. Chem.*, 2019, **84**, 2330–2338; (h) L. Song, L. Zhu, Z. Zhang, J.-H. Ye, S.-S. Yan, J.-L. Han, Z.-B. Yin, Y. Lan and D.-G. Yu, *Org. Lett.*, 2018, **20**, 3776–3779; (i) M. Ito, A. Osaku, A. Shiibashi and T. Ikariya, *Org. Lett.*, 2007, **9**, 1821–1824.
- (a) I. Pavlinov, E. M. Gerlach and L. N. Aldrich, *Org. Biomol. Chem.*, 2019, **17**, 1608–1623; (b) K.-J. Liu, Z. Wang, L.-H. Lu, J.-Y. Cheng, Y.-W. Lin, Z. Cao, X. Yu and W.-M. He, *Green Chem.*, 2021, **23**, 496–500; (c) X. Wang, Q. Wang, Y. Xue, K. Sun, L. Wu and B. Zhang, *Chem. Commun.*, 2020, **56**, 4436–64439; (d) Y. Zhao, X. Niu, H. Yang, J. Yang, Z. Wang and Q. Wang, *Chem. Commun.*, 2022, **58**, 8576–8579; (e) S. Jin, L. Wang, H. Han, X. Liu, Z. Bu and Q. Wang, *Chem. Commun.*, 2021, **57**, 395–362; (f) Q. H. Shi, Y.-H. Wang, X.-R. Wang, W.-H. Zhang, F.-L. Tian, L.-J. Peng, Y. Zhou and X.-L. Liu, *Chem. Front.*, 2023, **10**, 3307–3312.



- 8 C. J. Gerry and S. L. Schreiber, *Nat. Rev. Drug Discovery*, 2018, **17**, 333–352.
- 9 (a) T. Flagstad, G. Min, K. Bonnet, R. Morgentin, D. Roche, M. H. Clausen and T. E. Nielsen, *Org. Biomol. Chem.*, 2016, **14**, 4943–4946; (b) D. J. Foley, A. Nelson and S. P. Marsden, *Angew. Chem., Int. Ed.*, 2016, **55**, 13650–13657; (c) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.
- 10 (a) H. Braunstein, S. Langevin, M. Khim, J. Adamson, K. Hovenkotter, L. Kotlarz, B. Mansker and T. K. Beng, *Org. Biomol. Chem.*, 2016, **14**, 8864–8872; (b) T. K. Beng and A. Moreno, *New J. Chem.*, 2020, **44**, 4257–4261; (c) T. K. Beng, M. Bauder, M. J. Rodriguez and A. Moreno, *New J. Chem.*, 2018, **42**, 16451–16455; (d) K. Hovenkotter, H. Braunstein, S. Langevin and T. K. Beng, *Org. Biomol. Chem.*, 2017, **15**, 1217–1221; (e) T. K. Beng and A. Moreno, *RSC Adv.*, 2020, **10**, 8805–8809; (f) T. K. Beng, M. Rodriguez and C. Borg, *RSC Adv.*, 2022, **12**, 17617–17620; (g) J. Garcia, J. Eichwald, J. Zesiger and T. K. Beng, *RSC Adv.*, 2022, **12**, 309–318; (h) T. K. Beng, C. Borg and M. Rodriguez, *RSC Adv.*, 2022, **12**, 28685–28691; (i) T. K. Beng, J. Garcia, J. Eichwald and C. Borg, *RSC Adv.*, 2023, **13**, 14355–14360.
- 11 (a) D. S. Hamilton and D. A. Nicewicz, *J. Am. Chem. Soc.*, 2012, **134**, 18577–18580; (b) H. Shigehisa, M. Hayashi, H. Ohkawa, T. Suzuki, H. Okayasu, M. Mukai, A. Yamazaki, R. Kawai, H. Kikuchi, Y. Satoh, A. Fukuyama and K. Hiroya, *J. Am. Chem. Soc.*, 2016, **138**, 10597–10604; (c) L. Ferrand, Y. Tang, C. Aubert, L. Fensterback, V. Mouries-Mansuy, M. Petit and M. Amatore, *Org. Lett.*, 2017, **19**, 2062–2065.
- 12 (a) H. Nakatsuji, Y. Sawamura, A. Sakakura and K. Ishihara, *Angew. Chem., Int. Ed.*, 2014, **53**, 6974–6977; (b) H. Egami, J. Asada, K. Sato, D. Hashizume, Y. Kwato and Y. Hamashima, *J. Am. Chem. Soc.*, 2015, **137**, 10132–10135; (c) M. Wilking, C. G. Daniliuc and U. Hennecke, *Chem.–Eur. J.*, 2016, **22**, 18601–21807; (d) S. E. Denmark, P. Ryabchuk, M. T. Burk and B. B. Gilbert, *J. Org. Chem.*, 2016, **81**, 10411–10423; (e) J. D. Griffin, C. L. Cavanaugh and D. A. Nicewicz, *Angew. Chem., Int. Ed.*, 2017, **56**, 2097–2100.
- 13 (a) D. Karila, L. Leman and R. H. Dodd, *Org. Lett.*, 2011, **13**, 5830–5833; (b) B. N. Hemrick, K. Shen and Q. Wang, *J. Am. Chem. Soc.*, 2016, **138**, 5813–5816; (c) J. Xie, Y.-W. Wang, L.-W. Qi and B. Zhang, *Org. Lett.*, 2017, **19**, 1148–1151.
- 14 (a) R. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2012, **134**, 12462–12465; (b) R. Zhu and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 12655–12658.
- 15 A. R. Alcantara and P. D. de Maria, *Curr. Green Chem.*, 2018, **5**, 88.
- 16 T. K. Beng and R. E. Gawley, *J. Am. Chem. Soc.*, 2010, **132**, 12216.
- 17 (a) X. Qiao, D. L. Cheney, R. S. Alexander, A. M. Smallwood, S. R. King, K. He, A. R. Rendina, J. M. Luettgen, R. M. Knabb, R. R. Wexler and P. Y. S. Lam, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4118–4123; (b) M. A. Larsen, E. T. Hennessy, M. C. Deem, Y. Lam, J. Sauri and A. C. Sather, *J. Am. Chem. Soc.*, 2020, **142**, 726–732.
- 18 A. Calcaterra, L. Mangiardi, G. D. Monache, D. Quaglio, S. Balducci, S. Berardozi, A. Iazzetti, R. Franzini, B. Botta and F. Ghirga, *Molecules*, 2020, **25**, 414.
- 19 (a) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214–8264; (b) D. O'Hagan, *J. Fluorine Chem.*, 2010, **131**, 1071–1081; (c) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. L. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506; (d) T. Fujiwara and D. O'Hagan, *J. Fluorine Chem.*, 2014, **167**, 16–29; (e) R. Berger, G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, *Chem. Soc. Rev.*, 2011, **40**, 3496–3508; (f) E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 2832–2842.
- 20 For selected examples, see (a) Y. Zhao, C. Ni, F. Jiang, B. Gao, X. Shen and J. Hu, *ACS Catal.*, 2013, **3**, 631–634; (b) J. Gui, Q. Zhou, C.-M. Pan, Y. Yabe, A. C. Burns, M. R. Collins, M. A. Ornelas, Y. Ishihara and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 4853–4856; (c) H. Watanabe, M. Takemoto, K. Adachi, Y. Okuda, A. Dakegata, T. Fukuyama, I. Ryu, K. Wakamatsu and A. Orita, *Chem. Lett.*, 2020, **49**, 409–412.
- 21 For selected examples, see (a) S. E. Denmark and A. J. Cresswell, *J. Org. Chem.*, 2013, **78**, 12593–12628; (b) M. Nambo and C. M. Crudden, *Angew. Chem., Int. Ed.*, 2014, **53**, 742–746; (c) M. Nambo, Z. T. Ariki, D. Canseco Gonzalez, D. D. Beattie and C. M. Crudden, *Org. Lett.*, 2016, **18**, 2339–2342; (d) M. Nambo, E. C. Keske, J. P. G. Rygus, J. C.-H. Yim and C. M. Crudden, *ACS Catal.*, 2017, **7**, 1108–1112; (e) Z. T. Ariki, Y. Maekawa, M. Nambo and C. M. Crudden, *J. Am. Chem. Soc.*, 2018, **140**, 78–81; (f) R. R. Merchant, J. T. Edwards, T. Qin, M. M. Kruszyk, C. Bi, G. Che, D.-H. Bao, W. Qiao, L. Sun, M. R. Collins, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, P. Nuhant and P. S. Baran, *Science*, 2018, **360**, 75–80; (g) W. Miao, Y. Zhao, C. Ni, B. Gao, W. Zhang and J. Hu, *J. Am. Chem. Soc.*, 2018, **140**, 880–883; (h) F. Takahashi, K. Nogi and H. Yorimitsu, *Org. Lett.*, 2018, **20**, 6601–6605; (i) J. C.-H. Yim, M. Nambo, Y. Tahara and C. M. Crudden, *Chem. Lett.*, 2019, **48**, 975–977; (j) M. Nambo, Y. Tahara, J. C.-H. Yim and C. M. Crudden, *Chem.–Eur. J.*, 2019, **25**, 1923–1926; (k) T.-Y. Yu, Z.-J. Zheng, J.-H. Bai, H. Fang and H. Wei, *Adv. Synth. Catal.*, 2019, **361**, 2020–2024; (l) J. M. E. Hughes and P. S. Fier, *Org. Lett.*, 2019, **21**, 5650–5654; (m) Y. Maekawa, Z. T. Ariki, M. Nambo and C. M. Crudden, *Org. Biomol. Chem.*, 2019, **17**, 7300–7303; (n) M. Nambo, J. C.-H. Yim, L. B. O. Freitas, Y. Tahara, Z. T. Ariki, Y. Maekawa, D. Yokogawa and C. M. Crudden, *Nat. Commun.*, 2019, **10**, 4528; (o) P. Chatelain, A. Sau, C. N. Rowley and J. Moran, *Angew. Chem., Int. Ed.*, 2019, **58**, 14959–14963; (p) Y. Xia, L. Wang and A. Studer, *Angew. Chem., Int. Ed.*, 2018, **57**, 12940–12944; (q) Y. Xia and A. Studer, *Angew. Chem., Int. Ed.*, 2019, **58**, 9836–9840; (r) M. Nambo, Y. Maekawa and C. M. Crudden, *ACS Catal.*, 2022, **12**, 3013–3032; (s) M. Nambo, Y. Maekawa and C. M. Crudden, *ACS Catal.*, 2022, **12**, 3013–3032.
- 22 (a) D. A. Everson and D. J. Weix, *J. Org. Chem.*, 2014, **79**, 4793–4798; (b) T. Moragas, A. Correa and R. Martin, *Chem.–Eur. J.*, 2014, **20**, 8242–8258; (c) C. E. I. Knappke, S. Grupe,



- D. Gärtner, M. Corpet, C. Gosmini and von W. Jacobi, *Chem.-Eur. J.*, 2014, **20**, 6828–6842; (d) D. J. Weix, *Acc. Chem. Res.*, 2015, **48**, 1767–1775; (e) J. Gu, X. Wang, W. Xue and H. Gong, *Org. Chem. Front.*, 2015, **2**, 1411–1421; (f) E. Richmond and J. Moran, *Synthesis*, 2018, **50**, 499–513; (g) L.-C. Campeau and N. Hazari, *Organometallics*, 2019, **38**, 3–35; (h) A. H. Cherney and S. E. Reisman, *J. Am. Chem. Soc.*, 2014, **136**, 14365–14368; (i) D. A. Everson, R. Shrestha and D. J. Weix, *J. Am. Chem. Soc.*, 2010, **132**, 920–921; (j) D. A. Everson, B. A. Jones and D. J. Weix, *J. Am. Chem. Soc.*, 2012, **134**, 6146–6159; (k) D. P. Bassler, A. Alwali, L. Spence, O. Beale and T. K. Beng, *J. Organomet. Chem.*, 2015, **780**, 6; (l) T. K. Beng, K. Sincavage, A. W. V. Silaire, A. Alwali, D. P. Bassler, L. E. Spence and O. Beale, *Org. Biomol. Chem.*, 2015, **13**, 5349–5353.
- 23 For examples of reductive cross-coupling of alkyl aryl sulfones with aryl halides under nickel catalysis, see (a) J. M. E. Hughes and P. S. Fier, *Org. Lett.*, 2019, **21**, 5650–5654; (b) W. Miao, C. Ni, P. Xiao, R. Jia, W. Zhang and J. Hu, *Org. Lett.*, 2021, **23**, 711–715.

