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Iridium-catalyzed reductive sulfonamidation of alkoxy aryl alkynes†

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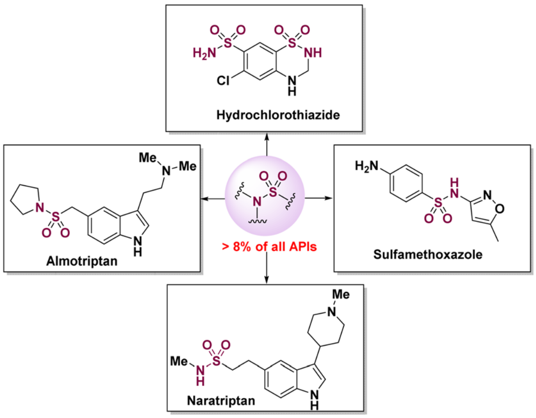
Sulfonamides are valuable structural building blocks, bioactives, and pharmaceuticals. While there have been great achievements in the sulfonamidation of alkyl and alkenyl carbon, the sulfonamidation of alkynyl carbon has not been studied. Herein, we report the synthesis of *N*-benzylated sulfonamides from alkoxy aryl alkynes and sulfonamides enabled by Ir-catalyzed reductive sulfonamidation using HCO_2H as a hydrogen donor. This process was performed under mild conditions, resulting in the transformation of a variety of substituted benzene, heteroaromatic, and aliphatic sulfonamides. Particularly, the structural diversification of valdecoxib and zonisamide showcased the utility of this protocol.

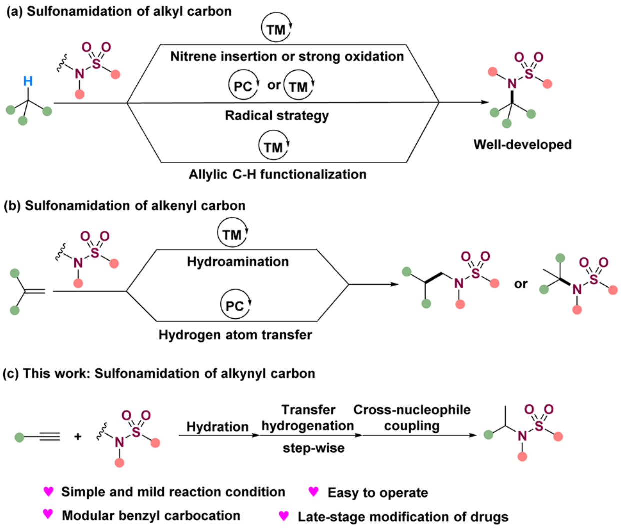
Introduction

Sulfonamides are not only valuable structural building blocks in synthetic intermediates, but are also commonly found in biological and pharmaceutical fields.[1] For instance, sulfonamides of almotriptan,[2] sulfamethoxazol,[3] hydrochlorothiazide,[4] and naratriptan[5] have found applications in the treatments of heavy migraine headache, urinary tract infections, and high blood pressure, respectively (Scheme 1). The latest statistics show that over 8% active pharmaceutical ingredients (APIs) contain sulfonamide skeletons, which have special physicochemical properties of metabolic stability.[6] Therefore, the extensive application of sulphonamides in medicinal chemistry has attracted the attention of chemists in the synthesis and functionalization of sulfonamides in recent decades.[7]

Reactions of primary sulfonamides with aliphatic halides,[8] alcohols,[9] and carbonyls[10] present classical strategies for the synthesis of sulfonamides, in which the organic,[11] inorganic,[12] Ir,[13] Ru,[14] Rh,[15] and other metal[16] catalysts are employed. Coupling of primary sulfonamides with aryl halides,[17] boronic acids,[18] and diaryliodonium triflate[19] constitutes another efficient approach to sulphonamide synthesis, where Cu,[20] Pd,[21] and Ni[22] metals are commonly utilized as catalysts. Direct sulfonamidation of alkyl carbon provides an atom- and step economy strategy for sulfonamide synthesis, with commendable substrate scope and efficiency (Scheme 2a).[23] However, the inevitable use of hypervalent iodine reagents or strong oxidation,[24] excessive equivalents of oxidants,[25] and poor



Scheme 1 Drugs containing sulfonamide motifs.



Scheme 2 Sulfonamidation of differential hybridized carbons.

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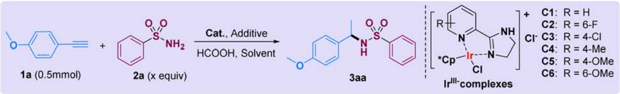
regioselectivity[26] limit the application of this strategy. Approaches to sulfonamide synthesis based on the sulfonamidation of alkenyl carbon *via* classical hydroamination or hydrogen atom transfer of alkenes are attractive alternatives (Scheme 2b).[27] Notably, asymmetric sulfonamidation of alkenyl carbon for the synthesis of enantioenriched sulfonamides *via* hydrogen atom transfer has also be established.[28] While there have been great achievements with regards to sulfonamidation of alkyl and alkenyl carbon, the sulfonamidation of alkynyl carbon has not been studied.

With our continuous research on transfer hydrogenation with Cp*Ir complexes,[29] *N*-alkylation[30] or *para*-Friedel–Crafts alkylation[31] were achieved from alkynes *via* hydration and transfer hydrogenation. In a previous work, a relatively stable benzyl carbocation was generated from alkynes *via* a hydration, transfer hydrogenation, and successive dehydroxylation process, which might be captured by primary or secondary sulfonamides to deliver a variety of *N*-benzylated sulfonamides. Using alkynes as substrates comes with various challenges: (a) although hydration of alkynes had been developed in our

Table 1 Optimization of the synthesis of sulfonamide **3aa**[a]



Entry	Cat.	Additive (equiv.)	**2a** (*x* equiv.)	Solvent	Yield **3aa**[b] (%)
1	**C3**	TsOH (0.6)	1.0	H_2O	38
2	**C3**	TsOH (0.6)	1.0	DMF	N.D.
3	**C3**	TsOH (0.6)	1.0	TFEA	N.D.
4	**C3**	TsOH (0.6)	1.0	MeCN	N.D.
5	**C3**	TsOH (0.6)	1.0	*p*-Xylene	N.D.
6	**C3**	TsOH (0.6)	1.0	Dioxane	N.D.
7	**C3**	TsOH (0.6)	1.0	TFEA/H_2O[c]	36
8	**C3**	TsOH (0.6)	1.0	TFEA/H_2O[d]	42
9	**C3**	TsOH (0.6)	1.0	TFEA/H_2O[e]	22
10	**C3**	TsOH (0.6)	1.0	TFEA/H_2O[f]	Trace
11	**C3**	TsOH (0.6)	1.0	*p*-Xylene/H_2O[d]	30
12	—	TsOH (0.6)	1.0	TFEA/H_2O[d]	N.D.
13	**C1**	TsOH (0.6)	1.0	TFEA/H_2O[d]	40
14	**C2**	TsOH (0.6)	1.0	TFEA/H_2O[d]	37
15	**C4**	TsOH (0.6)	1.0	TFEA/H_2O[d]	37
16	**C5**	TsOH (0.6)	1.0	TFEA/H_2O[d]	45
17	**C6**	TsOH (0.6)	1.0	TFEA/H_2O[d]	41
18	**C5**	TsOH (0.6)	1.2	TFEA/H_2O[d]	45
19	**C5**	TsOH (0.6)	1.4	TFEA/H_2O[d]	46
20	**C5**	TsOH (0.6)	1.6	TFEA/H_2O[d]	46
21	**C5**	TsOH (0.6)	1.8	TFEA/H_2O[d]	48
22	**C5**	TsOH (0.6)	2.0	TFEA/H_2O[d]	77
23	**C5**	TsOH (0.6)	2.5	TFEA/H_2O[d]	70
24	**C5**	TsOH (0.6)	3.0	TFEA/H_2O[d]	76
25	**C5**	—	2.0	TFEA/H_2O[d]	N.D.
26	**C5**	$PhSO_3H$ (0.6)	2.0	TFEA/H_2O[d]	52
27	**C5**	R^1SO_3H (0.6)[g]	2.0	TFEA/H_2O[d]	44
28	**C5**	MSA (0.6)	2.0	TFEA/H_2O[d]	59
29	**C5**	R^2SO_3H (0.6)[g]	2.0	TFEA/H_2O[d]	35
30	**C5**	**TsOH (0.2)**	**2.0**	**TFEA/H_2O**[d]	**81 (79)**
31	**C5**	TsOH (0.4)	2.0	TFEA/H_2O[d]	80
32	**C5**	TsOH (0.8)	2.0	TFEA/H_2O[d]	46
33	**C5**	TsOH (1.0)	2.0	TFEA/H_2O[d]	43
34	**C5**	TsOH (1.5)	2.0	TFEA/H_2O[d]	29
35	**C5**	TsOH (2.0)	2.0	TFEA/H_2O[d]	18
36[h]	**C5**	TsOH (0.2)	2.0	TFEA/H_2O[d]	63
37[i]	**C5**	TsOH (0.2)	2.0	TFEA/H_2O[d]	42
38[j]	**C5**	TsOH (0.2)	2.0	TFEA/H_2O[d]	N.D.

[a] Reaction conditions: **1a** (0.5 mmol), Cat. (1.0 mol%), HCO_2H (10.0 equiv.), and solvent (1.5 mL) for 12 hours at 80 °C (under air). [b] Yield was determined by NMR with dimethyl terephthalate as the internal standard. [c] The ratio of the mixed solvent was 1 : 8 (v/v). [d] The ratio of the mixed solvent was 1 : 4 (v/v). [e] The ratio of the mixed solvent was 1 : 2 (v/v). [f] The ratio of the mixed solvent was 1 : 1 (v/v). [g] R_1 = 4-Cl-Ph; R_2 = 2-naphthyl. [h] 60 °C. [i] 100 °C. [j] Without HCO_2H.

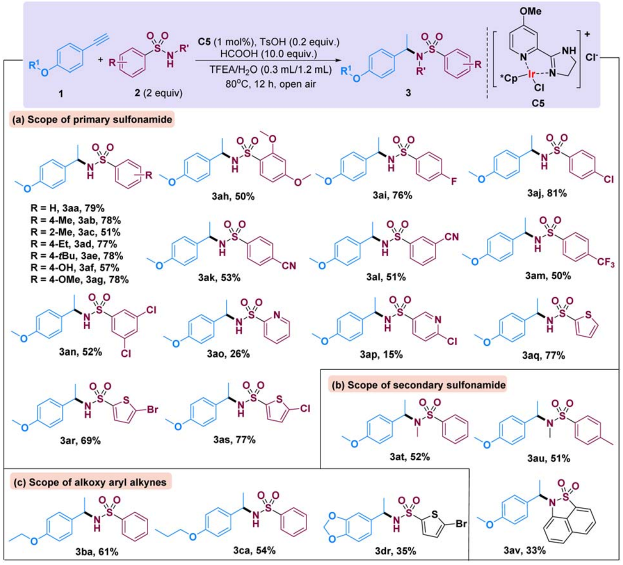
previous work,[31] there is a risk of deactivation of hydration using primary or secondary sulfonamides as nucleophilic reagents; (b) a similar outcome of poisoning subsequent transfer hydrogenation is possible under these reaction conditions; (c) a weaker nucleophilic property is noted while using nitrogen atoms as a nucleophilic reagent under acidic conditions, and using sulfonamides as nucleophilic agents will likely have similar related issues, hindering the final cross nucleophilic coupling process. Despite these difficulties, through protracted and unremitting efforts, herein, we realized the reductive sulfonamidation of alkynes with primary and secondary sulfonamides using metal catalysis, which provides inspiration for the synthesis of diversified sulfonamides (Scheme 2c).

Results and discussion

We initially examined the reductive sulfonamidation of alkynes by employing 4-ethynylanisole **1a** and benzene sulfonamide **2a** as model substrates, Cp*Ir complexes as catalyst,[32] and HCO_2H as a hydrogen donor (Table 1). Interestingly, the desired product **3aa** was produced at a 38% yield using H_2O as a solvent and TsOH as an additive (Table 1, entry 1). Screening of further reaction parameters indicated that the H_2O and Cp*Ir catalyst were essential for successful reductive sulfonamidation (Table 1, entries 2–11). Increasing the ratio of TFEA would decrease the yield of **3aa** (Table 1, entries 7–10). For instance, the yield of **3aa** was reduced to trace even though the ratio of TFEA and H_2O was loaded over 1 : 1 (Table 1, entry 10). Additionally, catalyst optimization (Table 1, entries 12–17) showed that the Cp*Ir complex **C5** could slightly enhance the sulfonamidation process leading to a 45% yield of the product **3aa** (Table 1, entry 16). Satisfyingly, increasing the loading of **2a** would sharply improve the yield of **3aa** (Table 1, entries 18–24). Of note, the control experiment demonstrated that a Lewis acid was crucial for this reductive sulfonamidation process (Table 1, entries 25–35) and decreasing the loading of TsOH to 0.2 equiv. resulted in the best yield of **3aa** (Table 1, entry 30). However, decreasing or increasing the reaction temperature was harmful to the production of **3aa** (Table 1, entries 36 and 37). Control experiment showed that HCO_2H was the essential hydrogen donor in this transformation, indicating that H_2O only act as a reaction media (Table 1, entry 38).

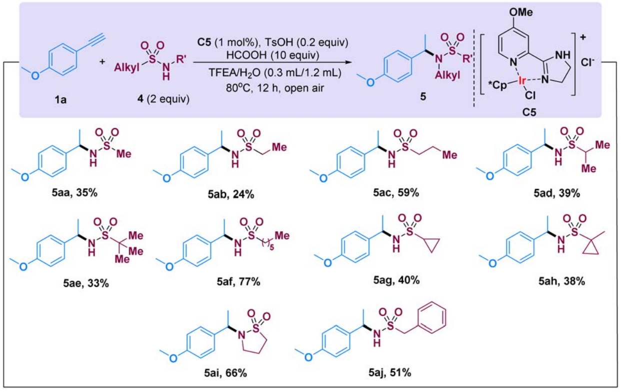
With the successfully optimized conditions, the substrate scope with respect to aryl alkynes and aryl sulfonamides was investigated (Table 2). As anticipated, aryl sulfonamides with electron-donating groups at differential positions were well tolerated, including methyl, ethyl, *tert*-butyl, hydroxyl, and methoxy, delivering the corresponding products (**3ab–3ag**) in good to excellent yields. Additionally, di-substituted aryl sulfonamide (**2h**) also performed well in this system. Aryl sulfonamides with electron-withdrawing groups, such as fluorine (**2i**), chlorine (**2j**, **2n**), nitrile (**2k**, **2l**), and trifluoromethyl (**2m**), were also efficient substrates to afford similar yields of the desired products (**3ai–3an**). However, significantly different yields were achieved with heteroaromatic sulfonamides (**2o–2s**) as substrates. For instance, low yield (15–26%) of corresponding products **3ao**, **3ap** were obtained using pyridine sulfonamides as substrates, while 2-thiophene-sulfonamides delivered the desired products **3aq–3as** in good yields (69–77%). This difference could be attributed to the difference in the density of π electrons. Interestingly, switching the primary aryl sulfonamides to secondary aryl sulfonamides also allowed the formation of the desired products (**3at–3av**) in moderate yields. Furthermore, other alkoxy-substituted aryl alkynes (**2b–2d**) were

Table 2 Substrate scope of aromatic sulfonamides and alkoxy aryl alkynes[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), **C5** (1.0 mol%), HCO_2H (10.0 equiv.), and TFEA (0.3 mL), H_2O (1.2 mL) for 12 hours at 80 °C, and isolated yield.

Table 3 Substrate scope of alkyl sulfonamides[a]



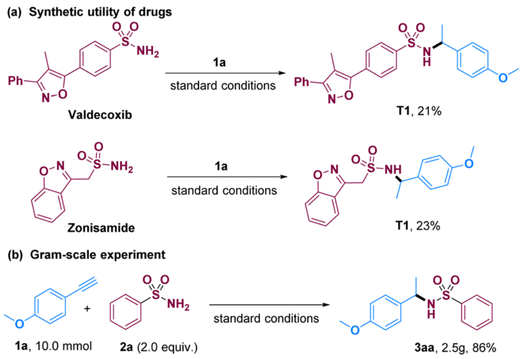
[a] Reaction conditions: **1a** (0.5 mmol), **4** (1.0 mmol), **C5** (1.0 mol%), HCO_2H (10.0 equiv.), and TFEA (0.3 mL), H_2O (1.2 mL) for 12 hours at 80 °C, and isolated yield.

also good substrates in the iridium catalyzed reductive sulfonamidation process.

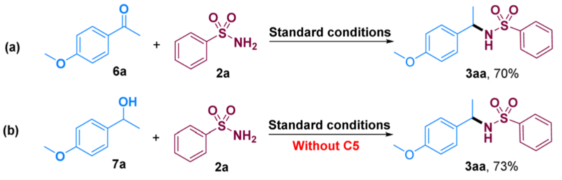
Having established the conversion of aromatic sulfonamides into diversified sulfonamides, this method was extended to employ alkyl sulfonamides as substrates (Table 3). In comparison with aryl sulfonamides, the corresponding products (**5aa–5ah**, **5aj**) were delivered in relatively lower yields using differential primary alkyl sulfonamides as substrates. Surprisingly, a better yield (66%) of sulfonamide **5ai** was delivered by using secondary cyclic aliphatic sulfonamide of 1,3-propanesultam as a substrate.

Following success in developing a broad range of sulfonamides, we then explored the synthetic applications of this method. First, we investigated the derivatization of drugs containing the sulfonamide scaffold, which are of interest in medicinal chemistry. As shown in Scheme 3a, valdecoxib (COX-2 inhibitor)[33] and zonisamide (used as an adjunctive therapy in adults with partial-onset of seizures)[34] could be easily converted into *N*-benzyl sulfonamides. Moreover, the model reaction was scaled to a 10.0 mmol reaction and it delivered 2.5 g of the sulfonamide **3aa** in 86% yield, which exhibited potential synthetic application in the organic chemistry industry (Scheme 3b).

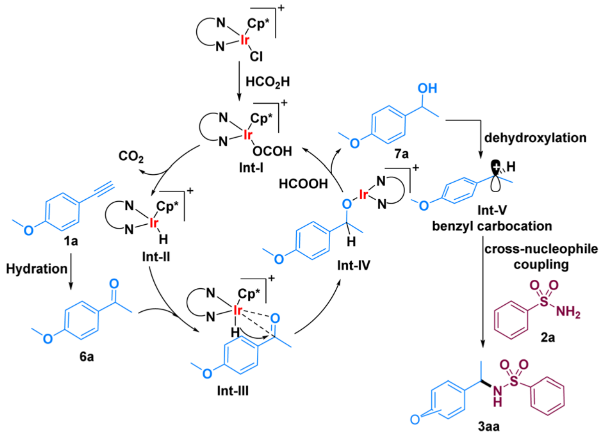
To gain more insights into the reaction mechanism, control experiments were performed. According to our previous work,[35] hydration of alkynes proceeded smoothly under acidic conditions to generate ketone and alcohol intermediates. Therefore, the ketone **6a** and sulfonamide **2a** were employed as substrates under standard conditions, resulting in a 70% yield of **3aa** (Scheme 4a). Moreover, subjecting alcohol **7a** and sulfonamide **2a** to the standard conditions in the absence of **C5** resulted in a 73% yield of **3aa** (Scheme 4b).



Scheme 3 Derivatization of drugs and gram-scale experiment.



Scheme 4 Control experiments.



Scheme 5 Proposed mechanism.

Based on the reaction result and control experiments (Scheme 4), a possible mechanism was proposed (Scheme 5). The mechanism is characterized by a catalytic cycle that includes hydration and a transfer hydrogenation process that was completed to generate the intermediate alcohol **7a**. Subsequently, carbocation occurred by dehydroxylation of **7a** under acidic conditions, which was followed by cross-nucleophile coupling with sulfonamide to produce the desired product **3aa**.

Conclusions

In conclusion, we have shown the sulfonamidation of alkoxy aryl alkynes with viable sulfonamides for the synthesis of diverse *N*-benzylated sulfonamides. This modular Cp*Ir complex-catalyzed reductive sulfonamidation synthesis was achieved under mild conditions. The reaction can be conducted at gram scale in air. Sulfonamide drugs of valdecoxib and zonisamide could also be employed as substrates and converted into *N*-benzyl sulfonamides. The good substrate suitability, wide range of functional group tolerance, scale-up performance, and mild reaction conditions provide evidence of the potential for the application of this reductive sulfonamidation transformation in rapid structural diversification of bioactive molecules.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Yuqiu Liang, Chengxiu Liu, and Penghao Wei: investigation, data curation, validation, visualization, manuscript, and ESI† writing and editing. Youchun Li and Lu Ouyang: conceptualization, funding acquisition, project administration, resources, supervision, visualization, revising the manuscript and the ESI.†

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) J. M. Dorn, M. Alpern, C. McNulty and G. W. Volcheck, Sulfonamide Drug Allergy, *Curr. Allergy Asthma Rep.*, 2018, **18**, 38; (*b*) Q. Zhang, Z. Xia, S. Joshi, V. E. Scott and M. F. Jarvis, Optimization of ADME properties for sulfonamides leading to the discovery of a T-type calcium channel blocker, ABT-639, *ACS Med. Chem. Lett.*, 2015, **6**, 641; (*c*) P. Devendar and G. Yang, Sulfur-containing agrochemicals, *Top. Curr. Chem.*, 2017, **375**, 1; (*d*) K. A. Scott and J. T. Njardarson, Analysis of US FDA-Approved Drugs Containing Sulfur Atoms, *Top. Curr. Chem.*, 2018, **376**, 5.

2 (*a*) J. Pascual and C. Vila, Almotriptan: a review of 20 years' clinical experience, *Expert Rev. Neurother.*, 2019, **19**, 759; (*b*) S. Gupta, A. Perla, A. Roy, J. G. Vitore, K. Bharathi, S. Salave, D. Rana, A. Sharma, R. Rathod, H. Kumar and D. Benival, In Vivo Evaluation of Almotriptan malate Formulation through Intranasal Route for the Treatment of Migraine: Systematic Development and Pharmacokinetic Assessment, *AAPS PharmSciTech*, 2023, **24**, 32.

3 (*a*) A. Stern, H. Green, M. Paul, L. Vidal and L. Leibovici, Prophylaxis for pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients, *Cochrane Database Syst. Rev.*, 2014, **10**, 1465–1858; (*b*) Y. Duan, X. Zhang, W. Deng, S. Wang, J. Hu, X. Wang, W. Li and B. Chen, The first reported pulmonary nocardiosis caused by Nocardia gipuzkoensis resisted to trimethoprim/sulfamethoxazol (TMP-SMZ) in an immunocompetent patient, *J. Glob. Antimicrob. Resist.*, 2004, **37**, 214.

4 (*a*) B.-J. H. van den Born, R. Olde-Engberink and L. Vogt, Hydrochlorothiazide and the Risk of Malignant Melanoma, *JAMA Intern. Med.*, 2018, **178**, 1425; (*b*) H. Sternlicht and G. L. Bakris, Hydrochlorothiazide as the Diuretic of Choice for Hypertension, *J. Am. Coll. Cardiol.*, 2016, **67**, 390.

5 (*a*) P. Tfelt-Hansen, Naratriptan is as effective as sumatriptan for the treatment of migraine attacks when used properly. A mini-review, *Cephalalgia*, 2021, **41**, 1499; (*b*) N. T. Mathew, Naratriptan: a review, *Expert Opin. Inv. Drug.*, 1999, **8**, 687.

6 (*a*) C. Zhao, K. P. Rakesh, L. Ravidar, W.-Y. Fang and H.-L. Qin, Pharmaceutical and medicinal significance of sulfur (SVI)-Containing motifs for drug discovery: A critical review, *Eur. J. Med. Chem.*, 2019, **162**, 679; (*b*) A. S. Kalgutkar, R. Jones and A. Sawant, in *Metabolism, Pharmacokinetics and Toxicity of Functional Groups: Impact of the Building Blocks of Medicinal Chemistry on ADMET*, ed. Smith, D. A., Royal Society of Chemistry, Cambridge, UK, 2010, p. 210.

7 (*a*) Y. Chen, Recent Functionalizations of Primary Sulfonamides, *Synthesis*, 2016, **48**, 2483; (*b*) D. Joseph, M. A. Idris, J. Chen and S. Lee, Recent Advances in the Catalytic Synthesis of Arylsulfonyl Compounds, *ACS Catal.*, 2021, **11**, 4169; (*c*) T. C. Das, S. A. Quadri and M. Farooqui, Recent advances in synthesis of sulfonamides: A review, *J. Chem. Biol. Interfaces*, 2018, **8**, 194; (*d*) O. M. Mulina, A. I. Ilovaisky and A. O. Terent'ev, Oxidative Coupling with S–N Bond Formation, *Eur. J. Org Chem.*, 2018, **2018**, 4648; (*e*) S. Ghosh, P. P. Pal and A. Hajraa, *N*-Heteroarylation of Sulfonamides: An Overview, *Adv. Synth. Catal.*, 2023, **365**, 3020.

8 (*a*) V. A. Azov, D. Janott, D. Schlüter and M. Zeller, Tuning of tetrathiafulvalene properties: versatile synthesis of *N*-arylated monopyrrolotetrathiafulvalenes via Ullmann-type coupling reactions, *Beilstein J. Org. Chem.*, 2015, **11**, 860; (*b*) S. J. Gharpure, D. Anuradha, J. V. Prasad and P. Srinivasa Rao, Stereoselective Synthesis of cis-2,6-Disubstituted Morpholines and 1,4-Oxathianes by Intramolecular Reductive Etherification of 1,5-Diketones, *Eur. J. Org Chem.*, 2015, **2015**, 86.

9 M. Dryzhakov, E. Richmond and J. Moran, Recent advances in direct catalytic dehydrative substitution of alcohols, *Synthesis*, 2016, **48**, 935.

10 (*a*) L. Li, B. Zhou, Y. H. Wang, C. Shu, Y. F. Pan, X. Lu and L. W. Ye, Zinc-Catalyzed Alkyne Oxidation/C–H Functionalization: Highly Site-Selective Synthesis of Versatile Isoquinolones and β-Carbolines, *Angew. Chem., Int. Ed.*, 2015, **54**, 8245; (*b*) Y.-M. Wang, N. C. Bruno, Á. L. Placeres, S. Zhu and S. L. Buchwald, Enantioselective synthesis of carbo-and heterocycles through a CuH-catalyzed hydroalkylation approach, *J. Am. Chem. Soc.*, 2015, **137**, 10524; (*c*) H. Alinezhad, H. Yavari and F. Salehian, Recent advances in reductive amination catalysis and its applications, *Curr. Org. Chem.*, 2015, **19**, 1021.

11 (*a*) Q. Xu, Q. Li, X. Zhu and J. Chen, Green and Scalable Aldehyde-Catalyzed Transition Metal-Free Dehydrative *N*-Alkylation of Amides and Amines with Alcohols, *Adv. Synth. Catal.*, 2013, **355**, 73; (*b*) S.-S. Weng, K. Hsieh and Z. Zeng, $PhI(OCOCF_3)_2$-catalyzed nucleophilic substitution of aromatic propargyl alcohols, *Tetrahedron*, 2015, **71**, 2549; (*c*) M. Zhuang and H. Du, Chiral Brønsted acid catalyzed enantioselective intermolecular allylic aminations, *Org. Biomol. Chem.*, 2014, **12**, 4590.

12 Q.-Q. Li, Z.-F. Xiao, C.-Z. Yao, H.-X. Zheng and Y.-B. Kang, Direct alkylation of amines with alcohols catalyzed by base, *Org. Lett.*, 2015, **17**, 5328.

13 (*a*) P. Qu, C. Sun, J. Ma and F. Li, The *N*-alkylation of sulfonamides with alcohols in water catalyzed by the water-soluble iridium complex {Cp*Ir[6, 6′-(OH) 2bpy](H$_2$O)}[OTf]$_2$, *Adv. Synth. Catal.*, 2014, **356**, 447; (*b*) L. Lu, J. Ma, P. Qu and F. Li, Effective recognition of different types of amino groups: from aminobenzenesulfonamides to amino-(*N*-alkyl) benzenesulfonamides via iridium-catalyzed *N*-alkylation with alcohols, *Org. Lett.*, 2015, **17**, 2350; (*c*) S. Kerdphon,

X. Quan, V. S. Parihar and P. G. Andersson, C–N Coupling of Amides with Alcohols Catalyzed by N-Heterocyclic Carbene–Phosphine Iridium Complexes, *J. Org. Chem.*, 2015, **80**, 11529; (*d*) Q. Zou, C. Wang, J. Smith, D. Xue and J. Xiao, Alkylation of amines with alcohols and amines by a single catalyst under mild conditions, *Chem.–Eur. J.*, 2015, **21**, 9656.

14 T. T. Dang, B. Ramalingam and A. M. Seayad, Efficient ruthenium-catalyzed *N*-methylation of amines using methanol, *ACS Catal.*, 2015, **5**, 4082.

15 P. Satyanarayana, G. M. Reddy, H. Maheswaran and M. L. Kantam, Tris (Acetylacetonato) Rhodium (III)-catalyzed α-alkylation of Ketones, β-alkylation of Secondary Alcohols and Alkylation of Amines with Primary Alcohols, *Adv. Synth. Catal.*, 2013, **355**, 1859.

16 (*a*) H. Hikawa, N. Matsuda, H. Suzuki, Y. Yokoyama and I. Azumaya, *N*-Benzylation/Benzylic C–H Amidation Cascade by the (η^3-Benzyl) palladium System in Aqueous Media: An Effective Pathway for the Direct Construction of 3-Phenyl-3,4-dihydro-(2*H*)-1,2,4-benzothiadiazine 1,1-Dioxides, *Adv. Synth. Catal.*, 2013, **355**, 2308; (*b*) M. Sharif, J. Opalach, P. Langer, M. Beller and X.-F. Wu, Oxidative synthesis of quinazolinones and benzothiadiazine 1,1-dioxides from 2-aminobenzamide and 2-aminobenzenesulfonamide with benzyl alcohols and aldehydes, *RSC Adv.*, 2014, **4**, 8; (*c*) P. Trillo, A. Baeza and C. Najera, Direct Nucleophilic Substitution of Free Allylic Alcohols in Water Catalyzed by $FeCl_3 \cdot 6H_2O$: Which is the Real Catalyst, *ChemCatChem*, 2013, **5**, 1538; (*d*) X. Xu, H. Wu, Z. Li, X. Sun and Z. Wang, Iron oxide-silver magnetic nanoparticles as simple heterogeneous catalysts for the direct inter/intramolecular nucleophilic substitution of π-activated alcohols with electron-deficient amines, *Tetrahedron*, 2015, **71**, 5254.

17 (*a*) J. Baffoe, M. Y. Hoe and B. B. Touré, Copper-mediated *N*-heteroarylation of primary sulfonamides: synthesis of mono-*N*-heteroaryl sulfonamides, *Org. Lett.*, 2010, **12**, 1532; (*b*) R. Hosseinzadeh, M. Tajbakhsh, M. Mohadjerani and M. Alikarami, Copper-catalysed *N*-arylation of arylsulfonamides with aryl bromides and aryl iodides using KF/Al_2O_3, *J. Chem. Sci.*, 2021, **122**, 143; (*c*) X. Han, Cross coupling of 3-bromopyridine and sulfonamides ($R^1NHSO_2R^2 \cdot$ R^1= H, Me, alkyl; R^2= alkyl and aryl) catalyzed by CuI/1,3-di (pyridin-2-yl) propane-1,3-dione, *Tetrahedron Lett.*, 2010, **51**, 360; (*d*) X. Wang, A. Guram, M. Ronk, J. E. Milne, J. S. Tedrow and M. M. Faul, Copper-catalyzed *N*-arylation of sulfonamides with aryl bromides under mild conditions, *Tetrahedron Lett.*, 2012, **53**, 7; (*e*) B. Tan, Y. Teo and A. H. Seow, Low catalyst loadings for ligand-free copper (I)-oxide-catalyzed *N*-arylation of methanesulfonamide in water, *Eur. J. Org Chem.*, 2014, **2014**, 1541.

18 (*a*) M. Nasrollahzadeh, A. Rostami-Vartooni, A. Ehsani and M. Moghadam, Fabrication, characterization and application of nanopolymer supported copper (II) complex as an effective and reusable catalyst for the CN bond cross-coupling reaction of sulfonamides with arylboronic acids in water under aerobic conditions, *J. Mol. Catal. A*, 2014, **387**, 123; (*b*) S. Y. Moon, J. Nam, K. Rathwell and W. Kim, Copper-catalyzed Chan-Lam coupling between sulfonyl azides and boronic acids at room temperature, *Org. Lett.*, 2014, **16**, 338; (*c*) J. C. Vantourout, L. Li, E. Bendito-Moll, S. Chabbra, K. Arrington, B. E. Bode and A. J. Watson, Mechanistic insight enables practical, scalable, room temperature Chan-Lam *N*-arylation of *N*-aryl sulfonamides, *ACS Catal.*, 2018, **8**, 9560.

19 S. Y. Moon, M. Koh, K. Rathwell, S. H. Jung and W. S. Kim, Copper-catalyzed *N*-arylation of *tert*-butyl *N*-sulfonylcarbamates with diaryliodonium salts at room temperature, *Tetrahedron*, 2015, **71**, 1566.

20 Q. Li, L. Xu and D. Ma, Cu-Catalyzed coupling reactions of sulfonamides with (hetero) aryl chlorides/bromides, *Angew. Chem., Int. Ed.*, 2022, **134**, e202210483.

21 (*a*) P. Innocenti, H. Woodward, L. O'Fee and S. Hoelder, Expanding the scope of fused pyrimidines as kinase inhibitor scaffolds: synthesis and modification of pyrido [3,4-*d*] pyrimidines, *Org. Biomol. Chem.*, 2015, **13**, 893; (*b*) A. J. DeAngelis, P. G. Gildner, R. Chow and T. J. Colacot, Generating active "L-Pd (0)" via neutral or cationic π-allylpalladium complexes featuring biaryl/bipyrazolylphosphines: synthetic, mechanistic, and structure-activity studies in challenging cross-coupling reactions, *J. Org. Chem.*, 2015, **80**, 6794; (*c*) M. Khalaj, M. Ghazanfarpour-Darjani, M. R. Talei Bavil Olyai and S. F. Shamami, Palladium nanoparticles as reusable catalyst for the synthesis of *N*-aryl sulfonamides under mild reaction conditions, *J. Sulfur Chem.*, 2016, **37**, 211; (*d*) S. S. Chourasiya, A. A. Wani, C. M. Nagaraja, A. K. Chakraborti and P. V. Bharatam, *N*-(acridin-9-yl) arenesulfonamides: Synthesis, quantum chemical studies and crystal structure analysis to establish the tautomeric preferences, *Tetrahedron*, 2018, **74**, 3634; (*e*) J. Becica, D. P. Hruszkewycz, J. E. Steves, J. M. Elward, D. C. Leitch and G. E. Dobereiner, High-throughput discovery and evaluation of a general catalytic method for *N*-arylation of weakly nucleophilic sulfonamides, *Org. Lett.*, 2019, **21**, 8981.

22 (*a*) T. Kim, S. J. McCarver, C. Lee and D. W. MacMillan, Sulfonamidation of aryl and heteroaryl halides through photosensitized nickel catalysis, *Angew. Chem., Int. Ed.*, 2018, **130**, 3546; (*b*) J. M. Blackburn, A. L. Gant Kanegusuku, G. E. Scott and J. L. Roizen, Photochemically-mediated, nickel-catalyzed synthesis of *N*-(hetero) aryl sulfamate esters, *Org. Lett.*, 2019, **21**, 7049; (*c*) R. T. McGuire, C. M. Simon, A. A. Yadav, M. J. Ferguson and M. Stradiotto, Nickel-Catalyzed Cross-Coupling of Sulfonamides With (Hetero) aryl Chlorides, *Angew. Chem., Int. Ed.*, 2020, **59**, 8952; (*d*) R. T. Simons, G. E. Scott, A. G. Kanegusuku and J. L. Roizen, Photochemically mediated nickel-catalyzed synthesis of *N*-(Hetero) aryl sulfamides, *J. Org. Chem.*, 2020, **85**, 6380; (*e*) T. T. Zhao, H. N. Qin and P. F. Xu, Light-Promoted Nickel-Catalyzed C–O/C–N Coupling of Aryl Halides with Carboxylic Acids and Sulfonamides, *Org. Lett.*, 2023, **25**, 636.

23 (*a*) Y. Chen, Recent Functionalizations of Primary Sulfonamides, *Synthesis*, 2016, **48**, 2483; (*b*) S. Ghosh,

P. Paramita Pal and A. Hajra, *N*-Heteroarylation of Sulfonamides: An Overview, *Adv. Synth. Catal.*, 2023, **365**, 1; (*c*) H. Wu, X. Chen, N. Sun and A. Sanchez-Mendoza, Recent developments in the synthesis of N-aryl sulfonamides, *Synth. Commun.*, 2021, **51**, 2287.

24 (*a*) G. Pelletier and D. A. Powell, Copper-Catalyzed Amidation of Allylic and Benzylic CsH Bonds, *Org. Lett.*, 2006, **8**, 6031; (*b*) Z. Wang, Y. Zhang, H. Fu, Y. Jiang and Y. Zhao, Efficient Intermolecular Iron-Catalyzed Amidation of C–H Bonds in the Presence of *N*-Bromosuccinimide, *Org. Lett.*, 2008, **10**, 1863; (*c*) J. A. Halfen, Recent Advances in Metal-Mediated Carbon-Nitrogen Bond Formation Reactions: Aziridination and Amidation, *Curr. Org. Chem.*, 2005, **9**, 657; (*d*) H. Lai, J. Xu, X. Liu and D. Zha, A dual strategy of direct C(sp^3)-H sulfonamidation by cross-dehydrogenative coupling and oxidative hydroxylation -condensation, *Tetrahedron*, 2024, **160**, 134022.

25 (*a*) P. Becker, T. Duhamel, C. Martínez and K. Muñiz, Designing Homogeneous Bromine Redox Catalysis for Selective Aliphatic C–H Bond Functionalization, *Angew. Chem., Int. Ed.*, 2018, **57**, 5166; (*b*) D. A. Powell and H. Fan, Copper-catalyzed amination of primary benzylic C–H bonds with primary and secondary sulfonamides, *J. Org. Chem.*, 2010, **75**, 2726; (*c*) S. R. Guo, P. S. Kumar and M. Yang, Recent advances of oxidative radical cross-coupling reactions: direct α-C(sp^3)–H bond functionalization of ethers and alcohols, *Adv. Synth. Catal.*, 2017, **359**, 2.

26 (*a*) A. M. Kazerouni, T. A. F. Nelson, S. W. Chen, K. R. Sharp and S. B. Blakey, Regioselective Cp*Ir (III)-catalyzed Allylic C–H Sulfamidation of Allylbenzene Derivatives, *J. Org. Chem.*, 2019, **84**, 13179; (*b*) R. J. Harris, J. Park, T. A. F. Nelson, N. Iqbal, D. C. Salgueiro, J. Bacsa, C. E. MacBeth, M.-H. Baik and S. B. Blakey, The Mechanism of Rhodium Catalyzed Allylic C–H Amination, *J. Am. Chem. Soc.*, 2020, **142**, 5842; (*c*) W. Pin Teh, D. C. Obenschain, B. M. Black and F. E. Michael, Catalytic Metal-free Allylic C–H Amination of Terpenoids, *J. Am. Chem. Soc.*, 2020, **142**, 16716.

27 (*a*) H. Qin, N. Yamagiwa, S. Matsunaga and M. Shibasaki, Bismuth- and Hafnium-Catalyzed Hydroamination of Vinyl Arenes with Sulfonamides, Carbamates, and Carboxamides, *Chem.–Asian J.*, 2007, **2**, 150; (*b*) G. Richard, O. Justin, L. Joo Ho, K. C. Michael and J. Kyung Woon, Chemoselective hydroamination of vinyl arenes catalyzed by an NHC-amidate-alkoxide Pd (II) complex and *p*-TsOH, *Tetrahedron Lett.*, 2013, **54**, 4083; (*c*) Z. S. Qureshi, K. M. Deshmukh, P. J. Tambade, K. P. Dhake and B. M. Bhanage, Amberlyst-15 in Ionic Liquid: An Efficient and Recyclable Reagent for Nucleophilic Substitution of Alcohols and Hydroamination of Alkenes, *Eur. J. Org Chem.*, 2010, **2010**, 6233.

28 (*a*) C. B. Roos, J. Demaerel, D. E. Graff and R. R. Knowles, Enantioselective Hydroamination of Alkenes with Sulfonamides Enabled by Proton-Coupled Electron Transfer, *J. Am. Chem. Soc.*, 2020, **142**, 5974; (*b*) Y.-X. Ji, J. Li, C.-M. Li, S. Qu and B. Zhang, Manganese-Catalyzed N–F Bond Activation for Hydroamination and Carboamination of Alkenes, *Org. Lett.*, 2021, **23**, 207; (*c*) B. G. Hejna, J. M. Ganley, H. Shao, H. Tian, J. D. Ellefsen, N. J. Fastuca, K. N. Houk, S. J. Miller and R. R. Knowles, Catalytic Asymmetric Hydrogen Atom Transfer: Enantioselective Hydroamination of Alkenes, *J. Am. Chem. Soc.*, 2023, **145**, 16118.

29 (*a*) Y. Wei, Y. Liang, R. Luo and L. Ouyang, Recent advances of Cp*Ir complexes for transfer hydrogenation: focus on formic acid/formate as hydrogen donors, *Org. Biomol. Chem.*, 2023, **21**, 7484; (*b*) L. Ouyang, R. Miao, Z. Yang and R. Luo, Iridium-catalyzed Reductive Amination of Carboxylic Acids, *J. Catal.*, 2023, **418**, 283; (*c*) Y. Xia, S. Wang, R. Miao, J. Liao, L. Ouyang and R. Luo, Synthesis of *N*-alkoxy Amines and Hydroxylamines via the Iridium-catalyzed Transfer Hydrogenation of Oximes, *Org. Biomol. Chem.*, 2022, **20**, 6394; (*d*) L. Ouyang, Y. Xia, R. Miao, J. Liao and R. Luo, Iridium-catalyzed reductive etherification of α,β-unsaturated ketones and aldehydes with alcohols, *Org. Biomol. Chem.*, 2022, **20**, 2621; (*e*) N. Luo, Y. Zhong, H. Shui and R. Luo, pH-Mediated Selective Synthesis of *N*-Allylic Alkylation or *N*-Alkylation Amines with Allylic Alcohols via an Iridium Catalyst in Water, *J. Org. Chem.*, 2021, **86**, 15509.

30 L. Ouyang, Y. Liang, S. Wang, R. Miao, J. Liao, Z. Yang and R. Luo, Iridium-catalyzed reductive hydroamination of terminal alkynes in water, *J. Catal.*, 2023, **427**, 115096.

31 (*a*) R. Luo, Y. Liang, S. Wang, J. Liao and L. Ouyang, Iridium-catalyzed selective *para*-C-alkylation of anilines/phenols with aryl alkynes, *J. Catal.*, 2023, **428**, 115184; (*b*) L. Ouyang, Y. Liang, S. Wang, J. Liao and R. Luo, Access of arylmethanes via iridium-catalyzed deoxygenative cross-coupling of aryl ketones with anilines/phenols, *J. Catal.*, 2024, **433**, 115492.

32 Z. Yang, Q. Zhu, R. Luo, Q. Xiang, J.-T. Liu, J.-K. Yang and W. Tang, Iridium-catalyzed highly efficient chemoselective reduction of aldehydes in water using formic acid as the hydrogen source, *Green Chem.*, 2017, **19**, 3296–3301.

33 (*a*) D. Ormrod, K. Wellington and A. J. Wagstaff, Valdecoxib, *Drugs*, 2002, **62**, 2059; (*b*) Y. Bluhm, R. Raudazus, A. Wagner, N. Urban, M. Schaefer and K. Hill, Valdecoxib blocks rat TRPV2 channels, *Eur. J. Pharmacol.*, 2022, **915**, 174702.

34 (*a*) J. C. Martínez-Ávila, A. G. Bartolomé, I. García, I. Dapía, H. Y. Tong, L. Díaz, L. Puerra, J. Frías, A. J. Carcás Sansuan and A. M. Borobia, Pharmacometabolomics applied to zonisamide pharmacokinetic parameter prediction, *Metabolomics*, 2018, **14**, 70; (*b*) C. Li, L. Xue, Y. Liu, Z. Yang, S. Chi and A. Xie, Zonisamide for the Treatment of Parkinson Disease: A Current Update, *Front. Neurosci.*, 2020, **14**, 574652.

35 N. Luo, Y. Zhong, J.-T. Liu, L. Ouyang and R. Luo, An Efficient Hydration and Tandem Transfer Hydrogenation of Alkynes for the Synthesis of Alcohol in Water, *Synthesis*, 2020, **52**, 3439.