JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

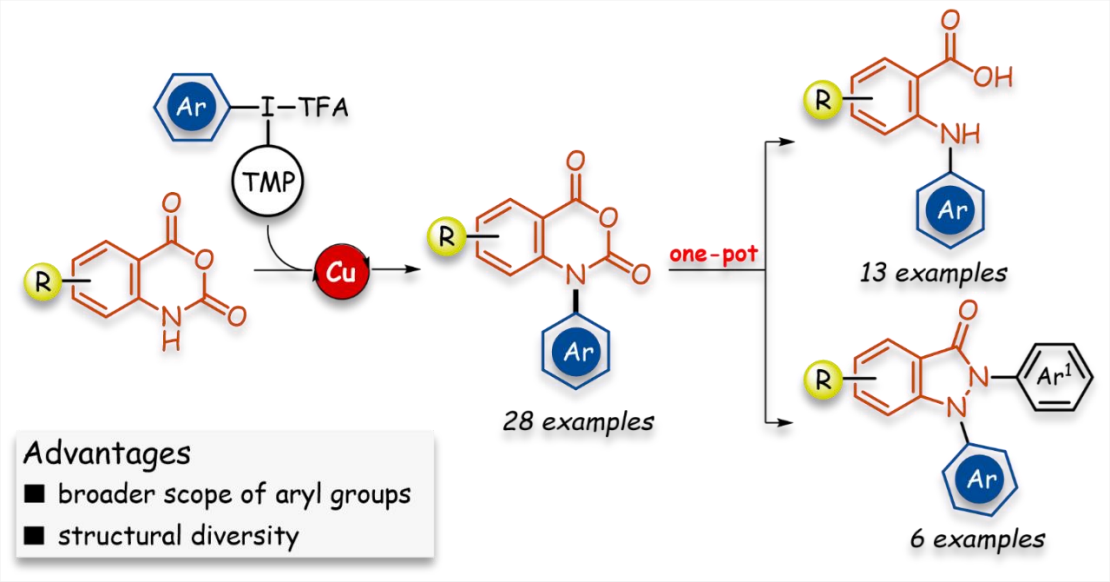
Utilization of Aryl(TMP)iodonium Salts for Copper-Catalyzed *N*-Arylation of Isatoic Anhydrides: An Avenue to Fenamic Acid Derivatives and *N,N′*-Diarylindazol-3-ones

Raktim Abha Saikia, Khanindra Talukdar, Debabrat Pathak, Bipul Sarma, and Ashim Jyoti Thakur*

Chapter 5

Copper-catalyzed *N*-Arylations of Isatoic Anhydrides

Abstract: The chapter describes a general method for copper-catalyzed *N*-arylation of isatoic anhydride with unsymmetrical iodonium salt at room temperature. The developed catalytic protocol is mild and operationally simple; and aryl(TMP)iodonium trifluoroacetate is employed as arylating partner. The methodology offers the broad applicability of both structurally and electronically diverse aryl groups from aryl(TMP)iodonium salts to access *N*-arylated isatoic anhydrides in moderate to excellent yields (61-92%). Moreover, the substituted isatoic anhydrides are equally compatible too with the protocol. To demonstrate the synthetic utilities of the *N*-arylation process, we also report an alternative approach for biologically relevant fenamic acid derivatives and *N,N′*-diarylindazol-3-ones under one-pot economical system. In addition, the scale-up synthesis of flufenamic acid is also illustrated.



Saikia, R. A., Talukdar, K., Pathak, D., Sarma, B., and Thakur, A. J. Utilization of Aryl(TMP)iodonium Salts for Copper-catalyzed *N*-Arylation of Isatoic Anhydrides: An Avenue to fenamic acid derivatives and *N,N′*-diarylindazol-3-ones. *The Journal of Organic Chemistry,* 88(6):3567-3581, 2023.

5.1 Introduction

5.1.1 Isatoic anhydride as a valuable synthon in organic synthesis

2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-diones, commonly known as isatoic anhydrides **1** and their derivatives are important heterocyclic compounds and key intermediates for the architecture of many pharmaceutically important scaffolds in medicinal chemistry [1–7]. Reported by Friedländer and Wleügel in 1883, the heterocycle was synthesized from anthranil and ethyl chloroformate and named as anthranilic carboxylic acid [1]. Later, Kolbe named the compound as "*isatoic acid*" since he synthesized it by oxidation of isatin; and finally, Erdmann recommended the name "*isatoic anhydride*" in 1899 [1]. Though the direct appearance of this moiety in natural product and pharmaceuticals have not been found yet, it serves as a primary synthon for many biologically active molecules. For example, fenamic acid derivatives **2** [non-steroidal anti-inflammatory drugs (NSAIDs)] [8–9], benzimidazoquinazolines **3** (anti-tuberculosis agents) [10], tryptanthrins **4** [11], 1,4-benzodiazepines **5** (against *trypanosoma brucei*) [12], penicinotam **6** (potent insecticidal properties) [13], etc. are all biologically potent scaffolds and these compounds can be synthesized from isatoic anhydrides (Figure 5.1).

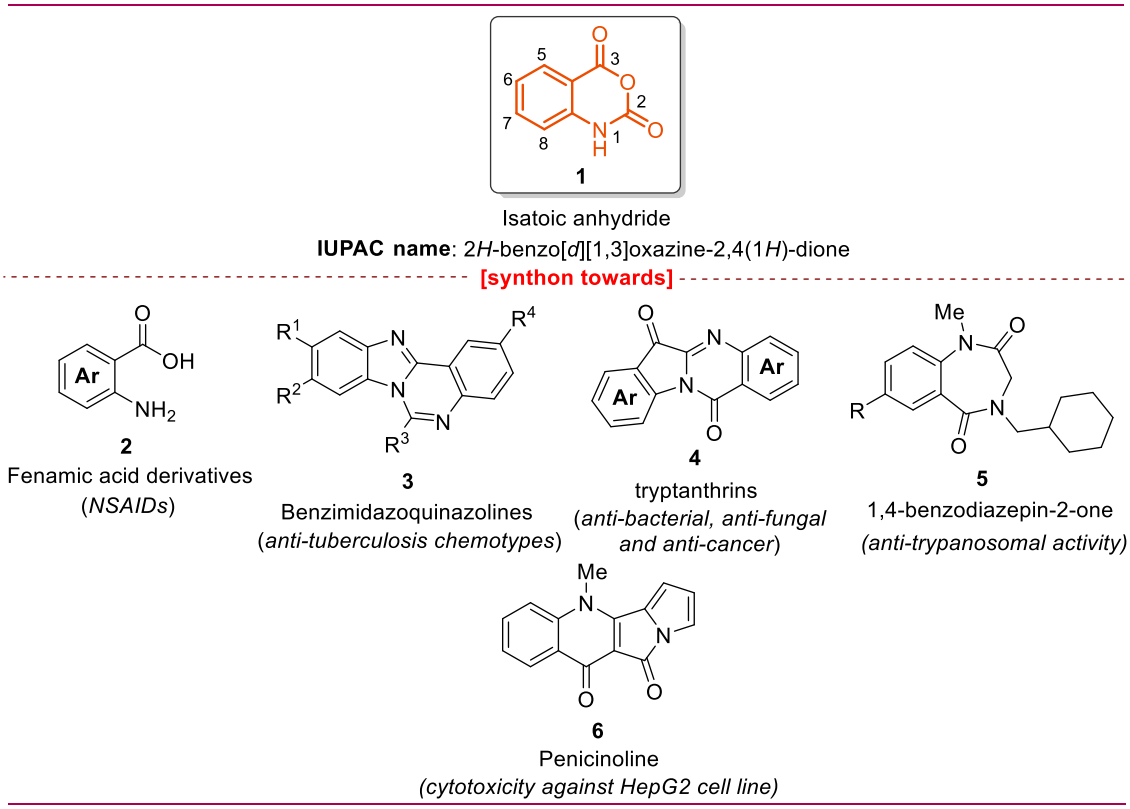
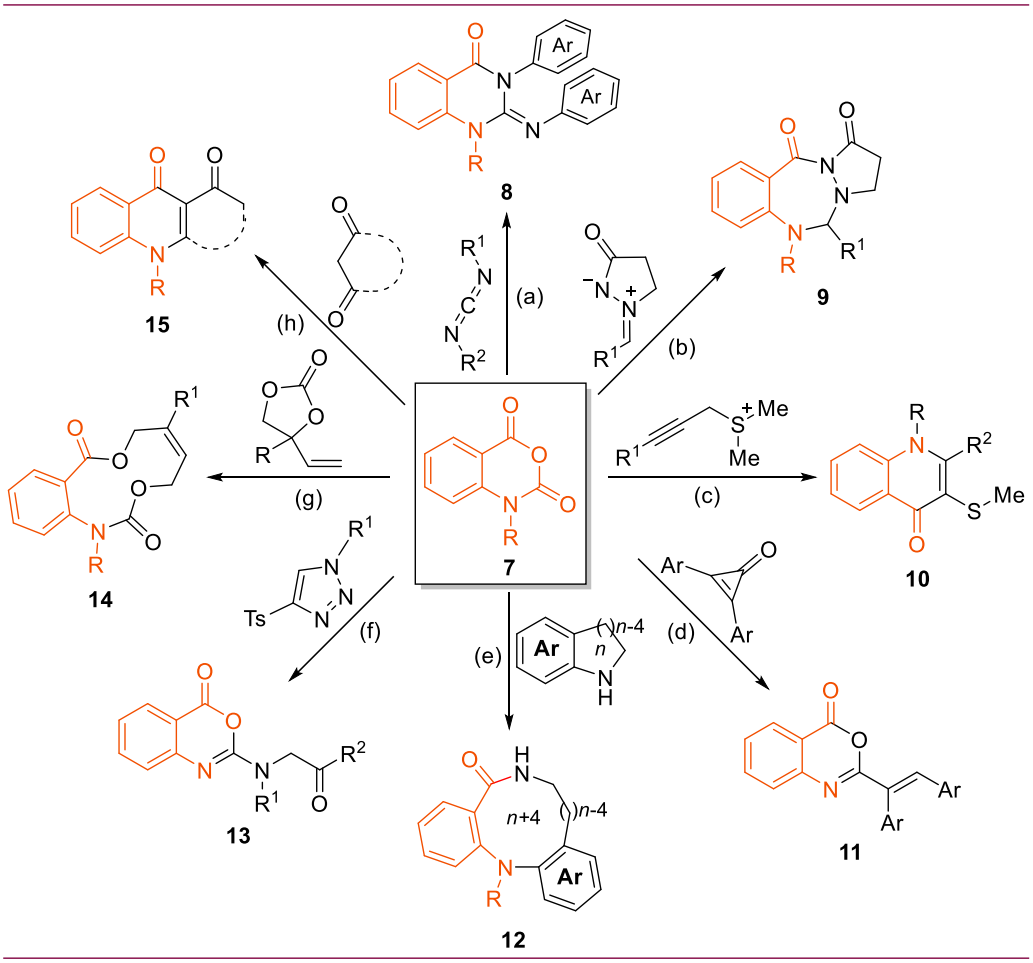


Figure 5.1 Biologically useful scaffolds where isatoic anhydrides are used

Due to the presence of an electrophilic anhydride group on isatoic anhydride nucleus, the heterocylic moiety has been exploited widely with diverse nucleophiles in the early 2000s [14], as mentioned in the review article by Kappe [1] and Coppola [15], independently. In the last decades, isatoic anhydrides have also been utilized as an important building block in construction of many new heterocylic molecules and compounds having medium-to-large membered rings [16-23] (Scheme 5.1).



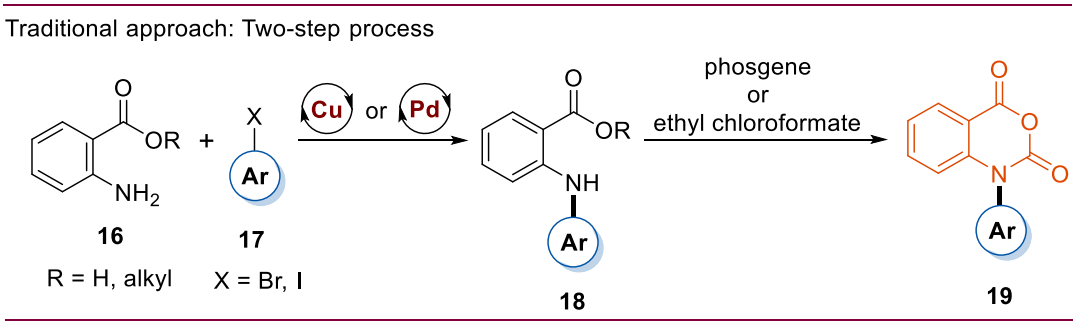
Scheme 5.1 Diversification of isatoic anhydrides with various reagents: (a) $Ni(PPh_3)_2Cl_2$ (10 mol%), Zn (30 mol%), MeCN, 100 °C, 10 h; (b) $Ph_2P(O)OH$ (10 mol%), 80 °C, ethyl propionate; (c) DMAP (2 equiv.), MeCN, 60 °C, 5 h; (d) Ag_2O (10 mol%), Na_2CO_3 (1 equiv.), HFIP (3 equiv.), PhMe, 100 °C, 16 h; (e) NaHMDS (1.1 equiv.), THF, 15 min, μw, 100 °C; (f) $Rh_2(Oct)_4$ (20 mol%), DCE, 100 °C, 1 h; (g) $Pd(PPh_3)_4$ (2.5 mol%), PPh_3 (10 mol%), EtOAc, 60 °C, 13 h; and (h) Et_3N (4.0 equiv), CH_3CN (0.5 M), 3 Å mol sieves, 85 °C, 13 h.

Because of the acidic N–H group on isatoic anhydride nucleus, both alkylation and arylation of the N–H group is quite possible. The alkylation of isatoic anhydrides has been quite well-explored and easily accessible under basic conditions [24–25],

although the anhydride group is prone to decarboxylation in many circumstances. Contrary to this, the arylation of isatoic anhydrides is relatively less explored; few reports are found for the *N*-arylation of isatoic anhydrides and limitations especially on the arylation scope are noticed in those studies [26–29]. Therefore, developing a general and versatile strategy for the *N*-arylation of isatoic anhydride and its broad scope of arylation is highly beneficial.

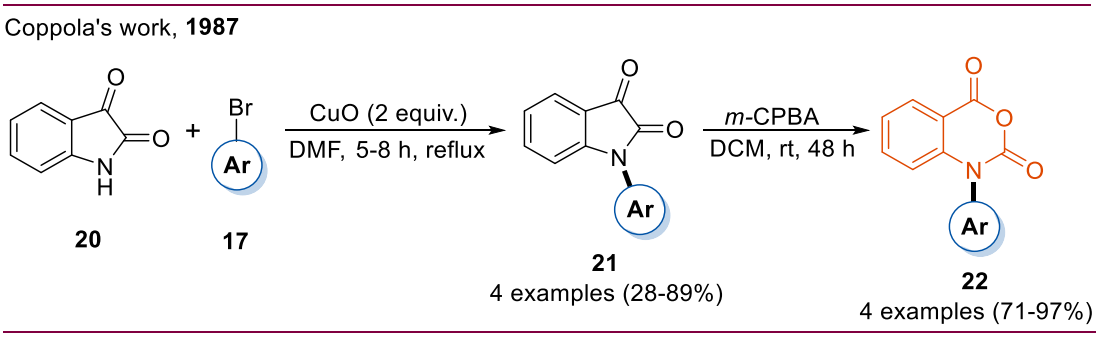
5.1.2 Previous methods to obtain *N*-arylated Isatoic anhydrides

The classical entry for these *N*-aryl isatoic anhydrides is through two-step *de novo* cyclization process: i) Ullmann condensation between *o*-aminobenzoic acid **16** and aryl halides **17**, ii) cyclization to form the anhydride linkage using phosgene or ethyl chloroformate (scheme 5.2) [26]. The major drawbacks associated with these routes are reductive dehalogenation of *o*-halobenzoic acid, harsh reaction conditions, low-yields, and use of toxic reagents.



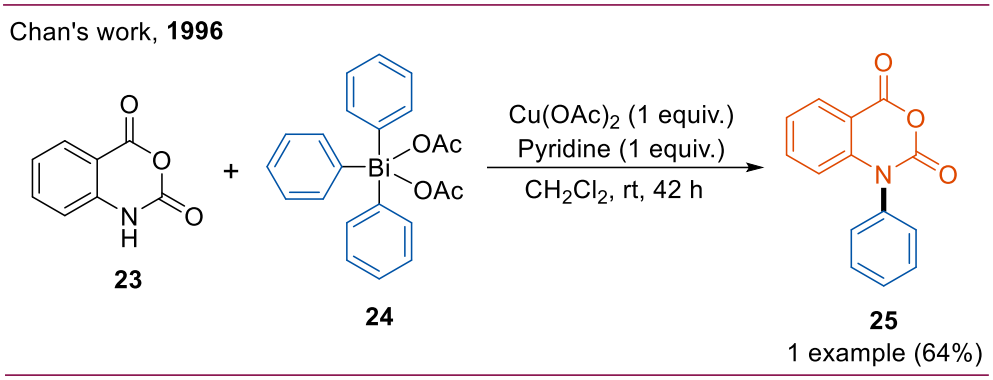
Scheme 5.2 C–N coupling/ring-closing approach

Later, Coppola introduced another two-step indirect route from isatin **20** in 1987 (scheme 5.3) [27]. In that report, Coppola mentioned that direct *N*-arylation of isatoic anhydride with aryl bromide under the same copper-mediated methodology had failed.



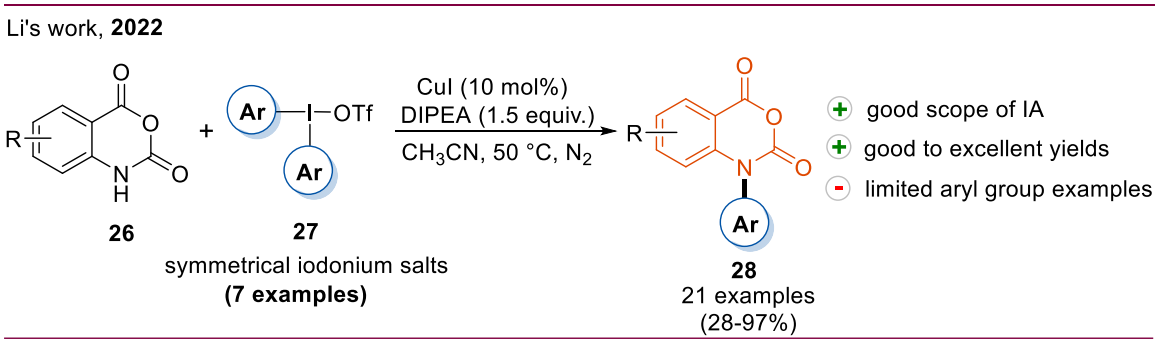
Scheme 5.3 *N*-arylation of indole/ring expansion

As these two-step methods have their own advantages and limitations, an alternative complementary approach is the direct functionalization of the isatoic anhydride nucleus without hampering the reactive anhydride fragment. Chan back in 1996 developed a direct approach for *N*-arylation of isatoic anhydride **23** under copper-catalysed condition with triarylbismuth as an arylating precursor **24** (Scheme 5.4) [28]. He mentioned only one example and stoichiometric amount of copper source was utilized.



Scheme 5.4 Direct *N*-arylation approach with triarylbismuth as aryl source

Concurrent to our ongoing work in this chapter, very recently Li and co-workers achieved a breakthrough with diaryliodonium salts **27** under copper-catalyzed conditions (Scheme 5.5) [29]. This methodology discussed broad scope of the functionalized isatoic anhydrides and symmetrical diaryliodonium salts were utilized in the arylation scope. As simple symmetrical iodonium salts were used, the examples of aryl groups were limited, and no diversity of aryl scope including electron-donating and electron-withdrawing groups were mentioned in that study.



Scheme 5.5 Recent development with symmetrical diaryliodonium salts

In this chapter, unsymmetrical iodonium salt i.e. aryl(TMP)iodonium salts are explored explore as arylating partners for the *N*-arylation of isatoic anhydrides. The strategic methodology is intended to enhance the scope of arylation with respect to aryl(TMP)iodonium salts and to demonstrate higher functional group tolerance. Furthermore, one-pot methodologies are designed to access fenamic acid derivatives and *N,N'*-diarylindazol-3-ones to demonstrate the synthetic utility of *N*-arylated isatoic anhydride intermediate.

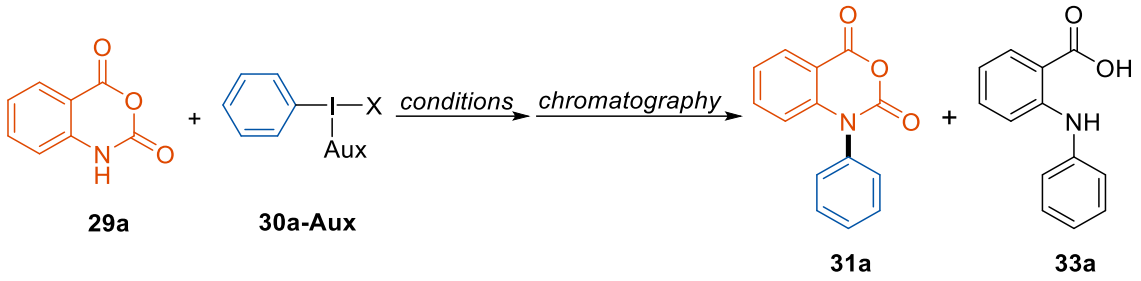
5.2 Optimization

5.2.1 Initial screening for of *N*-arylation of isatoic anhydrides

The carefully chosen and crucial optimization studies are presented in Table 5.1. The initial investigations of our desired transformation were started by using the model substrates isatoic anhydride **29a** and both diphenyliodonium triflate **30a-OTf** and phenyl(2,4,6-trimethoxyphenyl)iodonium trifluoroacetate or phenyl(TMP)iodonium trifluoroacetate **30a-TMP** as the arylating partner. A series of optimizations were performed to obtain an effective metal-free condition during our preliminary attempts, but regretfully no arylation product **31a** was observed in the presence of either weak or strong bases (entries 2-7). A trace amount of **31a** was noticed with DIPEA at elevated temperature of 100 ℃ (entry 6). Moreover, the application of previous metal-free methods of *N*-arylation of diaryliodonium salts failed with this heterocylic nucleus (entry 7) [30–32]. As the base-mediated approach was not successful, we attempted the reaction under the condition mentioned in chapter 4. Accordingly, when the reaction of **30a-TMP** with **29a** in presence of copper iodide (CuI) and potassium phosphate (K_3PO_4) at room temperature was carried out, we were pleased to observe positive result (entry, 10). However, after purification by column chromatography (silica gel, mesh 60-120), formation of the *N*-phenylated anthranilic acid product **33a** (side product) in 36% yield was also noticed along with **31a** (42% yield). The side product **33a** was noticed in minimal amount during the reaction period, however the substantial appearance of **33a** during column chromatographic purification can be rationalized as decarboxylation of **31a** under the slight acidic medium (silica gel, mesh 60-120). To prevent the decarboxylation process and maintain the yield of the reaction, various stationary phases were checked, and the best choice was flash chromatography (silica gel, 230-

400 mesh) under polar eluent (DCM/ethyl acetate). With the choice of proper chromatographic purification, trace amount of decarboxylation was noticed and the desired product **33a** was obtained in 73% yield (entry 9). The reaction demonstrated excellent selective transfer of the phenyl group from **30a-TMP-TFA** salt to the nitrogen nucleus and the presence of TMP-arylated product was not observed.

Table 5.1 Optimization of the reaction conditions[a]



Entry	30a-Aux (equiv.)	Aux/X	Solvent	Base (equiv.)	Cu (x mol%)	*T* (°C)	*t* (h)	Yield[b] (%)
1	**30a-OTf** (1)	Ph/OTf	Toluene	Na_2CO_3 (1.1)	-	100	24	ND
2	**30a-OTf** (1)	Ph/OTf	DMAc	NaH (2)	-	rt	24	ND
3	**30a-OTf** (1)	Ph/OTf	Toluene	K_3PO_4 (1.1)	-	100	12	ND
4	**30a-OTf** (1)	Ph/OTf	Toluene	Et_3N (1.1)	-	100	12	ND
5	**30a-OTf** (1)	Ph/OTf	Toluene	*t*BuOK (1.1)	-	100	12	ND
6	**30a-TMP** (1)	Ph/OTf	Tolune	DIPEA (1.1)	-	100	12	trace
7	**30a-TMP** (1)	TMP/TFA	DCE	KF (2)	-	70	12	ND
8	**30a-TMP** (1)	Ph/OTf	DCE	K_3PO_4 (1.2)	CuI (10)	rt	24	66
9	**30a-TMP** (1)	TMP/TFA	DCE	K_3PO_4 (1.2)	CuI (10)	rt	24	73
10	**30a-TMP** (1)	TMP/TFA	DCE	Et_3N (1.2)	CuI (10)	rt	3	82
11	**30a-TMP** (1)	TMP/TFA	DCE	Na_2CO_3 (1.2)	CuI (10)	rt	5	68
12	**30a-TMP** (1)	TMP/TFA	DCE	K_2CO_3 (1.2)	CuI (10)	rt	5	66

13	**30a-TMP** (1)	TMP/TFA	DCE	DBU (1.2)	CuI (10)	rt	3-4	71
14	**30a-TMP** (1)	TMP/TFA	DCE	Et_3N (1.2)	CuI (10)	70	3	80
15	**30a-TMP** (1)	TMP/TFA	DCE	Et_3N (1.2)	CuI (5)	rt	3	66
16	**30a-TMP** (1)	TMP/TFA	Toluene	Et_3N (1.2)	CuI (10)	rt	3-4	65
17	**30a-TMP** (1)	TMP/TFA	CH_3CN	Et_3N (1.2)	CuI (10)	rt	3-4	78
18	**30a-TMP** (1)	TMP/TFA	DCM	Et_3N (1.2)	CuI (10)	rt	3-4	80
19	**30a-TMP** (1)	TMP/TFA	DCE	Et_3N (1.2)	$Cu(OTf)_2$ (10)	rt	3-4	71
20	**30a-TMP** (1)	TMP/TFA	DCE	Et_3N (1.2)	$Cu(OAc)_2$ (10)	rt	3-4	68
21	**30a-TMP** (1)	TMP/TFA	DCE	Et_3N (1.2)	CuCl (10)	rt	3-4	78
22	**30a-TMP** (1)	TMP/TFA	DCE	Et_3N (1.2)	CuBr (10)	rt	3	84
23	**30a-TMP** (1)	TMP/TFA	DCE	Et_3N (1.2)	CuBr (5)	rt	3	88
24	**30a-TMP** (1.2)	TMP/TFA	DCE	Et_3N (1.2)	CuBr (2.5)	rt	12	78

[a]Reaction conditions: **29a** (0.2 mmol), **30a-Aux** salt (x equiv.), base (x equiv.) and copper salt (x mol%) were added in a dry Schlenk tube. [b]Isolated yields. ND implies not detected. rt i.e., room temperature.

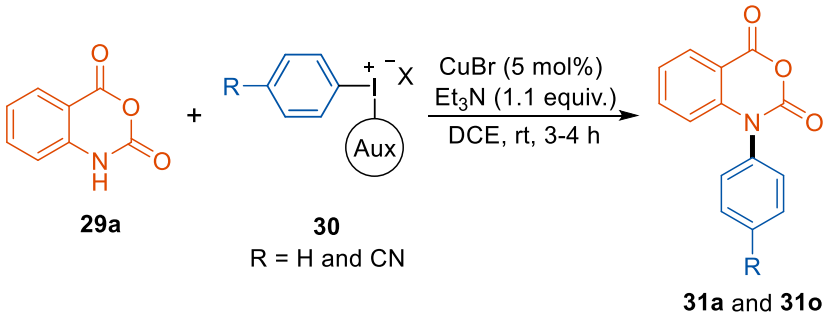
As the essence of copper was realized, a variety of inorganic and organic bases were screened again (entries 10-13). Among all optimized bases, Et_3N delivered better conversion of **31a** in 82% yield and the required reaction duration was also significantly less (entry 10). No further improvement on the yield of **31a** was observed while either elevating the reaction temperature or decreasing the amount of catalyst CuI (entries 14 and 15). At room temperature, solvents such as DCM and ACN could be useful too and comparatively good conversion was achieved in these solvents, however; lower yield was achieved in toluene due to solubility problems at room temperature (entries 16-18). As both copper(I) and copper(II) catalysts facilitated the formation of **31a**, the detailed examination of copper sources revealed that CuBr afforded a comparatively higher yield (85%) of **31a** than other catalysts

(entries 19-22). Interestingly, the reduction of the catalyst amount of CuBr from 10 mol% to 5 mol% did not improve the yield of the reaction and afforded the product **31a** in 88% (entry 23). Further decreasing the amount of CuBr to 2.5 mol%, slight loss of the yield was noticed, and completion of the reaction took longer duration (entry 24).

5.2.2 Selection of counter-anions and suitable auxiliary for unsymmetrical iodonium salt

Symmetrical iodonium salt, diphenyliodonium salt (**30a-OTf**) was applicable with the reaction conditions, affording 82% of **31a** (Table 5.2, entry 1). Iodonium salt with counter-anion tetrafluoroborate (**31a-BF_4**) was equally tolerated and demonstrated 78% conversion of **31a** (entry 2). Other auxiliaries based iodonium salts such as anisyl (An) and mesiyl (Mes) were screened too. The mesityl-iodonium salt **30a-Mes** exhibited better chemoselective arylation (entry 3), while anisyl-iodonium salt **30a-An** showed poor conversion of **31a** and gave mixture of arylated products (entry 4).

Table 5.2 Investigation of phenylation and 4-cyanophenylation[a]



Entry	30	Aux/X	R	T (°C)	*t* (h)	Yield[b] (%)
1	**30a-OTf**	Ph/OTf	R = H	rt	3	82
2	**30a-BF_4**	Ph/BF_4	R = H	rt	3	78
3	**30a-Mes**	Mes/OTf	R = H	rt	3	81
4	**30a-An**	An/OTf	R = H	rt	3	45
5	**30a-TMP**	TMP/OTs	R = H	60	3	82
6	**30o-TMP**	TMP/TFA	R = CN	rt	3	65
7	**30c-OTf**	Ph/OTf	R = CN	rt	3-4	36
8	**30c-Mes**	Mes/TFA	R = CN	rt	3-4	53
9	**30c-An**	An/OTf	R = CN	rt	3-4	trace
10	**30b-TMP-OTs**	TMP/OTs	R = CN	rt	3-4	62

[a]Reaction conditions: **29a** (0.1 mmol), diaryliodonium salt **30** (0.1 mmol), Et_3N (1.2 equiv.), CuBr (5 mol%) and solvent (0.1 M) were added in a Schlenk tube. [b]Isolated yields.

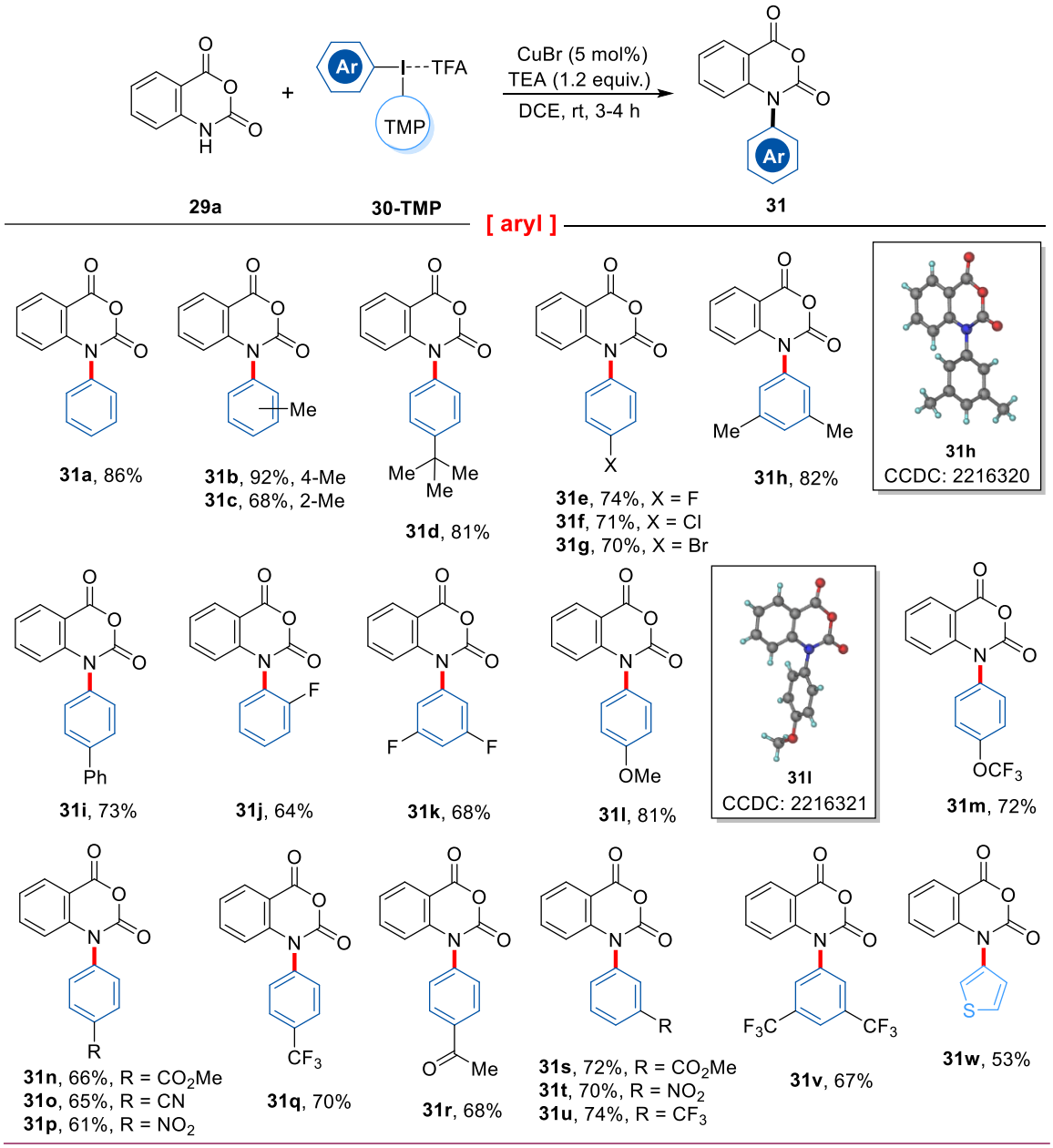
Similarly, arylation with an electron-withdrawing aryl moiety i.e., 4-cyanophenylation was tested prior to exploring the substrate scope of iodonium salts (entries 6-10). The arylated product **31o** was the major (65% yield) in case of TMP-TFA iodonium salt (**30o-TMP**), while mesityl-iodonium salt (**30c-Mes**) and TMP-OTs salt (**30c-TMP-OTs**) delivered the desired product **31o** in 53% and 62%, respectively (entries 8 and 10). The auxiliary studies showed that both mesityl- and TMP-iodonium salts were applicable, but TMP-iodonium salts were selected for arylation scope. Due to easier synthetic approach, unified synthetic route to obtain diverse functionalized (electron-rich and electron-donating) aryl groups and higher chemoselectivity, TMP-iodonium salts are highly beneficial as arylating partner among other auxiliary iodonium salts or symmetrical iodonium salts. As our reaction discovery process aimed to expand the arylation scope of isatoic anhydrides, our study basically focused on the reactivity of the aryl(TMP)iodonium salts and its applications with diverse examples.

5.3 Substrate scope

5.3.1 Scope of aryl(TMP)iodonium salts

With the optimized conditions using 5 mol% CuBr and 1.2 equivalents of Et_3N (TEA) at room temperature, the efficacy of the developed protocol was examined by varying the functionalized aryl groups of aryl(TMP)iodonium salts with isatoic anhydride **29a** (Table 5.3). Repeating the reaction for the model substrates on 0.3 mmol scale provided the product **31a** in 86% yield. Simple weakly-activating aryl groups 4-tolyl, 2-tolyl and 4-*tert*-butyl afforded corresponding arylated products **31b**, **31c** and **31d** respectively in good to excellent yields (68-91%). However, lower yield was observed in case of *ortho*-tolyl (product **31c**) due to the steric factor and the result was in same line of previous reports. Aryl moieties with weakly-deactivating halogen-substitution demonstrated good chemoselectivity and furnished the products **31e**-**31g** in good yields. In case of *m*-xylyl, the product (**31h**) could be obtained in 82% yield. Extended aromatic ring such as biphenyl (**31i**) could be arylated too with excellent selectivity. Apart from 4-F-phenyl example (**31e**), other fluorinated arenes such as *ortho*-fluoro (**31k**) and 3,5-difluoro (**31l**) substituted aryl scaffolds were incorporated into the isatoic anhydride nucleus and afforded the products in 64% and 68% yields, respectively. Aromatic ring bearing electron-rich

Table 5.3 Scope of the aryl groups derived from aryl(TMP)iodonium salts[a,b]



[a]Reaction conditions: **29a** (0.3 mmol), **30-TMP** salt (0.3 mmol), CuBr (5 mol%), TEA (1.2 equiv.) and dry DCE (0.1 M) were added to a Schlenk tube. [b]Isolated yields.

groups such as 4-OMe and 4-OCF_3 were easily transfered to the isatoic anhydride nucleus and provided the products **31l** and **31m** respectively in good yields. The complicated part in the scope of arylation is the incorporation of aryl rings with EW groups (EWG). In case the scope of symmetrical iodonium salts; it requires costly synthetic precursors [33]. In our study, aryl(TMP)iodonium salts with strong or weak EWG aryl moieties were equally feasible with the methodology. *Para*-substituted EWGs such as 4-CO_2Me (**31n**), 4-CN (**31o**) and 4-NO_2 (**31p**) owning aromatic rings

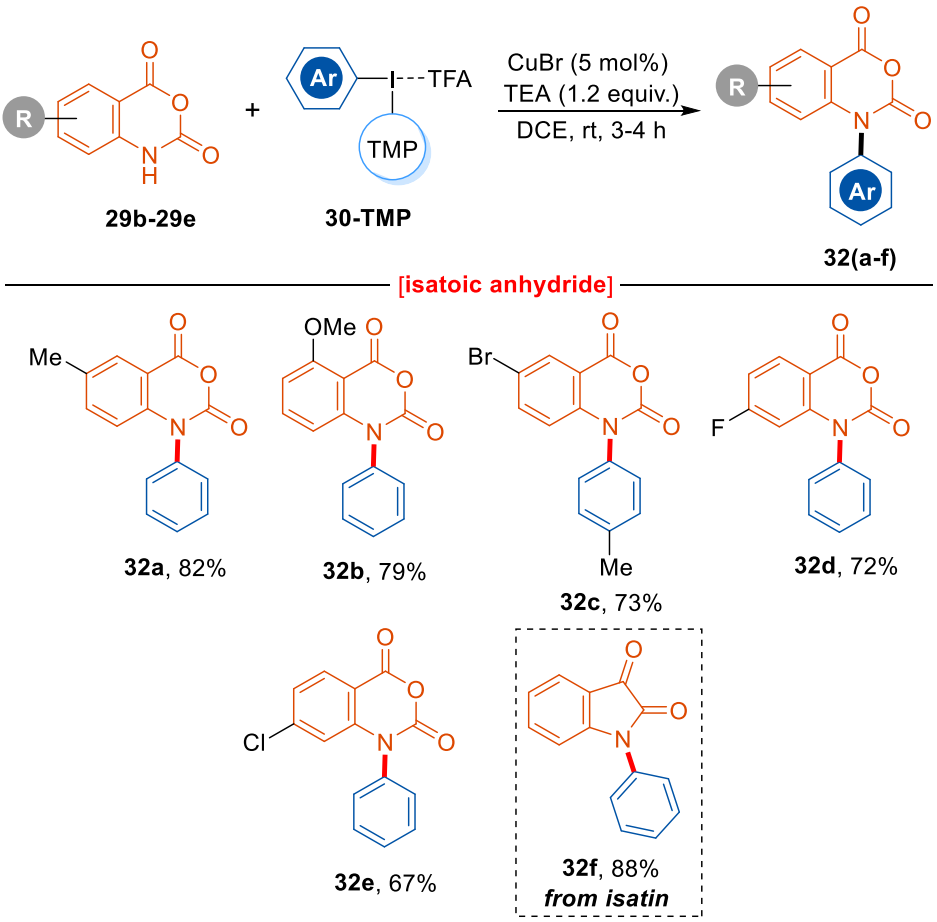
were implemented effectively from its corresponding TMP-iodonium salts, however, they exhibited moderate yields in comparison to EDGs. Similarly, the application of the examples of 4-CF_3-phenyl (**31q**) and 4-acetyl-phenyl (**31r**) further highlighted the robustness of the method with respect to the EWG aryl rings. EWGs on the *meta*-position of the aryl partner worked well with methods and featured the functional groups 3-CO_2Me (**31s**), 3-NO_2 (**31t**) and 3-CF_3 (**31u**) in moderate yields. TMP-iodonium salt with 3,5-bis(trifluoromethyl) also unveiled the selective transfer of the functionalized aryl group and afforded the product **31v** in 67% yield. Notably, TMP-iodonium salt with a heteroaryl group, such as 3-thienyl showed selective arylation to give product **31w** in 53% yield. Moreover, the structures of **31h** and **31l** were supported by single crystal X-ray structural elucidation.

5.3.2 Scope of isatoic anhydrides

Subsequently, the influence of other functional groups on the attached benzenoid ring of the isatoic anhydride moiety were checked by applying electronically variable isatoic anhydrides (**29b**-**29e**) (Table 5.4). The efficacy was tested through either phenylation from phenyl(TMP)iodonium trifluoroacetate **30a-TMP** or 4-methyl-phenylation from (*p*-tolyl)(TMP)iodonium trifluoroacetate **30b-TMP**. Having a methyl group on the C^6-position of isatoic anhydride ring afforded smooth transformation to phenylated product **32a** in 82% yield. Similarly, good yield of arylated product **32c** was obtained in case of 6-Br-isatoic anhydride with iodonium salt **30b-TMP**. An example of isatoic anhydride bearing 5-OMe group was demonstrated in this study and the iodonium salt **30a-TMP** underwent selective phenylation to furnish the product **32b** in 79% yield. This example shows advantageous result with respect to the previous study [29], as the 5-methoxy-isatoic anhydride failed to give arylated product with symmetrical iodonium salt. Weakly-deactivating halide groups (-F and -Cl) on the 7-position of isatoic anhydride were reacted with the iodonium salt **30a-TMP** and provided the arylated products **32d** and **32e** in 72% and 67% yields, respectively. As isatin comprises of similar amidic linkage like isatoic anhydride, we were expecting that the N−H group of isatin would undergo arylation too under our optimized reaction conditions. Pleasingly, the isatin

nucleus also showed similar reactivity with the protocol for *N*-arylation and offered the product **32f** in excellent yield of 88%.

Table 5.4 Scope of the substituted isatoic anhydrides[a,b]



[a]Reaction conditions: **29a-29e** or isatin (0.3 mmol), **30-TMP** salt (0.3 mmol), CuBr (5 mol%), TEA (1.2 equiv.) and dry DCE (0.1 M) were added to a Schlenk tube. [b]Isolated yields.

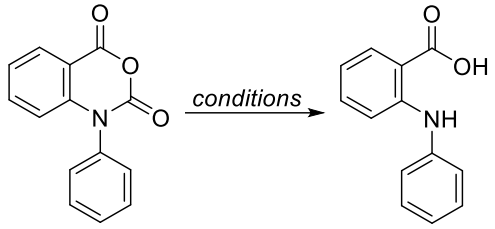
5.4 Application of *N*-arylated isatoic anhydrides as intermediate

5.4.1 Synthesis of fenamic acid derivatives

As the *N*-substituted isatoic anhydrides are active synthons to access other organic scaffolds, we became interested in demonstrating the synthetic utility of the *N*-arylated isatoic anhydrides. Fenamic acid derivatives or *N*-aryl anthranilic acids are known for their activity as nonsteroidal anti-inflammatory drugs (NSAIDs) and clinical candidates. It could be obtained from isatoic anhydrides too *via* stepwise *N*-arylation and decarboxylation [9–10]. Though the previously known decarboxylation step required a harsh condition, such as 15% HCl under reflux conditions; in this study the reaction conditions was re-optimized to cleave the

anhydride bond under mild reaction conditions (Table 5.5). With the optimized decarboxylation process (entry 5), the one-pot sequential approach for fenamic acid derivatives were explored with various isatoic anhydrides and functionalized aryl(TMP)iodonium salts without isolating the *N*-arylated product.

Table 5.5 Optimization for decarboxylation[a]



32a **33a**

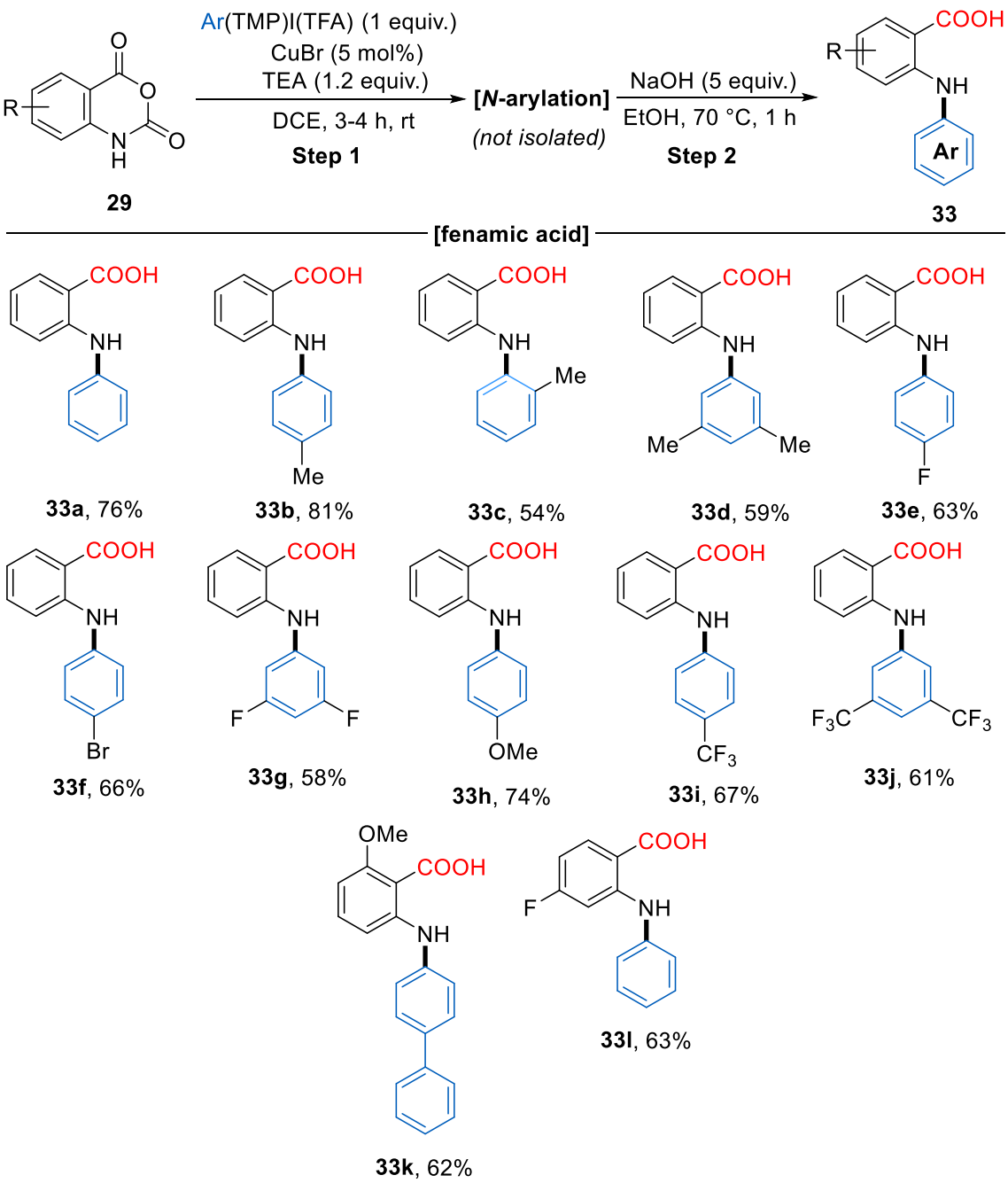
Entry	conditions	yield[b] (%)
1	H_2O, reflux	NR
2	15% HCl, 100 °C, reflux	72
3	i) EtOH, NaOH (1 equiv.), 70 °C, 1 h ii) 2N HCl acid-workup	68
4	i) EtOH, NaOH (2 equiv.), 70 °C, 1 h ii) 2N HCl acid-workup	72
5	**i) EtOH, NaOH (5 equiv.), 70 °C, 1 h ii) 2N HCl acid-workup**	**78**
6	i) EtOH, NaOH (10 equiv.), 70 °C, 1 h ii) 2N HCl acid-workup	76

[a]Reaction conditions: **32a** (0.2 mmol) was added to a Schlenk tube. [b]Isolated yields.

With the best optimized condition for the one-pot system, simple fenamic acid **33a** was obtained in 76% yield (Table 5.6). Changing iodonium salt containing other groups such as functionalized 4-tolyl, 2-tolyl and 3,5-dimethylphenyl easily worked with the one-pot method and afforded the substituted FA products **33b**, **33c** and **33d** respectively in good yields. Derivatives with 4-fluoro (**33e**) and 4-bromo (**33f**) were successfully synthesized from the corresponding iodonium salts **30e-TMP** and **30g-TMP** respectively. Electron-donating (**33h**) and electron-withdrawing (**33i**) group on the phenyl ring were compatible too with the reaction conditions and provided the products in moderate yields. Examples of multiple-fluorinated aryl moieties were demonstrated by showcasing the selective insertion of 3,5-difluoro-phenyl and 3,5-bis(trifluromethyl)-phenyl groups and obtaining the fenamic acid derivatives **33g** and **33j** in 58% and 61% yields, respectively. Other isatoic anhydrides possessing 5-

methoxy and 7-fluoro substituents were also compatible with the one-pot system and established the scope of the isatoic anhydrides (**33k** and **33l**).

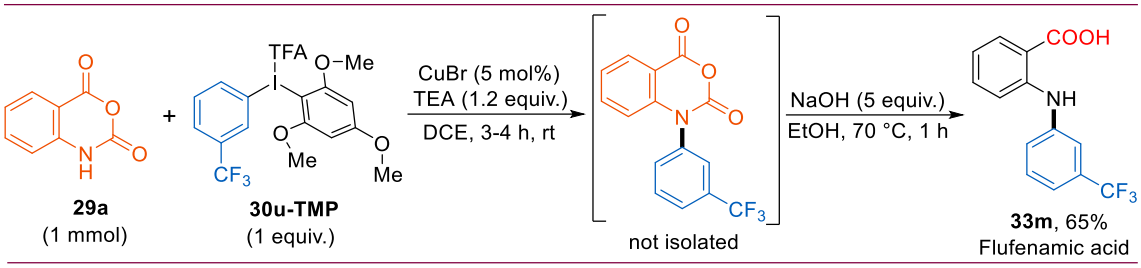
Table 5.6 Examples of fenamic acid derivatives[a,b]



[a]Reaction conditions: step 1: **29** (0.3 mmol), Ar(TMP)I(TFA) (0.3 mmol), CuBr (5 mol%), Et_3N (1.2 equiv.) and dry DCE (0.1 M) were added to a Schlenk tube; and step 2: removal of DCE, then NaOH (5 equiv.) in EtOH (5 mL). [b]All yields are isolated yield.

To illustrate the practical usefulness of the one-pot methodology for fenamic acid derivatives, we successfully synthesized flufenamic acid, an NSAID from isatoic

anhydride on a scale of 1 mmol and the product **33m** was formed in 65% yield (Scheme 5.6).



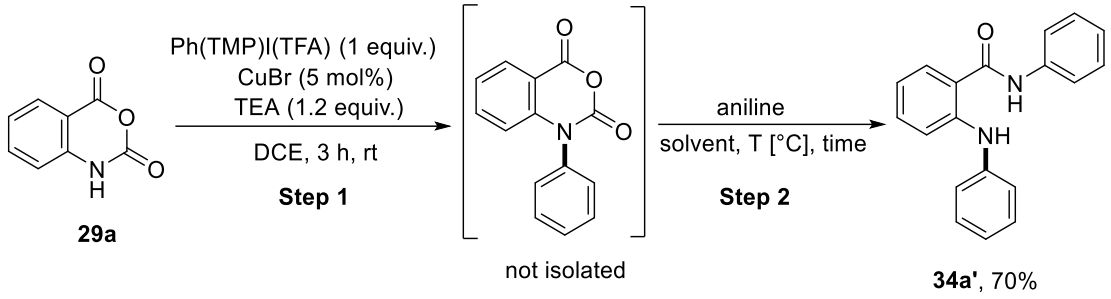
Scheme 5.6 Synthesis of flufenamic acid

5.4.2 Synthesis of *N,N'*-diarylindazol-3-ones

Furthermore, another synthetic utility of *N*-arylated isatoic anhydrides were demonstrated by establishing an alternative route to *N,N'*-diarylindazol-3-ones in a stepwise manner. Earlier, Wie and co-workers reported a pot-economical methodology from isatoic anhydride where they utilized arylboronic acids as coupling partner [34]. The sequential steps involved in their one-pot approach were decarboxylative amination followed by Chan-Lam C-N coupling with excess amount of aryl boronic acids and then dehydrogenative N-N bond formation by Zhou's method [35]. In our approach, the sequence is slightly different; the direct *N*-arylation of isatoic anhydride with our optimized protocol followed decarboxylative amination and then Zhou's method. This approach has some advantages in comparison to Wie's method as no excess amounts of arylating source is used and it requires a lesser extent of overall reaction duration.

Prior to application of Zhou's method in a one-pot process, the reaction conditions to obtain *N*-phenyl-2-(phenylamino)benzamide by *in-situ* preparation of *N*-phenylated isatoic anhydride was optimized (Table 5.7). The optimized condition to achieve **34a'** required slightly elevated temperature (70 ℃) (entries 1-6) and ethyl acetate was found to be a better choice of solvent (entries 7-9). The N-N bond formation step by Zhou's method from the precursor *N*-aryl-2-(arylamino)benzamide moiety could be performed in two ways: either by isolating *N*-aryl-2-(arylamino)benzamide product or in a one-pot system by applying the three-step sequentially (*N*-arylation/decarboxylation/N-N bond formation).

Table 5.7 Reaction condition for *N*-phenyl-2-(phenylamino)benzamide[a]

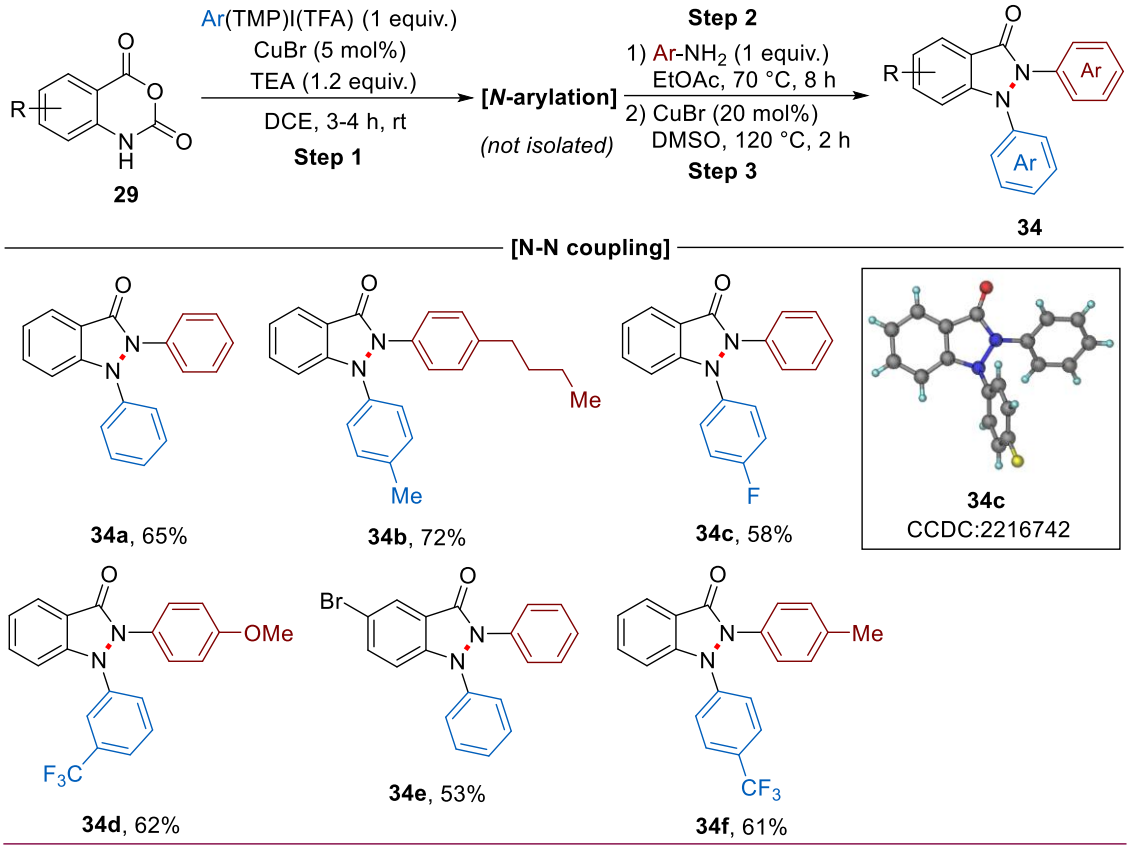


entry	aniline (x equiv.)	solvent	T (°C)	*t* (h)	yield[b]
1	1	EtOAc	rt	24	trace
2	1	EtOAc	70	12	70
3	1.5	EtOAc	70	12	71
4	1	EtOAc	100	12	62
5	1	EtOAc	70	6	68
6	**1**	**EtOAc**	**70**	**8**	**70**
7	1	ACN	70	8	65
8	1	Toluene	80	8	58
9	1	DCE	70	8	61

[a]Reaction conditions: : step 1: **29a** (0.1 mmol), diaryliodonium salt **30a-TMP** (0.1 mmol), Et_3N (1.2 equiv.), copper salt (5 mol%) and DCE (0.1 M) were added to a Schlenk tube, and step 2: removal of DCE, aniline (x equiv.) in solvent (3 mL). [b]Isolated yields.

Later, the substrate scope of isatoic anhydrides, aryl amines; and aryl(TMP)iodonium salts were established with the optimized one-pot process (Table 5.8). Iodonium salts containing aryl groups with electron-rich (**34b**) and electron-withdrawing (**34c**, **34d** and **34f**) worked smoothly with reaction conditions and afforded the arylated indazol-3-one derivatives in moderate yields. The demonstrated examples were a combination of electron-rich aryl amines and iodonium salts possessing both electron-rich and electron-deficient aryl groups. The previously challenged electron-deficient aryl moieties could be easily applied with this protocol (examples **34c**, **34d** and **34f**). The product **34c** is further clarified by single crystal X-ray structural elucidation. Isatoic anhydride with sensitive functional group like 6-Br, which is prone to react with copper-catalyzed conditions also tolerated the reaction conditions and provided the product **34e** in 53% yield.

Table 5.8 Examples of *N,N'*-diarylindazol-3-ones[a,b]

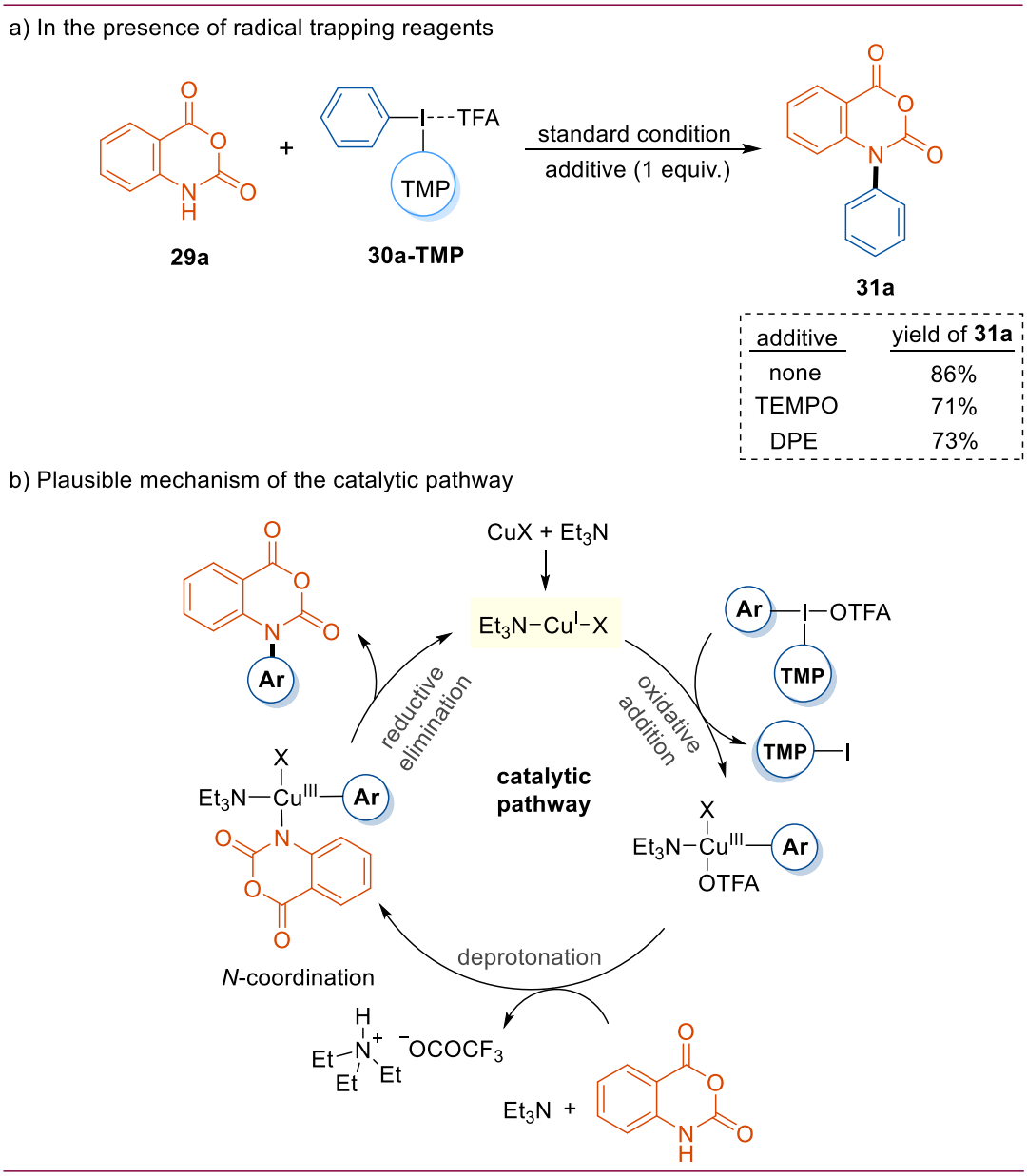


[a]Reaction conditions: step 1: **29** (0.3 mmol), Ar(TMP)I(TFA) salt (0.3 mmol), CuBr (5 mol%), Et_3N (1.2 equiv.) and dry DCE (0.1 M) were added to a Schlenk tube; step 2: removal of DCE, then Ar-NH_2 (1 equiv.) in EtOAc (5 mL) and step 3: removal of EtOAc, CuBr (20 mol%) in 2 mL DMSO. [b]Isolated yields.

5.5 Mechanism of the reaction

In general, the mechanism for Cu-catalyzed *N*-arylation reactions with either symmetrical or unsymmetrical iodonium salts proceeds *via* ionic pathway [33-34]. In our case, the controlled experiments for a possible radical pathway were performed with radical tapping reagents such as TEMPO and DPE (Scheme 5.7). In both the cases, the optimal formation of **31a** was observed and thus the possibility of the mechanism *via* radical pathway was not expected. Though, several reports already established the mechanism for Cu-catalyzed arylation with mesityl-auxiliary based iodonium salts; but possible steps involved are almost similar for aryl(TMP)iodonium salts too. The most important step is the formation of Cu(III)-aryl species from Cu(I) precursor *via* selective elimination of 2-iodo-1,3,5-trimethoxybenzene (TMP-I). Apart from its basic nature during deprotonation of the N–H proton of isatoic anhydride, triethyl amine (TEA) perhaps helps in the formation of Et_3N-Cu^I-X catalytic species. After the N-coordination of nitrogen nucleus with

Cu(III) aryl species, the reductive elimination facilitates the formation of final product **31a**.



additive	yield of **31a**
none	86%
TEMPO	71%
DPE	73%

Scheme 5.7 a) Controlled experiments, and b) plausible mechanism

5.6 Summary of the chapter

In conclusion, this chapter introduces the utilization of aryl(TMP)iodonium salts as a robust arylating partner for the *N*-arylation of isatoic anhydrides under mild and operationally simple Cu-catalyzed method. The developed strategy is highly flexible towards the wide scope of both isatoic anhydrides and aryl(TMP)iodonium salts. Due to the synthetic advantages of unsymmetrical iodonium salt with TMP-auxiliary, the

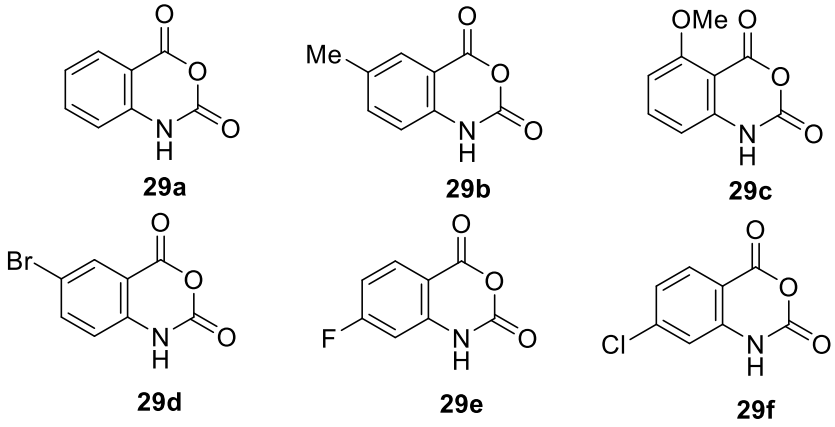
method allows diverse choices of aryl groups possessing electron-rich and electron-donating functional groups and affords broad examples of *N*-arylated isatoic anhydrides. The protocol is equally applicable for wide variation of substituted isatoic anhydrides too. The synthetic utility of *N*-arylated isatoic anhydrides is further explored to access fenamic acid derivatives and *N,N'*-diarylindazol-3-ones *via* an alternative two-step approach. Devising the one-pot system and employing *N*-arylation of isatoic anhydrides as an intermediate step, substantial examples of both fenamic acid derivatives and *N*-arylated indazol-3-ones are demonstrated, including the synthesis of an NSAID i.e., flufenamic acid.

5.7 Experimental section

All reactions were performed in oven-dried Schlenk-tubes or round bottom flasks under ambient conditions, unless otherwise stated. Dichloromethane (DCM), 1,2-dichloroethane (DCE) and acetonitrile (ACN) were dried by refluxing over CaH_2 under nitrogen condition and stored over 4Å molecular sieves. Toluene and 1,4-dioxane were dried utilising conventional drying procedures using sodium/benzophenone as indicator and stored over 4Å molecular sieves. All chemicals were purchased from commercial suppliers and used as received unless otherwise stated. Utilized bases such as NaOH, Cs_2CO_3, K_3PO_4 and KO^{t}Bu were stored in a desiccator. *meta*-Chloroperbenzoic acid (*m*-CPBA) (Aldrich, >77% active oxidant) was dried at room temperature over high vacuum for 1 hour and titrated by iodometric titration prior to use in the synthesis of diaryliodonium salts. Thin Layer Chromatography (TLC) analyses were performed on pre-coated Merck silica gel $60F_{254}$ plates using UV (λ= 254 nm) light and/or with $KMnO_4$-stain. **Column chromatography performed in this work was very crucial, 230-400 mesh silica gel (Merck and SRL) using the gradient system, freshly distilled DCM, and ethyl acetate mixture as eluent.** All NMR data were recorded in a 400 MHz instrument at 298 K using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts are given in ppm relative to the residual solvent peak (^{1}H NMR: $CDCl_3$ δ 7.26 and sometimes δ 1.56 ($CDCl_3$-water) and in DMSO-d_6 δ 2.50 and δ 3.3 (DMSO-water); ^{13}C NMR: $CDCl_3$ δ 77.16, DMSO-d_6 δ 39.52) with multiplicity (bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sep = septet, m = multiplet, app = apparent), coupling constants (*J*) (in Hz) and integration. The raw NMR data were

processed by MestReNova software. Single crystal X-ray diffraction data were recorded using a Bruker APEX-II CCD Diffractometer using MoKα radiation (λ= 0.71073 Å).

5.7.1 Isatoic anhydrides in this study



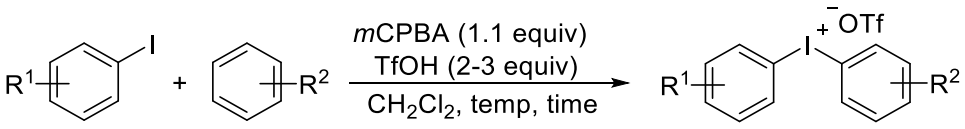
The isatoic anhydrides (**29a**-**29f**) utilized in this work are commercially available and purchased from suppliers.

5.7.2 Synthesis of diaryliodonium salts

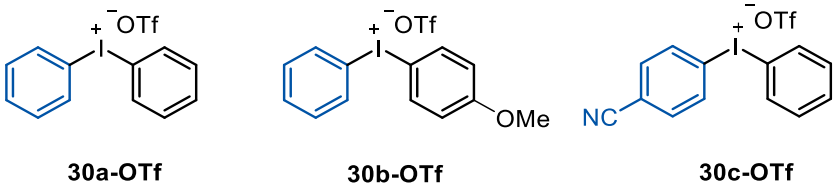
The diaryliodonium salts synthesized in this work (Table 5.9) are previously well-explored and the analytical data (especially ^{1}H NMR spectroscopy) those diaryliodonium salts were matched with literature.

Table 5.9 Synthesized diaryliodonium salts in this work

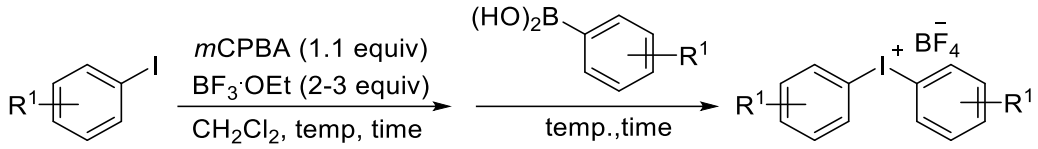
Method I [73, chapter 1]



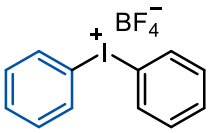
Synthesized diaryliodonium salts:



Method II [72, chapter 1]

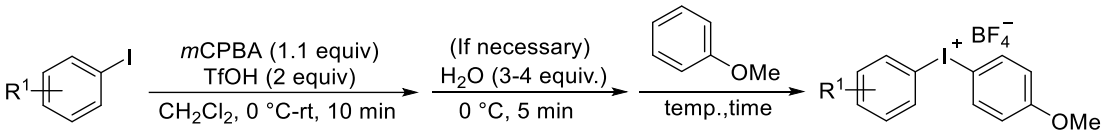


Synthesized diaryliodonium salts:

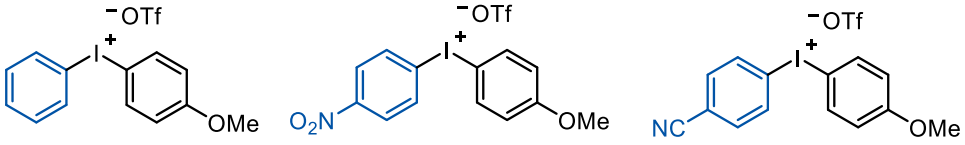


30a-BF$_4$

Method III [45, chapter 1]

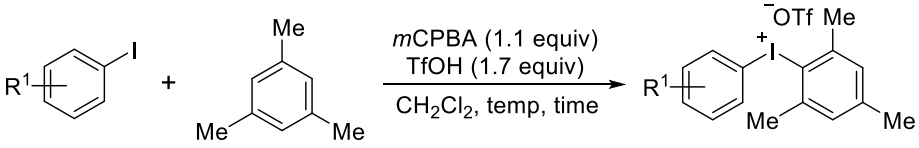


Synthesized diaryliodonium salts:



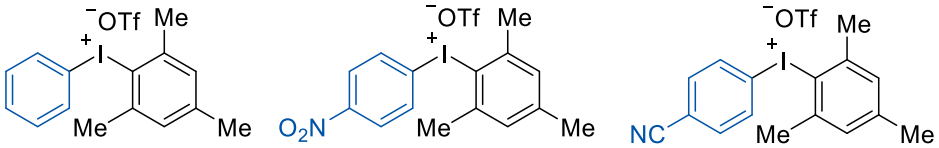
30a-An **30b-An** **30c-An**

Method IV [65, chapter 1]



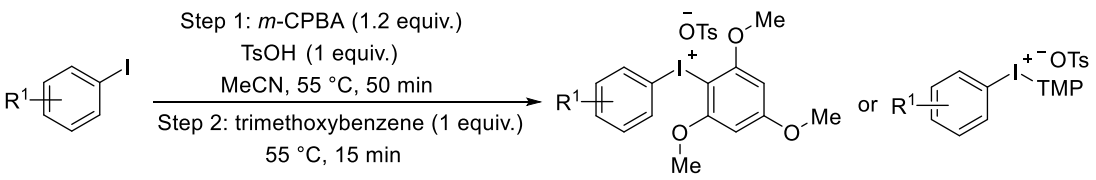
R^1= EDG or EWG

Synthesized diaryliodonium salts:

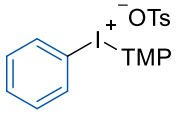


30a-Mes **30b-Mes** **30c-Mes**

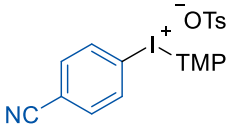
Method V [77, chapter 1]



Synthesized diaryliodonium salts:

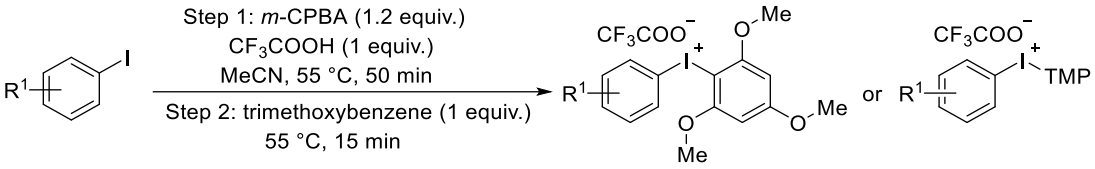


30a-TMP-OTs

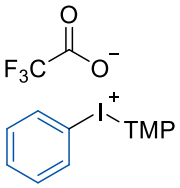


30b-TMP-OTs

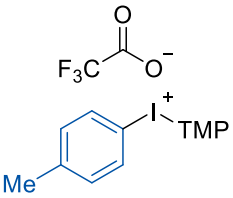
Method VI [79, chapter 1]



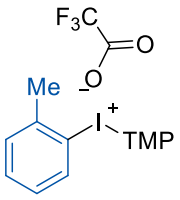
Synthesized diaryliodonium salts:



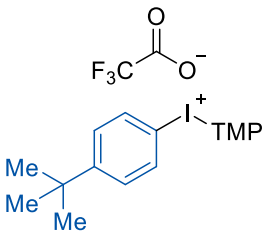
30a-TMP



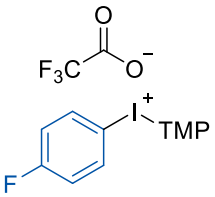
30b-TMP



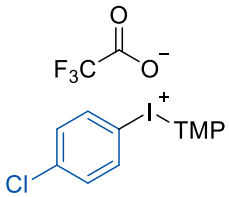
30c-TMP



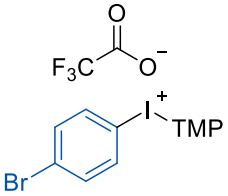
30d-TMP



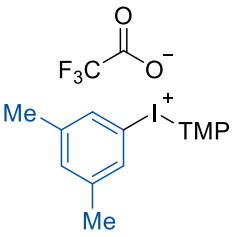
30e-TMP



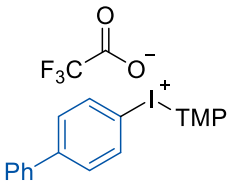
30f-TMP



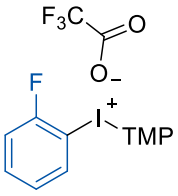
30g-TMP



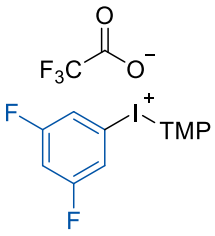
30h-TMP



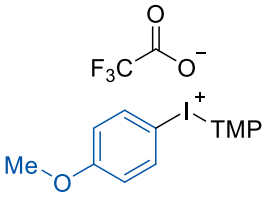
30i-TMP



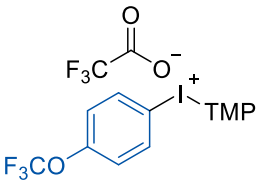
30j-TMP



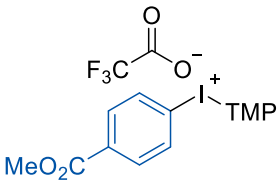
30k-TMP



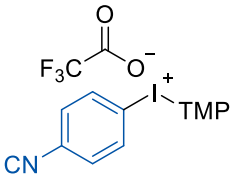
30l-TMP



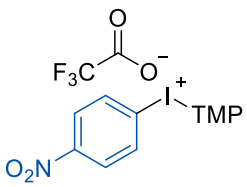
30m-TMP



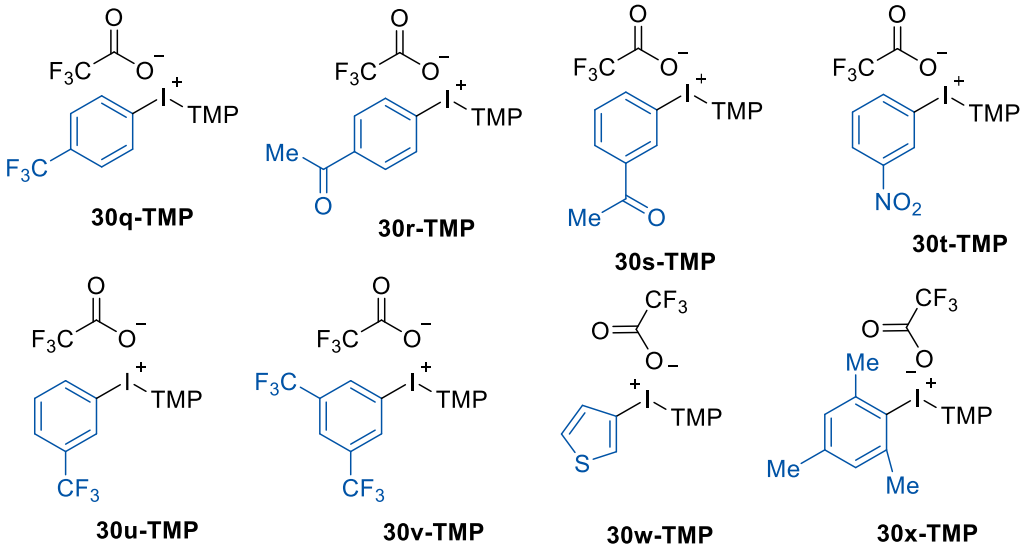
30n-TMP



30o-TMP

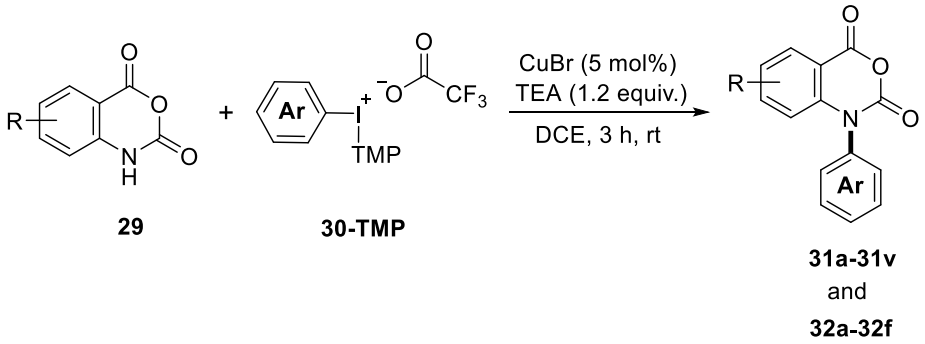


30p-TMP



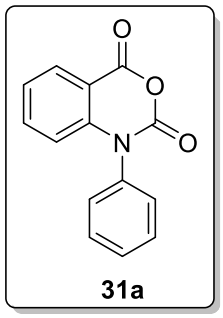
5.8 Synthesis and characterization of *N*-arylated isatoic anhydrides

5.8.1 General procedure A (GP-A): *N*-Arylation of isatoic anhydrides



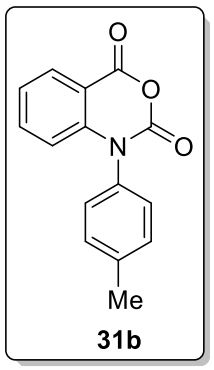
To an oven-dried Schlenck-tube, isatoic anhydrides **29** (0.3 mmol), diaryliodonium salt **30-TMP** (0.3 mmol, 1 equiv.), CuBr (0.015 mmol, 0.05 equiv.) and Et_3N (0.36 mmol, 1.2 equiv.) were added. After adding toluene (3 mL, 0.1 M), the tube was sealed and allowed to stir at room temperature. The reaction mixture was stirred for 3-5 h (completion was checked by TLC). The reaction mixture was then passed through Celite and washed with minimal EtOAc (15-20 mL). The organic mixture was then work-up with water followed by brine wash. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then, the crude product was purified using flash column-chromatography (using 230-400 mesh silica with eluent 30:1 DCM/ethyl acetate) to obtain the desired *N*-arylated product (**31a-31v** and **32a-32f**).

1-phenyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31a)** [27–29]



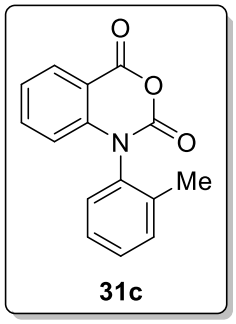
In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30a-TMP** (145.26 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31a** as white solid (61.7 mg, 0.258 mmol, 86%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 8 Hz, 2H), 7.56-7.64 (m, 4H), 7.38-7.40 (m, 2H), 7.31 (t, J = 8 Hz, 1H), 6.58 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 147.2, 143.1, 136.8, 135.4, 130.6, 130.4, 129.9, 128.5, 124.3, 115.6, 111.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{10}NO_3$ 240.0660; found 240.0645.

1-(p-tolyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31b)** [29]



In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30b-TMP** (149.4 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31b** as white solid (69.8 mg, 0.276 mmol, 92%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 8 Hz, 1H), 7.57 (t, J = 8 Hz, 1H), 7.41(d, J = 8 Hz, 2H), 7.24-7.31 (m, 3H), 6.61 (d, J = 8 Hz, 1H), 2.48 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.6, 147.4, 143.2, 140.1, 136.8, 132.7, 131.2, 130.3, 128.2, 124.2, 115.7, 111.1, 21.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{12}NO_3$ 254.0817; found 254.0798.

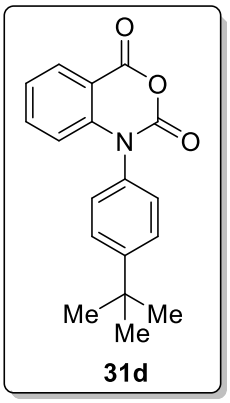
1-(o-tolyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31c)**



In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30c-TMP** (149.4 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31c** as white solid (51.6 mg, 0.204 mmol, 68%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 8 Hz, 1H), 7.59 (t, J = 8 Hz, 1H), 7.42-7.50 (m, 3H), 7.32 (t, J = 8 Hz, 1H), 7.28 (s, 1H), 6.47 (d, J = 8 Hz, 1H), 2.19 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.5, 146.7, 142.5, 137.1, 136.5, 134.1, 132.1, 130.6, 130.3, 128.5,

128.2, 124.4, 115.1, 111.1, 17.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{12}NO_3$ 254.0817; found 254.0802.

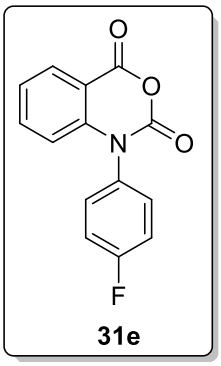
1-(4-(tert-butyl)phenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(33d)** [29]



31d

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30d-TMP** (162 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31d** as white solid (72 mg, 0.243 mmol, 81%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 8 Hz, 1H), 7.63 (d, J = 8 Hz, 2H), 7.58 (t, J = 8 Hz, 1H), 7.29 (d, J = 8 Hz, 4H), 6.61 (d, J = 8 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 153.1, 147.3, 143.3, 136.8, 132.6, 130.3, 127.8, 127.6, 124.2, 115.8, 111.1, 34.9, 31.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{18}NO_3$ 296.1286; found 296.1276.

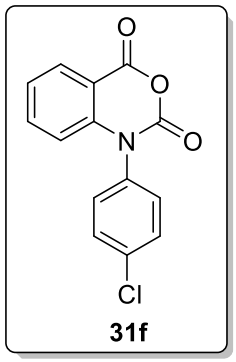
1-(4-fluorophenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31e)** [28,29]



31e

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30e-TMP** (150.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31e** as white solid (57.1 mg, 0.222 mmol, 74%). Reaction duration: 4 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8 Hz, 1H), 7.58-7.61 (m, 1H), 7.31-7.40 (m, 5H), 6.58 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0 ($J_{C\text{-}F}$ =250 Hz), 158.2, 143.0, 136.9, 131.3, 130.6, 124.4, 117.9, 117.6, 115.4, 111.2. ^{19}F NMR (376 MHz, DMSO-d_6): δ -112.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_9NO_3F$ 258.0566; found 258.0549.

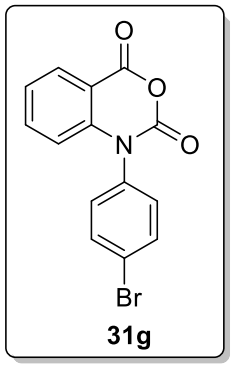
1-(4-chlorophenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31f)** [29]



31f

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30f-TMP** (156 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31f** as white solid (58.2 mg, 0.213 mmol, 71%). Reaction duration: 4 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 8 Hz, 1H), 7.60-7.62 (m, 3H), 7.31-7.35 (m, 3H), 6.59 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 147.1, 142.7, 137.0, 136.1, 133.8, 130.9, 130.6, 130.0, 124.5, 115.4, 111.20. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_9NO_3Cl$ 274.0270; found 274.0250.

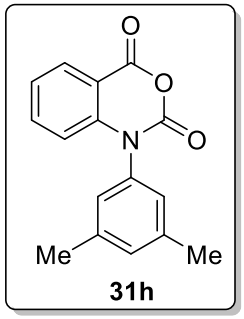
1-(4-bromophenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31g)** [29]



31g

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30g-TMP** (168.9 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31g** as white solid (66.8 mg, 0.21 mmol, 70%). Reaction duration: 4 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 2H), 7.59 (t, J = 8 Hz, 1H), 7.31 (t, J = 8 Hz, 1H), 7.26 (d, J = 8 Hz, 2H), 6.57 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 147.0, 142.7, 137.4, 134.4, 133.9, 130.6, 130.3, 124.5, 124.2, 115.4, 111.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_9NO_3Br$ 317.9765; found 317.9754.

1-(3,5-dimethylphenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31h)** [28,29]

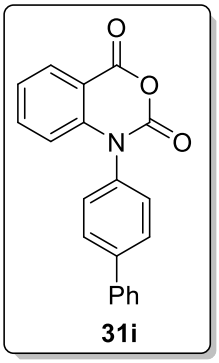


31h

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30h-TMP** (153.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31h** as white solid (65.7 mg, 0.245 mmol, 82%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 8 Hz, 1H), 7.58 (t, J = 8 Hz, 1H), 7.29 (t, J = 8 Hz, 1H), 7.20 (s, 1H), 6.98 (s, 2H), 6.61 (d, J = 8 Hz, 1H), 2.42 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 147.3, 143.2, 140.6, 136.7, 135.2, 131.6, 130.2, 125.8, 124.1, 115.8,

111.0, 21.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{14}NO_3$ 268.0973; found 268.0958.

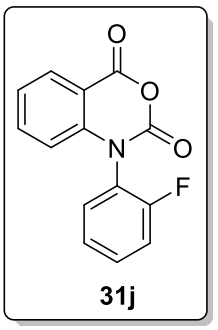
1-([1,1'-biphenyl]-4-yl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31i)**



31i

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30i-TMP** (168 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31i** as white solid (69 mg, 0.219 mmol, 73%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 8 Hz, 1H), 7.84 (d, J = 8 Hz, 2H), 7.67 (d, J = 8 Hz, 2H), 7.60-7.64 (m, 1H), 7.52 (t, J = 8 Hz, 2H), 7.44-7.47 (m, 3H), 7.33 (t, J = 8 Hz, 2H), 6.70 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 147.3, 143.1, 139.6, 136.9, 134.4, 130.5, 129.3, 129.0, 128.8, 128.1, 127.3, 124.3, 115.7, 111.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{14}NO_3$ 316.0973; found 316.0942.

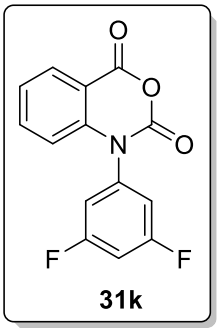
1-(2-fluorophenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31j)**



31j

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30j-TMP** (150.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31j** as white solid (49.3 mg, 0.192 mmol, 64%). Reaction duration: 5 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 8 Hz, 1H), 7.58-7.64 (m, 2H), 7.32-7.45 (m, 4H), 6.60 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 158.1, 157.1, 146.6, 142.3, 137.1, 132.1, 132.1, 130.6, 130.5, 125.8, 125.7, 124.6, 122.9, 122.8, 117.7, 117.5, 114.9, 111.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ -120.10 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_9NO_3F$ 258.0566; found 258.0562.

1-(3,5-difluorophenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31k)**

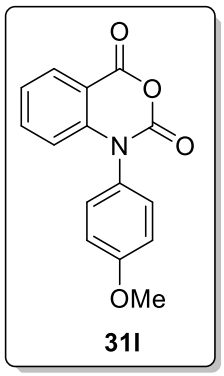


31k

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30k-TMP** (15 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31k** as white solid (56.1 mg, 0.203 mmol, 68%). Reaction duration: 5 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^{1}H NMR

(400 MHz, $CDCl_3$): δ 8.23 (d, J = 8 Hz, 1H), 7.65 (t, J = 8 Hz, 1H), 7.36 (t, J = 8 Hz, 1H), 7.06-7.11 (m, 1H), 6.98-7.00 (m, 2H), 6.63 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8 (dd, $J_{C\text{-}F}$ = 251 Hz & 14 Hz), 157.8, 146.6, 142.1, 137.1, 130.8, 124.8, 115.1, 112.9, 112.8, 112.7, 112.6, 111.1, 106.4, 106.2, 105.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -105.5 ppm. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_8NO_3F_2$ 276.0472; found 276.0458.

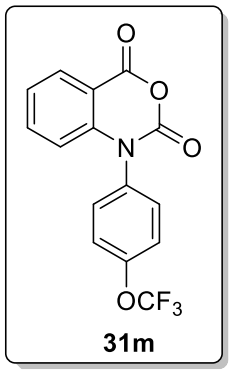
1-(4-methoxyphenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31l)** [28,29]



31l

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30l-TMP** (154.2 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31l** as white solid (65.4 mg, 0.243 mmol, 81%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8 Hz, 1H), 7.58 (t, J = 8 Hz, 1H), 7.28-7.30 (m, 3H), 7.12 (d, J = 8 Hz, 2H), 6.63 (d, J = 8 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 158.5, 147.5, 143.4, 136.8, 130.3, 129.6, 127.8, 124.2, 115.7, 111.2, 55.6. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{12}NO_4$ 270.0766; found 270.0743.

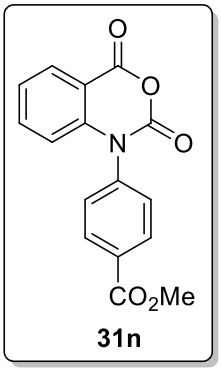
1-(4-(trifluoromethoxy)phenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31m)**



31m

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30m-TMP** (170.4 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31m** as white solid (69.8 mg, 0.216 mmol, 72%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 8 Hz, 1H), 7.62 (t, J = 8 Hz, 1H), 7.44-7.50 (m, 4H), 7.34 (t, J = 8 Hz, 1H), 6.58 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 149.9, 147.1, 142.7, 137.0, 133.6, 130.6, 130.4, 124.6, 122.8, 115.3, 111.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ -57.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_9NO_4F_3$ 324.04083; found 324.0463.

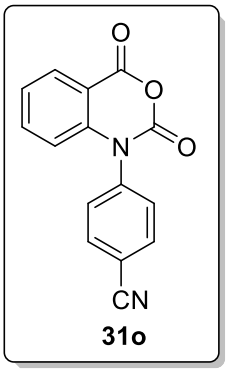
***methyl 4-(2,4-dioxo-2H-benzo[d][1,3]oxazin-1(4H)-yl)benzoate* (31n)**



31n

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30n-TMP** (162.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31n** as white solid (58.8 mg, 0.198 mmol, 66%). Reaction duration: 5 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 8 Hz, 2H), 8.20 (d, J = 8 Hz, 1H) 7.57 (t, J = 8 Hz, 1H), 7.48 (d, J = 8 Hz, 2H), 7.31 (t, J = 8 Hz, 1H), 6.53 (d, J = 8 Hz, 1H), 3.98 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.8, 158.1, 146.9, 142.5, 139.3, 137.0, 131.9, 130.6, 128.8, 124.6, 115.3, 111.2, 52.5. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{12}NO_5$ 297.0637; found 297.0629.

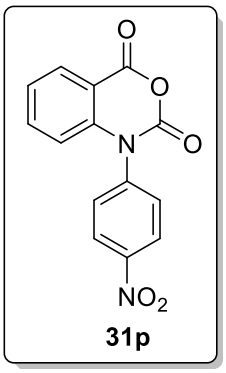
***4-(2,4-dioxo-2H-benzo[d][1,3]oxazin-1(4H)-yl)benzonitrile* (31o)**



31o

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30o-TMP** (152.8 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31o** as white solid (51.5 mg, 0.195 mmol, 65%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 8 Hz, 1H), 7.96 (d, J = 8 Hz, 2H), 7.61 (t, J = 8 Hz, 1H), 7.56 (d, J = 8 Hz, 2H), 7.37 (t, J = 8 Hz, 1H) 6.53 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 146.7, 142.1, 139.3, 137.1, 134.5, 130.9, 130.0, 124.9, 117.4, 115.0, 114.3, 111.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_9N_2O_3$ 265.0613; found 265.0605.

***1-(4-nitrophenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione* (31p)**

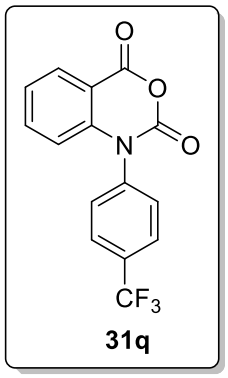


31p

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30p-TMP** (158.7 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31p** as white solid (52 mg, 0.183 mmol, 61%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, J = 8 Hz, 2H), 8.26 (d, J = 8 Hz, 1H) 7.62-7.65 (m, 3H), 7.38 (t, J = 8 Hz, 1H), 6.55 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 157.7, 148.4, 146.7, 142.0, 140.8, 137.1, 130.9, 130.2, 125.9, 125.0, 115.0, 111.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_9N_2O_5$ 285.0511; found 285.0494.

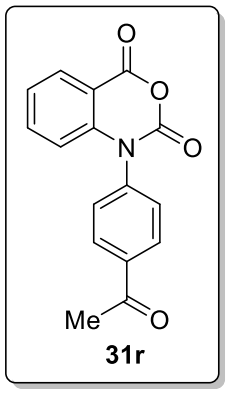
1-(4-(trifluoromethyl)phenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31q)**



31q

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30q-TMP** (165.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31q** as white solid (64 mg, 0.210 mmol, 70%). Reaction duration: 5 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8 Hz, 1H), 7.92 (d, *J* = 8 Hz, 2H), 7.60 (t, *J* = 8 Hz, 1H), 7.56 (d, *J* = 8 Hz, 2H), 7.35 (t, *J* = 8 Hz, 1H), 6.55 (d, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 146.9, 142.4, 138.5, 137.0, 132.7, 132.4, 132.1, 131.7, 130.7, 129.4, 127.8, 124.7, 122.0, 115.2, 111.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.88. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_9NO_3F_3$ 308.0534; found 308.0522.

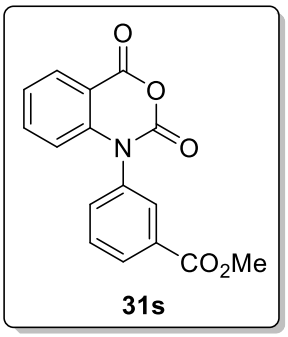
1-(4-acetylphenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31r)**



31r

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30r-TMP** (157.8 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31r** as white solid (57.3 mg, 0.204 mmol, 68%). Reaction duration: 4 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8 Hz, 3H), 7.59 (d, *J* = 8 Hz, 1H), 7.51 (d, *J* = 8 Hz, 2H), 7.33 (t, *J* = 8 Hz, 1H), 6.56 (d, *J* = 8 Hz, 1H), 2.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 158.1, 146.9, 142.5, 139.3, 138.2, 137.0, 130.6, 130.5, 129.1, 124.6, 115.3, 111.2, 26.7. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{12}NO_4$ 282.0766; found 282.0764.

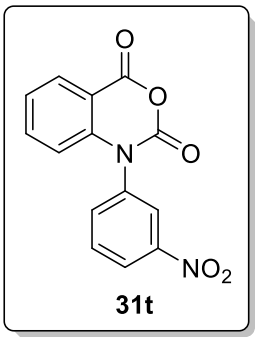
methyl 3-(2,4-dioxo-2H-benzo[d][1,3]oxazin-1(4H)-yl)benzoate **(31s)**



31s

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30s-TMP** (162.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31s** as white solid (58.8 mg, 0.198 mmol, 72%). Reaction duration: 5 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 8 Hz, 1H), 8.23 (d, J = 8 Hz, 1H), 8.08 (s, 1H), 7.74 (t, J = 8 Hz, 1H), 7.57-7.61 (m, 2H), 7.33 (t, J = 8 Hz, 1H), 6.54 (d, J = 8 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 158.1, 147.1, 142.7, 137.0, 135.6, 133.1, 132.9, 131.0, 130.8, 130.6, 129.9, 124.5, 115.4, 111.2, 52.5. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{12}NO_5$ 298.0715; found 298.0694.

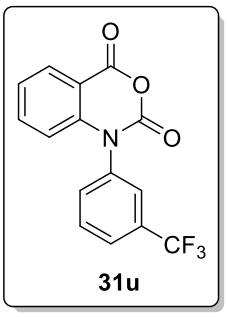
1-(3-nitrophenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31t)**



31t

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30t-TMP** (158.7 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31t** as yellow solid (52 mg, 0.183 mmol, 70%). Reaction duration: 5 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, J = 8 Hz, 1H), 8.32-8.33 (s, 1H) 8.25-8.28 (m, 1H), 7.88 (t, J = 8 Hz, 1H), 7.77-7.80 (m, 1H), 7.64 (t, J = 8 Hz, 1H), 7.38 (t, J = 8 Hz, 1H), 6.55 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 149.5, 146.9, 142.1, 137.2, 136.4, 135.1, 131.6, 131.0, 125.0, 124.5, 115.0, 111.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_9N_2O_5$ 285.0511; found 285.0502.

1-(3-(trifluoromethyl)phenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(31u)**

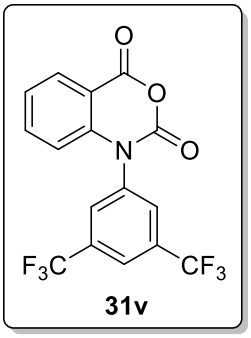


31u

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30u-TMP** (165.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31u** as white solid (64 mg, 0.210 mmol, 74%). Reaction duration: 5 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^1H NMR

(400 MHz, $CDCl_3$): δ 8.23 (d, J = 8 Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 7.80 (t, J = 8 Hz, 1H), 7.69 (s, 1H), 7.60-7.64 (m, 2H), 7.35 (t, J = 8 Hz, 1H), 6.53 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 147.0, 142.5, 137.1, 136.0, 133.1, 132.8, 132.4, 131.4, 130.7, 126.9, 125.9, 124.7, 121.8, 115.2, 111.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.5. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_9NO_3F_3$ 308.0534; found 308.0508.

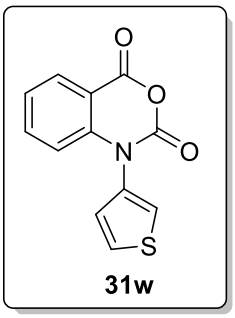
***1-(3,5-bis(trifluoromethyl)phenyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione* (31v)**



31v

In accordance with **GP-A**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30v-TMP** (186 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **31v** as white solid (75 mg, 0.199 mmol, 67%). Reaction duration: 5 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8 Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 7.80 (t, J = 8 Hz, 1H), 7.69 (s, 2H), 7.67 (t, J = 8 Hz, 1H), 7.40 (t, J = 8 Hz, 1H), 6.50 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 146.8, 141.9, 137.4, 136.9, 134.5, 131.1, 129.7, 125.1, 124.1, 114.7, 111.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_8NO_3F_6$ 376.0408; found 376.0392.

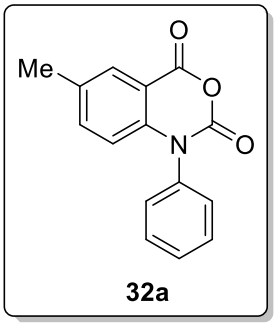
1-(thiophen-3-yl)-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (3w)



31w

In accordance with GP-A, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30w-TMP** (148 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (50 µL, 0.36 mmol) were used, and the following conditions gave the title compound **31w** as white solid (40 mg, 0.63 mmol, 53%). Reaction duration: 5 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate) gave. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8 Hz, 1H), 7.57-7.62 (m, 2H), 7.37-7.38 (m, 1H), 7.30 (t, J = 8 Hz, 1H), 7.08-7.09 (m, 1H), 6.71 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 146.9, 143.0, 137.1, 132.6, 130.3, 127.6, 125.9, 124.5, 124.4, 115.5, 111.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_8NO_3S$ 246.0224; found 246.0216.

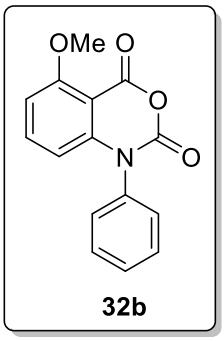
6-methyl-1-phenyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(32a)** [29]



32a

In accordance with **GP-A**, 6-methyl-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione **29b** (53.2 mg, 0.3 mmol), **30a-TMP** (145.26 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **32a** as white solid (62.2 mg, 0.246 mmol, 82%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.56-7.65 (m, 3H), 7.36-7.38 (m, 3H), 6.47 (d, J = 8 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 147.3, 141.03, 137.8, 135.5, 134.4, 130.5, 130.0, 129.8, 128.5, 115.6, 110.9, 20.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{12}NO_3$ 254.0817; found 254.0810.

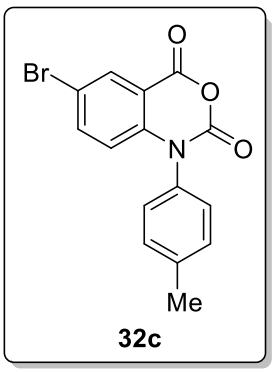
5-metheoxy-1-phenyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(32b)**



32b

In accordance with **GP-A**, 5-methoxy-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione **29b** (57.9 mg, 0.3 mmol), **30a-TMP** (145.26 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **32b** as white solid (63.8 mg, 0.237 mmol, 79%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.65 (m, 4H), 7.37-7.39 (m, 2H), 7.13-7.16 (m, 1H), 6.51 (d, J = 8 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6,156.2, 147.1, 137.2, 135.6, 130.6, 129.9, 128.5, 125.7, 117.2, 110.9, 56.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{12}NO_5$ 270.0766; found 270.0768.

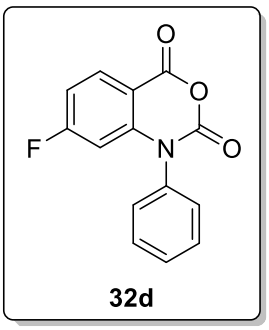
6-bromo-1-(p-tolyl)-2H-benzo[d][1,3]oxazine-2,4(1H)-dione **(32c)** [29]



32c

In accordance with **GP-A**, 6-bromo-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione **29d** (72.6 mg, 0.3 mmol), **30b-TMP** (149.4 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **32c** as white solid (72.7 mg, 0.219 mmol, 73%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.62 (dd, J = 8 & 3 Hz, 1H), 7.41 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 1H), 6.49 (d, J = 8 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 146.8, 142.2, 140.5, 139.6, 132.5, 131.4, 128.0, 117.6, 117.0, 112.6, 21.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{11}NO_3Br$ 331.9922; found 331.9917.

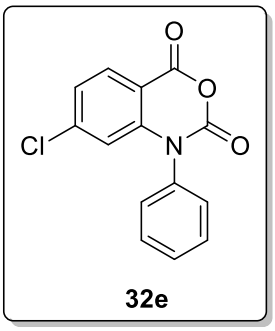
***7-fluoro-1-phenyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione* (32d)** [29]



32d

In accordance with **GP-A**, 7-fluoro-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione **29e** (54.3 mg, 0.3 mmol), **30a-TMP** (145.26 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **32d** as white solid (55.5 mg, 0.216 mmol, 72%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, J = 8 & 3 Hz, 1H), 7.61-7.67 (m, 3H), 7.37-7.38 (m, 2H), 7.01 (t, J = 8 Hz, 1H), 6.26 (dd, J = 8 & 4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8 (d, $J_{C\text{-}F}$ = 258 Hz), 157.4, 147.0, 145.4, 145.3, 135.0, 133.5, 133.4, 130.8, 112.4 (d, $J_{C\text{-}F}$ = 23 Hz), 107.6, 103.1 (d, $J_{C\text{-}F}$ = 23 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -113.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_9NO_3F$ 258.0566; found 258.0552.

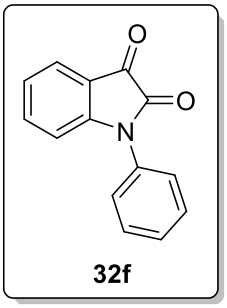
***7-chloro-1-phenyl-2H-benzo[d][1,3]oxazine-2,4(1H)-dione* (32e)** [29]



32e

In accordance with **GP-A**, 7-chloro-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione **29f** (59.2 mg, 0.3 mmol), **30a-TMP** (145.26 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **32e** as white solid (55 mg, 0.201 mmol, 67%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8 Hz, 1H), 7.62-7.68 (m, 3H), 7.36-7.38 (m, 2H), 7.26-7.28 (m, 1H), 6.56 (d, J = 4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 146.9, 144.0, 134.9, 131.8, 130.8, 130.3, 128.4, 124.9, 115.7, 109.5. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_9NO_3Cl$ 274.0270; found 274.0266.

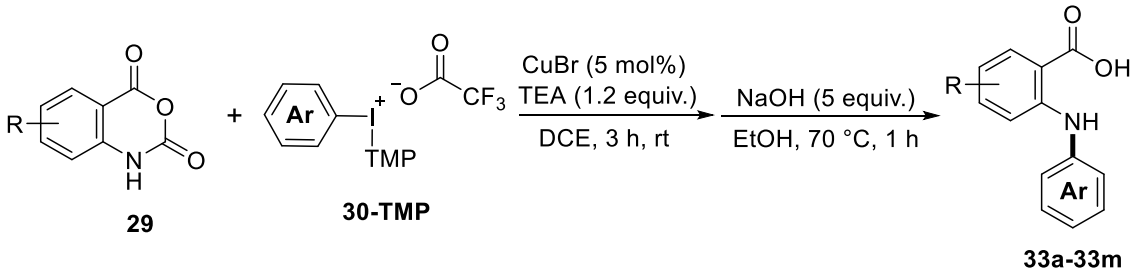
***1-phenylindoline-2,3-dione* (32f)** [28]



32f

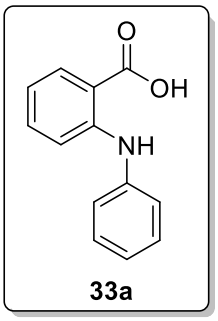
In accordance with **GP-A**, isatin (44.1 mg, 0.3 mmol), **30a-TMP** (145.26 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol) and Et_3N (46 µL, 0.33 mmol) were used, and the following conditions gave the title compound **32a** as dark orange solid (58.9 mg, 0.264 mmol, 88%). Reaction duration: 3 h. Purification method: flash column chromatography (30:1 DCM/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8 Hz, 1H), 7.54-7.60 (m, 3H), 7.43-7.49 (m, 3H), 7.19 (t, J = 8 Hz, 1H), 6.92 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.8, 157.3, 151.7, 138.3, 132.9, 129.9, 128.8, 126.0, 125.6, 124.3, 117.5, 111.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{10}NO_2$ 224.0711; found 224.07010.

5.8.2 General procedure B (GP-B): One-pot system for fenamic acid derivatives



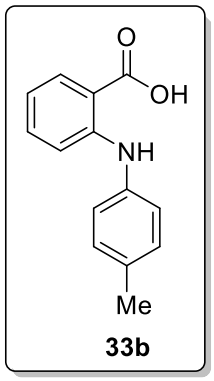
To an oven-dried Schlenck-tube, isatoic anhydride **29** (0.3 mmol), diaryliodonium salt **30-TMP** (0.3 mmol, 1 equiv.), CuBr (0.015 mmol, 0.05 equiv.) and Et_3N (0.36 mmol, 1.2 equiv.) were added. After adding toluene (3 mL, 0.1 M), the tube was sealed and allowed to stir at room temperature. The reaction mixture was stirred for 3-5 h (completion was checked TLC). The reaction mixture was concentrated under reduced pressure and NaOH (1.5 mmol, 5 equiv.) was added to the reaction vessel. After addition of EtOH (5 mL), the reaction vessel was placed on a pre-heated oil-bath at 70 °C. The reaction was stirred for 1 h duration. The ethanol was evaporated under reduced pressure and the crude was then acidified with 2N HCl solution and worked-up with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then, the crude product was purified using conventional column-chromatography (using 60-120 mesh silica with the eluent 20% hexane/ethyl acetate) to obtain the desired product (**32a**-**32m**).

2-(phenylamino)benzoic acid **(33a)** [38–40]



In accordance with **GP-B**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30a-TMP** (145.26 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33a** as white solid (61.7 mg, 0.258 mmol, 76%). Reaction duration: 4 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.00 (bd s, 1H), 9.63 (bs, 1H), 7.91 (d, J = 8 Hz, 1H), 7.34-7.41 (m, 3H), 7.22-7.24 (m, 3H), 7.07 (t, J = 8 Hz, 1H), 6.78 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 152.2, 145.7, 139.3, 137.1, 134.7, 128.3, 126.6, 122.6, 118.9, 117.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{12}NO_2$ 214.0868; found 214.0871.

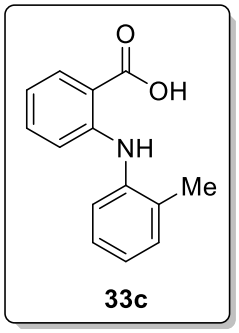
2-(p-tolylamino)benzoic acid **(33b)** [39]



33b

In accordance with **GP-B**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30b-TMP** (149.4 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33b** as light brown solid (55.2 mg, 0.243 mmol, 81%). Reaction duration: 4 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.23 (bs, 1H), 8.03 (d, J = 8 Hz, 1H), 7.32 (t, J = 8 Hz, 1H), 7.13-7.19 (m, 5H), 6.72 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 149.5, 137.5, 135.1, 134.0, 132.5, 131.2, 130.0, 123.8, 116.6, 113.8, 109.8, 20.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{14}NO_2$ 228.1024; found 228.1023.

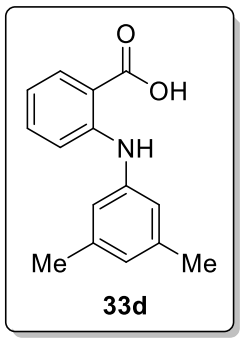
2-(p-tolylamino)benzoic acid **(33c)**



33c

In accordance with **GP-B**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30c-TMP** (149.4 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33c** as yellowish solid (36.8 mg, 0.162 mmol, 54%). Reaction duration: 5 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (bs, 1H), 8.08 (d, J = 8 Hz, 1H), 7.31-7.37 (m, 3H), 7.24 (t, J = 8 Hz,1H), 7.16 (t, J = 8 Hz,1H), 6.88 (d, J = 8 Hz,1H), 6.75 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 149.7, 138.6, 135.2, 133.5, 132.5, 131.1, 126.7, 125.2, 124.9, 116.5, 113.7, 109.7, 18.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{14}NO_2$ 228.1024; found 228.1018.

2-((3,5-dimethylphenyl)amino)benzoic acid **(33d)**

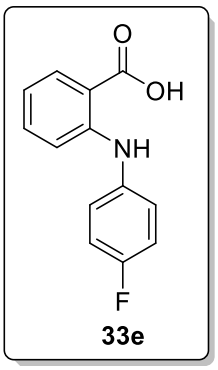


33d

In accordance with **GP-B**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30h-TMP** (153.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33d** as white solid (42.7 mg, 0.177 mmol, 59%). Reaction duration: 5 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.00 (bs, 1H), 9.58 (bs, 1H), 7.90 (d, J = 8 Hz, 1H), 7.38 (t, J = 8 Hz, 1H), 7.23 (d, J = 8 Hz, 1H),

6.85 (s, 2H), 6.75 (t, *J* = 8 Hz, 1H), 6.70 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 147.7, 140.8, 139.0, 134.5, 132.3, 125.2, 119.5, 117.5, 114.3, 112.8, 21.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}NO_2$ 242.1181; found 242.1180.

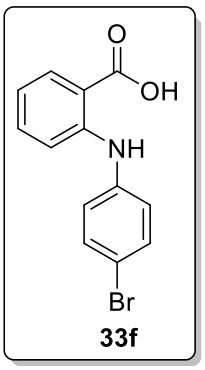
***2-((4-fluorophenyl)amino)benzoic acid* (33e)**



33e

In accordance with **GP-B**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30e-TMP** (150.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33e** as yellowish solid (43.7 mg, 0.189 mmol, 63%). Reaction duration: 5 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.23 (bs, 1H), 8.06 (d, *J* = 8 Hz, 1H), 7.36 (t, *J* = 8 Hz, 1H), 7.24-7.27 (m, 2H), 7.08 (t, *J* = 8 Hz, 2H), 7.05 (d, *J* = 8 Hz, 1H), 6.77 (t, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 159.8 ($J_{C\text{-}F}$ = 243 Hz), 149.6, 136.2, 135.3, 132.5, 125.9, 125.85, 117.0, 116.3, 116.1, 113.5, 109.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{11}NO_2F$ 232.0773; found 232.0772.

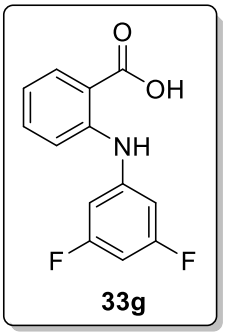
***2-((4-bromophenyl)amino)benzoic acid* (33f)** [40]



33f

In accordance with **GP-B**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30e-TMP** (150.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33f** as beige solid (57.8 mg, 0.198 mmol, 66%). Reaction duration: 5 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.26 (bs, 1H), 8.05 (d, *J* = 8 Hz, 1H), 7.46 (d, *J* = 8 Hz, 2H), 7.37 (t, *J* = 8 Hz, 1H), 7.13-7.20 (m, 3H), 6.79 (t, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 148.3, 139.5, 135.3, 132.7, 132.4, 124.4, 117.7, 116.5, 114.0, 110.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{11}NO_2Br$ 291.9973; found 223.09954.

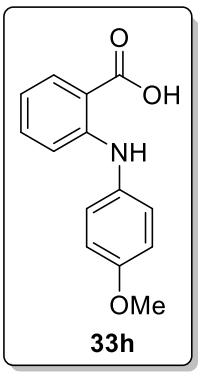
***2-((3,5-difluorophenyl)amino)benzoic acid* (33g)**



33g

In accordance with **GP-B**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30k-TMP** (15 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33g** as white solid (43.3 mg, 0.174 mmol, 58%). Reaction duration: 6 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.29 (bs, 1H), 9.64 (bs, 1H), 7.94 (d, J = 8 Hz, 1H), 7.49 (t, J = 8 Hz, 1H), 7.41 (d, J = 8 Hz, 1H), 6.90-6.96 (m, 3H), 6.74 (t, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.87, 163.6 (dd, $J_{C\text{-}F}$ = 189 & 13 Hz), 144.9, 144.8, 144.8, 134.5, 132.3, 120.2, 116.9, 116.0, 102.3 (d, $J_{C\text{-}F}$ = 23 Hz), 97.1 (t, $J_{C\text{-}F}$ = 21 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -109.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{10}NO_2F_2$ 250.0679; found 250.0677.

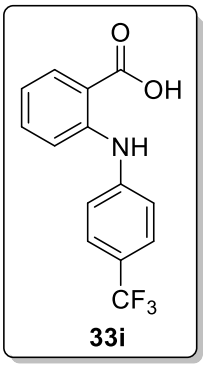
***2-((4-methoxyphenyl)amino)benzoic acid* (33h)** [39,40]



33h

In accordance with **GP-B**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30l-TMP** (154.2 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33h** as beige solid (54 mg, 0.222 mmol, 74%). Reaction duration: 5 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (bs, 1H), 8.05 (d, J = 8 Hz, 1H), 7.33 (t, J = 8 Hz, 1H), 7.21-7.24 (m, 2H), 6.95-6.97 (m, 3H), 6.70-6.74 (m, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 157.0, 150.5, 135.2, 126.4, 116.3, 114.7, 113.5, 109.4, 55.5 HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{14}NO_3$ 244.0973; found 244.0963.

***2-((4-(trifluoromethyl)phenyl)amino)benzoic acid* (33i)**

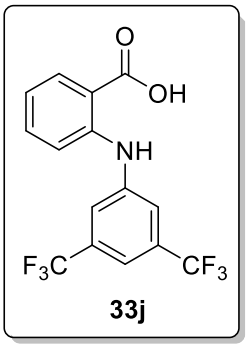


33i

In accordance with **GP-B**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30q-TMP** (165.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33i** as yellowish solid (56.7 mg, 0.201 mmol, 67%). Reaction duration: 4 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (bs, 1H), 8.09 (d, J = 8 Hz,

1H), 7.59 (d, *J* = 8 Hz, 2H), 7.32-7.44 (m, 4H), 6.88 (t, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 172.8, 146.9, 143.9, 126.7, 125.1 (J_{C-F} = 32 Hz), 120.7, 118.8, 114.9, 112.0. ^{19}F NMR (376 MHz, $CDCl_3$): *δ* -62.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{11}NO_2F_2$ 282.0741; found 282.0724.

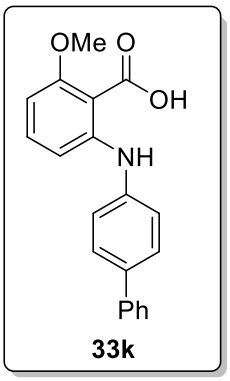
***2-((3,5-bis(trifluoromethyl)phenyl)amino)benzoic acid* (33j)**



33j

In accordance with **GP-B**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30v-TMP** (186 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33j** as yellowish solid (63.9 mg, 0.183 mmol, 61%). Reaction duration: 4 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 13.29 (bs, 1H), 9.70 (bs, 1H), 7.96 (d, *J* = 8 Hz, 1H), 7.77 (s, 2H), 7.49-7.53 (m, 2H), 7.38 (d, *J* = 8 Hz, 1H), 7.01 (t, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 169.5, 144.6, 144.0, 134.3, 132.3, 132.3, 131.8 (J_{C-F} = 32 Hz), 127.7, 125.0, 122.3, 121.1, 119.6, 117.6, 117.3, 113.9. ^{19}F NMR (376 MHz, DMSO-d_6): *δ* -61.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{10}NO_2F_6$ 350.0615; found 350.0612.

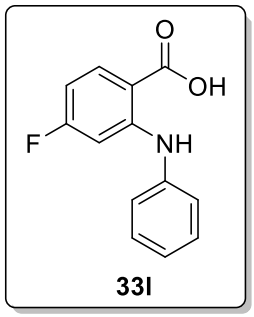
***2-([1,1'-biphenyl]-4-ylamino)-5-methoxybenzoic acid* (33k)**



33k

In accordance with **GP-B**, 5-methoxy-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (57.9 mg, 0.3 mmol), **30i-TMP** (168 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33k** as white solid (57.8 mg, 0.198 mmol, 62%). Reaction duration: 5 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 13.24 (bs, 1H), 9.25 (bs, 1H), 7.59-7.64 (m, 4H), 7.42-7.45 (m, 3H), 7.29-7.36 (m, 2H), 7.23 (d, *J* = 8 Hz, 2H), 7.11-7.14 (m, 1H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 169.8, 151.9, 142.0, 140.4, 140.2, 133.7, 129.3, 128.0, 127.1, 126.4, 121.9, 119.8, 118.1, 115.6, 115.2, 55.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{18}NO_3$ 320.1286; found 320.1288.

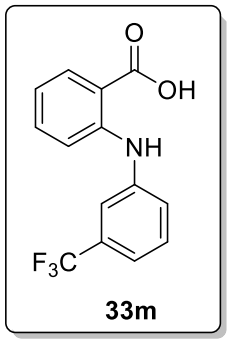
***4-fluoro-2-(phenylamino)benzoic acid* (33l)**



33l

In accordance with **GP-B**, 7-fluoro-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (54.3 mg, 0.3 mmol), **30a-TMP** (145.26 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33l** as beige solid (43 mg, 0.186 mmol, 63%). Reaction duration: 5 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.13 (bs, 1H), 9.88 (bs, 1H), 7.99 (t, J = 8 Hz, 1H), 6.58 (t, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.7, 166.3 ($J_{C\text{-}F}$ = 247 Hz), 150.1, 150.0, 140.0, 135.3, 130.1, 124.5, 122.8, 109.4, 104.9 ($J_{C\text{-}F}$ = 23 Hz), 99.6 ($J_{C\text{-}F}$ = 27 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ -104.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{11}NO_2F$ 232.0773; found 232.0761.

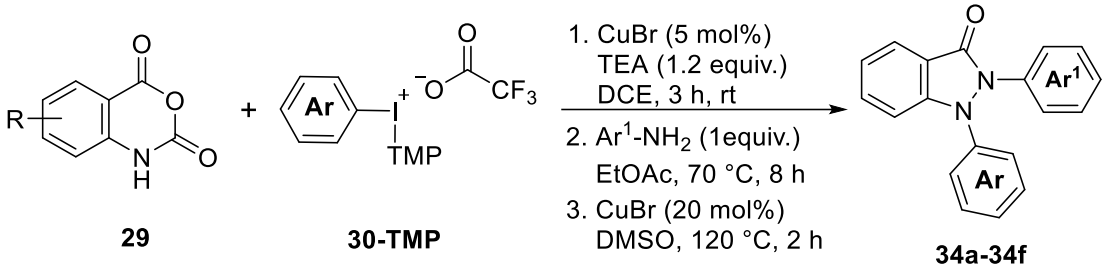
***2-((3-(trifluoromethyl)phenyl)amino)benzoic acid* (33m)** [39]



33m

In accordance with **GP-B**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30q-TMP** (165.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), Et_3N (46 µL, 0.33 mmol) and NaOH (60 mg, 1.5 mmol) were used, and the following conditions gave the title compound **33m** as yellowish solid (54.8 mg, 0.194 mmol, 65%). Reaction duration: 5 h. Purification method: column chromatography (4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.41 (bs, 1H), 8.09 (d, J = 8 Hz, 1H), 7.42-7.47 (m, 3H), 7.35 (d, J = 8 Hz, 1H), 7.26 (t, J = 8 Hz, 1H), 6.85 (t, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.0, 147.7, 141.2, 135.4, 132.7, 131.9 ($J_{C\text{-}F}$ = 32 Hz), 129.9, 125.3, 120.2, 118.8, 118.3, 114.2, 111.3. ^{19}F NMR (376 MHz, DMSO-d_6): δ -61.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{11}NO_2F_2$ 282.0741; found 282.0729.

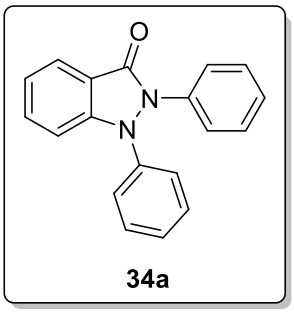
5.8.3 General procedure C: One-pot system for *N,N′*-diarylindazol-3-ones



29 **30-TMP** **34a-34f**

To an oven-dried Schlenck-tube, isatoic anhydride **29** (0.3 mmol), diaryliodonium salt **30-TMP** (0.3 mmol, 1 equiv.), CuBr (0.015 mmol, 0.05 equiv.) and Et_3N (0.36 mmol, 1.2 equiv.) were added. After adding toluene (3 mL, 0.1 M), the tube was sealed and allowed to stir at room temperature. The reaction mixture was stirred till for 3-5 h (checked by TLC). The reaction mixture was concentrated under reduced pressure and aniline (1.5 mmol, 5 equiv.) was added to the reaction vessel. After addition of EtOAc (5 mL), the reaction vessel was placed on a pre-heated oil-bath at 70 ℃. The reaction was stirred for 8 h duration. The ethyl acetate was evaporated under reduced pressure and then CuBr (0.06 mmol, 0.2 equiv.) was added to the vessel along with 2 mL of DMSO. Again, the tube was placed on a pre-heated oil-bath at 120 ℃ and stirred for 2 h. The reaction mixture was worked-up with EtOAc and ice-cold water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then, the crude product was purified using conventional column-chromatography (using 60-120 mesh silica with the eluent 10-20% hexane/ethyl acetate) to obtain the desired product (**34a**-**34f**).

1,2-diphenyl-1,2-dihydro-3H-indazol-3-one **(34a)** [36,37]

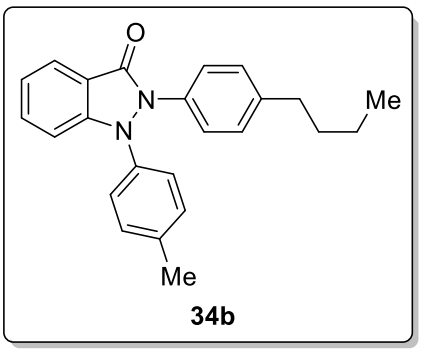


34a

In accordance with **GP-C**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30a-TMP** (145.26 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), and Et_3N (46 µL, 0.33 mmol); followed by aniline (28 µL, 0.3 mmol) and then, CuBr (8.6 mg, 0.06 mmol) were used, and the following conditions gave the title compound **34a** as white solid (55.8 mg, 0.195 mmol, 65%). Purification method: column chromatography (5:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8 Hz, 1H), 7.52 (d, J = 8 Hz, 2H), 7.42 (d, J = 8 Hz, 1H), 7.19-7.28 (m, 7H), 7.09-7.17 (m, 3H), 7.05 (t, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 150.2, 142.3, 135.9, 133.0, 129.65, 128.8, 127.5, 125.9, 124.5, 124.2, 123.4,

123.3, 118.3, 112.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{15}N_2O$ 287.1184; found 287.1176.

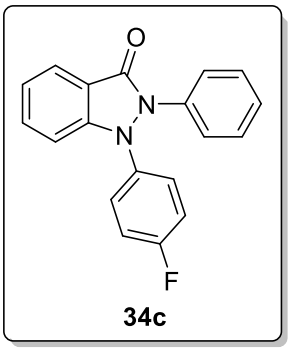
2-(4-butylphenyl)-1-(p-tolyl)-1,2-dihydro-3H-indazol-3-one **(34b)**



34b

In accordance with **GP-C**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30b-TMP** (149.4 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), and Et_3N (46 µL, 0.33 mmol); followed by aniline (28 µL, 0.3 mmol) and then, CuBr (8.6 mg, 0.06 mmol) were used, and the following conditions gave the title compound **34b** as beige solid (76.9 mg, 0.216 mmol, 72%). Purification method: column chromatography (5:1 hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8 Hz, 1H), 7.37-7.41 (m, 3H), 7.14 (t, J = 8 Hz, 1H), 7.03-7.08 (m, 7H), 2.44 (t, J = 8 Hz, 2H), 2.19 (s, 3H), 1.42-1.49 (m, 2H), 1.18-1.26 (m, 2H), 0.81 (t, J = 8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 150.3, 140.7, 139.7, 137.4, 133.4, 132.8, 130.1, 128.7, 124.3, 123.5, 123.1, 118.3, 112.41, 35.1, 33.3, 22.3, 21.0, 13.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{25}N_2O$ 357.1966; found 357.1968.

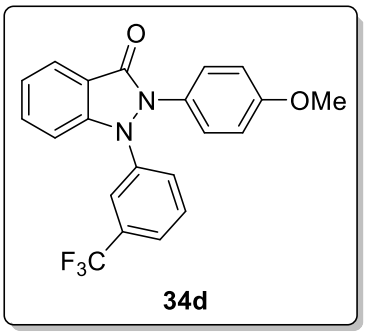
1-(4-fluorophenyl)-2-phenyl-1,2-dihydro-3H-indazol-3-one **(34c)** [37]



34c

In accordance with **GP-C**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30e-TMP** (150.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), and Et_3N (46 µL, 0.33 mmol); followed by aniline (28 µL, 0.3 mmol) and then, CuBr (8.6 mg, 0.06 mmol) were used, and the following conditions gave the title compound **34c** as white solid (52.9 mg, 0.174 mmol, 58%). Purification method: column chromatography (5:1 hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8 Hz, 1H), 7.43-7.50 (m, 3H), 7.27 (t, J = 8 Hz, 2H), 7.18-7.21 (m, 3H), 7.09 (t, J = 8 Hz, 1H), 7.04 (d, J = 8 Hz, 1H), 6.96 (t, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 162.6, 160.3, 150.54, 138.4, 135.6, 133.1, 128.9, 126.4, 126.3, 126.1, 124.5, 123.6, 123.5, 118.3, 116.7, 116.5, 112.4. ^{19}F NMR (376 MHz, DMSO-d_6): δ -113.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{14}N_2OF$ 305.1090; found 305.1083.

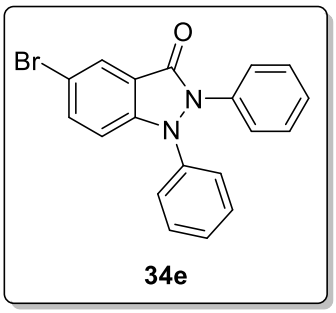
***2-(4-methoxyphenyl)-1-(3-(trifluoromethyl)phenyl)-1,2-dihydro-3H-indazol-3-one* (34d)**



34d

In accordance with **GP-C**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30u-TMP** (165.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), and Et_3N (46 µL, 0.33 mmol); followed by *p*-anisidine (36.9 mg, 0.3 mmol) and then, CuBr (8.6 mg, 0.06 mmol) were used, and the following conditions gave the title compound **34d** as white solid (71.4 mg, 0.186 mmol, 62%). Purification method: column chromatography (5:1 hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8 Hz, 1H), 7.35-7.50 (m, 7H), 7.22 (t, J = 8 Hz, 1H), 7.09 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 2H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 158.1, 149.5, 143.0, 133.1, 132.1 ($J_{C\text{-}F}$ = 33 Hz), 128.4, 127.5, 125.4, 124.6, 124.2, 123.9, 121.3, 118.4, 114.4, 112.0, 55.4. ^{19}F NMR (376 MHz, DMSO-d_6): δ -62.7. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{16}NO_2F_3$ 385.1163; found 385.1158.

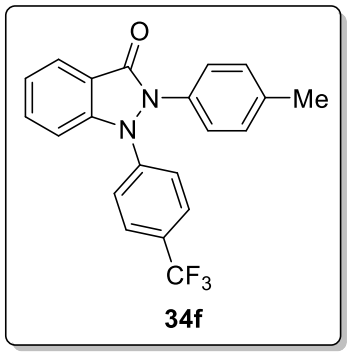
***5-bromo-1,2-diphenyl-1,2-dihydro-3H-indazol-3-one* (34e)** [36]



34e

In accordance with **GP-C**, 6-bromo-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione (72.6 mg, 0.3 mmol), **30a-TMP** (145.26 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), and Et_3N (46 µL, 0.33 mmol); followed by aniline (28 µL, 0.3 mmol) and then, CuBr (8.6 mg, 0.06 mmol) were used, and the following conditions gave the title compound **34e** as white solid (58 mg, 0.159 mmol, 53%). Purification method: column chromatography (5:1 hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.55 (d, J = 8 Hz, 1H), 7.45 (d, J = 8 Hz, 2H), 7.25-7.31 (m, 5H), 7.10-7.15 (m, 3H), 6.96 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 148.6, 140.3, 136.1, 135.2, 133.6, 130.0, 129.0, 127.2, 126.5, 125.6, 123.4, 120.1, 116.6, 114.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{14}N_2OBr$ 365.0289; found 365.0282.

***2-(p-tolyl)-1-(4-(trifluoromethyl)phenyl)-1,2-dihydro-3H-indazol-3-one* (34f)**



34f

In accordance with **GP-C**, isatoic anhydride **29a** (48.9 mg, 0.3 mmol), **30q-TMP** (165.6 mg, 0.3 mmol), CuBr (2.2 mg, 0.015 mmol), and Et_3N (46 μL, 0.33 mmol); followed by *p*-toluidine (32 mg, 0.3 mmol) and then, CuBr (8.6 mg, 0.06 mmol) were used, and the following conditions gave the title compound **34f** as white solid (67.4 mg, 0.183 mmol, 61%). Purification method: column chromatography (5:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8 Hz, 1H), 7.54 (d, J = 8 Hz, 2H), 7.47 (t, J = 8 Hz, 1H), 7.32-7.37 (m, 4H), 7.22 (t, J = 8 Hz, 1H), 7.19 (d, J = 8 Hz, 1H), 7.08 (d, J = 8 Hz, 2H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 149.2, 145.5, 136.2, 133.3, 133.2, 129.7, 126.8 ($J_{C\text{-}F}$ = 33 Hz), 124.7, 124.0, 123.9, 123.2, 118.4, 111.9, 20.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{16}N_2OF_3$ 369.1214; found 369.1218.

5.9 Representative ^{1}H and ^{13}C NMR spectra

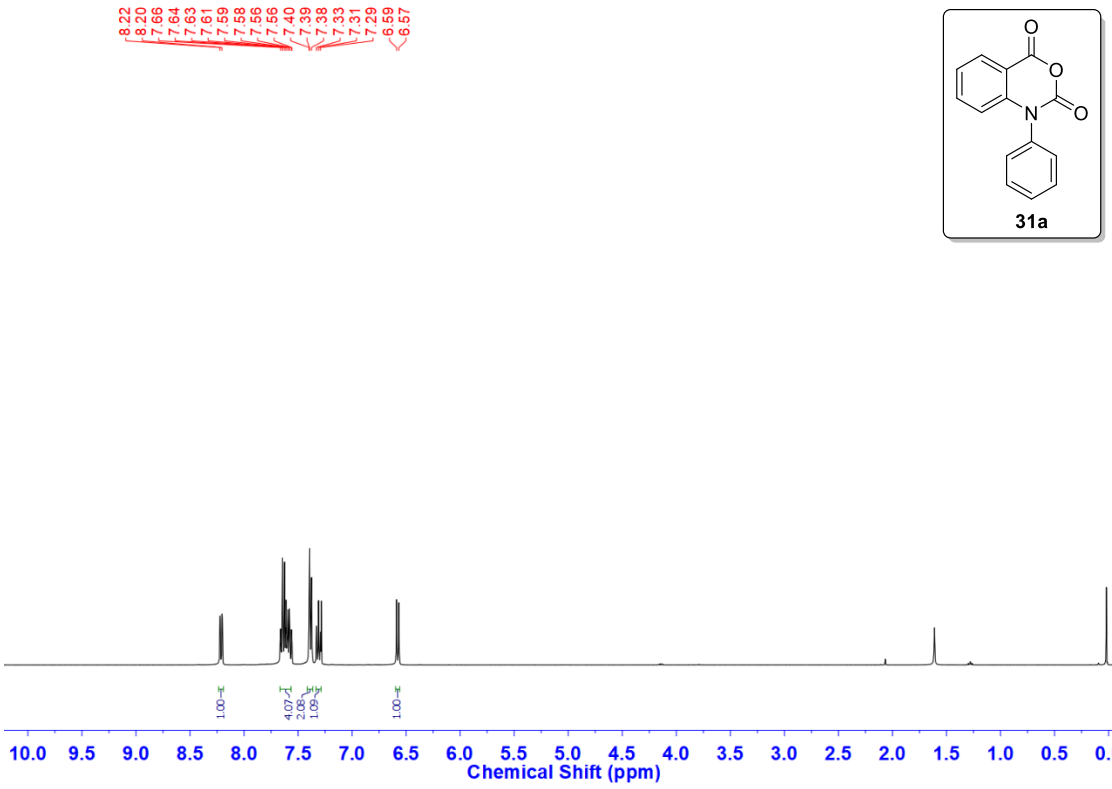


Figure 5.2 ^{1}H NMR spectrum of **31a** ($CDCl_3$, 400 MHz, 298 K)

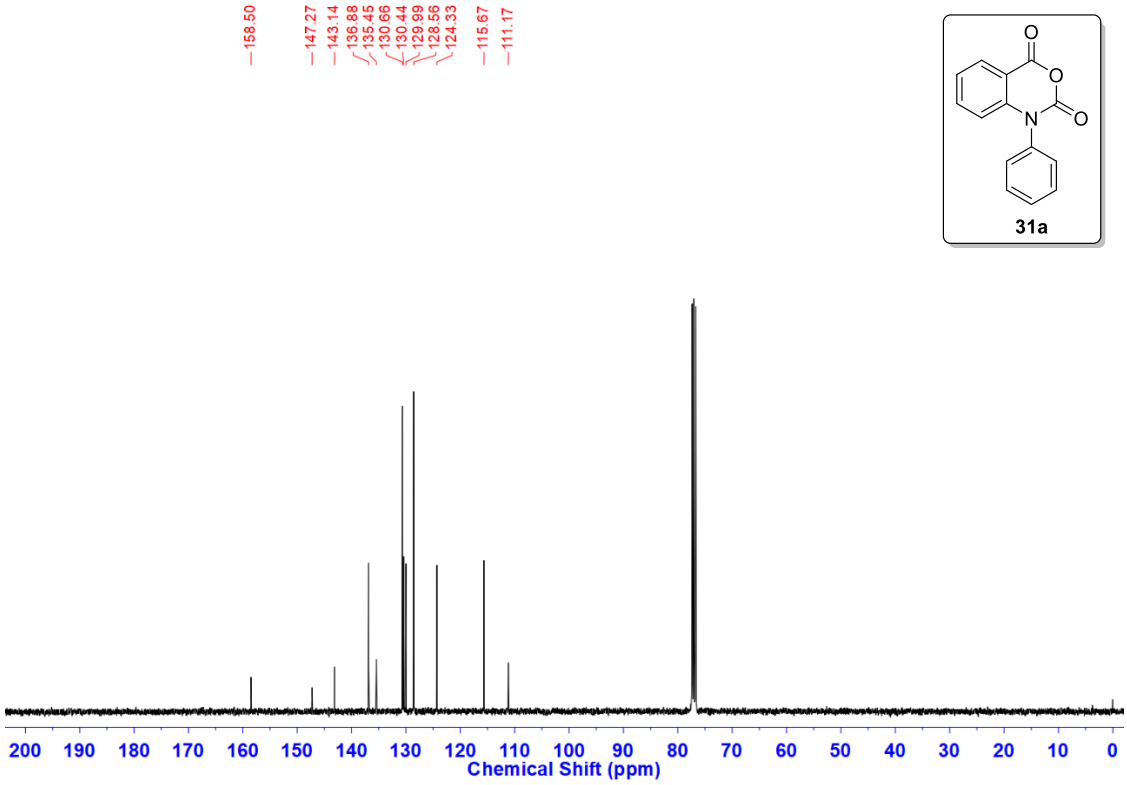


Figure 5.3 ^{13}C NMR spectrum of **31a** ($CDCl_3$, 100 MHz, 298 K)

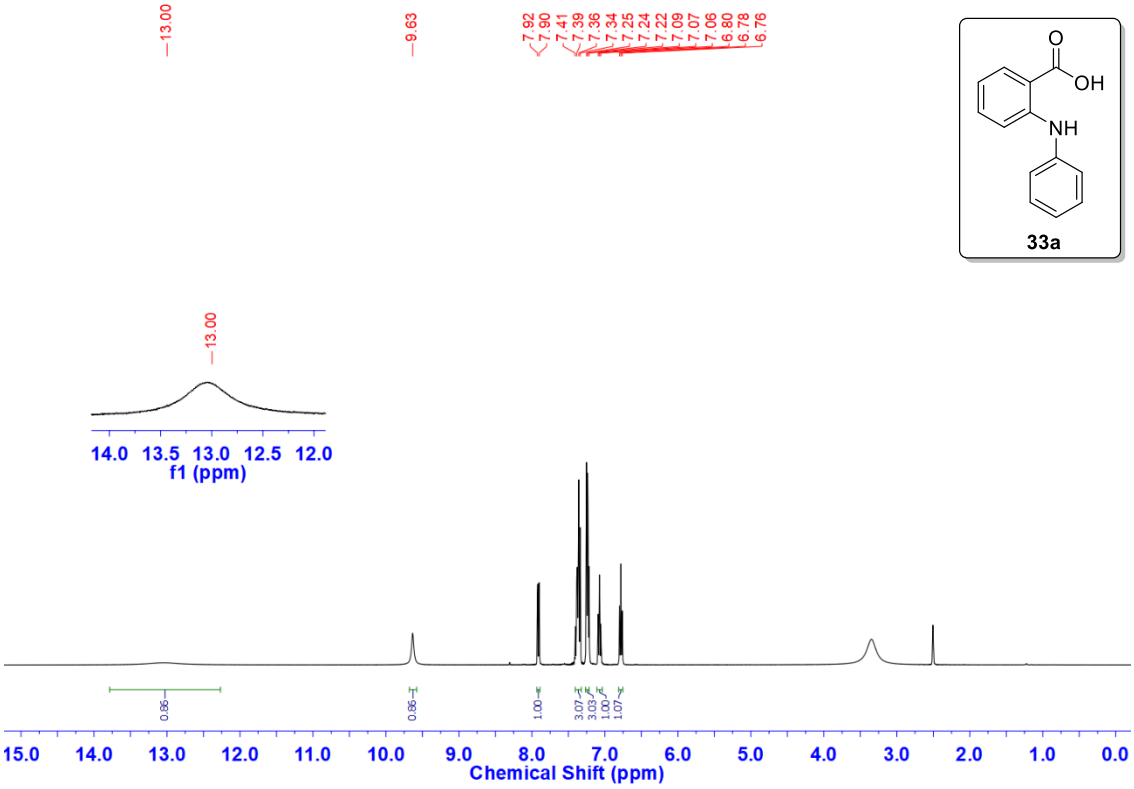


Figure 5.4 ^{1}H NMR spectrum of **33a** (DMSO-d_6, 400 MHz, 298 K)

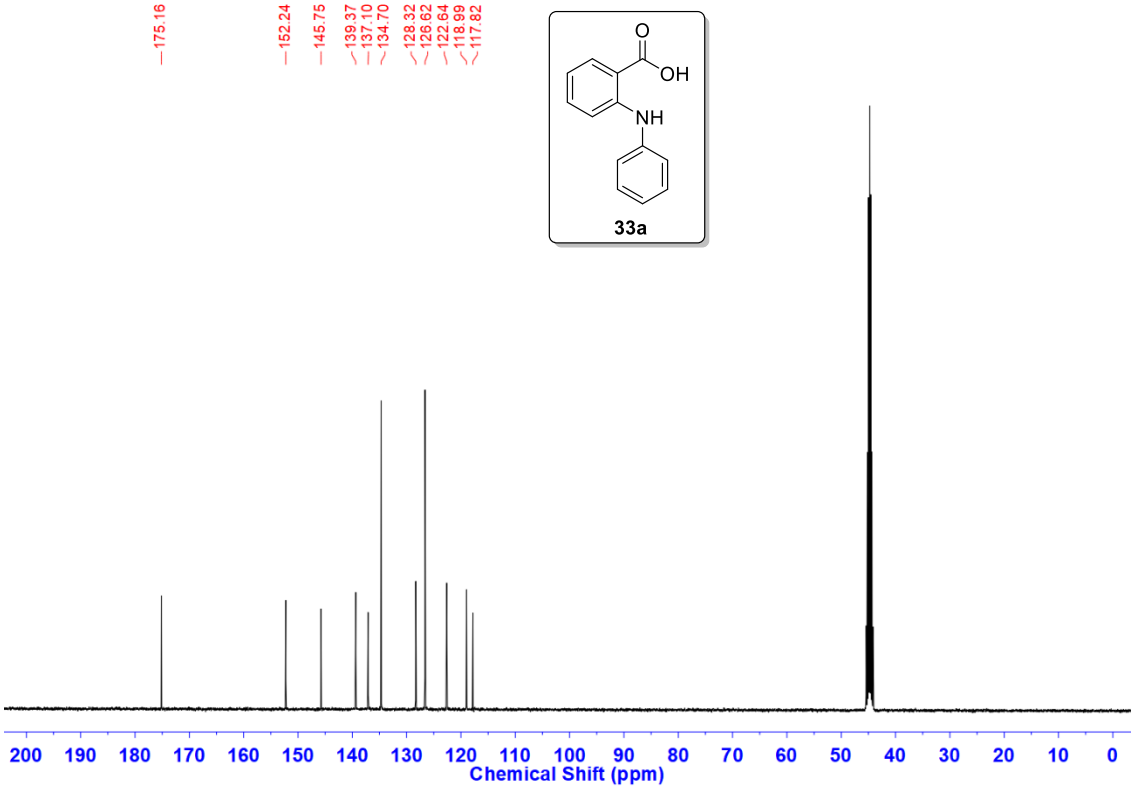


Figure 5.5 ^{13}C NMR spectrum of **33a** (DMSO-d_6, 100 MHz, 298 K)

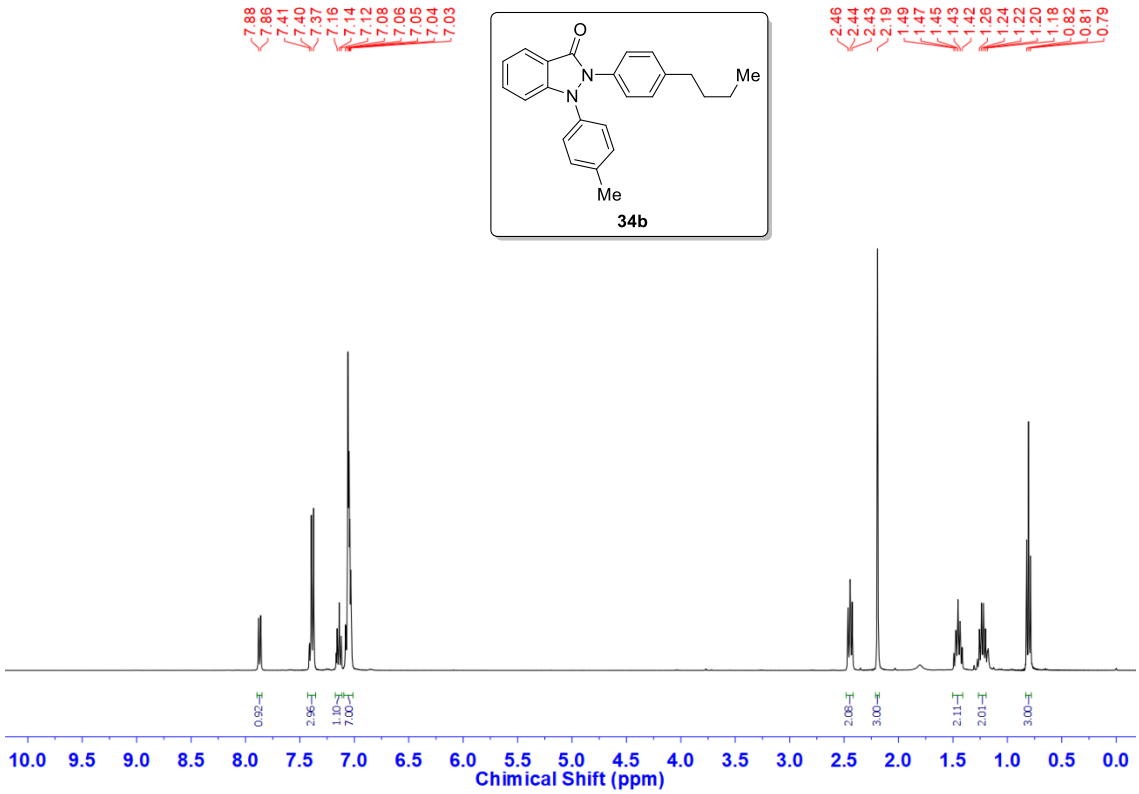


Figure 5.6 ^{1}H NMR spectrum of **34b** ($CDCl_3$, 400 MHz, 298 K)

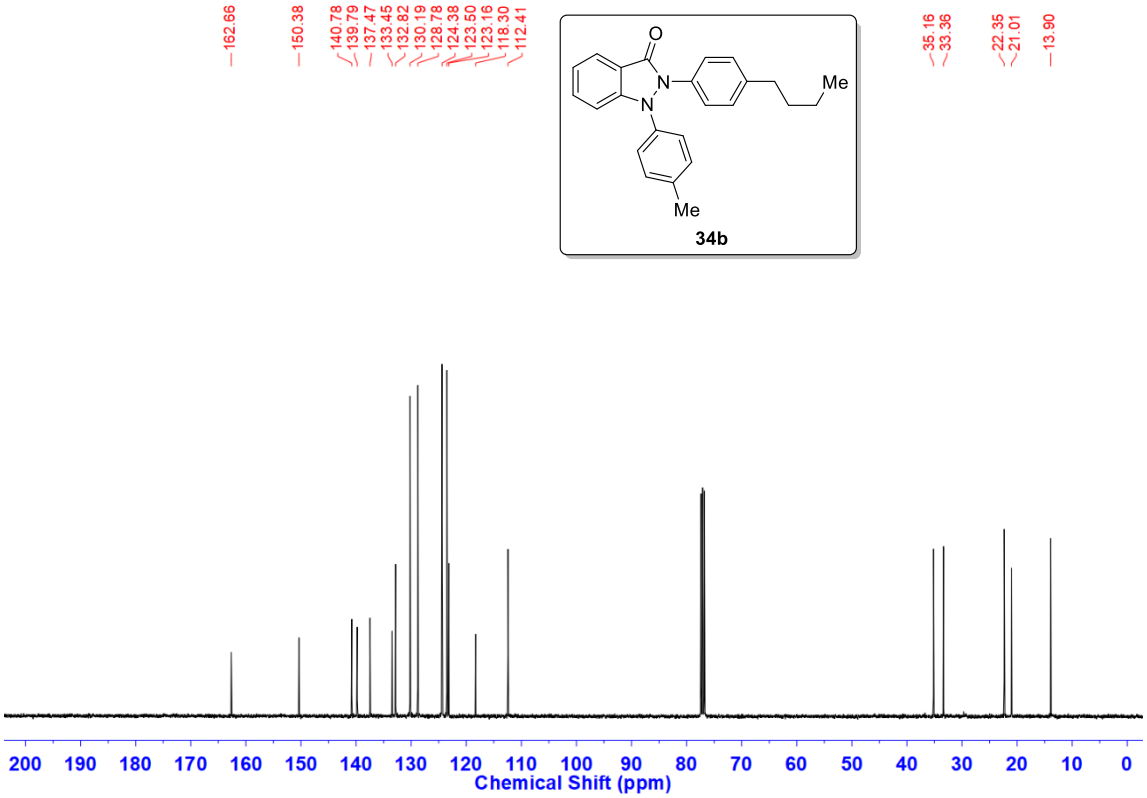


Figure 5.7 ^{13}C NMR spectrum of **34b** ($CDCl_3$, 100 MHz, 298 K)

5.10 Bibliography

[1] Tashrifi, Z., Mohammadi-Khanaposhtani, M., Biglar, M., Larijani, B., and Mahdavi, M. Isatoic anhydride: A fascinating and basic molecule for the synthesis of substituted quinazolinones and benzo di/triazepines. *Current Organic Chemistry*, 23(10):1090–1130, 2019.

[2] Kappe, T. and Stadlbauer, W. Isatoic anhydrides and their uses in heterocyclic synthesis. In, *Advances in Heterocyclic Chemistry*, volume 28, pages 127–182. Elsevier, 1981.

[3] Roy, S. R. Isatoic anhydride. *Synlett*, 2011(10):1479–1480, 2011.

[4] Brouillette, Y., Martinez, J., and Lisowski, V. Chemistry of Ring-Fused Oxazine-2,4-diones. *European Journal of Organic Chemistry*, 2009(21):3487-3503, 2009.

[5] Huang, G., Roos, D., Stadtmueller, P., and Decker, M. A simple heterocyclic fusion reaction and its application for expeditious syntheses of rutaecarpine and its analogs. *Tetrahedron Letters*, 55(26):3607–3609, 2014.

[6] Fessler, A. B., Fowler, A. J., and Ogle, C. A. Directly quantifiable biotinylation using a water-soluble isatoic anhydride platform. *Bioconjugate Chemistry*, 32(5):904–908, 2021.

[7] Odion, E. E., Ajibosin, G., and Usifoh, C. O. One-pot synthesis of *N*-benzyl-2-aminobenzoic acid *via* ring opening of isatoic anhydride derivative, and its antibacterial screening. *Journal of Pharmacy & Bioresources*, 18(3):192–195, 2021.

[8] Savjani, J. K., Mulamkattil, S., Variya, B., and Patel, S. Molecular docking, synthesis, and biological screening of mefenamic acid derivatives as anti-inflammatory agents. *European Journal of Pharmacology*, 801:28–34, 2017.

[9] Puspaningtyas, A. Drug Development of Mefenamic Acid Derivatives as Analgesic by Molecular Approach. *International Journal of Pharmaceutical and Clinical Research*, 9(2):123–130, 2017.

[10] Jadhavar, P. S., Patel, K. I., Dhameliya, T. M., Saha, N., Vaja, M. D., Krishna, V. S., Sriram, D., and Chakraborti, A. K. Benzimidazoquinazolines as new potent anti-TB chemotypes: Design, synthesis, and biological evaluation. *Bioorganic Chemistry*, 99:103774, 2020.

[11] Teja, C., Ramanathan, K., Naresh, K., Vidya, R., Gomathi, K., and Nawaz, F. R. Design, Synthesis, and Biological Evaluation of Tryptanthrin Alkaloids as Potential anti-Diabetic and Anticancer Agents. *Polycyclic Aromatic Compounds* 2021:1-21, 2021.

[12] Clark, R. L., Clements, C. J., Barrett, M. P., Mackay, S. P., Rathnam, R. P., Owusu-Dapaah, G., Spencer, J., and Huggan, J. K. Identification and development of the 1,4-benzodiazepin-2-one and quinazoline-2,4-dione scaffolds as sub-micromolar inhibitors of HAT. *Bioorganic & Medicinal Chemistry*, 20(20):6019–6033, 2012.

[13] Shao, C. L., Wang, C. Y., Gu, Y. C., Wei, M. Y., Pan, J. H., Deng, D. S., She, Z. G., and Lin, Y. C. Penicinoline, a new pyrrolyl 4-quinolinone alkaloid with an unprecedented ring system from an endophytic fungus Penicillium sp. *Bioorganic & Medicinal Chemistry Letters*, 20(11):3284–3286, 2010.

[14] Staiger, R. P. and Miller, E. B. Isatoic anhydride IV. Reactions with various nucleophiles. *The Journal of Organic Chemistry*, 24(9):1214–1219, 1959.

[15] Coppola, G. M. The chemistry of isatoic anhydride. *Synthesis*, 1980(07):505–536, 1980.

[16] Zhang, Z., Qin, Z., Chang, W., Li, J., Fan, R., Wu, X., Guo, R., Xie, X., and Zhou, L. Nickel-Catalyzed Decarboxylative Cyclization of Isatoic Anhydrides with Carbodiimides: Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones. *Advanced Synthesis & Catalysis*, 362(14):2864–2869, 2020.

[17] Li, C., Wang, C. S., Li, T. Z., Mei, G. J., and Shi, F. Brønsted Acid-Catalyzed (4+3) Cyclization of *N,N′*-Cyclic Azomethine Imines with Isatoic Anhydrides. *Organic Letters*, 21(3):598–602, 2019.

[18] Chen, Q., Pan, Y., Yue, T., Yang, W., Liu, H., and Zheng, J. [4+ 2]-Annulation of Prop-2-ynylsulfonium Salts and Isatoic Anhydrides: Access to 3-Methylthio-4-quinolones. *Organic Letters*, 22(15):6096–6100, 2020.

[19] Yang, M., Wang, J., Lv, W., Ba, D., Cheng, G., and Wang, L. Synthesis of 2-Alkenyl-4*H*-1,3-Benzoxazin-4-Ones through HFIP-Mediated Decarboxylative [4+2]-Annulation of Isatoic Anhydrides with Cyclopropenones under Silver Catalysis. *Advanced Synthesis & Catalysis*, 363(16):4085–4090, 2021.

[20] Costil, R., Lefebvre, Q., and Clayden, J. Medium-Sized-Ring Analogues of Dibenzodiazepines by a Conformationally Induced Smiles Ring Expansion. *Angewandte Chemie International Edition*, 129(46):14794–14798, 2017.

[21] Pal, K., Hoque, A., and Volla, C. M. Rh-Catalyzed Denitrogenative Reaction of *N*-Sulfonyl-1,2,3-triazoles with Isatoic Anhydrides and Oxadiazolones. *Chemistry–A European Journal*, 24(11):2558–2564, 2018.

[22] Wu, H. H., Fan, X. Z., Tang, Z., Zhang, H., Cai, L. Y., Bi, X. F., and Zhao, H. W. Palladium-Catalyzed Formal (5+6) Cycloaddition of Vinylethylene Carbonates with Isatoic Anhydrides for the Synthesis of Medium-Sized *N,O*-Containing Heterocycles. *Organic Letters*, 23(7):2802–2806, 2021.

[23] Khalifa, M. M., Philkhana, S. C., and Golden, J. E. Synthesis of Ring-Fused, *N*-Substituted 4-Quinolinones Using *p*Ka-Guided, Base-Promoted Annulations with Isatoic Anhydrides: Total Synthesis of Penicinotam. *The Journal of Organic Chemistry*, 85(2):464–481, 2019.

[24] Beutner, G. L., Kuethe, J. T., and Yasuda, N. A practical method for preparation of 4-hydroxyquinolinone esters. *The Journal of Organic Chemistry*, 72(18):7058–7061, 2007.

[25] Verma, E., Patil, S., and Gajbhiye, A. Convenient Novel Method to Access *N*-Benzylated Isatoic Anhydride: Reaction Behaviour of Isatoic Anhydride with 4-Chlorobenzyl Chloride in the Presence of Bases. *ACS Omega*, 6(12):8346–8355, 2021.

[26] Hardtmann, G. E., Koletar, G., and Pfister, O. R. The chemistry of 2*H*-3,1-benzoxazine-2,4(1*H*)-dione (isatoic anhydrides). The synthesis of *N*-substituted 2*H*-3,1-benzoxazine-2,4(1*H*)-diones. *Journal of Heterocyclic Chemistry*, 12(3):565–572, 1975.

[27] Coppola, G. M. *N*-Arylation of isatins. A direct route to *N*-arylisatoic anhydrides. *Journal of Heterocyclic Chemistry*, 24(5):1249–1251, 1987.

[28] Chan, D. M. Promotion of reaction of N–H both with triarylbismuth and cupric acetate. *Tetrahedron Letters*, 37(50):9013–9016, 1996.

[29] Wu, X. X., He, Y., Zhao, X. J., and Li, G. Copper-Catalyzed Electrophilic Arylation of Isatoic Anhydride with Diaryliodonium Salts for Synthesis of *N*-Phenylated Isatoic Anhydrides. *Asian Journal of Organic Chemistry*, 11(7):e202200155, 2022.

[30] Sandtorv, A. H. and Stuart, D. R. Metal-free synthesis of aryl amines: beyond nucleophilic aromatic substitution. *Angewandte Chemie International Edition*, 128(51):16044–16047, 2016.

[31] Purkait, N., Kervefors, G., Linde, E., and Olofsson, B. Regiospecific *N*-arylation of aliphatic amines under mild and metal-free reaction conditions. *Angewandte Chemie International Edition*, 130(35):11597–11601, 2018.

[32] Tinnis, F., Stridfeldt, E., Lundberg, H., Adolfsson, H., and Olofsson, B. Metal-free *N*-arylation of secondary amides at room temperature. *Organic Letters*, 17(11):2688–2691, 2015.

[33] Bielawski, M., Aili, D., and Olofsson, B. Regiospecific one-pot synthesis of diaryliodonium tetrafluoroborates from arylboronic acids and aryl iodides. *The Journal of Organic Chemistry*, 73(12):4602–4607, 2008.

[34] Neerbye Berntsen, L., Nova, A., Wragg, D. S., and Sandtorv, A. H. Cu-catalyzed N^3-Arylation of Hydantoins Using Diaryliodonium Salts. *Organic Letters*, 22(7):2687-2691, 2020.

[35] Soldatova, N. S., Semenov, A. V., Geyl, K. K., Baykov, S. V., Shetnev, A. A., Konstantinova, A. S., Korsakov, M. M., Yusubov, M. S., and Postnikov, P. S., Copper-Catalyzed Selective *N*-Arylation of Oxadiazolones by Diaryliodonium Salts. *Advanced Synthesis & Catalysis*, 363(14):3566-3576, 2021.

[36] Liu, S., Xu, L., and Wei, Y. One-pot, multistep reactions for the modular synthesis of *N,N′*-diarylindazol-3-ones. *The Journal of Organic Chemistry*, 84(3):1596–1604, 2018.

[37] Dai, G., Yang, L., and Zhou, W. Copper-catalyzed oxidative dehydrogenative N–N bond formation for the synthesis of *N,N′*-diarylindazol-3-ones. *Organic Chemistry Frontiers*, 4(2):229–231, 2017.

[38] Pellón, R. F., Carrasco, R., and Rodés, L. Synthesis of *N*-phenylanthranilic acids using water as solvent. *Synthetic Communications*, 23(10):1447-1453, 1993.

[39] Wolf, C., Liu, S., Mei, X., August, A. T., and Casimir, M. D. Regioselective copper-catalyzed amination of bromobenzoic acids using aliphatic and aromatic amines. *The Journal of Organic Chemistry*, 71(8):3270-3273, 2006.

[40] Maradolla, M. B., Mandha, A., and Garimella, C. M. Regioselective copper-catalysed amination of halobenzoic acids using aromatic amines. *Journal of Chemical Research*, 2007(10):587-589, 2007.