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Mechanochemical Ni-Catalysed Arylation of *ortho*-Hydroxyarylenaminones: Synthesis of Isoflavones

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Abstract: This work describes two new synthetic methods for the preparation of isoflavones following the Ni-catalysed domino arylation reactions of the vast range of ortho-hydroxyarylenaminones utilising aromatic bromides as well as carboxylic acids. The presented protocols tolerated significant variation of all coupling partners and enabled synthesis of isoflavone library of twenty-three representatives. This is the first communicated precedent where the mechanic energy was utilised in the synthesis of isoflavones following the domino cyclisation mode.

Keywords: Isoflavones; Arylation; Catalysis; Mechanochemistry; Methodology

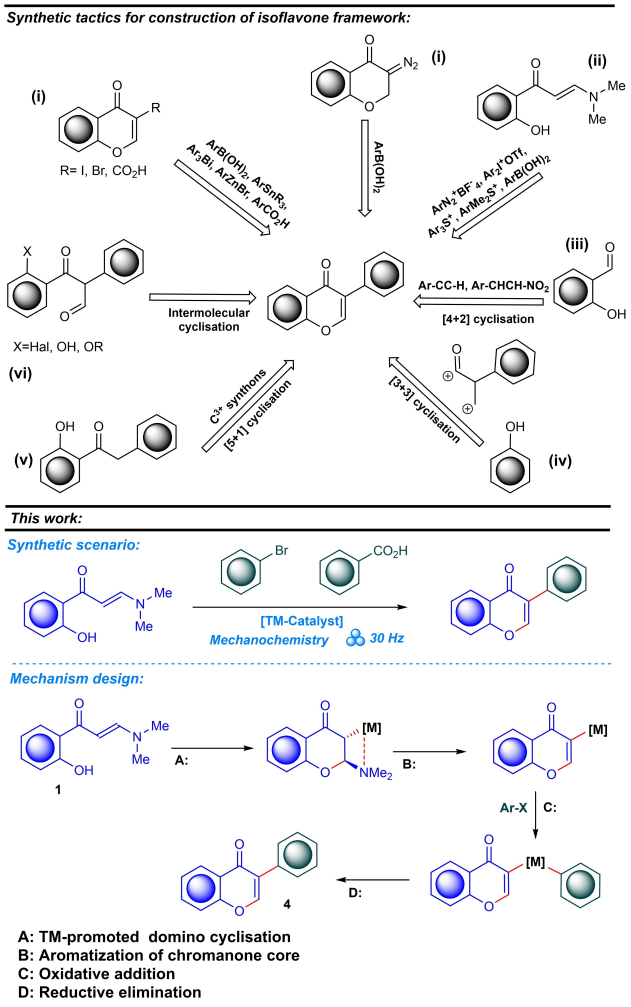
Introduction

Heterocyclic compounds play a key role in the development of drugs, drug-like scaffolds and are abundantly presented in a substantial portion of marketed drugs. Chromone heterocyclic core can also be found in biologically relevant natural products and numerous biologically active compounds with a wide spectrum of important activities.[1] Among all these, one has to highlight the chromone containing antibacterial agents, antifungal agents, anti-cancer agents, antioxidants, anti-HIV compounds, anti-ulcer agents, immunostimulants, biocides, wound healing agents, anti-inflammatory drugs and immune stimulation agents.[1] Chromone heterocycle system reflects the properties of multiple pharmaceuticals, and its structural changes offer a prominent level of valuable diversity in finding new therapeutics.[1] Isoflavonoids

(3-arylchromones) in turn are drug-like scaffolds which are widely applied in medicinal chemistry, life science and food production.[1e,2]

Besides the medicinal applications chromone framework showcases several ranges of reactivity which renders its presence in numerous building-blocks commonly used for the construction of many other heterocycles. The chromone system is dynamic and can easily enter various photofield reactions that result in the formation of different compound classes.[3] The γ-benzopyrone framework is also considered a masked 1,3-CCC-dielectrophile and thus can enter reactions with numerous nucleophiles, in particularly following the ANRORC mechanism.[4]

The synthetic routes, currently known to build-up the 3-arylchromone framework, can be divided into six main tactics (Scheme 1). The first one is bolstered upon (i) the range of C–C couplings between 3-halogenchromones or chromone-3-carboxilyc acids utilising the set of appropriate reagents, among those



Scheme 1. General methods for synthesis of isoflavones and our concept.

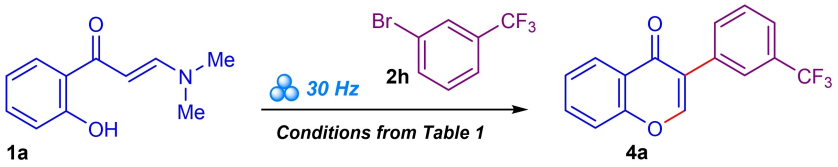
are aryl boronic acids,[5] aryl tin and triaryl bismuth regents,[6] aryl zinc bromide reagents[7] and aromatic carboxylic acids.[8] Another way to obtain 3-arylchromones is a C–C cross-coupling mode catalysed by palladium following the reaction between arylboronic acids and 3-diazo-2,3-dihydro-4H-1-benzopyran-4-one.[9] The second important strategy is (ii) the annulation of the γ-pyrone core by the essence of the arylation/domino cyclization of ortho-hydroxyarylenaminones utilising different arylation agents (aryldiazonium salts, diaryliodonium salts and arenesulfonyl chlorides following visible light-mediated protocols; aryl boronic acids in the presence of iodide catalysed by Pd salts).[10,11] The synthesis of 3-arylchromones can also be carried out by (iii) the [4+2]-cyclization reactions between salicylaldehyde and 1,2-CC-building blocks.[12] Other cyclisation modes like (iv) [3+3]-cyclization[13] and (v) [5+1]-cyclization,[14] are also presented in the contemporary literature and often used for the construction of the title heterocyclic system. (vi) Intermolecular cyclisation of suitable linear predecessors is another pathway to construct the isoflavone heterocyclic cores.[15] Many of the tactics illustrated here are methods that involve laborious procedures, expensive and toxic reagents; in some cases, they exert low tolerance to the essential functional groups and possess insufficient atom and step economy.

Therefore, there is an increasing need for synthetic packages capable of meeting the existing challenges of succinct preparation of isoflavones. A current trend in contemporary organic chemistry suggests exploring greener, cheaper, and more efficient methods through which one can generate significant variations of privileged organic molecules. We recently expanded the pool of abbreviated tactics for the photoredox preparation of isoflavones by two methods utilising Eosin Y and $Ru(bpy)_3Cl_2$ catalysts respectively, based on the arylation of ortho-hydroxyarylenaminones by the aryldiazonium and diaryliodonium salts.[10a] Both synthetic routes exhibit high yields and a good functional group tolerance. As we continue to seek strategies for preparation of isoflavone,[10] we hypothesized that isoflavone framework can be assembled following our synthetic scenario (Scheme 1). This implied direct arylation of ortho-hydroxyarylenaminones by bromo compounds and carboxylic acids under the green mechano-milling conditions (Scheme 1). Our mechanistic hypothesis, that is illustrated in the Scheme 1, indicates that under the transition metal catalysis the ortho-hydroxyarylenaminone unit is expected to undergo the domino metalation event by an appropriate transition metal complexes forming the organometallic intermediate which in turn can be further functionalised by an appropriate arylation agent.

Results and Discussion

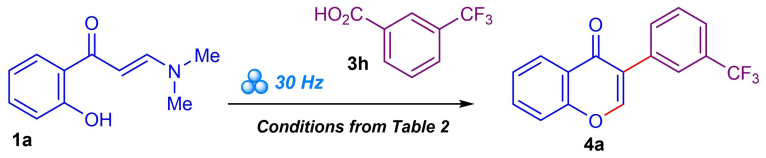
In order to formulate optimum reaction conditions, we selected two model reactions and performed a set of trial experiments, as the starting point of this research (Tables 1, S1). Namely, after the manipulation with reaction parameters, among those are catalysts, ligands, solvents, bases, etc., which resulted in nearly hundred preliminary experiments (Some of the experiments are illustrated in SI). We tested a diversity of copper, rhodium, ruthenium, palladium and nickel salts (Table 1, Entries 1–31, Table 2 and Scheme 2). We noticed that some of the nickel and palladium salts in combination with nitrogen-containing ligands (Scheme S4, **L1**–**L7**) under mechano-milling conditions facilitated the expected arylation reaction of

Table 1. Optimization of the reaction conditions.



entry	reaction components	frequency/ time	yield (%) **4a**
1	CuF_2 (0.1 equiv.), DABCO (1.3 equiv.), **L1** (0.1 equiv.), r.t.	30 Hz/90 min	21
2	$Cu(OTf)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L1** (0.1 equiv.), r.t.	30 Hz/90 min	38
3	$Cu(OTf)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L2** (0.1 equiv.), r.t.	30 Hz/90 min	27
4	$Cu(O_2CCF_3)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L2** (0.1 equiv.), r.t.	30 Hz/90 min	29
5	$Cu(OTf)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L3** (0.1 equiv.), r.t.	30 Hz/90 min	17
6	$Cu(OTf)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L4** (0.1 equiv.), r.t.	30 Hz/90 min	trace
7	$Cu(OTf)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L5** (0.1 equiv.), r.t.	30 Hz/90 min	0
8	$Cu(OTf)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L6** (0.1 equiv.), r.t.	30 Hz/90 min	0
9	$Cu(OTf)_2$ (0.1 equiv.), DABCO (1.3 equiv.), r.t.	30 Hz/90 min	0
10	$Rh(COD)_2BF_4$ (0.1 equiv.), DABCO (1.3 equiv.), **L3** (0.1 equiv.), r.t.	30 Hz/90 min	0
11	$RuCl_3$ (0.1 equiv.), DABCO (1.3 equiv.), **L2** (0.1 equiv.), r.t.	30 Hz/90 min	34
12	$RuCl_3$ (0.1 equiv.), DABCO (1.3 equiv.), **L5** (0.1 equiv.), r.t.	30 Hz/90 min	27
13	$(CH_3CN)_4Pd(OTf)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L2** (0.1 equiv.), r.t.	30 Hz/90 min	68
14	$Ni(OTf)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L2** (0.1 equiv.), r.t.	30 Hz/90 min	30
15	$NiBr_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L2** (0.1 equiv.), r.t.	30 Hz/90 min	32
16	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L1** (0.1 equiv.), r.t.	30 Hz/90 min	53
17	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L2** (0.1 equiv.), r.t.	30 Hz/90 min	49
18	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L3** (0.1 equiv.), r.t.	30 Hz/90 min	25
19	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L4** (0.1 equiv.), r.t.	30 Hz/90 min	27
20	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L5** (0.1 equiv.), r.t.	30 Hz/90 min	28
21	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L6** (0.1 equiv.), r.t.	30 Hz/90 min	trace
22	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L7** (0.1 equiv.), r.t.	30 Hz/90 min	0
23	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L8** (0.1 equiv.), r.t.	30 Hz/90 min	0
24	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), **L9** (0.1 equiv.), r.t.	30 Hz/90 min	0
25	$Ni(OTf)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[7]uril (0.1 equiv.), r.t.	30 Hz/90 min	77
26	$NiCl_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[7]uril (0.1 equiv.), r.t.	30 Hz/90 min	0
27	$NiBr_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[7]uril (0.1 equiv.), r.t.	30 Hz/90 min	59
28	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[7]uril (0.1 equiv.), r.t.	30 Hz/90 min	79
29	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[7]uril (0.05 equiv.), r.t.	30 Hz/90 min	80
30	**$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[6]uril (0.05 equiv.), r.t.**	**30 Hz/90 min**	**82**
31	$(CH_3CN)_4Pd(OTf)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[6]uril (0.05 equiv.), r.t.	30 Hz/90 min	84
	Reactions in solution		
32	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[6]uril (0.05 equiv.), dichloromethane, reflux.	—/24 h	0
33	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[6]uril (0.05 equiv.), CH_3CN, reflux.	—/24 h	0
34	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[6]uril (0.05 equiv.), 1,4-dioxane, reflux.	—/24 h	0
35	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[6]uril (0.05 equiv.), DMF, 80 °C.	—/24 h	0
36	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[6]uril (0.05 equiv.), DMF, 110 °C.	—/24 h	17
37	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[6]uril (0.05 equiv.), DMA, 90 °C.	—/24 h	35
38	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[6]uril (0.05 equiv.), DMA, 130 °C.	—/24 h	23

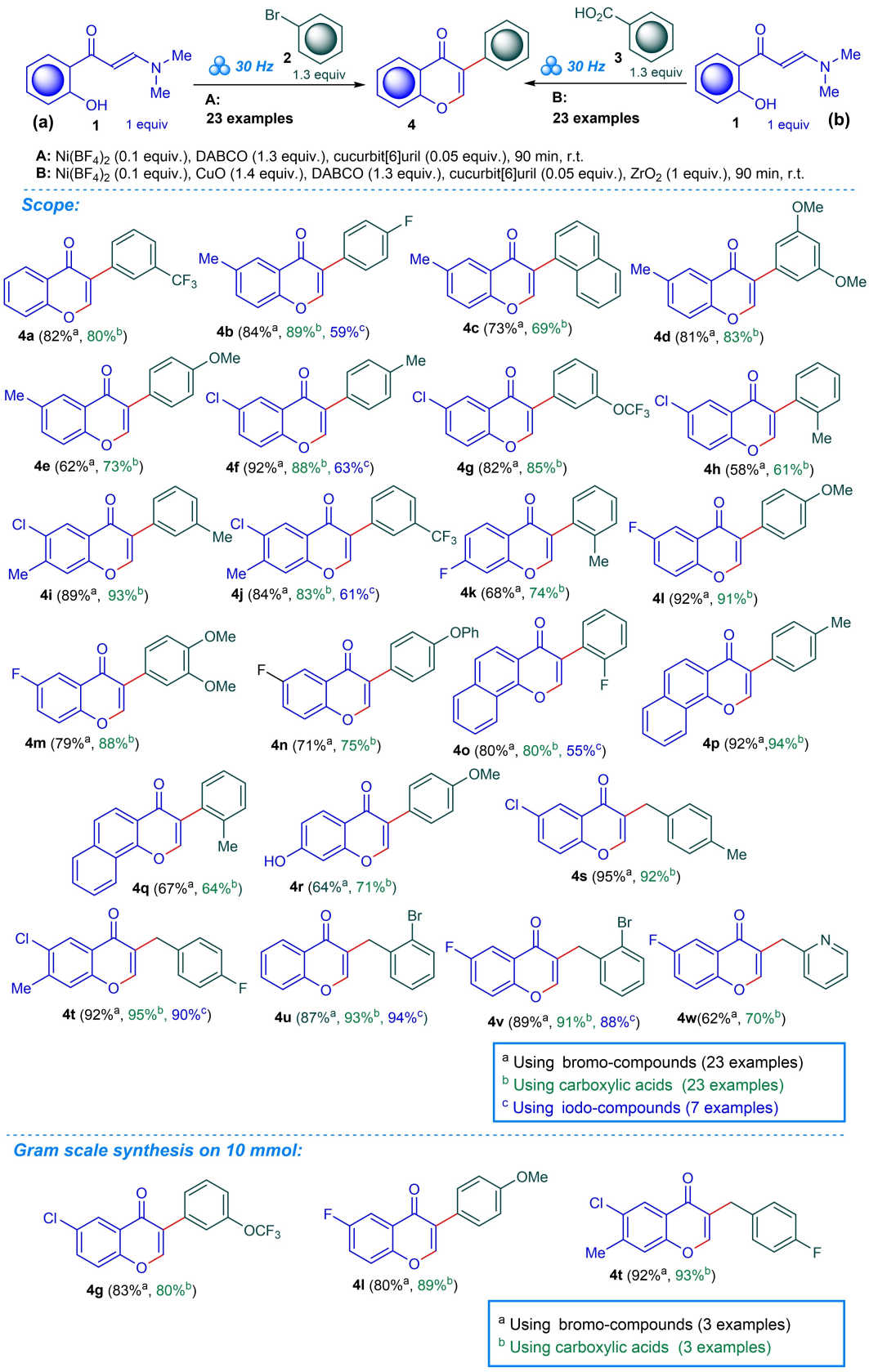
Table 2. Optimization of the reaction conditions.



entry	reaction components	frequency/ time	yield (%) **4 a**
1	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), cucurbit[6]uril (0.05 equiv.), r.t.	30 Hz/ 90 min	0
2	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), CuI (1.4 equiv.), ZrO_2 (1.0 equiv.), cucurbit[6]uril (0.05 equiv.), r.t.	30 Hz/ 90 min	0
3	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), $CuSO_4$ (1.4 equiv.), ZrO_2 (1.0 equiv.), cucurbit[6]uril (0.05 equiv.), r.t.	30 Hz/ 90 min	27
4	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), $CuCl_2$ (1.4 equiv.), ZrO_2 (1.0 equiv.), cucurbit[6]uril (0.05 equiv.), r.t.	30 Hz/ 90 min	21
5	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), $CuBr_2$ (1.4 equiv.), ZrO_2 (1.0 equiv.), cucurbit[6]uril (0.05 equiv.), r.t.	30 Hz/ 90 min	59
6	**$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), CuO (1.4 equiv.), ZrO_2 (1.0 equiv.), cucurbit[6]uril (0.05 equiv.), r.t.**	**30 Hz/ 90 min**	**80**
7	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), CuO (1.4 equiv.), ZrO_2 (1.0 equiv.), cucurbit[7]uril (0.05 equiv.), r.t.	30 Hz/ 90 min	81
8	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), CuO (1.4 equiv.), cucurbit[6]uril (0.05 equiv.), r.t.	30 Hz/ 90 min	0
Reactions in solution			
9	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), CuO (1.4 equiv.), ZrO_2 (1.0 equiv.), cucurbit[6]uril (0.05 equiv.), CH_3CN, reflux.	—/24 h	0
10	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), CuO (1.4 equiv.), ZrO_2 (1.0 equiv.), cucurbit[6]uril (0.05 equiv.), 1,4-dioxane, reflux.	—/24 h	0
11	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), CuO (1.4 equiv.), ZrO_2 (1.0 equiv.), cucurbit[6]uril (0.05 equiv.), DMF, 110 °C.	—/24 h	21
12	$Ni(BF_4)_2$ (0.1 equiv.), DABCO (1.3 equiv.), CuO (1.4 equiv.), ZrO_2 (1.0 equiv.), cucurbit[6]uril (0.05 equiv.), DMA, 100 °C.	—/24 h	33

model ortho-hydroxyarylenaminone by corresponding aryl bromide and thus the formation of the desired model isoflavone **4 a** (Table 1, Entries 13, 16, 17).

We identified the nitrogen-containing ligands (Scheme S5, **L1**, **L2**) which visibly contributed to the efficiency of this synthetic protocol. Unexpectedly, when we switched our attention to cucurbit[n]urils[16] – supramolecular entities capable to encapsulate small molecules, we observed an increase of the overall yields (Table 1, Entries 25–31). In the case of other supramolecular compounds[17] like calix[4]arene (**L8**) calix[5]arene (**L9**) the title reaction experienced a failure. The best outcome for the direct Ni-catalysed arylation of the model ortho-hydroxyarylenaminone by corresponding bromo compound was seen when we took ortho-hydroxyarylenaminone (1.0 mmol, 1.0 equiv.), bromo compound (1.3 equiv.) using $Ni(BF_4)_2$ (0.1 equiv.) as catalyst and as base DABCO (1.4 equiv.); addition of cucurbit[6]uril (0.05 equiv.) permitted to increase visibly the efficiency of this reaction. These conditions allowed for the preparation of the model compound **4 a** in 82% yield (Table 1, Entry 30). Of note, cucurbit[7]uril (Table 1, Entries 28, 29), that due to its larger inner void we considered more a molecular container, appeared similarly operational as cucurbit[6]uril and gave the model compound in 80% yield (Table 1, Entry 29). The same conditions with $Pd(OTf)_2$ and cucurbit[6]uril delivered the model compound in 84% yield (Table 1, Entry 31). However, for the scope and limitation studies we opted for the less costly cucurbit[6]uril and a corresponding nickel salt. When we started the search of the optimum reaction conditions for the second synthetic protocol, the starting point was the conditions that had already been developed; further we manipulated with additives (Table S1, Entries 1–8). We also noted that additives as well as base play a significant role in both synthetic schemes. It is obvious that according to the expected mechanism the aryl part of the carboxylic acid should be allocated onto the Ni-nuclei, this reaction should proceed via the decarboxylation. Thus, we considered copper salts as an additive to promote this transformation (Table S1, Entries 2–8). Finally, applying 1.3 equiv. of DABCO, 1.4 equiv. of CuO, and



Scheme 2. Scope of the isoflavones synthesis.

1.0 equiv. of ZrO_2 which is responsible for the high yield of the corresponding isoflavone (Table S1, Entry 8). Overall, as for the arylation of ortho-hydroxyarylenaminones by carboxylic acids the best outcome of the model reaction was observed when we utilised $Ni(BF_4)_2$ (0.1 equiv.) as a catalyst and DABCO (1.3 equiv.) as a base, cucurbit[6]uril (0.05 equiv.) as a presumptive ligand with CuO (1.4 equiv.) as a reagent for decarboxylative oxidation and ZrO_2 (1.0 equiv.) as an additive (Table S1, Entry 7). Absence of the zirconium oxide led to the failure of the title reaction (Table S1, Entry 8). This reaction requires 1.3 excess of the corresponding acid. The model isoflavone was obtained under these reaction conditions in 80% yield. In both cases with the mentioned reaction compositions the model reactions relinquished to finish in 90 minutes at room temperature. It is noteworthy that the wet conditions (the reactions were performed in numerous organic solvents) were not operational in the case of both synthetic protocols and did not deliver any product. The reactions in a solution for both protocols experienced a failure.

To our delight, the diverse set of aryl bromides and benzyl bromides (Scheme S1) as well as aromatic and benzyl carboxylic acids (Scheme S3) were reactive within these synthetic protocols and afforded a library of twenty-three chromone derivatives. The developed protocols exhibited functional group compatibility and a broad substrate scope with respect to both counterparts. Such functional groups on the phenyl framework as Me, CF_3, OMe, OPh, OCF_3, Br, F and 2-naphtyl as well as several benzyls including 2-methylen-pyridine showed tolerance for the title synthetic protocols. Of note, we also tested the behaviour of the corresponding iodides (Scheme S4) within the frames of the first protocol; for aryl iodides the titled protocol was operational enabling the preparation of the compounds **4b**, **4f**, **4j**, **4o**, albeit in lower yields. In the case of the used benzyl iodides, we observed no significant drop of the yields (**4t**–**4v**). It is important to highlight the high efficiency of these synthetic methodologies enabling the preparation of the final products in 58–93% yields. These two synthetic protocols not only showed a tolerance towards a broad range of functional groups but were also scalable to 10 mmol quantities and enabled the preparation of three representatives in gram quantities. Unfortunately, several heterocyclic reagents we attempted to introduce into this protocol experienced a failure. In turn, in the case of the cinnamyl bromides and cinnamic acids, we did not observe the formation of the desired products.

Density functional theory calculations are performed to gain mechanistic insight into the reaction. The mechanism starts with the coordination of ortho-hydroxyarylenaminones with $Ni(BF_4)_2$ to generate **vdW1**. In the starting $Ni(BF_4)_2$, each BF_4 has two fluorine atoms interacting with the metal center (the geometry around Ni is square planar). When ortho-hydroxyarylenaminones binds with the metal center, it causes the interaction of one BF_4 unit to break apart partially. In the resultant complex **vdW1**, olefin carbon is coordinating with the metal atom on one side whereas the other side of the Ni atom, is occupied by two fluorine atoms of a BF_4 ligand. The energy released in this step is 27.28 kcal mol^{-1}. Next, cyclization takes place in **vdW1** when oxygen atom attacks on an olefinic carbon with concomitant loss of BF_4 anion ligand from the metal center. The activation barrier for this cyclization is 40.26 kcal mol^{-1}. Ni atom polarizes the C=C bond for nucleophilic attack but the barrier is still high probably due to two main reasons (a) a ligand is lost from the metal center (b) the attacking nucleophile (OH) gets positive charge as a result of the attack. The O–C bond distance in the transition state is 1.47 Å. The transition state is late in nature where the geometry of the transition state is resembling more to the product than the reactant. Such a reaction is expected to be endothermic according to Hammond postulate. Indeed, this is the case, where the energy of the reaction is 39.44 kcal mol^{-1}. The **Int1** (product of the cyclization step) is then converted to **Int2** when phenyl bromide interacts with the metal center. This interaction takes places through bromine atom of phenyl bromide with the Ni atom. The **Int2** is marginally lower in energy than **Int1** (by 0.68 kcal mol^{-1}). A transition state for oxidative addition of phenyl bromide on nickel atom through concerted mode is located at a barrier of 7.42 kcal mol^{-1} from **Int2**. The C–Br bond is elongated to 2.11 Å from 1.95 Å in **Int2**. The C–Ni and Br–Ni bond lengths in the **TS2** are 2.17 and 2.30 Å. The oxidative additions step is exothermic by 2 kcal mol^{-1}. The next step involves the migration of NMe_2 group from the from the freshly formed ring to the metal center (Ni) but before entering this step, a slight reorientation of the ligands around the metal center is observed to generate **Int4** from **Int3**. In turn, the structure **Int4** is 3.90 kcal mol^{-1} higher in energy than **Int3**.

The migration of NMe_2 group from carbon to metal center has an activation barrier of 41.93 kcal mol^{-1} (From **Int4**). The C–N and M–N bond distances are 2.55 and 1.85 Å respectively. The barrier is quite high which is mainly due to the significant breakage of C–N bond in the transition state. The C–N bond distance in the transition state is 2.55 Å. Moreover, with the breakage of the C–N bond, the vicinal C–M bond is also affected significantly. Both these factors lead to increase in the kinetic barrier for this migration. This migration is slightly endothermic by 0.51 kcal mol^{-1}. In the subsequent step, a hydrogen atom from the carbon metal center is shifted to the amine moiety which results in regeneration of the double bond. A transition state for this proton shift is

located at a barrier of 7.50 kcal mol^{-1} from **Int6**. Moreover, the product of the reaction (**Int7**) lies about 4.43 kcal mol^{-1} lower in energy than **Int6**. The C–H and N–H distances in **TS4** are 1.23 and 1.53 Å, respectively. These two steps (involving **TS3** and **TS4**) can theoretically take place in a single step where NMe_2 and H can simultaneously leave the vicinal carbons (through a four membered transition state) in the form of NMe_2H but all attempts to locate such transition state experienced a failure. It has been previously shown that such transition states generally have very high kinetic demand (>50 kcal mol^{-1}). Therefore, it is believed that this two-step process is kinetically favorable as compared to a single step elimination of NMe_2H.

The last step in this cycle is reductive elimination. The reductive elimination step requires proper placement of the leaving groups. **Int 7** generated from the last step undergoes a reorientation of ligands to generate **Int8**. Formation of **Int8** from **Int7** is thermodynamically favorable by 2.46 kcal mol^{-1}. A transition state for the reductive elimination is located at a barrier of 1.10 kcal mol^{-1} from **Int8**. The kinetic barrier for the reductive elimination is quite low because the leaving groups are well oriented in close proximity of each other, and there is little movement for these groups to eliminate. The concerted transition state for reductive elimination regenerated Ni^{2+} from Ni^{4+}.[18] The C–C bond forming during this step has a bond length of 2.27 Å in the transition state whereas the C–Ni bond lengths (being broken) are 1.94 Å each. The reductive elimination step has high exothermicity; the energy of reaction for this step is −45.18 kcal mol^{-1} (Figure 1).

The synthesis of isoflavones via the arylation by carboxylic acids most probably proceeds the similar pathway, that is presented in the Scheme 3. The only difference is that the first step in this cascade involves copper oxide which promotes the oxidative decarboxylation. Copper is a metal of choice for the many decarboxylation reactions.[19] Of note, not all known cases of decarboxylation demand elevated temperatures, there are examples decarboxylation reactions occurring under photoredox as well as mechano-milling conditions at room temperature.[20]

Conclusion

Finally, in order to exclude the possible participation of the chromone as an intermediate in both scenarios, the chromone **8** was reacted with 1-bromo-4-fluorobenzene and 4-fluorobenzoic acid under the developed optimum reaction conditions (Scheme 4a,b). The title reactions experienced a failure.

In summary, we successfully developed for the first time the direct mechanochemical Ni-catalysed arylation of ortho-hydroxyarylenaminones by utilising bromo compounds and carboxylic acids. These new strategies allowed for the efficient and concise preparation of many structurally diverse isoflavones. We performed an in-depth study of the application range of the strategies developed and extended the substitution schemes of chromone derivatives and substituted aryl moieties. We also compared the advantages of both approaches in terms of efficiency and scalability.

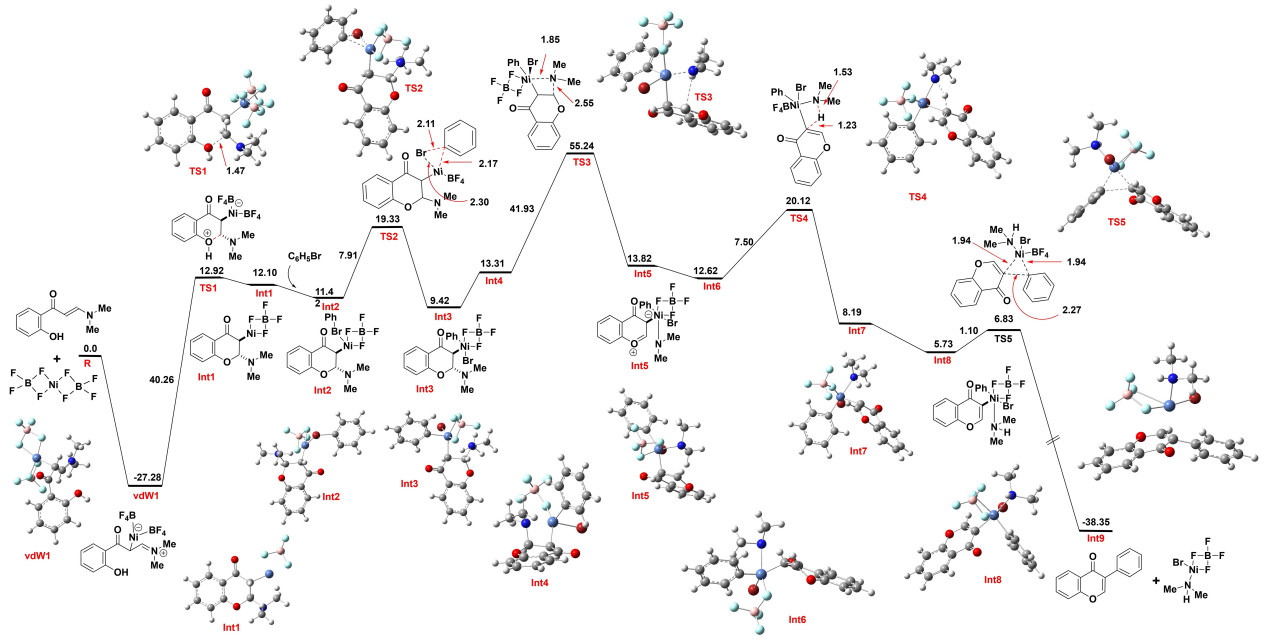
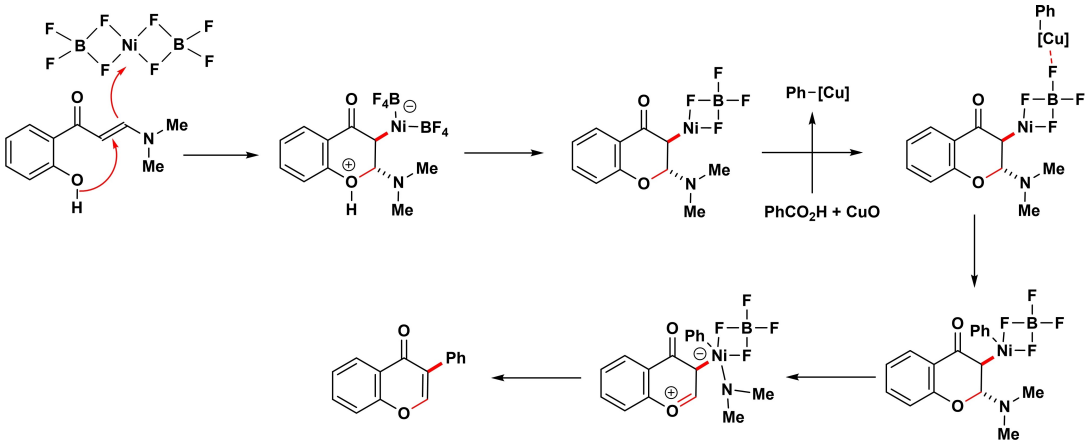
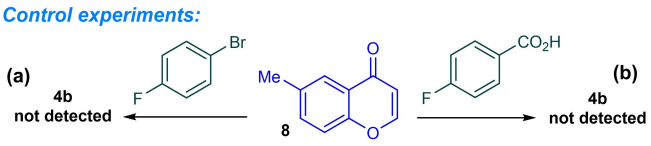


Figure 1. Energy profile of Ni (II) catalyzed coupling of ortho-hydroxyarylenaminones with aryl-bromide.



Scheme 3. Proposed reaction mechanism for carboxylic acids.



Scheme 4. Control experiments.

Experimental Section

General: Commercially available starting materials, reagents, catalysts, anhydrous and degassed solvents were used without further purification. Flash column chromatography was performed with Merck Silica gel 60 (230–400 mesh). The solvents for column chromatography were distilled before the use. Thin layer chromatography was carried out using Merck TLC Silica gel 60 F_{254} and visualized by short-wavelength ultraviolet light or by treatment with potassium permanganate ($KMnO_4$) stain. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker 250, 400 and 500 MHz at 20 °C. All ^1H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for $CHCl_3$ (7.26 ppm) and DMSO (2.50 ppm). All $^{13}C\{^1H\}$ NMR spectra were reported in ppm relative to residual $CHCl_3$ (77.00 ppm) or DMSO (39.70 ppm) and were obtained with ^1H decoupling. Coupling constants, *J*, are reported in Hertz (Hz). Gas chromatographic analyses was performed on Gas Chromatograph Mass Spectrometer GCMS-QP2010 Ultra instrument. Mechanochemical synthesis was performed using the Retsch MM400 mill using the standard kit. Liquid chemicals were dosed using gas tight micro syringes. Isolation of obtained compounds was achieved by column chromatography on Silica gel. All commercially available compounds were purchased from appropriate vendors.

General procedure for the synthesis of isoflavones 4 by the reaction of ortho-hydroxyarylenaminones 1 and bromides 2. In a dry box, to 5 mL grinding vessel (made of stainless) equipped with two balls (made of stainless, diameter: 5 mm) was placed consequently ortho-hydroxyarylenaminone (1.0 mmol, 1.0 equiv.), $Ni(BF_4)_2$ (23 mg, 0.1 mmol, 0.1 equiv.), DABCO (146 mg, 1.3 mmol, 1.3 equiv.), cucurbit[6]uril (50 mg, 0.05 mmol, 0.05 equiv.); then an appropriate bromo substrate (1.3 mmol, 1.3 equiv.) was added and the reaction vessel was properly capped. Finally, the reaction vessel was installed on the mill and subjected to milling at 30 Hz for 90 minutes. After completion of the reaction, the content of the vessel was generously treated with distilled water, filtrated and finally properly dried in vacuum. The resulted crude was directly subjected to gradient flash chromatography on silica gel to isolate the desired chromone derivative.

The gram scale synthesis was performed on 10 mmol of the starting ortho-hydroxyarylenaminone in 25 mL grinding vessel using two 10 mm balls.

The arylation by corresponding iodo-compounds was achieved following the same procedure.

General procedure for the synthesis of isoflavones 4 by the reaction of ortho-hydroxyarylenaminones 1 and carboxylic acids 3. In a dry box, to 5 mL grinding vessel (made of stainless) equipped with two balls (made of stainless, diameter: 5 mm) was placed consequently ortho-hydroxyarylenaminone (1.0 mmol, 1.0 equiv.), $Ni(BF_4)_2$ (23 mg, 0.1 mmol, 0.1 equiv.), CuO (111 mg, 1.4 mmol, 1.4 equiv.), ZrO_2 (122 mg, 1.0 mmol, 1.0 equiv.), DABCO (146 mg, 1.3 mmol, 1.3 equiv.), cucurbit[6]uril (50 mg, 0.05 mmol, 0.05 equiv.); then an appropriate carboxylic acid (1.3 mmol, 1.3 equiv.) was added and the reaction vessel was properly capped. Finally, the reaction vessel was installed on the mill and subjected to milling at 30 Hz for 90 minutes. After completion of the reaction, the content of the vessel was generously treated with distilled water, filtrated and finally properly dried in vacuum. The resulted crude was directly subjected to gradient flash chromatography on silica gel to isolate the desired chromone derivative.

The gram scale synthesis was performed on 10 mmol of the starting ortho-hydroxyarylenaminone in 25 mL grinding vessel using two 10 mm balls.

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