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# Domino Transformations of 3-Fluoro-1,2,4-Triazine Derivatives towards Spirocyclic and Fused Pyridines

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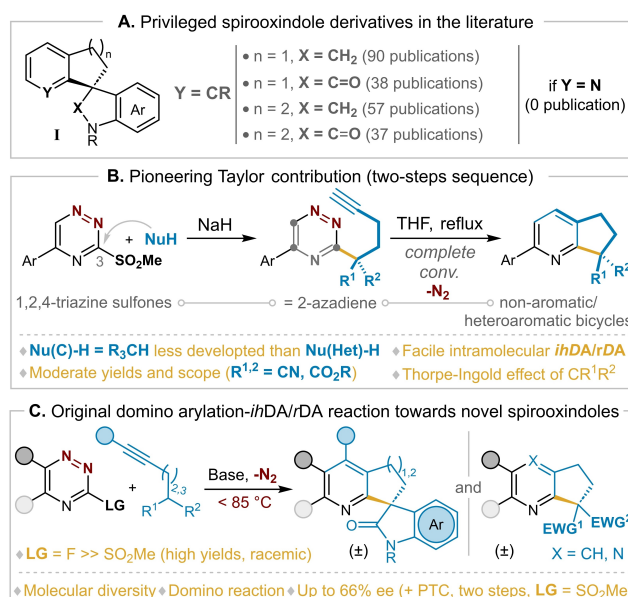
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**Abstract:** A domino  $S_NAr$ -*ihDA/rDA* reaction was developed from rarely exploited 3-fluoro-1,2,4-triazines with bifunctional alkyne tethered nucleophiles to construct various fused non-aromatic/heteroaromatic bicycles in yields ranging from 56 to 99%, notably within the family of valuable spirooxindole derivatives. In this study, the challenging enantioselective phase-transfer catalyzed arylation of a sulfonyl-triazine was also demonstrated with up to 66% ee. In both racemic and asymmetric processes, the nature of the leaving group at C3 was key to successfully achieve these sequences.

**Keywords:** Aromatic substitution; Cycloaddition; Domino reactions; Phase-transfer catalysis; Spiro compounds



**Scheme 1.** Towards fused non-aromatic/heteroaromatic bicycles: background and new plans.

Spirooxindoles are the core structures of several bioactive and naturally occurring compounds.<sup>[1]</sup> In that domain, the oxindole-derived tetracyclic architectures depicted in Scheme 1A (**I**, Y=CR) have elicited various investigations aiming either at the elaboration of bioactive products in this family, or the development of original methodologies allowing to construct various analogues.<sup>[2,3]</sup> Although pyridine derivatives are recognized as privileged structures in medicinal chemistry,<sup>[4]</sup> this azaarene is surprisingly absent in tetracyclic compounds such as **I** (Y=N) likely due to the lack of suited synthetic strategy.

The domino *inverse-electron-demand hetero-Diels-Alder/retro-Diels-Alder (ihDA/rDA)* reaction taking place between a 1,2,4-triazine, as a 2-azadiene, and a dienophile is a well-established and powerful cyclo-

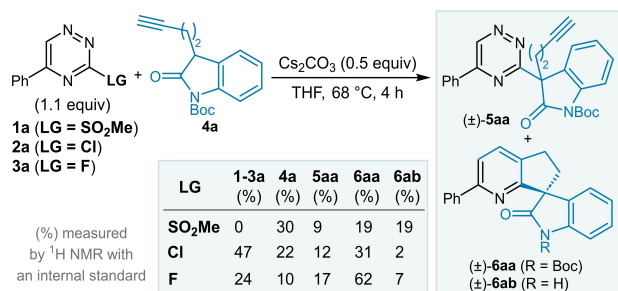
addition strategy to construct pyridine derivatives (Scheme 1B).<sup>[5]</sup> A significant amount of work has been dedicated to the development of  $S_NAr$  reaction at C3 of 3-methylsulfonyl-1,2,4-triazines by means of bifunctional hetero-nucleophiles (**Nu(Het)-H**, Nu=O, S, N)/dienophile,<sup>[6]</sup> allowing the subsequent, often stepwise, intramolecular *ihDA/rDA* reaction of an alkyne tether thereby constructing biorelevant fused non-aromatic/heteroaromatic bicycles.<sup>[5]</sup>

However, a similar strategy with a carbon-nucleophile (**Nu(C)-H = R<sub>3</sub>CH**)/dienophile is much less developed. Taylor has elegantly pioneered the nucleophilic

addition of malonate derivatives to 1,2,4-triazine sulfones (Scheme 1B).<sup>[7]</sup> In a second step, the authors demonstrated that the intramolecular *ihDA/rDA* reaction of the alkyne tether gave a five-membered ring formation benefited from a Thorpe-Ingold effect. Accordingly, the cycloaddition occurred at a rather low temperature (<70 °C), in contrast to the 150–200 °C usually required in other instances.<sup>[5]</sup> Unfortunately, the scope of this original C–C bond construction and stepwise strategy is rather limited, and led to yields from low to moderate (<50%) over two steps with regard to the nature of nucleophiles (good yield of 80% was only obtained with a malononitrile derivative).

In line with our program aiming at exploring the 3D-chemical space of valuable fused non-aromatic/hetero-aromatic bicycles,<sup>[8]</sup> we questioned whether well-designed bifunctional oxindole and malonate derivatives could add to C3 of activated 1,2,4-triazines under soft basic conditions (Scheme 1C). Thus, the subsequent intramolecular *ihDA/rDA* reaction could be triggered by the alkyne pendant in order to access, in a practical domino fashion, spiro-cyclic and unprecedented structures with a pyridine ring akin to **I** (Y=N). To reach this objective and overpass the actual limitation of the S<sub>N</sub>Ar reaction on 3-methylsulfonyl-1,2,4-triazines with carbon-nucleophiles, the nature of the leaving group was questioned. According to this endeavor, we are delighted to report our achievement in this direction which displays salient characteristic such as (1) the original and efficient use of 3-fluoro-1,2,4-triazines as bifunctional platform,<sup>[9]</sup> (2) whose reactivity allowed an efficient domino S<sub>N</sub>Ar-*ihDA/rDA* reaction to take place overcoming the previously observed limitations, (3) onto cyanomalonate and oxindole C-nucleophile derivatives en route to spirocyclic products in this last case. Furthermore, the first use of an 1,2,4-triazine in an enantioselective arylation sequence by phase-transfer catalysis (PTC) is reported.<sup>[10,11]</sup>

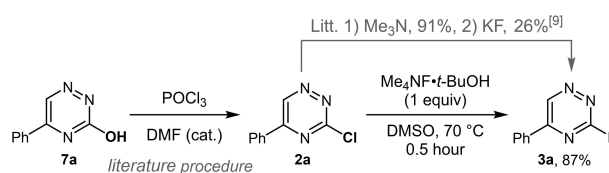
At the onset, the required bifunctional alkyne-tethered-oxindole derivative **4a** was synthesized by a straightforward alkylation of the oxindole, followed by a *N*-Boc protection (Scheme 2, see Supplementary Information – SI). Then, a mixture of triazine sulfone **1a** (1.1 equivalent) and oxindole **4a** has been heated in



Scheme 2. Preliminary investigations.

THF in the presence of cesium carbonate (0.5 equivalent, *vide infra*) as a base, in order to generate a cesium enolate as transient species. The S<sub>N</sub>Ar reaction took place as testified by the formation of a small amount of the addition-product **5aa** (9% measured by <sup>1</sup>H NMR). It was also observed 19% of both the cycloaddition *N*Boc spirocyclic product **6aa** and the corresponding *NH*-derivative **6ab**, likely originated from a base-promoted *N*-Boc deprotection of **6aa**.<sup>[12]</sup> This result shows that a rather facile intramolecular *ihDA/rDA* reaction occurred in a domino fashion even at 68 °C despite the steric bulk of the oxindole moiety. Unfortunately, several unidentified compounds were also observed on the crude NMR mixture among which 30% of starting oxindole **4a** was recovered without any traces of the triazine sulfone **1a**. On the other hand, the 3-chloro-triazine **2a** was investigated as starting material and the formation of the expected products **5aa**, **6aa** and **6ab** were observed but in moderate yields (14%, 31%, 2% respectively). In this case, the 3-chloro-triazine **2a** proved to be less reactive and more stable as 47% of **2a** was recovered. However, the oxindole **4a** was largely consumed (22% left). Obviously, a balance between reactivity and stability of starting materials has to be found to perform this domino sequence. To our delight, the 3-fluoro-triazine **3a** provided products **5aa**, **6aa** and **6ab** in 4 hours in good yields of 17%, 62% and 7% respectively, and a rather clean crude NMR spectrum. This preliminary investigation highlighted a marked and unique reactivity of 3-fluoro-triazine **3a** which allows the orchestration of the multiple C–C bond formation of the domino S<sub>N</sub>Ar-*ihDA/rDA* reaction from the rather sterically hindered bifunctional oxindole-alkyne **4a**, without a significant decomposition of the otherwise base sensitive starting materials.

Despite the common use of 3-sulfone-1,2,4-triazines as S<sub>N</sub>Ar partner, the similar exploitation of 3-fluoro-1,2,4-triazines has only been investigated in a S<sub>N</sub>Ar reaction with ammonia on a single starting material (*i. e.* **3a**).<sup>[9]</sup> Unfortunately, the synthesis of the 3-fluoro-1,2,4-triazine derivative **3a** required two steps from 3-chloro-triazines **2a** with a low overall yield (Scheme 3).<sup>[9]</sup> After some efforts, it was found that the Sandford's procedure,<sup>[13]</sup> by means of Me<sub>4</sub>NF•*t*-BuOH reagent, allowed a smooth transformation of the chloro-precursor **2a** into the 3-fluoro-triazine **3a** in a high yield of 87% on multi-millimoles scale and in a short period of time. Accordingly, we built a library of novel 3-fluoro-



Scheme 3. Access to 3-fluoro-1,2,4-triazine precursors.

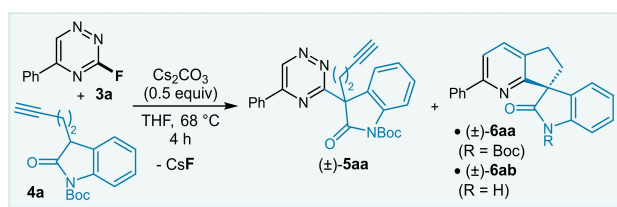
triazines **3** by this sequence en route to the investigation of their unique reactivity (see SI and Scheme 4), from a series of 3-chloro triazines **2** which was prepared according to known procedures from the corresponding alcohols such as **7a** (or the corresponding tautomer), either commercially available or easily accessible.

First of all, we optimized this original strategy leading to novel spirooxindole **6aa** (Table 1). For this purpose, we paid attention on the global  $S_NAr$  yield being the sum of products **5aa**, **6aa** and **6ab**. Cesium carbonate proved to be the best base tested for this transformation in 4 hours of reaction (entries 2–4, see SI for details). By increasing the amount of  $Cs_2CO_3$  from 0.5 to 1.5 equivalents, only a slight rise of yield was observed for the formation of **5aa–6aa–6ab** mixture at 68 °C (81% versus 88% overall yields measured by  $^1H$  NMR, entries 1 and 2). Worthy of note, the use of 0.5 equivalent of  $Cs_2CO_3$  minimized the decomposition

of starting materials (entry 1, 28% of **3a** and 10% of **4a** left). However, a lower amount of  $Cs_2CO_3$  (0.2 equiv.) led to a slower reaction (68% **5aa–6aa–6ab**, entry 5). Using  $CsHCO_3$  (0.5 equiv.) instead of  $Cs_2CO_3$  afforded a modest transformation (entry 6, 18% of **5aa–6aa–6ab** mixture). At that point, we hypothesized that the liberated fluorine anion can also deprotonate the oxindole **4a**. Indeed, the use of  $CsF$  (1.5 equiv.) instead of  $Cs_2CO_3$  proved to be a competent base for this domino transformation with a slower reaction rate (**5aa–6aa–6ab** mixture: 71% in 4 hours and 95% in 16 hours, entries 7–8), although a significant Boc-deprotection event into **6ab** was measured (24% after hours 16 hours). Neither transformation nor decomposition of starting materials was observed without base underlying that the *ihDA/rDA* cycloaddition benefited from the intramolecular process (entry 9). Eventually, other solvents such as acetonitrile and the greener 2-methylTHF (entries 10–11, **5aa–6aa–6ab** 73–72% overall yields) could be used as well, but the less polar aromatic solvents such toluene gave lower yields (entries 12–13). Eventually, the fluoro-triazine platform **3a**, was completely transformed into the cycloaddition spiro-product **6aa** in excellent 89% NMR yield in only 4 hours by rising the temperature from 68 to 80 °C (entries 14).

With this optimized and convenient protocol in hands, the model substrate **6aa** was obtained in 88% isolated yield on a small scale and 76% on 1 mmol scale (Scheme 4A). Controlled experiments with *NH* and *NMe* oxindoles **4b–c** showed formation of traces of products **6ab–6ac**, demonstrated thereby the importance of the *NBoc* moiety in order to decrease the  $pK_a$  of the hydrogen  $\alpha$  to the lactam function. However, a simple *NBoc* deprotection in the presence of TFA allowed the synthesis of the *NH*-oxindole **6ab** in 93% yield. Substituted *NBoc*-oxindole precursors **4d–e** were also tolerated to give rise to the formation of the corresponding products **6ad–6ae** in high 80–98% yields. Functionalized alkyne precursors **4f–g** furnished the corresponding spirocyclic compounds with a methyl (**6af**, 87%) and a bromine substituent (**6ag**, 68%) at C4 of the pyridine ring. Interestingly, from a synthetic strategy point of view, this latter case **6ag** may offer further functionalization at C4 through various crossed coupling reactions.<sup>[6b]</sup> However, with these more substituted alkyne precursors, an extra heating time (4–19 hours after filtration of  $Cs_2CO_3$ ) was required in order to complete the *ihDA/rDA* sequence. 1,2,4-triazine starting materials **3b–g**,<sup>[14]</sup> variously substituted at C5 by aryl (**3b–e**) or heteroaryl (**3f–g**) pendants, provided uneventfully the corresponding spirocyclic pyridines **6ba–6ga** in yields ranging from 76% to 91% (Scheme 4B). The C5-6 disubstituted triazine **3h** was also easily transformed into the pyridine **6ha** in an excellent 97% yield. Accordingly, any early modification of both partners **3** and **4** can be exploited in order

**Table 1.** Optimization of the domino  $S_NAr$ -*ihDA/rDA* reaction.



Entry	Deviation from initial conditions	Yield (%) <sup>[a]</sup> <b>5aa, 6aa, 6ab</b> <sup>[b]</sup>
1	None	17, 62, 7
2	$Cs_2CO_3$ (1.5 equiv.) as a base	18, 70, 10
3	$K_2CO_3$ (1.5 equiv.)	15, 36, 4
4	$K_3PO_4$ (1.5 equiv.)	14, 64, 15
5	$Cs_2CO_3$ (0.2 equiv.)	18, 43, 7
6	$CsHCO_3$ (0.5 equiv.)	7, 10, 1
7	$CsF$ (1.5 equiv.), 4 h	26, 41, 4 <sup>[c]</sup>
8	$CsF$ (1.5 equiv.), 16 h	2, 69, <sup>[d]</sup> 24
9	No base	0, 0
10	In 2-MeTHF as solvent	14, 50, 9
11	In MeCN	7, 54, 21
12	In PhMe	7, 20, 15
13	In $PhCF_3$	7, 31, 14
14	80 °C instead of 68 °C	traces, 89, 8

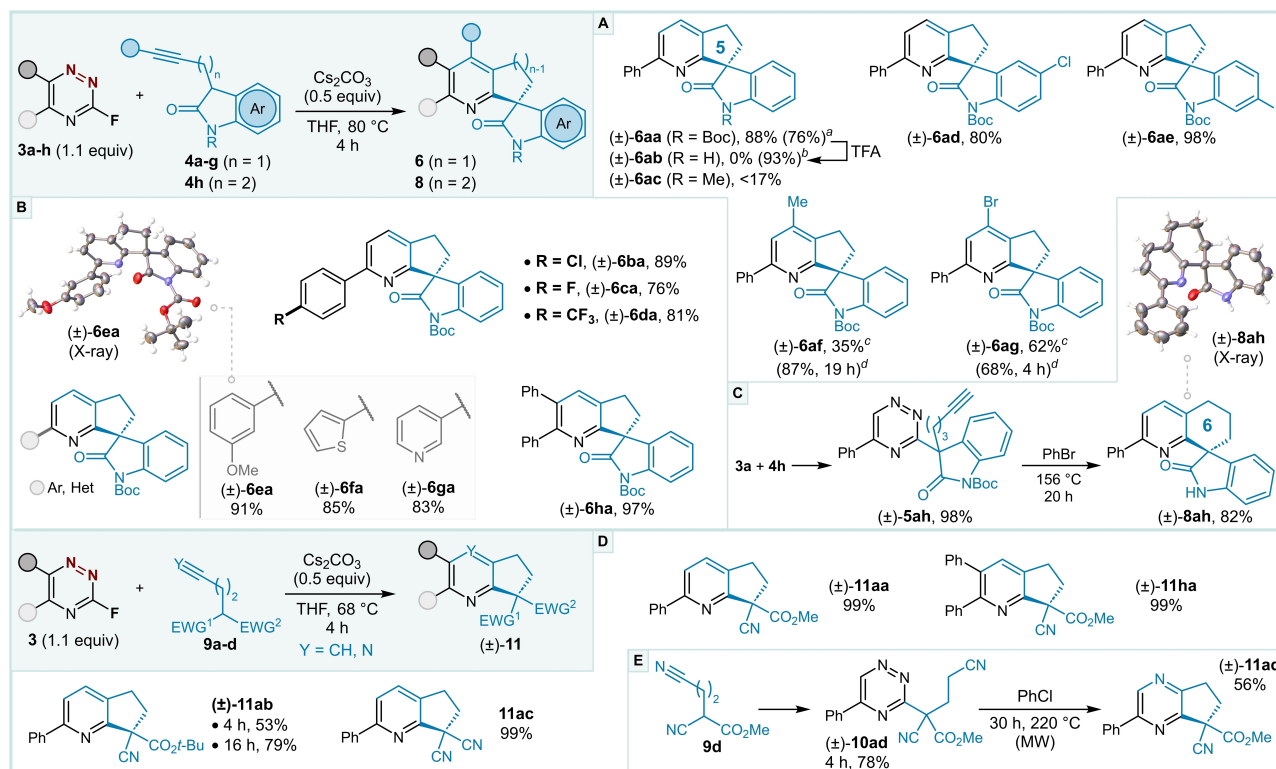
Reaction performed at 0.1 M (versus **4a**) with triazine **3a** (1.1 equiv.) on 0.1–0.2 mmol scale at 68 °C (oil bath temperature).

<sup>[a]</sup> NMR yield determined on the crude by  $^1H$  NMR and an internal standard.

<sup>[b]</sup> Remaining **3a**, **4a** (estimated by  $^1H$  NMR and an internal standard) in entry 1 (28%, 10%), entries 2 and 14 (traces), entry 3 (62%, 43%), entry 4 (17%, 0), entry 5 (56%, 42%), entry 6 (90%, 61%), entry 7 (65%, 31%), entry 8 (11%, 5%).

<sup>[c]</sup> **6aa** (20%), **6ab** (47%) in the presence of  $CsHCO_3$  (1 equiv.) and  $CsF$  (1.5 equiv.).

<sup>[d]</sup> 24% of *NH*-spiro-product **6ab** in 16 hours but traces in 4 hours.



**Scheme 4.** Scope and limitation. Reaction performed at 0.1 M (*versus* 4) on 0.1–0.2 mmol scale in THF as solvent; isolated yields (%) after purification by column chromatography. [a] Carried out on 1 mmol scale. [b] *N*-Boc deprotection of 6aa: Trifluoroacetic acid (TFA, 12 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 20 °C. [c] 65% and 15% of uncyclized addition products 5af and 5ag were also observed respectively after 4 hours at 80 °C. [d] Isolated yields of 6af and 6ag after 19 h and 4 h respectively at 80 °C in THF after filtration of the mineral base.

to eventually realize a convergent synthesis of these spiro-products 6 thanks to the key domino *S<sub>N</sub>Ar-ihDA/rDA* reaction en route to chemical diversity. Furthermore, we tackled the more challenging formation of fused 6,6-membered ring by means of a homologated oxindole-alkyne precursor 4h (Scheme 4C).<sup>[5,7b]</sup> Albeit the *S<sub>N</sub>Ar* reaction took place efficiently, to give 5ah in a high 98% NMR yield, the *ihDA/rDA* sequence did not occur at 80 °C. After a simple filtration of the mineral base, the crude product 5ah cyclized at 156 °C to form the six-membered fused bicyclic architecture in a high over all 82% isolated yield as a *NH*-product 8ah (ascertained by X-ray analyses),<sup>[14]</sup> because the *N*Boc did not survive these heating conditions.

In order to probe and expand the scope of the domino synthesis of these non-aromatic heteroaromatic compounds, we used cyanomalonate 9a and malononitrile 9c substituted by an alkyne pendant (Scheme 4D). A facile domino *S<sub>N</sub>Ar-ihDA/rDA* reaction took place in 4 hours to provide products 11aa, 11ha and 11ac in excellent 99% isolated yields. More hindered cyano *tert*-butyl esters 9b was also tolerated, to give product 11ab in good 79%, at the expense of a longer reaction time of 16 hours likely due to a slower *S<sub>N</sub>Ar* step. Interestingly, the cyanomethyl ester 9d, having nitrile

pendant potentially sensitive to a retro-Michael event, led to a smooth aromatic substitution reaction to form the corresponding addition product 10ad in 78% yield (Scheme 4E). Although the nitrile functional group is known to be a very challenging dienophile with 1,2,4-triazines,<sup>[5]</sup> usually requiring a rather rigid C(*sp*<sup>2</sup>)-rich backbone,<sup>[15]</sup> a slow but successful cycloaddition reaction took place at 220 °C in chlorobenzene as solvent, upon microwave heating, furnishing the corresponding pyrazine 11ad in descent 56% yield.

In spite of numerous asymmetric processes were developed for C–C bond formation upon phase-transfer catalysis (PTC) conditions,<sup>[10]</sup> the enantioselective arylation reaction has been achieved only few times.<sup>[11]</sup> The pioneering contribution of Jørgensen highlighted the possibility of PT-catalyzed enantioselective arylation of keto esters by means of electron-poor fluoro-nitroarenes and a fluoro-pyrimidine.<sup>[16]</sup> This sequence was extended to  $\alpha$ -amino acids and 3-aryloxindoles as nucleophiles and arene chromium complexes as electrophiles by Maruoka.<sup>[17]</sup> Interestingly, Togni reported a racemic PT-catalyzed *S<sub>N</sub>Ar* involving 2,4-dichloropyrimidines as electrophiles but a single example led to the corresponding 3-pyrimidinyl oxindole in 60% ee.<sup>[18]</sup>

Based on this background knowledge, we wondered whether an enantioselective heteroarylation step could be integrated in our domino  $S_NAr$ -*ihDA/rDA* reaction based on a PTC approach, highlighting thereby 1,2,4-triazines electrophiles are new players in that field. Considering the challenge of this approach, cyanomalonate derivative **9a** was chosen as model substrate at first. In our hands, and after an intensive screening of PTC conditions, including variation of chiral ammonium salts and nucleophiles, rather disappointing yields and ee were obtained (see SI for the overall investigation). Eventually, to our delight, the Lygo's *tropos*-catalyst **12** outperformed markedly the other organocatalysts.<sup>[19]</sup> The addition of methyl cyanomalonate **9a** took place efficiently even at 0 °C. A two steps sequence was used, including a filtration of the insoluble base before heating for the subsequent cycloaddition steps, in order to prevent degradation events (Scheme 5A). With this tactic, 10 mol% of the PT-catalyst **12** and  $Cs_2CO_3$  (1.5 equiv.) allowed an enantioselective  $S_NAr$  reaction of cyanomalonate **9a** to sulfone triazine **1a** followed by the likely non-racemizing *ihDA/rDA* sequence, to furnish the fused-pyridine product **11aa** in 59% ee and an overall 99% yield. However, to our surprise, although fluoro triazine **3a** proved to be very reactive in these conditions (with  $Cs_2CO_3$  at 0 °C), a dropped in ee to 30% was observed. Moreover, the chloro triazine **2a** gave rise to **11aa** in 40% ee albeit in low 43% yield. It seems that the nature of the C3-leaving group markedly influences the enantioselective outcome of the arylation reaction, without being favored for **3a** with the expected best leaving group (LG=F). Nevertheless, the promising outcome with triazine sulfone **1a** was slightly improved to 66% ee by performing the reaction at -20 °C in toluene by means of  $KOH/K_2CO_3$  as bases (lower temperature giving a much slower process). With the more hindered

oxindole **4a** as nucleophile, the PT-catalyzed arylation reaction took place to sulfone triazine **1a** in moderate but promising yields of 39% (**6aa**, 58% yield). The more reactive fluoro triazines **3a** allowed an asymmetric reaction at 0 °C furnishing thereby similar 40% ee (**6aa**, 53% yield).

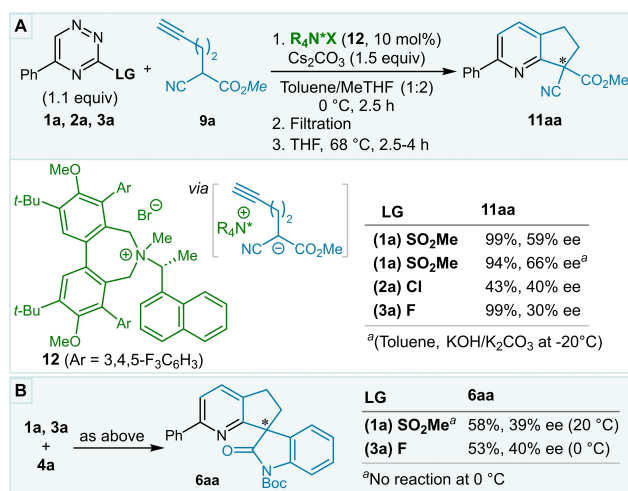
In conclusion, we described the superiority of 3-fluoro-1,2,4-triazine platforms to achieve an original domino  $S_NAr$ -*ihDA/rDA* reaction with only 0.5 equivalent of  $Cs_2CO_3$  which opens a straightforward route to non-aromatic/heteroaromatic bicycles, among which the construction of valuable spirooxindole architectures was allowed. An enantioselective PT-catalytic approach afforded a proof of principal of the first use of a 1,2,4-triazine as a new player in enantioselective heteroarylation sequence in up to 66% ee, and showed a more puzzling leaving group effect at C4 (F *versus*  $SO_2Me$ ) on both reactivity and enantioselectivity. The development and improved construction and use of 3-fluoro-1,2,4-triazine derivatives in heterocycles synthesis is currently under investigation with a focus on asymmetric processes.

## Experimental Section

**Typical procedure for the synthesis of the fused non-aromatic/heteroaromatic spirocycle 6aa.** In a microwave reaction vial equipped with a cross shaped stir bar, oxindole derivatives with an alkyne moiety **4a** (30.0 mg, 0.105 mmol, 1.0 equiv.), 3-fluoro-1,2,4-triazine **3a** (20.3 mg, 0.116 mmol, 1.1 equiv.) were dissolved in 1.05 mL of anhydrous THF (0.1 M) under nitrogen. Then,  $Cs_2CO_3$  (17.1 mg, 0.053 mmol, 0.5 equiv.) was added in one portion. The vial was sealed and heated for 4 h at 80 °C (oil bath temperature). The yellow color of the reaction mixture turned to a slight brown solution. At room temperature, the reaction mixture was filtered out on a short pad of silica gel and rinsed with 10 mL of EtOAc as eluent. The filtrate was concentrated under reduced pressure, and the NMR yield was measured on the crude product by <sup>1</sup>H NMR by means of  $Bn_2O$  as an internal standard. The residue was purified by flash column chromatography on silica gel to afford spirooxindole **6aa** (38.3 mg, 88%).

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Scheme 5. Enantioselective phase-transfer catalysis.

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