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RESEARCH ARTICLE OPEN ACCESS

An Asymmetric Aryne-capture Cascade Process: Tunable and Regiodivergent Synthesis of Chiral 2-Aminobenzylamines by a Three-Component Reaction

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Received: 24 November 2025 | **Revised:** 24 December 2025 | **Accepted:** 21 January 2026

Keywords: aryne | asymmetric synthesis | multicomponent reactions | rearrangement | regiodivergent

ABSTRACT

Despite the growing interest in arynes as versatile synthetic intermediates, their use in stereoselective reactions that deliver chiral products remains rare. Here, we describe the first example of a stereoselective cascade reaction of arynes with aryl amines and chiral sulfinimines, which efficiently furnishes 2-aminobenzylamine products via a tandem aryne capture–electrophile quench–rearrangement cascade. The observed stereochemical outcomes indicate that the high levels of asymmetric induction, achieved during the electrophile quench with Ellman sulfinimines, arise from an open transition state, favored in strongly coordinating solvents. Mechanistic studies support the operation of two competing rearrangement processes in the final step, viz., intermolecular methyl migration and Smiles-type rearrangement. Crucially, the reaction conditions can be tuned to access either 2-aminobenzylamine regioisomers with highselectivity: high concentration favors the methyl-migration product, while more dilution and/or the incorporation of electron withdrawing groups on the aryl amine steer the reaction toward the Smiles rearrangement pathway.

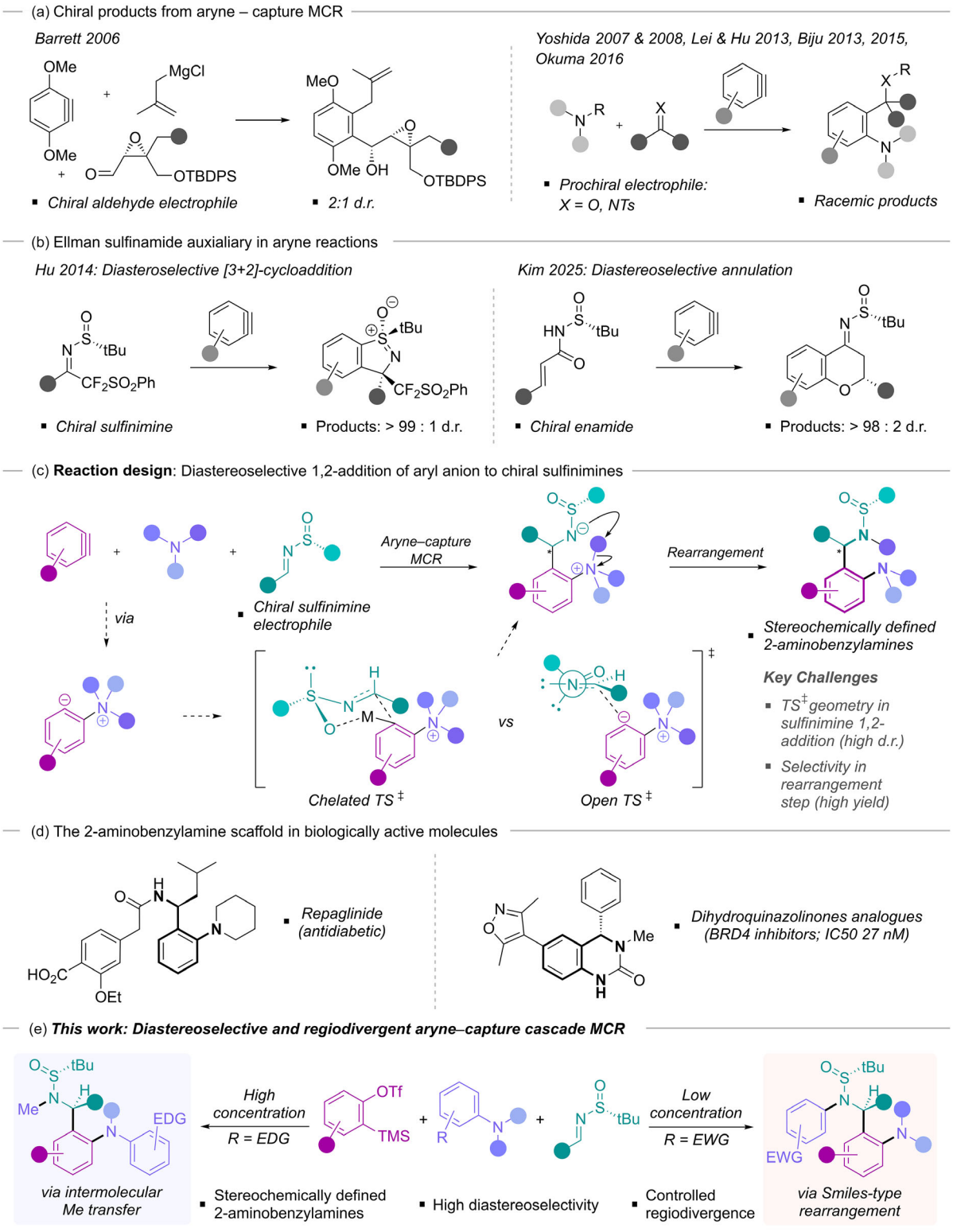
1 | Introduction

Multicomponent reactions (MCR) are well precedented as valuable tools for the creation of molecular diversity and the generation of compound libraries [1–6]. The "one-pot," bond-forming cascade intrinsic to MCR processes allows for highly efficient structural variation around core scaffolds, allowing for a broad canvas of chemical space to be routinely accessed by simple variation of the reaction components. Since Kobayashi's seminal report of mild conditions for aryne generation [7, 8], the reactivity of arynes (and other strained alkynes) has been widely and successfully exploited in a range of reactions [9, 10], including a number of MCR processes triggered by aryne capture [11, 12]; these transformations allow access to diverse arene-based chemical scaffolds with great efficiency.

However, despite the wealth of interest in these reactive species there are few reports of asymmetric reactions involving arynes [13]; in particular, enantioselective reactions remain elusive [14–16], partly due to the incompatibility of fluoride with many chiral Lewis acids, but also due to the high reactivity of the aryne partners, which often undergo competing reactions with spectator reagents and ligands. Notwithstanding these inherent challenges, a small number of diastereoselective aryne-capture MCR have been reported [17–20].

Our attention was drawn to aryne-capture MCR that provide access to 1,2-substituted, arene-based chiral products. Although several methods employing prochiral electrophiles have been reported [21–27], using either aldehydes [21–23, 25–27], ketones [24–26], or imines [22], only a limited number of approaches furnish non-racemic products [17] (Scheme 1a). Ellman's *t*Bu-sulfinamide

Dedicated to Professor Steven V. Ley CBE FMedSci FRS on the celebration of his 80th birthday.



SCHEME 1 | Context for asymmetric aryne MCR. (a) Aryne-capture MCR precedents giving chiral products. (b) Examples of the use of Ellman's sulfinamide auxiliary in aryne-capturereactions. (c) Our reaction design for the diastereoselective ayne-capture three-component reaction affording chiral 2-aminobenzylamine products. (d) Examples of the 2-aminobenzylamine scaffold in biologically active molecules. (e) This work: diastereoselective and regiodivergent aryne-capture cascade three-component reaction.

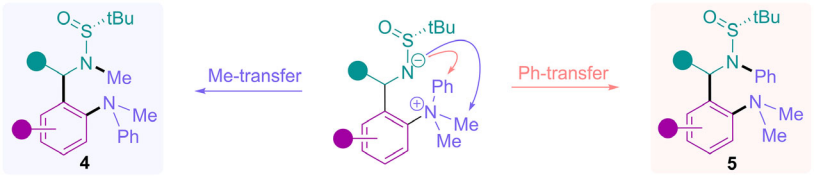
auxiliary, widely used for the asymmetric 1,2-addition of nucleophiles to chiral sulfinimines [28–31], has also been employed successfully in diastereoselective aryne-capture reactions, albeit not as a simple electrophile in a 1,2-addition process (Scheme 1b) [32, 33]. Thus, we envisaged that replacing the prochiral aldehyde electrophile commonly used in aryne-capture MCR with analogous chiral sulfinimines would provide efficient asymmetric induction in the key C—C bond-forming step, thereby enabling a novel approach to

asymmetric aryne-capture MCR. Arynes being prone to react with amine nucleophiles [11, 12], a diastereoselective aryne–capture MCR strategy for the synthesis of chiral 2-aminobenzylamines was devised, involving the sequential reaction of arynes with amines and chiral sulfinimines. We anticipated that amine selection would be critical for reaction success: primary and secondary amines bear acidic protons which could compete with the electrophile quench; silyl amines used by Yoshida [21, 22] alleviate this issue but are not commercially available; we therefore opted for tertiary amines. Following aryne-capture by the tertiary amine and addition of the resulting aryl anion to the chiral sulfinimine, a rearrangement-prone zwitterionic intermediate would be formed [34], which would subsequently furnish chiral 2-aminobenzylamine products (Scheme 1c).

The majority of bioactive molecules, and a high proportion of marketed medicines, contain nitrogen atoms in heterocycles, amines, or amide moieties [35, 36]. The targets of our synthetic strategy, 2-aminobenzylamines, are a privileged molecule structure with clinical and commercial significance, often seen in marketed or candidate drugs [37, 38] (Scheme 1d). At the time we commenced our study, no efficient methods for the preparation of 2-aminobenzylamine derivatives were reported; for instance, the 2-aminobenzylamine moiety of Repaglinide is prepared in a multistep synthesis from 2-chlorobenzonitrile [39], while in the case of dihydroquinazoline BRD4 inhibitors, 2-aminobenzophenone serves as the precursor [38]. We report here the successful realization of our asymmetric aryne-capture strategy, delivering a novel diastereoselective and regiodivergent aryne-capture cascade MCR, allowing telescoped, one-pot access to chiral 2-aminobenzylamine derivatives (Scheme 1e).

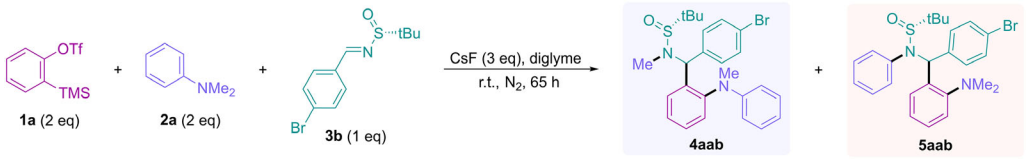
2 | Results and Discussion

Owing to the demonstrated ability of quaternary aryl ammonium salts to engage in Smiles-type rearrangements [26, 27, 40, 41], tertiary aryl amines were selected as the nucleophilic partner for the development of our aryne-capture MCR. Initial screening



SCHEME 2 | Regiodivergent rearrangement process.

TABLE 1 | Development of reaction conditions.

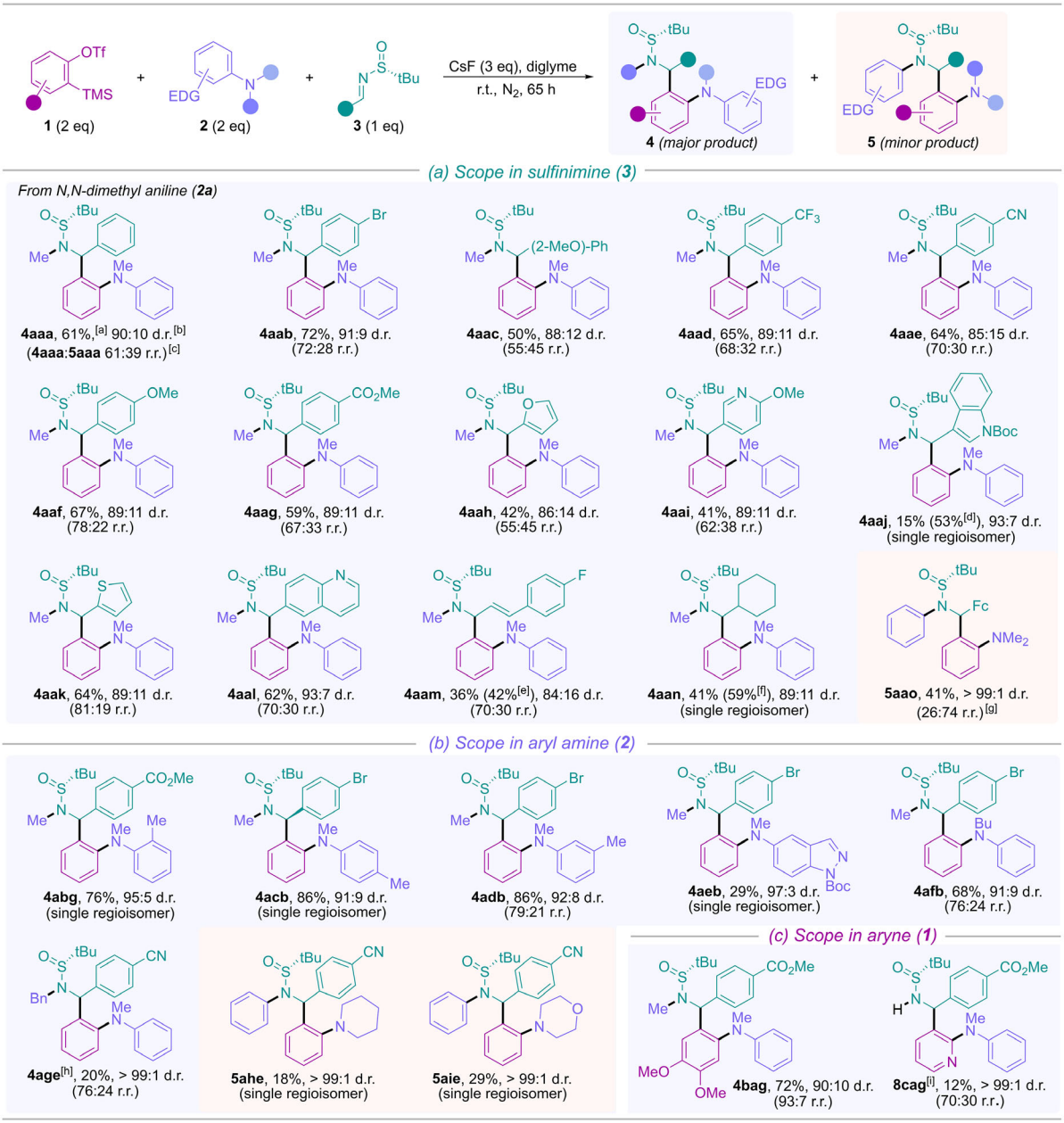


Entry	Variation from standard conditions	4aab		5aab	
		Yield, %[a]	d.r.[a]	Yield, %[a]	d.r.[a]
1	acetonitrile	5	ND	<1	ND
2	DME	63	91:9	20	ND
3	anisole	0	NA	0	NA
4	dioxane	0	NA	0	NA
5	THF	9	95:5	4	ND
6	None	72[b]	92:8	28[b]	>99:1
7[c]	17 h, **1a** (1 eq), **2a** (1 eq), **3b** (1.05 eq)	29	93:7	10	>99:1
8[d]	**1a** (1.5 eq), **2a** (1.5 eq)	59[b]	92:8	18	>99:1
9	TBAT	22	ND	4	ND
10	TBAF	4	ND	0	NA
11	KF	0	NA	0	NA
12	**Tol-3b** instead of **3b**	0	NA	60[e]	78:22[f]

[a]Estimated from ^{1}H NMR.
[b]Isolated yield.
[c]61% conversion of **1a**, 44% conversion of **3b**.
[d]79% conversion of **3b**.
[e]Sulfinyl deprotected amine **6aab** was isolated.
[f]Estimated from ^{1}H NMR of crude toluene sulfinamide product.

of reaction conditions using *N*,*N*-dimethylaniline (**2a**) and sulfinimine **3a** (Table S1) indicated that upon sequential reaction of benzyne with **2a** and **3a** both Me and Ph groups of the triggering arylamine nucleophile could migrate giving rise to products **4** and **5**, respectively (Scheme 2). Although migration of either Me or Ph substituent could be anticipated [40, 42], we envisaged that the rearrangement might be more selective, mirroring the selective aryl migration reported in alkoxide-initiated rearrangement processes [26, 27]. However, we were pleased to observe that the product expected from the previously reported Truce–Smiles pathway [41] was not detected. This initial screen also revealed that significant amounts of side product **C** [43] was formed, arising from protonation of intermediate **A** (Scheme 5c).

We were confident that judicious choice of solvents (Table 1, entries 1–6) (e.g., acetonitrile—Table 1, entry 1—is known to be a proton source in aryne reactions [44–46]) and tuning of the benzyne stoichiometry (Table 1, entries 6–8) would enhance the conversion of sulfinimine **3b** into products **4aab** and **5aab**. We were pleased to observe that, using diglyme and 2 equivalents of benzyne, **3b** was converted quantitatively into products **4aab** and **5aab** after 65 h (Table 1, entry 6); gratifyingly, both of the products were isolated with high levels of diastereopurity (92:8



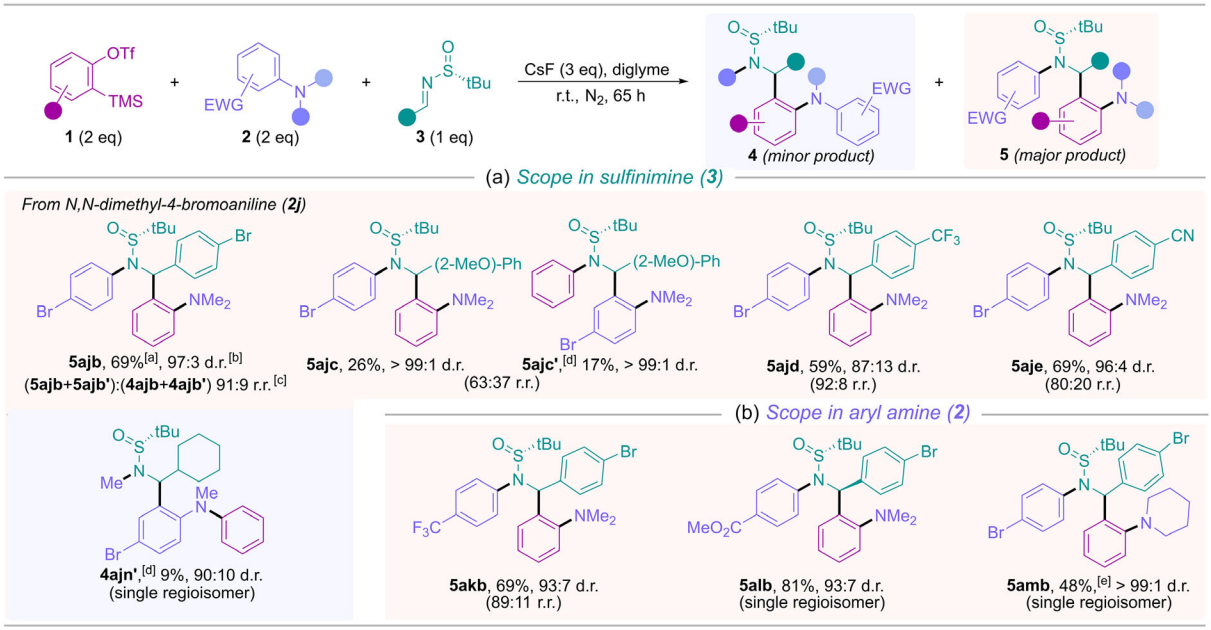
SCHEME 3 | Scope of the reaction using electron rich aryl amines. (a) Isolated yield. (b) Diastereomeric ratios (d.r.) were determined from ^{1}H NMR of isolated product. (c) Regioisomeric ratios (r.r.) of compounds **4** and **5** were determined from isolated yields of isomers **4** and **5**. (d) **4aaj** was obtained in 53% yield based on recovered **3j**. (e) **4aam** was obtained in 42% yield based on recovered **3n**. (f) **4aan** was obtained in 59% yield, based on recovered **3n**. (g) r.r. was determined from crude material. (h) **4aae** (approx. 5%) was also observed. (i) Product of the Me group rearrangement (**4cag**) was not observed and demethylated compound **8cag** was obtained as the major product of the reaction (12% yield). r.r. was determined from the isolated yield of **8cag** and **5cag**.

and >99:1 d.r., respectively). The long reaction time required to reach full conversion of **1a** (i.e., Table 1, entry 7: only 61% conversion of **1a** after 17 h) was attributed to the poor solubility of CsF in diglyme under strictly anhydrous conditions. Attempts to increase the fluoride solubility using crown ethers were not pursued due to their known propensity to absorb moisture, and the requirement to handle crown ethers in a glovebox was deemed detrimental to the practicality of the reaction. Alternatively, the variation in fluoride source (Table 1, entries 9–11) did not improve the outcome of the reaction. Despite the use of excess aryne, no further arylation of products **4** and **5** was observed, and diphenyldimethylammonium triflate **C** was formed as a side product, although the proton source could not be clearly identified. Notably, DME (Table 1, entry 2) gave similar, albeit slightly inferior, results to diglyme (83% vs. 100% combined yield of **4** + **5**), and its use in place of high-boiling diglyme could therefore provide a more practical alternative, facilitating the workup. The use of the Davis *p*-toluenesulfinamide auxiliary [47, 48] (Table 1, entry 12) did not improve the diastereoselectivity of the transformation, but did give complete control in the regiochemistry of the terminal rearrangement step, giving phenyl rearrangement product **5** exclusively (78:22 d.r.).

With a robust aryne–MCR protocol in hand, a range of sulfinimines **3** were screened (Scheme 3a, see also Scheme S1), using benzyne precursor **1a** and *N*,*N*-dimethylaniline (**2a**), providing sulfinamide products **4** and **5**, generally as the major and minor product, respectively (55:45–100:0 regioisomeric ratio [r.r.] **4**:**5**), with the exception of ferrocenyl sulfinimine **3o** which gave aryl rearrangement product **5aao** as the major regioisomer. Aryl sulfinimines **3a**–**3g** were converted into products with high efficiency (overall yield of **4** + **5** > 84%) giving products **4aaa**–**4aag** in good yields (50%–72%) with good functional group tolerance and little negative impact from steric and electronic effects of the aryl group substituent. Heteroaryl sulfinimines **3h**–**3l**, respectively, featuring furyl, pyridyl, indolyl, thiophenyl, and quinolinyl moieties, proved to be less reactive, giving **4aah**–**4aal** in moderate yields (15%–64%). Alkenyl and alkyl sulfinimines (**3m**, **3n**, see also Scheme S5) reacted sluggishly: although compounds **4aam** and **4aan** were obtained in 36% and 41% yield, respectively, other alkenyl sulfinimines gave mixtures of inseparable isomers in low yield, while other alkyl sulfinimines were unreactive. In all cases, compounds **4aaa**–**4aan** were obtained with good levels of diastereoselectivity (84:16–93:7 d.r.) and the minor products **5** were obtained as single diastereoisomers (see SI).

A range of electron rich aryl amines (**2b**–**2i**) were next evaluated in the reaction (Scheme 3b); the expectation was that the formation of compound **5** would be disfavored, thereby increasing the regioselectivity of the reaction. We were, therefore, pleased to observe that using dimethyl-substituted aryl amines **2b**–**2e**, the regioselectivity of the reaction was improved (up to 100:0 r.r.): *ortho*-, *meta*-, and *para*-toluidines **2b**–**2d** gave corresponding compounds **4** in excellent 76%–86% yield, while more sterically demanding indazole **2e** gave compound **4aeb** in moderate yield. Using differentially *N*-substituted aryl amines **2f** and **2g**, it was observed that the smaller (Me) group was transferred exclusively over the bulkier (Bu) group, while the Bn moiety was transferred preferentially over the Me group. Aryl amines bearing no *N*-methyl substituents such as piperidine **2h** and morpholine **2i** were found to be less reactive (see also Scheme S6) and gave compounds **5ahe** and **5aie**, respectively, arising from the migration of the aryl ring exclusively. Finally, the use of tertiary amines bearing no aryl substituents (Scheme S6) did not afford products **4** or **5**, notably poor conversion of sulfinimine **3** was achieved and significant quantities of ammonium salts (**C**) were observed.

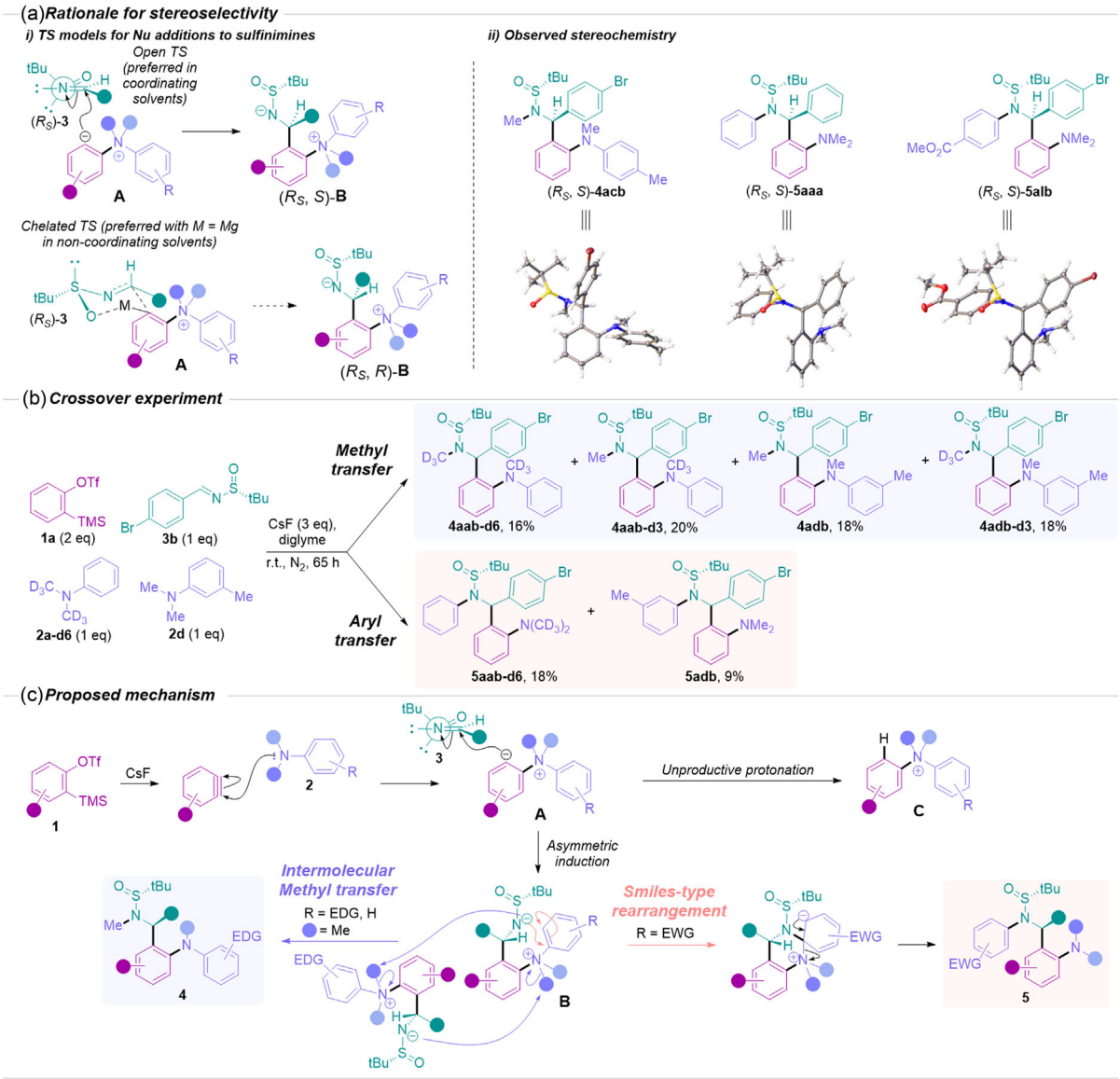
The scope in aryne was briefly evaluated (Scheme 3c, see also Scheme S7). Using dimethoxy-aryne precursor **1b**, sulfinamide product **4bag** was obtained in yield and diastereoselectivity comparable to analog **4aag** obtained from unsubstituted aryne, but



SCHEME 4 | (a) Isolated yield. (b) Diastereomeric ratios (d.r.) were determined from ^{1}H NMR of isolated product. (c) Regioisomeric ratios (r.r.) of compounds **4** (+ **4′**) and **5** (+ **5′**) were determined from isolated yields of isomers **4**, **4′**, **5**, and **5′**. (d) Compounds **4′** and **5′** arise from aryl to aryl proton transfer of the unsymmetrical benzene anion intermediate (**A** to **A′**, see Scheme S3); (e) **5amb** was isolated in 83% yield based on recovered **3b**.

with much improved regioselectivity (93:7 r.r. vs. 67:33 r.r.) indicating a strong influence of the aryne substituents on the rearrangement pathway. The use of *ortho*-substituted arynes (Scheme S7) was unsuccessful giving diarylammonium products exclusively, likely due to the increased steric hindrance preventing reaction with sulfinimine electrophiles. Pyridyne precursor **1c** afforded demethylated compound **8cag** as the major product of the reaction, while product **4cag** was not formed.

Following evaluation of the sulfinimine scope using electron rich aryl amines, electron deficient aryl amines **2j**–**2m** bearing electron withdrawing groups (EWG) were next screened in the reaction (Scheme 4, see also Scheme S6). The electronic control exerted by the aromatic ring electron withdrawing substituents was anticipated to bias the reaction in favor of the production of **5**, via aryl ring migration. Experimentation confirmed this hypothesis: aryl amines **2j**–**2m** bearing bromo, ester, or trifluoromethyl electron withdrawing groups afforded **5** (43%–81% yield) as the major product of the reaction and with high diastereoselectivity (>87:13 d.r.). Using bulkier cyclohexyl sulfinimine **3n**, however, provided Me-shift product **4ajn′** as the single regioisomer, suggesting that, as previously observed with bulkier aryne precursor **1b** which gave product **4bag** with increased r.r., migration of the phenyl ring is strongly influenced by steric factors. Another peculiarity in the reaction was observed arising from proton exchange in the diaryldimethylammonium zwitterion **A**, which yielded products **4′** and **5′** via zwitterion **A′** when EWG are present on aryl amine **2** (see SI, Scheme S3), although generally as minor products. Broad functional group tolerance was observed in both the sulfinimine and arylamine components of the reaction (Schemes 3 and 4): alkenyl, bromide, ether, ester, nitrile, carbamate, and hetaryl moieties being compatible with the process. Moreover, the sulfinyl chiral auxiliary can be readily removed using HCl (see Section S10), further asserting the synthetic utility of this transformation.



SCHEME 5 | Mechanistic investigations. (a) i) Two models for the stereoselective nucleophile addition to chiral *t*Bu-sulfinimines. ii) Crystal structures of products **4acb**, **5aaa** and **5alb** match the outcome of the open transition state model. (b) The crossover experiment shows that the methyl transfer is an intermolecular process whilst the aryl transfer is exclusively intramolecular. (c) Proposed mechanism for our 3-component reaction.

2.1 | Mechanistic Investigations

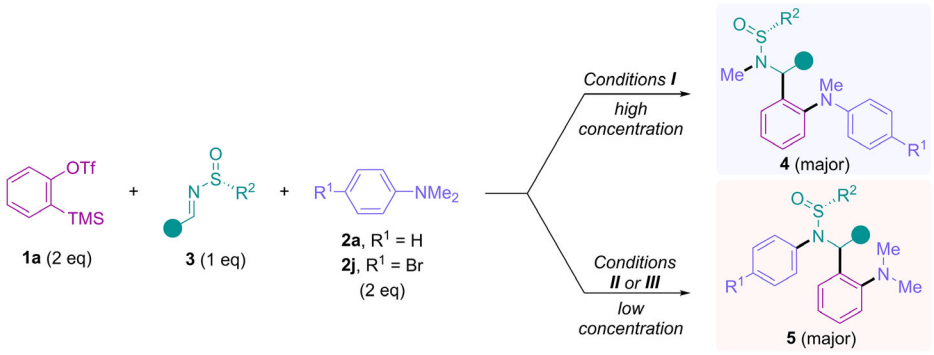
Several models have been described to rationalize the stereoselective outcome of the 1,2-addition of nucleophiles to chiral sulfinimines [28–31]. An open transition state has been shown to be favored in coordinating solvents whereas a chelated transition state is preferred when using Grignard reagent nucleophiles in non-coordinating solvents. Thus, we hypothesized that addition of nucleophile **A** to the *re* face of sulfinimine (R_S)-**3** via an open transition state would be favored in our reaction solvent (diglyme), affording products with an (R_S, *S*) configuration (Scheme 5ai). Crystal structures obtained for compounds **4acb**, **5aaa**, and **5alb** confirmed the stereochemistry of the products, validating our hypothesis (Scheme 5aii).

Certain reactions suggested to us that the Me-migration pathway (leading to compounds **4**) could be an intermolecular process. For example, using amine **2g** (Scheme 3), traces of compound **4aae** (which could not be formed by an intramolecular process) were observed, alongside major product **4age**. In order to probe the mechanism further, a crossover experiment using aryl amines **2a-d6** and **2d** (Scheme 5b) was undertaken (see also Section S9). Regarding Me-transfer compound **4**, a near-equimolar mixture of 4 products (**4aab-d6**, **4aab-d3**, **4adb**, and **4adb-d3**) was obtained in 73% yield (see also Figures S1 and S2). Formation of compounds **4aab-d3** and **4adb-d3** (which can only be obtained by an intermolecular process) shows that the Me transfer affording **4** must proceed, at least in part, intermolecularly, as demonstrated by Biju [40]. Products **4adb** and **4aab-d6** could, however, be formed either inter- or intramolecularly, but if both pathways were in operation, different quantities of products formed only by an intermolecular path (**4adb-d3** and **4aab-d3**, 36% yield), and of products that can be formed from both pathways (**4adb** and **4aab-d6**, 36% yield) would be expected. Since this was not the case (a 1:1 ratio was observed), we presume that the Me transfer (an intramolecularly disfavored 6-endo-tet pathway according to Baldwin's rules) occurs exclusively via an intermolecular process (Scheme 5c). Regarding formation of product **5**, only products **5adb** and **5aab-d6** were obtained (see also Figures S3 and S4); the absence of products that could only be formed intermolecularly (**5adb-d6** and **5aab**) confirms that the aryl migration proceeds exclusively intramolecularly via a Smiles-type rearrangement pathway (Scheme 5c). Moreover, since both **4** and **5** arise from a single chiral intermediate **B**, their formation could be expected to proceed with the same level of diastereoselectivity, as epimerization of product **4** or **5** is unlikely under the reaction conditions. However, the observation that **5** is consistently obtained in higher d.r. compared to **4** suggests that the intramolecular Smiles-type rearrangement affords **5** through diastereoselective consumption of intermediate **B** [49], thereby enriching **B** in the minor diastereoisomer. Consequently, if **4** is not generated via diastereoselective consumption of **B**, the reduced d.r. of **B** would translate into **4** being obtained in lower d.r. This interpretation is consistent with the further decrease in the d.r. of **4** when the reaction is tuned to favor the formation of **5** (see Table S2).

2.2 | Control of Regiodivergence

Since the methyl and aryl substituents migrate via inter- and intramolecular reactions respectively, high reaction concentration would be expected to favor formation of compound **4** while formation of compound **5** should be preferred in dilute reaction conditions. Altering the concentration of the reaction (Table S2) confirmed this trend, and compound **4aab** was obtained with

TABLE 2 | Control of regiodivergence.



Entry	3	Conditions[a]	4 Isolated yield, %	5 Isolated yield, %	r.r. (4:5)[b]
1	**3b**	**I**	91	7	93:7
		II	8	69	10:90
2	**3d**	**I**	79	3	96:4
		II	5	59	8:92
3	**3e**	**I**	94	5	94:6
		II	11	69	14:86
4	**Tol-3b**	**III**	0	60[c]	0:100

[a]Conditions — **I**: amine **2a** (1.0 M in diglyme), CsF (3 eq), r.t., N_2, 65 h. **II**: amine **2j** (0.125 M in diglyme), CsF (3 eq), r.t., N_2, 65 h. **III**: amine **2a** (0.125 M in diglyme), CsF (3 eq), r.t., N_2, 65 h, toluene sulfinamide **Tol-3b**.
[b]Regioisomeric ratios (r.r.) of compounds **4** and **5** were determined from isolated yields of isomers **4** and **5**.
[c]Sulfinyl deprotected amine **6aab** was isolated.

93:7 r.r. at high concentration (1 M in **2a**), while **5aab** was obtained preferentially (69:31 r.r.) under more dilute conditions (ca. 30 mM in **2a**). We thus sought to take advantage of the dependence of the reaction's regioselectivity on both concentration and aryl amine electronic characteristics to achieve further control of the regiodivergent rearrangement process (Table 2). Using sulfinimines **3b**, **3d**, and **3e** in highly concentrated reaction conditions (conditions **I**), corresponding products **4** were obtained in high yields (79%–94%) and with high regioselectivity (93:7–96:4 r.r.), while using more dilute reaction conditions and electron deficient amine **2b** (conditions **II**), products **5** were obtained preferentially (86:14–92:8 r.r.) and in good yields (59%–69%). Additionally, selective formation of compound **5** over **4** can be achieved using a toluene sulfinamide auxiliary (conditions **III**); using **Tol-3b** gave exclusive formation of rearrangement compound **5** (Table 2, entry 4).

3 | Conclusions

In summary, we have described an aryne-capture/nucleophilic addition/rearrangement cascade three-component reaction providing chiral 2-aminobenzylamine products (**4** and **5**) in high yield and high diastereoselectivity. Mechanistic investigations confirmed that products, **4** and **5**, are formed via an intermolecular Me-migration process and a Smiles-type rearrangement, respectively (Scheme 5c). Stereoselective reaction with chiral *t*Bu-sulfinimines **3** is presumed to occur via an open transition state and afforded compounds **4** with moderate diastereoselectivity while Smiles-type rearrangement products **5** were obtained in high d.r. The reaction can be tuned to favor the formation of either compound **4** (high concentration, electron-rich aryl amines) or **5** (dilute reaction conditions, electron-deficient aryl amines). The broad scope in sulfinimines **3** (15) and aryl amines **2** (13) successfully employed in the reaction, featuring a wide range of functional groups, demonstrates the potential of this method for efficient and rapid generation of molecular diversity.

4 | Experimental Section

A 10-mL Schlenk flask was charged with CsF (114 mg, 0.75 mmol, 3 eq), a glass stopper was fitted, vacuum was applied (approx. 5 mbar), and the Schlenk flask was flame dried (butane blowtorch for approx. 30 s or until free flowing CsF was obtained). Once cooled to room temperature, the flask was filled with nitrogen, a stir bar was added, and the Schlenk flask was briefly heated (10–15 s) with the blowtorch (the PTFE-coated stir bar could melt if added at the same time as CsF and subjected to flame drying for prolonged time) under vacuum (approx. 5 mbar). After cooling to room temperature, the flask was filled with nitrogen and fitted with a suba seal. (Then, when solid reagents were used, they were added to the flask and the flask was evacuated and then filled with nitrogen.) Then, dry diglyme (4 mL), sulfinimine **3** (0.25 mmol, 1.0 eq), *N*-arylamine **2** (0.5 mmol, 2.0 eq), and 2-(trimethylsilyl)aryl triflate **1** (0.5 mmol, 2.0 eq) were added sequentially and the suspension was stirred at r.t. for 65 h. The mixture was then filtered over celite (10 g), the celite pad was rinsed with DCM (25 mL), and the filtrate was evaporated under reduced pressure (the bulk of the diglyme was distilled off by heating the crude material under vacuum (approx. 5 mbar)). The resulting crude material was then purified by silica gel column chromatography affording products **4** and **5** (residual diglyme was often present in purified samples and could be removed under high vacuum or with an aqueous wash).

Author Contributions

Julien Doulcet conceived the project, designed, and carried out the aryne reaction experiments. **Noah Wright**, **Priscilla Ogunmola**, and **Bara Mala** performed the synthesis of sufinimine starting materials. X-ray crystallography analysis was performed by **Nathan R. Halcovitch**. **Joseph B. Sweeney**, and **Julien Doulcet** wrote the manuscript, supervised the project, and secured the funding (Lancaster University).

Acknowledgments

We thank Lancaster University for funding (no grant ID).

Funding

This work was supported by the Lancaster University.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supporting Scheme S1**: Synthesis of tBu-sulfinimines. **Supporting Scheme S2**: D-labelling experiment (to attest of the presence of aryl anion **A** after 65 h). Yields were determined by NMR. 2H NMR was performed and did not reveal the presence of **C**-d1. **Supporting Scheme S3**: Rationale for formation of products **4′** and **5′**. **Supporting Scheme S4**: Plausible rationale explaining the diastereoselective consumption of **B** via a Smiles-type rearrangement. For both diastereoisomers of **B**, the conformers were drawn to maximise pseudo-equatorial substituents, and the sulfinamide was depicted in its preferred conformation (with a N lone pair antiperiplanar to the S–O bond, consistent with stabilising negative hyperconjugation ($n_N \rightarrow \sigma^*_{S-O}$)[9]). **Supporting Scheme S5**: Unsuccessful sulfinimines. **Supporting Scheme S6**: Unsuccessful arylamines (* this rearrangement has been previously reported by Greaney et al.[10]). **Supporting Scheme S7**: Unsuccessful aryne precursors. **Supporting Scheme S8**: Photographic guide for reaction set up: A) Vacuum gauge showing the 5 mBar vacuum used to dry the CsF; B) CsF loaded (CsF looks tacky) to a non-dried 10-mL Schlenk flask, equipped with a glass stopper. C) Schlenk flask containing dried free flowing CsF. Procedure: the Schlenk flask shown in B was flame-dried under 5 mBar vacuum (30 s, or until CsF looks free flowing). D) Schlenk flask containing dried CsF and stir bar under 5 mBar vacuum – Procedure: under a positive flow of N_2, the glass stopper was removed and the stir bar was added to the Schlenk flask, then the glass stopper was fitted again, the Schlenk flask was placed under vacuum, and flame dried for 15 s (longer exposition of PTFE coated stir bars to flame drying can result in melting of the PTFE). E) Schlenk flask containing dried CsF, dried stir bar and solid reagents under 4 mBar vacuum – Procedure: Under a positive flow of N_2, the glass stopper was removed and solid reagents (here sulfinimine **3b**, and aryl amine **2j**) were added, the suba seal was then fitted to Schlenk flask, then the Schlenk flask was evacuated (gauge showing 4 mBar). F) A pale cloudy mixture (suspension of CsF) obtained upon stirring under N_2. Procedure: the Schlenk flask containing the solid reagents and a stir bar was filled with N_2, liquid reagents were added (here diglyme and aryne precursor 1a were added sequentially) through the suba seal using a syringe. G) A yellow cloudy mixture (suspension) obtained after 65 h of stirring under N_2 at r.t. H) An example of a failed reaction due to moisture from non-dried N,N-dimethyl aniline (2a): after 65 h stirring under N_2 at r.t., a clear pale yellow solution (with insoluble particles stuck to the glass) was obtained. **Supporting Fig. S1**: Identification of Me-shift products **4**. **Supporting Fig. S2**: Determination of the ratio of **4aab**-**d6**, **4adb**, **4aab**-**d3**, **4db**-**d3**. **Supporting Fig. S3**: Identification of aryl-shift products **5**. **Supporting Fig. S4**: Determination of the ratio of **5aab**-**d6** and **5adb**. **Supporting Table S1**: Initial optimisation of MCR reaction. **Supporting Table S2**: Effect of concentration.