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3-Alkyl-1,2,4-triazines as Heterocyclic Platforms for Organocatalytic Enantioselective Benzylic C-H Functionalization

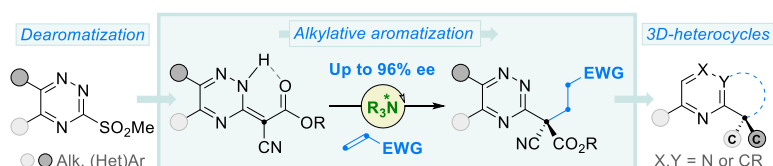
Anthony Lapray^a, Marie-Aude Hiebel,^b Sylvain Oudeyer,^a Jean-François Lohier,^c Franck Suzenet^{b*} and Jean-François Brière^{a*}

^aCNRS, INSA Rouen Normandie, Univ Rouen Normandie, Normandie Univ, CARMEN UMR 6064, INC3M FR 3038, F-76000 Rouen, France

^bUniversité d'Orléans, CNRS, ICOA, UMR 7311, Orléans, France

^cNormandie Univ, ENSICAEN, UNICAEN, CNRS, CRISMAT, 14000 CAEN, France

*Emails : franck.suzenet@univ-orleans.fr; jean-francois.briere@insa-rouen.fr

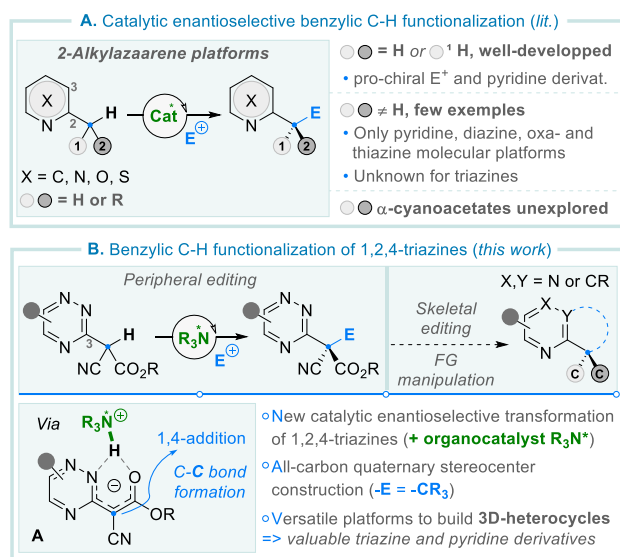


ABSTRACT: The α -3-(1,2,4-triazine)- α -cyanoacetate derivatives exhibit a unique and well-defined dearomatized structure undergoing efficient organocatalytic aromatization-alkylation sequences with Michael acceptors in order to construct an all-carbon tetrasubstituted stereocenter with high ees. These new players in the field of enantioselective catalytic benzylic C-H functionalization afford versatile molecular platforms towards the construction of valuable 3D-heterocycles.

Azaarenes connected to an α -stereogenic center are valuable three-dimensional (3D) heterocyclic substructures of medically relevant bioactive molecules, among which the pyridine ring motif and derivatives stand out.¹ In that domain, the catalytic enantioselective benzylic C-H functionalization of 2-alkylazaarenes has emerged as a powerful asymmetric method for building chemical diversity, while also affording great opportunities for reactivity investigations (Scheme 1A).² The reaction of 2-alkylazaarene nucleophiles having an unsubstituted ($R^{1,2} = H$) or monosubstituted ($R^1 \neq H, R^2 = H$) benzylic carbon is well-developed by metal or organic catalysis,^{3,4} especially with pro-chiral electrophiles (E^+), giving rise to the formation of a secondary or tertiary stereocenter.² However, the enantioselective construction of an all-carbon quaternary stereocenter ($R^{1,2} \neq H$ and $E^+ = CR_3$) remains a difficult task, and few precedents succeeded to overcome the challenging formation and functionalization of a trisubstituted 2-alkylazaarene anion in a stereocontrolled manner.^{5,6} In 2016, Palomo reported a Brønsted base catalyzed α -functionalization of pyridine and pyrazine N -oxides by achieving an efficient asymmetric Michael reaction, a transformation also extended to C-N bond formation.⁷ Then, Chen, Wang and co-workers developed a stereoselective Mannich reaction of 2-(cyanomethyl)-benzothiazole and benzoxazole heterocycles with imines, as pro-chiral electrophiles, with good enantiomeric and diastereomeric excesses.^{8,9} Yin, recently reported copper-catalyzed alkylations of α -(2-pyridine)- α -methylacetate.¹⁰ In that context, we sought to develop novel 2-alkylazaarenes as versatile molecular platforms for benzylic C-H functionalization to construct an all-carbon quaternary stereocenter, a motif frequently found in natural products and pharmaceutically active $C(sp^3)$ -rich heterocyclic architectures.^{6,11}

The 1,2,4-triazine derivatives are not only versatile building blocks as masked 2-aza-dienes (vide infra) but also important heterocycles in medicinal and agro-chemistry.¹² However, to the best of our knowledge, they have never been involved in an enantioselective benzylic functionalization process.

Scheme 1. Synthetic Plan and Context of Benzylic C-H Functionalization

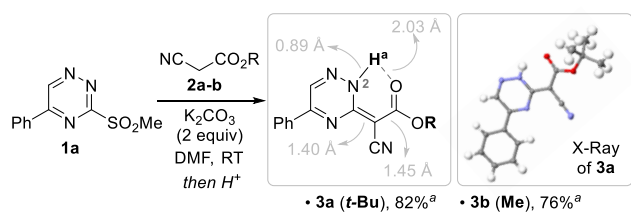


We hypothesized that a well-designed C3-substituted 1,2,4-triazine (Scheme 1B), having a benzylic disubstituted carbon, could be involved into a catalytic asymmetric C-C bond construction towards the formation of an all-carbon quaternary

stereocenter. Being aware of the previous use of α -arylated- α -cyanoacetates in asymmetric alkylation reactions,¹³ we designed our triazine in order to form the putative anion **A** under Brønsted base catalysis. However, the surprising absence of α -(2-pyridine) or α -(2-pyrimidine)- α -cyanoacetate derivatives in the literature involving asymmetric C-C or C-X bond constructions (Scheme 1A, X = C³R or N³), raised the question of their potential reactivity in enantioselective catalysis (Scheme 1B). We are pleased to report on α -3-(1,2,4-triazine)- α -cyanoacetate derivatives as new players in the field of enantioselective catalytic benzylic C-H functionalization, based on a unique dearomatization event. Furthermore, following this peripheral editing approach, the 1,2,4-triazine backbone was exploited in a series of domino *inverse-electron-demand hetero-Diels-Alder/retro-Diels-Alder (ihDA/rDA)* reactions in a logic of skeletal editing tactic.¹⁴ Thereby, these triazine derivatives pave the way to the synthesis of enantioenriched semi-saturated fused pyridine ring systems, as valuable architectures in medicinal chemistry.^{1,12,15}

At the onset of the project, the precursors **3a-b** turned out to be readily available by carrying out a regular condensation of methyl or *tert*-butyl- α -cyanoacetates **2a-b** with the model 3-methylsulfonyl-5-phenyl-1,2,4-triazine **1a** (Scheme 2).¹⁶ After a simple acidic work-up, the corresponding products **3a-b** were easily isolated with excellent yields of 76-82% on gram-scale. As sometimes mentioned in the literature,¹⁶ a downfield shift of ¹H NMR signal around 13.5 ppm (H^a) was observed. To our surprise, X-ray diffraction analyses revealed, a completely dearomatized triazine ring with a N²-H bond as a dienamine motif, a unique behavior of this family of azaarenes.^{17,18} Interestingly, an intramolecular hydrogen bond with the carbonyl group secures the formation of a single stereoisomer for the tetrasubstituted alkene moiety. Accordingly, this original property of the α -triazines α -cyanoacetates **3a-b** gives credit to the formation of the putative catalyst-bond intermediate **A** (Schemes 1B and 2), upholding our initial hypothesis of a stereoredefined pronucleophile.

Scheme 2. Initial and Unexpected Observations During Precursors synthesis



^aStructures of **3a-3b** were ascertained by X-ray analyses

Then, we tackled the unprecedented enantioselective alkylation-aromatization process of **3a** upon organocatalysis. An extensive screening of chiral Brønsted bases **5** (20 mol% in CH₂Cl₂, 6 h) was performed to promote the model Michael reaction of **3a** to methyl vinyl ketone (MVK) **4a** (Table 1, see also Supplementary Information – SI). Although quinine **5a** gave a low enantiomeric excess (ee) of 2%, cupreines **5b-e** proved to be competent bifunctional organocatalysts affording up to 82% ee with amine **5e** (74% yield of the corresponding product **6a**),¹⁹ provided that a bulky group such as a pyrimidine derivative (PYR) is present on the alcohol at C9 position. This outcome is reminiscent of the previous observations of the Deng group during their investigation of the reactivity of α -arylated- α -cyanoacetates with Michael acceptors.^{13b, 13c} The OTIPS-protected

catalyst **5f** was inefficient in these conditions, demonstrating the key role of the phenol moiety. Beside CH₂Cl₂ as the solvent (entries 1-3), the optimization endeavor showed an improved ee of 92% in MeCN (entry 3). Nevertheless, a decreased temperature resulted in a slow reaction rate due to the limited solubility of precursor **3a** in MeCN at 0 °C (entry 4). Finally, a mixture of MeCN/CH₂Cl₂ (3/1) allowed us to obtain a homogenous solution, leading to a complete conversion at 0 °C in 16 hours and excellent 95% ee with 10 mol% of catalyst **5e** (entry 5). Although a better 97% ee was measured at -20 °C, a slower transformation occurred at this temperature (62% yield in 16 hours, entry 6).

Table 1. Screening of Organocatalysts and Optimization

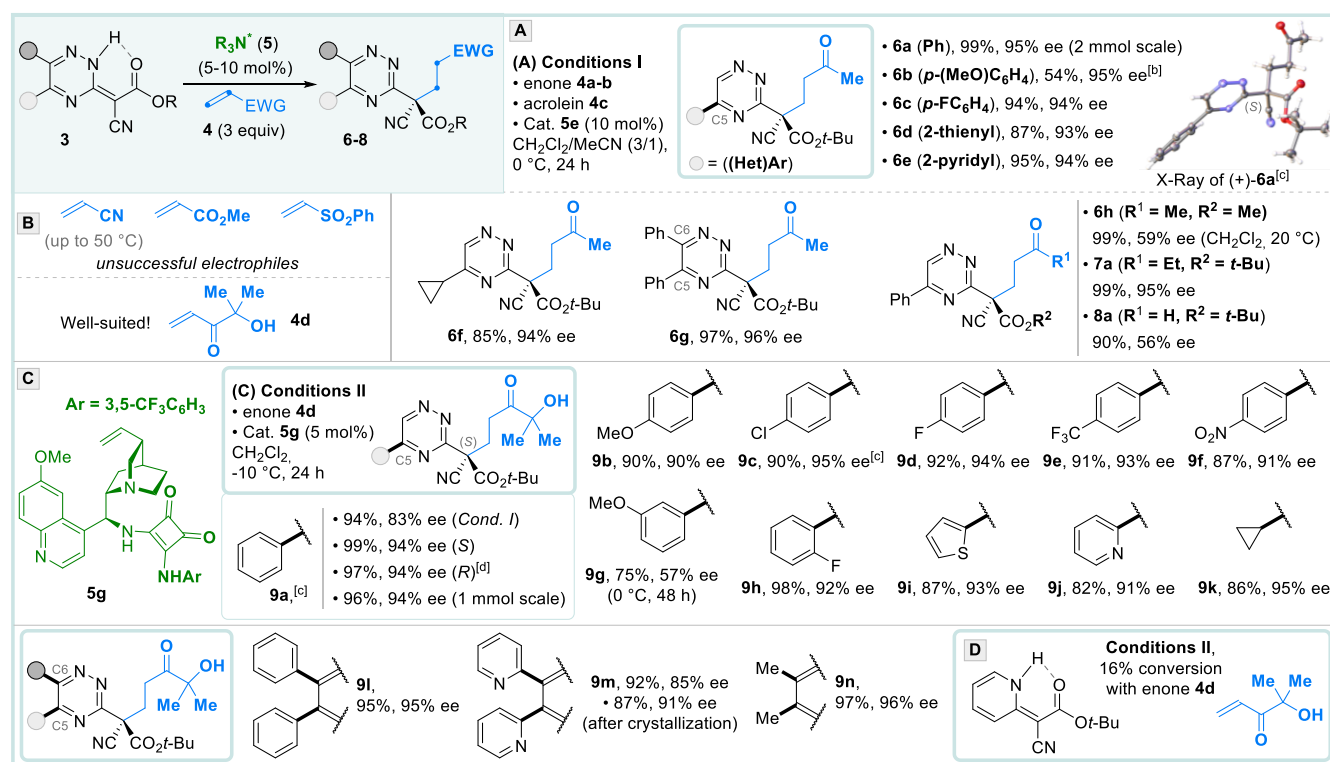
Entry	Solvent (M)	Time, Temp. (h, °C)	Yield ^[b] (%)	ee ^[c] (%)
1 ^a	THF (0.1)	6, 20	16	79
2 ^a	PhMe (0.1)	6, 20	52	56
3 ^a	MeCN (0.1)	6, 20	75	92
4 ^a	MeCN (0.1)	6, 0	43	95
5 ^e	MeCN/CH ₂ Cl ₂ ^d	16, 0	99	95
6 ^a	MeCN/CH ₂ Cl ₂ ^d	16, -20	62	97

• **5a** (R¹ = Me, R² = H), 75%, 2% ee
 • **5b** (R¹ = H, R² = H), 35%, 31% ee
 • **5c** (R¹ = H, R² = allyl), 84%, 77% ee
 • **5d** (R¹ = H, R² = CHPh₂), 65%, 72% ee
 • **5e** (R¹ = H, R² = PYR), 74%, 82% ee
 • **5f** (R¹ = TIPS, R² = PYR), 0%

^aCarried out with **3a** (0.1 mmol, 0.1-0.2 M), MVK **4a** (3 equiv) and catalyst **5e** (20 mol%). ^bYield determined by ¹H NMR on the crude product by an internal standard. ^[c]Analyzed by chiral HPLC analysis. ^[d]MeCN/CH₂Cl₂ (3/1, 0.2 M). ^e10 mol% of catalyst **5e**.

In order to investigate this innovative alkylation-aromatization sequence, we undertook the synthesis of a series of novel dearomatized α -triazine- α -cyanoacetate precursors **3** (Scheme 3). To our delight, a large array of triazines **3** were easily accessible as stable products under user-friendly conditions (like in conditions of Scheme 2, see also SI), that provide a good starting point for our investigation of the organocatalytic alkylation-aromatization sequence. The Michael addition reaction to MVK **4a** as the electrophile took place efficiently (>93% ee, Scheme 3A) from triazines **3a-3f** despite the presence of either electron-rich or electron-poor aryl substituents at C5 (**6a-6c**, 54-94%, 94-95% ee). Likewise, the pyridyl and thienyl heterocycles (**6d-6e**, 87-95%, 93-94% ee) as well as a cyclopropyl moiety (**6f**, 85%, 94% ee) all gave rise to excellent yields and enantiomeric excess. The model reaction giving rise to **6a** was validated on a 2 mmol scale without any decrease in the efficacy (99% yield, 95% ee), and the absolute configuration (*S*) was ascertained by X-Ray analysis. In the same vein, C5-C6 disubstituted precursor **3g** led to the corresponding products **6g** in 97% yield and excellent 96% ee. The reactivity of the less hindered methyl ester derivative **3h** with MVK turned out to be more difficult, due to a solubility issue, and required the use of CH₂Cl₂ as solvent. Nevertheless, these conditions afforded **6h** in only 59% ee, a decreased selectivity with respect to the more hindered *t*-Bu ester **6a** in similar conditions (82% ee, see Table 1 with catalyst **5e**).

Scheme 3. Scope and Limitation



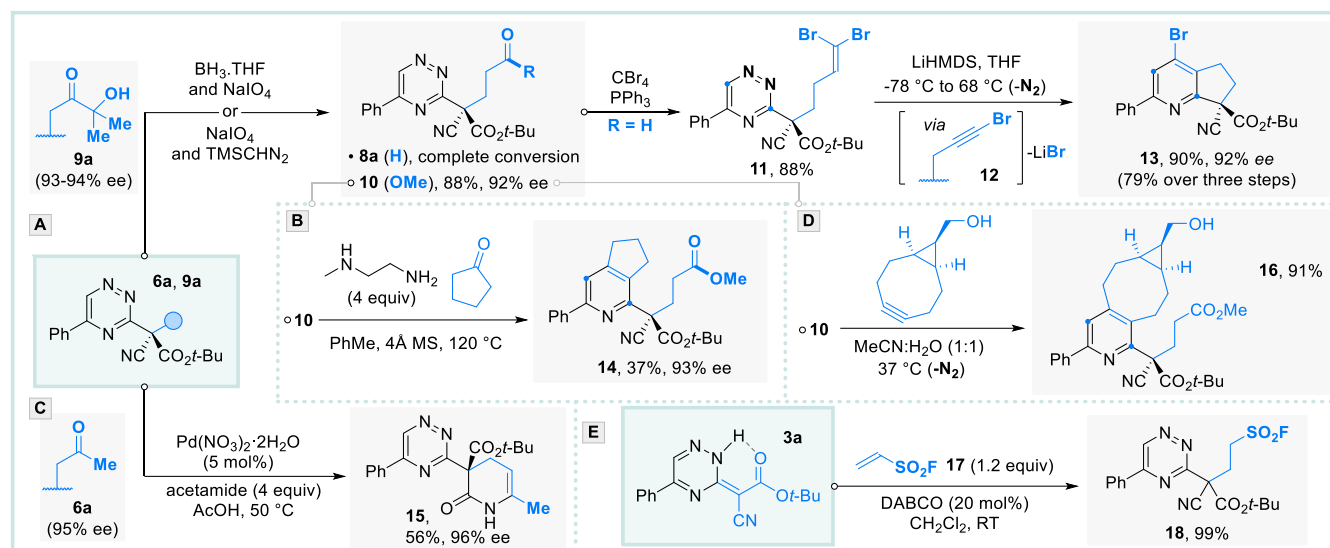
Scope and limitation. [a] **Conditions I**: **3** (0.2 mmol, 0.2 M), Enones or acrolein as Michael acceptors **4a-c** (3 equiv), organocatalyst **5e** (10 mol%), CH₂Cl₂/MeCN (3/1), 0 °C, 24 hours; **Conditions II**: **3** (0.2 mmol, 0.2 M), Michael acceptor **4d** (3 equiv), organocatalyst **5g** (5 mol%), CH₂Cl₂, -10 °C, 24 hours. Isolated yields (%) are given after purification by column chromatography and ee determined by chiral HPLC. [b] Conversion of 54% was measured due to solubility issue of the precursor. [c] The absolute configuration of compounds **6a** and **9c** were determined by X-ray analyses,¹⁷ or by chemical transformations (see SI) and the other absolute configurations were supposed by analogy with regard to fact that all derivatives are (+) dextrorotatory. [d] Carried out with the pseudo enantiomer of catalyst **5g'**, namely the squaramide derived *epi*-amino quinidine.

The more sterically hindered ethyl vinyl ketone was also well-tolerated, giving **7a** in 99% yield and 95% ee, while the polymerization-sensitive acrolein electrophile undertook a smooth Michael addition to provide product **8a** with 90% yield, but in lower 56% ee (*vide infra*).^{13c} Then, we investigated the scope of the reaction on a variety of electrophiles (Scheme 3B). The dearomatized triazine **3a**, which is rather stable, was not sufficiently reactive for a 1,4-conjugate addition (*conditions I*) on methyl acrylate, acrylonitrile or vinyl sulfone as less reactive Michael acceptors. On the other hand, capitalizing on the insightful pioneering contribution of Palomo and co-workers,^{13h,20} we were delighted to observe that the versatile α' -hydroxy enone **4d** afforded the corresponding adduct **9a** in promising 83% ee and 94% yield (Scheme 3C, *conditions I*). A slight modification of the reaction conditions (*conditions II*: CH₂Cl₂, -10 °C) resulted in excellent 94% ee (**9a**-*S*) with a complete conversion with only 5 mol% of the squaramide quinine-derived organocatalyst **5g**, even on 1 mmol scale. Importantly, a complete pseudo-enantiomeric effect was measured, giving rise to the formation of the *R*-enantiomer of adduct **9a** in 94% ee (97% yield), by means of the quinidine-derived organocatalyst **5g'** (see SI for the induction model and catalytic cycle). This enantioselective transformation into adducts **9** proved to be highly general giving rise to ees ranging from 90 to 95% (82-98% yields) for C5-substituted (**9b-9f** and **9h-9k**) and C5-C6-disubstituted products (**9l-9n**) regardless of the nature of the *para*-

and *ortho*-substituted aryl, heteroaryl and alkyl moieties. As illustrated with product **9m**, the ee could be enhanced from 85% to 91% by a simple crystallization. Worthy of note, compounds with a pyridyl (**6e**, **9j** and **9m**) or a nitro moiety (**9f**) that are known to interact in a competitive fashion with a bifunctional organocatalyst like **5g**, were well-tolerated in those conditions. As an exception, the product **9g** with a *meta*-methoxy phenyl part was isolated with only 57% ee and a low conversion even at 0 °C. This unique outcome might be correlated with the poor solubility of compound **3g** in the reaction mixture. Importantly, a preliminary investigation revealed a poor reactivity of α -3-(2-pyridine)- α -cyanoacetate derivative highlighting the uniqueness of the 1,2,4-triazine as molecular platforms for enantioselective additions (Scheme 3D).²¹

Then, we ventured to probe the synthetic potential of the original substrates **3a**, **6** and **9** (Scheme 4).¹² Based on literature protocols (Scheme 4A),^{13h,20} the precursor **9a** was transformed into the corresponding aldehyde **8a** (conversion >99%) or methyl ester **10** (88%, 92% ee), through straightforward reduction-oxidation sequences. The versatility of the α' -hydroxy ketone functional group advantageously complements the first and unsuccessful attempts to prepare the derivatives **8a** and **10** from methyl acrylate or acrolein as electrophiles (see Schemes 3A-B).

Scheme 4. Diversity-oriented Synthetic Transformations Thanks to Peripheral and Skeletal Editing Tactics



The aldehyde pendant of **8a** underwent a facile interrupted Ramirez-Corey-Fuchs sequence, initiated by the synthesis of the 1,2-dibromoalkene **11** (88% yield) by means of the non-basic $\text{CBr}_4/\text{PPh}_3$ reagents, followed by the *in-situ* formation of the bromo alkyne **12** thanks to LiHMDS promoted elimination reaction.²² Upon gentle heating of the reaction mixture at 68 °C, a smooth one-pot *ihDA/rDA* reaction took place from **12** to furnish the fused pyridine **13** in 90% yield (79% yield over three steps) with high 92% ee. This sequence likely benefits from the Thorpe-Ingold effect of the quaternary stereocenter facilitating the intramolecular cycloaddition reaction,²³ taking place otherwise around 150–200 °C.¹² Furthermore, the bromine atom at C4 of the pyridine ring affords numerous opportunities for functionalization events. On the other hand, the more stable ester precursor **10** underwent a smooth intermolecular *ihDA/rDA* reaction at 120 °C towards the construction of pyridine **14** in 37% yield (non-optimized) in 93% ee, thanks to the extrapolation of Taylor's enamine based procedure (Scheme 4B).²⁴ These successful *ihDA/rDA* sequences highlight the many opportunities available for constructing valuable semi-saturated fused pyridine ring systems,¹² and for executing transformations in the logic of skeletal editing of triazines.¹⁴ In quest of expanding the portfolio of the peripheral chemical transformations of these triazine substrates, the palladium-catalyzed hydration of the nitrile functional group of **6a** was undertaken (Scheme 4C).²⁵ Interestingly, the thus obtained amide group spontaneously cyclized to the ketone moiety to eventually furnish the corresponding piperidine derived lactam **15** in 56% yield, a valuable heterocycle in medicinal chemistry. Recently, the 1,2,4-triazine derivatives were developed as potent bioorthogonal tools thanks to their reactivity with strained dienophiles.²⁶ Inspired by the seminal contribution of Webb,^{26a} we were delighted to observe that a smooth *ihDA/rDA* reaction occurred between triazine-ester **10** and the well-established bicyclo[6.1.0]non-4-yne (BCN) in MeCN/H₂O at 37 °C to afford the cyclo-adduct **16** in 91% yield (Scheme 4D). The sulfur(VI) fluoride exchange (SuFEx) reaction is another bioorthogonal click reaction.²⁷ In this context, we demonstrated the possibility to install the SO₂F functionality through a facile Michael reaction to ethylene sulfonyl fluorides **17** giving rise to the corresponding product **18** in quantitative yield (Scheme 4E). These preliminary synthetic investigations

show how versatile these chiral 1,2,4-triazine platforms are to build molecular complexity in the field of valuable chiral azaarenes.

In conclusion, we highlighted a unique dearomatized 1,2,4-triazine structure **3** obtained upon the facile nucleophilic addition-elimination sequence with α -cyanoacetates from accessible precursors **1**. The readily available α -3-(1,2,4-triazine)- α -cyanoacetate derivatives **3** in their dearomatized form underwent highly enantioselective organocatalytic Michael reaction while subsequently forming an all-carbon quaternary stereocenter during the rearomatization event. Additionally, these triazines proved to be very versatile molecular platforms towards the construction of various chiral (fused) aza-heterocycles. These new players in the field of enantioselective catalytic benzylic C-H functionalization reaction are expected to pave the way to other C-C or C-X bond forming processes to build further chemical diversity within the valuable 3D-azaarenes family, especially alongside the 1,2,4-triazine moieties that can be utilized in skeletal editing tactics.¹⁴

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization data, NMR spectra, and X-Ray analyses (CCDC).

AUTHOR INFORMATION

Corresponding Author

Jean-François Brière - CNRS, INSA Rouen Normandie, Univ Rouen Normandie, Normandie Univ, CARMEN UMR 6064, INC3M FR 3038, F-76000 Rouen, France; orcid.org/0000-0002-1381-4535; E-mail: jean-francois.briere@insa-rouen.fr (www.lab-cobra.fr/equipes/heterocycles/, e-CatCH group).

Franck Suzenet - Université d'Orléans, CNRS, ICOA, UMR 7311, Orléans, France; orcid.org/0000-0003-1394-1603; E-mail: franck.suzenet@univ-orleans.fr

Authors

Anthony Lapray - INSA Rouen Normandie, Univ Rouen Normandie, CNRS, Normandie Univ, CARMeN UMR 6064, INC3M FR 3038, F-76000 Rouen, France; orcid.org/0009-0005-5081-7769

Marie-Aude Hiebel - Université d'Orléans, CNRS, ICOA, UMR 7311, Orléans, France; orcid.org/0000-0001-9476-9176

Sylvain Oudeyer - Univ Rouen Normandie, INSA Rouen Normandie, CNRS, Normandie Univ, CARMeN UMR 6064, INC3M FR 3038, F-76000 Rouen, France ; orcid.org/0000-0001-8238-800X

Jean-François Lohier - Normandie Univ, ENSICAEN, UNICAEN, CNRS, CRISMAT, 14000 CAEN, France; orcid.org/0000-0001-6339-4797

Authors Contributions

All authors have given approval to the final version of the manuscript.

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