Prayogik Rasayan

Cascade Synthesis of 1,1-Dicyanocyclopropanes via Sulfur Ylide-Mediated [2+1] Annulation Reaction in Batch and Continuous Flow

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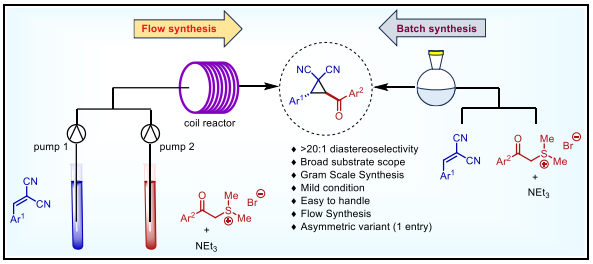
Abstract

We have developed a highly diastereoselective synthetic protocol for the preparation of densely functionalized cyclopropanes. The reaction involves the coupling of in situ generated sulfur ylide, acting as C1 synthon, with activated olefin, serving as C2 synthon, via a [2+1] annulation pathway. This versatile methodology is applicable both in batch and continuous flow processes, offering high functional group tolerance and scalability to gram quantities. Furthermore, an asymmetric variant of this reaction has been successfully achieved using chiral sulfur ylides, expanding its synthetic utility.

Keywords: Cyclopropane, *S*-ylide, Cascade Synthesis, Diastereoselective, Flow Synthesis



1. Introduction

For over a century, cyclopropanes, characterized by their highly strained three-membered ring structure, have captured significant interest due to their distinctive and versatile reactivity. These three-membered rings are found in various natural products and play a crucial role as building blocks in diverse fields such as organic synthesis, drug discovery, and materials science.[1,2] The diverse nature of cyclopropanes, often allows them to act as versatile chemical entities, in several [n+3] annulations reactions.[3] Their intrinsic ability to undergo ring opening, rearrangement, and cycloaddition reactions has made donor-acceptor cyclopropanes[4] stand out among various three-membered cyclic derivatives. The relevance of cyclopropanes extends beyond synthetic key intermediates[5], several studies have already confirmed promising bioactivity and pharmaceutical applications of compounds embedded with cyclopropane cores. Apparently, *trans*-Chrysanthemic acid (Figure 1, A) containing cyclopropane as their fundamental core shows insecticidal properties whereas Abacavir (B) and Efavirenz (C) drugs are prone to anti-retroviral pharmaceutical activity. Moreover, the anti-insomnia drug, Tasimelteon (D) and anti-diabetic drug, Saxagliptin (E) are well known for their tremendous bioactivity in several reports. (Figure 1)[6]

Several methodologies have been documented for the preparation of cyclopropanes including Corey-Chaykovsky cyclopropanation[7a], Simmons-Smith cyclopropanation[7b], direct addition–cyclization of β-halogenated carbonyl compounds, etc.[7] Besides, the use of ylide chemistry to synthesize a wide variety of cyclopropanes has piqued the interest of many scientific communities in the last few years.[8] Several attempts have been made using sulfur and pyridinium ylides as C1 synthons to develop cyclopropanes from dicyano-styrene derivatives.

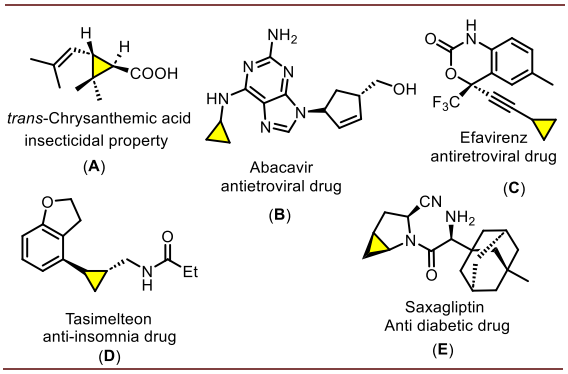


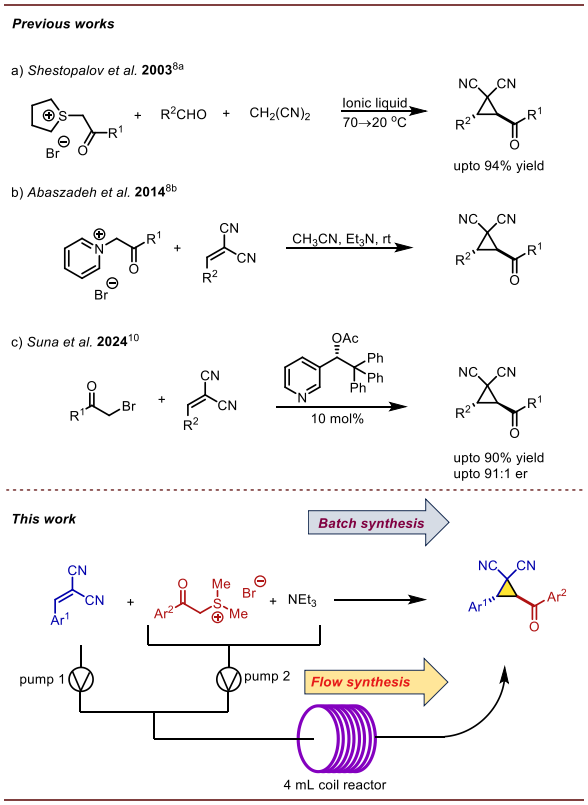
Figure 1: Biologically Active Compounds Contains Cyclopropane

Consequently, Shestopalov *et al*.[8a] in 2003 were able to demonstrate a one-pot synthesis of substituted 1,1-dicyanocyclopropanes using tetrahydrothiophene as mediators (Scheme 1a). In contrast, Abaszadeh *et al.* in 2014 used pyridine as a mediator in assistance with ultrasound to synthesize such derivatives with few substrate generalities (Scheme 1b).[8b] However, these results lead to the use of ultrasound irradiation to produce cyclopropanes. Additionally,

many asymmetric versions of cyclopropanes have also been well documented either by incorporating organocatalysts or by using chiral pyridines as mediators.[9] Recently, Suna *et al.* have reported an asymmetric synthesis of cyclopropanes with moderate enantioselectivity by introducing chiral pyridines in catalytic amounts (Scheme 1c).[10]

Lately, many groups have used SMe_2 as a mediator in various reactions and found it efficient for annulation reactions.[11] Building on this understanding, we hypothesized that SMe_2 could serve as a mediator in our annulation reaction. Herein, we carried out an extensive investigation into an alternative method for synthesizing the cyclopropane moiety via in-situ generation of S-ylides. This methodology has been utilized in both batch as well as in the continuous flow synthesis approach (Scheme 1).

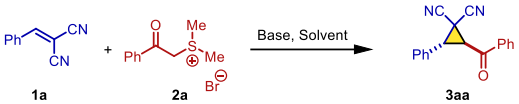
Scheme 1: Selective recent development for the synthesis of cyclopropane



2. Result and discussion

We began our investigation with dicyano-styrene **1a** and pre-formed sulfonium salt **2a** in the presence of base. Initially, we screened several organic and inorganic bases to get the maximum yield (Table 1, entries 1-7). Pleasingly, it was found that the 1,1-dicyanocyclopropanes **3aa** were generated in all different base conditions in good to moderate yield. However, NEt_3 emerged as the most effective base for this cascade process (Table 1, entry 1). We then turned our attention to optimizing the solvent, screening both polar and non-polar solvents (Table 1, entries 8-13) for our reaction protocol. During our investigation, it was found that $CHCl_3$ as a solvent was most suitable for this annulation reaction. Furthermore, to understand the reaction mechanism, some control experiments were carried out with phenacyl bromide instead of **2a** at room temperature and elevated temperature (Table 1, entries 14 and 15). Surprisingly, trace amount of product formation takes place even at higher temperature which predominatly demonstrates the pivotal role of sulphur as mediator in this cascade protocol. The diastereoselectivity of **3aa** was confirmed by crude ^{1}H NMR spectroscopy. The *trans*-geometry of the products was determined based on ^{1}H NMR coupling constants[12] and further validated by comparison with previously reported data.[10]

Table 1: Optimization of reaction conditions[a]



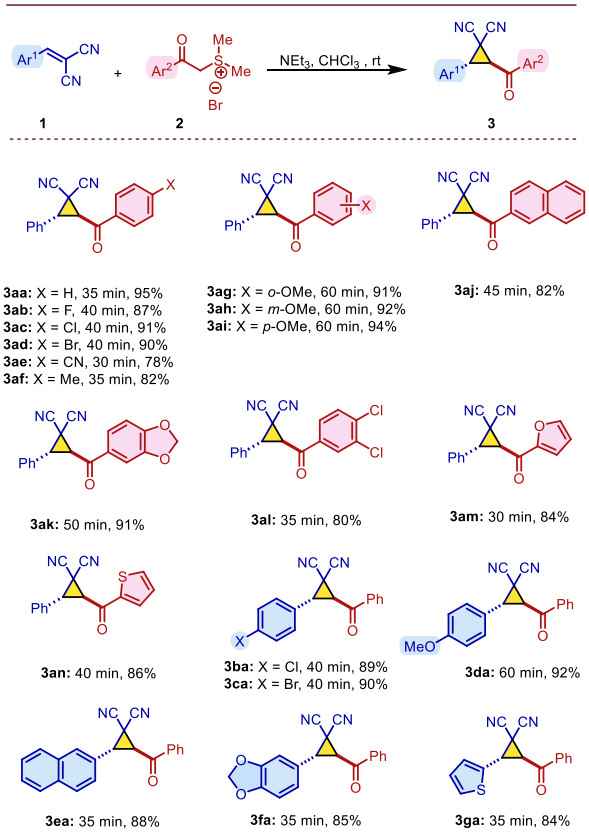
entry	solvent	base	time (min)	yield[b] (%)
1	CH_3CN	NEt_3	60	88
2	CH_3CN	DIPEA	50	87
3	CH_3CN	DBU	30	85
4	CH_3CN	DBN	45	82
5	CH_3CN	DABCO	60	84
6	CH_3CN	Cs_2CO_3	60	75
7	CH_3CN	Na_2CO_3	240	72
8	DCM	NEt_3	40	83
9	**$CHCl_3$**	**NEt_3**	**35**	**95**
10	EtOAc	NEt_3	45	85
11	MeOH	NEt_3	50	86
12	THF	NEt_3	50	70
13	toluene	NEt_3	60	82
14[c]	$CHCl_3$	NEt_3	60	trace
15[d]	$CHCl_3$	NEt_3	60	trace

[a]Reaction Condition: **1a** (0.1 mmol, 1 equiv.), **2a** (0.11 mmol, 1.1 equiv.), base (0.1 mmol, 1 equiv.), solvent (1 mL) at rt. [b]Isolated yield. [c]Phenacyl bromide is used instead of **2a**. [d]The reaction was conducted at 50 °C. dr was determined to be >20:1 for all cases by ^{1}H NMR of the crude reaction unless specified.

Now, with the optimized condition in our hand, we then examine the substrate generality of our devised cascade protocol. Initially, dicyano-styrene **1a** was investigated with a series of pre-formed sulfonium salts **2** derived from α-bromoketones (Scheme 2). At first, *para*-substituted halogen groups on α-bromoacetophenones (**2b-2d**) were employed, resulting in excellent yield and diastereoselectivity in all cases. Followed by a strong electron-withdrawing *para*-cyano group (**2e**) was introduced revealing a comparable reactivity with good yield. Next, the donating *para*-methyl group (**2f**) was tested delivering a high yield of **3af** with a similar reaction rate. We then focussed our attention on the introduction of the +R directing group at various positions of α-bromoketones **2**. To our delight substituted -OMe groups at *ortho*-, *meta*-, and *para*-positions of aryl ring (**2g-2i**) proceeded smoothly in this cascade reaction giving in excellent yields with slightly lowered reaction rates (**3ag-3ai**).

Next, bicyclic groups like 2-naphthyl (**3aj**) and piperonyl (**3ak**) groups were explored with this strategy without any significant loss in yield and selectivity. Moreover, 3,4-dichloro substituted aryl moiety (**2l**) was employed constructively in our cascade

Scheme 2: Scope of the [2+1] annulation between dicyano-styrene **1** and sulfonium salt **2**



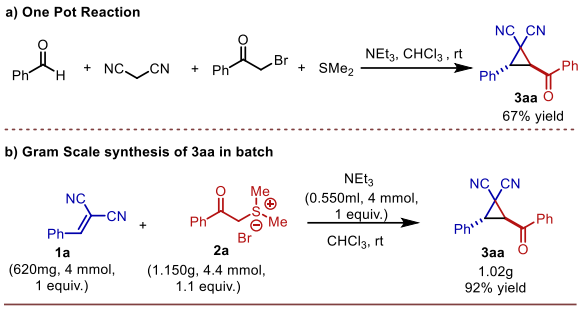
Reaction Conditions: **1** (0.3 mmol), **2** (0.33 mmol), NEt_3 (0.3 mmol), 3 ml of $CHCl_3$ at rt. The dr was determined to be >20:1 for all cases by ^1H NMR of the crude reaction unless specified.

strategy. Surprisingly, electronically and sterically distinctive five-membered heterocycles i.e., 2-furyl (**3am**) and 2-thienyl (**3an**) groups were also prepared with excellent yield.

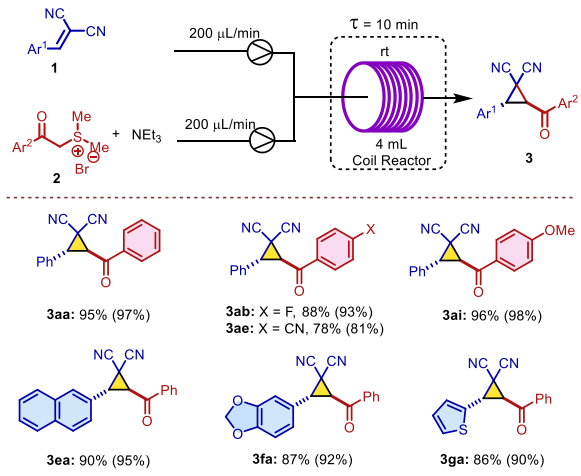
Later, we investigated the same protocol with a different styrene system derived from aryl aldehydes. It was observed that both *para*-Cl (**1b**) and *para*-Br (**1c**) substituted styrene systems were well tolerated producing satisfactory results. The aryl ring with electron-donating methoxy group at *para*-position (**1d**) delivers higher reaction yields of corresponding product **3da**. Furthermore, 2-naphthyl **(3ea),** piperonyl (**3fa**), and 2-thienyl (**3ga**) derivatives were also prepared efficiently showcasing its broad substrate variability.

Afterward, a one-pot synthesis of 1,1-dicyanocyclopropanes **3aa** was performed using benzaldehyde and malononitrile (precursor of **1a**) with dimethyl sulfide and bromoacetophenone (precursor of **2a**). This one-pot multicomponent study takes 6 hours to complete at room temperature with a satisfactory isolated yield of 67% (Scheme 3a). Next, a scale-up synthesis was also attempted with optimized reaction conditions, which produced 1.02 g of (**3aa**) (92%) with excellent diastereoselectivity (Scheme 3b).

Scheme 3: a) One pot reaction; b) Gram scale synthesis



Scheme 4: Synthesis of **3** in continuous flow



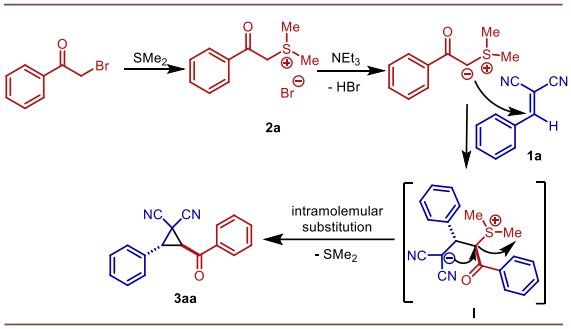
Reaction Conditions: **1** (0.1 M in $CHCl_3$), **2** (0.12 M in MeOH), NEt_3 (0.1 M in MeOH), room temperature. The yield written in the parenthesis was determined by ^1H NMR of the crude reaction mixture after workup. The dr was determined to be >20:1 for all cases by ^1H NMR of the crude reaction.

To further investigate the applicability of the developed method, we applied it to a continuous flow process. Recently, such processes have gained prominence in the pharmaceutical industry due to their advantages in terms of efficiency and sustainability. The flow system we used, consisted of a stainless-steel coil reactor (4 mL) with binary pumps connected to a 0.1 M solution of **1a** in methanol and 0.12 M solution of **2a** along with 0.1 M triethylamine in methanol (Scheme 4). Methanol was specifically chosen for the sulfonium salt due to its higher solubility in this solvent. Pleasingly, the cyclopropane derivatives have different substitutions on aryl (Ar^1 and Ar^2) and were successfully synthesized in flow conditions. Cyclopropane derivatives with para-fluoro, cyano, and methoxy at Ar^2 providing good to excellent yields. Subsequently, we varied the group on Ar^1 of dicyano-styrene **1** under flow conditions. Surprisingly, 2-

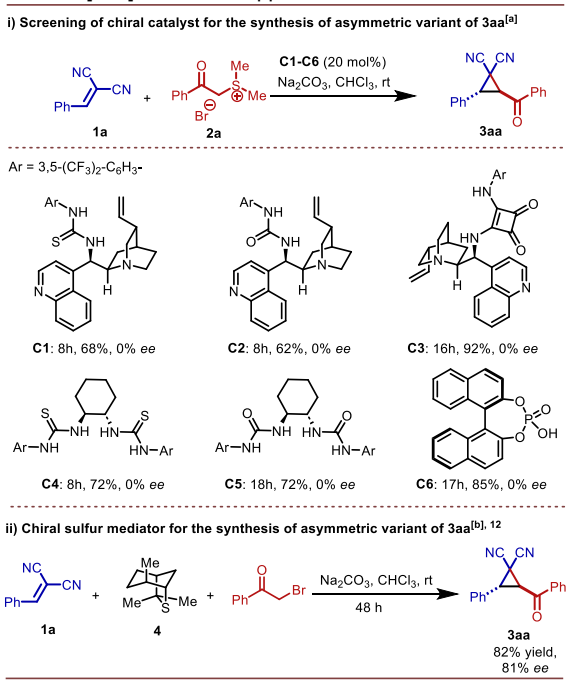
naphthyl (**3ea**), piperonyl (**3fa**), and 2-thienyl (**3ga**) consisting cyclopropanes were successfully obtained (Scheme 4).

The plausible mechanism of the cascade reaction is shown in Scheme 5. Initially, in-situ sulfur ylide is generated in the presence of base which attacks on activated olefin **1a** to produce adduct **I**. Next, intramolecular cyclization via carbanion affords the desired product **3aa** with the removal of the dimethyl sulfide mediator.

Scheme 5: Plausible mechanism of [2+1] annulation reaction.



Scheme 6: Attempt to develop an asymmetric variant of the cascade [2+1] annulation approach.



[a]Reaction Conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), Na_2CO_3 (0.1 mmol), **C1-C6** (0.02 mmol) and 1 mL of $CHCl_3$ at rt. [b](+)-isothiocineole (0.12 mmol) was used in one-pot reaction. The dr was determined to be >20:1 for all cases by ^1H NMR of the crude reaction unless specified.

To obtain enantioenriched **3aa**, our cascade protocol was carried out with dicyano-styrene **(1a)** and sulfonium salt **(2a)** in the presence of a mild inorganic base (Na_2CO_3) using chiral catalysts (Scheme 6). Initially, we tested *Cinchona* derived bifunctional catalysts (**C1-C3**) at room temperature and found that the reaction afforded the desired product **(3aa)** with excellent yield and diastereoselectivity with no enantioselectivity. Further, cyclohexane-diamine derived *H*-bond donor catalysts (**C4** and **C5**) have been employed in the reaction which is also not effective on enantioselective formation of cyclopropane. Next, chiral phosphate catalyst **C6** was tested in this cascade process but no enantiomeric excess was observed (Scheme 6). Later, chiral sulfur **4** was introduced instead of SMe_2. Pleasingly, the one-pot cascade reaction using chiral (+)-isothiocineole **4** as a mediator resulted in the production of enantioenriched *trans*-**3aa**.

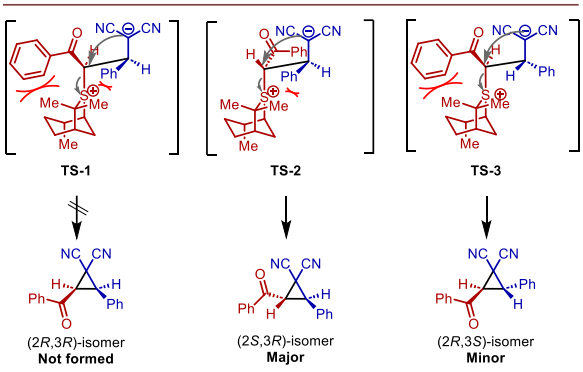


Figure 2: Proposed reaction pathways to *trans*-selective cyclopropane.

The absolute stereochemistry of the compounds was established by comparing their optical rotations with previously reported values for a model compound (3aa).[13] The formation of the *trans*-product was further confirmed based on our prior research. The observed enantioselectivity can be rationalized by examining the proposed transition states (**TS-1**, **TS-2**, and **TS-3**) depicted in Figure 2. In **TS-1**, steric repulsions between the COPh group and the methyl group, as well as between the phenyl and methyl groups of chiral sulfur **4**, likely hinder the formation of the *cis*-product, which was not detected under the optimized conditions. Conversely, **TS-2**, where such steric interactions are minimized between the COPh and methyl groups, facilitates the formation of the major *trans*-product (2*S*,3*R*). Meanwhile, in **TS-3**, a steric clash between the COPh and methyl groups contributes to the formation of the minor *trans*-product (2*R*,3*S*). As a result, the cascade reaction predominantly yields the *trans*-**3aa** (2*S*,3*R*) as the major product.

3. Conclusions

In summary, we have developed a cascade approach utilizing dicyano-styrene and sulfonium salts to synthesize cyclopropane derivatives through a [2+1] annulation strategy. This protocol exhibits broad functional group tolerance and excellent substrate scope, with isolated yields ranging from moderate to high and remarkable diastereoselectivity. The practicality of the reaction was demonstrated through gram-scale synthesis. Furthermore, continuous flow methods were explored, enabling the production of several cyclopropane

derivatives without any loss of diastereoselectivity. Additionally, enantioenriched 1,1-dicyanocyclopropanes were successfully synthesized using chiral sulfur.

4. Acknowledgements

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5. Notes and References

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6. About the author(s)

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