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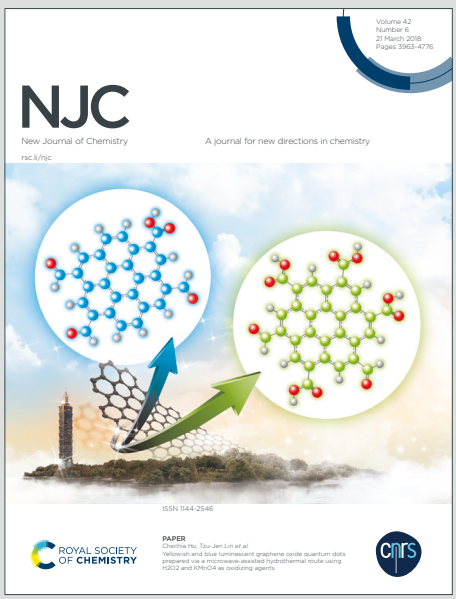

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COMMUNICATION

A Highly Diastereoselective Spiro-Cyclopropanation of 2-arylidene-1,3-indanediones and dimethylsulfonium ylides

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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A highly diastereoselective spiro-cyclopropanation reaction of 2-arylidene-1,3-indanediones and dimethylsulfonium ylides has been developed via a base-induced annulation. This efficient and simple protocol features simple operations, mild conditions and excellent functional group compatibility. A variety of structurally interesting spiro-cyclopropanes were prepared in excellent yields and diastereomeric ratios (up to 97% yield and 20:1 d.r.). Also, a ring expansion of the cyclopropanation product to quickly deliver a complex indeno[1,2-c]pyridazine structure showcased an interesting application of this method.

Introduction

Cyclopropanes are an important class of small molecules and are present in various biologically active compounds, natural products and pharmaceuticals.[1-5] Especially, cyclopropane can act as configurationally stable bioisosteric replacement of a double bond and, in general, it can improve metabolic stability, lipophilicity and solubility of the potential drug candidate.[6-8] Therefore, efficient synthetic methods for this highly strained system have been in high demand in synthetic organic community. Conventionally, cyclopropanation has been achieved by several classical methods[1, 9-12] such as cyclization of diazo compounds, carbine insertion of alkenes and Michael initiated ring closure of ylides with olefins. Among them, Ylides, including arsonium[13], sulfonium[14-24], and pyridinium ylides[25-27] (Scheme 1) are one of the promising active units for constructing cyclopropane skeletons. Sulfur ylides, one of the widely utilized reagents in synthetic organic chemistry has been reported to participate in cyclization reactions with different electro-deficient unsaturated functional groups.[14-24, 28] Sulfur ylides have also been found to undergo formal [2+1] annulation with 2-arylidene-1,3-indanediones to produce spiro-cyclopropanation products (Scheme 1). However, the method reported by Roy suffers from low diastereoselectivity (Scheme 1).[29] Additionally, Maleki developed a stereoselective one-pot cyclopropanation, but complex catalyst, L-Proline functionalized nanomagnetic organocatalyst LPSF (Fe_3O_4\SiO_2\propyltriethoxysilane\L-proline), needs to be utilized (Scheme 1).[30] The high nucleophilicity of the dimethylsulfonium ylide, as demonstrated by Mayr's reactivity parameters, would provide ample driving force to overcome the barriers for the nucleophilic addition process.[17, 20] As a Michael acceptor, 2-arylidene-1,3-indanediones are highly reactive 1,1-diactivated alkenes and have been used extensively as acceptors in organo-catalytic reactions for the synthesis of spirocyclic compounds. It is interesting to employ 1,1-diactivated alkenes developing cycloaddition reactions which led to highly substituted spiro-cyclopropane derivatives.[31-39] Herein, we would like to report our study on a highly efficient and diastereoselective spiro-Cyclopropanation of 2-arylidene-1,3

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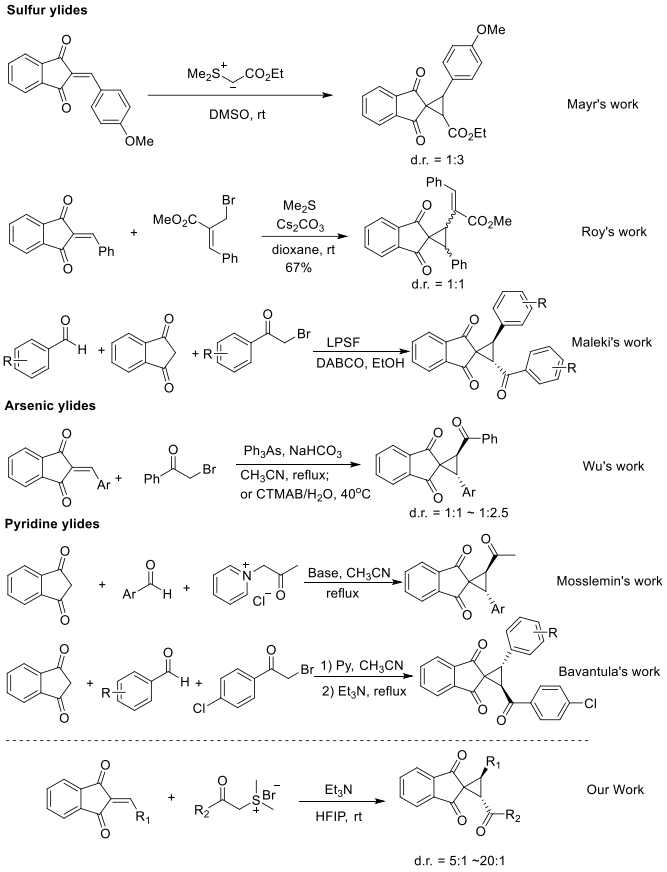
indanediones and dimethylsulfonium ylides under mild conditions (Scheme 1).

Scheme 1. Spiro-Cyclopropanation of 2-arylidene-1,3-indanediones and dimethylsulfonium ylides



Results

Our investigation started by studying the cyclopropanation of 2-benzylidene-indene-1,3-dione (**1a**) and dimethyl-sulfonium ylide (**2a**) as model substrates (Table 1). It is worth noting that as a Michael acceptor, 2-arylidene-1,3-indanediones are highly reactive 1,1-diactivated alkenes and have been used extensively as acceptors for the synthesis of spirocyclic compounds. It is interesting to employ 1,1-diactivated alkenes for the development of annulation reactions which led to highly substituted spiro-cyclopropane derivatives. After extensive screening of different solvents and bases, we were able to achieve the optimal condition. When 1.2 equivalents of Et_3N was utilized as the base and HFIP as the solvent at room temperature, 81% yield of the desired product was formed with greater than 20:1 diastereomeric ratio (Entry 14, Table 1). Hexafluoroisopropanol (HFIP) has emerged as an important solvent with interesting properties that allows it to promote a unique reactivity. In this context, HFIP has been reported to activate carbonyl compounds, epoxides, alcohols, halides, phenols and, more recently, alkynes or alkenes; however, the latter are still underexplored.[40-44]

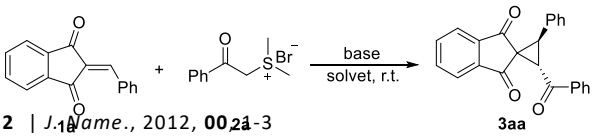


Table 1. Optimization of reaction conditions

Entry [a]	Base	Solvent	d.r. [b]	Yield (%) [c]
1	Cs_2CO_3	MeCN	20 : 3	51
2	Cs_2CO_3	HFIP	20 : 4	72
3	Cs_2CO_3	MeOH	>20 : 1	63
4	Na_2CO_3	HFIP	20 : 6	37
5	Et_3N	HFIP	>20 : 1	81[d]
6	DMAP	HFIP	20 : 2	50
7	DBU	HFIP	>20 : 1	38
8	Et_3N	MeCN	20 : 4	60
9	Et_3N	1,4-Dioxane	>20 : 1	70
10	Et_3N	MeOH	>20 : 1	45
11	Et_3N	TFE	4 : 20	24

[a] Reaction conditions: **1a** (0.22 mmol) with **2a** (0.26 mmol) and base (0.26 mmol) in 2 mL solvent. [b] Diastereomeric ratio (d.r.) was determined by ^1H NMR analysis. [c] NMR yields; they were determined by ^1H spectra using 1,3,5-trimethoxybenzene as an internal standard. [d] Yield of isolated product.

With the optimized conditions in hand, we studied the scope and limitation of this annulation reaction with various substituted 2-arylidene-1,3-indanediones and dimethylsulfonium ylides (Table 2). To our delight, this reaction exhibits excellent functional group compatibility. Both electron withdrawing and donating groups on 2-arylidene-1,3-indanediones were very well tolerated. For instance, 2-arylidene-1,3-indanediones bearing *o*-MeOPh, and 2,4-ClPh in the vicinal position (2 and 14) provided excellent yields and diastereomeric ratios. A naphthyl-substituted and heterocycle-incorporated 1,3-indanediones (19-22) were also efficiently transformed into their desired products with good yields. To explore the scope of dimethylsulfonium ylides, we employed a series of dimethylsulfonium ylides bearing different substituted phenyl rings. Interestingly, dimethylsulfonium ylide bearing an electron donating group such as *p*-MePh on the phenyl ring (24) gave a higher yield, whereas *p*-MeOPh group (25) furnished the desired product with a poor yield. The dimethylsulfonium ylides bearing electron withdrawing groups on the phenyl ring such as *m*-Cl and *o*-NO_2 (26 and 28) generated the corresponding annulation products with reduced yields. Alkyl- and aromatic heterocycle-containing dimethylsulfonium ylides (31-34) were successfully converted into the desired products with good yields and diastereomeric ratios. In order to emphasize the applicability of the protocol, we synthesized the annulation product **3aa** on a gram scale (starting with 1.00 g of **1a** to obtain **3aa** in 74% yield) under the optimized conditions (Scheme 2).

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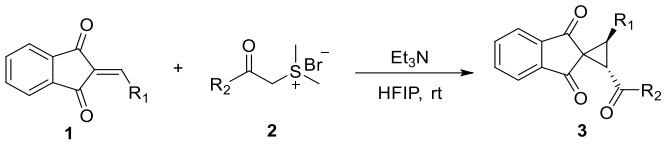

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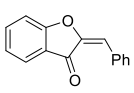
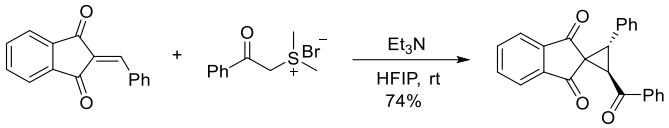
Table 2. Substrate Scope for Spiro-Cyclopropanation. [a]

Entry	R_1	R_2	Product	d.r. [b]	Yield (%) [c]
1	Ph	Ph	**3aa**	>20:1	81
2	*o*-MePh	Ph	**3ab**	>20:1	79
3	*m*-MePh	Ph	**3ac**	>20:1	43
4	*p*-MePh	Ph	**3ad**	>20:1	59
5	*o*-MeOPh	Ph	**3ae**	>20:1	79
6	*m*-MeOPh	Ph	**3af**	>20:1	97
7	*p*-MeOPh	Ph	**3ag**	>20:1	59
8	2,5-MeOPh	Ph	**3ah**	>20:1	96
9	*p*-^{t}BuPh	Ph	**3ai**	>20:1	85
10	*p*-MeSPh	Ph	**3aj**	>20:1	59
11	*o*-ClPh	Ph	**3ak**	>20:1	94
12	*m*-ClPh	Ph	**3al**	>20:1	73
13	*p*-ClPh	Ph	**3am**	>20:1	61
14	2,4-ClPh	Ph	**3an**	>20:1	70
15	*m*-NO_2Ph	Ph	**3ao**	>20:1	60
16	*p*-NO_2Ph	Ph	**3ap**	>20:1	83
17	2-Furyl	Ph	**3aq**	>20:1	44
18	2-Thienyl	Ph	**3ar**	20:7	34
19	3-Pyridinyl	Ph	**3as**	20:4	76
20	1-Naphthyl	Ph	**3at**	20:4	42
21	3-Phenylpropynyl	Ph	**3au**	>20:1	71
22	3-Phenylpropenal	Ph	**3av**	>20:1	60
23	Cyclohexyl	Ph	**3aw**	20:3	88
24	Ph	*p*-MePh	**3ba**	20:2	94
25	Ph	*p*-MeOPh	**3ca**	>20:1	36
26	Ph	*m*-ClPh	**3da**	20:2	58
27	Ph	*p*-BrPh	**3ea**	>20:1	89
28	Ph	*o*-NO_2Ph	**3fa**	>20:1	31
29	Ph	*m*-NO_2Ph	**3ga**	>20:1	71
30	Ph	*p*-CNPh	**3ha**	>20:1	97
31	Ph	2-Thienyl	**3ia**	20:7	66
32	Ph	2-Naphthyl	**3ja**	20:2	95
33	Ph	Me	**3ka**	>20:1	67
34	Ph	Et	**3la**	>20:1	95
35	Ph	OEt	**3ma**	20:9	45
36			**3na**	20:18	31

[a] Reaction conditions: **1** (0.22 mmol) with **2** (0.26 mmol) and Et_3N (0.26 mmol) in 2 mL HFIP. [b] Diastereomeric ratio (d.r.) was determined with the help of NMR. [c] Isolated yield after column chromatography purification.

Scheme 2. Scale-up Reaction of Model Substrates.



1a (1.00g) **2a** **3aa** (1.12g)

Based on our study and literature reports,[14, 45, 46] a plausible mechanism for the [2+1] annulation of 1,3-indanedione derivatives **1** with dimethylsulfonium ylide **2A** is proposed in Scheme 2. Under basic conditions, sulfonium salt **2** first isomerizes into sulfonium ylide **2A**. The Michael addition reactions occurs through a nucleophilic attack of the carbanion of **2A** to the electrophilic Michael acceptor center on 1,3-indanedione **1**, leading to betaine intermediates **2B** and **2C**. Then, a S_N2-type of cyclization of **2B** would smoothly afford the trans-product **3** with the concomitant release of the dimethyl sulfide. In contrast, the cis-product, 3' from the cyclization of 2C would not proceed, owing to the severe steric repulsion between the acyl group (R_1CO) and the substituent R_2 on 2C. Consequently, intermediate **2C** could be converted into cyclization precursor **2B** through reversible intramolecular proton transfer via the sulfonium ylide **2D**, finally forming the trans-product **3**. To our delight, we successfully obtained the X-ray crystallography data for compound **3ag** which confirmed the trans-structure (Scheme 3).[49]

In addition, we conducted three one-pot reactions for the formation of the desired cyclopropanation product **3aa** (Scheme 4). 1,3-indanedione was generated in situ from **4** and **5** in reaction 1, and dimethylsulfonium ylide was formed in situ from **6** and **7** in reaction 2. In reaction 3, both 1,3-indanedione and dimethylsulfonium ylide were generated in situ. Notably, the desired product from the one-pot reaction, **3aa** was obtained in a moderate yield in comparison to our stepwise condition, whereas the diastereomeric ratios remained excellent (>20:1).

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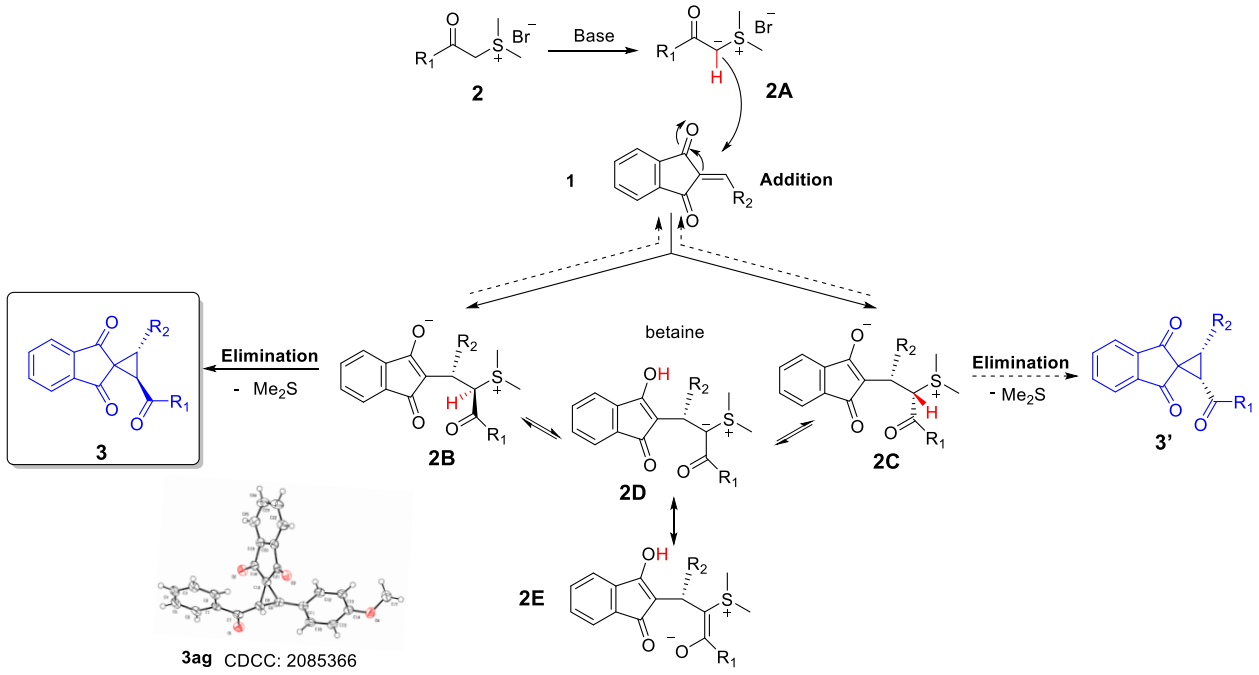
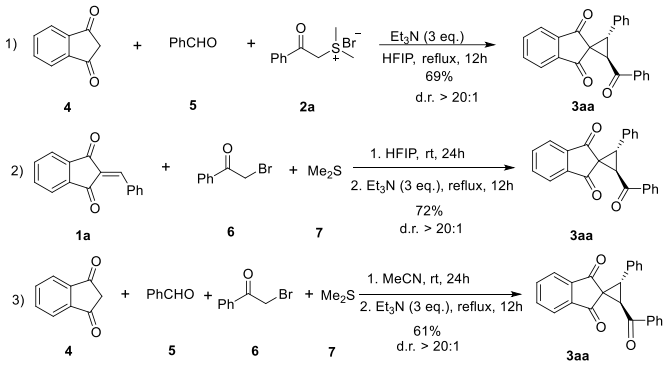
Scheme 3. Mechanism of Ylide-Mediated Cyclopropanations

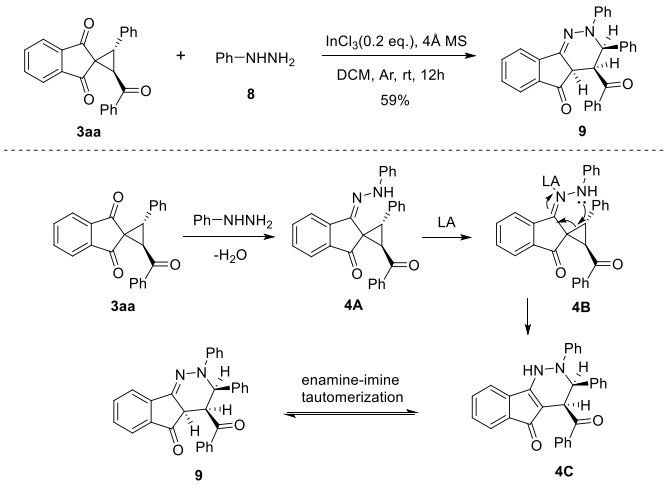


Scheme 4. Different Methods for One-pot Spiro-Cyclopropanation.



To demonstrate the applicability of this method, we carried out an annulation reaction of the cyclopropanation product **3aa** with an aryl hydrazine (Scheme 4). When the reaction is catalyzed by Lewis acid $InCl_3$ under inert atmosphere and room temperature, **3aa** converts into the corresponding ring-expanded product **9** in a good yield and its relative configuration was confirmed by ROESY in NMR. On the basis of other literature reports[47, 48] and our experimental outcomes, a plausible mechanism for this reaction was proposed, clarifying the observed pyridazine ring formation (Scheme 5).

Scheme 5. Further Transformations of **3aa** to Indeno[1,2-c]Pyridazine Derivatives and the Mechanism



Conclusion

In summary, we have developed an efficient and highly diastereoselective route for the synthesis of spiro-cyclopropanes via a base induced annulation reaction of 2-arylidene-1,3-indanediones and dimethylsulfonium ylides. In most of the examples, trans-products were formed in high diastereomeric ratio and chemical yields. Additionally, a ring expansion of cyclopropanes for the synthesis of indeno[1,2-c]pyridazine has also been realized. We believe that this protocol serves as a simple tool for the rapid and selective synthesis of complex and strained spiro-cyclopropanes and their derivatives.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

This work was supported by the National Research Projects Cultivation Project (No. 2019-21GP05), and the Hubei Provincial

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College Students' Platform for Innovation and Entrepreneurship Training Program (No. S202010927044). The authors are also grateful to College of Science and Health, and the chemistry department of William Paterson University.

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49. Crystallographic data for **3ag** has been deposited with the Cambridge Crystallographic Data Centre as

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