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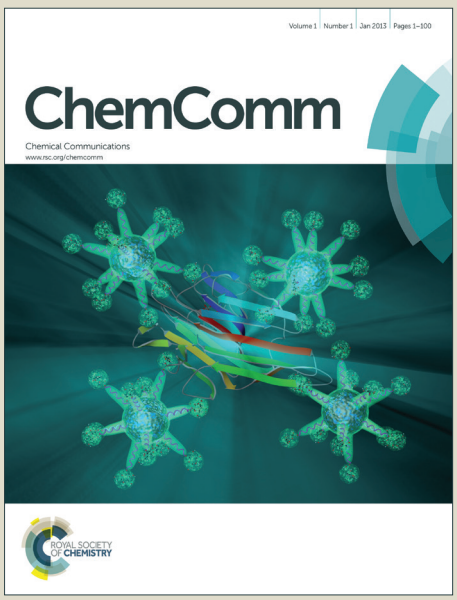

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A Facile Formal [2+1] Cycloaddition of Styrenes with alpha-Bromocarbonyls catalyzed by Copper: An Efficient Synthesis of Donor-Acceptor Cyclopropanes

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Reactions of 2-bromoesters and styrenes underwent [2+1] cycloaddition reactions, i.e., cyclopropanation, to produce donor-acceptor (D-A) cyclopropanes through radical addition-ring closure process. In this reaction, the combination of copper(II) complex and amines is found to be a good catalyst system to obtain cyclic compounds in high yields. This reaction provides an efficient protocol to synthesize D-A cyclopropanes, which are very important building blocks in organic synthesis.

Cyclopropanations have been studied extensively for many decades. A vast amount of cyclopropyl functional groups can be found in natural compounds possessing biological activities[1], pharmaceuticals[2], agrochemicals[3] and other synthetic intermediates[4]. Among cyclopropane structures, donor-acceptor (D-A) cyclopropanes are currently widely utilized
intermediates in synthetic organic chemistry since they can easily undergo a ring-opening reaction in the presence of a Lewis acid to produce a [3 + n] annulation product[5].
The selective preparations of functionalized cyclopropanes are accomplished by reacting olefins with carbonyl derivatives[6]. For example, a vast array of cyclopropyl derivatives can be enantioselectively synthesized[8] through the Simmons–Smith reaction[7] and the generation of organometallic carbenoids through the reactions of diazo compounds and transition metal catalysts. A Michael initiated ring closure reaction (MIRC) is another option for the preparation of cyclopropanes[9]. One of the advantages of using a MIRC for cyclopropanation is that stable halocarbonyl compounds instead of diazo compounds can be reacted with electron deficient olefins (Michael acceptors) under mild conditions. Although the MIRC is a very convenient process for cyclopropanations, electron deficient α,β-unsaturated carbonyl, nitro or sulfonyl compounds (not styrene derivatives) can only be utilized in MIRC reactions.

We recently reported that the reaction of alpha-bromocarbonyl compounds with styrenes gives tertiary-alkyl olefinations in good yields via an atom transfer radical addition (ATRA) and a subsequent dehydrohalogenation (Heck-like reaction)[10]. During the course of our research in radical chemistry, we also found that cyclopropanation can occur via an ATRA-initiated ring closure reaction. Unlike MIRC, which is initiated by the generation of anionic species **A**, our current cyclopropanation methodology begins with the reaction of halocarbonyl compounds **1** and a copper(I) salt[10,11] to generate radical species **C** (Scheme 1). A key to success for both the MIRC and our reaction methodology involves the ring-closing step of intermediate **B** or **D,** which is generated from the addition of **A** or **C** to olefin (**2** or **2′**). The advantages of using halocarbonyl compounds **1** include 1) a facile generation of radicals without any excess initiator, 2) an easy preparation (simple bromination of carbonyl compounds or many commercially available sources), and 3) a good susceptibility for added functional groups, which provides new opportunities or possibilities for the synthesis of D-A cyclopropanes **3**. There are reports in the literature where halocarbonyl compounds **1** are utilized as a cyclopropanation reagent[12], which includes the efficient cyclopropanation of [60] fullerene under mild conditions (Bingel reaction)[13]. However, a general methodology for the catalytic synthesis of D-A cyclopropanes **3** with **1** has not yet been established. In this context, we envisaged a formal [2+1] cycloaddition of halocarbonyl compounds **1** with styrene derivatives **2** using a copper(II) catalyst to afford D-A cyclopropanes **3**.

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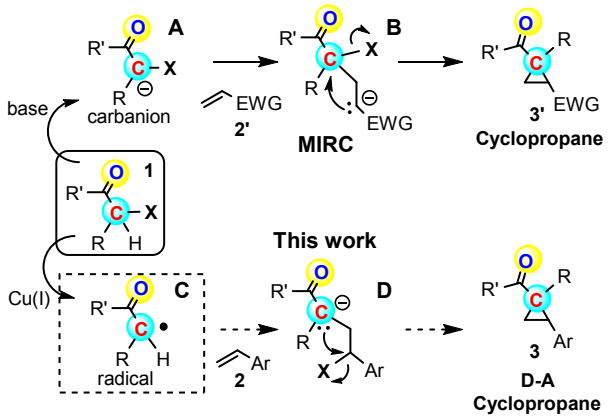
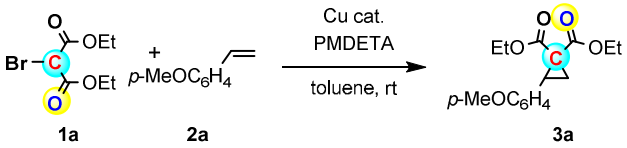


Scheme 1 The difference between MIRC and our formal [2+1] cycloaddition.

As we expected, bromomalonate **1a** selectively provided cyclopropane **3a** in the presence of *p*-methoxystyrene **2a**, CuI, PMDETA *N*,*N*′,*N*″,*N*‴,*N*‴-pentamethyldiethylenetriamine (PMDETA), and toluene as a solvent at room temperature (Table 1, Run 2). Without a catalyst or an amine, no reaction occurred (Run 1). **1a** reacts with Cu(I) to produce the corresponding alkyl radical species for the ATRA initiated ring closure reaction. CuI gave 32% yield, whereas cationic copper catalyst, $[Cu(I)(MeCN)_4]BF_4$, gave 81% yield (Runs 2 and 3). Cu(II) catalysts are not suitable for the generation of alkyl radicals from bromocarbonyl compounds **1** without reducing reagents; however, $[Cu(II)(H_2O)_6](BF_4)_2$ and $Cu(II)Cl_2$ underwent cyclopropanation efficiently (Runs 4 and 5). Although various copper(I) catalysts were screened, $[Cu(II)(H_2O)_6](BF_4)_2$ gave the highest yield (90%, Run 5). In this reaction, any reductants, such as low-valent metals, Sn(II), glucose, hydrazine, and ascorbic acid, were not used to generate active Cu(I) species from Cu(II) species but Cu(I) is considered to be a real active catalyst in this reaction[11]. Weiss and co-workers have reported that excess amine can reduce Cu(II) to Cu(I)[14]. Therefore, PMDETA could act as a reductant and showed the best yield of all alkylamines tested. We suspected that this reaction occurs through carbene species, but dimerization of **1** to give fumaric acid ester was not detected. In addition, the reaction presented here did not occur in the presence of 2,2,6,6-tetramethylpiperidine 1-Oxyl(TEMPO), which could indicate the radical reaction (alkylated TEMPO was detected[10c]).

Under the best conditions shown in Table 1 Run 5, styrenes **2** was able to react with bromocarbonyl compounds **1** in moderate to excellent yields at room temperature (Table 2). 2-Bromomalonate derivatives **1** smoothly reacted with *p*-methoxystyrene (**2a**) and gave the products **3b**–**3e**. Bromomalonic acid allyl ester leading to **3d** has double bonds in the molecule; however, the double bonds did not

Table 1 Optimization.



1a 2a 3a

Run	Cu cat.	Yield of **3a** (%)
1	none	0
2	CuI	32
3	$[Cu(MeCN)_4]BF_4$	81
4	$CuCl_2$	52
5	$[Cu(H_2O)_6](BF_4)_2$	**90**

All reactions were carried out for 20 h in toluene with 10 mol% Cu salt, PMDETA (1.2 equiv), **1a** (2.0 equiv.) and **2a** (1.0 equiv.). Yields were determined by ^{1}HNMR.

affect the yields. This reaction is expected to involve a radical reaction; nevertheless, the double bonds remained intact. Bulky malonate esters led to **3e** in moderate yield, and highly bulky malonate having *t*-Bu groups did not undergo cyclization. Malonamide leading to **3g** was very unstable during the reaction, and the corresponding dehalogenated product was produced instead of cyclopropane **3g**. Interestingly, unsymmetrical bromoesters leading to **3h** and **3i** enabled stereoselective cyclopropanations with 59:41 and 85:15 for trans:cis selectivity, respectively. In the MIRC reaction of bromo-phosphonomalonates, cis-cyclopropylphosphonates were the main products; however, our reaction gave trans-selectivity in spite of similar steric bulkiness between sulfonyl and phosphonate groups[15]. The cyclopropanation can be applied to various styrenes **2** with dimethyl bromomalonate (**1b**) in moderate to good yields. Methoxy- and methyl-substituted styrenes leading to **3j**–**3m** resulted in good yields. Simple styrene easily undergoes a polymerization reaction in the presence of alkyl radicals; however, 79% of **3n** was obtained. Although, according to our previous results[10], electron deficient styrenes were not suitable for the reaction with tertiary-alkyl radicals, the reactions proceeded smoothly and gave the corresponding products **3o**–**3r** in moderate to good yields. β-Substituted styrenes were not reacted, whereas α-methylstyrene gave the cyclopropane **3s** in 76% yield.

The D-A cyclopropanes **3** obtained by the proposed copper-catalyzed cycloaddition are useful building blocks that can be easily transformed into a wide variety of functionalized cyclo-compounds by taking advantage of the versatile reactivities of **3** (Scheme 2)[16]. For example, syntheses of cyclic amidine **4**[17] and tetrahydrofuran **5**[18] via Lewis acid catalyzed [3+2] cycloadditions of donor-acceptor cyclopropane **3n** and imine or aldehyde have

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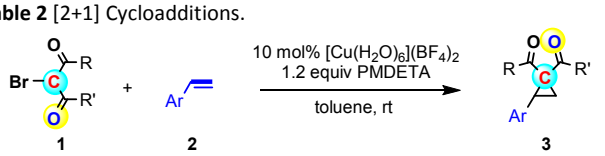
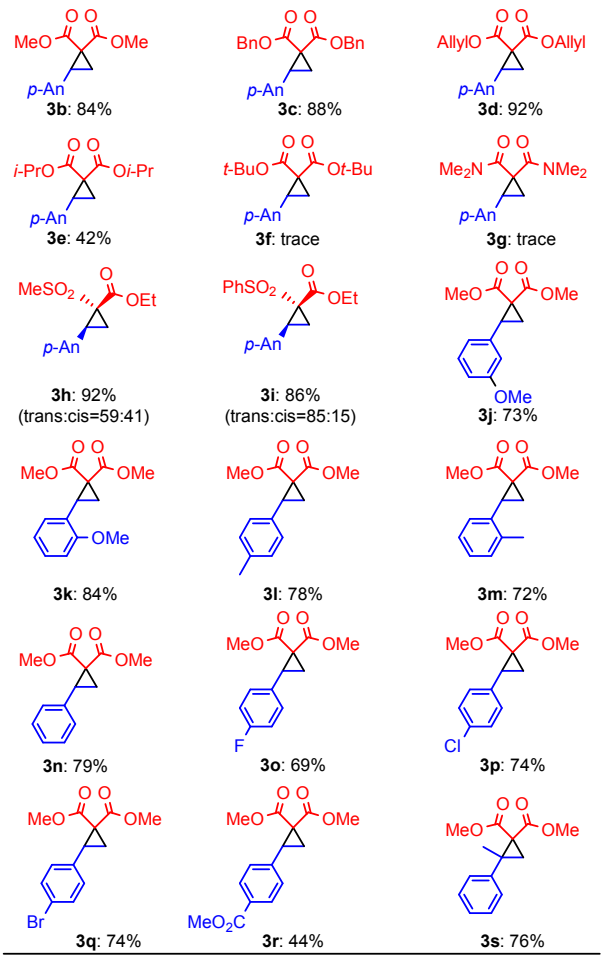
been achieved. **3n** also can be transformed into cyclopropane hemimalonate

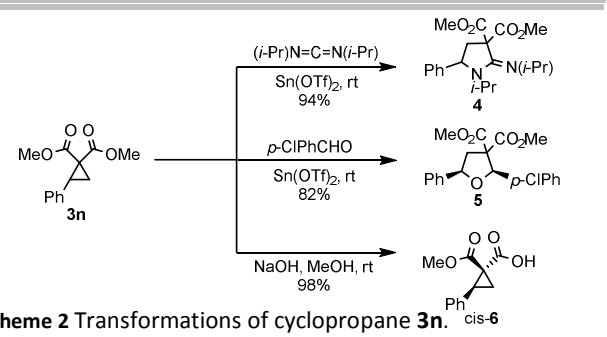
Table 2 [2+1] Cycloadditions.



Yield of **3**



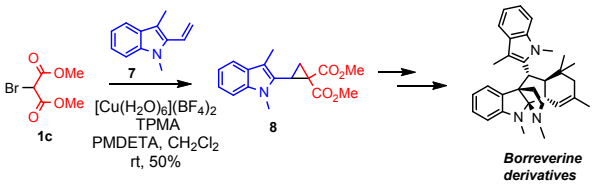
All reactions were carried out for 20 h at rt in toluene with 10 mol% $[Cu(II)(H_2O)_6](BF_4)_2$, PMDETA (1.2 equiv), **1** (2.0 equiv.) and **2** (1 equiv.). Isolated yields.



Scheme 2 Transformations of cyclopropane **3n**.

6 stereoselectively, which is a useful reactant for a nucleophilic ring-opening reaction using internal carboxylic acid activation[19].We also tried the reaction with α-chloromalonate but no reaction occurred. In the case of α-bromo-β-ketoesters, no cyclopropanes were obtained.

The rationale behind the attention accorded cyclization chemistry has been based, in part, on its potential to streamline routes towards valuable synthetic targets. Thus, we tried to synthesize the core structure of borreverine[20]. Borreverine alkaloid, which demonstrates antimicrobial action in vitro, has a cyclopropyl-substituted core structure **8** (Scheme 3). This core can be synthesized from the unstable vinylated indole **7**. One of the most serious problems in cyclopropanation reaction is the use of an unstable olefin as a starting material. In rhodium catalyzed cyclopropanation with diazoesters, almost all vinylated compounds can be reacted to produce cyclopropanes; however, 2-vinylated indole **7** was not suitable for the reaction because the vinylated indole is too unstable to react with diazoesters in good yield[20a]. In this case, our copper catalyzed system successfully gave 50% yield of the borreverine core **8** from **7**.



Scheme 3 Synthesis of the core **8** of borreverine.

Conclusions

In conclusion, we found a copper-catalyzed cycloaddition of bromocarbonyl compounds **1** and styrenes **2** to produce D-A cyclopropanes **3**, which are useful building blocks in organic synthesis. Current our formal [2+1] cycloaddition of 2-bromoester **1** with styrene **2** through a radical mechanism is very rare because **1** is generally used for MIRC reaction with Michael acceptor such as α,β-unsaturated carbonyl-, and nitro compounds. The reaction developed in this study provides facile access to a series of core structures of natural products. Further investigations, including asymmetric cycloaddition and mechanistic studies, are currently underway.

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