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Multicomponent 1,3-Bifunctionalization of Donor–Acceptor Cyclopropanes with Arenes and Nitrosoarenes

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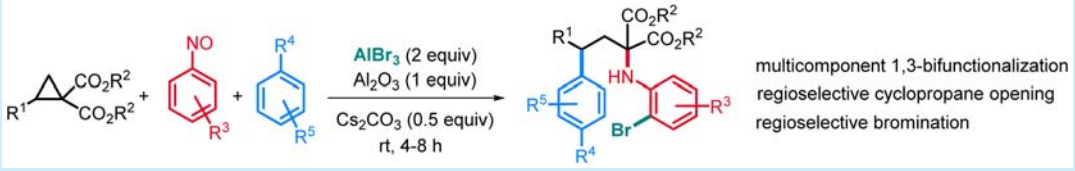
Supporting Information



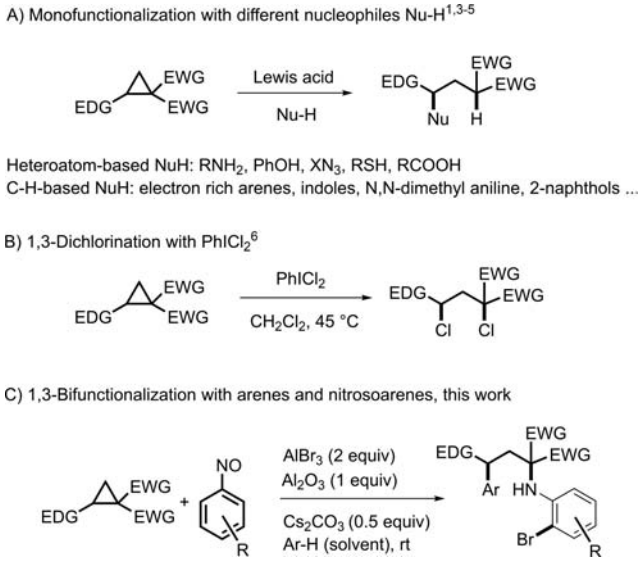
ABSTRACT: $AlBr_3$-mediated multicomponent 1,3-bifunctionalization of donor–acceptor cyclopropanes using arenes and nitrosoarenes as coupling partners is presented. In the cascade, a C–C, a C–N, and a C–Br bond is formed. Reactions are easy to conduct and proceed under mild conditions. The γ,γ-disubstituted N-arylated α-amino esters obtained as products are readily further chemically modified rendering the method valuable.

Donor–acceptor (DA) cyclopropanes are popular and powerful building blocks in organic synthesis.[1] Pioneering work by Wenkert and Reißig appeared in the 1970s and 1980s.[2] Since, the chemistry of DA cyclopropanes gained great attention. Due to their high π character, inherent angle strain, and intrinsic torsional strain, DA cyclopropanes participate in different reactions such as ring openings, annulations, or rearrangements.[1] Among these reaction types, ring opening of DA cyclopropanes is of particular interest as it provides direct access to scaffolds, which are valuable for the preparation of biologically active compounds.[1]

Ring opening reactions of DA cyclopropanes are generally conducted in the presence of a Lewis acid, which coordinates to the acceptor substituent thereby activating the 3-membered ring. Attack by the nucleophile then takes place at the carbon atom next to the donor substituent. Various heteroatom-based as well as carbon nucleophiles have been used for this purpose.[3−5] The resulting negative charge associated with the acceptor substituent is typically neutralized by trapping with a proton leading to monofunctionalization of the former cyclopropane ring (Scheme 1A). Preparative more valuable is the 1,3-bifunctionalization. In such cases the ensuing anion gets trapped by an electrophile other than a proton. This has been achieved in formal cycloadditions of cyclopropanes where ring opening occurs by ambident reagents that react as nucleophiles and also bear an electrophilic site.[1]

However, noncyclizing 1,3-bifunctionalization of DA cyclopropanes using two noninterlinked reaction components, one as an electrophile and the other as a nucleophile, is very rare. Along these lines, Werz and co-workers showed an elegant work where treatment of DA cyclopropanes with $PhICl_2$ under mild conditions leads to 1,3-dichlorination of the activated cyclopropane (Scheme 1B).[6] We herein disclose a four-component 1,3-bifunctionalization of DA cyclopropanes involving arenes as nucleophiles and nitrosoarenes as electrophiles in the presence of $AlBr_3$ as a Lewis acidic reagent to provide γ,γ-diaryl-N-arylated amino ester derivatives that are of importance for pharmaceutical and agrochemical industry (Scheme 1C).[7]

Scheme 1. Ring Opening Reactions of DA Cyclopropanes



Within the framework of our program devoted to the development of nitrosoarene chemistry,[8] we recently disclosed stereospecific [3 + 3] annulation of DA cyclopropanes with nitrosoarenes in the presence of $MgBr_2$ to afford tetrahydroquinolines (see mechanistic discussion below).[9] Inspired by this

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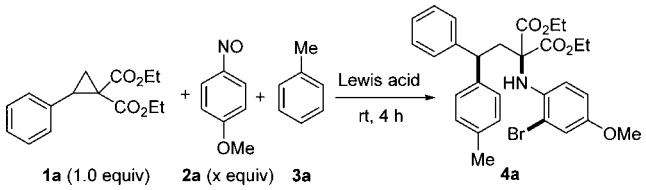
result, we commenced the present study by examining the reaction between diethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1a**) and easily prepared *p*-methoxynitroso-benzene (**2a**) as model substrates in the presence of a superstoichiometric amount of a Lewis acid under different conditions (Table 1).

Table 1. Optimization Studies



1a (1.0 equiv) **2a** (x equiv) **3a** **4a**

entry[a]	2a (equiv)	Lewis acid (equiv)	yield[b] (%)
1	1.5	$AlBr_3$ (1.5)	32
2	1.5	$AlBr_3$ (2.0)	43
3	1.5	$AlBr_3$ (2.5)	38
4	1.5	$FeBr_3$ (2.0)	22
5	1.5	$InBr_3$ (2.0)	30
6	2.0	$AlBr_3$ (2.0)	48
7	2.5	$AlBr_3$ (2.0)	45
8[c]	2.0	$AlBr_3$–Al_2O_3 (2.0)	54
9[c,d]	**2.0**	**$AlBr_3$-Al_2O_3 (2.0)**	**58**
10[c,e]	2.0	$AlBr_3$–Al_2O_3 (2.0)	46

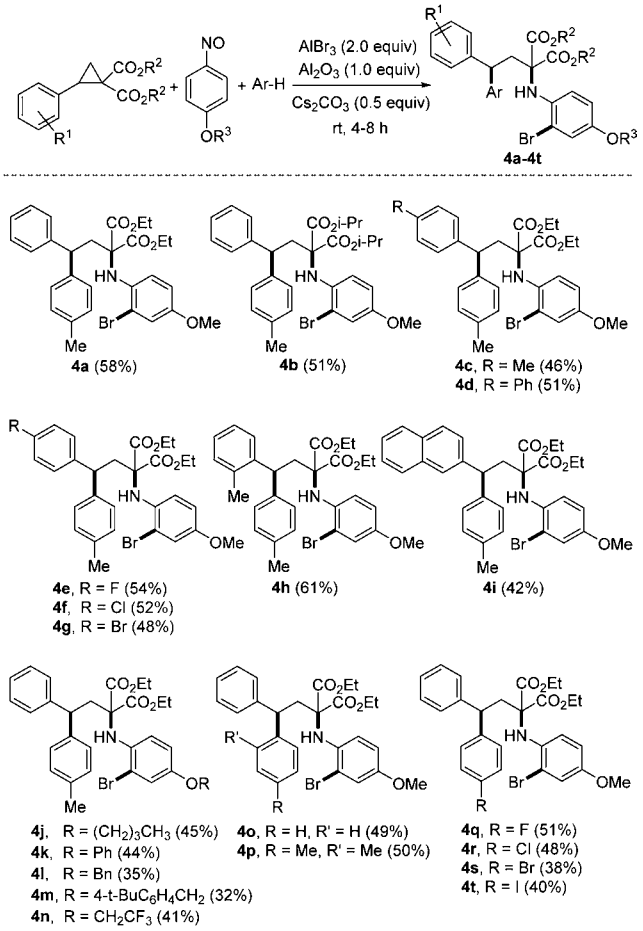
[a]0.5 mL of **3a** was used. [b]Isolated yield. [c]1.0 equiv of Al_2O_3 was used. [d]0.5 equiv of Cs_2CO_3 was used. [e]1.0 equiv of Cs_2CO_3 was used.

Reaction of **1a** and **2a** with 1.5 equiv of $AlBr_3$ in toluene (**3a**) at 25 °C for 4 h afforded α-amino malonate **4a** in 32% isolated yield as a regioisomerically pure compound (Table 1, entry 1). The amazing cascade comprises regioselective γ-Friedel–Crafts type arylation of the DA cyclopropane by the solvent and α-amination with the nitrosoarene. Amination is followed by N–O bond cleavage with concomitant *ortho*-bromination of the *N*-aryl group. The yield of **4a** could be increased to 43% by using 2.0 equiv of $AlBr_3$ (Table 1, entry 2). However, a further increase in the stoichiometry of $AlBr_3$ resulted in a decreased yield (Table 1, entry 3). Various Lewis acids were screened next. With $MgBr_2$, $AlCl_3$, AlI_3, $CuBr_2$, $NiBr_2$, and $ZnBr_2$, the targeted cascade does not occur (not shown in Table 1). $FeBr_3$ and $InBr_3$ provided **4a** albeit in lower yields (22% and 30%, Table 1, entries 4 and 5).

With the observation that a small amount of **1a** remained unreacted after full consumption of the nitrosoarene component, the amount of **2a** was increased. Addition of 2.0 equiv of **2a** provided complete conversion of **1a** affording the targeted product **4a** in 48% yield (Table 1, entry 6). Increasing the amount of **2a** does not further improve the result (Table 1, entry 7). Gratifyingly, when the reaction was carried out by using a mixture of $AlBr_3$ and Al_2O_3, yield of **4a** was improved to 54% (Table 1, entry 8, Al_2O_3 was added to trap traces of water and acid). A further improvement was achieved by adding 0.5 equiv of Cs_2CO_3 (acts as buffer), and **4a** was isolated in 58% yield (Table 1, entry 9). Increasing the amount of Cs_2CO_3 leads to a worse result (Table 1, entry 10).

With the optimized reaction conditions in hand (Table 1, entry 9), we next investigated the scope and limitations of the method by using various racemic DA cyclopropanes in combination with *p*-methoxynitrosobenzene (**2a**) and toluene (**3a**) as reaction partners. Results are presented in Scheme 2. The activating ester functionality in the DA cyclopropane was varied first, and the isopropyl ester **1b** gave **4b** in 51% yield. To

Scheme 2. Scope of the Multicomponent 1,3-Bifunctionalization of DA Cyclopropanes



investigate electronic effects exerted by the donor substituent in the DA cyclopropane component, the phenyl group in the parent **1a** was replaced by substituted aryl groups. Neither electron-donating nor electron-withdrawing substituents at the para-position of the phenyl ring affected the efficiency of this cascade, and the corresponding products **4c–g** were obtained in 46–54% yield. Moreover, steric effects seem to be less important as *o*-tolyl cyclopropane **1h** gave **4h** in 61% yield. The naphthyl congener **1i** worked and the desired product **4i** was isolated in moderate yield.

Next, the scope of the reaction was examined with respect to the nitrosoarene component. We found only oxygen-containing electron-donating groups at the para-position of the nitrosobenzene to be tolerated. Alkoxy- and aryloxy-substituted nitrosoarenes reacted with **1a** in the presence of **3a** to give the corresponding α-amino malonates **4j–m** in moderate to good yields. Notably, even with the electron-poorer *p*-(2,2,2-trifluoroethoxy)-nitrosobenzene, the reaction occurred smoothly and **4n** was isolated in 41% yield. However, *ortho*- and *meta*-methoxy nitrosobenzene did not work in the cascade. We then investigated the scope of the four component cascade reaction by varying the arene component used as a solvent. Electronically neutral benzene and moderately electron donating *m*-xylene underwent smooth reaction resulting in the formation of the corresponding products **4o** and **4p** in 49% and 50% yield, respectively. The structure of **4o** was unambiguously confirmed by X-ray analysis (Figure 1). Quite surprisingly, haloarenes

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participated well in the reaction furnishing products **4q–t** with complete para-regioselectivity in moderate to good yields.

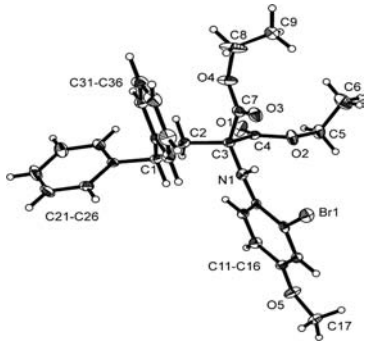
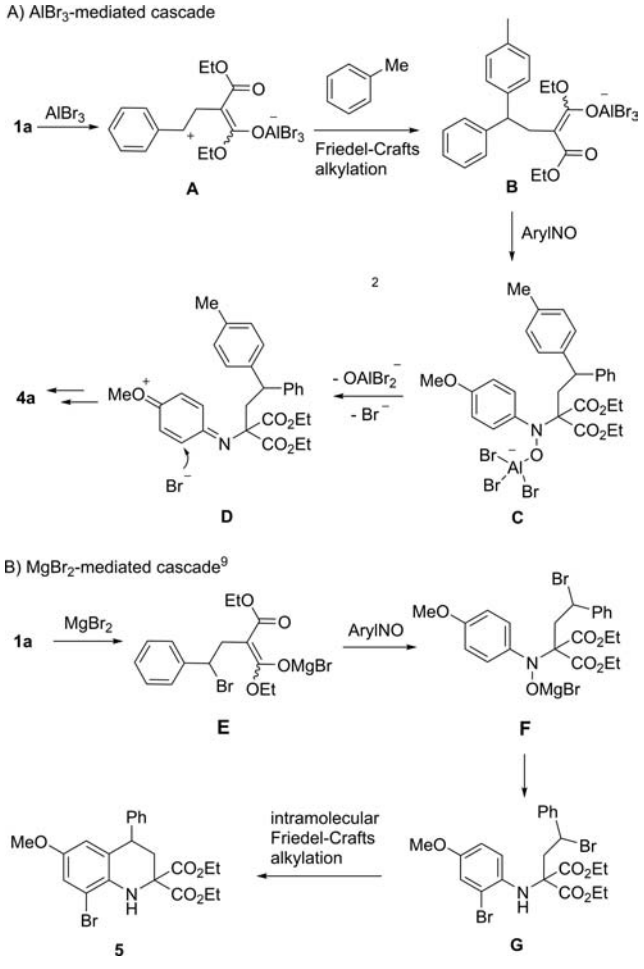


Figure 1. Crystal structure of compound **4o** (50% ellipsoid probability).

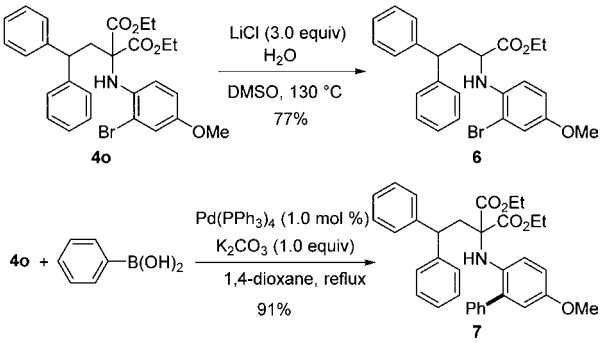
On the basis of our previous work[9] and literature reports,[10] a plausible mechanism for the multicomponent 1,3-bifunctionalization of DA cyclopropanes reaction is suggested in Scheme 3. Ring-opening of the DA cyclopropane **1a** with $AlBr_3$ generates the reactive benzylic cation **A**,[11] which directly undergoes Friedel–Crafts type alkylation at the para-position of toluene (**3a**). The resulting enolate **B** further reacts with *p*-methoxynitrosobenzene to **C**. N–O bond cleavage assisted by the methoxy group leads to **D**, which is then trapped by the bromide anion. Tautomerization eventually provides **4a**. Notably, as previously shown[9] reaction with $MgBr_2$ occurs via a different pathway. Ring-opening with $MgBr_2$ provides the benzylic bromide **E** stereospecifically, and intermolecular reaction with the solvent is suppressed (also if an arene is used as solvent). As in the Al-chemistry, the Mg-enolate is then α-aminated by the nitrosoarene to give **F**. *ortho*-Bromination and N–O bond cleavage provide **G**, which further reacts via an intramolecular Friedel–Crafts alkylation to give **5**. Hence, the difference in the bromination aptitude of the Lewis acid in the initial ring-opening step determines the reaction outcome to give either the 1,3-bifunctionalization products **4** or tetrahydroquinolines **5**.

Scheme 3. Plausible Mechanism: $AlBr_3$ and $MgBr_2$ Show Chemodivergent Chemistry



To demonstrate the synthetic value of the method, we investigated follow-up chemistry using **4o** as a substrate (Scheme 4). When **4o** was subjected to Krapcho decarboxylation conditions, *N*-arylated α-amino ester **6** was obtained in 77% isolated yield, and **4o** also engaged in a Suzuki–Miyaura coupling with phenylboronic acid to provide **7** in 91% yield.

Scheme 4. Follow-up Chemistry



In conclusion, we have reported a new type of multicomponent 1,3-bifunctionalization of DA cyclopropanes with arenes and nitrosoarenes in the presence of $AlBr_3$ to provide γ,γ-disubstituted *N*-arylated α-amino ester derivatives. $AlBr_3$ acts as a Lewis acid and also as a bromide anion donor in the regioselective arene bromination step. In these cascades, a C–C bond along with one C–N bond and one C–Br bond are formed. Importantly, $AlBr_3$ and $MgBr_2$ show chemodivergent reactivity. Whereas $MgBr_2$ activates the DA cyclopropane to give a benzylic bromide, $AlBr_3$ generates the corresponding benzylic cation. The high reactivity of the cation as compared to the bromide allows for intermolecular Friedel–Crafts type alkylation of the arene. The trapping of the benzylic cation also works with electron-poorer halogenated arenes that are used as solvents. Reactions are easy to conduct and occur under mild conditions in a short time (4–8 h).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02815.

Experimental details, characterization data for the products, and supplementary crystallographic data CCDC 1475169 (**4o**) (PDF)

X-ray data for **4o** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) When enantioenriched **1g** was reacted with **2a** and **3a** under standard reaction conditions we found complete loss of stereochemical information, and α-amino malonate **4g** was obtained in racemic form.

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