Annulations

International Edition: DOI: 10.1002/anie.201604373
German Edition: DOI: 10.1002/ange.201604373

Lewis Acid Catalyzed Selective Reactions of Donor–Acceptor Cyclopropanes with 2-Naphthols

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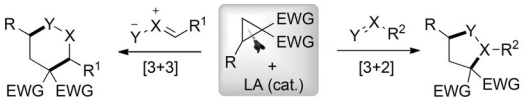
Abstract: *Lewis acid-catalyzed reactions of 2-substituted cyclopropane 1,1-dicarboxylates with 2-naphthols is reported. The reaction exhibits tunable selectivity depending on the nature of Lewis acid employed and proceed as a dearomatization/rearomatization sequence. With $Bi(OTf)_3$ as the Lewis acid, a highly selective dehydrative [3+2] cyclopentannulation takes place leading to the formation of naphthalene-fused cyclopentanes. Interestingly, engaging $Sc(OTf)_3$ as the Lewis acid, a Friedel–Crafts-type addition of 2-naphthols to cyclopropanes takes place, thus affording functionalized 2-naphthols. Both reactions furnished the target products in high regioselectivity and moderate to high yields.*

Donor–acceptor (D–A) cyclopropanes are a versatile class of three-atom building blocks owing to the exceptional reactivity of the cyclopropane moiety and the vicinal arrangement of the donor and acceptor groups.[1] The cyclopropane ring can be cleaved under Lewis acid conditions (because of the high ring strain of ≈ 27.5 kcal mol^{-1}),[2] thus generating 1,3-zwitterionic intermediates which can undergo formal cycloaddition reactions and also react with both nucleophiles and electrophiles. The interception of D–A cyclopropanes with carbon–carbon double bonds under Lewis acid activation can result in cyclopentannulation reactions by formal [3+2] cycloaddition reactions [Eq. (1); EWG = electron-withdrawing group].[3,4] Five-membered heterocycles can easily be accessed by the trapping of D–A cyclopropanes with aldehydes/imines.[5] Moreover, D–A cyclopropanes can undergo reaction with several 1,3-dipoles in a formal [3+3] annulation reaction resulting in the synthesis of functionalized six-membered heterocycles.[6]



(1)

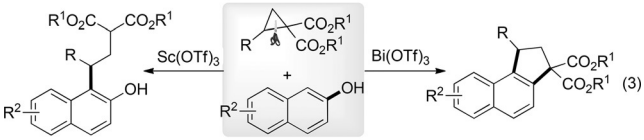
The Lewis acid catalyzed ring-opening of D–A cyclopropanes using nucleophiles is one of the straightforward methods for rapid access to 1,3-bifunctional compounds.[1d] A variety of heteroatom-containing nucleophiles and electron-rich aromatic compounds are known to add to D–A cyclopropanes activated by Lewis acids [Eq. (2)]. The ring-opening reactions of D–A cyclopropanes using phenols and amines were demonstrated by the group of Charette.[7,8] Subsequently, the enantioselective scandium(III)-catalyzed ring-opening reactions of D–A cyclopropanes with nucleophiles such as amines, alcohols, thiols, and carboxylic acids, were recently uncovered by Feng and co-workers.[9] Regarding the addition of carbon nucleophiles, the addition of indoles to D–A cyclopropanes was reported by the groups of Kerr and Johnson.[10] In addition, the Lewis acid catalyzed reactions of D–A cyclopropanes with malononitriles by a domino ring-opening/cyclization strategy was recently disclosed by the group of Ghorai.[11] Herein, we report the Lewis acid catalyzed reactions of D–A cyclopropanes with 2-naphthols as the nucleophilic source. The reaction follows a dearomatization/rearomatization strategy and is highly tunable [Eq. (3); Tf = trifluoromethanesulfonyl]. By employing $Bi(OTf)_3$ as the Lewis acid for the cyclopropane activation, the reaction afforded naphthalene-fused cyclopentanes through a highly selective dehydrative [3+2] cyclopentannulation. It is envisioned that the reaction proceeds by way of a dual activation mode, where bismuth(III) activates both the D–A cyclopropane and 2-naphthol. With $Sc(OTf)_3$ as the Lewis acid, selectivity was switched to functionalized 2-naphthols formed by the Friedel–Crafts-type addition of 2-naphthols to cyclopropanes. It may be mentioned that the 1,3-bifunctional derivatives obtained by the ring-opening of D–A cyclopropanes are present as a core structure in some of the biologically and pharmaceutically active molecules.[12]

Ring opening of D–A cyclopropanes with nucleophiles

(2)

Nu = amines, phenols, thiols, acids, indoles, malononitriles etc.

Selective reactions of D–A cyclopropanes with 2-naphthols (this work)



(3)

Friedel–Crafts type addition
Sc^{III} activates the cyclopropane

dehydrative [3+2] annulation
dual activation using Bi^{III}

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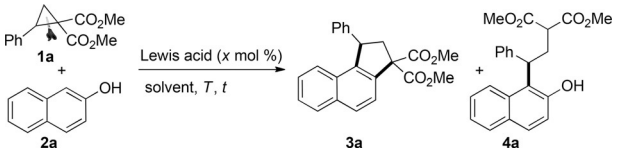
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201604373.

The present study commenced with the treatment of the D–A cyclopropane **1a** with 2-naphthol (**2a**) under Lewis acid catalyzed reaction conditions (Table 1). Interestingly, when **1a** and **2a** were mixed with $Bi(OTf)_3$ in CH_2Cl_2 at 30 °C for 24 hours, the reaction afforded the cyclopentane-fused naphthalene **3a** in 63% yield and the 2-naphthol derivative **4a** in 35% yield (entry 1).[13] The cyclopentane **3a** was formed by the dehydrative [3+2] reaction whereas the **4a** resulted from the Friedel–Crafts addition of **2a** to **1a**. The reaction did not proceed at all when performed at 0 °C, and reaction at 45 °C did not improve either the yield or selectivity (entries 2 and 3). A rapid solvent screening revealed that the reaction was sluggish in THF, but gave comparable results in other chlorinated solvents such as $CHCl_3$ and DCE (entries 4–6). Other Lewis acids such as $Cu(OTf)_2$ and $In(OTf)_3$ were not beneficial in the present reaction although $In(OTf)_3$ reversed the selectivity to give **4a** (entries 7 and 8). Gratifyingly, when the reaction was carried out using a mixture $Bi(OTf)_3$ and KPF_6, the reaction furnished **3a** in 84% yield and **4a** in 12% yield (entry 9).[14] Slight modification in the reaction conditions resulted in the selective formation of **3a** in 83% yield upon isolation (entry 10). Moreover, the reaction carried out with $Yb(OTf)_3$ as the Lewis acid afforded **4a** in 44% yield in high selectivity (entry 11). Finally, use of $Sc(OTf)_3$ resulted in the exclusive formation of **4a** in 84% yield upon isolation (entry 12).[15]

Table 1: Optimization of the reaction conditions.[a]

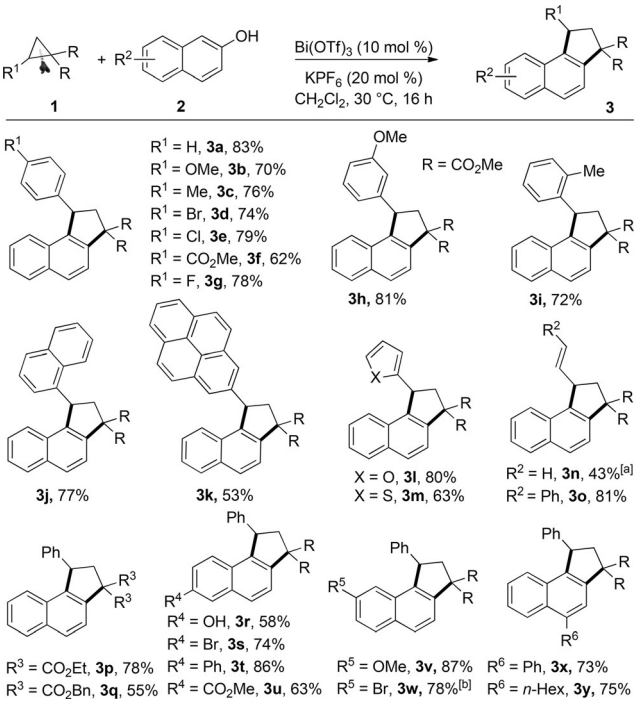


Entry	Lewis acid (*x* mol%)	Solvent	*T* [°C]	*t* [h]	Yield [%][b] **3a**/**4a**
1	$Bi(OTf)_3$ (20)	DCM	30	24	63/35
2	$Bi(OTf)_3$ (20)	DCM	0	24	<5/<5
3	$Bi(OTf)_3$ (20)	DCM	45	24	62/36
4	$Bi(OTf)_3$ (20)	THF	30	24	<5/<5
5	$Bi(OTf)_3$ (20)	$CHCl_3$	30	24	61/32
6	$Bi(OTf)_3$ (20)	DCE	30	24	61/34
7	$Cu(OTf)_2$ (20)	DCM	30	24	48/38
8	$In(OTf)_3$ (20)	DCM	30	24	31/67
9[c]	$Bi(OTf)_3 + KPF_6$	DCM	30	16	84/12
10[d]	$Bi(OTf)_3 + KPF_6$	DCM	30	16	86 (83)/8 (<5)
11	$Yb(OTf)_3$ (20)	DCM	30	24	<5/44
12[e]	$Sc(OTf)_3$ (20)	DCM	30	12	<5/86 (84)

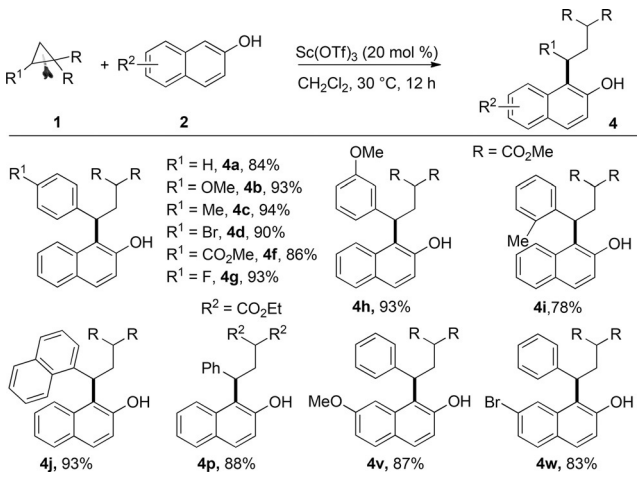
[a] All reactions were carried out with 0.25 mmol of **2a** and 0.3 mmol of **1a** in 1.0 mL solvent unless otherwise specified. [b] The yields were determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as the internal standard. Yield within parentheses are those of the products isolated from the reaction run on a 0.5 mmol scale. [c] Reaction performed using 20 mol% of $Bi(OTf)_3$ and 20 mol% of KPF_6. [d] Reaction carried out using 0.275 mmol of **1a**, 10 mol% of $Bi(OTf)_3$, and 20 mol% of KPF_6. [e] Reaction carried out using 1:1 ratio of **1a** and **2a**. DCM = dichloromethane, THF = tetrahydrofuran.

With the optimized reaction conditions in hand, we then examined the substrate scope of both the reactions. First, we evaluated the scope of the bismuth(III)-catalyzed reaction (Scheme 1). A series of D–A cyclopropane substrates having electron-releasing and electron-withdrawing substituents at the 4-position of the benzene ring on the donor terminus of **1** underwent smooth cyclization, thus resulting in the formation of the corresponding cyclopentannulated products in good yields (**3a**–**g**). Moreover, substitution at the 3-position and 2-position of the benzene ring are well tolerated (**3h**, **3i**), and substrates having substituents such as naphthyl, pyrenyl, and heteroaromatic substitution at the donor site of **1** afforded the desired product in moderate to good yield (**3j**–**m**). In addition, the vinyl cyclopropane derivatives also afforded the cyclopentane derivatives in moderate to good yield (**3n**, **3o**). In the case of vinyl cyclopropane **1n**, the Friedel–Crafts addition product was isolated in 20% yield. The alkoxycarbonyl moiety in **1** was also variable, and did not affect the outcome of the reaction (**3p**, **3q**). Then, we studied the scope of the reaction with substituted 2-naphthols. Various substituted 2-naphthol derivatives readily underwent the dehydrative [3+2] annulation reaction, thus furnishing the expected product in good yields (**3r**–**y**).[16] In the case of product **3w**, the structure was confirmed using single-crystal X-ray analysis.[17]

Then, we studied the scope of the scandium(III)-catalyzed Friedel–Crafts-type reaction (Scheme 2). As in the case of the bismuth(III)-catalyzed reaction, a series of electronically dissimilar D–A cyclopropanes, with different substitution patterns, smoothly added to 2-naphthol under scandium(III) catalysis to afford the 1-functionalized 2-naphthol in good



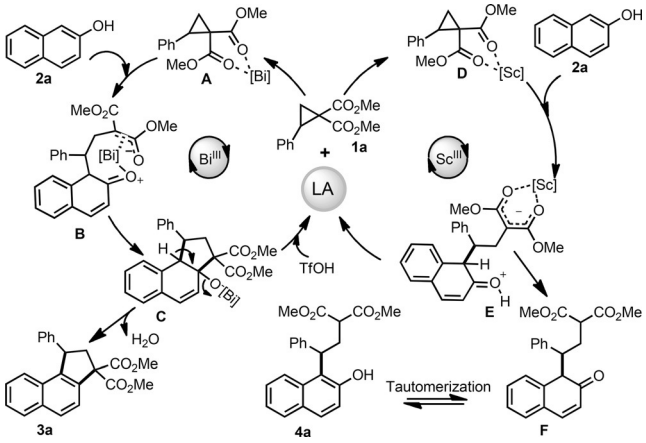
Scheme 1. Scope of the bismuth(III)-catalyzed dehydrative [3+2] cyclopentannulation. General reaction conditions: **1** (0.55 mmol), **2** (0.50 mmol), $Bi(OTf)_3$ (10.0 mol%), KPF_6 (20.0 mol%), CH_2Cl_2 (2.0 mL), 30 °C and 16 h. Yields of isolated product are given. [a] 20% of the Friedel–Crafts addition product was also isolated. [b] Structure confirmed by X-ray analysis.[15]



Scheme 2. Scope of the scandium(III)-catalyzed Friedel–Crafts-type reaction. General reaction conditions: **1** (0.50 mmol), **2** (0.50 mmol), $Sc(OTf)_3$ (20.0 mol%), CH_2Cl_2 (2.0 mL), 30 °C and 12 h. Yields of isolated product are given.

yields (**4a**–**j**). Moreover, the ethyl ester moiety in **1** did not affect the outcome of the reaction (**4p**), and the substitution on the naphthol ring was also tolerable (**4v**, **4w**).[18]

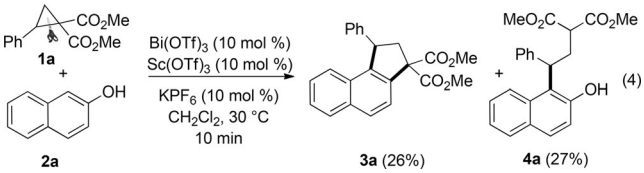
A plausible mechanism of this tunable Lewis acid catalyzed reaction is shown in Scheme 3. The activation of



Scheme 3. Proposed mechanism of the reaction.

1a using Bi^{III} possibly generates the intermediate **A**, which makes the cyclopropane ring labile. Addition of **2a** to **A** generates the zwitterionic intermediate **B**, where Bi^{III} activates the carbonyl group for nucleophilic attack (possibly, the malonate anion still interacts with Bi^{III}). Intramolecular aldol reaction generates the cyclopentane intermediate **C**, which eliminates a molecule of water to form the product **3a**, with the regeneration of the Bi^{III} catalyst.[19] In contrast, activation of **1a** using Sc^{III} generates the intermediate **D** (similar to **A**). The nucleophilic addition of **2a** to **D** generates the zwitterionic intermediate **E**, where Sc^{III} is activating the diester moiety. Intramolecular proton transfer generates the enone **F**, which tautomerizes to the thermodynamically more stable **4a**. The mechanistic difference between the two Lewis acid catalyzed reactions may be due to the remarkable dual effect of Bi^{III} in activating the D–A cyclopropane (generating **A**) as well as the 2-naphthol (generating **B**), which eventually results in the dehydrative [3+2] annulation reaction. Notably, Sc^{III} activates only the D–A cyclopropane (generating **D**).

To get insight into the Lewis acid activity of bismuth(III) and scandium(III) in the same flask, an experiment was performed by mixing **1a** and **2a** under the optimized reaction conditions using both catalysts [Eq. (4)]. When the reaction was quenched after 10 minutes, **3a** was formed in 26% yield and **4a** was formed in 27% yield. The 1:1 formation of **3a** and **4a** demonstrates Lewis acid activation at the same rate. Similar results were obtained when the reaction was quenched after 5 minutes.[15]



In conclusion, selective Lewis acid catalyzed reactions of D–A cyclopropanes with 2-naphthols have been demonstrated. The use of $Bi(OTf)_3$ resulted in a dehydrative [3+2] annulation reaction to furnish naphthalene-fused cyclopentanes.[20] Employing $Sc(OTf)_3$ as the Lewis acid resulted the Friedel–Crafts-type addition to afford 1-functionalized 2-naphthols. Both reactions took place with high selectivity.

Acknowledgments

This activity was supported by Science and Engineering Research Board (SERB-DST), Government of India (Grant No.SR/S1/OC/12/ 2012). A.T.B. thanks the Humboldt Foundation for an equipment grant. T.K. and M.T. thank CSIR for the SPM fellowship and SRF respectively, and T.R. thanks DST for the Inspire fellowship. We thank Dr. P. R. Rajamohanan for the excellent NMR support and Dr. B. Santhakumari for the HRMS data.

Keywords: annulations · arenes · Lewis acids · reaction mechanisms · small ring systems

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 10061–10064
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[15] For details, see the Supporting Information.
[16] The reaction of a D–A cyclopropane with 1-naphthol did not furnish either the cyclopentannulated product [using $Bi(OTf)_3$] or Friedel–Crafts product [using $Sc(OTf)_3$] under the present reaction conditions.
[17] CCDC 1439638 (**3w**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[18] When the Friedel–Crafts product **4a** was exposed to $Bi(OTf)_3$)/KPF_6 catalytic system, the annulation leading to the formation of **3a** was not observed. In this case, **4a** was recovered quantitatively.
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Received: May 5, 2016
Published online: July 8, 2016

