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A novel ring-opening reaction of methylenecyclopropanes with aromatic amines catalyzed by Lewis acids

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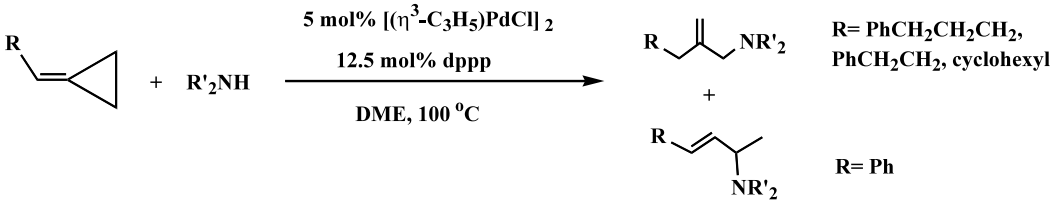
Abstract—Methylenecyclopropanes (MCPs) can react with aromatic amines to give the corresponding homoallylic amines in good to high yields in the presence of Lewis acids. The substituents on the benzene ring of the MCPs or the aromatic amines can affect significantly the reaction rate.

Carbon–nitrogen bond formation is one of the most important processes in organic synthesis. The addition of the nitrogen–hydrogen (N–H) bond of amines to carbon–carbon multiple bonds, hydroamination, is a convenient method for this purpose.[1] Of many carbon–carbon multiple bond containing substrates, methylenecyclopropanes (MCPs) are the ideal building blocks to realize hydroamination. MCPs undergo a variety of ring-opening reactions because the relief of ring strain provides a potent thermodynamic driving force. For example, Yamamoto et al.[2] reported that MCPs can react with amines in the presence of a Pd(II) catalyst (Scheme 1). This Pd(II)-catalyzed hydroamination of MCPs mainly proceeds via a Markovnikov-type addition followed by distal bond cleavage. On the other hand, reactions of benzylidenecyclopropane with amines form exclusively a different type of hydroamination product via an *anti* Markovnikov-type addition followed by proximal bond cleavage before the formation of a π-allylpalladium under the same conditions. Although this reaction offers a method towards allylic amines, it must be carried out at 100°C for 3 days. The severe conditions therefore limit its practical utilization in organic synthesis.

As well as amines, in the presence of a Pd catalyst, MCPs can also react with many other reactants such as ROH,[3] malonate derivatives,[4] carbon dioxide,[5] aldehydes,[6] imines,[7] R_3SiH,[8] R_3SnH,[9] $R_2B\text{-}BR_2$,[10] $R_3Si\text{-}BR_2$,[11] $R_3Si\text{-}CN$,[12] olefins,[13] active methyne and methylene[14] compounds to afford different ring-opening adducts depending on the nature of the reactants.

In contrast to Pd-promoted MCPs reactions, to the best of our knowledge, little attention has been paid to Lewis acid-promoted MCP reactions.[15] Herein, we wish to report novel ring-opening reactions of MCPs with aromatic amines catalyzed by a Lewis acid which offers a way to produce homoallylic amines under relatively mild reaction conditions.



Scheme 1.

Keywords: methylenecyclopropanes (MCPs); aromatic amines; aliphatic amines; ring-opening reaction; Lewis acids.

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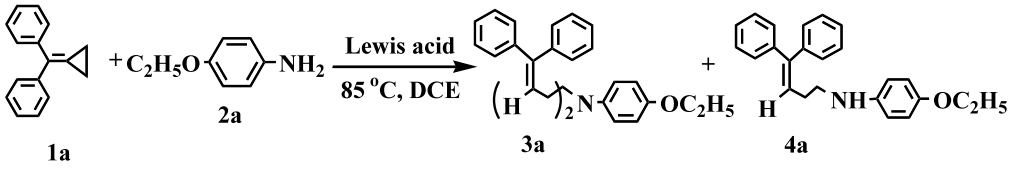
At the beginning we used diphenylmethylenecyclopropane **1a** and *p*-phenetidine **2a** as the substrates to examine the reaction in the presence of a Lewis acid. As a result, we found that two homoallylic amines: the monoalkylated product **4** and the dialkylated product **3** were produced. Various $M(OTf)_x$ type Lewis acids and traditional Lewis acids such as $AlCl_3$, $BF_3{\cdot}Et_2O$ were tested in this reaction. The results are summarized in Table 1. We found that $Sn(OTf)_2$ is the best Lewis acid for this reaction. The reaction can be completed within 24 h at 85°C in CH_2ClCH_2Cl (Table 1, entry 1). $Yb(OTf)_3$, $Sc(OTf)_3$ and $Cu(OTf)_2$ are less active than $Sn(OTf)_2$ (Table 1, entries 2–4). $BF_3{\cdot}Et_2O$ is also a good Lewis acid for this reaction (Table 1, entry 6).

Then we carried out the reactions of **1a** with various amines in the presence of $Sn(OTf)_2$ at 85°C in CH_2ClCH_2Cl. The results are summarized in Table 2. We found that aromatic amines reacted smoothly to give the products in good to high yields (Table 2, entries 1, 2, 4, 6, 8, 9 and 10). On the other hand, no reaction occurred when aliphatic amines were used (Table 2, entries 3, 5, 7 and 11). Moreover, benzene substitution of the aromatic amines can affect significantly the reaction rate. For example, the reactions of **1a** with 3,5-dichloroaniline **2c** or 3-(trifluoromethyl)aniline **2e**,[16] 3-fluoroaniline **2i**, 3-nitroaniline **2j** are much faster than that of **1a** with aniline **2b**, and gave much higher yields of the dialkylated homoallylic amines **3** under the same conditions without formation of the monoalkylated products **4** because they are very rapidly transformed to produce **3**. Moreover, the reaction rate of **1a** with **2a** is very similar to that of **1a** with **2b**. Thus, the dialkylated homoallylic amine products **3** and monoalkylated homoallylic amine products **4** were obtained in similar yields (Table 2, entries 1 and 6). Based on these results, we can conclude that electron-withdrawing groups on the benzene ring of the aromatic amines accelerate the reaction to afford exclusively the dialkylated homoallylic amine products **3**.

In order to clarify the effect of the steric hindrance of aromatic amines on this novel ring-opening reaction, we selected 1,1′-binaphthyl-2,2′-diamine **2l** which has two amino groups (Scheme 2). Theoretically this reaction could produce five adducts, but in fact only three adducts were formed under our conditions. Product **3l** does not react further with **1a** to give the corresponding tetrakis-alkylated homoallylic amines products, while the monoalkylated homoallylic amine product **4l** can be further alkylated on the other amino group with **1a** to afford **3l′**. The results are shown in Scheme 2. We believe that this phenomenon can be explained by the large steric hindrance of the dialkylated amino group which blocks out further reactions of another amino group with **1a**.

Besides **1a**, we also examined the reactions of various MCPs with **2e** which has an electron-withdrawing group on the benzene ring in the presence of $Sn(OTf)_2$. As can be seen from Table 3, both aromatic MCPs and aliphatic MCPs can react with **2e** to give the products in high yields. The reaction of (di-*p*-tolyl)methylenecyclopropane **1b** with **2e** proceeds quickly within 5 h at 85°C to give **3m** in quantitative yield (100%) (Table 3, entry 2). Moreover, the reaction of [di(*p*-methoxyphenyl)]methylenecyclopropane **1f** with **2e** can even proceed at room temperature (17°C) to produce the two corresponding adducts **3q** and **4q** in quantitative yield as well (100%) (Table 3, entry 6). However, we found that only **1f** having a methoxy group on the benzene ring has such high reactivity. Compared to those MCPs having electron-donating groups on the benzene ring, the reaction of 2-chlorobenzophenylmethylenecyclopropane **1d**, which instead has an electron-withdrawing group on the benzene ring, required a higher temperature (85°C) and prolonged reaction time (48 h) to complete the reaction with **2e**, albeit in a low yield (Table 3, entry 4). In addition to aromatic methylenecyclopropanes, aliphatic methylenecyclopropanes such as *p*-phenylcyclohexylmethylenecyclopropane **1c** and methylheptylmethylenecyclopropane **1e**

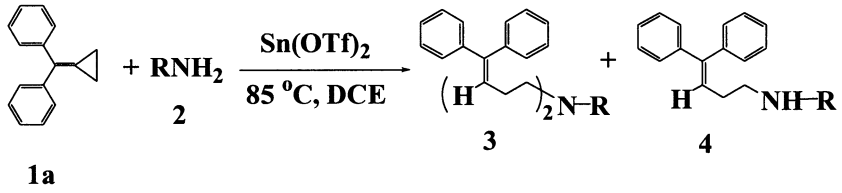
Table 1. The effects of the Lewis acid on the reaction of **1a** with **2a**

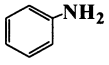
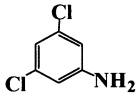
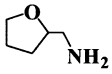
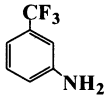
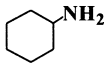
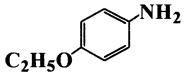
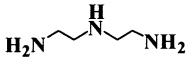
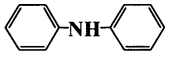
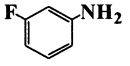
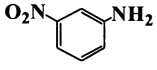
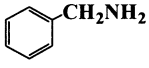


Entry	Lewis acid	Yields (%)[a]	
		3a	**4a**
1	$Sn(OTf)_2$	38	40
2	$Yb(OTf)_3$	13	41
3	$Sc(OTf)_3$	13	45
4	$Cu(OTf)_2$	8	21
5	$AlCl_3$	–	7
6	$BF_3{\cdot}Et_2O$	32	38

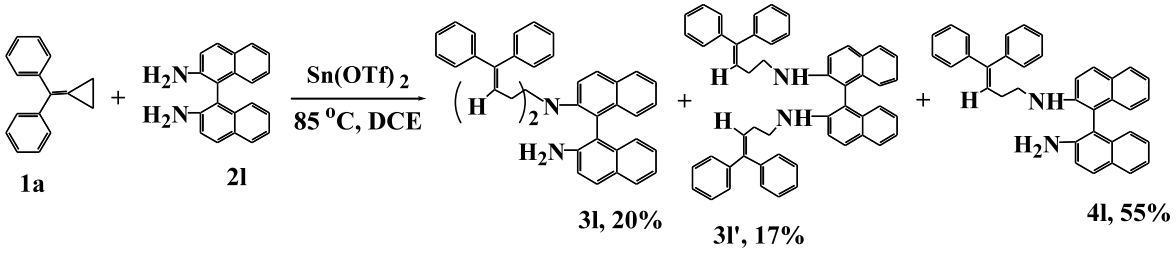
[a] Isolated yield.

Table 2. The reactions of **1a** with RNH_2 in the presence of the Lewis acid $Sn(OTf)_2$ (10 mol%)



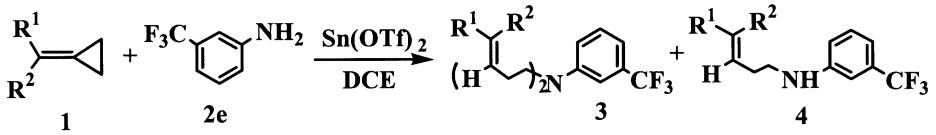
Entry	RNH_2		Time(h)	Yields(%)[a]	
				3	4
1		2b	24	3b (43)	4b (36)
2		2c	24	3c (85)	-
3		2d	24	-	-
4		2e	24	3e (100)	
5		2f	24	-	-
6		2a	24	3a (38)	4a (40)
7		2g	24	-	-
8		2h	12	3h (46)	
9		2i	24	3i (89)	-
10		2j	24	3j (95)	-
11		2k	24	-	-

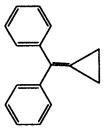
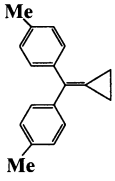
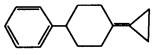
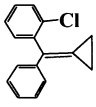
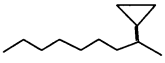
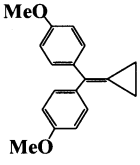
[a] Isolated yield



Scheme 2.

Table 3. The reactions of MCPs with **2e** in the presence of Lewis acid $Sn(OTf)_2$ (10 mol%)



Entry	MCPS		Time (h)	Temp (^oC)	Yield/(%)[a]	
					3	4
1		1a	24	85	3e (100)	
2		1b	5	85	3m (100)	
3		1c	24	85	3n (36)	4n (53)
4		1d	48	85	3o (10) *E:Z*= 15:1	4o (51) *E* only
5		1e	24	85	3p (66) *E:Z*= 11:1	4p (21) *E* only
6		1f	24	17	3q (89)	4q (11)

[a] Isolated yield

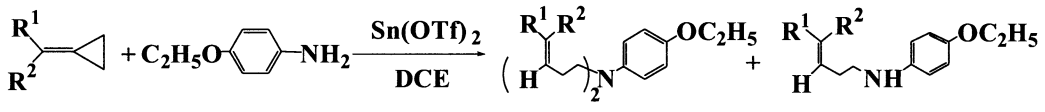
also react with **2e** to give the corresponding products in high yields (Table 3, entries 3 and 5). At the same time, we chose **1d** and **1f** to react with **2a**, which has an electron-donating group on the benzene ring, in order to testify our results further (Table 4). Evidently under the same conditions, the reaction rate of **1d** with **2a** is slow, but the reaction rate of **1f** with **2a** is fast (Table 4).

Accordingly, in order to improve the yields and reaction rates, two requirements are needed in the reactions of MCPs and $ArNH_2$: (1) electron-donating groups on the benzene ring of MCPs. (2) Electron-withdrawing groups on the benzene ring of RNH_2.

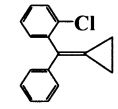
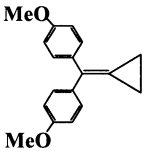
A plausible mechanism for this novel ring-opening reaction of MCPs with $ArNH_2$ is shown in Scheme 3. The MCPs first coordinate with the Lewis acid to give cation **5**, which immediately rearranges to the ring-opened cation **6**.[17] The subsequent nucleophilic attack of $ArNH_2$ on **6** affords the adduct **7**. The final product is formed after proton migration. Aliphatic amines can deactivate Lewis acids used in this reaction because they can strongly coordinate to Lewis acids. Thus, this ring-opening reaction cannot take place when aliphatic amines are used as the substrates.

In conclusion, we have discovered a novel transformation of MCPs with aromatic amines in the presence of Lewis acids. This reaction affords two types of adducts: mono- and dialkylated amino products in good to high yields depending on the substrates. This process can provide a novel and efficient route to the synthesis of homoallylic amines. Efforts are in progress to elucidate the mechanistic details of this reaction and to disclose its scope and limitations.

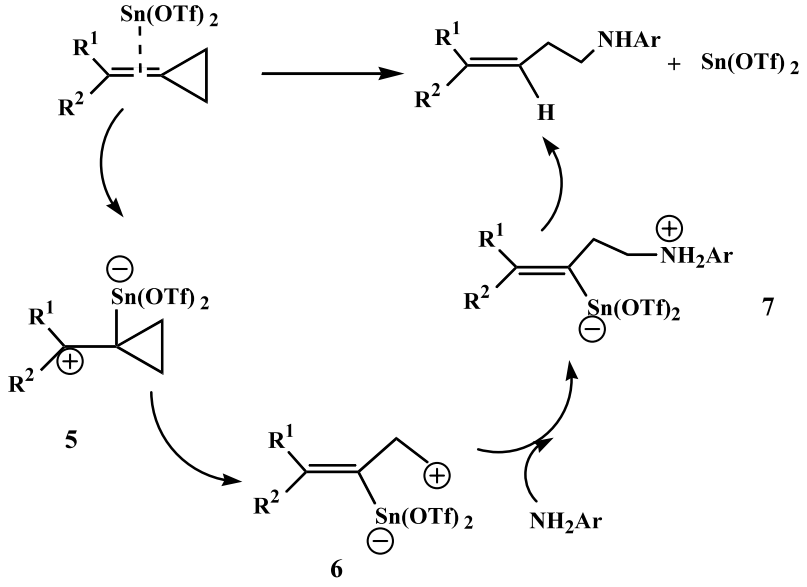
Table 4. The reaction of **2a** with MCPs in the presence of Lewis acid $Sn(OTf)_2$ (10 mol%)



1 2a 3 4

Entry	MCPS		Time (h)	Temp (^oC)	Yields (%)[a] 3	Yields (%)[a] 4
1		1d	48	85	-	4r (4) *E* only
2		1f	24	17	3s (56)	4s (39)

[a]Isolated yield



Scheme 3.

Acknowledgements

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16. Typical reaction procedure: **1a** (185 mg, 0.9 mmol), **2e** (48 mg, 0.3 mmol), and $Sn(OTf)_2$ (13 mg, 10 mol%) were suspended in anhydrous CH_2ClCH_2Cl (2 ml) under argon. The mixture was stirred at 85°C for 24 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2) using EtOAc/hexane (1:100) as the eluent to yield **3e** (0.172 g, 100%) as a colorless solid. [*N*,*N*-Di-(1,1-diphenyl-1-butenyl)-3-(trifluoromethyl)]aniline **3e**: mp: 118–120°C; IR (neat) 1609 (m), 1495 (m), 1454 (m), 1322 (s), 1120 (s), 850 (w), 761 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.4 (m, 4H), 3.3 (t, 4H, $J=7.6$ Hz), 6.1 (t, 2H, $J=7.5$ Hz), 6.4 (m, 1H), 6.7 (s, 1H), 6.8–7.4 (m, 22H); MS (EI): m/z 573 (M^+, 0.3), 380 (54), 167 (100), 129 (61), 91 (53); anal. calcd for $C_{39}H_{34}NF_3$ (%): C, 81.68; H, 5.93; N, 2.44. Found: C, 81.72; H, 6.09; N, 2.41%.
17. The fast rearrangement of cation **5** to **6** has been well documented, inter alia, see: Carey, F. A.; Tremper, H. S. *J. Am. Chem. Soc.* **1969**, *91*, 2967.