Aluminum Bis(trifluoromethylsulfonyl)amides: New Highly Efficient and Remarkably Versatile Catalysts for C–C Bond Formation Reactions**

Andreas Marx and Hisashi Yamamoto*

Lewis acids are powerful tools in many different reactions such as Diels Alder reactions, aldol synthesis, and the Sakurai reaction. The aim is now to develop more reactive Lewis acidic species that catalytically promote these synthetically valuable transformations.^[1] Metal triflates (triflate = OTf) are employed as Lewis acids to promote important carbon carbon bond formation reactions since the trifluoromethylsulfonyl (Tf) group is one of the strongest neutral electron withdrawing groups.^[1, 2] However, a major limitation of the known metal triflates is the synthesis of highly valuable homoallyl alcohols (for example, **8**) by the Lewis acid promoted reaction of aldehydes with inexpensive and non toxic allyl trimethylsilane [Eq. (1)]. The formation of such homoallyl alcohols necessitates the use of allyl tin reagents instead.^[3, 4]

Attempts to develop more reactive Lewis acidic species for this transformation by modification of the triflate ion with more electron withdrawing counterions have failed.^[5] Herein we report the first successful development of new versatile catalysts derived from the superacid bis(trifluoromethylsulfonyl)amine (Tf₂NH)^[6] that promote allylation and other important reactions with unprecedented efficiency.

Recently, ytterbium triflate (Yb(OTf)₃) was shown to promote the reaction between aldehydes and allyl tributyltin reagents but that allyl silanes were unaffected by this reagent.^[7] Attempts to develop a more reactive Lewis acid by modification of the triflate ions with the more electron withdrawing counterion bis(trifluoromethylsulfonyl)amide (bistriflylamide) failed.^[5] The desired homoallyl alcohol **8** was only formed in trace amounts and generated TMSNTf₂ (TMS = trimethylsilyl) as a side product, which is believed to be the actual promoter for this reaction. This proposal is supported by our finding that catalytic amounts of TMSNTf₂^[8] or Tf₂NH (**1**), which generates TMSNTf₂ in situ through reaction with **2**, form **8** in moderate yield along with substantial amounts of undesired products (Table 1, entries 1 and 2).

Similar results were obtained when (iPrO)₂Ti(NTf₂)₂^[9] and Al(NTf₂)₃^[9] were employed (Table 1, entries 3 and 4). These

[*] Prof. Dr. H. Yamamoto, Dr. A. Marx
Graduate School of Engineering, Nagoya University, CREST
Japan Science and Technology Corporation (JST)
Furo cho, Chikusa, Nagoya 464 8603 (Japan)
Fax: (+81) 52 789 3222
E mail: j45988a@nucc.cc.nagoya.u.ac.jp

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Table 1. Reaction of benzaldehyde and allyl trimethylsilane to give **8** using various catalysts [Eq. (1)].

Entry	Catalyst	Conditions	Yield [%] ^[a]
1	TMSNTf ₂	20 °C, 3 h	53
2	HNTf ₂	20 °C, 3 h	52
3	(<i>i</i> PrO) ₂ Ti(NTf ₂) ₂	78 °C, 3 h	45
4	Al(NTf ₂) ₃	20 °C, 3 h	35 ^[b]
5	Me ₂ AlNTf ₂	20 °C, 3 h	93 ^[c]

[a] Yield of isolated products. [b] Precipitation of Al(NTf₂)₃ at 78 °C. [c] No reaction at 78 °C.

promoters afford an undesired side product in substantial amounts (37 % and 41 %, respectively), which was identified as the recently reported side product formed when BF₃·OEt₂ was used as a promoter.^[10] By taking mechanistic considerations for the formation of this undesired reaction product into account we suspected that the catalyst must be exhibiting exceedingly high reactivity for a clean promotion of this process. Therefore, a less reactive catalyst should be more suited for the clean allylation of aldehydes with allyl trimethylsilane. Indeed, we found that 5 mol % of Me₂AlNTf₂ (**3**), readily prepared by treatment of a solution of Me₃Al with one equivalent of commercially available Tf₂NH, catalyzes the smooth addition of allyl trimethylsilane (**2**) to benzaldehyde (**4**), and yields **8** in 93 % yield after acidic work up. We further investigated the scope of the reaction toward the aromatic aldehyde (**5**), the less reactive aliphatic aldehyde hexanal (**6**), and the hindered aldehyde trimethylacetaldehyde (**7**). The results are summarized in Table 2.

Aromatic aldehydes were allylated in excellent yields and short reaction times. Aliphatic aldehydes were allylated in good yields with the same catalyst loading (5 mol %), but in order to suppress the formation of side products lower reaction temperatures were required, which resulted in longer reaction times.^[11]

We further investigated the general scope of Me₂AlNTf₂ in catalytic C–C bond forming reactions. Catalytic pentadienyl

ation of aldehydes is still a challenging topic in organic synthesis. Strong Lewis acids such as TiCl₄ and BF₃·OEt₂ applied in stoichiometric amounts commonly yield the desired pentadienylated alcohols **13–16** in only moderate yields, and, depending on the applied reaction conditions, mixtures of γ and ϵ substituted products are obtained.^[12] However, 5 mol % of **3** is sufficient to effect the addition of 5 trimethylsilyl 1,3-pentadiene (**12**) to aldehydes and gave **13–16** (Table 2) in excellent, and up to now unprecedented, yields. Furthermore, the addition proceeds in high selectivity, thus the ϵ substituted adducts were formed exclusively. Next, we explored the use of **3** in the catalytic Mukaiyama aldol reaction^[13] and found that treatment of various aldehydes with the silyl enol ether **17** in the presence of 2 mol % **3** gave rise to good yields of the desired aldol products **18–21** (Table 2). We further investigated the use of this remarkably active catalyst in other addition reactions of **17** and found that **3** supersedes any previously reported Lewis acid. Employment of only 2 mol % allows a smooth cross aldol reaction between simple ketones to yield the desired adducts **22** and **23** under mild reaction conditions (Scheme 1).^[14]

Scheme 1. Cross aldol reaction between ketones and Michael addition catalyzed by 2 mol % **3**. Reaction conditions: ketone (1 equiv), silyl enol ether **17** (1.1 equiv), 2 mol % **3**, CH₂Cl₂, 45 °C, 3 h. Desilylation: 1N HCl/THF. The yields in parentheses are of isolated products.

Table 2. Carbon–carbon bond formations catalyzed by Me₂AlNTf₂

Aldehyde	Nucleophile		

[a] Aldehyde (1 equiv), **2** (1.1 equiv), 5 mol % **3**, CH₂Cl₂, 20 °C, 3 h (aromatic aldehydes) or 40 °C, 10–20 h (aliphatic aldehydes). Desilylation: 1N HCl/THF. [b] The yields in parentheses are of isolated, purified products. [c] Aldehyde (1 equiv), **12** (1.1 equiv), 5 mol % **3**, CH₂Cl₂, 78 °C, 3–20 h. Desilylation: tetrabutylammonium fluoride (TBAF) in THF. [d] Aldehyde (1 equiv), **17** (1.1 equiv), 2 mol % **3**, CH₂Cl₂, 78 °C, 3–20 h. Desilylation: 1N HCl/THF.

Interestingly, when α,β unsaturated ketones are employed under the same reaction conditions a catalytic 1,4 addition is observed to yield the Michael adducts **24** and **25** in excellent yields without any evidence for 1,2 addition (Scheme 1).^[15]

Apart from the remarkable ability of **3** to catalyze C–C bond formation with unprecedented efficiency and versatility, more subtle aspects of this aluminum derived species appeared. Thus, substitution of both methyl groups in Me₂AlNTf₂ by suitable ligands should allow the design of tailor made catalysts. Initially, we aimed to design a suitable catalyst that would recognize and activate a less shielded carbonyl functionality to undergo chemoselective aldol reaction with the less shielded substrate. This is a challenging task, since many known promoters of the Mukaiyama aldol reaction trigger the formation of reactive silyl species

that catalyze the reaction with loss of selectivity.^[13b] A successful achievement of a chemoselective aldol reaction would indicate and favor a Lewis acid catalyzed reaction mechanism over a reaction pathway catalyzed by reactive silyl species. Aluminum 2,6 diphenylphenoxides such as methyl aluminum bis(2,6 diphenylphenoxide) (MAPH) have been shown to be suitable for the recognition of less hindered aldehydes. Thus, compound **26** (Scheme 2) should be suitable for this purpose.^[16, 17]

Scheme 2. Design of a catalyst for the chemoselective aldol reaction.

As expected, treatment of an equimolar mixture of hexanal (**6**) and trimethylacetaldehyde (**7**) with **17** in the presence of 5 mol % of **3** effected only a moderate preference for the less hindered aldehyde (Table 3, entry 1). In marked contrast, the reaction of **17** promoted by **26** yielded the aldol product of the

Table 3. Chemoselective aldol reactions.^[a]

Entry	Aldehyde	Cat.	Ratio ^[b]
1	CHO vs. CHO	3	74:26 ()
2	CHO vs. CHO	26	99:1 (84 %)
3	CHO vs. CHO	26	57:43 ()
4	CHO vs. CHO	26	93:7 (79 %)
5	CHO vs. CHO	26	99:1 (84 %)
6	CHO vs. CHO	26	92:8 (67 %)

[a] Aldehydes (1 equiv each), **17** (1 equiv), 5 mol % catalyst, CH₂Cl₂, 78 °C. Desilylation: 1N HCl/THF [b] Determined by ¹H NMR analysis. The yield is given in parentheses.

less hindered aldehyde in 84 % yield, and only trace amounts of the trimethylacetaldehyde derived product were detected by ¹H NMR analysis (Table 3, entry 2). Table 3 further demonstrates that **26** is able to promote the highly selective functionalization of a variety of substrates and exhibits the scope of this process as well as its limitations. While **26** fails to differentiate between hexanal and cyclohexanecarboxaldehyde, higher selectivity is found when the more hindered 2 phenylpropionaldehyde is employed instead (Table 3, entries 3 and 4). Furthermore, **26** is able to perform the chemoselective aldol reaction between cyclohexanecarboxaldehyde and trimethylacetaldehyde or 2 phenylpropionalde

hyde (Table 3, entries 5 and 6, respectively). These findings indicate that the bulky aluminum reagent **26** acts as a highly reactive Lewis acid when it promotes the presented reactions, and thus selectivity can be introduced by suitable ligands.

In conclusion, we have developed a new class of aluminum bis(trifluoromethylsulfonyl)amides as highly reactive and versatile Lewis acidic catalysts for a variety of important C–C bond forming reactions. In addition, we were able to design a ligand scaffold in a rational approach to ensure the selective recognition and activation of a desired substrate, thus indicating that the aluminum species act directly as reactive Lewis acids. Considering the wide applications found for strong electron withdrawing counterions such as triflates, there is a high probability that metal bistriflylamides will prove to be valuable in the development of new Lewis acids for important organic transformations. The correlation of the catalytic ability of aluminum bistriflylamides with the electronic and steric properties of the ligand sphere should allow the development of Lewis acidic catalysts for enantioselective processes.

Experimental Section

Me₂AlNTf₂ (**3**) was readily prepared by treatment of Me₃Al (100 μL of 0.5 M solution in toluene) with 1 equivalent of commercially available Tf₂NH (100 μL of 0.5 M solution in CH₂Cl₂) in CH₂Cl₂ (4.0 mL) at room temperature (gas evolution) for 30 min with rigorous exclusion of air and moisture and was used without further purification.

Typical procedure for the reaction of aldehydes with allyl trimethylsilane: Benzaldehyde (**4**, 100 μL, 1.00 mmol) and allyl trimethylsilane (**2**, 175 μL, 1.10 mmol) were added at –20 °C under argon to a solution of Me₂AlNTf₂ (**3**, 0.05 mmol) in CH₂Cl₂ (4.0 mL). After stirring the reaction mixture for 3 h, 1N HCl (2.0 mL) and THF (2.0 mL) were added and the reaction was allowed to warm to room temperature. The reaction mixture was stirred for 30 min, poured into NaHCO₃ solution, and extracted with diethyl ether. The combined organic extracts were dried over MgSO₄, concentrated, and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/10) to give **8** (138 mg, yield 93 %) as a colorless liquid that shows identical spectral and analytical data with those in ref. [18]

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