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A Lewis acid/metal amide hybrid as an efficient catalyst for carbon–carbon bond formation†

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While Lewis acids and metal amides are among the most frequently used metal species, they are believed to be incompatible when combined. Here we describe a Lewis acid/metal amide hybrid, which contains electron-withdrawing groups and basic and bulky nitrogen functional groups in the same metal complex, as a novel catalyst. We have synthesized $\text{In}(\text{N}(\text{SiMe}_3)_2)_2\text{Cl}$ ($\text{In}(\text{HMDS})_2\text{Cl}$) and $\text{In}(\text{HMDS})_2\text{OTf}$ as Lewis acid/metal amide hybrids, which showed excellent catalytic activity for the reaction of nitrones with terminal alkynes to give synthetically useful propargyl hydroxylamines. It is noted that neither the Lewis acids (InCl_3 , $\text{In}(\text{OTf})_3$) nor the metal amides ($\text{In}(\text{HMDS})_3$) have activity; only the hybrids worked well, and the catalytic activity of the hybrids was shown to be much higher than that of previously reported catalysts for this reaction. The concept of a Lewis acid/metal amide hybrid as a catalyst may be expanded to broad acid/base catalysis.

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Introduction

Lewis acids have often been used in organic chemistry as promoters (stoichiometric use) and catalysts (catalytic use).^{1,2} Friedel–Crafts acylation and alkylation with AlCl_3 are typical examples;³ more recently, several stereoselective reactions catalyzed by Lewis acids have been developed.^{4,5} On the other hand, lithium diisopropylamide (LDA) and potassium hexamethyldisilazide (KHMDS) are typical examples of metal amides;^{6,7} these amides abstract acidic protons to generate nucleophilic species such as carbanions for carbon–carbon bond-forming reactions (Fig. 1A). Thus, while Lewis acids and metal amides are among the most frequently used metal species, these are acids and bases, and have been believed to be incompatible when combined.^{1,2,8}

In Lewis acids, the metal parts play key roles, and stronger electron-withdrawing counter anions such as halides and trifluoromethanesulfonate (triflate), which lower the LUMO energy of the metal complexes and thus increase the Lewis acidity of the metals, have been investigated. On the other hand, nitrogen atoms play key roles in metal amides. Indeed, nitrogen atoms have two functions, nucleophilicity and basicity.⁸ To utilize only the base function, sterically bulky metal amides have been developed.^{6,7} Here, we report a Lewis acid/metal amide hybrid, which contains electron-withdrawing groups and

basic and bulky nitrogen functional groups in the same metal complex (Fig. 1B). The hybrid is expected to work as a Lewis acid as well as a Brønsted base.^{9,10}

Results and discussion

Indium is in group 13, and $\text{In}(\text{III})$ is one of the most stable oxidation states. InCl_3 and $\text{In}(\text{OTf})_3$ are known as typical $\text{In}(\text{III})$ Lewis acids.¹ On the other hand, $\text{In}(\text{N}(\text{SiMe}_3)_2)_3$ ($\text{In}(\text{HMDS})_3$) is known as a typical In amide.^{11–13} We prepared $\text{In}(\text{HMDS})_2\text{Cl}$ as an $\text{In}(\text{III})$ Lewis acid/amide hybrid.¹⁴ The preparation was conducted by mixing 1 equiv. of InCl_3 and 2 equiv. of KHMDS in THF at room temperature. After 12 h, the mixture was filtered, and purification by sublimation and recrystallization gave pure $\text{In}(\text{HMDS})_2\text{Cl}$; its structure was confirmed by X-ray crystallographic analysis (Fig. 2).¹⁵

Next, to demonstrate the catalytic activity of this $\text{In}(\text{III})$ Lewis acid/amide hybrid, a model reaction of nitrones with terminal

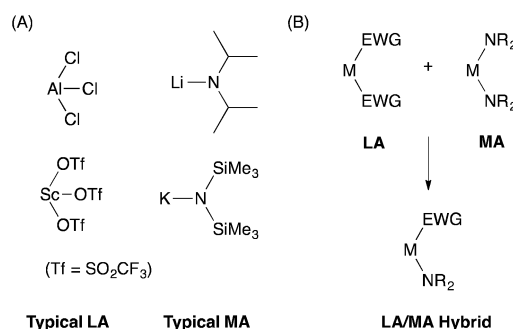


Fig. 1 (A) A typical Lewis acid (LA) and metal amide (MA); (B) a Lewis acid/metal amide hybrid (LA/MA hybrid).

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† Electronic supplementary information (ESI) available: NMR study of the In catalyst structure, general experimental procedures, DFT calculations of the LUMO energy levels of the In complexes, and physical data of the products. CCDC 928541. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4sc01332h



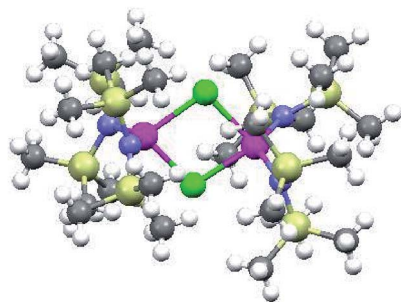


Fig. 2 The structure of $\text{In}(\text{N}(\text{SiMe}_3)_2)_2\text{Cl}$ ($\text{In}(\text{HMDS})_2\text{Cl}$) from X-ray crystallographic analysis.

alkynes was examined.^{16–19} The catalytic addition of terminal alkynes to nitrones provides an efficient route to propargyl hydroxylamines, which can be further transformed into isoxazolines²⁰ and aziridines²¹ *via* intramolecular cyclization. In the literature, only a couple of catalyst systems have been reported for this reaction. Carreira *et al.* are pioneers and have shown that the combination of $\text{Zn}(\text{OTf})_2$ (10 mol%) and $^i\text{Pr}_2\text{NEt}$ (25 mol%) is a suitable catalyst system.¹⁶ It was also reported that the combination of InBr_3 (15 mol%) and $^i\text{Pr}_2\text{NEt}$ (20 mol%) is an alternative catalyst system.¹⁸ In both cases, however, the combination of a Lewis acid and a tertiary amine was needed. While the reaction also proceeded in the presence of a sub-stoichiometric amount of Et_2Zn (20 mol%),¹⁸ in all these cases,

relatively high loading amounts of Lewis acids (10–20 mol%) and external tertiary amines (20–25 mol%) were required to catalyze the reaction.²² We selected the reaction of nitrone **1a**, derived from benzaldehyde and benzyloxyamine, with phenylacetylene **2a** as a model, and several catalysts were examined (Table 1).

When 5 mol% of InCl_3 , $\text{In}(\text{HMDS})_3$, or $\text{In}(\text{OTf})_3$ was used at 40 °C for 3 h, the reaction did not proceed at all (entries 1–3). On the other hand, in the presence of $\text{In}(\text{HMDS})_2\text{Cl}$, the reaction proceeded smoothly under identical reaction conditions to give the desired compound in 84% yield (entry 4). We further examined other indium salts. When $\text{In}(\text{HMDS})\text{Cl}_2$ was used, the product was obtained in 5% yield (entry 5); however, in the presence of $\text{In}(\text{HMDS})_2\text{OTf}$ ²³ and $\text{In}(\text{HMDS})(\text{OTf})_2$, the product yields were 88% and 86%, respectively (entries 6, 7). The use of 2,2,6,6-tetramethylpiperidide (TMP) in place of HMDS ($\text{In}(\text{TMP})_2\text{OTf}$) gave a 12% yield of the product (entry 8), while the corresponding alkoxide ($\text{In}(\text{O}^t\text{Bu})_2\text{OTf}$) gave no product (entry 9). $\text{In}(\text{O}^i\text{Pr})_3$ was also found to give no product (entry 10). We further examined the catalytic activity of these $\text{In}(\text{III})$ Lewis acid– $\text{In}(\text{III})$ amide hybrids at a loading of 1 mol% at 25 °C for 3 h (Table 1).

We found that $\text{In}(\text{HMDS})_2\text{OTf}$ showed the highest activity among the hybrids. The order of catalytic activity is as follows: $\text{In}(\text{HMDS})_2\text{OTf} > \text{In}(\text{HMDS})_2\text{Cl} \gg \text{In}(\text{HMDS})(\text{OTf})_2$, $\text{In}(\text{HMDS})\text{Cl}_2$, $\text{In}(\text{TMP})_2\text{OTf} > \text{In}(\text{O}^t\text{Bu})_2\text{OTf}$. It is noted that neither the Lewis acid (InCl_3 , $\text{In}(\text{OTf})_3$) nor the metal amide ($\text{In}(\text{HMDS})_3$)

Table 1 Screening of Indium catalysts^a

| Entry | Catalyst | Yield ^b (%) | |
|-------|---|-----------------------------|--|
| | | 5 mol%, 40 °C (condition A) | 1 mol% 25 °C (condition B) |
| 1 | InCl_3 | 0 | — |
| 2 | $\text{In}(\text{HMDS})_3$ | 0 | — |
| 3 | $\text{In}(\text{OTf})_3$ | 0 | — |
| 4 | $\text{In}(\text{HMDS})_2\text{Cl}$ | 84 | 7 |
| 5 | $\text{In}(\text{HMDS})\text{Cl}_2$ ^d | 5 | <5 ^c |
| 6 | $\text{In}(\text{HMDS})_2\text{OTf}$ ^e | 88 | 38 (92) ⁱ , 35 ^j |
| 7 | $\text{In}(\text{HMDS})(\text{OTf})_2$ ^f | 86 | <5 |
| 8 | $\text{In}(\text{TMP})_2\text{OTf}$ ^g | 12 | <5 |
| 9 | $\text{In}(\text{O}^t\text{Bu})_2\text{OTf}$ ^h | 0 | — |
| 10 | $\text{In}(\text{O}^i\text{Pr})_3$ | 0 | — |

^a The reaction of **1a** with **2a** was performed for 3 h at 40 °C or 25 °C in THF using the indium catalyst shown in the table following condition A or B. Condition A: **1a** (0.50 mmol) and **2a** (0.55 mmol) were used in the presence of the indium catalyst (0.025 mmol), and the reaction concentration was 0.2 M. Condition B: **1a** (1.0 mmol) and **2a** (1.1 mmol) were used in the presence of the indium catalyst (0.010 mmol), and the reaction concentration was 0.4 M. ^b Isolated yield. ^c NMR yield. ^d The In catalyst was prepared *in situ* by mixing InCl_3 and KHMDS (1 : 1). ^e The In catalyst was prepared *in situ* by mixing $\text{In}(\text{HMDS})_2\text{Cl}$ and AgOTf (1.1 : 1). ^f The In catalyst was prepared *in situ* by mixing $\text{In}(\text{OTf})_3$ and KHMDS (1 : 1). ^g The In catalyst was prepared *in situ* by mixing $\text{In}(\text{OTf})_3$ and LiTMP (1 : 2). ^h The In catalyst was prepared *in situ* by mixing $\text{In}(\text{OTf})_3$ and KO^tBu (1 : 2). ⁱ The reaction was performed for 18 h. ^j The reaction was performed using a catalyst solution obtained after filtration of precipitate (AgCl).



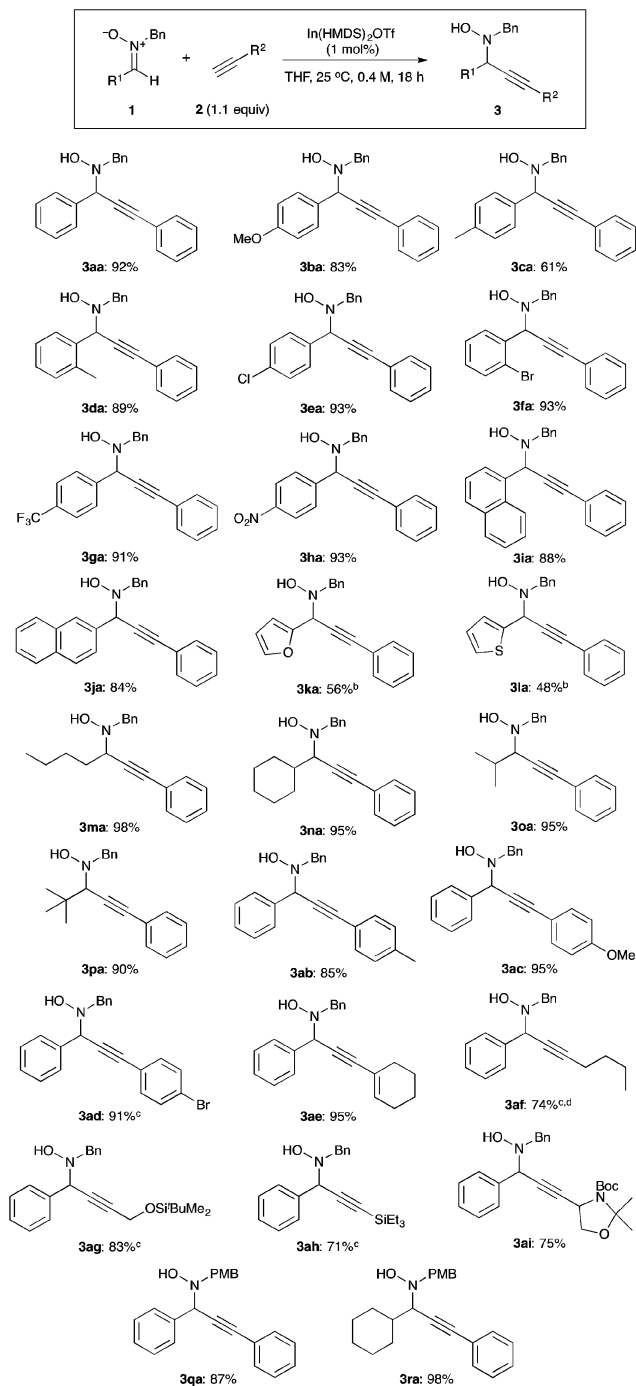


Fig. 3 Substrate scope of the reaction of nitrones with terminal alkynes using $\text{In}(\text{HMDS})_2\text{OTf}$ as the catalyst. ^a The reaction of **1** (1.0 mmol) with **2** (1.1 mmol) was performed in THF (0.4 M) at 25 °C using $\text{In}(\text{HMDS})_2\text{OTf}$ (1 mol%) prepared from $\text{In}(\text{HMDS})_2\text{Cl}$ (0.012 mmol) and AgOTf (0.010 mmol) unless otherwise noted. ^b 5 mol% of the In catalyst was used. ^c The reaction was performed at 40 °C. ^d The reaction was performed for 36 h.

showed any activity for the reaction, and that only the Lewis acid/metal amide hybrids gave the desired products. Moreover, the order of the catalytic activity among the hybrids is remarkable, and an exquisite balance between Lewis acidity and amide basicity is a key for high catalytic activity.²⁴

Substrate scope of the reaction of nitrones with terminal alkynes using $\text{In}(\text{HMDS})_2\text{OTf}$ as the catalyst was surveyed under the optimized reaction conditions (Fig. 3). $\text{In}(\text{HMDS})_2\text{OTf}$ (1 mol%) worked well with a wide variety of substrates to provide the desired propargyl hydroxylamines. The addition reaction of *N*-benzyl nitrones **1** derived from benzaldehyde derivatives bearing electron-donating substituents (**1b–1d**) with phenylacetylene **2a** proceeded to give the desired adducts (**3ba–3da**) in good yields. The nitron bearing electron-withdrawing groups (**1e–1h**) were more reactive, and high yields were obtained under the same reaction conditions (**3ea–3ha**). The bulkier nitrones with 1- and 2-naphthyl groups (**1i**, **1j**) were also applicable to the addition reaction (**3ia**, **3ja**), and nitrones prepared from heteroaromatic aldehydes (**1k**, **1l**) gave the desired products (**3ka**, **3la**). The reactions using the nitrones prepared from several primary, secondary, and tertiary aliphatic aldehydes (**1m–1p**) proceeded smoothly to give the desired adducts in high yields (**3ma–3pa**). Several terminal alkynes **2** could also be used in this reaction. Phenylacetylene derivatives bearing electron-donating and electron-withdrawing substituents on the phenyl group (**2b–2d**) gave high yields (**3ab–3ad**). While a terminal alkyne bearing an alkenyl substituent (**2e**) was successfully employed in the desired reaction (**3ae**), alkynes bearing alkyl groups (**2f**, **2g**) and a triethylsilyl group (**2h**) were less reactive, but high yields were obtained at higher temperature (**3af–3ah**). The terminal alkyne-bearing oxazolidine moiety (**2i**) reacted without losing any protecting group (**3ai**). The *p*-methoxybenzyl group could also be employed as a protecting group on the nitrogen atom (**3qa**, **3ra**).²⁵

The efficiency of the Lewis acid/metal amide hybrid catalyst was also demonstrated in a gram-scale experiment using 0.1 mol% of the catalyst. In the presence of 0.1 mol% of $\text{In}(\text{HMDS})_2\text{OTf}$, **1a** reacted with **2a** in THF at 25 °C for 36 h to give the desired propargyl hydroxylamine **3aa** in 90% yield (Fig. 4).

A proposed catalytic cycle of this reaction is shown in Scheme 1. Initially, terminal alkyne **2** is activated by $\text{In}(\text{HMDS})_2\text{X}$ ($\text{X} = \text{Cl}$ or OTf) to form indium acetylide **I**. This step was independently confirmed by NMR analysis. It is noted that the Brønsted basicity of $\text{In}(\text{HMDS})_2\text{X}$ enables this process and that this step does not proceed at all using a conventional Lewis acid such as InCl_3 and $\text{In}(\text{OTf})_3$. Acetylide **I** then reacts with nitron **1** to give adduct **III** via addition step **II**, in which the Lewis acidity of the indium bearing electron-withdrawing group X is important to activate nitron **1**. Thus, both the Lewis acidity and Brønsted basicity of $\text{In}(\text{HMDS})_2\text{X}$ are crucial for this reaction, and moreover, an exquisite balance between the Lewis acidity and Brønsted basicity of the Lewis acid–metal amide hybrids is also key for this reaction. Finally, adduct **III** reacts with $\text{HN}(\text{HMDS})_2$ to give product **3** along with the regeneration of $\text{In}(\text{HMDS})_2\text{X}$.²⁶

In addition to being a conceptual advance and having a high catalytic activity, this Lewis acid/metal amide hybrid has another synthetic advantage as a catalyst in tandem-type reactions with other catalysts. In the presence of 5 mol% of $\text{In}(\text{HMDS})_2\text{Cl}$ and 20 mol% of AgOTf , **1a** reacted with **2a** to give a 4-isoxazoline derivative (**4aa**) directly in high yield (Fig. 5A).²⁰ Moreover, in the presence of 5 mol% of $\text{In}(\text{HMDS})_2\text{Cl}$ and 20 mol% of CuOTf , **1a** reacted with **2a** to give an aziridine



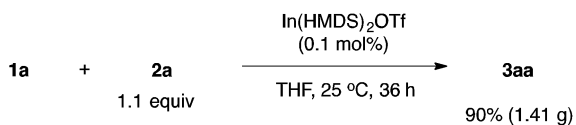
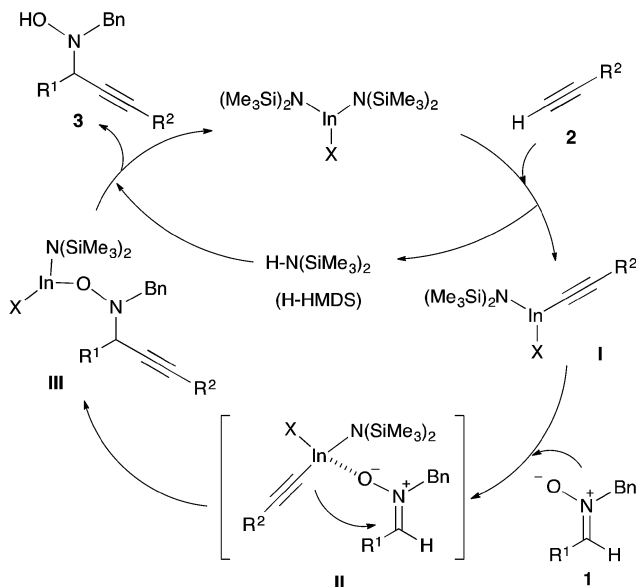


Fig. 4 A gram-scale synthesis using 0.1 mol% of the catalyst.



Scheme 1 A proposed catalytic cycle (X = Cl or OTf).

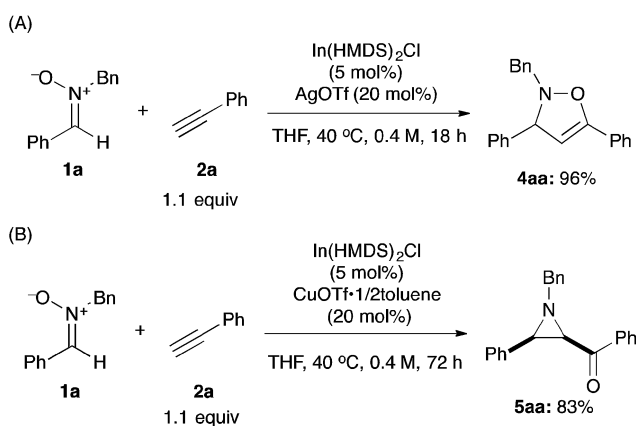


Fig. 5 Tandem addition/cyclization reactions leading to isoxazoline (A) and aziridine (B).

product (5aa) in high yield (Fig. 5B).²¹ In these cases, In(HMDS)₂X (the Lewis acid/metal amide hybrid) is compatible with Lewis acids such as AgOTf and CuOTf, and the tandem addition/cyclization reactions proceeded smoothly in one pot.²⁷

The concept of a Lewis acid/metal amide hybrid as a catalyst could be expanded to other acid/base catalyses. In preliminary results, In(HMDS)₂Cl was found to be effective for the reaction of 2a with aldehyde 7a (Fig. 6A). Moreover, In(HMDS)₂F was found to be an effective Lewis acid/metal amide hybrid catalyst for the reactions of 2a with 7b (Fig. 6B) and 2a with 7c (Fig. 6C).

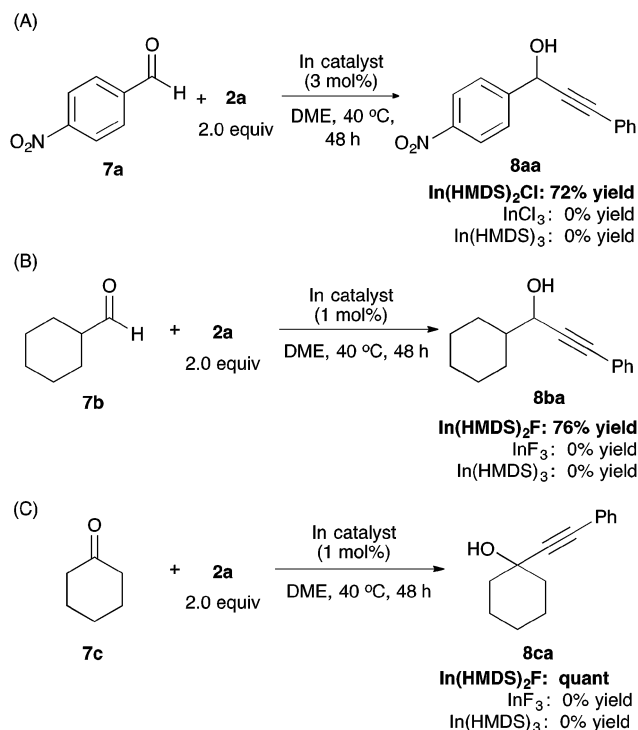


Fig. 6 Other Lewis acid–metal amide hybrids and catalyses.

Conclusions

We have synthesized In(HMDS)₂Cl and In(HMDS)₂OTf as In(III) Lewis acid/amide hybrids. These hybrids showed excellent catalytic activities for the reaction of nitrones with terminal alkynes to give synthetically useful propargyl hydroxylamines in good to high yields. It is noted that neither Lewis acids (InCl₃, In(OTf)₃) nor metal amides (In(HMDS)₃) have catalytic activity but only hybrids work well for this reaction. The catalyst loading is low (0.1–1 mol%) compared with those of the previous Lewis acid–tertiary amine systems (10–25 mol%), and the hybrid is compatible with other Lewis acids to realize tandem reactions in one pot. The concept of a Lewis acid/metal amide hybrid as a catalyst described in this paper may be expanded to broader acid/base catalysis and preliminary results were shown. Further investigations on this concept are currently underway in our laboratory.

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