Cooperative Catalysis

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Arylamine-Catalyzed Enamine Formation: Cooperative Catalysis with Arylamines and Acids**

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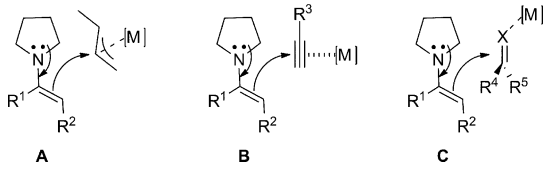
The explosive growth of organocatalysis has had a huge impact on asymmetric catalysis in the past decade.[1] Transition-metal catalysis, on the other hand, has been established for a long time as one of the most powerful methods in organic synthesis.[2] Aminocatalysis is a major field in organocatalysis. The combination of organocatalysis with the more traditional metal Lewis acid catalysis has emerged, aiming to achieve organic transformations that cannot be accomplished by organocatalysis or metal catalysis independently.[3] Although it promises huge potential, this research area has grown only slowly. The major challenge lies in the incompatibility of the catalysts, in particular, the combination of enamine catalysis with harder metal Lewis acid is very difficult. The circumvention of this problem would represent an important breakthrough, given the huge number of substrates that can be activated by the large variety of metal Lewis acids. Herein, we present the solution to this long-standing problem by using arylamines as the catalysts in enamine catalysis. Very importantly, we demonstrate that arylamines can serve as efficient amine catalysts in direct asymmetric aldol reactions. Furthermore, we have developed a highly chemo- and enantioselective three-component aza-Diels–Alder reaction by combining arylamines with metal Lewis acids.

The combination of enamine catalysis with metal Lewis acid catalysis was first reported by Ibrahem and Codava in 2006.[4] Since then, considerable progress has been made in this area, leading to a series of exciting discoveries.[3,5–9] However, these combinations were limited to soft metals, such as Cu^{I},[5] Ag^{I},[6] Au^{I},[7] Ir^{I},[8] and Pd^{0} or Pd^{II},[9] activating either π-allyl electrophiles or alkynes (Scheme 1, **A** and **B**).[10]



Scheme 1. Combination of enamine catalysis with metal catalysis.

Combining enamine catalysis with harder metal Lewis acid (Scheme 1, **C**) turned out to be very challenging because of acid–base self-quenching reactions, which render the catalysts inactive.[11] In asymmetric aminocatalysis involving either an enamine or an iminium intermediate, a chiral aliphatic secondary or primary amine serves as the catalyst. Aliphatic amines are hard bases, and thus likely to be compatible with softer metals based on the soft/hard approach, but less likely to be compatible with harder metals. We hoped to find an amine catalyst that is compatible with a large variety of metal Lewis acids to significantly extend the scope of enamine/metal Lewis acid catalysis, and to facilitate the development of a new research area of iminium/metal Lewis acid catalysis. We considered to use arylamines, such as aniline, because they have a much lower pK_a value (4–6) than aliphatic amines (9–11), and should be much softer because of the delocalization of the lone pair to the aromatic π system. It appeared to us that arylamines are ideal candidates for combination with harder metal Lewis acids. Despite their ubiquity in organic chemistry, arylamines have never been used in enamine catalysis.[12] This may be mainly due to the general understanding that the nucleophilicity of arylamines is much lower compared to aliphatic amines. However, List and co-workers suggested the formation of enamine intermediates from arylamines as a step in organocatalytic cascade reactions.[13] In a recent report, Gong and co-workers also suggested that an achiral arylamine played a crucial role in controlling the stereochemistry of a Friedländer condensation by forming an enamine intermediate.[14] We speculate that arylamines might be suitable to serve as an efficient amine catalyst in enamine catalysis in conjunction with a stronger metal Lewis acid. The lower nucleophilicity of enamines can be compensated by the following factors: 1) facilitated formation of enamine in the presence of a metal Lewis acid; 2) higher activation of the electrophiles by a metal Lewis acid.

The asymmetric aza-Diels–Alder reaction (ADAR) is the most convenient and powerful method to form nitrogen-containing heterocycles, which are one of the most important structural motifs in natural products, pharmaceuticals, and biosystems.[15] While the recent progress on normal-electron-demand ADARs based on dienamines and imine dienophiles

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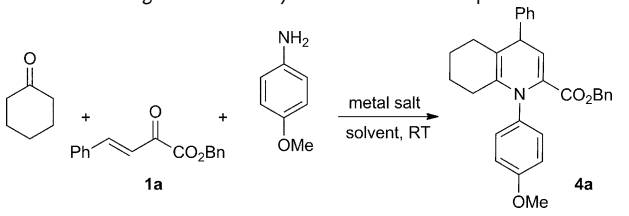
has been considerable,[16] little has been done in the development of inverse-electron-demand ADARs involving enamines as the dienophiles.[17] In 2008, Chen and co-workers reported the first two-component organocatalytic asymmetric inverse-electron-demand ADAR of carbonyl compounds.[17a] In this reaction, an aldehyde reacted with a preformed 1-azadiene that was activated by an N-sulfonyl group. To the best of our knowledge, there is no report on an enamine-based inverse-electron-demand ADAR reaction of ketones. Very recently, we developed an inverse-electron-demand hetero-Diels–Alder reaction (HDAR) of ketones with unsaturated ketoesters through an enamine/metal Lewis acid bifunctional approach.[18] Encourged by this success, we considered the development of a three-component inverse-electron-demand ADAR of β,γ-unsaturated α-ketoesters, cyclic ketones, and aromatic amines (Scheme 2). A three-component reaction would avoid the preformation of the dienophiles and the very troublesome preparation of unstable 1-azadienes.[19] This approach seemed very challenging, not only because a large number of possible side reactions, including aza-Michael addition, aldol reaction, Mannich reaction, HDAR, etc., might be involved in this multicomponent reaction, but also because both the ketone and the possible 1-azadiene intermediate are difficult substrates for this type of reactions. Ketones are much less reactive than aldehydes for as a result of both electronic and steric reasons; the possible 1-azadiene intermediates are less reactive than 1-azadienes that are activated by an N-sulfonyl group (see Chen et al.)[17] and the more commonly used 2-azadienes.[19] On the other hand, given the exceptional simplicity of this reaction and its potential impact on organic synthesis, we thought it was worthy of exploration. Arylamines, such as aniline, can reversibly form enamine intermediates (**2**) with cyclic ketones and thus serve as the enamine catalysts; on the other hand, they can also reversibly form 1-azadienes (**3**) with β,γ-unsaturated α-ketoesters (**1**) in the presence of a metal Lewis acid. The in situ formed 1-azadienes **3**, which can be strongly activated by a metal Lewis acid, can react with the enamine, leading predominately to an irreversible ADAR reaction under optimized conditions to give dihydropyridine **4** or tetrahydropyridine **5** (Scheme 2).

We started our investigation by screening a variety of metal salts for the three-component reaction of cyclohexanone, enone **1a**, and *p*-methoxyaniline in THF (Table 1). Most of the metal salts that were screened were able to catalyze the desired ADAR toward dihydropyridine **4a**. The corresponding tetrahydropyridine (**5**) was not isolated. Y(OTf)$_3$, Yb(OTf)$_3$, La(OTf)$_3$, and Zn(OTf)$_2$ displayed high activity for this ADAR with regard to reaction time (< 4 h) and yield (61–91 %); the formation of **4a** was confirmed using ^{1}H and ^{13}C NMR spectroscopy, DEPT, COSY, HSQC, and MS (HRMS and ESI) analyses.

After the development of a three-component ADAR reaction, we investigated an asymmetric version of this reaction. The availability of an asymmetric ADAR will

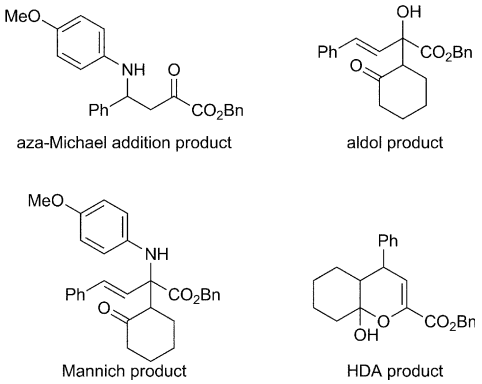
Table 1: Screening of metal catalysts for the three-component ADAR.[a]

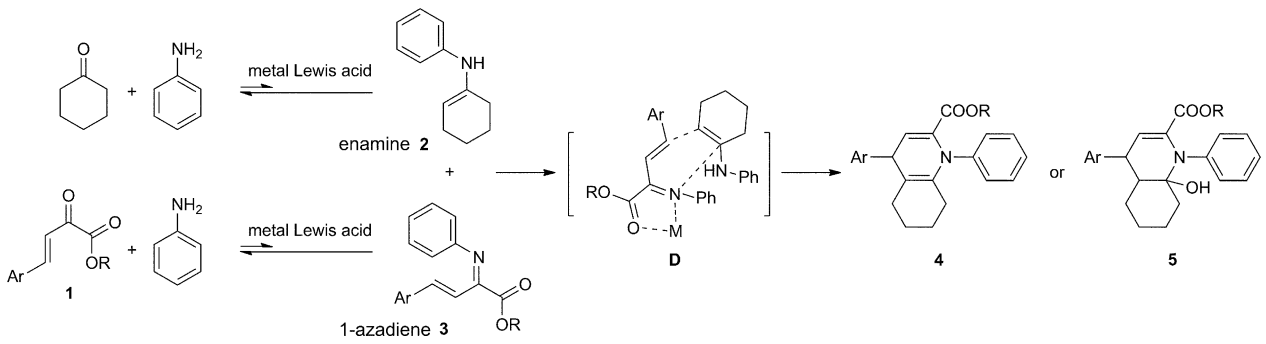


Metal	*t* [h]	Yield of **4a** [%][b]	Metal	*t* [h]	Yield of **4a** [%][b]
Y(OTf)$_3$	2	91	La(OTf)$_3$	12	61
Cu(OTf)$_2$	24	trace	Sc(OTf)$_3$	12	56
Yb(OTf)$_3$	3	85	Zn(OTf)$_2$	4	78
Eu(FOD)$_3$	36	0	YCl$_3$[c]	24	trace
In(SbF$_6$)$_3$	12	20			

[a] Reactions were performed with **1a** (0.1 mmol) and cyclohexanone (0.05 mL) in the presence of *p*-methoxyaniline (0.1 mmol) and metal salt (10 mol%) in THF (1 mL). [b] Yields were determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures. [c] Reaction was carried out in toluene (1 mL).

Possible products from side reactions:



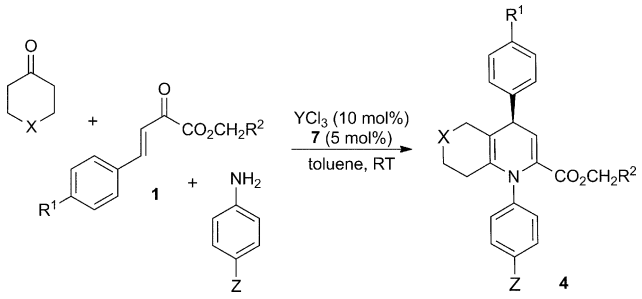


Scheme 2. Inverse-electron-demand aza-Diels–Alder reaction.

largely broaden the utility of this reaction. Since arylamines also act as a reactant in the reaction, the asymmetry can only be induced through the metal species. A general way to accomplish this is to use chiral ligands. We screened a number of ligands, including BOX, PyBOX, naphthol, and salen, in combination with $Y(OTf)_3$, $Yb(OTf)_3$, $La(OTf)_3$, and $Zn(OTf)_2$ (see the Supporting Information, Table S2). However, only low to modest enantioselectivities (< 42% *ee*) were obtained with decreased catalyst activity and/or increased occurrance of side reactions. We then investigated the possibility of using a chiral anion. Using chiral counterions to introduce high stereoselectivity in metal-catalyzed reactions was first achieved by Toste and co-workers in 2007.[20a] This strategy has been successfully applied to several reactions that were catalyzed by a metal with only one chiral anion.[20b–f] The success of reactions catalyzed by a metal with more than one chiral anion was however limited.[20g,h]

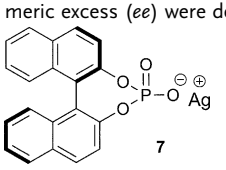
We initiated the study by combining a $M^{III}Cl_3$ with a simple chiral silver phosphate (**7**) for the three-component reaction of cyclohexanone, enone **1a**, and *p*-methoxyaniline. After extensive exploration of the reaction conditions including a screening of solvents and metals (see the Supporting Information, Tables S3 and S4), the combination of YCl_3 (10 mol%) and silver phosphate **7** (5 mol%) in toluene led to product **4a** with high enantioselectivity. We found that the silver phosphate **7** must be prepared at higher temperature (45°C) in order to obtain high enantioselectivity. Using the optimized conditions, we investigated the substrate scope of enone **1**, the arylamine, and the ketone (Table 2). The β,γ-unsaturated α-ketoesters with both electron-donating and electron-withdrawing aromatic substituents at the γ-position reacted smoothly with cyclohexanone and *p*-methoxyaniline to give the ADAR product **4** in very good to excellent enantioselectivity (87–96% *ee*) in good yields (68–90%; Table 2, entries 1–10). These reactions were highly chemoselective under the optimized conditions, leading to the dominating formation of ADAR products. In addition to the electron-rich *p*-methoxyaniline, more electron-deficient aniline (Table 2, entry 11), *p*-chloroaniline (entry 12), and *p*-bromoaniline (entry 13) all reacted with enone **1** ($R^1 = Cl$, $R^2 = H$) and cyclohexanone to produce the ADAR products **4k**–**4m** in very high enantioselectivity and chemoselectivity (93–96% *ee*, 68–72% yield). It is notable that when $Y(OTf)_3$ was used as the catalyst, the reaction of the much more electron-deficient *p*-nitroaniline gave the ADAR product quantitatively, however, when the chiral anion was used, the resulting phosphate was not strong enough to catalyze the ADAR (see the Supporting Information). Similar to cyclohexanone, heteroatom-containing dihydrothiopyran-4-one also underwent ADAR smoothly, giving **4n** in 93% *ee* and 73% yield (Table 2, entry 14). On the other hand, cyclopentanone and cycloheptanone reacted with enone and *p*-methoxyaniline, producing the ADAR products in good yields (91% and 70%, respectively) in the presence of $Y(OTf)_3$ (see the Supporting Information, Figure S1). However, when chiral anions were used, only modest enantioselectivity and chemoselectivity were achieved (see the Supporting Information, Figure S2). The absolute configuration of **4d** was established as (4*R*) by X-ray crystallography (see the Supporting Information for details). All other products **4** were assumed to have similar configurations as **4d**.

Table 2: Scope of asymmetric three-component inverse-electron-demand ADARs.[a]



Entry	X	Z	R^1	R^2	*t* [h]	**4**	Yield [%][b]	*ee* [%][c]
1	C	OMe	H	Ph	12	**4a**	72	89
2	C	OMe	H	H	12	**4b**	80	92
3	C	OMe	Me	Ph	12	**4c**	70	86
4	C	OMe	Cl	Ph	12	**4d**	90	93
5	C	OMe	Cl	H	12	**4e**	85	96
6	C	OMe	Br	Ph	12	**4f**	88	93
7	C	OMe	Br	H	12	**4g**	85	95
8	C	OMe	OMe	H	12	**4h**	78	93
9	C	OMe	NO_2	CH_3	12	**4i**	68	92
10	C	OMe	H	*p*-NO_2Ph	12	**4j**	80	87
11	C	H	Cl	H	24	**4k**	70	94
12	C	Cl	Cl	H	24	**4l**	68	96
13	C	Br	Cl	H	24	**4m**	72	93
14	S	OMe	Cl	H	24	**4n**	73	93

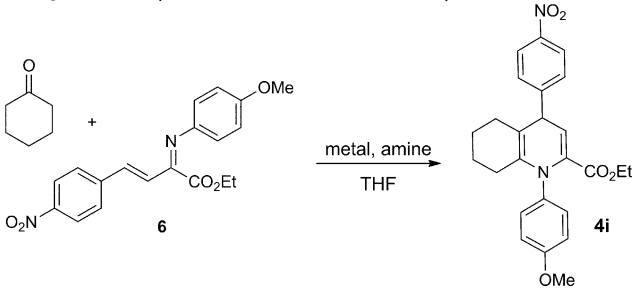
[a] The reactions were performed with 0.1 mmol of enone and 0.05 mL of cyclic ketone in the presence of 0.1 mmol of arylamine in 1 mL of toluene. [b] Yields refer to isolated product. [c] The values of enantiomeric excess (*ee*) were determined by chiral HPLC analysis.



In order to further illustrate the much better compatibility of arylamines with metal Lewis acids, we replaced the arylamine with an aliphatic amine (hexylamine) in the three-component reaction in the presence of $Y(OTf)_3$. The reaction became very messy. Starting enone **1a** was not completely consumed, even after two days, and no ADAR product was detected. On the other hand, when the metal Lewis acid ($Y(OTf)_3$) was replaced by a Brønsted acid (benzoic acid or phosphoric acid), similar results were obtained. These data clearly suggest the necessity of using both an arylamine and a metal Lewis acid in this reaction.

We believe that the arylamines participated in the reaction not only as reactants, but also as amine catalysts, activating the ketones through enamine intermediates. To better understand the catalytic role of the amines, we carried out the two-component reaction of 1-azadiene **6**[21] with cyclohexanone (Table 3). In the absence of an arylamine, with $Y(OTf)_3$ as the sole catalytic species, the reaction of **6** with cyclohexanone gave the ADAR product (**4i**) in less than 10% yield after 36 h, furthermore, a large amount of starting material **6** and the enone that results from the decomposition

Table 3: Two-component ADAR reaction and catalytic role of amines.

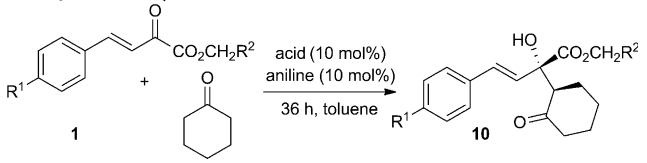


Entry	Metal salt	Amine	*t* [h]	Yield [%]
1	$Y(OTf)_3$	–	36	<10
2	$Y(OTf)_3$	*p*-methoxyaniline	24	70
3	–	*p*-methoxyaniline	48	–
4	$Y(OTf)_3$	*N*,*N*-dimethylaniline	36	<10
5	$Y(OTf)_3$	hexylamine	48	–
6	–	hexylamine	24	–

of **6**, was recovered (Table 3, entry 1). The reaction rate increased when aniline was added (Table 3, entry 2), and the transformation was complete within 24 h, giving **4i** in 70% yield. In the absence of a metal Lewis acid, **6** did not react with cyclohexanone (Table 3, entry 3). When *N*,*N*-dimethylaniline, a tertiary amine that is slightly more basic than aniline, was added to the reaction mixture (Table 3, entry 4), the reaction proceeded similarly to that summarized in entry 1, thus indicating that *N*,*N*-dimethylaniline did not act as a co-catalyst in this reaction. Regardless of whether $Y(OTf)_3$ was present or absent (Table 3, entries 5 and 6, respectively), the reaction did not give any ADAR product and starting material **6** was recovered when an aliphatic primary amine (hexylamine) was used. These data strongly support that the three-component ADAR is mediated by both a metal Lewis acid and an arylamine through the formation of enamine intermediates.

In order to further confirm that arylamines can serve as amine catalysts in enamine catalysis, we investigated the direct aldol reactions of enones **1** (Table 4) and isatin (Table 5) with cyclohexanone. The reactions could not be catalyzed by a metal Lewis acid or aniline alone. However, when a catalytic amount of aniline was combined with a metal Lewis acid ($Cu(OTf)_2$ and $Y(OTf)_3$, respectively), the reactions proceeded smoothly to give the desired aldol products (**10** and **11**, respectively) in good yields (entry 2 in Tables 4 and 5, respectively), thus indicating the power of this catalyst combination. Furthermore, aniline can be combined with a Brønsted acid to catalyze the aldol reaction of enone **1**. The asymmetric version of this reaction was effectively achieved through the use of chiral phosphoric acid **8** (Table 4, entries 3–6, 80–89% *ee*). On the other hand, combination of the chiral arylamine **9** with $Y(OTf)_3$ gave the product of the aldol reaction of isatin with excellent enantioselectivity (95% *ee*; Table 5, entry 3). These data suggest that an arylamine can serve as an amine catalyst in conjunction with either a metal Lewis acid or a Brønsted acid. The stereoselectivity can be introduced either through a chiral acid or a chiral amine. It should also be mentioned that when an alkylamine (hexylamine) was combined with $Y(OTf)_3$ for the aldol reaction of isatin, no reaction occurred, again illustrating the much better compatibility of arylamines with harder metal Lewis acids.

Table 4: Direct asymmetric aldol reaction of enone **1**.



Entry	R^1	R^2	Acid	Product	Yield [%]	d.r.	*ee* [%]
1[a]	Cl	H	$Cu(OTf)_2$	**10a**	2	–	–
2[b]	Cl	H	$Cu(OTf)_2$	**10a**	53	–	–
3	Cl	H	**8**	**10a**	82	12.5:1	89
4	H	H	**8**	**10b**	74	11:1	86
5	OMe	H	**8**	**10c**	75	10:1	80
6	NO_2	CH_3	**8**	**10d**	66	10:1	81

[a] Reaction was performed without aniline, in THF, 6 days. [b] Reaction was performed with aniline (20 mol%), in THF, 3 days.

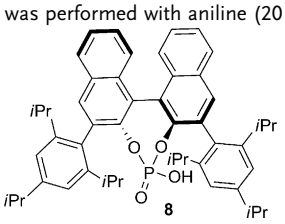
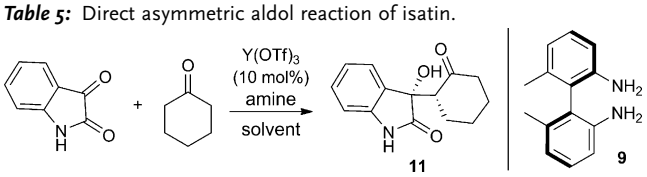


Table 5: Direct asymmetric aldol reaction of isatin.



Entry	Amine (mol%)	Solvent	*t* [h]	Yield [%]	d.r.[a]	*ee* [%]
1	–	THF	48	0	–	–
2	aniline (10)	THF	6	80	n.d.	n.d.
3	**9** (20)	toluene	12	79	10:1	95

[a] *syn*/*anti*. n.d. = not determined.

In conclusion, the combination of aminocatalysis with harder metal Lewis acids is difficult because of the aforementioned acid–base quenching reaction, which leads to inactivation of the catalysts. We have shown that the use of arylamines to replace the aliphatic amines that are generally used in aminocatalysis can circumvent the problem. Very importantly, we have demonstrated that in combination with either a Brønsted or a metal Lewis acid, arylamines can effectively act as amine catalysts and activate ketones through the formation of enamine intermediates. Using this new concept, a three-component inverse-electron-demand aza-Diels–Alder reaction of cyclic ketones with enones was developed through the combination of an arylamine with a stronger metal Lewis acid. The enantioselectivity of these reactions was achieved by using simple chiral anions. The availability of a large variety of arylamines, the nucleophilicity of which can be easily tuned through the introduction of different electronic groups at the aromatic ring(s), and the

possibility of inducing stereoselectivity through either a chiral amine or a chiral acid make this approach highly flexible, thus promising broad applications.

Experimental Section

General procedure for asymmetric aza-HDAR: A mixture of YCl_3 (3.9 mg, 0.02 mmol, 10 mol%), **7** (4.6 mg, 0.01 mmol, 5 mol%), and cyclic ketone (0.1 mL) was stirred at room temperature for 3 h in toluene (1 mL). The appropriate enone **1** (0.2 mmol, 1.0 equiv) and arylamines (0.2 mmol, 1.0 equiv) were then added. The resulting suspension was stirred at room temperature until the reaction was completed (monitored by TLC). The reaction mixture was filtered through a silica gel plug, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 4:1, *v*:*v*) to give the pure products. The *ee* values were determined by HPLC analysis on a chiral stationary phase. Full experimental details and characterization data (^{1}H NMR, ^{13}C NMT, DEPT, COSY, and HSQC spectroscopy, HPLC data, and high-resolution mass spectrometry) for all new compounds are included in the Supporting Information.

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