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Introduction

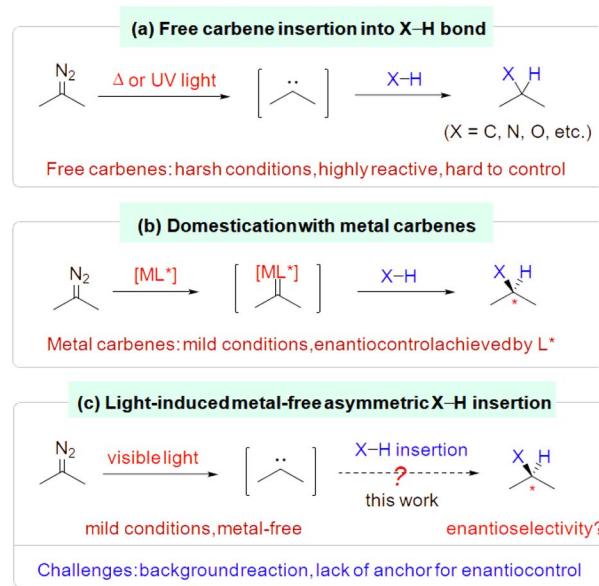
Insertion of a carbene into an H–X bond ($X = C, N, O$, etc.) is a well-known reaction that provides expedient access to functionalized organic molecules.^{1,2} However, free carbenes, conventionally generated from diazo compounds under harsh conditions (e.g., high temperature, UV irradiation), are highly reactive and hard to control regarding chemo- and stereoselectivity and functional group compatibility (Scheme 1a).^{1,3} In contrast, taming their reactivity by combining them with metals to form metal carbenes has allowed these insertion reactions to proceed not only under mild conditions with good functional group tolerance, but also with straightforward enantiocontrol *via* metal–ligand interactions (Scheme 1b).² Recently, free carbenes have been generated under mild conditions by deploying visible light irradiation of the corresponding diazo compounds, which allowed a wide range of insertion processes to take place without the aid of a metal catalyst.^{4–6} However, the leap toward a mild metal-free catalytic enantioselective insertion of a photo-generated free carbene into an H–X bond has yet to be achieved (Scheme 1c).

Visible-light-induced organocatalytic enantioselective N–H insertion of α -diazoesters enabled by indirect free carbene capture†

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While asymmetric insertion of metal carbenes into H–X ($X = C, N, O$, etc.) bonds has been well-established, asymmetric control over free carbenes is challenging due to the presence of strong background reactions and lack of any anchor for a catalyst interaction. Here we have achieved the first photo-induced metal-free asymmetric H–X bond insertion of this type. With visible light used as a promoter and a chiral phosphoric acid used as a catalyst, α -diazoesters and aryl amines underwent smooth N–H bond insertion to form enantioenriched α -aminoesters with high efficiency and good enantioselectivity under mild conditions. Key to the success was the use of DMSO as an additive, which served to rapidly capture the highly reactive free carbene intermediate to form a domesticated sulfoxonium ylide.

The key to tackling this formidable challenge is thought to involve finding a way (1) to outcompete or inhibit the facile racemic background reaction once the free carbene is generated and (2) to enable a metal-free chiral inducer to interact with the reaction partners to achieve effective enantiocontrol. Typically, free carbenes and the H–X bond insertion partners (such as amines, alcohols) either lack obvious anchors for catalyst interaction or have flexible conformations that make it difficult to achieve asymmetric induction.^{1–3} Moreover, many chiral



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Scheme 1 Introduction to insertion of carbenes into H–X bonds.



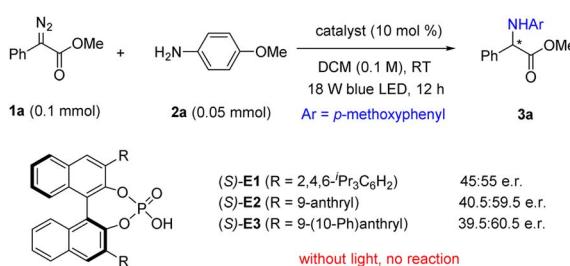
organocatalysts have polar H-X bonds that may not be compatible with free carbenes.^{7,8} In this context, here we report our progress using an indirect approach.

Results and discussion

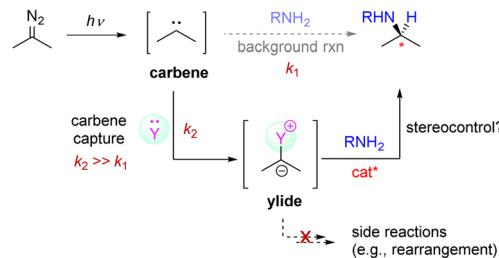
Reaction development

We started our preliminary study with α -diazoester **1a** as the carbene precursor and *para*-methoxy aniline as the reaction partner, aiming to achieve an asymmetric N-H insertion reaction (Scheme 2).^{9,10} Initially, we evaluated some typical chiral organocatalysts, including the cinchona alkaloid quinine, thiourea, urea, and squaramide. With blue light-emitting diode (LED) irradiation, these reactions proceeded smoothly at room temperature to form the desired N-H insertion product **3a** in excellent yields, but unfortunately, all in racemic forms (see Fig. S1 in ESI† for details). Next, we examined a few chiral phosphoric acids (CPAs, Scheme 2).¹¹ To our delight, these reactions showed some enantioselectivity. Of the CPAs tested, CPA **E3** led to the best enantioselectivity (39.5 : 60.5 e.r.). Notably, the reaction did not proceed without light. Further considerable efforts to screen other conditions, including solvents and temperature, did not improve the outcome.

The low enantioselectivity was believed to be primarily due to the facile background reactions of the free carbene. We hypothesized that the enantioselectivity would be improved if the free carbene, once generated, could be immediately captured by an additive Y to *in situ* generate a less-reactive intermediary carbenoid species (e.g., ylide),¹² which would react with the amine in a more controlled manner (Scheme 3). However, several requirements need to be fulfilled in this design. First, the additive should be strong enough to outcompete the amine so that it is able to alter the normal reactivity ($k_2 \gg k_1$) and thus shut down any background reaction. In addition, this intermediary carbenoid should have sufficient reactivity toward the amine partner in the presence of the organocatalyst, which in the meantime should be able to control the enantioselectivity during N-H bond insertion. Furthermore, the additive should not contain labile groups that can react with the free carbene to form side products (e.g., rearrangement products).¹³ Finally, with its likely use in a stoichiometric amount, the additive should be compatible with the organocatalyst and not affect the subsequent stereocontrol. Overall, these requirements have apparently made this design quite difficult to implement.



Scheme 2 Preliminary results.



Scheme 3 Design strategy involving carrying out carbene capture with an additive in order to inhibit any background reaction from occurring.

We hypothesized that the lone pair on sulfur, phosphorus, or halogen might be able to trap the free carbene, and the resulting ylides from these species could be both stable and reactive.¹² In particular, sulfur ylides have been used for asymmetric H-X bond insertion reactions.^{14,15} Thus, we examined PPh_3 , halobenzenes and sulfides, but they did not lead to any obvious improvement.¹⁶ However, use of DMSO resulted in a dramatic increase in enantioselectivity (to 78 : 22 e.r.). Other sulfoxides, including cyclic and aryl-substituted ones, were inferior (Fig. 1).

With DMSO, we next varied other parameters, including solvent, temperature, and concentration as well as the ester group used. Unfortunately, no improvement was obtained. We then turned our attention to any effect of the amount of DMSO on enantioselectivity. Since its main function in this reaction was to trap the free carbene, increasing its loading was thought to perhaps facilitate carbene capture, thus diminishing any racemic background reaction. However, DMSO is not a typical solvent for organocatalysis, as its high polarity may interrupt the catalyst–substrate interaction. Our initial use of four equivalents of DMSO (Fig. 1) was arbitrary and may not have been optimal due to the above two factors that lead to opposite effects to stereocontrol. Thus, we systematically evaluated the influence of DMSO loading (Fig. 2). As the DMSO loading was increased, the enantioselectivity initially increased significantly, but then gradually decreased. The highest enantioselectivity was obtained with 32 equivalents of DMSO (90 : 10 e.r.). Notably, decreasing the temperature or using LEDs with

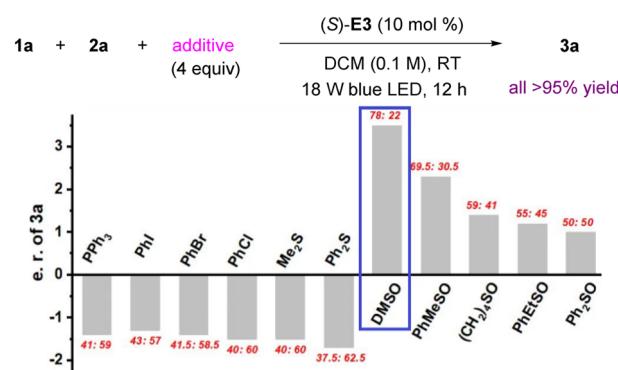


Fig. 1 Effect of additives.



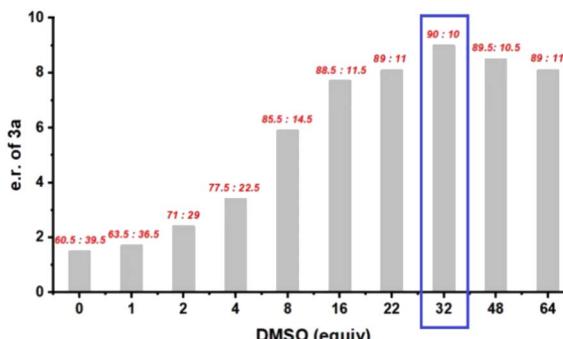
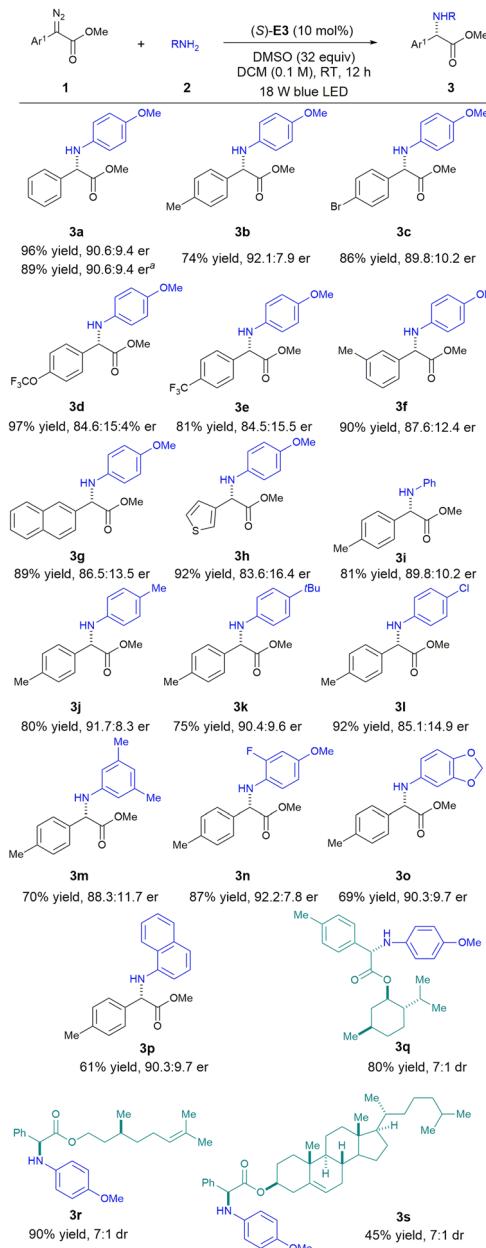


Fig. 2 Effect of DMSO loading.

different wavelengths did not improve the enantioselectivity (see Table S2[†] for details).

With the above optimized conditions, we next investigated the generality of this mild organocatalytic asymmetric carbene insertion protocol (Scheme 4). A wide range of α -aryl diazoacetates bearing different substituents reacted smoothly with *para*-methoxyaniline to give the desired α -aryl glycines in excellent yields with good enantioselectivities. The incorporation of a thiophene heterocycle at the α -position (**3h**) did not affect the reactivity. Various arylamines were also amenable to this protocol. Unfortunately, aliphatic amines were not compatible, as use of these compounds led to racemic products. This result can be explained by a strong background reaction occurring with the more basic aliphatic amines, and their high basicity levels may have also deactivated the CPA catalyst. Late-stage functionalization of some natural product derivatives was also feasible with this protocol (**3q–3s**). Some potentially reactive functional groups were well tolerated, and the desired products were all formed with good efficiency and stereocontrol. Note that substrate-directed stereocontrol of these molecules under metal-catalyzed or catalyst-free conditions have typically been difficult to achieve.^{5j} Finally, synthesis of **3a** on a scale of 2 mmol was equally efficient.

To determine more about the reaction mechanism, particularly the role of DMSO, we carried out some control experiments (Scheme 5). In the absence of amine and (*S*)-E3, the free carbene generated from diazoester **1a** was successfully trapped by DMSO to form the sulfoxonium ylide **4a** in 75% yield (Scheme 5a).^{12b,c} Without light, this step did not proceed, suggesting that light-induced free carbene generation was likely involved. Next, this ylide was treated with amine **2a** and catalyst (*S*)-E3, which rapidly reacted to form **3a** in 90% yield and 94.5 : 5.5 e.r. (Scheme 5b). These results confirmed the chemical and kinetic competence of the sulfoxonium ylide **4a** and also supported our design, shown in Scheme 2. We were also interested in probing any possible role of light in the C–N bond-forming step. Indeed, the reaction of **4a** with **2a** was very slow with the same light irradiation (Scheme 5c). This result suggested a possible lack of a significant role played by light in the second step of the standard protocol. Instead, the CPA catalyst was considered to be essential for activation and enantiocontrol of the sulfoxonium ylides.¹⁵ Finally, TEMPO was added to the

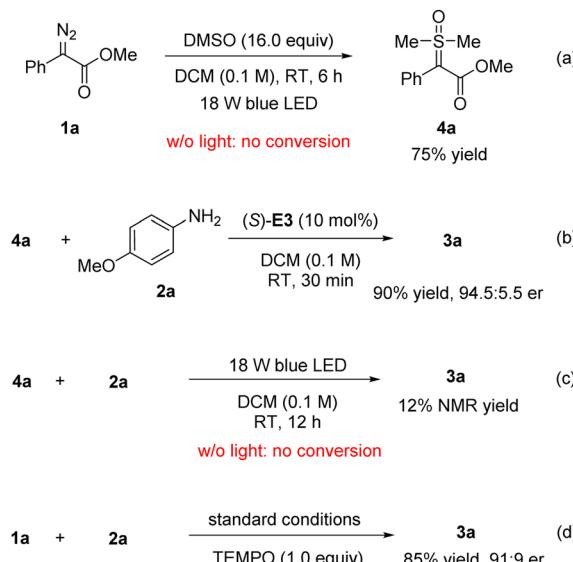


Scheme 4 Reaction scope: **1** (0.2 mmol), **2** (0.1 mmol), catalyst (0.01 mmol), DMSO (3.2 mmol), DCM (1.0 mL). ^aRun at a 2.0 mmol scale.

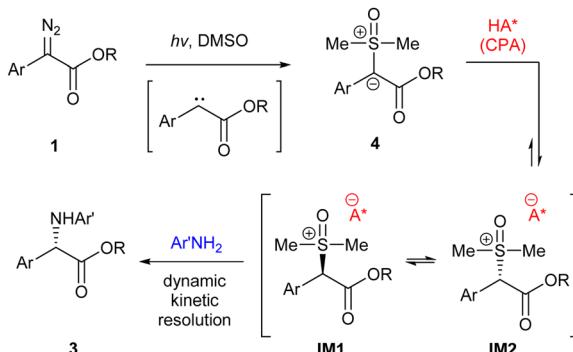
standard reaction of **1a** with **2a**; this addition had a very minor influence on the outcome (Scheme 5d), consistent with the involvement of singlet carbenes rather than of radicals or triplet carbenes in the reaction.^{6g}

A possible mechanism is proposed in Scheme 6. The reaction begins with photo-initiated free carbene formation and capture by DMSO to form sulfoxonium ylide **4**. Next, the chiral acid catalyst protonates the ylide to form sulfoxonium ions **IM1** and **IM2**, which are diastereometers and rapidly interconvert with each other. And finally, according to the mechanism, the chiral anion then directs the amine to react preferentially with one of the two diastereomers to form the enantioenriched product **3** via dynamic kinetic resolution.^{15b}





Scheme 5 Control experiments.



Scheme 6 Proposed mechanism.

Conclusions

In conclusion, we have developed a photo-induced metal-free enantioselective X–H insertion reaction of diazo compounds under mild conditions. Due to facile racemic background reactions and the lack of a robust anchor for catalyst interaction, the development of direct asymmetric insertion of free carbenes into X–H bonds remains a challenge, though highly desirable. Here, we have made progress indirectly in this regard by employing visible light as a promoter, a chiral phosphoric acid as a catalyst, and most importantly, a suitable additive. A range of α -diazoesters and arylamines successfully underwent one-pot asymmetric N–H insertion to form the desired enantioenriched α -aminoesters with high efficiency and good enantioselectivity. Key to the success was the use of a suitable amount of DMSO as an additive, which captured the free carbene in the form of a domesticated carbenoid, namely a sulfoxonium ylide, for the stereocontrolled N–H bond insertion. Control experiments provided solid evidence for the role of DMSO. The development of more direct and efficient metal-free

asymmetric X–H insertion reactions of free carbenes is ongoing in our laboratory.

Data availability

All experimental data is available within the article and the ESI.†

Author contributions

W. Guo: conceptualization, methodology, investigation, data curation, and writing of the original draft. Y. Zhou, H. Xie, X. Yue, and F. Jiang: resources. H. Huang, and Z. Han: writing-review. J. Sun: conceptualization, supervision, writing-review and editing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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16 Notably, opposite chiral induction was observed between the cases with sulfoxides and other additives. Indeed, the latter cases were the same as the situation without additive. Further studies indicated that under such conditions, non-

sulfoxide additives did not efficiently trap the free carbene. Therefore, their asymmetric induction was similar to that of free carbene. In contrast, sulfoxides were able to trap the free carbene, and thus asymmetric induction was *via* sulfoxonium ions and thus different from the others.

