The triplet state of deprotonated mesoionic carbene Breslow intermediates is thermally accessible: Distal difunctionalization of aldehydes

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The triplet state of deprotonated mesoionic carbene Breslow intermediates is thermally accessible: Distal difunctionalization of aldehydes

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INTRODUCTION

N-heterocyclic carbenes (NHCs), especially thiazol-2-ylidenes **A** [1] and 1,2,4-triazol-5-ylidenes **B**,[2] have long been known as organocatalysts for aldehyde transformations, such as the benzoin condensation, Stetter reaction, cycloadditions, Claisen rearrangement, etc. [3,4,5,6,7] (Fig 1a). These reactions occur via electron-pair-transfer processes through the so-called Breslow Intermediates (**BI**s).[8,9,10,11,12] The role of the **BI** in single electron transfer (SET) pathways was also established a long time ago in biosynthesis,[13] and expanded in the last decade to NHC-organocatalysis. [14,15,16,17] Among the important differences between the electron-pair-transfer and the SET pathways is that the first relies on the **BI**, whereas the second involves the deprotonated **BI** (**BI**$^{-}$).[18,19,20,21,22,23,24] Also noteworthy is the recent development of NHC/photoredox dual catalysis[25] involving acyl azolium salts **BI**$^{+}$,[26,27,28,29,30,31,32,33,34,35,36] as well as few reports[37,38,39] dealing with their excited state (**BI**$^{+*}$), both of which being the doubly oxidized deprotonated **BI** (Fig 1b). Obviously, the latter processes are based on the oxidizing power of the **BI**$^{+}$ and the **BI**$^{+*}$, whereas

NHC-organocatalysis via SET reaction depends on the reducing ability of **BI**$^{-}$ in the ground state. Herein we report that the excited triplet state of **BI**$^{-}$ (**BI**$^{-*}$) derived from 1,2,3-triazol-5-ylidenes (mesoionic carbenes, MIC) **D**[40,41] is thermally accessible, allowing for the catalytic distal difunctionalization of aryl aldehydes. At the formyl side, an oxidative esterification reaction takes place, concomitant with reduction of the aryl side. Here, three types of chemical transformation are demonstrated, namely hydro(deutero)defunctionalization, hydrogenation and reductive alkylation. (Fig. 1c).

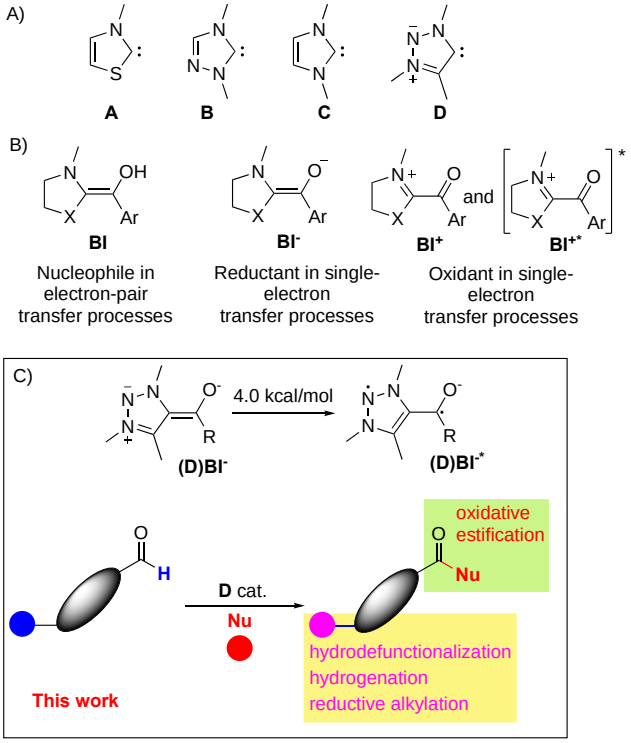


Figure 1 A) Carbenes considered in this study; B) Breslow Intermediate (**BI**), deprotonated Breslow Intermediate (**BI**$^{-}$), and acyl azolium intermediate in the ground state (**BI**$^{+}$) and the excited state (**BI**$^{+*}$); C) mesoionic carbene (**D**)-catalyzed distal difunctionalization of aryl aldehydes via the excited state of deprotonated Breslow Intermediate **(D)BI**$^{-*}$.

RESULTS AND DISCUSSION

To gain further insight into the electronic properties of **BI**s and **BI**$^{-}$s derived from **A**, **B**, **C**[42] and MICs **D**, we performed density functional theory (DFT) calculations at the PWPB95-D3/def2QZVPP//B3LYP-D3(BJ)/6-31G** + SMD (THF) level of theory. The adiabatic singlet-triplet gaps for **BI**s derived from classical NHCs **A**-**C** are greater

than 37.0 kcal/mol, whereas for the mesoionic carbene (**D)BI**,[43] it is only 23.7 kcal/mol (Fig. 2). The same trend is observed for the singlet-triplet gap of the corresponding deprotonated **BI**s (**BI$^-$s**). They vary from 26.1 to 28.7 kcal/mol for NHCs **A**-**C**, but the gap is strikingly as low as 4.0 kcal/mol for the mesoionic analogue (**D)BI**$^-$. The small S/T gap for (**D)BI** and (**D)BI**$^-$ is due to the polarized exocyclic CC bond,[43] which in the singlet state leads to a repulsion between the negatively charged carbon and adjacent oxygen. The SOMO of (**D)BI**$^{-}$***** has contributions from the π orbital of the triazole ring, the carbonyl and, interestingly, the phenyl ring. The SOMO-1 is mainly located on the π* orbital of the triazole ring and on the carbonyl group. From these computational results, we were confident that the very low singlet-triplet gap predicted for (**D)BI**$^-$ would allow access to the triplet form (**D)BI**$^{-}$***** without photoexcitation. Moreover, since the SOMO is at least partially located on the phenyl group of the aldehyde moiety, it implied that the ring has a radical anion character. Thus, we envisioned that if a leaving group is present on the aryl ring, it could be eliminated, affording a biradical **(D)BR***. DFT calculations predict that such compounds would have a singlet ground state 14.5 kcal/mol lower in energy than the triplet and should therefore be regarded as the zwitterionic compound **(D)ZW**, which should allow for distal difunctionalization of aryl aldehydes.

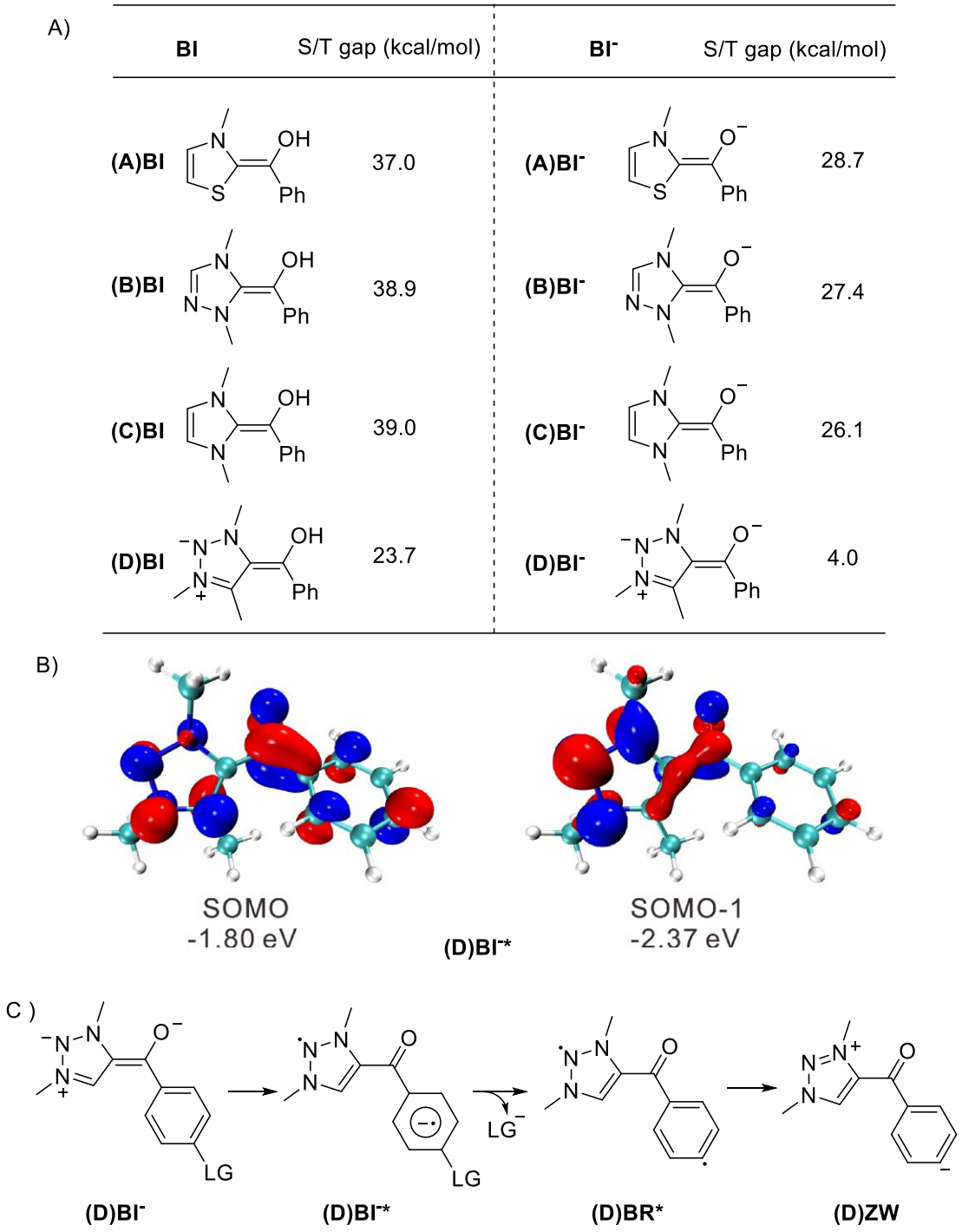
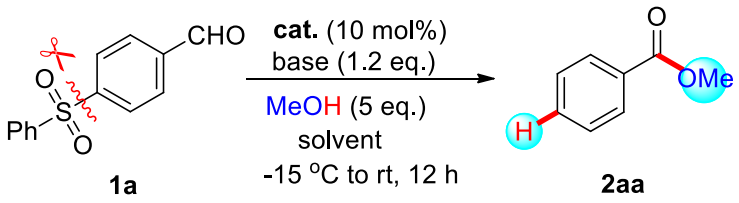


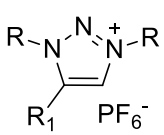
Figure 2 A) Singlet/triplet gap of **BI**s and **BI**$^{-}$s derived from carbenes **A-D**; B) SOMO and SOMO-1 of (**D)BI**$^{-}$*****, isovalue is 0.05; C) Postulated reaction sequence leading to the formation of the zwitterionic compound (**D)ZW**, allowing for difunctionalization of aryl aldehydes.

We capitalized on the potent leaving group ability of sulfonyl groups through single-electron reduction [44] to check our hypothesis. We first reacted 4-sulfonylbenzaldehyde **1a** with methanol in the presence of 10 mol% of a 1,2,3-triazolium salt as precatalyst, using a base to generate *in situ* the corresponding mesoionic carbene **D** and to deprotonate the ensuing Breslow Intermediate. With 4,5-unsubstituted triazolium **Cat$_a$** and **Cat$_b$**, methyl benzoate **2aa** was formed in 42 and 38% yield, respectively (Figure 3, entries 1-2). The leaving group was quantitatively recovered as benzenesulfinic acid ($PhSO_2H$). The yield in **2aa** significantly increased to 65 and 74% by using ester substituted triazolium salts **Cat$_c$** and **Cat$_d$**, (entries 3-4), which have proven to be the best catalysts for the previously reported MIC-catalyzed arylacylation of alkynes via SET.[45] Classical-NHCs were less efficient; only very low yields were obtained (entries 5-7). Base and solvent screening showed *t*-BuOK and *t*-BuOMe (MTBE) to be the best choices (entries 8-12). Reducing the amounts of MeOH or decreasing the reaction temperature gave lower yields (entries 13-15). A control experiment in the dark gave the same yield, which revealed that this reaction did not proceed via photoexcitation (entries 16). Note that the transformation of the 4-sulfonylbenzaldehyde **1a** into methyl benzoate **2aa**, involved a reductive desulfonylation at the aryl group and an oxidative esterification at formyl carbon, and is therefore overall redox-neutral.

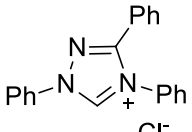


1a **2aa**

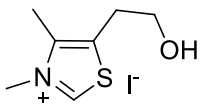
Entry	Cat.	Base	Solvent	yield[a]
1	**Cat$_a$**	*t*-BuOK	MTBE	38
2	**Cat$_b$**	*t*-BuOK	MTBE	42
3	**Cat$_c$**	*t*-BuOK	MTBE	65
4	**Cat$_d$**	*t*-BuOK	MTBE	74(71)
5	**Cat$_e$**	*t*-BuOK	MTBE	30
6	**Cat$_f$**	*t*-BuOK	MTBE	12
7	**Cat$_g$**	*t*-BuOK	MTBE	n.d.
8	**Cat$_d$**	MeOK	MTBE	35
9	**Cat$_d$**	Cs_2CO_3	MTBE	n.d.
10	**Cat$_d$**	*t*-BuOK	THF	51
11	**Cat$_d$**	*t*-BuOK	Dioxane	37
12	**Cat$_d$**	*t*-BuOK	$PhCF_3$	45
13[b]	**Cat$_d$**	*t*-BuOK	MTBE	38
14[c]	**Cat$_d$**	*t*-BuOK	MTBE	44
15[d]	**Cat$_d$**	*t*-BuOK	MTBE	50
16[e]	**Cat$_d$**	*t*-BuOK	MTBE	74



R= Mes, R_1=H **Cat$_a$**
R= Dipp, R_1=H **Cat$_b$**
R= Mes, R_1=COOMe **Cat$_c$**
R= Dipp, R_1=COOMe **Cat$_d$**
IMes•HCl **Cat$_e$**



Cat$_f$



Cat$_g$

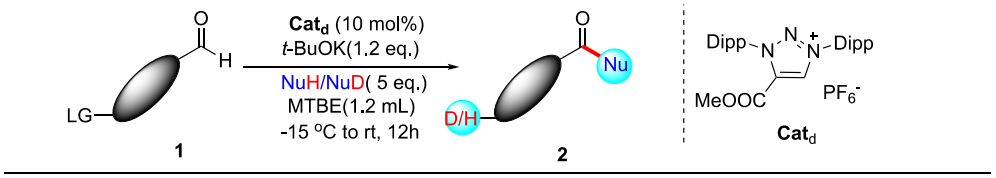
Figure 3 Optimization of the reductive desulfonylation and oxidative esterification. [a]Reaction carried out in 0.3 mmol scale. Yields were determined by ^{1}H spectroscopy with CH_2Br_2 as internal standard. Isolated yield is given in parentheses. [b]1.0 equiv

MeOH was used. [c]3.0 equiv MeOH was used. [d]Temperature was changed from -15 ^{o}C to 0 ^{o}C. [e]The reaction was performed in dark.

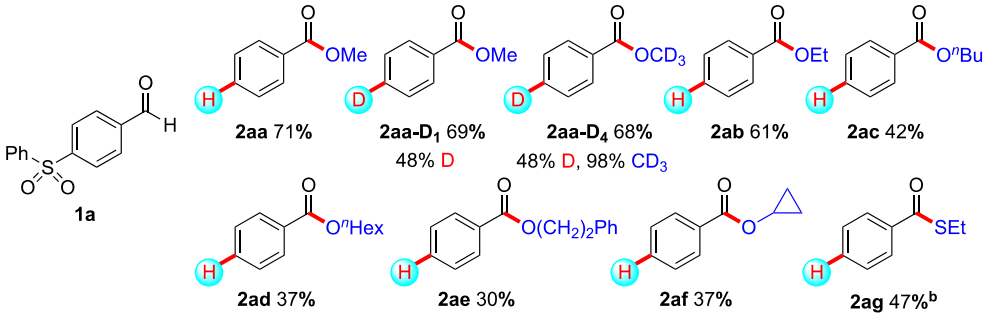
The scope of the MIC-catalyzed hydrodefunctionalization reaction was investigated under the optimized conditions. Treatment of **1a** with CH_3OD and CD_3OD gave deuterated products **2aa-D$_1$** and **2aa-D$_4$**, respectively. Note that the only partial deuteration at the phenyl ring is due to the presence of the formyl-H and MIC$^+$-H, which are exchangeable. Different nucleophiles were next employed. The yields decreased as the chain length and steric hindrance of the alcohols increase. Primary alcohols gave benzoate **2aa**-**2ae** in 30-71% yields. For secondary alcohols, only cyclopropanol gave the corresponding benzoate **2af** in 37% yield, while other alcohols gave trace products. When ethanethiol was employed with ethanol as proton source, *S*-ethyl benzothioate **2ag** could be isolated in 47% yield. We extended our investigations to sulfonyl-substituted aryl aldehydes **1b**-**1e**. When bromo, trifluoromethyl and methyl substituents were embedded on 4-sulfonylbenzaldehyde, using CH_3OD as deuterium source, the corresponding deuterodesulfonylation products **2b-D$_1$** – **2d-D$_1$** were isolated in 43-80% yields with deuteration levels of 50-53% at the 4-position. 5-Sulfonyl-2-thiophenecarbaldehyde **1e** gave deuterated product **2e-D$_1$** in 73% isolated yield. Other sulfonyl groups, such as methylsulfonyl (**1f**) and aminosulfonyl (**1g**) were converted less efficiently, giving benzoate **2aa** in 30 and 42% yield, respectively. Interestingly, the sulfonyl group can be placed in a more distal position, as shown by the desulfonylation of **1h, 1i** and **1j** which gave **2h** and **2i** in 27, 38 and 25 % yield, respectively.

The scope of the MIC-catalyzed hydrodefunctionalization and esterification of aryl aldehydes is not restricted to the sulfonyl functionality. Esters can also be used as the leaving group, as shown by the formation of the toluoate **2i** in 21% yield. Fluoride is also an attractive leaving group, since the reductive defluorination of trifluoromethylarenes is a versatile strategy for the construction of difluoromethylarenes.[46] When 4-trifluoromethyl substituted aryl aldehydes **1l** were employed, the corresponding 4-difluoromethylbenzoates **2l** was formed in 42%

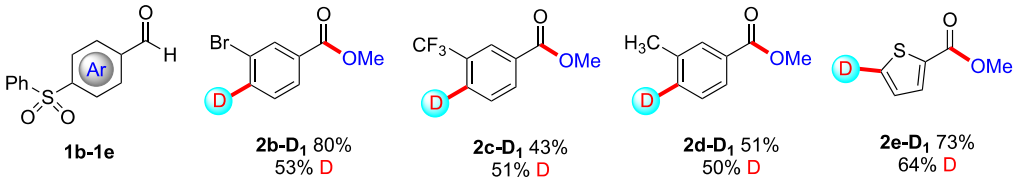
isolated yields. The 4-deuterodifluoromethylbenzoate **2l-D$_1$** was obtained in 40% yield and 60% deuteration level, using CH_3OD as deuterium source. When the trifluoromethyl group was placed in the *ortho*-position, the corresponding 2-difluoromethylbenzoate **2m** was obtained in 22% yield. Interestingly, when two trifluoromethyl groups were placed on the *ortho*- and *para*-positions, reductive defluorination selectively occurred on the *ortho*-position, giving 2-difluoromethyl-4-trifluoromethylbenzoate **2n** in 38% yield. Using CH_3OD as deuterium source, the deuterated analogue **2n-D$_1$** was isolated in 35% yield with 70% deuteration level.



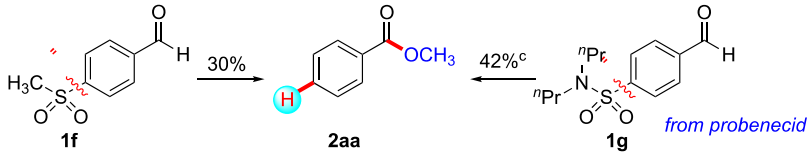
Desulfonylation with diffierent NuH/NuD



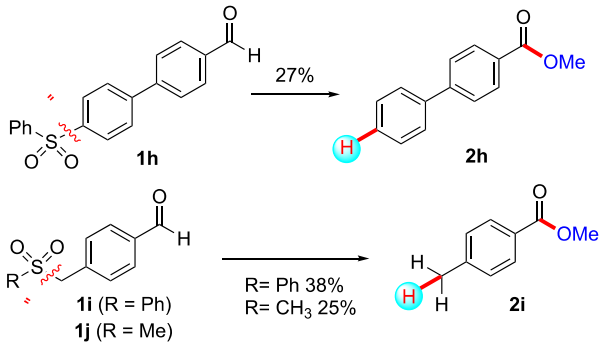
Desulfonylation from different aldehydes



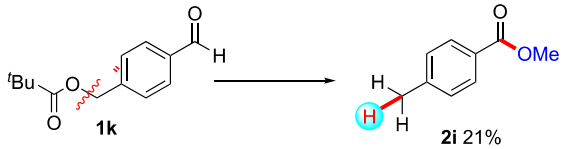
Desulfonylation from different sulfonyl leaving group



Desulfonylation from more distal position



Diffierent Leaving Groups:



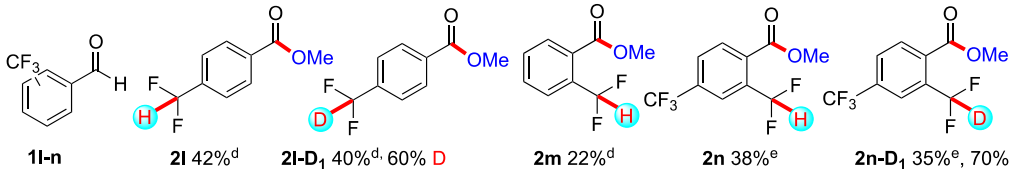


Figure 4 Scope of the MIC-catalyzed hydrodefunctionalization and esterification of aryl aldehydes. Reactions were carried out in 0.3 mmol scale. [b]3 equiv. EtOH, 2.5 equiv ^{t}BuOK, and 1.0 equiv EtSH were used. Isolated yields are given. [c]Temperature was changed from -15 °C to 0 °C. [d]**Cat$_C$** (20 mol%) was used as catalyst, 90 °C for 5 h. [e]**Cat$_C$** (20 mol%) was used as catalyst, 50 °C for 5 h.

We were curious to test whether the MIC-catalyzed distal difunctionalization of aryl aldehydes could be extended to other types of reduction processes. We first chose the hydrogenation reaction of azo compounds (Fig. 5). Under the optimized conditions, in the presence of methanol as the NuH agent, 4-azobenzaldehyde **3a** was converted into the corresponding hydrazine **4a** in 90% yield. By using CD_3OD as deuterium source, the deuterated product **4a-D$_3$** was obtained in 87% yield with a high deuteration level of 95%. Ethanol can also act as the NuH, affording **4b**, which was isolated in 67% yield. Azo derivatives with different substituents **3c**-**3f** also gave hydrazine derivatives **4c-f** in 47-76% yields. The azo group can also be placed in *meta*- and even a more distal position, giving the target products **4g-4h** in 50-61% yields. Note that these results allow to rule out a two-electron pathway via *p*- or *o*-quinodimethane.[47] These hydrogenation reactions can also be extended to other unsaturated substrates. When 4-benzoylbenzaldehyde **5** was used, the benzoyl group was reduced to the α-hydroxylbenzyl group while the formyl group was oxidized to an ester, giving **6** which was isolated in 40% yield. A dearomatization reaction was also observed for 9-anthraldehyde **7**, giving 9,10-dihydroanthracene-9-carboxylate **8** in 32% yield.[48,49]

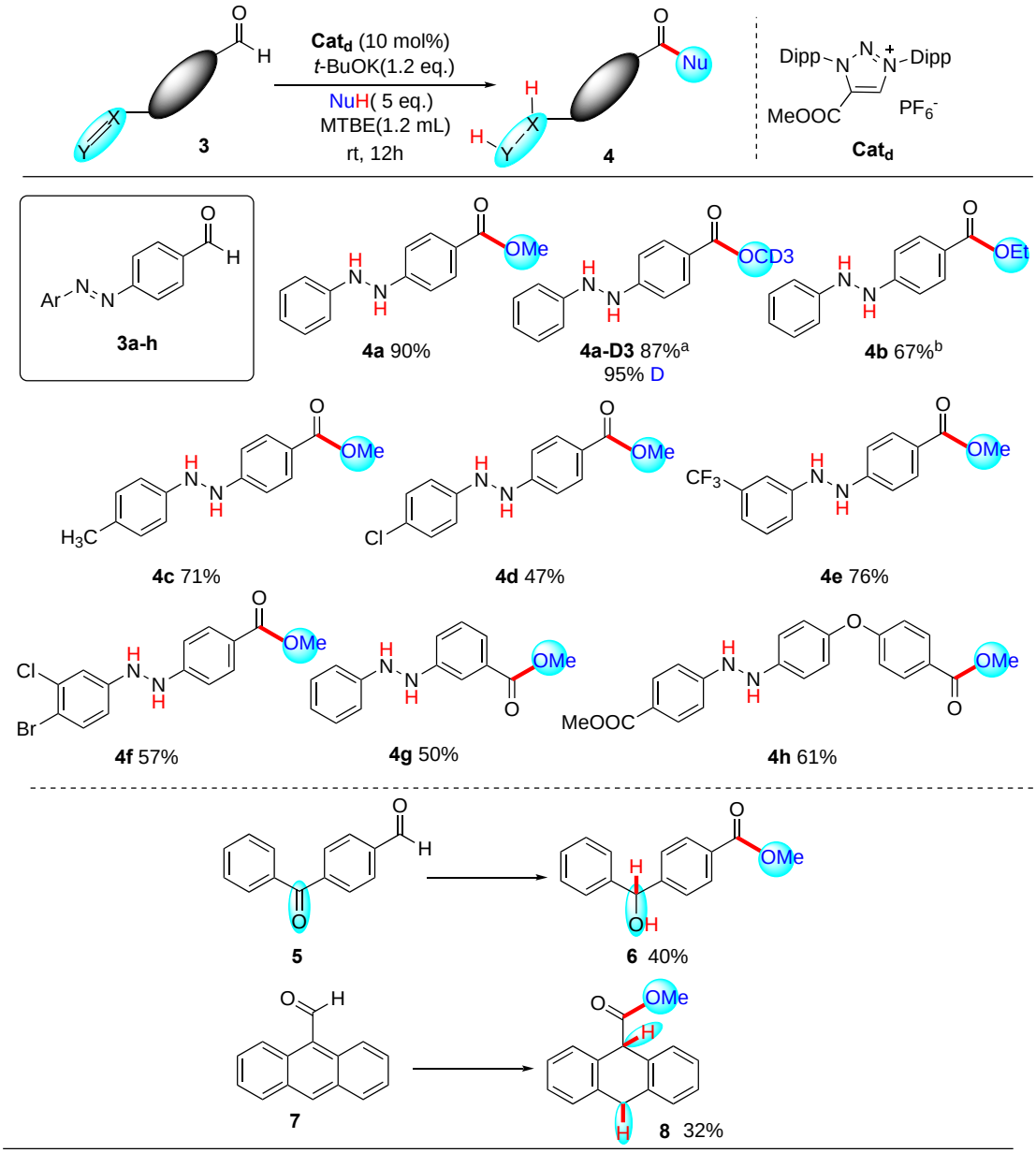


Figure 5 MIC-catalyzed hydrogenation reactions. Reactions carried out in 0.3 mmol scale. Isolated yields are given. [a]CD_3OD was used. [b]EtOH was used.

Lastly, we wanted to demonstrate that the process could allow for C-C bond formation, therefore adding complexity to aryl aldehydes (Fig. 6). To this end, we reacted 4-iodobenzaldehyde **9** under the optimized catalytic conditions with alkenes **10** in the presence of methanol. Gratifyingly, 2-vinylpyridine derivatives (**10a-c**), 2-vinylbenzothiazole (**10d**), and even methyl methacrylate (**10e**) reacted smoothly with 4-iodobenzaldehyde **9**, generating the desired products **11a-e** in 37-55% yields. Note

that in these cases, the second inversion of state could occur either just after the cleavage of the carbon-iodine bond, or after the addition to the alkene.

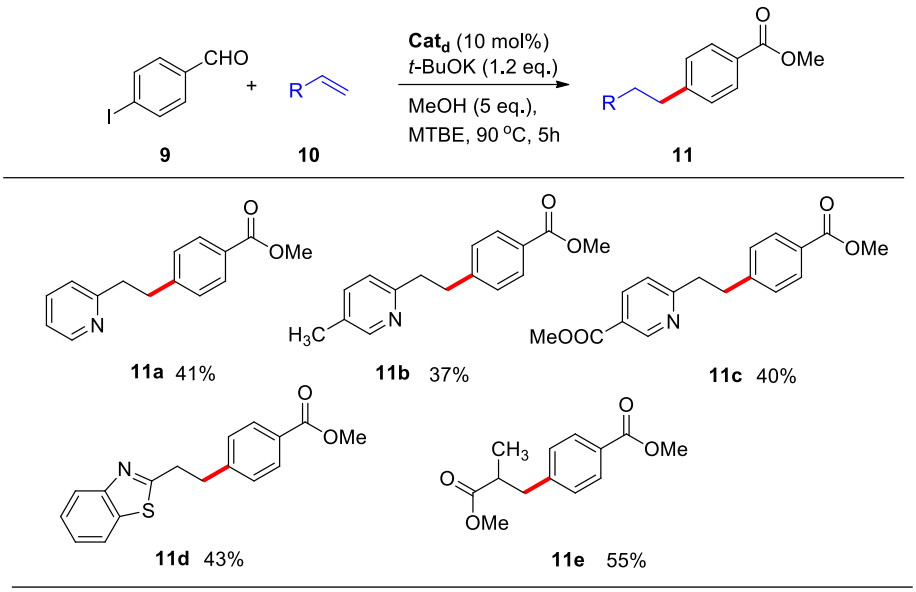


Figure 6 C-C bond formation, adding complexity to aryl aldehydes.

CONCLUSIONS

Photochemical reactions involving direct excitation of a substrate to its triplet state are well explored.[50] Recently, this area experienced a renaissance by exploiting a photosensitizer as a catalyst for energy transfer.[51,52,53] This work shows that the combination of aryl aldehydes with carbenes leads to low S/T gap adducts (Breslow Intermediates and their deprotonated forms) due to the radical-stabilization effect of carbenes.[54] The S/T gap is especially small with mesoionic carbenes, which results in their low activation energy and viability of thermal excitation. The resulting triplet state of deprotonated Breslow Intermediates enables tandem distal functionalization of aryl aldehydes. The reactivity of these biradicals is significantly different from that of the aforementioned photo-excited triplet substrates, which have a high activation energy, high reactivity and limited reaction patterns (Fig. 7). Synthetic strategies, based on the thermal accessibility of triplet states of other carbene-derived intermediates, such as azolium enolates, dienolates and homoenolates, are under current investigation.

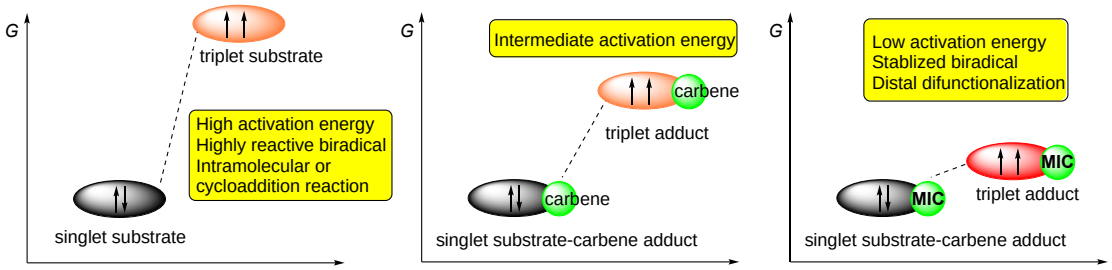


Figure 7 Carbenes, especially MICs, lead to adducts featuring low-lying triplet states.

Acknowledgments

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Author contributions

X.Y. and G.B. conceived and designed the project and wrote the manuscript with the help of M.M.. Z.Z., C.-Y.L., L.-L.Z., and W.L. conducted the experiments and analyzed the data. S.H. carried out the computational analyses. All authors provided comments on the experiments and the manuscript during its preparation.

Declaration of interest

The authors declare no competing interests.

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