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Enantioselective [2 + 2 + 2] cycloaddition of ketenes and carbon disulfide catalyzed by N-heterocyclic carbenes†

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The chiral N-heterocyclic carbene-catalyzed [2 + 2 + 2] cycloaddition of ketenes and carbon disulfide was realized to give the cycloadduct of 1,3-oxathian-6-ones in good yields with excellent enantioselectivities.

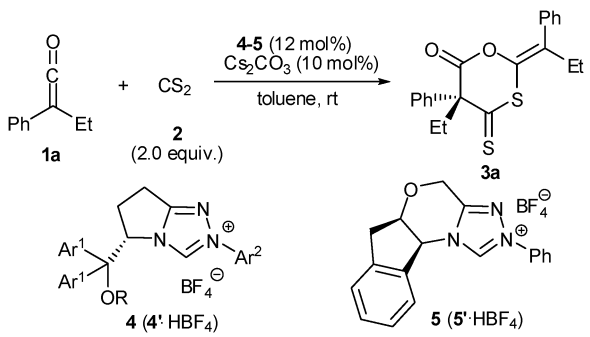
Carbon disulfide is an attractive C_1 building block for the synthesis of sulfur-containing organic compounds.[1] Particularly, the cycloadditions with carbon disulfide afford rapid construction of sulfur-heterocycles.[2] Although the Lewis bases-catalyzed[3] and organometallic compounds-catalyzed[4] cycloadditions with carbon disulfide have been widely reported, to the best of our knowledge, the enantioselective catalytic cycloaddition reaction with carbon disulfide remains unexplored.

Over the past two decades, N-heterocyclic carbenes (NHCs)[5] have been successfully used as reagents for heterocycles,[6] ligands for organometallic catalysts,[7] and Lewis base organocatalysts.[8–10] In the line of our NHC-catalyzed reactions, we found that NHCs are efficient catalysts for the cycloaddition reactions of ketenes.[11–13] In this communication, we wish to report an NHC-catalyzed cycloaddition of ketenes with carbon disulfide. Although the formation of the stable NHC-CS_2 adduct is well established,[14] our report shows that the NHC-catalyzed reaction with carbon disulfide is also feasible.

Firstly, the reaction of phenyl(ethyl)ketene (**1a**) with carbon disulfide was investigated (Table 1). In the presence of catalytic NHC **4a′**, generated freshly from its precursor **4a** and Cs_2CO_3, the reaction gave the corresponding [2 + 2 + 2] cycloadduct of 1,3-oxathian-6-one **3a**, which involving two molecules of ketene **1a** and one molecule of carbon disulfide, in 69% yield with 95% ee (entry 1). A series of NHCs derived from L-pyroglutamic acid were then screened (entries 2–8). NHCs **4b** and **4c** with diphenylmethyl group showed similar results as NHC **4a** (entries 2 and 3). NHC **4d** with two bulky aryl groups resulted in a dramatic decrease of enantioselectivity (entry 4). NHCs **4e** and **4f** with a free hydroxy group gave cycloadduct **3a** in moderate yields with varied ee values (entries 5 and 6). It is unexpected that NHCs **4g** and **4h** derived from mesityl hydrazine offered only trace cycloadduct **3a** (entries 7 and 8) with ketene dimer as the major byproduct. Further improvement of the reaction was realized by carrying out the reaction at −40 °C, which gave the cycloadduct **3a** in 99% yield with 96% ee (entry 9). Reaction catalyzed by the tetracyclic carbene **5′**, derived from aminoindanol, gave cycloadduct with 96% ee albeit in 24% yield (entry 10).

With the optimum reaction conditions in hand,[15] a variety of ketenes were then tested for the [2 + 2 + 2] cycloaddition reaction (Table 2). Aryl(alkyl)ketenes **1b** and **1c** with electron-withdrawing groups (Ar = 4-Cl, 4-BrC_6H_4) worked well to give the cycloadduct in good yields with excellent enantioselectivities (entries 2 and 3). Ketene **1d** with *p*-methylphenyl group afforded cycloadduct in 72% with 92% ee (entry 4).

Table 1 Screening of NHCs



Entry	**4** (Ar^1, Ar^2, R) or **5**[a]	Yield (%)[b]	ee (%)[c]
1	**4a** (Ph, Ph, TBS)	69	95
2	**4b** (Ph, 2-^{i}PrC$_6$H$_4$, TBS)	67	96
3	**4c** (Ph, Bn, TBS)	45	97
4	**4d** (2-naphtyl, 2-^{i}PrC$_6$H$_4$, TBS)	64	40
5	**4e** (Ph, Ph, H)	40	83
6	**4f** (3,5-$(CF_3)_2C_6H_3$, Ph, H)	49	99
7	**4g** (Ph, Mes, TMS)	trace	/
8	**4h** (3,5-$(CF_3)_2C_6H_3$, Mes, H)	trace	/
9[d]	**4b**	99	96
10	**5**	24	−96[e]

[a] NHC **4′–5′** was generated from the corresponding triazolium salt **4–5** in the presence of Cs_2CO_3 at room temperature for 1 h, and used immediately. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The reaction was carried out at −40 °C. [e] The minus ee value indicates a reversed enantioselectivity. Mes = mesityl.

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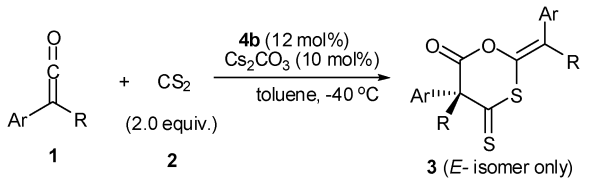
Table 2 Enantioselective NHC-catalyzed [2+2+2]cycloaddition reaction of ketenes with carbon disulfide

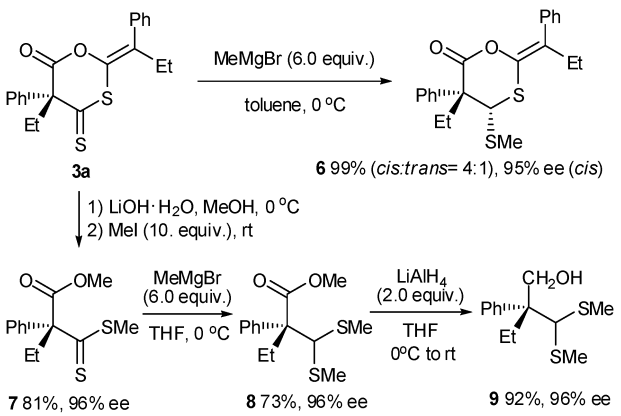


Entry	1 (Ar, R)	3	yield (%)[a]	ee (%)[b]
1	**1a** Ph, Et	**3a**	99	96
2	**1b** 4-ClC$_6$H$_4$, Et	**3b**	87	97
3	**1c** 4-BrC$_6$H$_4$, Et	**3c**	79	96
4	**1d** 4-MeC$_6$H$_4$, Et	**3d**	72	92
5	**1e** 4-MeOC$_6$H$_4$, Et	**3e**	NR (32)[c]	(93)[c]
6	**1f** 3-ClC$_6$H$_4$, Et	**3f**	71	94
7	**1g** 2-ClC$_6$H$_4$, Et	**3g**	NR	/
8	**1h** Ph, Me	**3h**	69	96
9	**1i** Ph, *n*-Pr	**3i**	94	92
10	**1j** Ph, *n*-Bu	**3j**	96	96
11	**1k** 4-ClC$_6$H$_4$, *i*-Pr	**3k**	NR	/

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Reaction carried at room temperature.

However ketene **1e** with strong electron-donating group (Ar = 4-MeOC$_6$H$_4$) gave only trace product at −40 °C, and 32% yield with 93% ee was observed at room temperature (entry 5). While ketene **1f** with *m*-chlorophenyl group worked well, ketene **1g** with *o*-chlorophenyl group did not (entries 6 and 7). The reaction of phenyl(alkyl)ketenes **1h**, **1i**, **1j** with different linear alkyl groups (R = Me, *n*-Pr or *n*-Bu) went smoothly (entries 8–10), but aryl(isopropyl)ketene **1k** afforded no cycloadduct (entry 11).[16]

Several chemical transformations of **3a** were summarized in Scheme 1. It is interesting that the addition of methyl Grignard reagent to cycloadduct **3a** gave exclusive cyclic thioacetal **6** in 99% yield with 95% ee, without ring-opened corresponding ketone or thioketone formed.[17] Alcoholysis of **3a** afforded the corresponding ester-thioester **7** in 81% yield. Again, selective methylation of **7** with Grignard reagent gave ester-thioacetal **8**. The β-hydroxy thioacetal **9** was obtained in 92% yield with 96% ee by selective reduction of **8** with LiAlH$_4$ in THF.



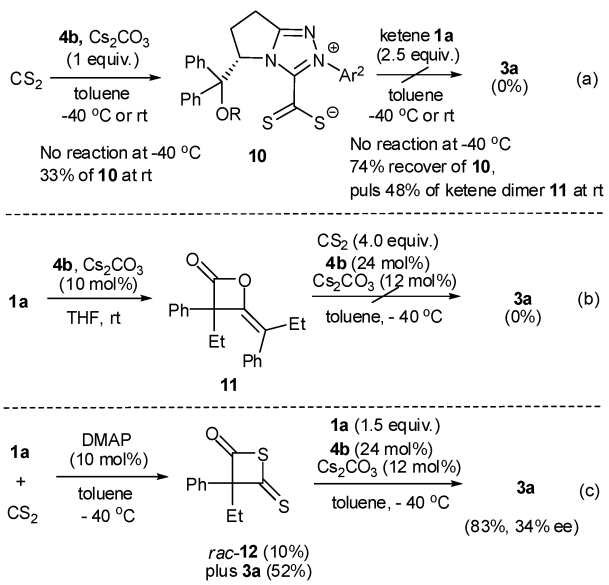
Scheme 1 Chemical transformations of **3a**.

The structure of cycloadduct *rac*-**3h**,[18] and the relative and absolute configuration of cyclic thioacetal (+)-*cis*-**6** were unambiguous established by the X-ray analysis of their crystals.[19]

Considering both reactions of NHC with ketenes and with carbon disulfide have been reported,[11,12,14] we tried to clarify whether this catalytic cycloaddition is initiated by addition of NHC to ketenes or carbon disulfide (Scheme 2). Although no reaction of NHC **4b′** and carbon disulfide was observed at −40 °C, the NHC-CS$_2$ adduct **10** was isolated in 33% at room temperature.[20] However no reaction of NHC-CS$_2$ adduct with ketene **1a** was observed at −40 °C or room temperature (reaction a). We have reported that NHCs could catalyze the dimerization of ketene **1a** to give lactone **11**.[8b] However, the further reaction of lactone **11** with CS$_2$ was found nonfeasible (reaction b). It is interesting that when the reaction of ketene **1a** and CS$_2$ was catalyzed by DMAP, 10% yield of [2+2] cycloadduct **12** was isolated along with 52% of the corresponding [2+2+2] cycloadduct **3a**. Furthermore, the cycloadduct **12** could react with one more molecule of ketene **1a** in the presence of catalytic NHC **4b′** to give the cycloadduct **3a** in good yield (reactions c).

Based on those observations, we proposed that the catalytic cycle is initiated by the addition of NHC to ketenes giving intermediate A, which reacts with CS$_2$ to afford intermediate B. Cyclization of intermediate B furnishes [2+2] cycloadduct **12**, but **12** could also go back to intermediate B in the presence of NHC. The reaction of one more molecule of ketene with intermediate B gives intermediate C, which is ring-closed to give final [2+2+2] cycloadduct **3** and regenerates the NHC catalyst (Fig. 1).

In conclusion, a highly enantioselective N-heterocyclic carbene-catalyzed [2+2+2] cycloaddition reaction of two molecules of ketenes with one molecule of carbon disulfide to give 1,3-oxathian-6-ones was developed. Control experiments revealed that the catalytic reaction is initiated by the addition of NHC to ketenes rather than carbon disulfide.



Scheme 2 Control experiments for mechanism investigation.

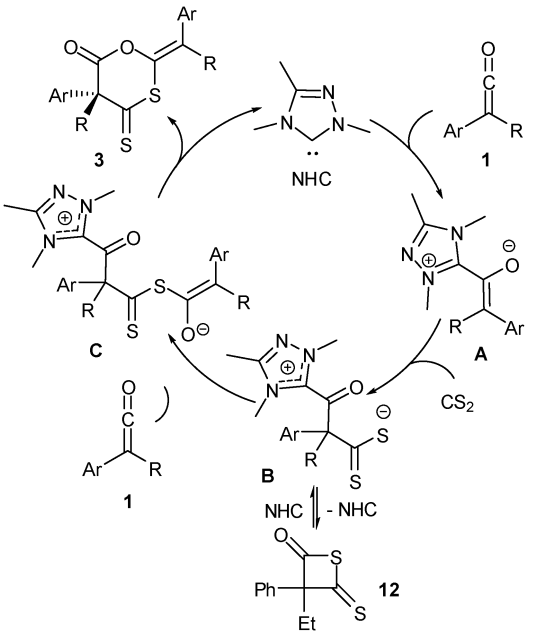


Fig. 1 Possible catalytic cycle.

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