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Methylenecyclopropane as C1 synthetic units: [1 + 4] cycloaddition *via* a nickel catalyst†

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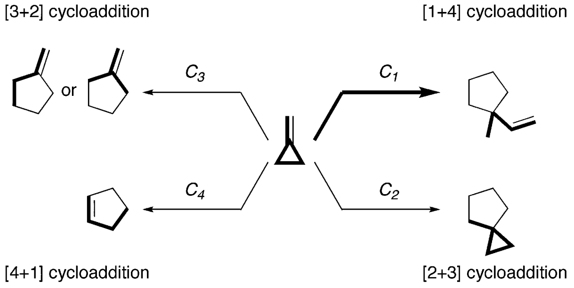
Nickel-catalyzed reactions of methylenecyclopropanes and thioanhydrides afford sulfur-containing heterocyclic compounds *via* [1 + 4] cycloaddition. The reactions represent a new use for methylenecyclopropane as a possible one-carbon building block to replace carbon monoxide, isocyanides, and Fischer carbene complexes.

In the presence of a transition metal catalyst, methylenecyclopropanes (MCPs) easily undergo a variety of reactions owing to a potent thermodynamic driving force originating from the relief of the cyclopropane ring strain.[1,2] Among the reactions of MCPs, a formal [3 + 2] cycloaddition, in which MCPs are incorporated as three-carbon (C3) synthetic units, provides facile synthetic access to structurally diverse five-membered carbo- and heterocyclic compounds. It has been a research subject of great interest (Scheme 1).[1,3,4] Furthermore, [2 + 3] cycloaddition and [4 + 1] cycloaddition have also been developed as alternative methods for assembling five-membered cyclic compounds; MCPs can also contribute as two-carbon (C2) and four-carbon (C4) synthetic units.[5,6] Although MCPs have been recognized as reactive building blocks for numerous transition metal-catalyzed transformations, no example of the use of MCPs as one-carbon (C1) synthetic units has appeared in the literature. We have set out to further explore transition metal-catalyzed cycloaddition of MCPs, motivated by their unique reactivity and possible use as a C1 building block in [1 + 4] cycloaddition as a surrogate for molecular compounds such as carbon monoxide,[7] isocyanides,[8] and Fischer carbene complexes.[9,10] Here, we report an unprecedented type of [1 + 4] cycloaddition of MCPs and thiophthalic anhydrides to afford thiophthalides.



Scheme 1 Reaction modes of methylenecyclopropane in cycloadditions affording five-membered ring compounds.

We recently demonstrated nickel-catalyzed decarbonylative cycloaddition of alkynes with five-membered heterocyclic compounds to give six-membered heterocyclic compounds.[11] The reactions consist of a substitution reaction in which a carbon monoxide is replaced by an alkyne acting as a C2 synthetic unit in a thiophthalic anhydride through catalysis. Through continuous study, we became intrigued by the use of various carbon–carbon unsaturated compounds as a reaction partner instead of an alkyne.[12] Thus, we examined decarbonylative addition of thiophthalic anhydrides to MCPs. We found that the reaction afforded an unexpected type of cycloadduct, thiophthalide, whose heterocyclic skeleton is found in materials such as pharmaceutical drugs and fluorescent probes for optical imaging.[13] The reaction of thiophthalic anhydride **1a** with MCP **2a** in the presence of Ni(cod)$_2$ (10 mol%), PPr$_3$ (20 mol%), and a Lewis acid (methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide, MAD) in refluxing toluene (130 °C) for 9 h initially provided thiophthalide **3aa** in 31% yield (Table 1, entry 1). Further exploration of ligands revealed that the use of PMe$_2$Ph improved the yield of **3aa** to 85% (entry 3). The use of other ligands such as PMe$_3$, PMePh$_2$, PPh$_3$, and PCy$_3$ resulted in lower yields of **3aa** (entries 2–6). We found that the use of MAD as an additive is crucial for efficient transformation (entries 7–9). In the absence of MAD, the reaction afforded **3aa** in 11% yield (entry 10).

The reaction of 2-naphthyl-substituted MCP **2a** with **1a** also afforded cycloadduct **3ab** in 82% isolated yield (Table 2). The molecular structure of **3ab** was unambiguously confirmed by X-ray single-crystal analysis, which showed that the cycloadduct is indeed a five-membered sulfur-containing heterocycle and has a *trans* configuration of the double bond (see ESI†). Cycloaddition of **1a** with aryl-substituted MCPs possessing an electron-donating and an electron-withdrawing group also afforded correspondingly substituted cycloadducts in high yields (**3ac**, 87%; **3ad**, 86%). Although MCPs such as 2-octyl-1-methylenecyclopropane and benzylidene cyclopropane failed to participate in the reaction, 2-methyl-2-phenyl-1-methylenecyclopropane reacted with **1a** to give **3ae** in 60% isolated yield.

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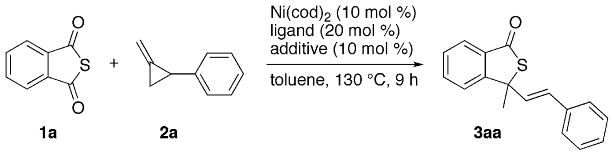
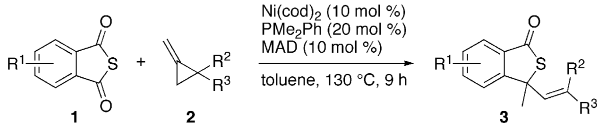
Table 1 Nickel-catalyzed [1 + 4] cycloaddition[a]



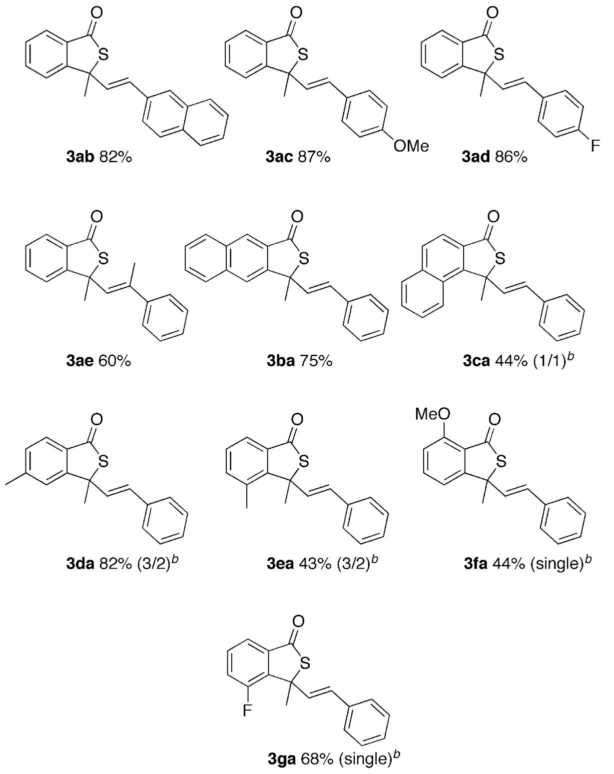
Entry	Ligand	Additive	Yield[b] (%)
1	PPr_3	MAD	31
2	PMe_3	MAD	55
3	PMe_2Ph	MAD	85
4	$PMePh_2$	MAD	74
5	PPh_3	MAD	32
6	PCy_3	MAD	10
7	PMe_2Ph	$ZnCl_2$	13
8	PMe_2Ph	$AlMe_3$	51
9	PMe_2Ph	$B(C_6F_5)_3$	64
10	PMe_2Ph	—	11

[a] All reactions were performed using Ni(cod)$_2$ (10 mol%), ligand (20 mol%), **1a** (0.4 mmol), and **2a** (0.2 mmol) at 130 °C for 9 h. [b] Isolated yields based on **2a**.

Table 2 Nickel-catalyzed cycloaddition of **1** with **2**



Products[a]

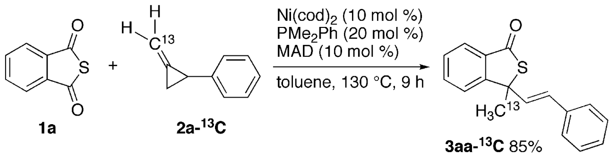


[a] Isolated yields given. [b] Ratio of regioisomers.

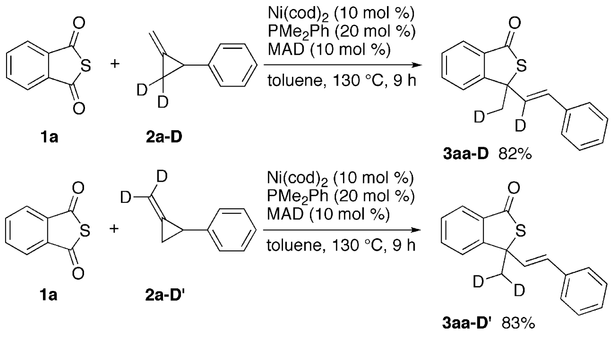
These results suggested that an aryl substituent on the cyclopropane ring of MCPs is crucial for the transformation. Cycloaddition of MCP **2a** with 2,3-naphthalenedicarboxylic thioanhydride gave **3ba** in 75% yield, whereas the reaction with 1,2-naphthalenedicarboxylic thioanhydride furnished **3ca**, consisting of regioisomers in a 1/1 ratio, in 44% yield. Thiophthalic anhydrides having various substituents were also examined in reaction with MCP **2a**. Thus, we found that a methyl substituent has little effect on the regioselectivity regardless of its substitution position (**3da** and **3ea**), whereas 4-methoxy and 4-fluoro substituents significantly affected the regioselectivity. Cycloadducts **3fa** and **3ga** were isolated as sole products in 44% and 68% yields, respectively. The observed regioselectivity is ascribed to preferential oxidative addition to nickel(0) of the more electron-deficient carbonyl moiety.

To gain further insight into the cycloaddition reaction mechanism, we performed additional experiments. We first examined the reaction of **1a** with MCP **2a–^{13}C**, the exomethylene carbon of which was ^{13}C enriched (Scheme 2). The results of ^{13}C NMR spectroscopy of the cycloadduct **3aa–^{13}C** revealed that an exomethylene of MCP **2a** was converted to a methyl group of **3aa** during the reaction. We next examined the reaction of **1a** with partially deuterated MCP **2a–D** or **2a–D′** (Scheme 3). The reaction of **1a** with **2a–D** afforded **3aa–D**, whereas that with **2a–D′** gave **3aa–D′**, suggesting that one of the methylene protons on the cyclopropane ring of MCP **2a** was rearranged to contribute to the methyl group of cycloadduct **3aa** through the nickel-catalyzed transformation.

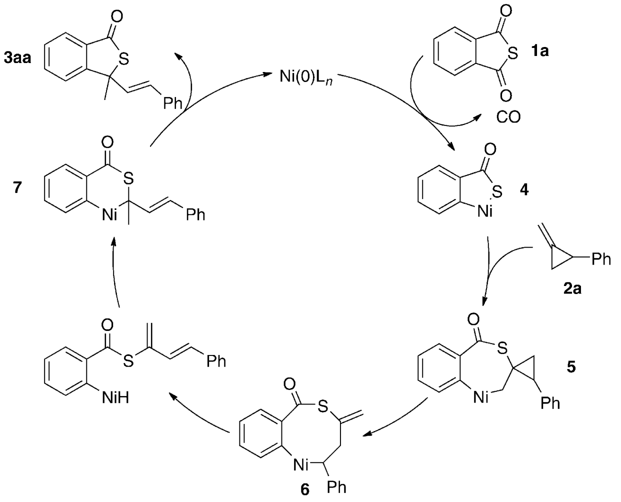
On the basis of these observations, we propose the following reaction mechanism for the present [1 + 4] cycloaddition (Scheme 4). Oxidative addition of **1a** to nickel(0) and subsequent decarbonylation afford nickelacycle **4**. MCP **2a** is then inserted into the thio–nickel bond to give intermediate **5**. With its cyclopropane unit, the carbon–nickel bond undergoes facile cyclopropylmethyl–homoallyl metal-type rearrangement to furnish nickelacycle **6**. After β-hydride elimination and insertion of the newly formed hydride–nickel bond to the carbon–carbon double bond, **6** furnishes thermally more stable six-membered



Scheme 2 Cycloaddition of **1a** with ^{13}C-enriched MCP **2a**.



Scheme 3 Cycloaddition of **1a** with deuterated MCP **2a**.



Scheme 4 A plausible reaction mechanism.

nickelacycle **7**, followed by reductive elimination to afford **3aa**. Notably, the quaternary carbon from MCP is incorporated into the newly formed five-membered ring by replacing a carbon monoxide of **1a** as a consequence of the process. The effects of MAD as the Lewis acid are not yet clear; however, we assumed that MAD might promote thio-nickelation of MCP by coordinating to the carbonyl oxygen of nickelacycle **4**.

In conclusion, we have developed a new type of cycloaddition of MCPs with thiophthalic anhydrides and a nickel catalyst in which a carbon monoxide is replaced with a quaternary carbon from MCP to give highly substituted thiophthalides. These are useful synthetic precursors for preparation of sulfur-containing five-membered heterocyclic compounds. These results highlight the potential of MCPs as C1 synthetic units in a cyclic compound. The use of MCPs as C1 synthetic units offers an advantage in introducing a quaternary carbon directly into a ring system, which allows MCPs to behave as if they were carbene species. Detailed studies that aim to elucidate the reaction mechanism, and efforts to expand the scope of the use of MCPs as C1 synthetic units, are underway.

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