[3+2] Cycloaddition Reaction of Cyclopropyl Ketones with Alkynes Catalyzed by Nickel/Dimethylaluminum Chloride**

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Transition-metal-catalyzed cycloaddition reactions have received increasing attention as straightforward methods for the synthesis of a five-membered-ring framework. The reaction of cyclopropanes having an unsaturated bond such as methylenecyclopropanes or vinylcyclopropanes has been studied intensively for use in the preparation of fivemembered-ring compounds by [3+2] cycloaddition with unsaturated compounds.^[1] However, the reaction of alkynes with alkylidenecyclopropanes,^[2] vinylcyclopropanes,^[3] and cyclopropyl imines^[4] gave only seven-membered-ring products by either [3+2+2] or [5+2] cycloadditions. To date, only one example of a nickel-catalyzed intermolecular [3+2] cycloaddition reaction of methylenecyclopropanes with alkynes to afford cyclopentene derivatives has been reported by Binger et al.,^[5a] although some intramolecular reactions have been known.^[5]

Previously, both the group of Montgomery as well as our group simultaneously reported that cyclopropyl ketones can react as a three-carbon unit in the presence of a nickel catalyst to give cyclopentane derivatives.^[6] In this reaction, a sixmembered oxa-nickelacycle played an important role as a key reaction intermediate and its molecular structure was determined by X-ray crystallography.^[7] Although enones reacted with the six-membered oxa-nickelacycle to give an η^3 -oxaallylnickel complex, alkynes did not react at all. In his pioneering work, Fujisawa and co-workers reported that the ring-opening reaction of cyclopropyl phenyl ketone with AlMe₃ to give butyl phenyl ketone is promoted by a nickel catalyst without ligands.^[8] This result indicates that organoaluminum reagents might play an important role in the oxidative addition of cyclopropyl phenyl ketone to nickel(0). Herein we report the nickel-catalyzed [3+2] cycloaddition

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reaction of cyclopropyl ketones with alkynes to give cyclopentenes in the presence of organoaluminum reagents.^[9]

In the presence of 10 mol % of $[Ni(cod)_2]$ and 100 mol %of AlMe₃, the reaction of cyclopropyl phenyl ketone (1a) with 2-butyne (2a) was conducted in THF at room temperature (Table 1, entry 1). The expected [3+2] cycloaddition reaction

Table 1:	Reaction optim	ization and cor [Ni(cod) ₂ additive R THF, RT,	ntrol studies] (10 mol%) . 18 h		D Ph
Entry	2	Additive	[mol %]	3	Yield [%] ^[b]
1	2a (R = Me)	AlMe ₃	100	3 aa	80
2	2a (none	-	3 aa	0
3	2a	Me ₂ AlOAc	100	3 aa	99
4	2a	Me ₂ AlOTf	100	3 aa	84
5	2a	Me ₂ AlCl	100	3 aa	100 (98)
6	2a	Me ₂ AlCl	20	3 aa	100
7	2a	AICI ₃	100	3 aa	0
8	2a	TiCl₄	100	3 aa	0

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2a AlCl ₃ 100 3 aa 0 2a TiCl ₄ 100 3 aa 0 2a ZnMe ₂ 100 3 aa 0
2a TiCl₄ 100 3aa 0 2a ZnMe₂ 100 3aa 0
2a ZnMe ₂ 100 3aa 0
0 2 a PCy ₃ 20 3 aa 0
1 2 b (R = Et) Me ₂ AlCl 100 3 ab 100
2 2 b Me ₂ AlCl 20 3 ab 29
$3^{[c]}$ 2b Me ₂ AlCl 20 3ab 100 (88)

[a] Unless otherwise specified, the reaction was performed on a 0.2 mmol scale. [b] Yield as determined by GC analysis of the crude reaction mixture. Yield of isolated product is given within parentheses. [c] The reaction mixture was stirred at 50 °C for 3 h. cod = 1,5-cyclooctadiene, Cy = cyclohexyl, Tf = trifluoromethylsulfonyl, THF = tetrahydrofuran.

occurred to give **3 aa** in 80 % yield.^[10] In the absence of AlMe₃, 3aa was not obtained at all, thus indicating that AlMe₃ is crucial for the reaction (entry 2). In the absence of alkynes, the nickel catalyst was immediately decomposed to give a black precipitate. When AlMe₃ was employed as an additive, the formation of undesired side-reaction products, such as the methylated compound and its derivatives, was inevitable because of the high reactivity of AlMe₃. Therefore, other additives were examined to suppress the formation of undesired side-reaction products. In the presence of Me₂AlOAc or Me₂AlOTf, the [3+2] cycloaddition of 1a with 2a gave 3aa in 99 and 84% yield, respectively (entries 3 and 4). Me₂AlCl was also very effective for the reaction (entry 5). Even a catalytic amount of Me₂AlCl was sufficient to give 3aa quantitatively (entry 6). Other Lewis acids such as AlCl₃, TiCl₄, and ZnMe₂ did not promote the reaction at all (entries 7–9).^[9] In the presence of PCy₃, no reaction occurred

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(entry 10). The reaction of **1a** with 3-hexyne (**2b**) proceeded to give **3ab** (entry 11). A decrease in the amount of Me₂AlCl from 100 mol% to 20 mol% lead to the low conversion and yield of **3ab** (entry 12). Thus, in the presence of 20 mol% of Me₂AlCl, the reaction was carried out at 50 °C and **3ab** was obtained quantitatively (entry 13).

We next examined the scope of this cycloaddition reaction. The reaction of **1a** with symmetric internal alkynes gave the corresponding cyclopentene derivatives in high yields (Scheme 1; **3aa–3ad**). Unsymmetric alkynes were also applicable for this reaction, and both 1-trimethylsilylpropyne (**2e**; $R^4 = TMS$, $R^5 = Me$) and 1-phenylpropyne (**2f**; $R^4 = Ph$, $R^5 = Me$) reacted with **1a** to give the corresponding cyclo-



Scheme 1. [3+2] Cycloaddition reaction of 1 with 2. Reaction conditions: cyclopropyl ketone (1.0 mmol), alkyne (3.0 mmol), [Ni(cod)₂] (0.1 mmol), and Me₂AlCl (0.2 mmol) in THF (1.0 mL) at 50 °C for 3 h. Yield of isolated product given; the regioisomer ratio is given in parentheses. The major product is depicted. [a] Run at 80 °C. [b] Used 40 mol% of Me₂AlCl. [c] Used 100 mol% of Me₂AlCl. [d] Used 100 mol% of Me₂AlOAc. [e] The isomer ratio of 1,4-*trans* (A)/1,4-*cis* (B)/1,5-*trans* (C) is given in parentheses. TIPS = triisopropylsilyl, TMS = trimethylsilyl.

pentenes (3ae, 3af) with high regioselectivity. The reaction of 1-trimethylsilyl-2-phenylacetylene (**2g**; $R^4 = Ph$, $R^5 = TMS$) with 1a gave a mixture of regioisomers, however, a reduced regioselectivity was observed compared with the reactions of either 2e or 2f. These results suggest that the regioselectivity might be controlled by the steric bulk of the substituents. The molecular structure of the major regioisomer of 3ag was determined by X-ray crystallography.^[11] Although terminal alkynes are prone to undergoing dimerization or trimerization in the presence of nickel(0) species, the cycloaddition of triisopropylsilyl acetylene (2h; $R^4 = TIPS$, $R^5 = H$) with 1a occurred to give the expected cyclopentene product as a single regioisomer (3ah).^[12] Use of activated alkynes of functional groups containing ester, ether, or carbonyl groups led to the recovery of starting material presumably because of the coordination to Me₂AlCl, thus decreasing its reactivity. The reaction of **1a** with 2-methyl-1-hexen-3-yne (**2i**; $R^4 = Et$, $R^5 = 2$ -propenyl) gave the expected cyclopentene derivatives 3ai in moderate vield.

A broad range of cyclopropyl aryl ketones were successfully employed for the cycloaddition reaction (3ba-3ga). Electronic variation on the phenyl ring of the cyclopropyl ketones had little effect on the reaction efficiency, except for the methoxy group. The methoxy group is supposed to decrease the reactivity of Me₂AlCl by coordinating to Me₂AlCl. Moreover, cyclopropyl 3-methoxyphenyl ketone (1d; $R^1 = 3$ -MeOC₆ H_4 , $R^2 = H$, $R^3 = H$) gave the product (3da) in 21% yield even in the presence of a stoichiometric amount of Me₂AlCl. Cyclopropyl 4-fluorophenyl ketone (1e; $R^1 = 4$ -FC₆H₄, $R^2 = H$, $R^3 = H$) was also converted into the desired product. Cyclopropyl 2-thienyl ketone (1 f; $R^1 = 2$ thienyl, $R^2 = H$, $R^3 = H$) also underwent the reaction to give 3 fa in moderate yield. Although the oxidative addition of $C_{sp^2}\!\!-\!\!F$ and $C_{sp^2}\!\!-\!\!S$ bonds in fluoroarenes and thiophenes, respectively, to nickel(0) is known,^[13,14] neither of them underwent the oxidative addition under the reaction conditions. Cyclopropyl methyl ketone (**1h**; $R^1 = Me$, $R^2 = H$, $R^3 = H$) reacted with 2c efficiently to give the expected product (3hc) in 69% yield with a stoichiometric amount of Me₂AlCl. This observation could be rationalized by the difference in coordination ability between **1a** and **1h**.^[15] Ethyl cyclopropanecarboxylate did not proceed the reaction at all.

Although the reaction of disubstituted cyclopropanes required a stoichiometric amount of Me2AlCl or Me2AlOAc, both 1i ($R^1 = Ph$, $R^2 = Me$, $R^3 = H$) and 1j ($R^1 = Ph$, $R^2 = Ph$, $\mathbf{R}^3 = \mathbf{H}$) also underwent the cycloaddition reaction with **2a**. The reaction of *trans*-1-benzoyl-2-methylcyclopropane (1k; $R^1 = Ph, R^2 = H, R^3 = Me$) or *trans*-1-benzoyl-2-phenylcyclopropane (11; $R^1 = Ph$, $R^2 = H$, $R^3 = Me$) with 2a each gave a mixture of three isomers: 1,4-trans (A), 1,4-cis (B), and 1,5trans (C; 3ka, 3la). In these reactions, Me₂AlOAc was more effective than Me₂AlCl. By monitoring the progress of the reaction of 1k with 2a using GC, it was observed that the isomer ratio of 3ka remained unchanged during the reaction. In addition, when two different mixtures of 3ka (A/B/C = 62:26:12 and 46:45:9) were heated at 50°C for 3 hours in the presence of 10 mol % of [Ni(cod)₂], 100 mol % of Me₂AlOAc, and 2a, the isomer ratio of 3ka also remained unchanged.^[11]

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Thus, it was found that isomers A and B did not undergo the interconversion under the catalytic reaction conditions.

Although both a stoichiometric amount of Me₂AlCl and a higher reaction temperature were required, dicyclopropyl ketone (1m) reacted with two molecules of 2a to yield dicyclopentenyl ketone 4 [Eq. (1)]. It is noteworthy that

cyclopentenyl cyclopropyl ketone was not observed at all in the reaction, which suggests that the second [3+2] cycloaddition occurs much faster than the first one. The intramolecular reactions of the [3+2] cycloaddition were unsuccessful,^[16] although ruthenium catalyst efficiently proceeded.^[17] Thus, nickel catalysts and ruthenium catalysts are complementary in [3+2] cycloaddition of cyclopropyl ketones with alkynes.

To gain deeper insight into the reaction mechanism, we examined the reaction of the isolable six-membered oxanickelacycle **5** with **2a** and Me₂AlCl. However, it ended up leading to very rapid generation of the π -allylnickel complex **6** [Eq. (2)].^[18] Thus, we synthesized the six-membered oxanickelacycle **7**, which does not contain 1,3-bis(2,6-diisopro-



pylphenyl)imidazol-2-ylidene (IPr) in its structure (Scheme 2). Elemental analysis showed the expected composition. The ¹H and ¹³C NMR chemical shifts of the nickel enolate moiety (-NiOC(2-vinylphenyl)=CH-) are in the range of those for reported nickel enolates.^[6a,7,19] The upfield shift of the vinyl group indicates the η^2 -coordination to nickel(II) center. The treatment of **7** with carbon monoxide (5 atm) led to the formation of the expected lactone **8** quantitatively,^[20] which is consistent with the structure of **7** depicted in Scheme 2. The stoichiometric reaction of **7** with **2a** and



Scheme 2. Synthesis and reactivity of 7.

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Me₂AlCl did not give **3ga** at all (Scheme 2), but **3ga** was produced in 56% yield in the catalytic reaction (Scheme 1). These results suggest that a six-membered oxa-nickelacycle intermediate does not seem to be generated in the [3+2] cycloaddition.^[7]

A plausible reaction path is depicted in Scheme 3. The coordination of the unsaturated bonds of cyclopropyl ketones and alkynes occurs to give the $\eta^2:\eta^2$ -coordinated nickel



Scheme 3. A plausible reaction pathway.

complex A. Organoaluminum reagents might enhance the coordination ability of cyclopropyl ketones toward the nickel(0) center by the coordination of the oxygen atom of the carbonyl group.^[21] The oxidative addition of the proximal carbon-carbon bond of the cyclopropyl ketones to nickel(0) occurs to give the nickelacyclobutane intermediate **B**. Recently, we reported the isolation of oxa-nickelacyclopentene by the oxidative cyclization of an alkyne and an aldehyde with nickel(0) promoted by Me₂AlOTf, in which the coordination of one oxygen atom of a OTf group to a nickel(II) center was observed.^[21] Thus, the substituent X of organoaluminum reagents such as Me,^[22] Cl,^[23] and OAc groups would also coordinate toward the nickel(II) center to stabilize the reaction intermediates by forming a chelate structure. The insertion of an alkyne into the carbon-nickel bond of B affords the nickelacyclohexene intermediate C. The experimental results of stoichiometric reactions with 7 and very rapid formation of 6 by the reaction of 5 with Me₂AlCl suggest that the generation of the intermediate **D** is unlikely. Reductive elimination from C gives the cyclopentene derivative $\mathbf{3}$ to regenerate nickel(0) species and organoaluminum reagents. The formation of 1,4-cis products in the reaction of 1,2-trans-disubstituted cyclopropanes was observed, which implies that a key step to invert the stereochemistry at the a position (marked carbon atom) must be included in the catalytic cycle. Thus, the interconversion between C and E might occur prior to the reductive elimination because the generation of η^1 -O-nickel enolate complex and its inversion of stereochemistry have been reported.^[19b, 24]

In summary, we have demonstrated the nickel-catalyzed intermolecular [3+2] cycloaddition reaction of cyclopropyl ketones with alkynes in the presence of organoaluminum reagents. The key to success is the organoaluminum reagents, which activate the carbonyl group of cyclopropyl ketones and stabilize the reaction intermediates. This reaction provides a new method for the synthesis of cyclopentene derivatives. Additional studies to elucidate the reaction mechanism and expand the reaction scope are underway in our laboratory.

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