

## [3+3] Cyclodimerization of Methylenecyclopropanes: Stoichiometric and **Catalytic Reactions of Nickel(0) with Electron-Deficient** Alkylidenecyclopropanes

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Received April 20, 2010

Summary: Stoichiometric treatment of Ni(cod)<sub>2</sub> with ethyl cyclopropylideneacetate (ECPA) in the presence of  $PCy_3$ resulted in an unpredicted formation of a Ni(0) complex bearing an (E,E)-1,2-bis(exo-alkylidene)cyclohexane ligand, which stemmed from the [3 + 3] cyclodimerization of ECPA. The reaction could be expanded to a Ni(0)-catalyzed [3 + 3]cyclodimerization reaction of ester-substituted methylenecyclopropanes, giving the corresponding cyclohexane derivatives in excellent yields.

Methylenecyclopropanes (MCPs) are strained reactive molecules, and transition-metal-catalyzed cyclodimerization or cycloaddition reactions of MCPs have provided an atomefficient, powerful strategy for the synthesis of a variety of cyclic compounds.<sup>1</sup> Nickel(0) is also known to catalyze cyclodimerization reactions of MCPs to afford cyclobutane and cyclopentane derivatives via [2 + 2] and [3 + 2] cyclo-dimerizations, respectively (Chart 1).<sup>2–4</sup> Pioneering work on the cyclodimerization of methylenecyclopropane in the presence of Ni(cod)<sub>2</sub>, giving a mixture of dispiro[2.1.2.1]octane ([2 + 2] product) and 5-methylenespiro[2.4]heptane ([3 + 2]product), was reported by Binger.<sup>2a</sup> The usage of maleic anhydride as an additive with the Ni(0) catalyst was found to be effective for the selective formation of the [3 + 2] cyclodimerization product,<sup>2c</sup> whereas the introduction of tertiary phosphines into the Ni(0) catalytic system resulted in the preferential formation of MCP trimers.<sup>2b</sup> Interestingly, employing dialkyl fumarates as the solvent in the Ni-catalyzed reaction was devised to give another dimer, 1,3-dimethylenecyclohexane, as a minor product.<sup>2c</sup> The selective [3 + 2]cyclodimerization of methylenecyclopropane, on the other hand, was also caused by treating with Pd(0) catalyst.<sup>3</sup> In contrast, the limiting studies of cyclodimerization reactions of substituted MCPs have been described thus far: the cyclodimerization of 1-methylene-2-vinylcyclopropane with Pd(0) catalysts was reported by Binger,<sup>4a</sup> and the reaction of

## Chart 1. Ni(0)-Catalyzed Cyclodimerization of Methylenecyclopropane and Proposed Intermediates



ethyl cyclopropylideneacetates in the presence of Ni catalysts was developed by Saito.<sup>4b</sup> Although a number of the cyclodimerizations of MCPs have been reported as described above, there is a very limiting example for [3 + 3] cyclodimerization in which two proximal C-C bonds are cleaved (Chart 1).<sup>4b</sup>

In these related reactions, some attempts to confirm the reaction intermediates have been made. Based on the isolation and characterization of a nickelacyclopentane intermediate (Chart 1, A) by using (bipy)Ni(cod) as a Ni(0) precursor, oxidative cyclization of methylenecyclopropane with Ni(0) has been regarded as a key reaction step.<sup>5</sup> The C-C bond cleavage of the cyclopropane ring could be achieved via  $\beta$ -carbon elimination of **A**, which is known as a "cyclopropyl-butenyl rearrangement", during the catalytic reaction. Another possibility was proposed that the oxidative addition of a proximal bond to Ni(0) took place at the initial stage of the reaction to give 2-methylene-1nickelacyclobutane (Chart 1, B), while the corresponding intermediate has not been isolated.<sup>6,7</sup> In addition, the sole example of a nickel(0) complex containing an  $\eta^2$ -methylenecyclopropane ligand has been reported.<sup>8</sup>

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<sup>(7)</sup> In contrast, the oxidative addition of a distal bond, affording 3-methylene-1-palladacyclobutane intermediate, occurred in the Pd(0)-catalyzed cyclodimerization reaction. See also ref 3.

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In the course of our continuous studies on the development of Ni-catalyzed transformation reactions and isolation of heteronickelacycle key intermediates,<sup>9</sup> we recently demonstrated that nickel(0) complexes bearing a strong  $\sigma$ -donor ligand, such as PCy<sub>3</sub> and IPr, promote oxidative addition of the cyclopropane ring adjacent to a carbonyl group to yield six-membered oxanickelacycles.<sup>10</sup> We therefore investigated the stoichiometric reaction of Ni(cod)<sub>2</sub> with ethyl cyclopropylideneacetate (**1a**; ECPA)<sup>11</sup> in the presence of PCy<sub>3</sub> in anticipation of smooth cleavage of a proximal carbon– carbon bond of the cyclopropane ring. It was, as a result, found that selective formation of a 1,2-bis(*exo*-alkylidene)cyclohexane framework was achieved as a result of a [3 + 3] cyclodimerization reaction via cleavage of two proximal C–C bonds (Chart 1).<sup>12–14</sup> We also herein report a novel Ni-catalyzed [3 + 3] cyclodimerization of electron-deficient alkylidenecyclopropanes.

In the presence of 2 equiv of PCy<sub>3</sub>, the reaction of **1a** with Ni(cod)<sub>2</sub> in toluene- $d_8$  at -15 °C led to the quantitative formation of an  $\eta^2$ -ECPA complex (**2a**) (Scheme 1). On further monitoring of the reaction at room temperature by means of NMR spectroscopy, the gradual decomposition of **2a** was observed, while no other reaction intermediates were detectable, to yield a 1:1 mixture of Ni(cod)<sub>2</sub> and an unexpected Ni(0) complex (**3a**). X-ray crystallography of **3a** 

(12) Formation of bis(*exo*-alkylidene)cyclohexanes via hydrolysis of titana- or zirconabicycles: (a) Nugent, W. A.; Calabrese, J. C. J. Am. Chem. Soc. **1984**, 106, 6422–6424. (b) Negishi, E.; Cederbaum, F. E.; Takahashi, T. Tetrahedron Lett. **1986**, 27, 2829–2832. (c) Nugent, W. A.; Thorn, D. L.; Harlow, R. L. J. Am. Chem. Soc. **1987**, 109, 2788–2796. (d) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. J. Am. Chem. Soc. **1989**, 111, 3336–3346. (e) Urabe, H.; Sato, F. J. Org. Chem. **1996**, 61, 6756–6757.



**Figure 1.** Molecular structures of **3a** with thermal ellipsoids at the 30% probability level. H atoms are omitted for clarity.

## Scheme 1. Reaction of 1a with Ni(cod)<sub>2</sub> in the Presence of PR<sub>3</sub>



revealed that an (E,E)-1,2-bis(exo-alkylidene)cyclohexane unit, which arose from the [3 + 3] cyclodimerization of **1a** via selective cleavage of the proximal C–C bond trans to the ethoxycarbonyl group, coordinated to the nickel atom in  $\eta^2:\eta^2$  fashion (Figure 1). The nickel center in **3a** adopted a tetrahedral coordination geometry, which is often observed in four-coordinated Ni(0) complexes.

By employing 2 equiv of PPh<sub>3</sub> instead of PCy<sub>3</sub> as a ligand, on the other hand, the corresponding  $\eta^2$ -ECPA complex (2a') was quantitatively obtained (Scheme 1). Unlike the  $PCy_3$ -ligated complex 2a, the isolated 2a' is stable, regardless of the presence or absence of a 1,5-COD molecule, in  $C_6D_6$ solution at room temperature, and therefore, it was not converted into further compounds at all. The X-ray crystallography of 2a' clearly demonstrated a three-coordinated Ni(0) structure coordinated by the  $\eta^2$ -ECPA and two PPh<sub>3</sub> molecules (Figure 2). Complex 2a' is the first example of a structurally well-defined nickel complex coordinated by an  $\eta^2$ -methylenecyclopropane derivative,<sup>8</sup> while some precedents for other transition-metal complexes having an  $\eta^2$ methylenecyclopropane ligand have been reported.<sup>15</sup> It should be mentioned that the reaction of 1a with 10 mol % of 2a' as a catalytic precursor gave the [3 + 2] cyclodimerization product 6a.16

In contrast, the reaction with 1-cyclopropylidene-2-propanone (1b) was found to proceed in a different manner.

(16) The [3 + 2] cyclodimerization of **1a** in the presence of Ni(cod)<sub>2</sub> and PPh<sub>3</sub> has been reported to yield the same product. See also ref 4b.

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<sup>(11)</sup> The unique role of 1a as a three-carbon source has also been developed in Ni-catalyzed [3+2+2] and [4+3] cycloaddition reactions. (a) Saito, S.; Masuda, M.; Komagawa, S. J. Am. Chem. Soc. 2004, 126, 10540-10541. (b) Komagawa, S.; Saito, S. Angew. Chem., Int. Ed. 2006, 45, 2446-2449. (c) Saito, S.; Takeuchi, K. Tetrahedron Lett. 2007, 48, 595-598. (d) Maeda, K.; Saito, S. Tetrahedron Lett. 2007, 48, 3173-3176. (e) Saito, S.; Komagawa, S.; Azumaya, I.; Masuda, M. J. Org. Chem. 2007, 72, 9114-9120. (f) Komagawa, S.; Yamasaki, R.; Saito, S. J. Synth. Org. Chem. Jpn. 2008, 66, 974-982. (g) Yamasaki, R.; Sotome, I.; Komagawa, S.; Azumaya, I.; Masu, H.; Saito, S. Tetrahedron Lett. 2009, 50, 1143-1145. (h) Komogawa, S.; Takeuchi, K.; Sotome, I.; Azumaya, I.; Masu, H.; Yamasaki, R.; Saito, S. J. Org. Chem. 2009, 74, 3323-3329. (i) Fukusaki, Y.; Miyazaki, J.; Azumaya, I.; Katagiri, K.; Komagawa, S.; Yamasaki, R.; Saito, S. Tetrahedron 2009, 65, 10631-10636. (j) Yamasaki, R.; Terashima, N.; Sotome, I.; Komagawa, S.; Saito, S. J. Org. Chem. 2010, 75, 480-483. (k) Saito, S.; Maeda, K.; Yamasaki, R.; Kitamura, T.; Nakagawa, M.; Kato, K.; Azumaya, I.; Masu, H. Angew. Chem., Int. Ed. 2010, 49, 1830-1833.

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**Figure 2.** Molecular structures of **2a**' with thermal ellipsoids at the 30% probability level. H atoms, except for those attached to C1, C3, and C4 carbon atoms, and the solvated molecules (0.5  $C_7H_8$ ) are omitted for clarity. C7A:C7B = 0.600(14):0.400(14).



**Figure 3.** Molecular structures of **4** with thermal ellipsoids at the 30% probability level. H atoms are omitted for clarity.

Scheme 2. Reaction of 1b with Ni(cod)<sub>2</sub> in the Presence of PCy<sub>3</sub>



Stoichiometric treatment of Ni(cod)<sub>2</sub> and PCy<sub>3</sub> with 2 equiv of **1b** led to the quantitative formation of a Ni(II) complex (**4**), although neither the corresponding  $\eta^2$ -olefin complex similar to **2a** nor the analogue of **3a** was observed through the reaction (Scheme 2). Unlike the case for complex **3a**, the 1,2-bis(*exo*-alkylidene)cyclohexane fragment in **4** coordinated to the nickel center in the  $\eta^1$ -oxo- $\eta^3$ -oxaallyl mode (Figure 3). Interestingly, treatment of (*E*,*E*)-**5b** with Ni(cod)<sub>2</sub> in the presence of PCy<sub>3</sub> smoothly afforded **4** while the reaction with its isomer, (*E*,*Z*)-**5b**, did not proceed (Scheme 2), which suggested that (*E*,*E*)-**5b** was a prior product in the stoichiometric [3 + 3] cyclodimerization reaction of **1b** (vide infra).

A catalytic application of the selective [3 + 3] cyclodimerization of **1a** was examined. The reaction of **1a** with a

Table 1. Ni(0)/PCy<sub>3</sub>-Mediated [3 + 3] Cyclodimerization of  $1^{a}$ 



<sup>*a*</sup> General conditions: [1] = 0.2 M. <sup>*b*</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. Cited yields in parentheses are of the isolated major regioisomer. <sup>*c*</sup> After slow addition of 1 (for 5 h) was terminated, the reaction mixture was further stirred for 1 h. <sup>*d*</sup>Ni(cod)<sub>2</sub> and PCy<sub>3</sub> (10 mol % each) were used.

catalytic amount of Ni(cod)<sub>2</sub> and PCy<sub>3</sub> (10 and 20 mol %, respectively) was conducted at room temperature, resulting in full consumption of 1a within 7 h. However, the expected [3+3] cycloaddition product (5a) was obtained in 38% yield and a [3 + 2] cyclopentane derivative (6a) was formed as a major product (Table 1, run 1). Elevating the reaction temperature (60 °C) improved the yield of 5a to 81% (run 2). Finally, slow addition of 1a to the toluene solution of a Ni(cod)<sub>2</sub> and PCy<sub>3</sub> mixture over 5 h led to the formation of 5a in 90% yield, and the major product, (E,E)-5a, was isolated in 70% yield (run 3). This catalytic reaction can be applied for primary, secondary, and tertiary ester-substituted MCPs to give the corresponding cyclohexane derivatives in excellent yields (runs 4-6). For esters 1a,c-e, the geometry of the [3 + 3] cyclodimerization product was highly controlled to be E, E, which was consistent with the geometry observed in the stoichiometric reaction. In contrast, the ketone derivative 1b required higher reaction temperature for its consumption, and the major product, (E,Z)-5b, was acquired in 50% yield (Table 1, run 7). The difference in diastereoselectivities of 5 between the reactions of 1a,c-e and that of 1b reflects the difference in structures of intermediates 3 and 4.

To elucidate the mechanism for the formation of the reaction side product **6**, the catalytic reaction with **1a** was monitored by NMR spectroscopy, revealing a nickelacyclohexane intermediate (**7a**) whose <sup>31</sup>P resonance appeared at 34.5 ppm (Scheme 3).<sup>17</sup> The generation of **7a** was also supported by exposing **7a** (prepared in situ) to carbon monoxide (5 atm), giving the expected six-membered ketone (**8**) with the concomitant formation of Ni(PCy<sub>3</sub>)(CO)<sub>3</sub> (Scheme 3).<sup>18</sup> These observations convinced us that **6a** stemmed from the reductive elimination of **7a**, which would be formed by the C=C bond insertion of **1a** into a Ni–C bond of a transient 2-alkylidene-1-nickelacyclobutane

<sup>(17)</sup> Except for the unidentified minor species ( $\delta_P$  32 ppm), resonances attributable to **7a** and free PCy<sub>3</sub> appeared as detectable signals in the <sup>31</sup>P NMR spectrum (see also Figures S1 and S2 in Supporting Information).

<sup>(18)</sup> The treatment of nickel compounds with carbon monoxide can yield  $[Ni(CO)_4]$  (extremely toxic) due to the addition of insufficient amounts of PCy<sub>3</sub>, careless handling, or an accident. The reaction mixture must be handled in a well-ventilated fume hood.

Scheme 3. Observation of the Nickelacyclohexane Intermediate 7a



species (C) (Scheme 4).<sup>6,19,20</sup> Although the  $\beta$ -carbon elimination of **7a** might occur in parallel to give the same [3 + 3] product **5a** as a result of the reductive elimination from a seven-membered nickelacycle, the results of the stoichiometric reaction to give **3a**, depicted in Scheme 1, and the suppression of the formation of **6a** by the slow addition of **1a** support the notion that oxidative addition of the proximal C–C bond to the electron-rich Ni(0) center would be a key reaction step, leading to the selective [3 + 3] cyclodimerization without the generation of **7a** (Scheme 4, left circle).

In summary, we have demonstrated the unique nickelcatalyzed [3 + 3] cyclodimerization of alkylidenecyclopropanes to yield 1,2-bis(*exo*-alkylidene)cyclohexanes in excellent yields.

(19) We could not rule out the possibility that 7a would be formed via another intermediate (**D**) by the oxidative cyclization of 1a with 2a.

Scheme 4. Plausible Mechanism for Catalytic Formation of 5a



Acknowledgment. We thank Prof. Shinichi Saito and Mr. Koichiro Kawakami (Tokyo University of Science) for the gift of some compounds and fruitful discussions. This work was supported by a Grant-in-Aid for Scientific Research (No. 21245028) and Encouragement for Young Scientists (B) (No. 21750102) from the MEXT.

Supporting Information Available: Text, figures, and CIF files giving detailed experimental procedures, analytical and spectral data for all new compounds, and crystallographic data for 2a', 3, and 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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