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Nickel-catalyzed [2 + 2] cycloaddition reaction using bisallenes

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Introduction

Cyclobutanes are privileged structural motifs for biologically important molecules [1], and their efficient synthesis has been major topics in synthetic organic chemistry. One of the most rapid and facile synthetic approaches to the functionalized cyclobutanes has been [2 + 2] cycloaddition reaction under photo irradiation, thermal conditions and metal catalysis [2,3]. In particular, allenes as "activated olefins" have been utilized as versatile C₂-components due to their strong affinity to metal complexes and successfully applied in [2 + 2] cycloaddition reaction mediated by various metal species [4]. For example, symmetric bisallenes with a Pd(0) catalyst gave "head to head" cycloadducts [5,6], whereas thermal conditions [6] or Rh catalysis [7] give "tail to tail" cycloadducts. Azabicyclo[3,1,1]heptane skeletons are effectively constructed under Au(I) catalysis [8] (Scheme 1).

These results indicate that bisallenes dramatically change their behavior and the observed reactivity and selectivity are highly dependent on the nature of catalysts or conditions. Therefore, other metal species would be an alternative tool for a new system. Previously, we have reported that the bisallenes are suitable precursors for stereoselective hydrocyanative cyclization [9]. Herein we focused on the reactivity of bisallenes with nickel species to provide a new protocol of [2 + 2] cycloaddition reaction producing highly functionalized cyclobutanes (Scheme 2). During the course of study, we realized that the allenes were suitable substrates for nickel-catalyzed cyclization [9,10] and cycloaddition [11]. Therefore, we next focused on the reactivity of bisallenes as π -compo-

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ABSTRACT

A nickel-catalyzed [2 + 2] cycloaddition of bisallenes has been described. Simple bisallenes are employed for the formation of "head to head" cycloadducts in the presence of Ni(0) with xantphos. The dienyl moiety in a product were applicable for various [4 + 2] cycloaddition reactions. Allene-allenamides under Nixantphos system gave the tricyclic compounds through sequential [2 + 2]-[4 + 2] cycloaddition reaction in highly stereoselective manner.

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nents for further application and investigated regio- and stereocontrolled [2+2] cycloaddition.

Results and discussion

In the beginning, **1a** with a catalytic amount of $Ni[P(OPh)_3]_4$ (10 mol%) in toluene was employed under thermal condition (Table 1). The reaction resulted in the formation of "head to head" product of 2a in only 5% yield after 18 h (entry 1). To improve the yield of 2a, ligand screening was next examined. The use of PCy₃ did not complete the reaction to give 2a only in 2% with a recovery of 1a in 53% yield (entry 2). On the other hand, PPh₃ accelerated the cycloaddition to complete within 1 h with affording 2a in 27% yield (entry 3). Arylphosphine such as MePPh₂ gave slight improvement in the yield of 2a (entry 4). In the case of bidentate phosphines, significant differences in their conversion were observed. For example, the use of BINAP and dppe (1,2-diphenylphosphinoethane) were resulted in low yield (entries 5 and 6), however dppb (1,2diphenylphosphinobutane) slightly improved the yield of 2a (entry 7). We were pleased to find that xantphos dramatically enhanced the reaction efficacy to complete within 1.5 h and the yield of 2a was increased to 87% (entry 8). Similar results were obtained when the reaction period was 15 min or the temperature was lowered to 50 °C (entries 9 and 10). The solvent effect using THF, CH₃CN, and 1,2-dichloroethane (DCE) was next investigated at 70 °C, however the positive improvements in the reaction rate or the chemical yield were not observed (entries 11-13). These results are summarized in Table 1.

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Scheme 1. Mode of [2 + 2] cycloaddition using bisallene.



Scheme 2. Ni-Catalyzed reaction using bisallene.

Table 1

Ligand effect in Ni-catalyzed [2 + 2] cycloaddition using 1a.



Entry	Ligand (mol%)	Condition ^a	Time h	Yield of 2a % ^b	Recov. of 1a % ^b
1	none	Toluene, 70 °C	18	5	0
2	PCy ₃ (20)	Toluene, 70 °C	20	2	53
3	PPh ₃ (20)	Toluene, 70 °C	1	27	0
4	$MePPh_2$ (20)	Toluene, 70 °C	1	36	0
5	(S)-BINAP (10)	Toluene, 70 °C	11	7	19
6	dppe (10)	Toluene, 70 °C	20	6	45
7	dppb (10)	Toluene, 70 °C	16	22	43
8	xantphos (10)	Toluene, 70 °C	1.5	87 ^c	0
9	xantphos (10)	Toluene, 70 °C	0.25	80 ^c	0
10	xantphos (10)	Toluene, 50 °C	0.25	76 ^c	0
11	xantphos (10)	THF, 70 °C	0.25	73	0
12	xantphos (10)	CH ₃ CN, 70 °C	0.25	16	0
13	xantphos (10)	DCE, 70 °C	0.25	39	0

^a The reaction concentration: 0.1 M.

 $^{\rm b}$ Yields are estimated by $^1{\rm H}$ NMR analysis using 2,2'-bipyridyl as an internal standard except for entries 8–10.

^c Isolated yield

Under optimum conditions, substrate scope using **1b-g** was next investigated (Scheme 3). Substituents on α position to nitro-



Scheme 3. Substrate scope under optimum conditions.

gen atom such as **1b,c** were both suitable for this intramolecular cycloaddition to give **2b,c** as a sole product in respective yields of 29% and 47%. A phenyl group on R_2 was also applicable and highly stereocontrolled product (**2d**) was exclusively obtained in 61% yield. The construction of carbocycle using **1e** was accomplished to give **2e** in 53% yield. A cyanoacetate was also applicable to give the corresponding adducts (**2f**) as a mixture of diastereomers (dr = 1:1). The substituent on R_1 dramatically decreased the reaction efficacy, and the reaction of **1g** gave lower conversion to **2g** only in 5% yield.

To study the reactivity of the two methylenes on a cyclobutane ring, we next investigated the transformations using **2a** (Scheme 4). Conjugate diene in **2a** shows enough reactivity to form cyclohexene ring *via* thermal and stereoselective [4 + 2] cycloaddition reactions, for example, the reaction with **3a** at 120 °C gave tetracyclic compound (**4a**) in 75% yield [6]. Benzyne generated from **3b** acted as a reactive dienophile to give **4b** in 41% yield after recrystallization. These structures were established by X-ray crystallographic analysis [12]. Cu-mediated dehydro Diels-Alder reaction [13] using **3c** gave **4c** in 49% yield. Finally, regio- and stereoselective Ni-catalyzed hydrocyanation [14] was investigated and gave a sole HCN adduct of **4d** in 54% yield [12].

Then, we next focused on allenamides [15] that have been utilized in intra- [16] and intermolecular [2 + 2] cycloaddition [17– 23] using various metal catalysts. In the case of allene-allenamides (**5**), their non-equivalent four C=C double bonds could be discriminated through selective interaction with Ni(0) species, however Ni-xantphos system using **5a** was ineffective to give any "*head to head*", "*head to tail*" or "*tail to tail*" [2 + 2] cycloadducts (**7a-c**) at all. On the other hand, intramolecular cycloaddition using **5b** smoothly proceeded to give a single product of **6b**, of which structure was confirmed to have tricyclic core by X-ray crystallographic analysis (**Scheme 5**) [12]. In case of **5c**, similar cycloaddition proceeded to give **6c** as a single diastereomer in 44% yield. Xantphos was also an essential ligand for this cycloaddition because the reactions without ligand or the use of PPh₃ or dppe instead were all ineffective to give any trace amount of **6** nor **7** at all.

The plausible reaction pathways for above reactions are proposed in Scheme 6. The [2 + 2] cycloaddition of **1a** would be trig-

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Scheme 4. Synthetic transformation of 2a.

Ni[P(OPh)3]4 (10 mol%) xantphos (10 mol%) TsN TsN toluene, 70 °C 5a: R = H 5b: R = Me 6a: R = H : 0% (0.5 h) 5c: R = iPr 6b: R = Me: 62% (0.5 h) 6c: R = iPr : 44% (1 h) TsN 7a: head to head 7b: head to tail 6b TsN not isolated 7c: tail to tail



Scheme 6. Plausible reaction mechanism.

Scheme 5. Ni-Catalyzed cycloaddition using 5.

would effectively promote the reductive elimination from the intermediates **A** and **B** to the corresponding cycloadducts [28,29].

gered by the formation of **A** reacting with inner allenyl C=C bonds of **1a** via oxidative cyclization, and the following reductive elimination gives *head to head* product of **2a** with a release of a Ni(0) catalyst. The formation of **A** would be critically prevented by the steric bulk of a substituent such as **1g** to decrease the cyclization efficacy. In case of allene-allenamide (**5b**), two possible nickelacycles **B1** and **B2** via homodimerization are proposed. The following reductive elimination would give "*tail to tail*" cycloadduct (**C**), [24] which could be transformed to **6b** through intramolecular Diels-Alder reaction.[25–27] The exclusive formation of **6b,c** suggests that the stereochemistry of red C=C bonds in both **B** and **C** would be critically controlled to be *E*-isomer for sequential [4 + 2] cycloaddition. In both cases, xantphos gave strong influence in conversion, which would be caused by its larger bite angle. This bisphosphine

Conclusions

In conclusion, we have developed a nickel-catalyzed [2+2] cycloaddition using bisallenes. The reaction pathways are highly dependent on the substrates. Symmetric bisallenes predominantly gave simple [2+2] adducts *via* "head to head" cycloaddition, whereas allene-allenamide substrates show unique reactivity to promote sequential [2+2]-[4+2] cycloaddition to give tricyclic compounds with highly stereoselective manner. These observations among the nickel catalysis have enough impact on synthetic chemistry, offering the alternative method for the synthesis of functionalized cyclolobutanes, and the further application is currently undergoing in our laboratory.

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Experimental section

Represened procedure for Ni-catalyzed [2 + 2] cycloaddition of 1a

A mixture of Ni[$P(OPh)_3$]₄ (23.5 mg, 0.018 mmol, 10 mol%), xantphos (10.4 mg, 0.018 mmol, 10 mol%) and **1a** (50.3 mg, 0.18 mmol) in toluene (1.8 mL, 0.1 M) was heated at 70 °C under argon atmosphere for 90 min. After the filtration of the reaction mixture through a celite pad, the organic solvents were removed under the reduced pressure. The resulting mixture was poured into silica gel and purified by column chromatography (hexane: AcOEt = 80:1 to 10:1) to give **2a** as colorless solid (43.6 mg, 0.16 mmol, 87%).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151168.

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