

Accepted Article

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Adv. Synth. Catal. 10.1002/adsc.201900719

Link to VoR: http://dx.doi.org/10.1002/adsc.201900719

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DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Regioselective [2+2+2] Cycloaddition Reaction Using Alleneynes with Simple Allenes under Nickel Catalysis

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201#######.((Please delete if not appropriate))

Abstract. A Ni-catalyzed [2+2+2] cycloaddition reaction between allene-ynes and various mono-, di- and trisubstituted allenes is described. This protocol effectively differentiates allenyl π components and shows broad substrate generality to give highly functionalized carbocycles. A DFT study played a key role in revealing a detailed reaction mechanism that controls site-, regio- and stereoselectivity, which are thought to originate in the substituent effect on π -bonds in the early transition state.

Keywords: allene; catalysis; cycloaddition; nickel; regioselective

Six-membered carbocycles are an important class of molecules in material and pharmaceutical sciences. Therefore the development of efficient approaches to obtain them has been an important issue in synthetic chemistry. Metal-catalyzed [2+2+2] cycloaddition reactions using alkynes and olefins have been considered as potential functionalized methods for producing 6membered rings in a single operation.^[1] On the other hand, allenes (C=C=C) are attractive components because the extra olefins in the products synthetic utility.^[2] enhance their However it is difficult to discriminate their π bonds. In fact, most of the reported examples of metal-catalyzed cycloaddition employ a single use of allenes as C2 units.^[3,4] Focusing on [2+2+2] cycloaddition,^[5,6] recent applications of Rh^[7,8] and B^[9] catalysis have revealed that 2 or 3 allenes can be used for the site-, regio- and stereoselective construction of 6-membered carbocycles (Scheme 1). While these transformations are highly attractive, further strategic modification is required to overcome substrate limitations and enhance product diversity. In this communication, we report a new protocol using two non-equivalent allenes in the site-, regio- and stereoselective [2+2+2] cycloaddition under nickel catalysis. DFT calculations are used to propose a detailed reaction pathway and the origin of these selectivities.



Scheme 1. Metal-catalyzed [2+2+2] cycloaddition using simple allenes.

We previously reported the Ni-catalyzed hydrocyanative cyclization of allene-yne to construct a 5-membered ring (Scheme 2).^[10] To our surprise, the reaction without a HCN source dramatically changed its behavior to give homo-dimerization product in 92% yield, exclusively. This result clearly shows that [2+2+2] cycloaddition uses 2 different π components of allenes, which are effectively incorporated into a cyclohexene ring in а regioselective manner.



Scheme 2. Ni-catalyzed reaction using allene-ynes.

Focusing on a 1,1-disubstituted allene, we next chose **2a** as a simple π -component to optimize the reaction conditions (Table 1). First, the reaction was performed in toluene at 100 °C, and the expected hetero-adduct of **3aa**^[11] was obtained in 84% yield as a single isomer with dimeric **4a** in 16% yield (entry 1). A survey of the reaction conditions using other phosphorous ligands (entries 2 and 3), or a lower temperature or concentration (entries 4 and 5) did not improve the product ratio. When the amount of **2a** (2 eq.) was reduced, both slower conversion and a decreased product ratio were observed (entry 6).

Table 1. Optimization.

TsN	$-t \cdot Bu + \underbrace{\bigcup_{i=1}^{N(i P(OPh)_{3}]_{4}}_{i \text{ toluene}} + \underbrace{\bigcup_{i=1}^{Me}}_{T_{SN}} + \underbrace{\bigcup_{i=1}^{Me}}_{i \text{ toluene}} + \underbrace{I_{SN}}_{i tol$	TsN t-Bu 4a	Ts t-Bu
Entry	Conditions	3aa	4 a
		(%)	(%)
1	100 °C, 0.5 h, 0.1 M	84	16
2	100 °C, 2 h, 0.1 M, P(OPh) ₃	70	22
	(40 mol%)		
3	100 °C, 0.5 h, 0.1 M, PPh ₃	78	14
	(40 mol%)		
4	70 °C, 7 h, 0.1 M	24	8
5	100 °C, 0.5 h, 0.05 M	72	13
6	100 °C, 2 h, 0.1 M ^{a)} , P(OPh) ₃	37	17
	(40 mol%)		

^{a)} 1) Two equiv of **2a** was used.

Next, the substituent effect in 1 was investigated. The steric bulk of R^1 substituents in **1** strongly affected the efficiency in the formation of 3 under optimum conditions (Scheme 3). For example, 1b containing an ethyl group gave **3ba** in 92% yield with **4b** in 7% yield. In the case of 1c, 3ca was exclusively obtained in 94% yield. On the other hand, the yield of 3da was 27% and **5da** was formed when R^1 was hydrogen (1d). The latter product suggests that an inner, rather than not a terminal, C=C bond in 1d is reactive in ring formation, as described in Scheme 2. These results clearly show that the steric bulk of R¹ strongly affects the formation of 3 by preventing the competing pathways to 4 and 5. The use of 1e, which contains a methyl at R^2 instead of a *t*-Bu group. remarkably decreased the regioselectivity to give \bar{a} mixture of 3ea and 6ea in 73% yield.



Scheme 3. Substituent effect of allene-yne (1).

Based on the above observations, the substrate scope was examined next (Scheme 4). The reaction using **2b** with **1a-c** also gave the corresponding adducts (3ab-3cb) in 64-90% yield. Oxygen- and carbontethered allene-ynes (1f-h) could all be used in this regioselective cycloaddition to give 3fa-3hb in 55-85% yield. Amino- and silvl functionalities in 2c,d were both suitable for regioselective cycloaddition. To our delight, 1,3-disubstituted allenes involving a phenyl group (2e,f) gave highly site-, regio- and stereocontrolled products (3ce, 3cf).^[11] In the reaction of allenamide (1i) with 2a, smooth conversion to 3ia was observed under basic media to avoid the decomposition of **1i** and/or **3ia**. A cyclic allene (**2g**) could also be used for the construction of a tricyclic system^[4d] in a single operation and **3cg** was obtained in 67% yield as an inseparable mixture of stereoisomers.[12]



Scheme 4. Substrate scope for [2+2+2] cycloaddition between 1 and 2.

To reveal the reaction pathway and the origin of regioselectivity, we performed a model calculation using the DFT method with **1a'**, 1,1-dimethylallene (DMA) and Ni[P(OMe)₃]₄ (Figure 1).^[13] The reaction starts with the formation of π -complex (**CP1**), and subsequent oxidative addition gives **INT1**. More

stable INT2 is provided by ligand substitution, and the choice of the reaction at the C_A - or C_B -Ni bond is a key issue for determining the regioselectivity. The more feasible pathway is estimated to have an activation barrier of 27.7 kcal/mol for TS2, cleaving a C_A-Ni bond. This pathway would take advantage of minimizing the steric repulsion between t-Bu and dimethyl groups. Subsequent ligation gives morestabilized INT4, which has a shorter distance between C_B and C_C in **TS3** to achieve reductive elimination at more-hindered carbons. The optimized structure of INT3 includes larger angle of C_B-Ni-C_D (140.7°) than C_B-Ni-C_C (98.9[°]) and longer distance between C_B and C_D than C_B and C_C . These values reasonably explain the regioselectivity in reductive elimination to complete the cycloaddition (Figure 2). Thus, the experimentally observed cycloadduct (PD) is obtained. The characteristic features of highly regioselective cycloaddition provided by DFT analysis are 1) a less-substituted $C_{sp}=CH_2$ bond of DMA reacts with **INT2**, 2) a less-bulky C_A -Ni bond reacts with DMA, and 3) bond formation between C_A and C_{sp} in DMA is a rate- and selectivity-determining step.[14]

The above mechanistic features are clearly in agreement with the observed regiochemistry. However, the result with 1e ($R^2 = Me$, Scheme 3) is consistent with the rules because its steric influence in transition state would be ineffective. Therefore, we next performed DFT calculations for eight possible TS_{A-H} to evaluate their activation energies (Figure 3). In the case of 1a', $TS_{C(t-Bu)}$ is the most feasible due to the lowest activation barrier of 27.74 kcal/mol, a described in Figure 1. However, the reduced steric repulsion between t-Bu and dimethyl groups it expected in TS_A , and a large energy difference was observed relative to TS_C , which suggests that the greater electrophilicity of the sp carbon in DMA^[14b] could be suitable for reacting with a C_{sp3}-Ni bond. On_ the other hand, 1g' gives two operative transition states, shown as TS_C and TS_G , which have respective barriers of 29.03 and 30.24 kcal/mol. These pathways would be competitive because of the small energy gap (1.21 kcal/mol), and both of their products were isolated as **3ea/6ea** in a ratio of 1/1.8 (Scheme 3).

Figure 1. Energy diagram for reaction pathway of [2+2+2] cycloaddition. Energies are calculated at the M06/LANL2DZ (Ni) and 6-31G* (others).



Figure 2. Optimized structure of INT3.







The above DFT analysis suggests that the structural modification of substrates would be a potential method for development of alternative reaction pathways and regioselectivities. Thus, we installed R_6 on an allenvel terminal (**1j-o**) to give a new reaction toward $\mathbf{TS}_{G(Me)}$ by preventing observed predicted $TS_{C(Me)}$, and the regioselectivity and products even with the use of mono-substituted allenes (2h,i). The reaction of 1 i with 2h gave the conjugated triene (6ih) in 45% yield while controlling two stereogenic centers to be trans. In the case of iPr and phenyl groups, the corresponding cycloadducts (6kh, **6lh**) were obtained in respective of yields of 40% and 86%. Substituted aromatic rings (1m,n) and linear alkyl group (2i) gave 6mh, 6nb, 6li and 6ki yields in of 26-52%. These results are summarized in Scheme 5.



Scheme 5. Effect of R^6 in regioselective [2+2+2] cycloaddition and substrate scope.

Finally, we investigated the reaction of **1a**,**o** with **2h** to provide additional information about the mechanism (Scheme 6). The reaction of **1a** gave both **3ah** and **6ah** without any selectivity, suggesting that both $\mathbf{TS}_{\mathbf{C}(t-Bu)}$ and $\mathbf{TS}_{\mathbf{G}(t-Bu)}$ would be operative because less-bulky **2h** could reduce the activation energy of the latter. The result using **1o** clearly indicates that both *t*-Bu and Me (R⁶) groups would provide higher energy barriers to prevent all possible TSs even with the use of **2h**.



Scheme 6. Reaction using 1a,o with 2h.

In conclusion, we realized a highly site-, regio- and stereoselective [2+2+2] cycloaddition using various allenes under nickel catalysis. All of the substituents on π -components exerted a significant influence to control the reactivity, selectivity and reaction pathway. A DFT calculation revealed the selectivity-determining step, which is strongly affected by the steric environment around π -bonds. The rational design of substrates can be important for controlling the activation barrier in this step, and a new and alternative reaction pathway was also developed. These achievements would provide strategic options in Ni catalysis and further applications are currently being investigated.

Experimental Section

General procedure for Ni-catalyzed [2+2+2] cycloaddition reaction. Synthesis of 3aa:

To a solution of **1a** (40.0 mg, 0.12 mmol) and **2a** (52 mg, 0.48 mmol) in toluene (1.2 mL) was added Ni[P(OPh)₃]₄ (5.7 mg, 0.012 mmol, 10 mol%), and the mixture was heated at 100 °C for 30 min under argon. After filtration through a Celite pad and removal of the solvents, the resulting crude product was purified by silica gel column chromatography (hexane/AcOEt = 40:1) to give **3aa** (44.5 mg, 0.1 mmol, 84%) as a pale yellow solid together with **4a** (6.4 mg, 0.096 mmol, 16%) as a white solid.

Acknowledgements

This work was supported by the Grant-in-Aid from the Japan Society for the Promotion of Science (JSPS) (Grant No. 17K08205).

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Adv. Synth. Catal. Year, Volume, Page – Page

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