Published in final edited form as:

Angew Chem Int Ed Engl. 2016 November 21; 55(48): 15091–15095. doi:10.1002/anie.201609489.

Nickel-Catalyzed Chemo- and Enantioselective Coupling Between Cyclobutanones and Allenes: Rapid Synthesis of [3.2.2] Bicycles

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Abstract

Herein an intramolecular Ni-catalyzed (4+2) coupling between cyclobutanones and allenes via C–C cleavage is reported, which provides a distinct approach to access [3.2.2] bicyclic scaffolds that are challenging to prepare through conventional approaches. The reaction is efficient, chemoselective and pH/redox neutral. Room temperature conditions and low catalyst loadings can be adopted. Excellent enantioselectivity is also achieved.

Graphical Abstract

An intramolecular Ni-catalyzed (4+2) coupling between cyclobutanones and allenes via C–C cleavage is reported, which provides a unique approach to access [3.2.2] bicyclic scaffolds. The reaction is efficient, chemoselective and pH/redox neutral. Excellent enantioselectivity is also achieved.

Keywords

allene; cycloaddition; nickel catalysis; cyclobutanone; C–C activation

Transition metal (TM)-catalyzed C–C cleavage reactions have recently emerged as attractive synthetic methods that offer unusual strategic disconnections for preparation of complex scaffolds.^[1] In particular, the couplings between a strained ketone and an unsaturated unit via C–C activation provide efficient access to various ring systems. Two complementary approaches have been developed to assist the coupling (Scheme 1): one involves oxidative addition of a TM, e.g. Rh^I, Ni⁰, Ru⁰, into a strained C–C bond, followed by 2 π insertion to complete the cycloaddition (path a);^[2] the other approach, pioneered by Murakami and co-

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workers,^[3a] utilizes a cyclometalation pathway to first form a five-membered metallacycle between the carbonyl group and the unsaturated unit, followed by β -carbon elimination and reductive elimination to furnish the ring (path **b**).^[3]

To date, a number of unsaturated units, including alkenes,^[2b,c,e,f,i] alkynes,^[2a,d,h] 1,3-dienes,^[3d,g] ketones/ aldehydes^[2k] and imines,^[2l] have been employed to couple with strained ketones through one or both pathways. In contrast, the use of allenes as a 2π unit would deliver an additional olefin moiety into the product for further derivatization,^[4] which unfortunately, has received much less attention. The challenge is likely due to that 1) allenes are generally less stable and tend to undergo dimerization catalyzed by TMs,^[5] and 2) control of the chemoselectivity in the allene-mediated reactions is nontrivial.^[6] Recently, we reported the first Rh-catalyzed cyclobutanone-allene coupling via path **a** involving oxidative addition into C–C bonds (Scheme 2a); however, instead of giving the desired (4+2) product, an unexpected (4+1) addition was found as the major reaction pathway, in which allenes serve as a one-carbon unit.^[7] Stimulated by this result, an intriguing question arose: how would allenes behave in a cyclometalation/ β -carbon elimination pathway (path **b**)? In other words, can (4+2) products be exclusively formed with allenes as a 2π unit in a C–C cleavage/coupling reaction? Driven by these questions, herein, we describe our systematic efforts on the development of a Ni-catalyzed chemo- and enantioselective intramolecular (4+2) coupling between cyclobutanones and allenes via C–C cleavage (Scheme 2b). This method provides a unique and efficient entry to functionalized [3.2.2] hetero- and carbocycles that are commonly found in natural products and other bioactive compounds (Figure 1).

Our study began using allene **1a** as the model substrate with Ni(cod)₂ as the precatalyst (Table 1). While bidentate ligands gave full conversions of the starting material, a complex mixture of unidentifiable products was obtained (entries 1–4). Given that the Ni(II) intermediate after cyclometalation would require an open coordination site for subsequent β -carbon elimination, the chelation of bidentate ligands would inhibit ligand dissociation; thus, it was envisioned that use of monodentate ligands should avoid this issue. Indeed, when PPh₃ was employed, which is known to undergo fast ligand dissociation,^[8] the desired (4+2) product (**2a**) bearing a 3-aza[3.3.2] scaffold was formed in 92% yield (entry 5). Other monodentate ligands, such as PCy₃, also afforded the desired product but in a slightly lower yield (entry 6). Halving the ligand loading did not affect the reaction efficiency, suggesting that only one phosphine is needed per metal (entry 7). A survey of solvent effects suggested toluene to be optimal (entries 8 and 9). Note that the catalyst loading can be further reduced to 5 and 2.5 mol% without significantly diminishing the yields (entries 10 and 11). In addition, the reaction run at room temperature also gave an excellent yield with a longer reaction time (entry 12).

With the optimized conditions (Table 1, entries 7 and 12) in hand, the scope of the Ni-catalyzed (4+2) coupling was explored. First, 1,1,3-trisubstituted allenes were found to be excellent coupling partners (Table 2, substrates **1a–1h**). Both cycloalkyl and *gem*-dialkyl substitution were well tolerated. When unsymmetrical allenes were employed, mixtures of E/Z isomers were obtained (**1g** and **1h**). For substrate **1h**, with a pendant benzyl ether substituent, lower reactivity (40% conversion) was observed under the standard conditions.

However, when the reaction concentration was increased to 0.15 M, the desired [3.2.2] bicycle **2h** was isolated in 81% yield. While attempts to use 1,3,3-trisubstituted and tetrasubstituted allenes (**1i** and **1m**) were unfruitful likely due to the steric hindrance in the cyclometalation step, 1,3-disubstituted allenes (**1i** and **1j**) proved to be suitable substrates. The diminished yields were attributed to the instability of the more exposed allene moiety under the reaction conditions. Not surprisingly, when mono-substituted allene **1k** was tested, only allene dimers were detected.

Next, variations on the cyclobutanone part were examined (Table 3). Besides methyl group (**2a**), other alkyl and aryl groups, such as ethyl (**2n**), propyl (**2o**), phenyl (**2p**), benzyl (**2q**) and benzyl ether (**2r**), were found compatible for this transformation. Due to the mild reaction conditions, an *unprotected primary alcohol* remained intact (**2s**). Cyclobutanone **1t** with hydrogen at the C3 position is also a competent substrate. In addition, cyclobutanone **2u** with a C2 substituent underwent selective C–C cleavage at the less hindered position offering the desired [3.2.2] bicycle with a 6:1 d.r.

In addition, substrates **1v** and **1w**, containing a *spirocyclic* center, were successfully employed to construct tricyclic scaffolds in good yields (entries 1 and 2, Table 4). While the cyclopentyl-based substrate (**1v**) showed no diastereoselectivity, the cyclohexane one (**1w**) nevertheless afforded a single diastereomer, whose structure was confirmed by X-ray crystallography.^[9] The nearly complete diastereoselectivity for **1w** suggested a highly ordered β -carbon elimination process possibly controlled by the chair conformation of the cyclohexane ring. Besides nitrogen tethers, carbon linkages were also investigated (entries 3–5, Table 4). While the sp^3 carbon linker (**1x**) gave the desired (4+2) product in a good yield,^[10] it is surprising that substrate **1y**, bearing an arene backbone, was found inactive. We reasoned that, although the arene linkage brings the cyclobutanone and allene closer to each other, the rigid backbone also causes the coordination of nickel with the two moieties more difficult due to the steric repulsion between the allene substituent (Me) and the metal. Thus, we further hypothesized that introduction of a weak coordinating group to the allene substituent would enhance its binding with nickel, and consequently provide better reactivity. Indeed, when the MeO-substituted analogue (**1z**) was employed, the desired benzo [2.2.2] bicycle was afforded in a reasonably good yield.

To control the absolute stereochemistry of the [3.2.2] products, the enantioselective variant of the reaction was explored (Table 5). A range of chiral monodentate phosphine ligands were examined (entries 1–6), and the highest e.r. was obtained with TADDOL-derived phosphoramidite **L6** (entry 6).^[11] Interestingly, the enantioselectivity is highly sensitive to the reaction concentration (entries 7–10);^[12] ultimately, a 79% yield and 96:4 e.r. were achieved when increasing the concentration from 0.03 to 1.0 M (entry 10). Further, use of mesitylene as solvent gave higher yield (entry 13). Other TADDOL-derived phosphoramidite ligands such as **L7** and **L8** were also tested and proved less efficient than **L6** (entries 14 and 15).

The scope of the enantioselective (4+2) cyclization was next studied (Table 6). Two important observations were made: 1) substrates with cycloalkyl and di-alkyl substituted allenes all provided good yields and high e.r. (**2a–2g**); 2) changing the substituent at the C3

position of cyclobutanone did not significantly disturb the enantioselectivity. The absolute stereochemistry was assigned based on the X-ray crystallographic structure of product **2aa**.^[9]

The Ni-catalyzed (4+2) cyclization is also scalable, and the product (**2a**) can undergo many facile transformations to access other structures or functional groups (Scheme 3). Application of this method in complex molecule synthesis is ongoing in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project was supported by NIGMS (R01GM109054) and the Welch Foundation (F 1781). G.D. is a Searle Scholar and Sloan fellow. Johnson Matthey is acknowledged for a generous donation of Rh salts. Prof. Dr. M. C. Young is thanked for proofreading the manuscript. We also thank Dr. V. Lynch and Dr. M. C. Young for X-ray structures.

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12. At high concentration, substrate **1a** only dissolved slowly during the course of the reaction. The resulting transient higher catalyst/substrate ratio may account for the higher enantioselectivity.

Figure 1. Representative natural products or pharmaceutical compounds containing [3.2.2] bicyclic skeleton.

Scheme 1.
Two C-C activation modes with cyclobutanones

[a] previous unexpected result with allenes:

[b] this work (*from path b*): **Scheme 2.**

Coupling of cyclobutanones with allenes

Scheme 3.
Synthetic Applications

Table 1

Selected optimization conditions with allene **1a**

Entry	Ni (mol%)	Ligand (mol%)	Temp (°C)	Solvent	Conv.(%)	Yield (%) ^[a]
1	10%	dppp (12)	100	Tol	100	0
2	10%	dppb (12)	100	Tol	100	0
3	10%	dppe (12)	100	Tol	100	0
4	10%	BINAP (12)	100	Tol	100	0
5	10%	PPh₃ (24)	100	Tol	100	92
6	10%	PCy ₃ (24)	100	Tol	100	80
7	10%	PPh ₃ (12)	100	Tol	100	92
8	10%	PPh ₃ (12)	100	THF	100	85
9	10%	PPh ₃ (12)	100	1,4-dioxane	100	86
10	5%	PPh ₃ (6)	100	Tol	100	91
11	2.5%	PPh ₃ (3)	100	Tol	75	71
12 ^[b]	10%	PPh ₃ (12)	25	Tol	100	91

^[a] Determined by ¹H NMR using mesitylene as the internal standard. PCy₃ = tricyclohexylphosphine. cod = 1,5-cyclooctadiene.^[b] 172 h.

Table 2

Substrate Scope on allene^[a]

^[a] Run on a 0.1 mmol scale with 10 mol% $\text{Ni}(\text{cod})_2$ and 12 mol% PPh_3 in 2.0 mL toluene at 100 °C for 24 h.

^[b] Room temperature for 72 h.

^[c] Number in parentheses is the yield based on recovered starting material (brsm).

$[\alpha]_{\text{D}}^{25}$ 0.7 mL toluene.

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Table 3

Substrate Scope on cyclobutanone^[a] ^[a] Run on a 0.1 mmol with 10 mol% Ni(cod)_2 and 12 mol% PPh_3 in 2.0 mL toluene at 100 °C for 24 h.^[b] Room temperature for 72 h.^[c] Number in parentheses is brsm yield.

Table 4

Substrate Scope on Backbone and Linkage^[a]

1
	1v	(±)-2v : (±)-2v' = 1 : 1 70%
2
	1w	(±)-2w 73% X-ray structure
3
	1x	(±)-2x 61% (76%) ^[b,c]
4
	1y	(±)-2y 0%
5
	1z	(±)-2z : (±)-2z' = 1.3 : 1 56% (70%) ^[c]

^[a]Run on a 0.1 mmol scale in a sealed 4 mL vial, using 10 mol% Ni(cod)₂ and 12 mol% PPh₃ in toluene (2.0 mL) at 100 °C for 24 h.^[c]Number in parentheses is brsm yield.

Table 5

Selected Optimization for the Enantioselective Reaction^[a]

Entry	Ligand	Solvent	Concentration	Yield ^[b]	e.r. ^[c]
1	L1	toluene	0.03 M	<5%	...
2	L2	toluene	0.03 M	62%	54.5:45.5
3	L3	toluene	0.03 M	32%	66.5:33.5
4	L4	toluene	0.03 M	35%	69:31
5	L5	toluene	0.03 M	89%	53:47
6	L6	toluene	0.03 M	51%	76:24
7	L6	toluene	0.015 M	59%	62.5:37.5
8	L6	toluene	0.1 M	60%	88:12
9	L6	toluene	0.4 M	61%	95:6
10	L6	toluene	1.0 M	79%	96:4
11	L6	THF	1.0 M	52%	88:12
12	L6	1,4-dioxane	1.0 M	75%	95:5
13	L6	mesitylene	1.0 M	82%	96:4
14	L7	toluene	1.0 M	60%	71.5:28.5
15	L8	toluene	1.0 M	90%	66.5:33.5

^a Run on a 0.03 mmol scale.

^b Determined by crude ¹H NMR using 1,1,1,2,2-tetrachloroethane as the internal standard.

^c Determined by HPLC analysis using a chiral stationary phase.

^d Not determined. (R)-SITCP = (11aR)-(+)-5,6,10,11,12,13-Hexahydro-5-phenyl-4H-diindeno[7,1-cd:1,7'-ef]phosphocin, (R)-MOP = (R)-(+)-2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl, DTBM = 3,5-di-tert-butyl-4-methoxyphenyl.

Table 6Substrate Scope of the Enantioselective (4+2) Cyclization^[a] ^[a] Run on a 0.1 mmol scale. Number in parentheses is brsm yield.