Cycloaddition

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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 nickel-catalyzed (4+2) coupling between cyclobutanones and allenes, by C–C cleavage, is reported. The reaction provides a distinct approach for accessing [3.2.2] bicyclic scaffolds which 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.

ransition metal catalyzed C–C cleavage reactions have recently emerged as attractive synthetic methods which offer unusual strategic disconnections for the preparation of complex scaffolds.^[1] In particular, the couplings between a strained ketone and an unsaturated unit by C–C activation provide efficient access to various ring systems. Two complementary approaches have been developed to facilitate such couplings (Scheme 1): one involves oxidative addition of



Scheme 1. Two C-C activation modes with cyclobutanones.

a transition metal (TM), for example, Rh^I, Ni⁰, and Ru⁰, into a strained C–C bond, followed by 2π insertion to complete the cycloaddition (path a).^[2] The other approach, pioneered by Murakami and co-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 atom elimination and reductive elimination to furnish the ring (path b).^[3]

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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,^[21] have been employed for coupling with strained ketones through either 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] and unfortunately, it has received much less attention. The challenge arises from: 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 rhodium-catalyzed cyclobutanone–allene coupling by path a involving oxidative addition to C–C bonds (Scheme 2a).



Scheme 2. Coupling of cyclobutanones with allenes.

However, instead of giving the desired (4+2) product, an unexpected (4+1) addition was found as the major reaction pathway, in which the allene serves as a one-carbon unit.^[7] Motivated by this result, an intriguing question arose: how would allenes behave in a cyclometalation/ β -carbon atom 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 nickel-catalyzed chemo- and enantioselective intramolecular (4+2) coupling between cyclobutanones and allenes by C–C cleavage (Scheme 2b). This method provides a unique and efficient entry to functionalized [3.2.2] hetero-

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

and carbocycles which are commonly found in natural products and other bioactive compounds (Figure 1).

Our study began by using the 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 nickel(II) intermediate after cyclometalation would require an open coordination site for subsequent β -carbon atom 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, a ligand 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

Table 1: Selected optimization conditions with allene 1 a.



Entry	Ni (mol%)	Ligand (mol%)	Т [°С]	Solvent	Conv. [%]	Yield [%] ^[a]
1	10	dppp (12)	100	toluene	100	0
2	10	dppb (12)	100	toluene	100	0
3	10	dppe (12)	100	toluene	100	0
4	10	BINAP (12)	100	toluene	100	0
5	10	PPh ₃ (24)	100	toluene	100	92
6	10	PCy ₃ (24)	100	toluene	100	80
7	10	PPh ₃ (12)	100	toluene	100	92
8	10	PPh ₃ (12)	100	THF	100	85
9	10	PPh ₃ (12)	100	1,4-dioxane	100	92
10	5	PPh ₃ (6)	100	toluene	100	91
11	2.5	PPh_3 (3)	100	toluene	75	71
12 ^[b]	10	PPh ₃ (12)	25	toluene	100	91

[a] Determined by ¹H NMR spectroscopy using mesitylene as the internal standard. [b] 72 h. BINAP = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl, cod = 1,5-cyclooctadiene, dppb = 1,4-bis(diphenylphosphino)butane, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis-(diphenylphosphino)propane, PCy₃ = tricyclohexylphosphine, THF = te-trahydrofuran, Ts = 4-toluenesulfonyl.

afforded the desired product but in a slightly lower yield (entry 6). Halving the ligand loading did not affect the reaction efficiency, thus 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 albeit with a longer reaction time (entry 12).

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

Table 2: Substrate scope with respect to allene.[a]



[a] Run on a 0.1 mmol scale with 10 mol% [Ni(cod)₂] and 12 mol% PPh₃ in 2.0 mL toluene at 100 °C for 24 h. [b] Room temperature for 72 h. [c] Number within parentheses is the yield based on recovered starting material (brsm). [d] 0.7 mL toluene.

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conversion) was observed under the standard reaction 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 (**11** and **1m**) were unfruitful, likely as a result of 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, the monosubstituted allene **1k** was tested, only allene dimers were detected.

Next, variations on the cyclobutanone unit were examined (Table 3). Besides a methyl group (2a), other alkyl and aryl groups, such as ethyl (2n), propyl (2o), phenyl (2p), benzyl





[a] Run on a 0.1 mmol with 10 mol% [Ni(cod)₂] and 12 mol% PPh₃ in 2.0 mL toluene at 100 °C for 24 h. [b] Room temperature for 72 h. [c] Number within parentheses is yield brsm.

(2q), and benzyl ether (2r), were found to be compatible for this transformation. Because of the mild reaction conditions, an unprotected primary alcohol remained intact (2s). The cyclobutanone 1t with hydrogen at C3 is also a competent substrate. In addition, the cyclobutanone 2u with a C2 substituent underwent selective C-C cleavage at the less hindered position, thus offering the desired [3.2.2] bicycle with a 6:1 d.r.

In addition, the substrates 1v and 1w, containing a spirocyclic center, were successfully employed to construct tricyclic scaffolds in good yields (Table 4, entries 1 and 2). While the cyclopentyl-based substrate 1v showed no diastereoselectivity, the cyclohexane 1w nevertheless afforded a single diastereomer, whose structure was confirmed by

Table 4: Substrate scope with respect to the backbone and linkage.^[a]



[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. Yield is that of the isolated product. [b] 1,4-Dioxane was used (2.0 mL). [c] Number within parentheses is yield brsm.

X-ray crystallography.^[9] The nearly complete diastereoselectivity for 1w suggested a highly ordered β -carbon atom elimination process possibly controlled by the chair conformation of the cyclohexane ring. Besides nitrogen tethers, carbon linkages were also investigated (entries 3-5). While the sp³-hybridized carbon linker 1x gave the desired (4+2) product in a good yield,^[10] it is surprising that the substrate 1y, bearing an arene backbone, was inactive. We reasoned that, although the arene linkage brings the cyclobutanone and allene closer to each other, the rigid backbone also makes coordination of nickel with the two moieties more difficult as a result of 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, an enantioselective variant of the reaction was

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Table 5: Selected optimization for the enantioselective reaction.^[a]



[a] Run on a 0.03 mmol scale. [b] Determined by ¹H NMR analysis on crude reaction mixture using 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-hex-ahydro-5-phenyl-4*H*-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.



explored (Table 5). A range of chiral monodentate phosphine ligands were examined (entries 1–6), and the highest e.r. was obtained with the TADDOL-derived phosphoramidite **L6** (entry 6).^[11] Interestingly, the enantioselectivity is highly sensitive to the reaction concentration (entries 7–10),^[12] and 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 a 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 dialkyl-substituted Table 6: Substrate scope of the enantioselective (4+2) cyclization.^[a]



[a] Run on a 0.1 mmol scale. Number within parentheses is yield brsm.

allenes all provided good yields and high e.r. values (**2a-g**); 2) changing the substituent at C3 of the cyclobutanone did not significantly disturb the enantioselectivity. The absolute stereochemistry was assigned based on the X-ray crystallographic structure of product **2aa**.^[9]

The nickel-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.

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Keywords: allenes \cdot C–C activation \cdot cycloaddition \cdot nickel \cdot small ring systems

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Scheme 3. Synthetic applications. DCM = dichloromethane, *m*CPBA = *m*-chloroperbenzoic acid.

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Bicycle, bicycle: An intramolecular nickelcatalyzed (4+2) coupling between cyclobutanones and allenes by C-C cleavage is reported that provides a unique approach for accessing [3.2.2] bicyclic scaffolds. The reaction is efficient, chemoselective, and pH/redox neutral. Excellent enantioselectivity is also achieved.

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