



Nickel-Catalyzed Ring-Opening Allylation of Cyclopropanols via Homoenolate

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mild and neutral conditions. The reaction displays linear selectivity for both linear and branched acyclic allylic carbonates and is also applicable to cyclic allylic carbonates, affording a variety of $\delta_{,\varepsilon}$ unsaturated ketones in moderate to good yields. Mechanistic experiments are in accord with a catalytic cycle involving decarboxylative oxidative addition of allylic carbonate to Ni(0),



alkoxide exchange with cyclopropanol, cyclopropoxide-to-homoenolate conversion on Ni(II), and C-C reductive elimination.

M etal homoenolates have proved to serve as versatile organometallic species for the synthesis of β -functionalized carbonyl compounds through interception with various electrophiles.¹ Among such transformations is the allylic substitution, which represents one of the most extensively explored C-C coupling reactions of organometallic reagents. Nakamura and Kuwajima demonstrated the reaction of preformed zinc homoenolate derived from 1-siloxy-1-alkoxycyclopropane with allylic chlorides under copper or nickel catalysis with $S_N 2'$ or $S_N 2$ selectivity, respectively, thus affording $\delta_{,\varepsilon}$ -unsaturated esters (Scheme 1a).² Recently, cyclopropanols have emerged as direct precursors to (catalytic) metal homoenolates for various C-C and C-heteroatom bond formations.^{1a-d} As one of the pioneering studies in this context, in 2012, Cha and co-workers reported ring-opening allylation of cyclopropanols with allylic halides or phosphates mediated by stoichiometric amounts of Et₂Zn and CuCN· 2LiCl (Scheme 1b).^{3,4} The reaction was proposed to involve reversible generation of zinc homoenolate from zinc cyclopropoxide and its transmetalation with copper. In parallel with the copper catalysis of the preformed zinc homoenolate, the reaction displayed high S_N2' selectivity.

Despite the significant progress in catalytic transformations of cyclopropanols via homoenolates, allylic substitution with S_{N2} or linear selectivity remains underdeveloped. Recent reports by Ma and co-workers on the palladium-catalyzed coupling between cyclopropanols and propargyl carbonates or 2,3-allenic carbonates suggest the feasibility of such transformations,⁵ while their studies underlined the difficulty of suppressing β -hydride elimination of palladium homoenolate to give enone as an undesirable byproduct.⁶ We report herein a nickel-catalyzed ring-opening coupling between cyclopropanols and various allylic carbonates with linear selectivity (Scheme 1c), which involves catalytically generated nickel homoenolate as the key intermediate^{7,8} and is complementary to Cha's

Scheme 1. Allylation of Metal Homoenolates

(a) Preformed stoichiometric Zn homoenolate



(b) In-situ generated Zn homoenolate

$$R^{1}_{\perp} \overset{OH}{\longrightarrow} + R^{2} \overset{X}{\longrightarrow} X \xrightarrow{\begin{array}{c} \text{Et}_{2} \text{Zn} (1 \text{ equiv}) \\ \text{CuCN-2LiCl} (1.5 \text{ equiv}) \\ \text{THF, -30 °C to rt} \end{array}} R^{1} \overset{V}{\underset{R^{2}}{\overset{R^{R}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}{\overset{R^{2}}}{\overset{R^{2}}{$$

(c) This work: Catalytically generated Ni homoenolate



Mild and neutral conditions

Complementary regioselectivity to Cha's allylation

Applicable to linear, branched, and cyclic carbonates

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allylation. The present reaction features neutral and noncryogenic conditions without using stoichiometric metal reagents and allows the use of linear, branched, and cyclic allylic carbonates, thus offering an approach to various $\delta_{,\varepsilon}$ unsaturated ketones that is complementary to others such as the conjugate addition of allyl nucleophiles⁹ or enolate alkylation with homoallyl electrophiles.¹⁰ The products are amenable to various derivatizations employing both the carbonyl and the olefin moieties as synthetic handles.

The present study commenced with exploration of the coupling between 1-phenylcyclopropanol (1a) and *tert*-butyl cinnamyl carbonate (2a) (Table 1). Our initial attempts

Table 1. Optimization of Reaction Conditions^a

ОН		Ni(cod) ₂ (10 mol %) ligand (10 mol %)	0
Ph 🗸	+ Ph' 💛 OBoc	solvent, 60 °C, 12 h	Ph
1a	2a		3aa
entr	v ligand	solvent	yield (%) ^b
1	none	THF	28
2	dppe	THF	32
3	dppp	THF	30
4	DPEphos	THF	29
5	Xantphos	THF	51
6	Xantphos	toluene	54
7	Xantphos	DMF	60
8	Xantphos	tBuOMe	69
9	Xantphos	MeCN	73
10 ^c	Xantphos	MeCN	76
11 ^{c,c}	Xantphos	MeCN	84

^{*a*}The reaction was performed using 0.10 mmol each of **1a** and **2a** (0.3 M). ^{*b*}Determined by GC using mesitylene as an internal standard. ^{*c*}The reaction was performed at 23 °C. ^{*d*}0.10 mmol of **1a** and 0.12 mmol of **2a** were used.

focused on palladium catalysts in light of their widespread use in allylic substitution as well as cyclopropanol-derived homoenolate chemistry.^{1a-d,5} However, these attempts gave the linear allylation product **3aa** only in low yield (<34%) along with undesirable byproducts such as acrylophenone or cyclopropyl cinnamyl ether, which would have been formed via β -hydride elimination of the palladium homoenolate⁵ or *O*allylation of the cyclopropanol, respectively (see Table S1). On the other hand, Ni(cod)₂ (10 mol %) was found to promote the reaction in THF at 60 °C to afford **3aa** in a moderate yield of 28% but without forming the above undesirable byproducts. Note also that the ring-opening isomerization of **1a** to propiophenone was largely suppressed.

While the use of common diphosphine ligands such as dppe, dppp, and DPEphos in combination with Ni(cod)₂ had negligible impact on the yield of **3aa** or proved even detrimental (see Table S2), Xantphos was found to improve the reaction efficiency to give **3aa** in 51% yield (entry 5). Upon screening of solvents with the Ni(cod)₂/Xantphos catalyst, MeCN was identified as the optimal solvent among others such as toluene, DMF, and *t*BuOMe, improving the yield of **3aa** to 73% (entries 6–9). The reaction temperature could be lowered to room temperature (23 °C) without a decrease in the efficiency (entry 10), and further improvement was achieved using a slight excess (1.2 equiv) of **2a**, affording **3aa** in 84% yield (entry 11). With the optimized catalytic system in hand, we first explored the reaction of various cyclopropanols with cinnamyl carbonate **2a** (Scheme 2). A series of 1-arylcyclopropanols

Scheme 2. Reaction of Various Cyclopropanols with Cinnamyl Carbonate $2a^a$



^aThe reaction was performed on a 0.3 mmol scale. ^bThe result of a 2 mmol scale reaction is shown in the parentheses.

participated in the desired allylation to afford the corresponding $\delta_{\ell}\varepsilon$ -unsaturated ketones 3aa-3ka in moderate to good vields (55-89%). A variety of substituents such as methyl, methoxy, trifluoromethyl, chloro, and bromo groups were tolerated on the para- or meta-position. A substituent on the ortho position, such as methoxy group, could also be tolerated, albeit with somewhat lower yield (see 3ia). The reaction of 1a could be performed on a 2 mmol scale to afford 3aa in 80% yield. 1-(2-Naphthyl)- and 2-thienyl-substituted cyclopropanols also smoothly participated in the reaction to afford the desired products 3ja and 3ka, respectively, in good yields. 1-Alkylcyclopropanols bearing primary or secondary alkyl groups were also amenable to the reaction with 2a, furnishing the desired products 3la and 3ma in good yields. Furthermore, 1,2-disubstituted cyclopropanols 1n and 10 underwent selective cleavage of the less substituted C-C bond to produce the α -branched ketone products **3na** and **30a**, respectively.

We next examined the reaction of 1a with various allylic carbonates (Table 2). Substituted cinnamyl carbonates smoothly participated in the allylation to afford the corresponding products in good yields (entries 1 and 2). An alkyl-substituted linear allylic carbonate also gave the linear allylation product in good yield (entry 3). Branched allylic carbonates derived from 1-(hetero)aryl allyl alcohols gave rise to the linear products in moderate to good yields (entries 4

entry	allyl carbonate	product	yield (%)
	R	Ph R	
1	2b ($R = 4$ -MeOC ₆ H ₄)	3ab	90
2	$2c (R = 4-FC_6H_4)$	3ac	77
3	2d (R = nPr)	3ad	80
	OBoc R	Ph R	
4	2a' (R = Ph)	3aa	71
5	2e (R = 3-pyridyl)	3ae	51
	OBoc	0	
	\wedge	Ar	
6	2f	3af(Ar = Ph)	72
7^b	2f	3jf(Ar = 2-Naph)	64
		Ph CO ₂ Et	
0	1	$\mathbf{R} = \mathbf{R} = \mathbf{R}$	00
8 0	$2\mathbf{g} (\mathbf{R} = \mathbf{P}\mathbf{n})$	3ag(E/Z = 70.24)	00 61
9	$\Delta \Pi (\mathbf{K} - (\mathbf{L}) - \mathrm{styryr})$	Sall(E/Z = 78.22)	01
	() _n	Ph	
		()n	
10^{c}	2i (n = 1)	3ai	70
11 ^c	2j (n = 0)	3aj	77
	OBoc	Ph	
	\sim	\smile	
12^c	2k	3ak	88
	OBoc		
	\searrow	Ph ///	
	Ph	Ph	
13c	21	39]	80

l'able	2.	Reaction	ot	la	with	Various	Ally	lic	Carbonate	:S
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^{*a*}The reaction was performed on a 0.3 mmol scale under the conditions in Table 1, entry 11. ^{*b*}1j was used instead of 1a, and the reaction was performed on a 0.6 mmol scale. ^{*c*}The reaction was performed without Xantphos.

and 5). Likewise, a tertiary allylic carbonate 2f underwent the reaction with 1a and 1j, producing the β -prenylated ketones 3af and 3jf, respectively, in moderate yields (entries 6 and 7). Furthermore, the reaction of 1a with branched allylic carbonates derived from the products of Morita–Baylis–Hillman reaction between aldehyde and acrylate ester also afforded the linear allylation products with moderate *E*-stereoselectivity with respect to the newly formed C=C bond (entries 8 and 9).

Under the standard conditions, the reaction of 1a with a cyclic allyl carbonate derived from cyclohex-2-en-1-ol (2i) was sluggish and gave the product 3ai only in 25% yield. Upon additional screening, the reaction was found to proceed smoothly in the absence of Xantphos, affording 3ai in 70%

yield (entry 10). The ligand-free conditions proved also effective for a five-membered allyl carbonate (2j) and a sixmembered tertiary allylic carbonate (2k), affording the corresponding products 3aj and 3ak, respectively, in good yields (entries 11 and 12). Notably, the reaction of 1a with *cis*configured cyclic carbonate 2l gave rise to the product 3al as a single diastereomer (entry 13). The diastereochemistry of 3al was assigned to be *trans*, which suggested stereochemical inversion as a mechanistic feature of the present allylation.

To gain insight into the reaction mechanism of the present ring-opening allylation, several experiments were performed. First, the reaction of a cinnamyl/cyclopropyl mixed carbonate 4 under the standard conditions afforded the $\delta_{\nu}\epsilon$ -unsaturated ketone **3aa** in good yield (Scheme 3a), which was most likely

Scheme 3. Mechanistic Experiments



initiated by oxidative addition of the cinnamyl moiety followed by decarboxylation, ring-opening of the resulting cyclopropoxide to homoenolate, and C-C bond-forming reductive elimination. The reaction of 4 in the presence of 1 equiv of cyclopropanol 1c afforded a mixture of 3aa and 3ca in 31% and 51% yields, respectively (Scheme 3b). This result indicates that exchange between the cyclopropoxide ligand derived from 4 and 1c is faster than the cyclopropoxide ring-opening and reductive elimination. On the other hand, in the presence of 1 equiv of cinnamyl carbonate 2b, the reaction of 4 afforded 3aa the major product (35%) along with a small amount of 3ab (7%) (Scheme 3c). This outcome suggests that alkoxide exchange between two distinct π -allylnickel(II) species derived from 4 and 2b could operate to some extent. Note that the possibility of intermolecular outer-sphere attack of nickel(II) homoenolate onto π -allylnickel(II) species could be ruled out as the mechanism of C-C bond formation by the exclusive formation of the trans-configured 3al from the cis-configured 2l, which would instead support the inner-sphere mechanism. The low combined yield (42%) could be attributed to the accumulation of allylnickel(II) tert-butoxide, which would not have a path to regenerate Ni(0) in the absence of cyclopropanol. Exposure of 1a to the standard conditions in the absence of 2a caused only sluggish ring-opening isomerization to propiophenone (Scheme 3d).

Scheme 4 illustrates a plausible catalytic cycle of the present nickel-catalyzed ring-opening allylation reaction. Oxidative

Scheme 4. Plausible Catalytic Cycle



addition of allyl carbonate 2 to a Ni(0) species and subsequent decarboxylation would form a π -allylnickel(II) *tert*-butoxide species **A**. Exchange of the *tert*-butoxide ligand of **A** with cyclopropanol 1 would give rise to a π -allylnickel(II) cyclopropoxide species **B**, which would rearrange to a π -allylnickel(II) homoenolate **C** through β -carbon elimination. C-C bond-forming reductive elimination of **C** would furnish the allylation product 3 while regenerating the Ni(0) species.

The δ, ε -unsaturated ketones obtained by the present allylation are amenable to further transformations utilizing both the olefinic and carbonyl functionalities, as illustrated in Scheme 5. With the geminal methyl groups at the olefinic

Scheme 5. Product Transformations



terminus, **3**jf proved to be a suitable substrate for FeCl₃catalyzed intramolecular carbonyl–olefin metathesis,¹⁰ affording the cyclopentene derivative **5** in 50% yield (82% brsm) (Scheme 5a). Epoxidation of **3aa** with *m*CPBA and subsequent treatment of the product **6** with *t*-BuOK resulted in the intramolecular addition of ketone enolate to the epoxide in a 5*exo-tet* fashion to afford the cyclopentanol derivative **7** (Scheme 5b).¹¹ Interestingly, the diastereoselectivity of the latter step was controlled by the amount of *t*BuOK added. Thus, the reaction in the presence of a large excess *t*BuOK (4 equiv) gave the diastereomer with cis configuration with respect to the benzoyl and phenyl groups with the diastereomeric ratio of 4:1.¹² By contrast, the use of a catalytic amount of t-BuOK (0.2 equiv) resulted in the opposite diastereomer with virtually perfect selectivity (trans/cis > 20:1). We speculate that chelation of the oxygen atoms of the enolate and the epoxide by a potassium cation during the cyclization step is responsible for the preferential formation of the more sterically congested *cis* isomer under the former conditions. Finally, we found that the treatment of 3aa with tBuOK (30 mol %) resulted in dehvdrative and dehvdrogenative cycloaromatization to give o-terphenyl (8) albeit in a moderate yield (Scheme 5c). To our knowledge, this is an unprecedented type of cycloaromatization, and its scope and mechanism will be the subject of further investigation.

In summary, we have developed nickel-catalyzed ringopening allylation of cyclopropanols with allylic carbonates to afford $\delta_{,\varepsilon}$ -unsaturated ketones under mild and neutral conditions. The reaction displays linear selectivity for both linear and branched acyclic allylic carbonates and is also applicable to cyclic allylic carbonates. The stereochemical probe and control experiments suggest that the reaction involves π -allylnickel(II) cyclopropoxide and its homoenolate isomer as the key intermediates. Further studies on catalytic transformations of cyclopropanols via homoenolates are underway in our laboratories.¹⁴

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02072.

Experimental procedures and spectral data of all new compounds. (PDF)

Accession Codes

CCDC 2090722 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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