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Letter

# Nickel-Catalyzed Isomerization/Allylic Cyanation of Alkenyl Alcohols

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**ABSTRACT:** Herein reported is a nickel-catalyzed isomerization/allylic cyanation of alkenyl alcohols, which complements current methods for the allylic substitution reactions. The specific diphosphite ligand and methanol as the solvent are crucial for the success for this transformation. A gram-scale regioconvergent experiment and formal synthesis of quebrachamine demonstrate the high potential of this methodology.

**S** ince cyano groups find potential utility in pharmaceuticals and biologically important compounds<sup>1</sup> and can be readily converted into a wide variety of functional groups such as amines, carboxylic acid derivatives, ketones, and so on,<sup>2</sup> their introduction is of great interest for chemists. In this context, cyanation of allylic alcohol and its derivatives has attracted increasing attention.<sup>3</sup> However, these methods suffer from the following drawbacks: (1) prior conversion of the allyl alcohols to the derivatives bearing good leaving groups is usually necessary,<sup>3a-c</sup> and (2) when a free allyl alcohol is used as the starting material, Lewis<sup>3d</sup> or Brønsted<sup>3e</sup> acids are often added to activate the hydroxyl group, which limits the functional group tolerance. Consequently, the development of unique and efficient redox-neutral strategies for the cyanation of allyl alcohol is highly desirable. Recently, we reported a dual catalytic cycle that merges the Ni-catalyzed allylic cyanation and asymmetric hydrocyanation.<sup>3f</sup> However, the alkenes must be installed at the neighborhood of the alcohol and thus only limited substrate scope is amenable. Therefore, we envisioned that it will be an interesting complement to our previous work if we could install the starting alkene at a different position of the starting alcohol to achieve the allylic cyanation via the alkene isomerization strategy, which has attracted considerable attention in the last decades.

Remote functionalization mediated by alkene isomerization is a powerful strategy for the construction of valuable molecules from readily available materials.<sup>4–9</sup> In this content, alkenyl alcohols are considered as versatile substrates for these transformations. The isomerization of alkenyl alcohols to ketones through olefin migration has been catalyzed by using various metals including Pd<sup>6</sup>, Rh<sup>7</sup>, Ru<sup>8</sup>, and Fe<sup>9</sup>. This process is usually triggered by the C==C bond insertion into metalhydride or metal-arylate species, followed by the iterative  $\beta$ -H eliminations and migratory insertions to change the site of metal along the chain and end up with the  $\beta$ -hydride elimination on the hydroxyl group to afford ketone (Scheme 1a).<sup>6,7b,8</sup>

Inspired by the isomerization of alkenyl alcohols to ketones, we wonder if the key intermediate B (Scheme 1b) could undergo other transformations, such as allylic substitution reactions (Scheme 1b, B to D) which have gained extra attention for C-C and C-X (X = N, O, S, etc.) bond formation,<sup>10</sup> instead of continuing to isomerize to ketone (Scheme 1b, B to C). Once achieved, this methodology can provide a novel synthetic pathway for allylic substitution reactions. Although it was feasible theoretically, some challenges must be addressed: (1) due to the strong thermodynamic driving force to furnish ketone when the migration of a double bond is initiated, trapping the allyl alcohol intermediate is challenging, and (2) combination of multistep by using a single catalytic system would offer the advantage of operational simplicity, leading to a higher step economy, yet it would pose extra difficulty to identify a catalyst that would exhibit sufficient reactivity and accurate selectivity in each of the key steps.

Based on the above assumptions and our previous work,<sup>36,11</sup> we envisaged that the system of acetone cyanohydrin and nickel allows the possibility of achieving this conversion because we have achieved migratory hydrocyanation and allylic cyanation in this system, respectively. Herein, we expect to

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Scheme 1. Catalytic Remote Functionalization of Alkenyl Alcohols

a) Previous work: alkenyl alcohol isomerization reactions



b) Design: switched chemoselectivity via allylic substitution reactions



c) This work: Catalytic isomerization/allylic cyanation of alkenyl alcohols



report the first Ni-catalyzed isomerization/allylic cyanation of alkenyl alcohols (Scheme 1c).

With the hypothesis in mind, we began our study by testing the reactivity of the model reaction undertaking different ligands in the presence of  $Ni(cod)_2$  and acetone cyanohydrin (Table 1). When commercially available ligands such as Dppe, Dppf, xantphos, DPEphos, BINAP, or  $P(OPh)_3$  were used, no desired product 2a was observed, and ketone 3a was detected in 26-47% yield (entries 1-6). Hypophosphite ligand L1 was ineffective for the conversion of alkenyl alcohol 1a to 2a (entry 7). Then, bidentate phosphite L2 and L3 were tested, and we were delighted to find the formation of 2a albeit with only 2 and 4% yield, respectively (entries 8 and 9). Solvent screening indicated that the polarity of the solvents plays a key role in the chemoselectivity. Non-polar solvents such as n-hexane and toluene led to large amounts of ketone 3a, while almost no desired product 2a was observed (entries 10 and 11). In addition to acetonitrile, polar solvents are beneficial to the formation of 2a (entries 12–16). It is worth mentioning that the desired product 2a will further undergo a hydrocyanation reaction to form the corresponding dinitrile compound when using water as a solvent (entry 17). When switching water to methanol as solvent, the yield of 2a was encouragingly increased to 69% (entry 18). The solvent effect phenomena might be attributable to methanol (a hydrogen-bonding solvent) accelerating the formation of the key intermediate  $\pi$ -allylmetal complex by lowering the activation barrier.<sup>12</sup> In order to improve the yield of 2a, we tried to adjust other reaction conditions. The yield was further improved to 80% while decreasing the catalyst loading to 2 mol % (entry 19). When shortening the reaction time to 3 h, 2a can be obtained with the same GC yield and 74% isolated yield (entry 20). Moreover, air stable catalyst Ni(4-tBu stb)313 was tested and proved to be efficient in this transformation (entry 21), while the catalytic system of NiCl<sub>2</sub>·6H<sub>2</sub>O and Zn was found inactive (entry 22). Additionally, as this isomerization/allylic cyanation features an enantioselective potential, an asymmetric version of Table 1. Reaction Optimization with Substrate 1a<sup>a</sup>



2	Dppf	1,4-dioxane/H <sub>2</sub> O <sup>g</sup>	ND	47
3	Xantphos	1,4-dioxane/H <sub>2</sub> O <sup>g</sup>	ND	28
4	DPEphos	1,4-dioxane/H <sub>2</sub> O <sup>g</sup>	ND	31
5	BINAP	1,4-dioxane/H <sub>2</sub> O <sup>g</sup>	ND	36
6 <sup>c</sup>	$P(OPh)_3$	1,4-dioxane/H <sub>2</sub> O <sup>g</sup>	ND	26
7	L1	1,4-dioxane/H <sub>2</sub> O <sup>g</sup>	ND	33
8	L2	1,4-dioxane/H <sub>2</sub> O <sup>g</sup>	2	28
9	L3	1,4-dioxane/H <sub>2</sub> O <sup>g</sup>	4	13
10	L3	<i>n</i> -hexane	ND	85
11	L3	toluene	5	62
12	L3	CH <sub>3</sub> CN	ND	27
13	L3	THF	2	24
14	L3	1,4-dioxane	2	24
15	L3	DMA	11	24
16	L3	DMF	24	20
17	L3	H <sub>2</sub> O	ND	9
18	L3	MeOH	69	trace
19 <sup>d</sup>	L3	MeOH	80	trace
20 <sup>e</sup>	L3	MeOH	$80(74)^{f}$	trace
21 <sup><i>h</i></sup>	L3	MeOH	72	trace
22 <sup>i</sup>	L3	MeOH	ND	ND

<sup>*a*</sup>The reactions were carried out at 80 °C for 12 h with 1a (0.1 mmol), Me<sub>2</sub>C(OH)CN (0.11 mmol), and solvent (0.3 mL) in the presence of Ni(cod)<sub>2</sub> (5 mol %) and ligand (5 mol %) under a N<sub>2</sub> atmosphere, ND = not detected. <sup>*b*</sup>The yields were determined by GC analysis using *n*-dodecane as the internal standard. <sup>*c*</sup>Ligand (10 mol %). <sup>*d*</sup>Ni(cod)<sub>2</sub> (2 mol %) and ligand (2 mol %). <sup>*e*</sup>Reaction time (3 h). <sup>*f*</sup>Isolated yield. <sup>*g*</sup>1,4-Dioxane/H<sub>2</sub>O (50/1, v/v). <sup>*h*</sup>Ni(<sup>4+tBu</sup>stb)<sub>3</sub> (2 mol %) instead of Ni(cod)<sub>2</sub>. <sup>*i*</sup>NiCl<sub>2</sub>·6H<sub>2</sub>O (2 mol %) and Zn (20 mol %) instead of Ni(cod)<sub>2</sub>.

this reaction was also carried out, yet no excellent enantioselectivity was presented (for more details, see Table S1).

We next investigated the scope of substrates with the optimized conditions (Table 1, entry 20). Whether the substituent on the phenyl group is an electron-withdrawing group or an electron-donating group, the corresponding allylic nitriles can be obtained in moderate to good yields (Scheme 2a, 2b-2j, 43-93%). Surprisingly, substrates bearing unprotected -OH or  $-NH_2$  were tolerated (2e and 2h). When  $R^1$  was a heterocyclic group such as thiophene, the product 2k was afforded in 52% yield. When  $R^1$  was naphthyl, the desired product 2l was obtained in 54% yield. Afterward, we focused on the impact of chain length on the reaction (Scheme 2b). Comparing the results of 2m-2s and 2a, we found that the longer the methylene intervals between the alkene and -OH, the lower the yield of the hydrocyanated product. Although the overall trend is declining, the yield can still reach 51% when

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products. <sup>b</sup>Reactions were conducted on a 0.1 mmol scale. <sup>c</sup>Reaction conducted at 50 °C for 12 h.

olefins migrate across eight carbons. Moreover, the *trans*internal olefin can provide 2t in 83% yield, and the *cis*-internal olefin 1u can also generate 2u in 67% yield (Scheme 2c). In order to figure out whether R<sup>1</sup> must be an aryl group, we designed 1v and 1w to give the corresponding 2v and 2w in 61 and 40% yield, respectively, indicating that conjugated non-aryl substituted substrates are also applicable in this catalytic system (Scheme 2d). Unexpectedly, primary alcohol 1x was tolerated in this transformation and tended to bring a branched allyl substituted product that then isomerizes to give 2x in 45% yield (Scheme 2e).

Furthermore, to illustrate the synthetic utility of this migration/allylic substitution reaction, a gram-scale regioconvergent reaction was conducted with 1:1:1:1 of regioisomers of alkenyl alcohols, furnishing 2a in 90% yield (Scheme 3a). The





<sup>a</sup>The reaction was carried out at 80 °C for 3 h with a mixture of **1a** (2.16 mmol, 350 mg), **1t** (2.16 mmol, 350 mg), **1a-1** (2.16 mmol, 350 mg), **1a-2** (2.16 mmol, 350 mg), Me<sub>2</sub>C(OH)CN (9.5 mmol, 808 mg), and MeOH (26 mL) in the presence of Ni(cod)<sub>2</sub> (2 mol %, 47.5 mg) and **L3** (2 mol %, 189.8 mg) under a N<sub>2</sub> atmosphere. <sup>b</sup>The reaction was carried out at 100 °C for 24 h with **1y** (0.1 mmol, 34.1 mg), Me<sub>2</sub>C(OH)CN (0.11 mmol, 9.4 mg), and MeOH (0.3 mL) in the presence of Ni(cod)<sub>2</sub> (5 mol %, 1.3 mg) and **L3** (5 mol %, 5.5 mg) under a N<sub>2</sub> atmosphere.

reported route for the total synthesis of the natural product quebrachamine<sup>14</sup> required five steps from the aldehyde to the key intermediate (2y). However, herein, our method streamlined the route to two steps from the same aldehyde via the Grignard reaction and isomerization/allylic cyanation reaction (Scheme 3b).

To gain more insight about this transformation, the reaction with 1m as substrate was monitored by <sup>1</sup>H NMR analysis by using mesitylene as an internal standard (see Table S2 and Figure S1). Allyl alcohol 1m-m (see Figure S1) was indeed the intermediate in this transformation and was nearly fully consumed within 30 min. In addition, several deuterium labeling experiments were carried out for further study (Scheme 4). The protected substrate 1a-P was submitted with fully deuterium-labeled acetone cyanohydrin under the standard reaction conditions and the corresponding product D-2a was gathered with the deuterium incorporated at C2 (0.01D), C3 (0.79D), C4 (1.65D), and C5 (2.48D) in 68% yield, proving an iterative  $\beta$ -H elimination/migratory insertion mechanism. D-2u was gathered with the deuterium incorporated at C2 (0.06D), C3 (0.68D), C4 (1.64D), C5-C6 (3.33D), and C7 (2.52D) in 49% yield using 1u-P as substrate.

### Scheme 4. Deuterium-Labeling Experiments



This result indicated that the isomerization of olefins is bidirectional and reflected the poor site selectivity for  $[H-NiL3^{II}-CN]$  migratory insertion.

Based on reaction monitoring profiles and deuterium labeling experiments, we proposed the mechanism of this reaction (Scheme 5). First, precatalyst Ni(cod)<sub>2</sub> undergoes ligand exchange with L3 to form active species I. Then, [H– NiL3<sup>II</sup>–CN] species II was generated through oxidative addition of acetone cyanohydrin with active species I. Species II would undergo hydronickelation of 1 to trigger a reversible sequence of  $\beta$ -H elimination/migratory reinsertion steps to access a series of alkyl–Ni(II)–CN intermediates (III, V, VI,

Scheme 5. Proposed Catalytic Cycle



etc.) along the alkyl chain. The subsequent  $\beta$ -H elimination of VI delivers the allyl alcohol VII. Subsequently, species I undergoes oxidative addition with the allyl alcohol VII and then would react with acetone cyanohydrin to generate species IX. Finally, reductive elimination of IX furnishes allylic nitrile 2 and regenerates Ni<sup>0</sup> complex I.

In summary, we reported the first nickel-catalyzed tandem isomerization/allylic cyanation reaction of alkenyl alcohols. This methodology provides a novel synthetic pathway for allylic substitution reaction. The catalytic system tolerated a variety of functional groups and proved to be efficient when olefin could migrate up to eight carbons. A gram-scale synthesis and a synthetic application demonstrated the potential of this transformation. Further mechanistic studies support a novel sequential alkene isomerization (chainwalking)/allylic cyanation pathway.

## ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02143.

Experimental procedures, characterization data, and copies of NMR spectra for all new products (PDF)

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#### Notes

The authors declare no competing financial interest.

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