

Letter

CN

26 examples

up to 99% yield

Supporting Information

Cat. [Ni]

. Toluene. 120 °C. 12 h

Lewis acid-free

Synthesis of Tertiary Benzylic Nitriles via Nickel-Catalyzed Markovnikov Hydrocyanation of α -Substituted Styrenes

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+ Me₂C(OH)CN

quaternary carbon center • high FG tolerance

Markovnikov selectivity

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ABSTRACT: The Markovnikov hydrocyanation of α -substituted styrenes enables the synthesis of tertiary benzylic nitriles under nickel catalysis. The Lewis-acid-free transformation features an unprecedented functional groups tolerance, including the -OH and $-NH_2$ groups. A broad range of tertiary benzylic nitriles were obtained in good to excellent yields. In addition, an asymmetric version of this reaction was preliminarily investigated.

N itriles are versatile building blocks in material science, organic synthesis, and the pharmaceutical industry, and therefore, synthetic methods of nitriles have been extensively investigated.¹ In nitrile chemistry, tertiary benzylic nitriles constitute not only very important synthetic intermediates² but also unique and specific scaffolds of biologically active compounds, such as Verapamil and PDE 4 inhibitor (Figure 1).³ In light of their interesting biological activities, a number of



Figure 1. Tertiary benzylic nitriles in pharmaceuticals.

synthetic methods have been developed for the construction of tertiary benzylic nitriles. Traditionally, this class of compounds has been prepared via double alkylations of benzylic nitriles,⁴ cyanation of tertiary benzylic alcohols or halides,⁵ or oxidative benzylic cyanation of aromatic hydrocarbons.⁶ Furthermore, S_NAr of aryl fluorides with secondary nitriles,⁷ Pd-catalyzed direct α -arylation of secondary nitriles with aryl halides,⁸ and Brønsted-acid-promoted hydrocyanation of arylalkenes⁹ have become powerful alternatives.

Catalytic alkene hydrocyanation represents one of the most conceptually straightforward processes for alkyl nitrile preparation.¹⁰ During the past decades, catalytic hydrocyanation has received considerable interest, with substantial progress. Various catalytic systems allowed for the conversion of alkene substrates like vinylarenes,¹¹ strained alkenes,¹² 1,3-dienes,¹³ allenes,¹⁴ and even unactivated aliphatic alkenes¹⁵ to nitrile products. A simple retrosynthetic analysis suggests that a Markovnikov-selective hydrocyanation of α -substituted styrenes would enable access to

tertiary benzylic nitriles. Although few contributions feature transition-metal-catalyzed hydrocyanation of α -substituted styrenes, the transformations are exclusively anti-Markovnikov selective. Morandi reported the Ni-catalyzed reversible transfer hydrocyanation of a broad range of alkenes.¹⁶ In particular, the hydrocyanation of α -methylstyrene led to the exclusive formation of the anti-Markovnikov product (Scheme 1a). A similar result was obtained by Studer and Liu using a Pd catalyst and Ni catalyst, respectively (Scheme 1b,c).17,18 Notably, the success of both transformations depends on the Lewis acid employed, which inherently limits the functional group tolerance. Conversely, Oestreich recently reported a transition-metal-free Markovnikov-selective irreversible transfer hydrocyanation also with the aid of boron Lewis acids (Scheme 1d).¹⁹ The use of a Lewis acid therefore appears to be critical under the reported conditions to either generate a Wheland intermediate or to promote reactivity and facilitate the metalmediated oxidative addition and reductive elimination events. On the other hand, the use of a Lewis acid also usually enhances the metal-mediated anti-Markovnikov regioselectivity.^{10c,d}

Despite these elegant contributions, the necessity to avoid the use of a Lewis acid is conspicuous to enhance the functional group tolerance, as no example with free -OH or $-NH_2$ groups has been so far reported. From an environment perspective, Lewis acid solid wastes would also be significantly reduced. Vogt et al. concluded that the hydrocyanation of styrene in the presence of Lewis acid and formation of the linear nitrile product is both thermodynamically and kinetically favored.¹¹¹ Therefore, to achieve the Markovnikov hydrocyanation of styrene derivatives, the use of Lewis acid should be avoided. Due to these accounts, we envisaged that the use of an appropriate

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Scheme 1. Catalytic Hydrocyanation of α -Substituted Styrenes

Previous works

 a) Ni-catalyzed anti-Markovnikov transfer hydrocyanation of α-methylstyrene (Morandi *et al.*)

b) Pd-catalyzed anti-Markovnikov transfer hydrocyanation of α-methylstyrene (Studer *et al.*)



 c) Ni-catalyzed anti-Markovnikov hydrocyanation of α-methylstyrene (Liu et al.)

$$Me \xrightarrow{Ph} + Zn(CN)_2 \xrightarrow{5 \text{ mol\% NiCl}_2, 6 \text{ mol\% dppf}}_{1.0 \text{ equiv. } Zn, 0.5 \text{ equiv. } Znl_2} \xrightarrow{CN}_{Me} \xrightarrow{Ph}_{75\% \text{ yield}}$$

d) Boron Lewis acid-catalyzed Markovnikov transfer hydrocyanation of α-substituted styrenes (Oestreich *et al.*)



This work

e) Lewis acid-free Ni-catalyzed Markovnikov hydrocyanation of α -substituted styrenes



ligand under Ni catalysis would be sufficient to free the transformation from any Lewis acid. Therefore, we report herein a Ni-catalyzed Markovnikov-selective hydrocyanation of α -substituted styrenes that does not require any Lewis acid to proceed (Scheme 1e).

To initiate our investigation, α -methylstyrene 1a was chosen as a model substrate with acetone cyanohydrin 2 as the HCN surrogate under nickel catalysis with a variety of phosphorus ligands (Table 1). Ligands L1–L3 and DIOP, which were previously proven to be effective in the asymmetric hydrocyanation reactions, ^{11cg,12a,13a,b} were examined. Very low yields of the desired product 3a was obtained with ligands L2, L3, and (*R*,*R*)-DIOP (Table 1, entries 1–4). Further investigations showed that commercially available phosphorus ligands (e.g., MonoPhos, Xantphos, and DPEphos) exhibited no reactivity in the formation of the desired product (Table 1, entries 5–7). It is worth mentioning that the DPEphos and Xantphos ligands

Table 1. Optimization of Reaction Conditions^a



3	L3	toluene	7
4	(R,R)-DIOP	toluene	5
5	(S)-MonoPhos	toluene	0
6	Xantphos	toluene	0
7	DPEphos	toluene	0
8	L4	toluene	10
9	L5	toluene	67
10	L6	toluene	80
11	L7	toluene	86
12	L8	toluene	84
13	L9	toluene	92(84) ^c
14	L10	toluene	10
15	L9'	toluene	0
16	L9	1,4-dioxane	44
17	L9	acetone	18
18	L9	DCE	0
19	L9	THF	5
20 ^d	L9	toluene	0
21 ^e	L9	toluene	0

^{*a*}Reaction conditions: **1a** (0.1 mmol), **2** (0.3 mmol), Ni(cod)₂ (5 mol %), ligand (5 mol %), solvent (0.3 mL), 120 °C, 12 h. ^{*b*}Determined by GC analysis using *n*-undecane as the internal standard. ^{*c*}Isolated yield. ^{*d*}NiCl₂. ^{*e*}NiBr₂·DME.

proved to be efficient in the metal-catalyzed transfer hydrocyanation reactions.^{16,17} Binaphthol-based diphosphite ligands L4–L9, which were previously proven to be effective in the asymmetric hydrocyanation of styrenes,²⁰ were then investigated (Table 1, entries 8–14). With a H substituent, some reactivity was observed (Table 1, entry 8). To our delight, when

phenyl rings were present instead, a dramatic increase of the yield from 10 to 67% was observed (Table 1, entry 9). This phenomena might be attributable to the increased bite angle which promotes reductive elimination (rate-determining step) of the product when a phenyl ring was present instead of H.¹ Consequently, we investigated the effects of substituents on the arene rings. The electron-withdrawing para-trifluoromethyl substituent in ligand L6 further improved the yield in the desired product to 80% (Table 1, entry 10). Both the para-tertbutyl-substituted ligand L7 and para-methoxy-substituted ligand L8 led to very good yield of the desired product (Table 1, entries 11 and 12). When the arene rings were substituted at both of the meta positions by methoxy groups (L9), an excellent 92% yield was obtained (Table 1, entry 13). Although tert-butyl groups were present instead, a dramatic decrease of the yield to 10% was observed, highlighting that the steric hindrance is most likely playing a preponderant role rather than electronics (Table 1, entry 14). In contrast, with ligand L9', with mismatched chiralities, no conversion was observed (Table 1, entry 15). We then investigated different solvents, but none appeared to be as efficient as toluene under the reaction conditions (Table 1, entries 16–19). The use of other nickel(II) precatalysts such as NiCl₂ and NiBr₂·DME simply led to no product formation (Table 1, entries 20 and 21). As a result, the optimal reaction conditions were established as $Ni(cod)_2/L9/toluene/120$ °C.

Under these optimized conditions, we explored the substrate scope of this nickel-catalyzed process (Scheme 2). Substrates bearing electron-neutral and electron-rich aryl substituents underwent effcient Markovnikov hydrocyanation, providing the corresponding desired products in good to excellent yields (3a-3j). However, substrates containing electron-withdrawing aryl substituents tended to provide hydrocyanated products in lower yields (31-3n). Substrates containing several functional groups, including halogen (3h), ester (3m), ethers (3c, 3i, 3g), thioether (3d), and sulfone (3n) were also suitable substrates for the transformation. Gratifyingly, the hydroxy substituent was extremely well tolerated (3i). The free amine was only moderately tolerated (3k) but still highlights the remarkable functional group tolerance of our protocol. In addition, substrates with heterocyclic substituents (such as thiophenyl and indolyl groups) proved to be efficient coupling partners to generate the corresponding products in excellent yields (3q and 3r). Moreover, the substrate employing the structurally complex estrone was also successfully converted into the desired product 3s in good yield. Besides the methyl substituted at the R position, a variety of alkyl-substituted styrenes were all suitable for the reaction, and the corresponding benzylic nitrile products (3t-3w) were obtained in 55–65% yields. Notably, -CN and $-CO_2Me$ functional groups were well tolerated (3v and 3w). Finally, the bicyclic substrate 1-methylene-1,2,3,4-tetrahydronaphthalene underwent efficient hydrocyanation, yielding the desired product in 70% yield (3x). Product 3y could be prepared in a moderate but synthetically useful yield with a 5/2diastereomeric ratio. Interestingly, vinyl-substituted alkene 1z was well tolerated and led to exclusive formation of the corresponding 1,2-adduct 3z in excellent yield. Unfortunately, no conversion was observed when the 1,1-dialkyl-substituted ethylene was employeded. These results indicated that the presence of either an aromatic ring or an unsaturated group is critical as a driving force for the reaction.

To demonstrate the synthetic utility of our transformation, we conducted a scale-up experiment and product transformations (Scheme 3). Gram-scale reaction of **10** was achieved, affording

Scheme 2. Substrate Scope^a



^{*a*}Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), Ni(cod)₂ (5 mol %), **L9** (5 mol %), toluene (0.5 mL), 120 °C, 12 h. Yields of isolated products after flash column chromatography.

Scheme 3. Gram-Scale Reaction and Further Product Transformations

a) Gram-scale experiment



the desired tertiary benzylic nitrile product **30** in a nearly quantitative yield (Scheme 3a). To prove the usefulness of the

nitrile products, the tetrahydro- β -carboline **3r**-**B** was smoothly obtained by applying the reduction of **3r** and the Pictet– Spengler cyclization sequence. Furthermore, the δ -disubstituted ε -caprolactam **3w**-**B** can be efficiently synthesized via selective hydrogenation of **3w** and an intramolecular condensation reaction procedure (Scheme 3b).

When measuring the selectivity outcome of the reaction, we were surprised to observe that our transformation features an enantioselective potential (eq 1). For example, when analyzing



the tertiary benzylic nitrile **3t**, a significant 33% ee was observed. This result disclosed that a more appropriate and efficient chiral ligand would therefore enhance the observed asymmetric induction in the Ni-catalyzed Markovnikov hydrocyanation of α -substituted styrenes. It should be noted that although many elegant methods for the synthesis of cyanide-bearing quaternary carbon stereogenic centers have been reported,²¹ there is, to the best of our knowledge, no precedent literature concerning an enantioselective hydrocyanation reaction to construct this chiral compound.

In summary, we have developed the first Lewis-acid-free Markovnikov hydrocyanation of α -substituted styrenes under Ni catalysis. The transformation enables the access to a broad range of tertiary benzylic nitriles in good to excellent yields and features an unprecedented functional groups tolerance, including the -OH and $-NH_2$ groups. The synthetic utility of the transformation was demonstrated in the preparation of ε -caprolactam and tetrahydro- β -carboline. The preliminary study of the asymmetric version of this reaction could offer the enantioselective potential of our transformation. Further investigations on the development of nickel-catalyzed highly enantioselective Markovnikov hydrocyanation of α -substituted styrenes are in progress.

ASSOCIATED CONTENT

Supporting Information

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Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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