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Ligand-Controlled Regiodivergent Nickel-Catalyzed Hydrocyanation of Silyl-Substituted 1,3-Diynes

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cyano-containing 1,3-envnes has been demonstrated with several downstream transformations.

1,3-Enynes are prominent structural motifs that are often found in many bioactive molecules and organic materials.¹ The 1,3-envne scaffold is also a versatile building block in synthetic organic chemistry.² Of note, 1,3-enynes with electron-withdrawing groups (i.e., esters, ketones) are particularly attractive as they bear the potential to be employed in the construction of thiophenes,³ isoxazoles,⁴ furans,⁵ pyrrolines,⁶ allenes,⁷ 1,3dienes,⁸ and many others. Among these active 1,3-enynes, the use of cyano-substituted ones was rarely reported, although particularly useful in annulation reactions. Indeed, cyanosubstituted 1,3-envnes enable the preparation of pharmaceutically interesting cyano-containing heterocycles.⁹ Obviously, the lack of efficient synthetic methods for cyano-containing 1,3envnes restricts their potential applications.¹⁰ It is therefore of high interest to develop efficient, highly regio- and stereoselective synthesis of cyano-containing 1,3-enynes.

bring divergent alkyne insertion modes, which in turn lead to

different regioselectivities. Moreover, the synthetic value of the

Recently, the transition-metal-catalyzed functionalization of 1,3-diynes has attracted increasing attention.¹¹ In the view of atom-efficient organic synthesis, the hydrofunctionalization of 1,3-diynes paved a new avenue for accessing functionalized 1,3enynes. Based on our continuous interest in catalytic hydrocyanation of unsymmetrical internal alkynes,¹² we envisioned that the hydrocyanation of 1-aryl-4-silyl-1,3-diynes (silyl activated 1,3-diynes) might be an efficient approach for the synthesis of cyano-substituted conjugated envnes because 1-aryl-4-silyl-1,3-diynes were readily available via Glaser coupling. The corresponding products could be easily derived through desilylation. In sharp contrast to the hydrocyanation of alkynes,¹³ the hydrocyanation of 1,3-diynes still remains elusive in the literature due to the intractable challenges in regio- and stereoselectivity control for unsymmetrical internal alkynes. Until now, only a limited number of special unsymmetrical internal alkynes have been hydrocyanated with high regio- and stereoselectivity.¹⁴ Obviously, the hydrofunctionalization of unsymmetrical 1-aryl-4-silyl-1,3diynes would pose extra difficulties in regard to monoalkynes: (a) Regioselectivity between two alkyne motifs (Scheme 1a, A);^{11a,b,e} (b) regioselectivity in each migratory insertion (Scheme 1a, B),^{11d} (c) selectivity between mono- and dihydrofunctionalization (Scheme 1a, C),^{11c} and (d) stereo-selectivity in each migratory insertion (Scheme 1a, D).

Despite the lack of examples involving the hydrocyanation of 1-aryl-4-silyl-1,3-diynes, significant advancements in the hydrofunctionalization of 1-aryl-4-silyl-1,3-diynes have been made over the past few decades. These hydrofunctionalizations usually occurred at one alkyne of the unsymmetrical 1,3-diynes with high regioselectivity (Scheme 1b). For example, hydro-amidation,^{11a} hydroesterification,^{11b} hydroboration,^{11f} and hydrosilylation,^{11e} of 1-aryl-4-silyl-1,3-diynes preferentially took place at the 1,2-C \equiv C (Scheme 1b, left). Furthermore, the Ge group reported a regiodivergent hydroboration of 1aryl-4-silyl-1,3-diynes in which the 1,2-C≡C bond inserted into either a cobalt-hydride or cobalt-boryl intermediate (Scheme 1b, left).^{11d} To the best of our knowledge, the only example concerning the selective hydrofunctionalization of the 3,4-C≡C bond of 1-aryl-4-silyl-1,3-diynes was reported by Krische and co-workers wherein α -hydroxy esters were constructed, and the reaction occurred exclusively at the silyl-substituted C≡C bond (Scheme 1b, right).^{11g} However, the regiodivergent hydrofunctionalization of aryl-/silyl-substituted 1,3-diynes is an alluring but rather demanding task, which may offer new tools for the construction of more

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complex molecules with high skeletal diversities.¹⁵ We herein describe a complementary strategy for the hydrofunctionalization of 1,3-diynes by showing that an appropriate ligand could help to control the regiodivergent hydrocyanation of 1-aryl-4-silyl-1,3-diynes (Scheme 1c).

With the aforementioned in mind, we commenced our study by investigating 1-phenyl-4-trimethylsilyl-butadiyne (1a), with acetone cyanohydrin 2 to identify reliable conditions for 1,3divne hydrocyanation. We first performed the reaction using $Ni(cod)_2$ and monophosphine ligands in toluene at 100 °C. The application of L1 proved to be futile, with only 19% conversion of 1a (Table 1, entry 2). L2 could also not afford the hydrocyanation product, albeit with 100% conversion of 1a (Table 1, entry 3). In the cases of L1 and L2, fluorescent products were formed which might be attributed to the oligomerization/polymerization of 1a.^{11a} Next, various bisphosphine ligands were evaluated (Table 1, entries 4-6). After extensive screening, we found that 1a could be fully converted to the monohydrocyanation product 3a using L5 (Table 1, entry 6). In order to further improve the reaction, we evaluated the influence of critical reaction parameters. We found that 1a could react with 2 to afford the monohydrocyanation product 3a in 93% GC yield with excellent selectivity in the presence of L5 at 50 °C (Table 1, entry 7). A slight tuning in the ligand environment would decrease the reaction efficiency (Table 1, entries 8-10). We also examined the effects of the phosphite ligands on the reaction efficiency. For monodentate phosphite ligand L9, 35% of 1a was consumed without any formation of the hydrocyanation product. Although using bisphosphite ligands led to unsatisfactory 3a/ 4a (Table 1, entries 12 and 13), an obvious enhancement in the selectivity toward 4a was observed. These promising results

Table 1. Reaction Optimization with Substrate $1a^{a,b}$



^{*a*}Reaction conditions (entries: 1–13): **1a** (0.1 mmol), Ni(cod)₂ (7.5 mol %), ligand (7.5 mol %), **2** (0.3 mmol), toluene (0.5 mL), 100 °C, 18 h. ^{*b*}Reaction conditions (entries: 14–16): **1a** (0.1 mmol), Ni(cod)₂ (12.5 mol %), ligand (25 mol %), **2** (0.3 mmol), toluene (0.5 mL), 100 °C, 14 h. ^{*c*}Conversion of **1a** was determined by GC analysis using *n*-dodecane as the internal standard. ^{*d*}The ratio of **3a** to **4a** was determined by GC and GC-MS analysis (for more details, see Supporting Information). ^{*c*}Yield refers to the major product and is determined by GC analysis using *n*-dodecane as the internal standard. ^{*f*}Isolated yield. ^{*g*}The reaction was carried out at 50 °C. ^{*h*}Ligand (15 mol %). N.D. = no detected. **L1** = PPh₃, **L2** = PCy₃, **L3** = Xantphos, **L4** = dppp, **L9** = P(OPh)₃.

encouraged us to divert to the regioselectivity. Next, we turned our attention to the phosphine—phosphite ligand. To our delight, **4a** could be obtained as a major product in 85:15 selectivity with **L12** (Table 1, entry 14). Further ligand screening revealed that ($S_{axr}S_rS$)-Bobphos **L14**¹⁶ could afford **4a** with good yield and excellent selectivity at 100 °C (Table 1, entry 16). It is noteworthy that synthetic methods for constructing enynyl silanes like **4a** were continuously refined.¹⁷ Eventually, a regiodivergent condition on nickel-catalyzed hydrocyanation of 1-aryl-4-silyl-1,3-diynes was identified.

With the optimized conditions for efficient switch between two alkyne sites in hand, we set out to explore the generalities of substrates of this divergent transformation. As shown in Scheme 2, aryl-substituted 1,3-diynes, including electron-rich, pubs.acs.org/OrgLett

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Scheme 2. Substrate Scope^a



Ar=

R=4-Ph, **3f**^b: 85% vield, 94:6 r.r.; **4f**^c: 53% vield, 6:94 r.r. R=4-F, **3g**: 82% yield, 95:5 r.r.; **4g**^c: 56% yield, 7:93 r.r. R=4-Cl. **3h**: 61% vield. 94:6 r.r.: **4h**^c: trace

R=H, **3a**: 91% yield, 94:6 r.r.; **4a**: 61% yield, 3:97 r.r. R=4-NMe₂, **3b**: trace; **4b**: 64%(57%)^f yield, 2:98(4:96)^f r.r. R=4-CF₃, **3j**: 73% yield, 91:9 r.r.; **4j**^c: 63% yield, 7:93 r.r. R=4-OMe, 3c: 95% yield, 98:2 r.r.; 4c: 65% yield, 5:95 r.r. R=4-SMe, 3d: 89% yield, 95:5 r.r.; 4d: 67% yield, 5:95 r.r. R=4-Me, 3e: 86% yield, 94:6 r.r.; 4e: 65% yield, 4:96 r.r.

R=4-Br, **3i**: 72% yield, 95:5 r.r.; **4i**^c: 57% yield, 8:92 r.r. R=4-CH₃(CO), **3k**: 89% yield, 97:3 r.r.; **4k**^{c,d,e}: 63% yield, 14:86 r.r. R=4-CO₂Me, **3I**^{d,g}: 79% yield, 89:11 r.r.; **4I**^{c,d,e}: 50% yield, 30:70 r.r. R=4-Cl, 3-CF₃, **3m**: 75% yield, 95:5 r.r.; **4m**^c: 49% yield, 7:93 r.r.



mmol scale. Unless with footnote, r.r. = the ratios of 3 to 4, and it was determined by GC and GC-MS analysis. Yield refers to the isolated major product. ^bNi(cod), (10 mol %), L5 (10 mol %), 24 h. ^cNi(cod), (15 mol %), L14 (30 mol %). ^dThe ratios of 3 to 4 were determined by NMR analysis. "The ratio of total monohydrocyanation products to 4 was determined by NMR analysis. "Ni(cod)₂ (15 mol %) and L12 (30 mol %). ^g70 °C.

-neutral, and -deficient functional groups, were well tolerated under condition A (3a-3m). Compared with 3, the yield and selectivity of 4 were slightly affected by the substituents (4a-4m). Electron-rich substrates could be smoothly converted to the corresponding product. For electron-deficient substrates, slight fine-tuning of the condition B was required to enhance the reactivity and selectivity. Moreover, using an electronwithdrawing group such as a carbonyl or ester group, the corresponding product 4 was obtained with poor selectivity because at least three monohydrocyanation products were generated (4k and 4l). The vinyl (1n) and internal alkynyl (10) groups, which would otherwise react under Ni-catalyzed hydrocyanations,^{13,18} remained untouched under both condition A and B. The naphthyl-substituted 1,3-diyne was also

tolerated (1p). 1,3-Enynes bearing oxygen- (1q and 1r), nitrogen- (1s-1u), and sulfur-containing (1x) heteroaryl substituents also produced the corresponding products in high yield and selectivity. It is worth mentioning that electrondeficient pyridyl-substituted 1,3-diyne 1v was exclusively tolerated under condition A. Due to the strong electrondonating and electron-withdrawing effects of the substrate, the products 3b and 4h were indicated as traces amounts. To further demonstrate the synthetic applications of this reaction, the estrone-derived diyne (1y) was subjected to our protocol, leading to 3y and 4y in 80% and 51% yield, respectively. Instead of a trimethylsilyl group, a dimethylphenylsilyl group was also well tolerated under both conditions. When alkyl- or TMS-substituted 1,3-diynes were employed, almost no

reaction was observed. This phenomenon might be attributable to the lack of $p-\pi$ hyperconjugative effect. Remarkably, **1b**, **1s**, and **1u** could all be converted to the corresponding product **4** with good yield and excellent selectivity when **L12** was used instead of **L14**.

To highlight the utility of this Ni-catalyzed hydrocyanation reaction, we conducted a gram-scale reaction of 1c and acetone cyanohydrin 2, and this reaction yielded enynyl nitrile 3c in 85% isolated yield with excellent selectivity (Scheme 3). We





^a(i) DIBAL-H, toluene, −78°C, 3 h; (ii) cyclohexanone, pyrrolidine, InCl₃, 4 Å molecular sieves, DCE, 80 °C, 20 h; (iii) NH₂NH₂·H₂O, K₂CO₃, DMA, 40 °C, 12 h; (iv) acetylacetone, DBU, DMF, 100 °C, 14 h; (v) 2-acetamidomalonate, DBU, DMF, r.t., 0.5 h.

also demonstrated that cyano-functionalized 1,3-envne 3c underwent desilylation and afforded 1,3-envne 5 containing a terminal alkyne unit. Moreover, enynyl nitrile 3a could be easily converted to enynals 6, which are important synthons in organic chemistry.¹⁹ As mentioned in the introduction, conjugated enynes with an electron-withdrawing group have been widely employed in the construction of cyclic or heterocyclic compounds. With this hydrocyanation of 1,3diynes protocol in hand, we are able to provide a diverse range of cyano-containing cyclic or heterocyclic products. For example, bicyclo[3.3.1]alkenone 7 was obtained in 92% yield by In-catalyzed intermolecular annulation of enamine with 1,3enyne 1c. Pyrazole (8) and pyrans (9 and 10) were also obtained under mild conditions. Interestingly, the trimethylsilyl group could be easily removed in these transformations. We also conducted a large-scale reaction of 1a and acetone

cyanohydrin 2, and this reaction yielded enynyl nitrile 4a in 54% isolated yield with excellent selectivity. Treatment of the divergent product 4a with 2-acetamidomalonate and DBU provided the 2,3-dihydro-1*H*-pyrroles 11 in 86% yield.

This divergent transformation displayed a remarkable selectivity that encouraged us to elucidate the reaction mechanism. First, we checked whether the Bobphos ligand was a monodentate or bidentate ligand with nickel, although it has been proved to coordinate as a bidentate ligand with either rhodium or palladium.^{16b} The reaction between Ni(cod)₂ and Bobphos (2.0 equiv) in toluene- d_8 was monitored by ³¹P NMR at room temperature. Compared with the ³¹P peaks of Bobphos (8.6 and 125.8 ppm), two new peaks were observed at 177.5 ppm (d, *J* = 124 Hz) and 66.0 ppm (d, *J* = 128 Hz) with two doublets (for more details, see the Supporting Information). These signals suggested that the Bobphos ligand may be a bidentate ligand with nickel in the reaction. To further understand the induced selectivity, we conducted density functional theory (DFT) calculations for this regiodivergent hydrocyanation reaction.²⁰ DFT calculations (for more details, see the Supporting Information) suggested that the anti-geometry of the [H-Ni(Dppf)-CN] complex preferentially inserted at 1,2-C=C, while the syn-geometry of the [H-Ni(Bobphos)-CN] complex (to reduce the cost of DFT calculations, L12 was used) inserted at 3,4-C=C, thus tuning the regioselectivity (Figure 1). The proposed mechanism was also shown in the Supporting Information.



Figure 1. Optimized geometries and quadrant diagrams of lowestenergy transition states for the alkyne insertion step with L5 or L12 as ligand. Refer to the SI for TSs leading to other isomers and for the origins of regioselectivity.

In summary, the Ni-catalyzed regiodivergent hydrocyanation of 1-aryl-4-silyl-1,3-diynes was successfully developed. The efficient switch between two alkyne sites depends on suitable steering ligands between diphosphine and the phosphine– phosphite ligand. Two kinds of enynyl nitriles can be synthesized in good yields with high regioselectivity from the same reactants. The obtained cyano-containing 1,3-enynes could easily undergo simple transformations to various cyanosubstituted heterocycles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01262.

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

Accession Codes

CCDC 1983075 and 2017792 contain 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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