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Enantioselective Olefin Hydrocyanation Without Cyanide

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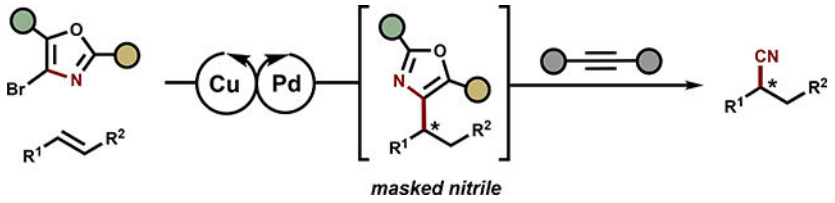
Abstract

The enantioselective hydrocyanation of olefins represents a conceptually straightforward approach to prepare enantiomerically enriched nitriles. These, in turn, comprise or are intermediates in the synthesis of many pharmaceuticals and their synthetic derivatives. Herein, we report a cyanide-free dual Pd/CuH-catalyzed protocol for the asymmetric Markovnikov hydrocyanation of vinyl arenes and the anti-Markovnikov hydrocyanation of terminal olefins in which oxazoles function as nitrile equivalents. After an initial hydroarylation process, the oxazole substructure was deconstructed using a [4+2]/retro-[4+2] sequence to afford the enantioenriched nitrile product under mild reaction conditions.

Graphical Abstract



Nitriles are a ubiquitous class of compounds present in many pharmaceuticals,[1] secondary metabolites,[2] and polymers.[3] Owing to their unique chemical reactivity, nitriles often serve as precursors to numerous additional important functional groups in organic synthesis, including *N*-heterocycles, carbonyl compounds, and amines.[4] Although nitriles can be accessed by many methods, the conversion of olefins to alkyl nitriles via transition metal-catalyzed olefin hydrocyanation represents one of the most conceptually straightforward processes. While hydrocyanation of feedstock olefins is conducted on a million-metric ton scale annually to produce nitrile precursors to polymers,[3] these protocols employ hydrogen cyanide and form almost exclusively achiral products. Despite the numerous improvements in the racemic hydrocyanation of olefin feedstocks[5] and fine chemicals,[6] the reaction

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Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, and characterization data for all new compounds including ^{1}H- and ^{13}C-NMR spectra, SFC and HPLC traces (PDF).

conditions and substrates employed in the analogous asymmetric variant of this transformation have advanced minimally since the seminal work by Jackson[7a] and RajanBabu.[7b–7d,7g]

Asymmetric olefin hydrocyanation is typically achieved through the formal addition of hydrogen cyanide, either generated *in situ* or employed directly in gaseous form, across an olefin facilitated by a chiral phosphine-ligated metal catalyst (Scheme 1A).[7–8] Aside from the potential safety concerns of working with hydrogen cyanide,[9] many of these asymmetric methods are limited to vinyl arenes and employ non-commercially available ligands.[7,10–11] Alternative methods to access enantioenriched nitriles, including C–H cyanation,[12] α-arylation of prefunctionalized nitriles[13] and enantioselective protonation of silyl ketene imines,[14] have also been developed employing various precursors.[15]

Our continued interest in enantioselective alkene hydrofunctionalization reactions led us to envision the development of a catalytic protocol to access enantioenriched α-alkyl-α-arylnitriles, represented by **3** (Figure 1B).[16–18] We proposed that the critical C–CN bond of the nitrile could be forged through an initial dual Pd/CuH-catalyzed asymmetric olefin hydroarylation[17] reaction using a *N*-heterocyclic compound as a nitrile surrogate, thus obviating the need to employ cyanide either directly or transiently formed. A subsequent thermal-[4+2]/retro-[4+2] sequence with the appropriate dienophile could furnish the enantioenriched nitrile. However, at the outset, it was unclear to us which *N*-heterocycle would best serve as a masked nitrile, since pyrimidines, pyrazines, oxazoles and several other heterocycles have all been shown to expel nitriles as byproducts in cycloaddition reactions with alkynes.[19–21] We reasoned that an oxazole, despite its limited precedent in forming nitriles,[19] would be an ideal nitrile precursor for this transformation as it does not introduce any regiochemical complications and is an electron-rich aza-diene.[21]

Figure 1C details our proposed dual Pd/CuH catalytic cycle for the aforementioned approach. Enantioselective hydrocupration of an olefinic substrate (**1**) by a CuH catalyst (**I**), generated *in situ* through the use of a Cu(I) salt, chiral phosphine ligand, and silane, would form an enantioenriched Cu(I) alkyl intermediate (**II**). Meanwhile, the Pd catalytic cycle would begin with oxidative addition of a ligated Pd(0) species (**III**) into a 2-halo-oxazole (**2**) forming complex **IV**. Stereospecific transmetallation of **II** with Pd species **IV** would result in an alkyl Pd(II) complex (**V**), which following reductive elimination furnishes an intermediate enantioenriched oxazole (**4**). The formed copper(I) halide (**VI**) could regenerate the active CuH catalyst after a σ-bond metathesis reaction in the presence of an appropriate base and silane.[17–18] For this approach to be successful, the rates of both catalytic cycles would need to be well aligned to prevent any deleterious side pathways or the racemization of the alkyl copper species **II**.[17] After this hydroarylation process, as depicted in Figure 1B, a subsequent thermal [4+2] cycloaddition between oxazole **4** and an alkyne would form a highly strained 7-oxa-2-azabicyclo[2.2.1]heptadiene derivative (**5**), and upon a retro-[4+2] cycloaddition the nitrile product is liberated along with an electron deficient furan (**6**). Thus, we reasoned that the judicious choice of a 2,5-disubstituted-4-halo-oxazole (**2**) coupling partner would be paramount to achieving both a highly enantioselective hydroarylation step and an efficient [4+2]/retro-[4+2] sequence.

Accordingly, we focused on finding a suitable halo-oxazole coupling partner (**2**) and a set of experimental reaction conditions for the asymmetric olefin hydrocyanation using styrene (**1a**) as a model substrate (Table 1). Our investigation of the optimal reaction conditions identified oxazole **2a** as an excellent nitrile surrogate and the commercially available alkyne **7a** as a suitable dienophile. When **2a** and **7a** were utilized in conjunction with $[Pd(cinnamyl)Cl]_2$, BrettPhos (**L3**), **P1**, NaOTMS, and $Me_2(Ph)SiH$, the desired nitrile **3a** was formed in high yield and enantioselectivity (entry 1, 96% ^1H NMR yield and 97:3 er), without isolation of the alkyl oxazole intermediate (**4**). Evaluation of a series of Cu salts and chiral bisphosphines (entries 1–5) led us to discover the air-stable Cu(I) precatalyst **P1**, which enabled the reaction to be set up without the use of an inert-atmosphere glovebox.[22] Use of the previously described (**S**)-DTBM-SEGPHOS-ligated CuCl precatalyst **P2**[18b] formed the desired product in similar yield but with considerably lower enantioselectivity (entry 2). Variation of the biarylphosphine backbone (entries 6–7) or the absence of a Pd-catalyst (entry 8) resulted in diminished yield or no product formation respectively. Examination of an alternative to **2a** as the nitrile surrogate highlighted the crucial role of the oxazole substituents in this transformation. Modification of the substituent at the 5-position from methyl to phenyl (**2b**) delivered nitrile **3a** in considerably lower yield and enantioselectivity, presumably due to the electron-poor nature of the corresponding alkyl oxazole intermediate (entry 9). While our previous reports on enantioselective olefin hydroarylation[18b] suggested that a 2-chloro-*N*-heterocycle was more efficient in the hydrofunctionalization reaction than the corresponding hetereoaryl bromide, use of **2c** in the current process resulted in minimal olefin hydrocyanation (entry 10). A variety of acetylene diester derivatives, such as the di-*n*-octyl substituted ester (**7b**), performed well as dienophiles. Notably, the judicious choice of dienophile coupling partner aided in the purification of the nitrile products (see below and the Supporting Information for details).

Having established appropriate reaction conditions for the asymmetric olefin hydrocyanation reaction, we investigated the scope of vinyl arene substrates (Scheme 1). Vinyl arenes bearing a substituent at the *para*-position, such as phenyl (**3b**), isobutyl (**3d**), or thiomethyl (**3e**), were well tolerated under the reaction conditions, resulting in good yields and enantioselectivity of the nitrile product. Facile enantiospecific hydrolysis could convert nitrile **3d** and **3g** to ibuprofen[10] and cicloprofen,[14] respectively, both of which are nonsteroidal anti-inflammatory drugs (NSAIDs).[23] A vinyl arene containing *ortho*-substitution was effectively converted to the nitrile (**3c**) in high yield and enantiopurity. Moreover, substrates containing heterocycles, including benzofuran (**3f**), indoline (**3h**), *N*-tosyl-indole (**3i**), carbazole (**3j**), pyrazole (**3k**), morpholine (**3m**), and *N*-Boc-piperzine (**3o**), were smoothly transformed to the nitrile product with excellent selectivity. Additionally, 1,2-disubstituted alkenes (Scheme 1B), a problematic substrate class for complementary Ni-catalyzed asymmetric olefin hydrocyanation methods,[7h] performed well under our reaction conditions (**3l** and **3m**). However, cyclic olefins were difficult substrates for this transformation. Nitrile **3n** was isolated in moderate yield and enantioselectivity when **1n** was subjected to the standard catalytic system. We hypothesized that this diminished yield may reflect a slower rate of transmetallation between the proposed organometallic species **II** and **IV**, potentially due to a more sterically congested transition state, or a slower rate of hydrocupration of **1n**. To further highlight the applicability of this formal olefin

hydrocyanation method to access medicinally relevant molecules, we synthesized an intermediate (**3o**) en route to **8**, a USP28 inhibitor (Scheme 1C). Conversion of **3o** to **8** could be achieved via reduction of the nitrile (**3o**) and acylation of the resulting primary amine.[24]

We were interested in extending this chemistry toward the anti-Markovnikov hydrocyanation of unactivated olefins. In line with our previous work,[18b] we anticipated the anti-Markovnikov hydrocyanation to be more challenging due to the higher hydrocupration barrier.[25] However, we were able to perform the hydrocyanation of terminal olefins without significantly modifying the standard reaction conditions (Scheme 2). Overall, this process tolerates the presence of a variety of important structural elements (**10a**–**10g**), including an ester (**10b**), dioxolane (**10c**), benzothiazole (**10e**), indole (**10f**) and an amide (**10g**). Furthermore, the corresponding alkyl nitriles were isolated in high yield and regioselectivity. Hydrocyanation of terminal alkene (**9d**) accentuated the degree of chemoselectivity for this process, which generated **10d** in good yield without any detectable hydrocyanation of the trisubstituted alkene. We further demonstrated the utility of this method by synthesizing the nitrile derivative (**10g**) of the cardiovascular drug Cilostazol (**11**), which could conceivably be converted to **11** following deprotection and tetrazole formation.[26] As previously mentioned, reduction of the halo-oxazole (**2**) and the olefinic coupling partner represents potential side reactions for this transformation. Formation of a significant amount of reduced **9g** was observed when the olefin was subjected to the standard reaction conditions. A decrease in the amount of **P1** utilized, from 6.0 to 4.0 mol%, was necessary to improve the efficiency of the dual CuH/Pd catalytic system and deliver amide **10g** as the major product.

Enantioenriched alkyl nitriles (**3**) often undergo epimerization or decomposition under a variety of acidic, basic and oxidative conditions, thus making further manipulation of the resulting nitrile product potentially challenging.[7f,27] To obviate these degradation pathways, we envisioned that the chiral alkyl oxazole (**4**) may serve as a stable masked nitrile in multistep organic synthesis, which could be revealed at a later stage under neutral reaction conditions (Scheme 3). To illustrate this concept, we employed 1,2-disubstituted olefin **1p** as a simple representative example. An initial asymmetric olefin hydroarylation reaction installed the oxazole substructure (**4p**), which was followed by silyl group removal, either under acid or fluoride-mediated conditions, and basic functionalization of the resulting phenol to yield oxazole **4p'** without any erosion of the enantioselectivity. A subsequent thermal cycloaddition sequence with alkyne **7b** revealed the nitrile (**3p**) with complete enantiospecificity. We believe that this strategy will be further applicable in more sophisticated contexts and numerous reaction manifolds that would otherwise result in decomposition of the nitrile substructure.

In summary, we have developed an asymmetric olefin hydrocyanation sequence that relies on an oxazole as surrogate for a nitrile, thus avoiding the use of any sources of cyanide in the reaction mixture. These reaction conditions developed were broadened to the anti-Markovnikov hydrocyanation of unactivated olefins. We anticipate that this strategy of employing an enantioenriched alkyl oxazole as a masked nitrile in multistep synthesis will find further utility in a variety of scenarios.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(27). In some substrates (3b and 3e) epimerization of the nitrile product was observed upon exposure to silica flash column chromatography, which could be avoided by altering the method of purification, see supporting information for details.

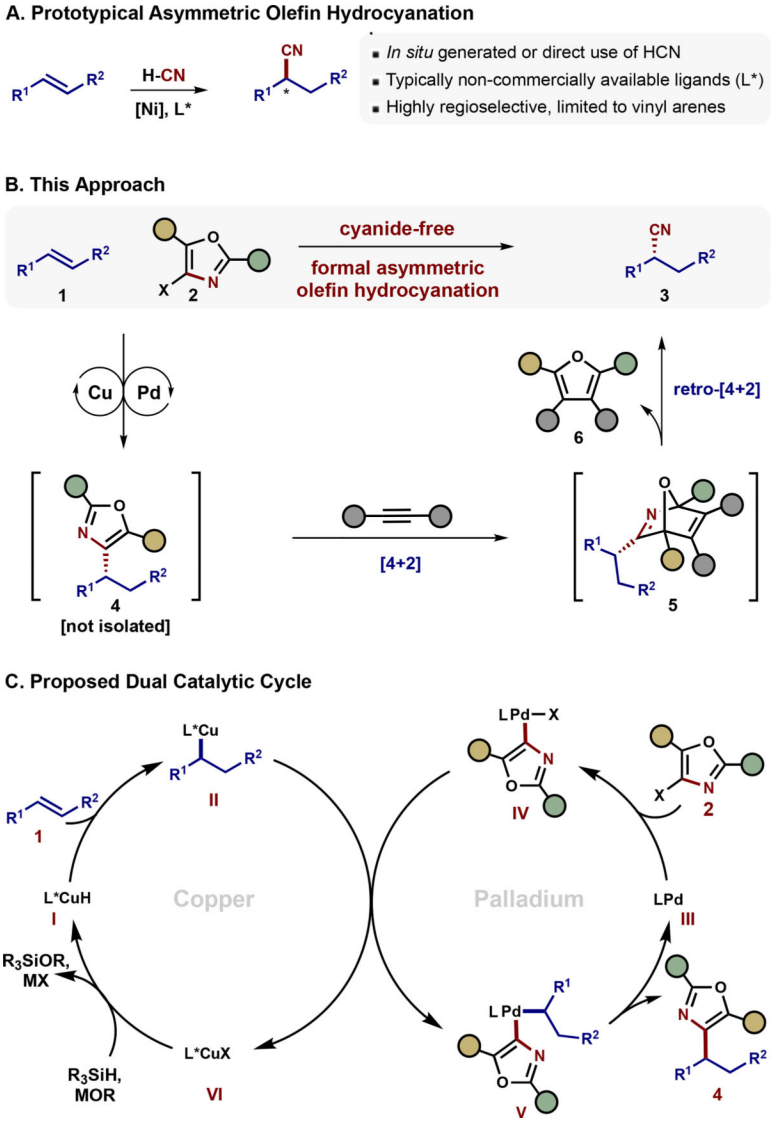
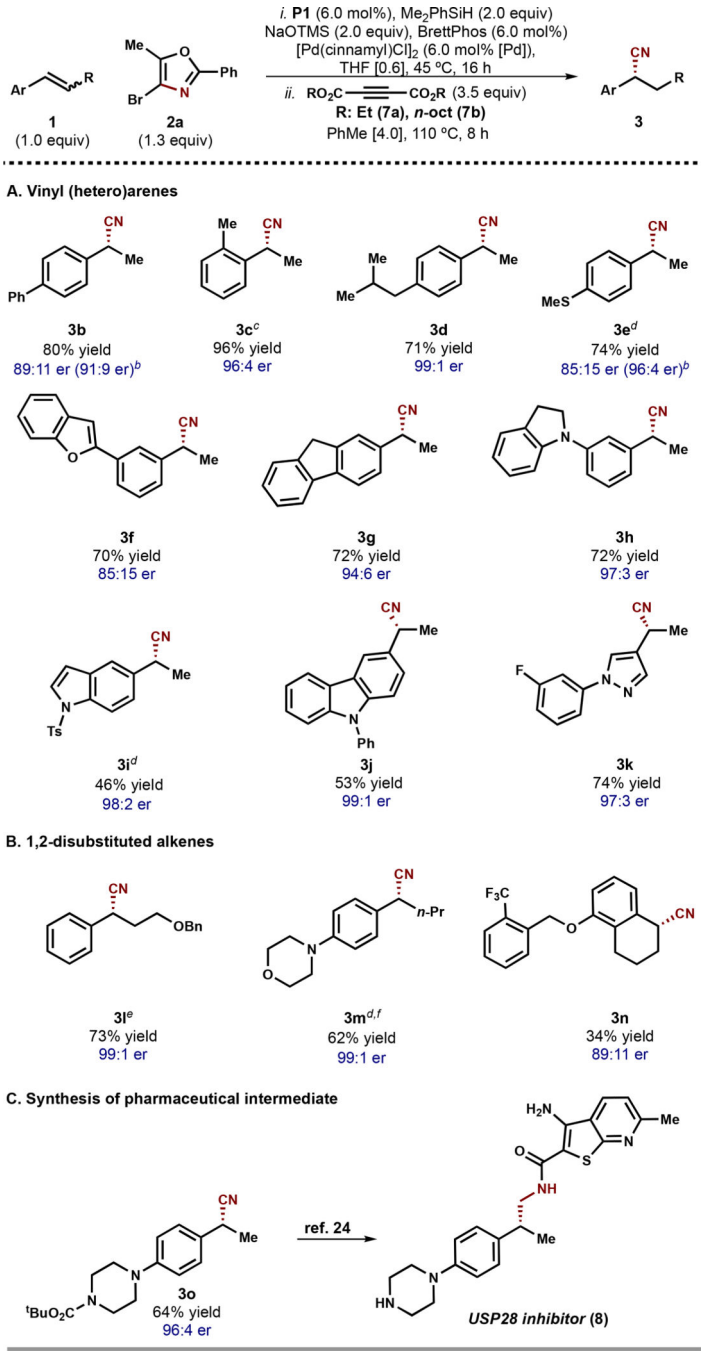


Figure 1.

A. Traditional approaches to asymmetric olefin hydrocyanation. **B.** Our dual Pd/CuH-catalyzed asymmetric olefin hydrocyanation using oxazoles as masked nitriles, followed by a thermal deconstruction of **4** to the enantioenriched nitrile. **C**. Proposed dual Pd/CuH catalytic cycles for the hydrofunctionalization process involving a 2-halo-oxazole (**2**).

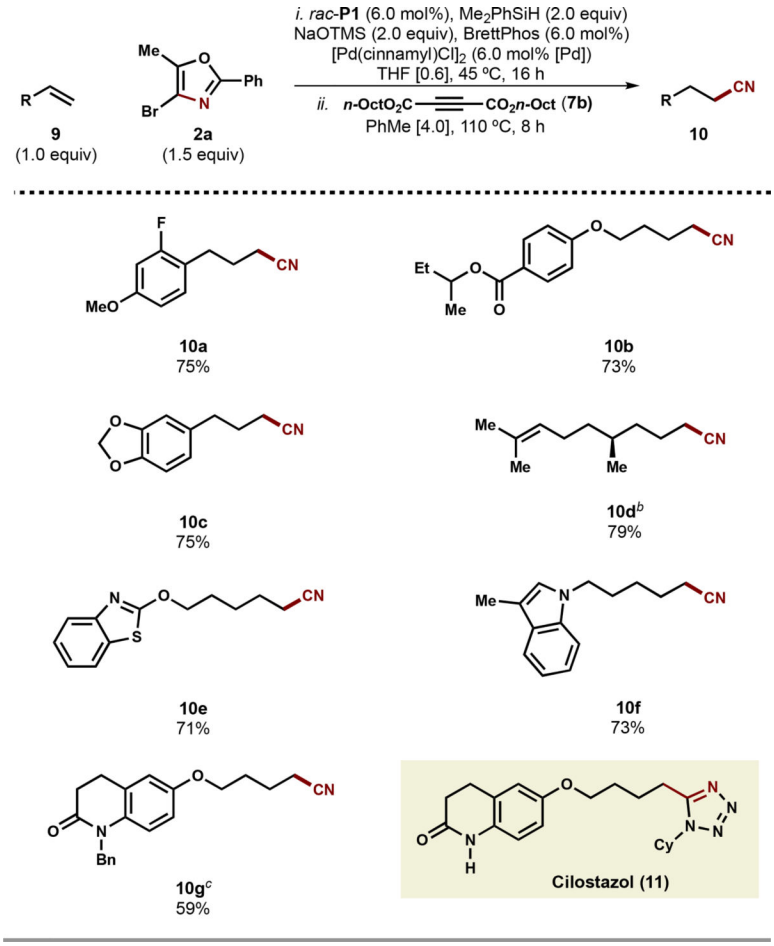


Scheme 1.

Substrate scope of the asymmetric Markovnikov hydrocyanation of vinyl arenes. [a]

[a]All yields represent the average of isolated yields from two runs purified by silica flash chromatography with 0.5 mmol alkene; alkyne (**7b**) was used unless otherwise noted, enantioselectivity determined by chiral SFC or HPLC. [b]Alternative purification was used, see supporting information for details. [c]Yield was determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard due to the volatility of the product.

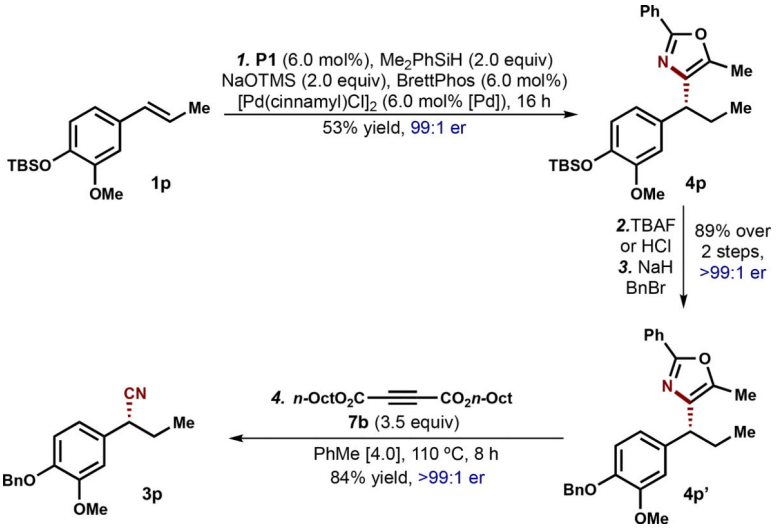
[d]Alkyne (**7a**) was used. [e] Intermediate oxazole **4l** was purified, isolated yield reported over two steps. [f]1.5 equiv of **2a** and 24 h at 45 ºC



Scheme 2.

Substrate scope for the anti-Markovnikov hydrocyanation of unactivated olefins.[a]

[a]All yields represent the average of isolated yields from two runs purified by silica flash chromatography with 0.5 mmol alkene. [b]Yield was determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard [c]4.0 mol% **P1**



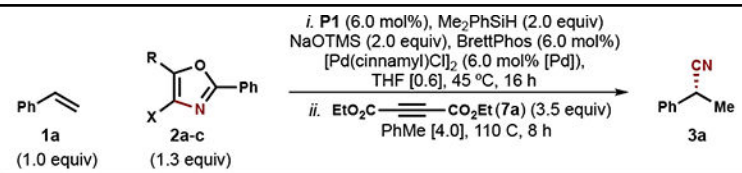
Scheme 3.

Enantioenriched oxazoles as masked nitriles in multistep synthesis

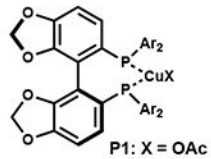
[a]Reagents and conditions: (1) Average of isolated yields from two runs on 0.5 mmol scale; (2) TBAF (1.5 equiv), THF [0.45], rt, 1.5 h or aq. 6 M HCl (5.0 equiv), THF [0.5], rt, 16 h; (3) NaH (1.2 equiv), BnBr (1.2 equiv), rt, 18 h, 89% or 81% over two steps, respectively >99:1 er; (4) **7b** (3.5 equiv), PhMe [4.0], 110 °C, 8 h, 84%, >99:1 er

Table 1.

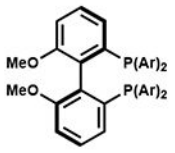
Optimization of the enantioselective hydrocyanation of styrene (**1a**).[a]



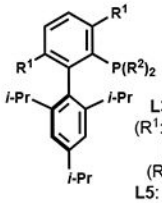
entry	variation from standard conditions	% yield	er
1	none, **2a** (X=Br, R=Me)	96%	97:3
2	**P2**	88%	80:20
3	6.0 mol% CuOAc + 7.0 mol% **L1**	94%	97:3
4	6.0 mol% $Cu(OAc)_2$ + 7.0 mol% **L1**	82%	72:28
5	6.0 mol% CuOAc + 7.0 mol% **L2**	81%	99:1
6	XPhos (**L4**)	61%	87:13
7	*t*-BuBrettPhos (**L5**)	14%	nd
8	no Pd and BrettPhos	0%	nd
9	**2b** (X=Br, R=Ph)	35%	90:10
10	**2c** (X=Cl, R=Me)	5%	nd



P1: X = OAc
P2: X = Cl
Ar= 3,5-(*t*-Bu)$_2$-4-MeOC$_6$H$_2$
(*S*)-DTBM-SEGPHOS (**L1**)



L2:
Ar= 3,5-(*t*-Bu)$_2$-4-MeOC$_6$H$_2$
(*R*)-DTBM-OMe-BIPHEP



L3: BrettPhos
(R^1: OMe, R^2: Cy)
L4: XPhos
(R^1: H, R^2: Cy)
L5: *t*-BuBrettPhos
(R^1: OMe, R^2: *t*-Bu)

[a]Reaction conditions: 0.2 mmol styrene (1.0 equiv), yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture, using 1,1,2,2-tetrachloroethane as internal standard. Enantiomeric ratio (er) was determined by chiral SFC. nd: not determined.