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Nickel-catalyzed regioselective hydrocyanation of terminal alkynes by assistance of a tosyl group

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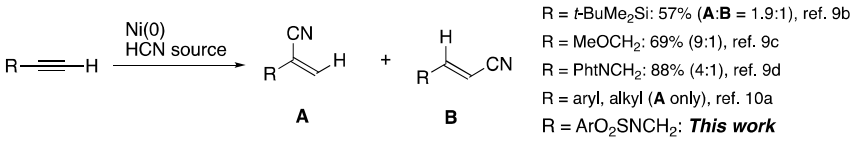
Abstract: Nickel-catalyzed regioselective hydrocyanation of terminal alkynes is described. A tosylamide functionality at the propargyl position was the most suitable group for controlling the regiochemistry for C–CN bond formation as well as rate enhancement. A gram-scale synthesis was achieved by minimizing the catalyst loading to 2 mol%. The major HCN adduct could be transformed to the corresponding indoline through construction of a benzylic quaternary carbon under iron catalysis.

Keywords: Alkynes, Hydrocyanation, Iron, Nickel, Sulfonamide

1. Introduction

A cyano group is equivalent to aminomethyl and formyl groups and carboxylic acids. Therefore, its introduction has been recognized as a key reaction for creation of biologically important compounds.[1] Nickel-catalyzed hydrocyanation[2,3] using various substrates such as olefins,[4] styrene derivatives,[5] conjugated dienes,[6] allenes[7,8] and alkynes,[9] is one of the most powerful cyanation protocols, although limited C–C multiple bonds have been shown to give high regioselectivity. Among terminal alkynes, neighboring functional groups such as silyl[9b] and oxygen functionalities[9c,d] have been influential for controlling the regioselectivity (Scheme 1). Recently, Liu and co-workers reported the hydrocyanation of terminal alkynes under Ni/Mn catalysis.[10a] In this article, we report the effect of sulfonamides on both regiocontrol and rate enhancement using inexpensive HCN precursors in a nickel-catalyzed hydrocyanation reaction.

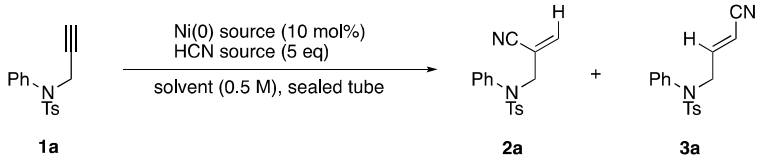
Scheme 1. Ni-catalyzed hydrocyanation of terminal alkynes



2. Result and discussion

Since sulfonamides are effective for stabilizing the organonickel (II) species,[11] we expected that chelation of the Ni(II) center in the hydronickelation step would control its regioselectivity. First, **1a** with a tosylamide at the propargylic position was chosen as a substrate and the reaction was performed in the presence of Ni(0) (10 mol%) with various HCN sources in toluene (Table 1). As expected, the sp alkynyl carbons were discriminable, and the reaction using acetonecyanohydrin (AC) (5 eq) at 100 °C for 2 h proceeded to give the corresponding HCN adducts in 37% yield as an inseparable mixture (**2a**:**3a** = 10:1) (entry 1). Since the efficacy of HCN release from AC seems to be lower, in-situ generation of HCN from TMSCN with alcohols was examined next. The use of MeOH increased the yield and the selectivity was 12.5:1. Trifluoroethanol (TFE) improved the conversion to 90% yield with 10:1 selectivity. With *t*-BuOH, the yield slightly decreased. Water also acted as a proton source instead of alcohols, however both the yield and selectivity decreased (entries 2-5). A shorter reaction time gave similar results and lower temperature gave slight improvement of the product ratio (entries 6 and 7). Solvent effect was examined at 100 °C, and 1,2-dichloroethane and THF gave similar results to toluene however CH_3CN gave no reaction even after 3 h (entries 8-10). Further optimization using TFE with TMSCN in toluene at 100 °C revealed that the external ligand such as PPh_3 and bipyridine was quite ineffective. Cheaper Ni(0) source such as $NiCl_2 \cdot 6H_2O$ [4b] and $Ni(acac)_2$ [10a] with metal reductants did not work at all (entries 11-14). These results indicate that TFE with TMSCN is the best HCN source and optimum condition (toluene, 100 °C) was adopted for further investigation.

Table 1. Optimization



1a **2a** **3a**

entry	Ni(0) source	HCN source (eq)	ligand (mol%)	solvent	conditions	yield (%) (**2a**:**3a**)
1	$Ni[P(OPh)_3]_4$	$Me_2C(OH)CN$ (5)	none	toluene	100 °C, 2 h	37 (10:1)
2	$Ni[P(OPh)_3]_4$	TMSCN (5), MeOH (5)	none	toluene	100 °C, 2 h	84 (12.5:1)
3	$Ni[P(OPh)_3]_4$	TMSCN (5), CF_3CH_2OH (5)	none	toluene	100 °C, 2 h	90 (10:1)
4	$Ni[P(OPh)_3]_4$	TMSCN (5), *t*-BuOH (5)	none	toluene	100 °C, 2 h	86 (10:1)
5	$Ni[P(OPh)_3]_4$	TMSCN (5), H_2O (5)	none	toluene	100 °C, 2 h	74 (8:1)
6	$Ni[P(OPh)_3]_4$	TMSCN (5), CF_3CH_2OH (5)	none	toluene	100 °C, 0.5 h	90 (10:1)
7	$Ni[P(OPh)_3]_4$	TMSCN (5), CF_3CH_2OH (5)	none	toluene	70 °C, 2 h	84 (11.7:1)
8	$Ni[P(OPh)_3]_4$	TMSCN (5), CF_3CH_2OH (5)	none	$(ClCH_2)_2$	100 °C, 0.5 h	88 (8:1)
9	$Ni[P(OPh)_3]_4$	TMSCN (5), CF_3CH_2OH (5)	none	THF	100 °C, 0.5 h	85 (10.5:1)
10	$Ni[P(OPh)_3]_4$	TMSCN (5), CF_3CH_2OH (5)	none	CH_3CN	100 °C, 3 h	0 (NR)
11	$Ni[P(OPh)_3]_4$	TMSCN (5), CF_3CH_2OH (5)	PPh_3 (20)	toluene	100 °C, 2 h	0 (NR)
12	$Ni[P(OPh)_3]_4$	TMSCN (5), CF_3CH_2OH (5)	bipyridine (10)	toluene	100 °C, 2 h	6 (11.8:1)
13	$NiCl_2 \cdot 6H_2O$, Zn[a]	TMSCN (5), CF_3CH_2OH (5)	none	toluene	100 °C, 2 h	0 (NR)
14	$Ni(acac)_2$, Mn[b]	TMSCN (5), CF_3CH_2OH (5)	none	toluene	100 °C, 2 h	0 (NR)

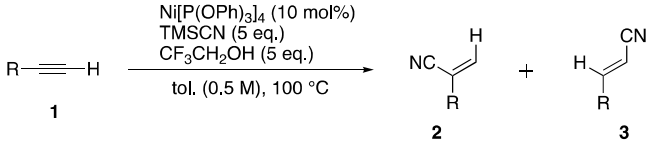
a) 40 mol%. b) 100 mol%

To optimize the suitable functional groups, the effect of acyl groups on nitrogen was examined (Table 2, entries 2-4). An acetyl instead of a Ts group gave lower conversion to give **2b** in 26% yield even after 3 h (entry 1 vs 2). Methyl carbamate (**1c**) gave lower conversion to give **2c** in 57% yield (entry 3). A methoxy instead of a methyl group on the $ArSO_2$ functionality slightly decreased the chemical yield to give **2d** in 82% yield (entry 4). When the amide functionality was replaced by methylene such as **1e**, both the product ratio and the yield decreased to give the corresponding adducts in 35% yield (5:1) (entry 5). An amine such as **1f** was found to be an unsuitable substrate, and no any HCN adducts were identified with recovery of **1f** in 50% yield (entry 6). This result suggests that NH function might have enough nucleophilicity to deactivate the Ni catalyst. In the case of phenylether (**1g**), the reaction proceeded smoothly, however its efficacy and selectivity (**2g**/**3g**) were both lower than those for **1a** (entry 7). These results suggest that SO_2N at the propargylic position is the most effective for regiocontrol and rate enhancement for Ni-catalyzed hydrocyanation.

Alkyl and acyl groups as well as hydrogen on tosylamide (R in **1h-k**) did not affect regioselective hydrocyanation and the major products **2h-k** were obtained at up to 10:1 within 2 h (entries 8-11). Aryl groups on tosylamide did not affect the

selectivity in **2l-n** (entries 12-14). However, an *ortho* methyl group in **1o** dramatically decreased the reactivity and only a trace amount of **2o** was obtained even after 9 h (entry 15). To clarify the effect of an SO_2 group, **1p** with two methylenes next to a triple bond was examined (entry 16). Although the reaction proceeded smoothly, the decreased selectivity in **2p** (6:1) suggests that the distance between a sulfonamide and a C–C triple bond is important for controlling the regiochemistry in the hydrometallation step. This reaction was sensitive to the steric environment around a C–C triple bond because an NTs_2 functionality in **1q** and a quaternary carbon in **1r** prevented the reactions (entries 17 and 18). As we assumed, simple terminal alkynes (**1s,t**) were unsuitable for regiocontrol because the lack of sulfonamide would be disfavored to discriminate sp carbons in the hydrometallation step (entries 19 and 20). Finally, internal alkynes with a PhNTs group (**1u-w**) were examined. They were reactive enough to promote hydrocyanation and their selectivity was up to 6:1 (entries 21-23).[9d]

Table 2. Substrate scope



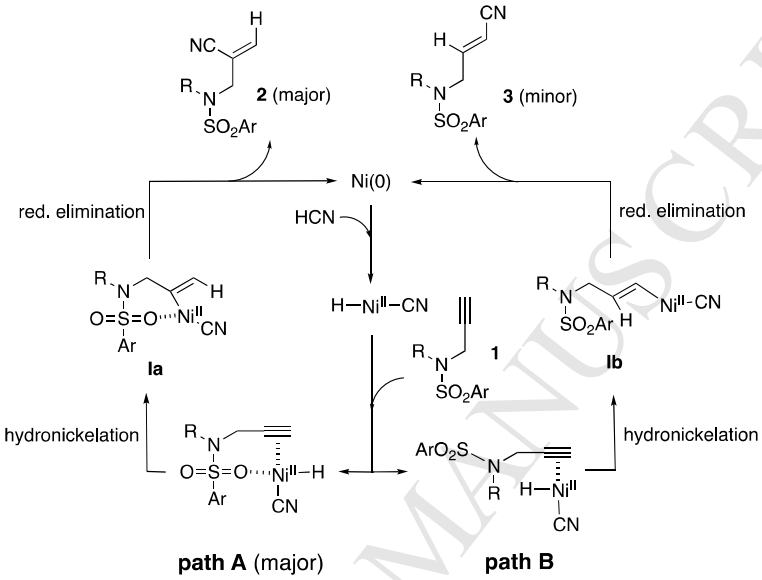
entry	substrate	time (h)	major product	yield (%) selectivity (**2**:**3**)[a]
1	**1a**: R = Ts	0.5		**2a**: 90% (10:1)
2	**1b**: R = Ac	3		**2b**: 26% (10:1)
3	**1c**: R = CO_2Me	1		**2c**: 57% (8:1)
4	**1d**: R = 4-MeOPhSO_2	1		**2d**: 82% (10:1)
5	**1e**: X = CH_2	1		**2e**: 35%[b] (5:1)
6	**1f**: X = NH	19		**2f**: 0%[c]
7	**1g**: X = O	2		**2g**: 59%[b] (7:1)
8	**1h**: R = Bn	2		**2h**: 97% (6:1)
9	**1i**: R = Me	1		**2i**: 84% (8:1)
10	**1j**: R = PhCO	1		**2j**: 74% (10:1)
11	**1k**: R = H	2		**2k**: 74% (9:1)
12	**1l**: R = 2-Br	6		**2l**: 83% (8:1)
13	**1m**: R = 2-I	2		**2m**: 65% (8:1)
14	**1n**: R = 4-MeO	1		**2n**: 83% (8:1)
15	**1o**: R = 2-Me	9		**2o**: trace[d]
16	**1p**	1		**2p**: 96% (6:1)
17	**1q**	21	no reaction	
18	**1r**	48	no reaction	
19	**1s**: R = Ph	2		**3s**: 76% (1:1.2)
20	**1t**: R = c-Hex	1		**2t**: 90% (2:1)
21	**1u**: R = Me	1		**2u**: 85% (2:1)
22	**1v**: R = Ph	1		**2v**: 95% (6:1)
23	**1w**: R = Me_3Si	7		**2w**: 47% (6:1)

a) Selectivity is determined by 1H NMR analysis.
b) Isolated yield. Selectivety is estimated from crude mixture.
c) Recovery of **1f**: 50%.
d) Recovery of **1o**: 98%.

Based on the above observations, we propose plausible reaction pathways (Scheme 2). The initial step is the oxidative addition of HCN to Ni(0). The resulting H–Ni^{II}CN species promotes hydronickelation to a terminal alkyne by controlling chelation between an SO_2 group and the Ni(II) center (path A).[11] As observed in **1f** vs. **1a**, this effect would be essential to enhance the efficacy of the reaction. This proposal is also consistent with the finding that steric bulkiness around the triple bond could prevent the hydronickelation step (**1o,q,r** vs **1a**). The

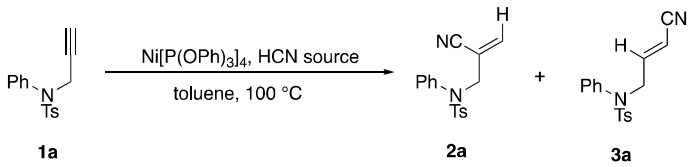
resulting alkenylnickel intermediate (**Ia**) would be smoothly transformed to **2a** *via* reductive elimination with the release of Ni(0) catalyst. In path B, chelation between the Ni center and an SO_2 group would be unlikely in **Ib**, and therefore this catalytic cycle does not act as a major pathway.

Scheme 2. Plausible reaction pathways



Since we realized the effect of a tosylamide group, two applications using **1a** and **2a** were next investigated. First, we investigated minimization of the catalyst loading and HCN source. When the reaction (toluene, 1.0 M) was carried out in the presence of 2 mol% of Ni(0) species, a longer reaction time was required to give the corresponding HCN adducts in 58% yield (**2a**:**3a** = 20:1) (entry 2). The HCN source could also be reduced to 2 eq. in a gram-scale reaction and **2a** was obtained in 60% yield after 22 h (entry 3). In contrast, with the use of inexpensive MeOH, the conversion was unfortunately lower to give **2a** in 30% yield (entry 4). These results are summarized in Table 3.

Table 3. Application to gram-scale synthesis



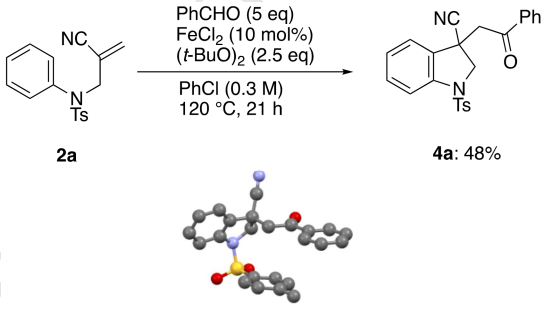
1a **2a** **3a**

entry	Ni catalyst (mol%)	HCN source	conc. (M)	time (h)	yield (%) and selectivity (**2a**:**3a**)
1	10	TMSCN: 5 eq, TFE: 5 eq	0.5	0.5	90% (10:1)
2	2	TMSCN: 5 eq, TFE: 5 eq	1.0	21	58% (20:1)[b)]
3[a)]	2	TMSCN: 2 eq, TFE: 2 eq	1.0	22	60% (14:1)[c)]
4[a)]	2	TMSCN: 2 eq, MeOH: 2 eq	1.0	20	30% (11:1)

a) One gram of **1a** was used. b) Recovery of **1a** was 23% yield. c) Recovery of **1a** was 22% yield.

The second application was the synthetic transformation of **2** to indoline skeleton (Scheme 3). Olefinic and aromatic carbons in **2a** can be connected by radical cyclization through aromatic CH bond cleavage.[12] Therefore, we focused on the construction of a quaternary carbon through iron-catalyzed indoline formation.[12b] The reaction using **2a**, $FeCl_2$ (10 mol%), PhCHO and $(t\text{-BuO})_2$ effectively proceeded to give **4a** in 48% yield and its structure was confirmed by X-ray crystallographic analysis.[13]

Scheme 3. Fe-catalyzed indoline formation



2a **4a**: 48%

X-ray crystallographic analysis of **4a**

In conclusion, we have found that sulfonamides at the propargylic position play key roles in the reactivity and selectivity in Ni-catalyzed hydrocyanation. This finding provides new insight into metal-catalyzed cyanation and could lead to further applications including the synthesis of biologically important compounds.

Experimental section:

Typical procedure for Ni-catalyzed hydrocyanation, synthesis of 2a: A mixture of TMSCN (0.19 mL, 1.5 mmol) and trifluoroethanol (0.11 mL, 1.5 mmol) was stirred

for 10 min at room temperature and then toluene (0.6 mL), **1a** (85.5 mg, 0.3 mmol) and $Ni[P(OPh)_3]_4$ (39.0 mg, 0.03 mmol, 10 mol%) were added. After being stirred for 0.5 h at 100 °C under argon, the reaction mixture was filtrated by celite pad to remove metallic salts and regioselectivity of the product was determined by ^1H NMR. The resulting crude mixture was charged on a silica gel pad to purify column chromatography (hexane:AcOEt = 5:1) and an inseparable mixture of **2a** and **3a** (83.8 mg, 0.27 mmol, 90%, 10:1) was obtained. Recrystallization of the mixture from hexane-AcOEt gave **2a** as a sole product.

Synthesis of 4a: To a solution of **2a** (46.7 mg, 0.15 mmol) in PhCl (0.5 mL, 0.3 M) were added $FeCl_2$ (3.0 mg, 0.015 mmol, 10 mol%), benzaldehyde (0.08 mL, 0.75 mmol) and di-*tert*-butylperoxide (0.07 mL, 0.375 mmol), and the reaction mixture was stirred for 21 h at 120 °C. After being cooled to room temperature, the reaction mixture was poured onto a silica gel pad to purify by flash column chromatography (hexane:AcOEt = 5:1) to give **4a** as a colorless solid (30.2 mg, 0.073 mmol, 48%).

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13. CCDC 1870352 (**4a**) contains the supplementary crystallographic data for this paper.

Graphical Abstract