Nickel-Catalyzed Reductive Arylation of Redox Active Esters for the Synthesis of α-Aryl Nitriles – Role of a Chlorosilane Additive

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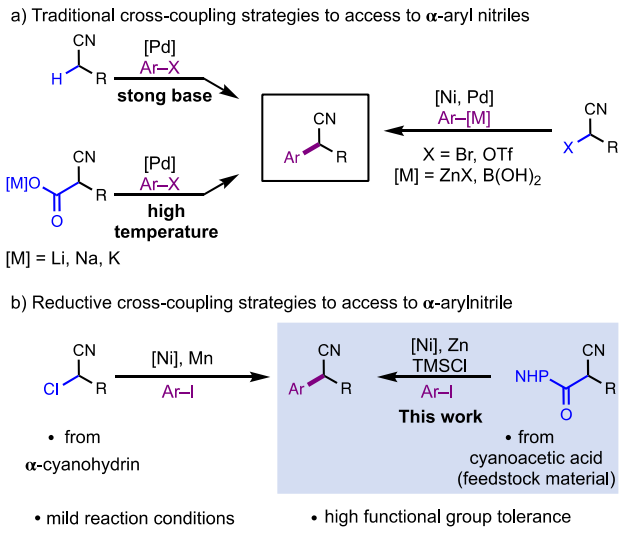
ABSTRACT: A nickel-catalyzed reductive cross-coupling of redox-active *N*-hydroxyphthalimide (NHP) esters and iodoarenes for the synthesis of α-aryl nitriles is described. The NHP ester substrate is derived from cyanoacetic acid, which allows for a modular synthesis of substituted α-aryl nitriles, an important scaffold in pharmaceutical sciences. Mechanistic studies reveal that decarboxylation of the NHP ester to the reactive radical intermediate is accomplished by a combination of a chlorosilane additive and Zn dust. The reaction exhibits a broad scope as many functional groups are compatible under the reaction conditions, including complex highly functionalized medicinal agents.

Scheme 1. α-Aryl nitrile synthesis via cross-coupling



Nickel-catalyzed reductive cross-couplings (RCC) have garnered considerable interest over the past decade since they allow for the construction of C–C bonds from two distinct electrophilic reagents.[1] Compared to traditional cross–coupling reactions, reductive methods tend to avoid the discrete formation of anionic species which often leads to milder reaction conditions that exhibit exceptional functional group tolerance. Thus, reductive cross-coupling reactions that target substrates containing base-sensitive functional groups are highly attractive as they elegantly showcase the advantages of this cross-coupling strategy. One such example that would benefit from this strategy is the synthesis of α-aryl nitriles. These scaffolds are of importance to the synthetic community due to their versatile nature as synthetic intermediates and their prevalence in pharmaceutical agents. Thus, considerable efforts have been dedicated to their synthesis.[2]

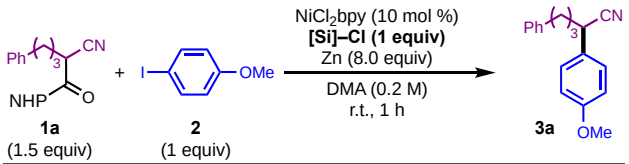
Traditionally, feedstock chemicals such as aliphatic nitriles[3] or cyanoacetate salts[4] can undergo α-arylation as a nucleophilic reagent in the presence of an aryl(pseudo)halide coupling partner with a transition-metal catalyst such as Pd (Scheme 1a, left). However, these established α-arylation methods require strongly basic reaction conditions and/or high temperatures to generate the nucleophilic coupling partner, which limits both their functional group compatibility and their use in late-stage diversification of complex molecules. In contrast, cross-coupling reactions using α-(pseudo)halo nitriles as electrophilic coupling partners address these limitations as the reactions tend to be milder. As such, α-(pseudo)halo nitriles have been elegantly employed in traditional[5] (Scheme 1a, right), and reductive[6,7] (Scheme 1b, left) cross-coupling reactions. The main drawback to these methods is that starting material preparation can be undesirable since they are typically synthesized from a cyanohydrin intermediate which requires the use of a toxic cyanide equivalent. As an alternative approach, we envisioned using cyanoacetic acid derived electrophiles in a RCC as these are feedstock starting materials and easily derivatized (Scheme 1b, blue box). Specifically, we envisioned using the redox properties of *N*-hydroxyphthalimide (NHP) esters to generate an α-cyano radical that can engage in Ni-catalyzed arylation.[8]

RCC reactions of NHP esters are powerful methods that have been used to prepare a diverse range of C–C bonds.[9] Notably, while there are many examples in the literature describing the functionalization of alkyl substituted NHP ester derivatives, examples of NHP esters bearing additional functional group

handles in the α–position are rare.[10] Herein we describe the development of a reductive decarboxylative arylation reaction of cyanoacetic-derived NHP esters. Mechanistic studies of the reaction revealed a unique reduction mechanism for the NHP ester substrate and indicated that an α-cyano radical intermediate is generated in the combined presence of a chlorosilane additive and Zn dust. This finding has implications on the field of NHP ester functionalization, as the role of halosilane additives in previous investigations are not fully understood.[9b]

We began reaction optimization by exploring the RCC of NHP ester **1a** and iodoarene **2**. Initial experiments led to low conversions of aryl iodide and none of the desired product **3a** (Table 1, entry 1). However, when 1 equivalent of a mono-chlorosilane additive such as TBSCl or TMSCl was added, low to moderate yields (24% and 55%, respectively) of α-aryl nitrile **3a** were obtained (Table 1, entries 2-3). Di– and tri–chlorosilanes generally resulted in increased product formation, with the notable exception of $Si(^tBu)_2Cl_2$, which resulted in no detectable formation of **3a** (Table 1, entries 4-7). Ultimately, when 3 equivalents of TMSCl were added in combination with $NiCl_2$bpy (10 mol %) as the pre-catalyst, and superstoichiometric Zn dust (8 equiv), **3a** was obtained in 82% yield (Table 1, entry 8).[11] Decreasing the amount of Zn to 2 equivalents resulted in reduced conversion to **3a** (Table 1, entry 9). The reaction is very rapid and occurs within 15 minutes at room temperature (*vide infra*), potentially signifying that rapid Zn-mediated reduction of the Ni catalyst is essential for productive catalysis. Control reactions in the absence of Ni, ligand or Zn resulted in no detectable product formation.

Table 1. Effect of chlorosilane additive



1a (1.5 equiv) **2** (1 equiv) **3a**

Entry	[Si–Cl]	yield **3a** (%)[a]	conv. **2** (%)[a]
1	None	0	16
2	TBSCl	24	53
3	TMSCl	55	66
4	$SiCyMeCl_2$	65	100
5	$Si(^iPr)_2Cl_2$	74	100
6	$Si(^tBu)_2Cl_2$	0	8
7	$SiPhCl_3$	75	100
8	**TMSCl (3 equiv)**	**83**	**100**
9[b]	TMSCl (3 equiv)	53	83

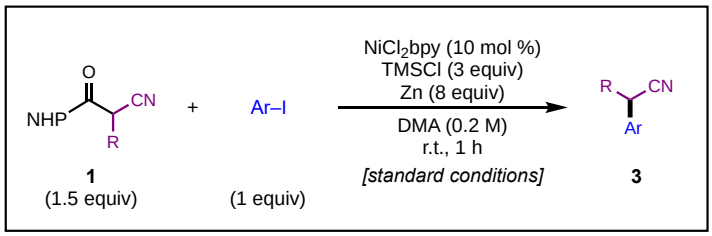
[a]Calibrated yields determined by GC-MS using dodecane as an internal standard. Reactions performed on a 0.1 mmol scale. [b]Reaction performed using 2 equiv Zn instead of 8 equiv.

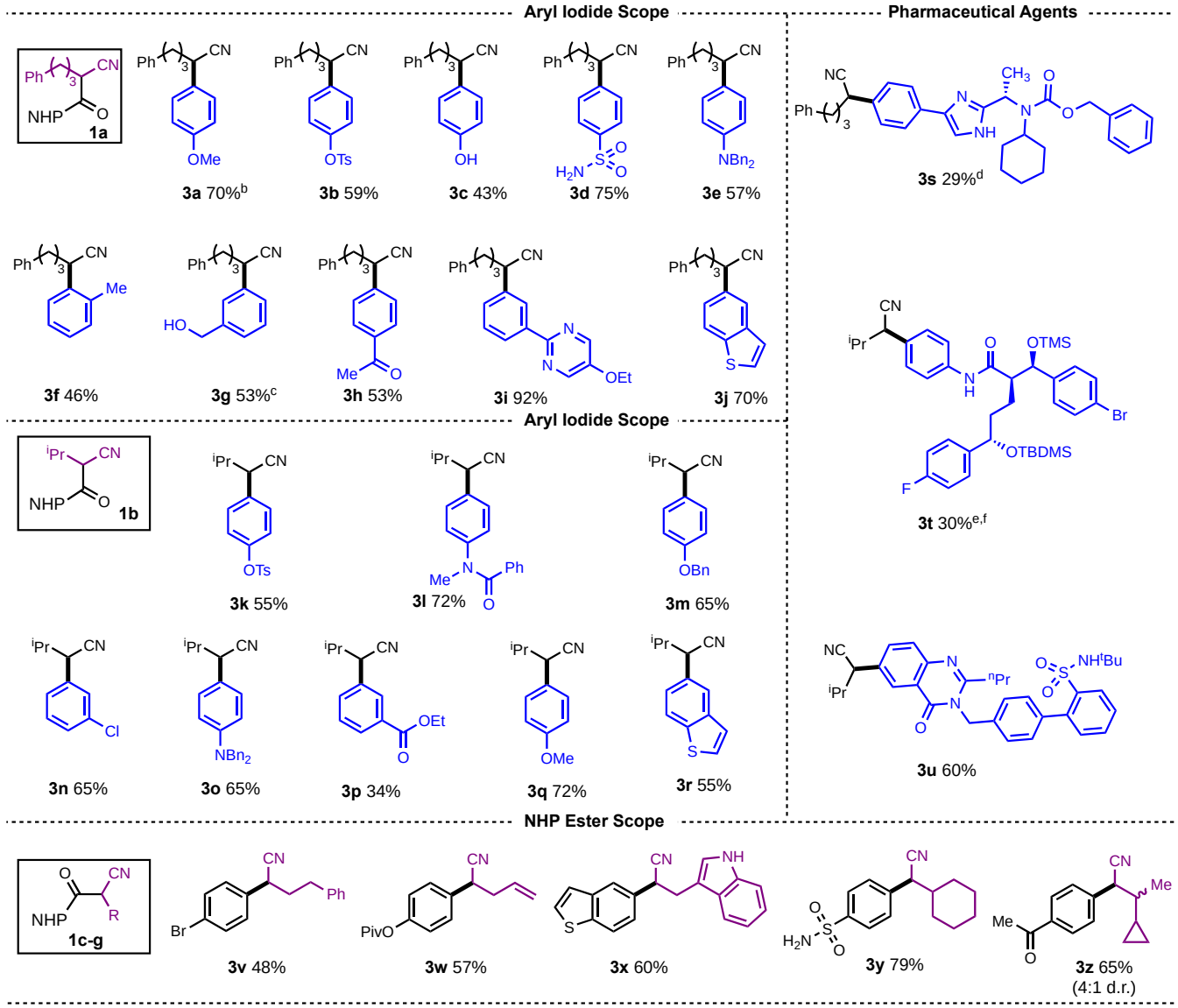
After establishing the optimal reaction conditions, we set out to explore the scope of the reaction (Scheme 2). Notably, the reaction was selective for aryl iodides over other common cross-coupling partners such as aryl bromides (**3t, 3v**), aryl chlorides (**3n**), aryl tosylates (**3b, 3k**), and aryl pivalates (**3w**). Functionalization at the other reactive position of these substrates was never observed.[12] Aryl iodides bearing base-sensitive functional groups were also compatible, including a phenol (**3c**), sulfonamide (**3d**, **3u**, **3y**), benzyl alcohol (**3g, 3t**), and ketone (**3h, 3z**).

Notably, the unprotected alcohols in **3c**, **3g**, and **3t** are silylated over the course of the reaction, and either the free alcohol (**3c**, **3g**), or the TMS-protected adduct (**3t**) can be isolated directly.[13] Aryl iodides containing *N*-heterocycles (**3i, 3s, 3u**) were efficiently cross-coupled, as well as 5-iodobenzothiophene (**3j**, **3r**). Tertiary amide substrate (**3l**), and secondary amide (**3t**) bearing a free N-H were good coupling partners. Strongly electron-donating groups on the iodoarene are tolerated such as alkoxy (**3a**, **3m**, **3q**) and amino (**3e**, **3o**) substituents. An ortho-substituted iodoarene gave the desired α-aryl nitrile (**3f**) in 46% yield. Structurally complex aryl iodides, bearing a diverse range of functional groups (**3s-u**) were also suitable substrates in the reaction, which highlights the synthetic utility of this method within the context of late-stage diversification. In particular, β-hydroxyamide **3t**, is an intermediate towards an anti-hypercholesterolemic compound which features a selective Ar-I over Ar-Br functionalization en route towards those medicinal agents.[14]

Other NHP esters of functionalized cyanoacetic acids can also be used in this transformation. α-Aryl nitriles with pendant alkyl chains (**3v**) or an allyl substituent (**3w**) were prepared in moderate to good yields from the corresponding NHP ester. Nitrile **3x** was prepared in good yield from the NHP ester containing a free N-H indole without requiring protecting group manipulations.[15] Bulky isopropyl (**3k-3r**, **3t, 3u)** and cyclohexyl (**3y**) substituted NHP esters were also suitable substrates for this transformation, as well as substrate **3z** bearing a cyclopropane ring.[16]

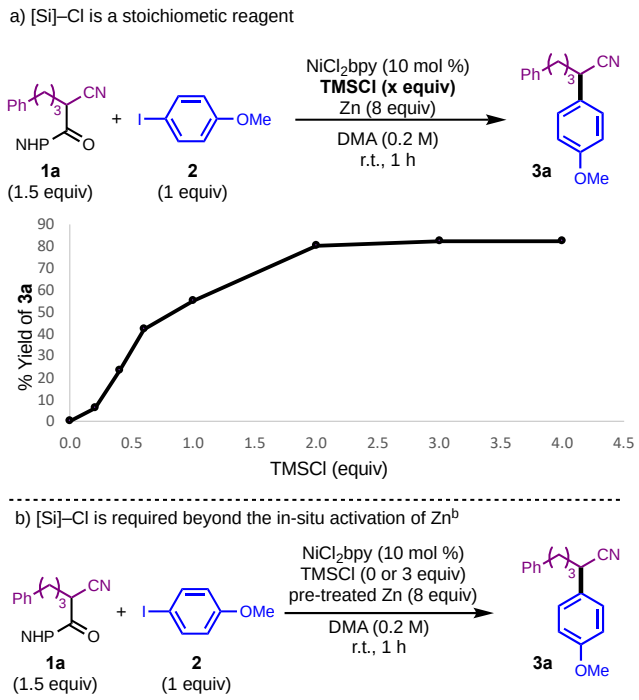
Scheme 2. Reaction Scope[a]





[a]Reactions performed on a 0.2 mmol scale. Yields reported are isolated yields after purification. [b]Reaction performed on 0.5 mmol scale. [c]Reaction worked up with TBAF (2.5 equiv). [d]Reaction performed on 0.1 mmol scale. [e]4 equiv TMSCl and 2 equiv **1b** were used. [f]ArI contained the free OH but was isolated as the OTMS adduct.

Scheme 3. Role of chlorosilane in product formation[a]



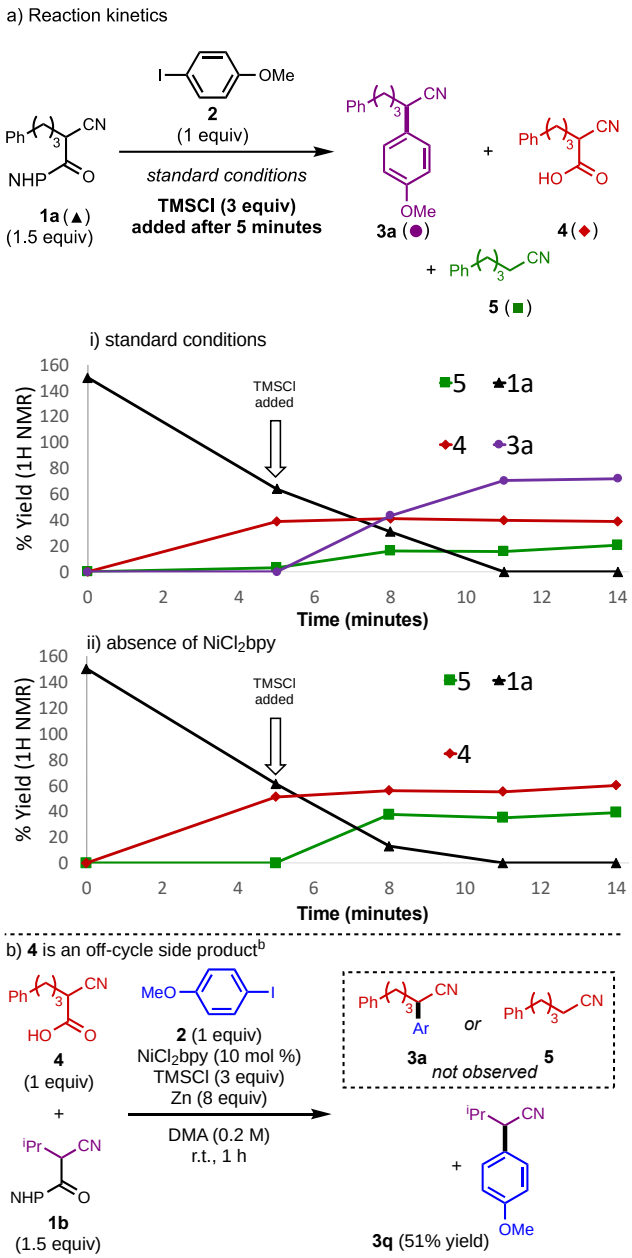
Entry	TMSCl (equiv)	conv. **2** (%)[a]	yield **3a** (%)[a]
1	0	11	0
2	3	100	82

[a]Reactions performed on 0.1 mmol scale. Calibrated yields determined by GC-MS using dodecane as the internal standard. [b]Pre-treated Zn was prepared by stirring with TMSCl (3 equiv) in DMA for 30 min. It was then filtered, washed with DMA, and dried in the glovebox before being added to the reaction under otherwise standard conditions.

Since the chlorosilane was an essential component to the reaction and, in its absence, no product was obtained (Table 1, entry 1), we set out to investigate its role. Chlorosilanes have been used as additives for other reductive cross-coupling reactions.[9b,17] These reports typically suggest that the chlorosilane acts as an *in-situ* activator for the stoichiometric metal reductant (Zn or Mn). While several reports use this reagent in catalytic amounts, some methods require stoichiometric (or near stoichiometric) quantities, which suggests a role beyond that of simply activating the reductant.[9b,17d,f,g,h,i] As the field of reductive cross-coupling continues to expand, detailed mechanistic understandings of the role of the components in these reactions will be essential to inspire future development.

Our initial mechanistic experiments demonstrated that TMSCl is necessary in stoichiometric amounts in the reaction (Scheme 3). As shown in Scheme 3a, we found that the yield of **3a** increases with increasing amounts of TMSCl. To investigate whether the role of TMSCl was simply to act as an *in-situ* activator for Zn, we pre-treated standard Zn dust[18] with TMSCl (3 equiv) and subsequently used this as the stoichiometric reductant in the reaction (Scheme 3b).[19] Notably, in the absence of additional TMSCl, **3a** was not observed which suggests that TMSCl plays a crucial role beyond solely acting as an activator for the metal reductant (Scheme 3b).[20]

Scheme 4. Reaction kinetics[a]



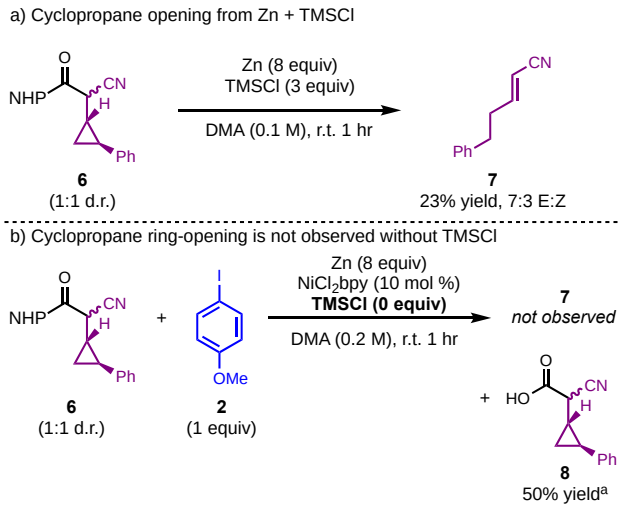
[a]Reactions performed on a 0.3 mmol scale. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Reaction performed on a 0.1 mmol scale.

To further understand the role of TMSCl, we studied the kinetics of the transformation, under slightly modified reaction conditions where TMSCl was added after 5 minutes (Scheme 4a, plot i). Interestingly, before the addition of TMSCl, we observed significant conversion of NHP ester **1a** (black triangle) to the carboxylic acid **4** (red diamond), along with trace amounts (ca. 3%) of decarboxylated side-product **5** (green square).[21] Product **3a** (purple circle) was not detected. Once TMSCl was added, however, we observed rapid formation of **3a**, along with increased amounts of

decarboxylated side-product **5** (ca. 20%). It is important to note that carboxylic acid **4** is generated as a result of background hydrolysis of NHP ester **1a**.[22] When the same experiment was conducted in the absence of $NiCl_2$bpy (Scheme 4a, plot ii), we observed a similarly rapid decomposition of NHP ester **1a** to carboxylic acid **4**. Decarboxylated side-product **5** was again not observed until TMSCl was added, at which point **1a** was rapidly converted to **5** (ca. 40% in under 3 minutes). Importantly, when **1a** is treated with TMSCl in DMA but in the absence of Zn, **4** was observed and **5** was not detected.[15] The most commonly accepted mechanism for NHP ester activation under Ni catalysis is through a single electron transfer (SET) from a low-valent Ni species ($Ni^{(I)}$ or $Ni^{(0)}$) which leads to decarboxylation and liberation of the alkyl radical.[8a,e,9a,d,h,23] The observation that **5** is formed in appreciable amounts (>5%) only after the addition of TMSCl suggests that reduction of the NHP ester **1a** to the α-cyano radical is mediated by a combination of chlorosilane and zinc.

To confirm that carboxylic acid **4** does not decarboxylate under the reaction conditions, we spiked **4** into a standard reaction between an alternative NHP ester substrate **1b** and 4-iodoanisole **2** (Scheme 4b). Decarboxylated side-product **5** and cross-coupled product **3a** were not detected, while the expected arylated product **3q** was still obtained in 51% ^{1}H NMR yield. Since **5** is not generated from carboxylic acid **4**, it is most likely being formed via direct conversion of the NHP ester **1a** to the α-cyano radical followed by subsequent reduction to the anion or HAT with a solvent molecule.[24]

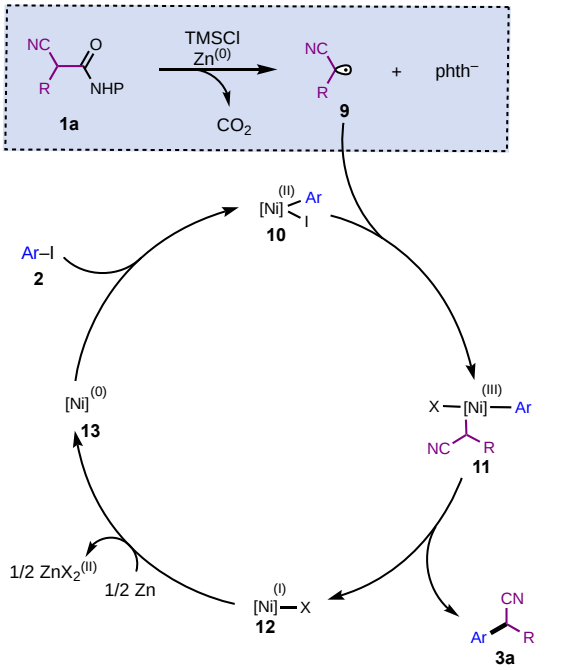
Scheme 5. Radical clock experiments



[a]Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

To further support the mechanistic hypothesis that TMSCl and Zn are responsible for α-cyano radical formation from **1a**, we conducted a series of radical clock experiments. First, we prepared cyclopropane containing NHP ester **6** and subjected it to TMSCl and Zn in DMA (Scheme 5a). The expected ring-opened acrylonitrile derivative **7** was isolated in 23% yield as a 7:3 E:Z mixture of isomers.[25,26] For comparison, when **6** was submitted to the standard reaction conditions in the absence TMSCl, **7** was not detected and carboxylic acid **8** was observed as the major product (Scheme 5b). Importantly, no arylated products were detected during this reaction. Subjecting cyclopropane substrate **6** to the standard reaction conditions in the presence of TMSCl, Zn, Ni and aryl iodide resulted in a complex mixture, and the expected δ-arylated product could not be isolated.

Scheme 6. Possible catalytic cycle



Based on these combined data and previous investigations,[27,28] a plausible catalytic cycle is shown in Scheme 6. NHP ester **1a** undergoes TMSCl mediated reduction by Zn to liberate the α-cyano radical **9** *via* loss of CO_2 and phthalimide anion ($phth^-$).[29] This radical is then captured by a Ni(II) oxidative addition complex **10** to generate Ni(III) intermediate **11**, which upon reductive elimination furnishes the desired product **3a** along with a Ni(I) species **12**. Single electron reduction generates the Ni(0) complex **13** which could undergo an oxidative addition with iodoarene **2** thereby restarting the catalytic cycle.[30] Since the consumption of NHP ester **1a** to α-cyano radical **9** is rapid and occurs in the absence of a nickel catalyst (Scheme 4), one explanation for the observed increase in yield when 8 equivalents of Zn are used (Table 1, entries 8 vs. 9) is that it enables rapid reduction of Ni(I) species **12** to a catalytically active Ni(0) species **13** and that this step is crucial in reducing the formation of side product **5**.

In conclusion, we have developed a Ni–catalyzed reductive cross-coupling reaction of cyanoacetic acid-derived NHP esters and iodoarenes to yield valuable α-aryl nitriles. The reaction conditions are mild and a broad scope of functional groups are tolerated as a result. A chlorosilane additive is necessary for the reaction to proceed and plays a crucial role in mediating NHP ester reduction and decarboxylation to a reactive α-cyano radical intermediate. In its absence, decarboxylation only occurs in trace amount (< 5%) and cross-coupling is not observed. The prevalence of chlorosilanes as additives in RCC reactions renders this finding significant for mechanistic understanding and further developments in this field. Studies involving an enantioselective version of the reaction, along with utilizing

other α-functionalized NHP ester derivatives are currently underway in our group.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Optimization details, experimental procedures, characterization of all products (file type, PDF)
NMR spectra (file type, PDF)

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All authors have given approval to the final version of the manuscript.

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[10] RCC reactions of NHP esters bearing an α-amino (See refs 9c, d, f, g, i) or an α-alkoxy (See refs 9b, c, g, h, i, j) substituent have been documented. However, examples of substrates bearing an electron-deficient group in the α–position are notably absent.

[11] See the supporting information for more detailed optimization.

[12] Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A-M.; Garg, N. K.; Percec, V. Nickel-Catalyzed Cross-Couplings Involving Carbon−Oxygen Bonds. *Chem. Rev.* **2011**, *111*, 1346-1416.

[13] Phenolic substrate **3c** was isolated as the free -OH due to the TMS group falling off during chromatography. Product **3g** was desilylated by addition of TBAF (1.0 M in THF, 2.5 equiv). **3t** was directly isolated as the OTMS adduct. See SI for details.

[14] a) Limanto, J.; Krska, S. W.; Dorner, B. T.; Vazquez, E.; Yoshikawa, N.; Tan, L. Dynamic Kinetic Resolution: Asymmetric Transfer Hydrogenation of α-Alkyl-Substituted β-Ketoamides. *Org. Lett.* **2010**, *12*, 512, 515. b) Limanto, J.; Lushi, T.; Dreher, S. D.; Dorner, B. T.; Naoki, Y.; Krska, S. W. Process for Preparing an Anti-Hypercholesterolemic Compound. U.S. Patent WO 2009054887. April 30, **2009**.

[15] See supporting information for more details.

[16] See supporting information for the complete scope of the reaction including substrates that were less tolerated.

[17] For reductive cross-coupling reactions that use a chlorosilane additive with a Mn reductant, see: a) Nimmagadda, S. K.; Korapati, S.; Dasgupta, D.; Malik, N. A.; Vinodini, A.; Gangu, A. S.; Kalidindi, S.; Maity, P.; Bondigela, S. S.; Venu, A.; Gallagher, W. P.; Aytar, S.; González-Bobes, F.; Vaidyanathan, R. Development and Execution of an Ni(II)-Catalyzed Reductive Cross-Coupling of Substituted 2-Chloropyridine and Ethyl 3-Chloropropanoate. *Org. Process Res. Dev.* **2020**, *24*, 1141-1148. b) Kadunce, N. T.; Reisman, S. E. Nickel Catalyzed Asymmetric Reductive Cross-Coupling between Heteroaryl Iodides and α-Chloronitriles. J. Am. Chem. Soc. **2015**, 137, 10480−10483. c) Johnson, K. A.; Biswas, S.; Weix, D. J. Cross-Electrophile Coupling of Vinyl Halides with Alkyl Halides. *Chem. Eur. J.* **2016**, *22*, 7399 – 7402; d) Shimkin, K. W.; Montgomery, J. Synthesis of Tetrasubstituted Alkenes by Tandem Metallacycle Formation/Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **2018**, *140*, 7074-7078. e) Tu, H-Y.; Wang, F.; Huo, L.; Li, Y.; Zhu, S.; Xhao, X.; Li, H.; Qing, F-L.; Chu, L. Enantioselective Three-Component Fluoroalkylarylation of Unactivated Olefins through Nickel-Catalyzed Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 9604-9611. f) Poremba, K. E.; Kadunce, N. T.; Suzuki, N.; Cherney, A. H.; Reisman, S. E. Nickel-Catalyzed Asymmetric Reductive Cross-Coupling To Access 1,1-Diarylalkanes. *J. Am. Chem. Soc.* **2017**, *139*, 5684-5687. For reductive cross-coupling using a chlorosilane with a Zn reductant, see: g) Lin, T.; Mi, J.; Song, L.; Gan, J.; Luo, P.; Mao, J.; Walsh, P. J. Nickel-Catalyzed Desymmetrizing Cross-Electrophile Coupling of Cyclic *Meso*-Anhydrides. *Org. Lett.* **2018**, *20*, 1191-1194. h) Lin, Z.; Lan, Y.; Wang, C. Synthesis of *gem*-Difluoroalkenes via Nickel-Catalyzed Reductive C–F and C–O Bond Cleavage. *ACS. Catal.* **2019**, *9*, 775-780. i) Chenniappan, V. K.; Peck, D.; Rahaim, R. Nickel catalyzed deoxygenative cross-coupling of benzyl alcohols with aryl-bromides. *Tetrahedron Letters*, **2020**, *61*, 151729. j) Arendt, K. M.; Doyle, A. G. Dialkyl Ether Formation by Nickal-Catalyzed Cross-Coupling of Acetals and Aryl Iodides. *Angew. Chem. Int. Ed.* **2015**, *54*, 9876-9880. h) Chandrachud, P. P.; Wojtas, L.; Lopchuk, J. M. Decarboxylative Amination: Diazirines as Single and Double Electrophilic Nitrogen Transfer Reagents. *J. Am. Chem. Soc.* **2020**, *142*, 21743-21750. i) Ze-Peng, Y.; Freas, D. J.; Fu, G. C. The Asymmetric Synthesis of Amines via Nickel-Catalyzed Enantioconvergent Substitution Reactions. *J. Am. Chem. Soc.* ASAP, doi: 10.1021/jacs.0c13034. For reductive cross-coupling using organic reductants, see Ref 9b

[18] The standard Zn dust used in the reaction was activated with dilute HCl; Fieser, L. F.; Fieser, M. Fieser and Fieser's Reagents for Organic Synthesis, Volume 1; John Wiley and Sons, Inc.: New York, 1967.

[19] Pre-treated Zn was prepared by stirring with 3 equiv of TMSCl in DMA for 30 min before being filtered, washed (DMA), and dried in the glovebox. It was then added to the reaction under otherwise standard conditions.

[20] Without additional TMSCl (Scheme 2b, entry 1) 11% of iodoarene **2** was consumed (using 10 mol % Ni catalyst), which

suggests that while the Ni catalyst is active, in the absence of TMSCl subsequent steps in the catalytic cycle are not operative.

[21] The unaccounted-for mass balance of NHP ester **1a** is likely due to loss of carboxylic acid **4** to the aqueous layer during the work up of the aliquots.

[22] During control reactions in the absence of TMSCl, N-hydroxyphthalimide is formed alongside carboxylic acid **4** and phthalimide is not detected. This suggests that carboxylic acid **4** arises *via* hydrolysis and not through a reductive mechanism.

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[25] The remainder of the mass balance in this reaction is very likely carboxylic acid **8**. An exact yield of **8** was not obtained as the compound was partially lost when the reaction mixture was filtered over Si upon workup.

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[29] The details of the interaction between NHP ester **1a** and TMSCl leading to decarboxylation are not yet fully understood. Experimental and computational studies are underway to clarify this interaction.

[30] Another plausible catalytic cycle involves radical capture by a Ni(0) species followed by oxidative addition of the resulting Ni(I) complex with the iodoarene. Both catalytic cycles are consistent with the data.