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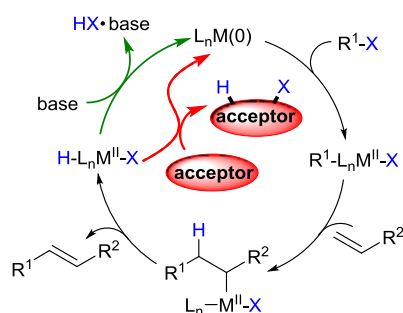
Unlocking Mizoroki-Heck Type Reactions of Aryl Cyanides Using Transfer Hydrocyanation as a Turnover-Enabling Step

Xianjie Fang[†], Peng Yu[†], Gabriele Prina Cerai and Bill Morandi*

Abstract: A new transfer hydrofunctionalization strategy to turnover $H-M(II)-X$ complexes has enabled both intra- and intermolecular Mizoroki-Heck (MH) type reactions of aryl cyanides that are challenging to realize under traditional, basic conditions. Initially, a cascade carbonickelation/MH reaction of 2-cyanostyrenes was achieved using a key alkyne transfer hydrocyanation step. Mechanistic experiments supported the proposed catalytic cycle, including the turnover-enabling transfer hydrocyanation step. The reactivity was then extended to the intermolecular MH reaction of benzonitriles and styrenes.

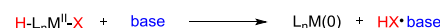
The Mizoroki-Heck (MH)¹ coupling between aryl electrophiles and alkenes has found widespread applications in organic synthesis.² The traditional mechanism of this reaction involves an initial oxidative addition, followed by insertion into an alkene and β -hydride elimination. The $H-M(II)-X$ species generated at the end of the catalytic cycle is then commonly converted back to a $M(0)$ species through the use of a base to enable catalytic turnover (Scheme 1).² A wide range of electrophiles, including halides,³ sulfonates,⁴ diazonium salts,⁵ and hydrazines,⁶ have been used in this mechanistic manifold. However, the MH coupling of less traditional electrophiles, such as ethers,⁷ amides⁸ or cyanides remains a major challenge in this area. Herein, we report a transfer hydrofunctionalization approach to catalyst turnover in MH reactions, a strategy that has enabled, for the first time, the use of a broad range of $Ar-CN$ electrophiles in both intra- and intermolecular MH reactions.

→ traditional base-mediated MH reaction: unknown when $X \equiv CN$
 → transfer approach reported herein: high efficiency when $X \equiv CN$



Scheme 1. Traditional MH mechanism compared to new approach.

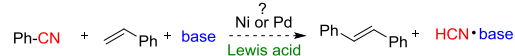
a) Ref. [2]: Traditional MH reactions use a base to regenerate $M(0)$



b) Ref. [13]: Oxidative addition of strong $C-CN$ is facilitated by Lewis acid co-catalysts



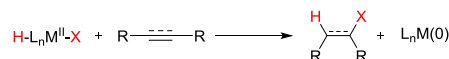
c) Unsuccessful preliminary experiments using a base



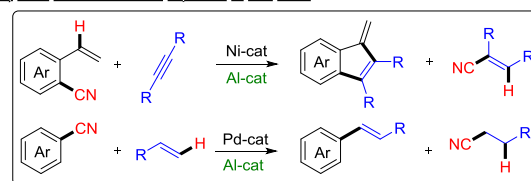
Results: no conversion using base only
low yield using base and Lewis acid

⇒ needs Lewis acid but only low reactivity in the presence of base

d) Our design to circumvent the use of base: transfer hydrofunctionalization



e) New transformations reported in this work



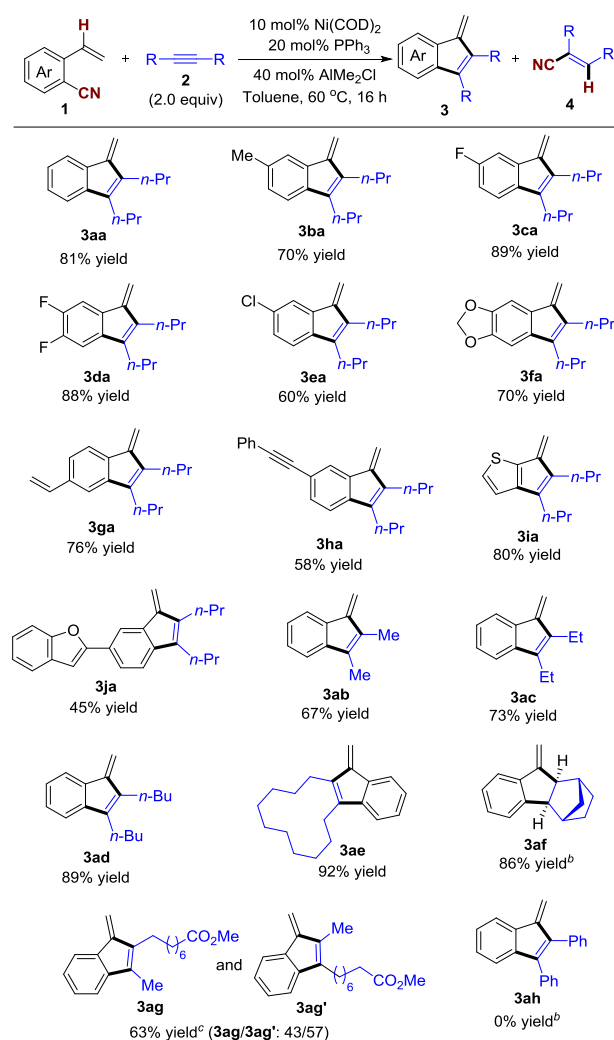
Scheme 2. Reaction design.

The MH-type coupling of $Ar-CN$ electrophiles would provide a complementary methodology for the construction of $C-C$ bonds because aromatic nitriles are widespread compounds that can be easily synthesized from inexpensive precursors (carboxylic acids, amides, aldoximes and methyl arenes) that are not derived from aryl halides.⁹ Aromatic nitriles also often bear substitution patterns that are complementary to aryl halides because the nitrile group, in contrast to halogens, directs aromatic ring functionalization reactions to the meta position due to its strongly electron withdrawing character.⁹ Additionally, the cyano group is unreactive under most cross-coupling conditions and can thus serve as a masked, orthogonal electrophile in a synthetic sequence.¹⁰ To the best of our knowledge, the only example of efficient MH reaction of cyanides has been realized by the group of Chatani¹¹ using a Rh catalyst under base-free conditions, but the scope of this reaction is limited to the use of vinylsilanes as coupling partners. The development of a MH-type coupling that can utilize a broad range of cyano electrophiles¹² and alkenes has been challenging, in part because the most efficient catalytic protocols to activate strong $C-CN$ bonds towards oxidative addition rely on the use of a Lewis acid co-catalyst (Scheme 2b),¹³ a strategy potentially incompatible with the use of bases in the traditional turnover-enabling step of the MH reaction (Scheme 2a). Accordingly, in preliminary experiments (Table S1), we did not observe any MH-type reactivity between benzonitrile and styrene in the presence

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of a base (Scheme 2c). Low reactivity (<10% yield) was observed when combining the use of a base with a Lewis acid under a wide range of reaction conditions, a result demonstrating that: (1) A Lewis acid is important to activate the C–CN bond and; (2) it is difficult to combine the use of Lewis acids with stoichiometric amounts of base due to the low compatibility of these reagents. In need of a new approach, we reasoned that transfer hydrocyanation¹⁴ could, in principle, provide a mechanistically distinct alternative to catalyst turnover in MH reactions (Scheme 2d and 2e) and circumvent the traditional use of base. Such an approach to regenerate the active catalytic species (Ni(0) or Pd(0)) is attractive because of its compatibility with the Lewis acid co-catalyst necessary for efficient oxidative addition of the C–CN bond. The incorporation of a transfer hydrocyanation step in the catalytic cycle would thus enable previously elusive transformations of R–CN and provide a complementary strategy for catalyst turnover in cross-coupling reactions.

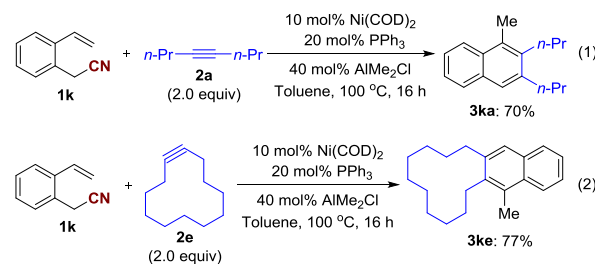


Scheme 3. Scope of the intramolecular MH-type reaction. Reactions carried out on 0.25 mmol scale in toluene (0.5 mL). Yield of isolated product. Yields of **4** are in the SI. ^aThis reaction was carried out at 100 °C. ^cThe isolated yields of two regioisomers.

As highlighted in our recent work,¹⁴ alkene hydrocyanation is a reversible process under Ni catalysis and Al co-catalysis, a feature that could complicate the realization of our novel approach to MH reactions. Therefore, we reasoned that the use of an alkyne instead of an alkene as acceptor for the transfer hydrocyanation step might favor the desired process because alkynes are more reactive towards H–Ni–CN, are less prone to undesired oligomerization and are irreversibly hydrocyanated.^{14,15} With this idea in mind, we designed an intramolecular MH-type reaction¹⁶ that relies on a domino alkyne carbonickelation-MH reaction-alkyne hydrocyanation. The elementary steps of this new reaction consist of an oxidative addition of the Ar–CN bond, alkyne insertion, alkene insertion, β -hydride elimination and catalyst regeneration through alkyne hydrocyanation. The higher reactivity of the alkyne in both the intermolecular insertion step and the hydrocyanation step should facilitate the realization of this novel approach to MH-type reactions.

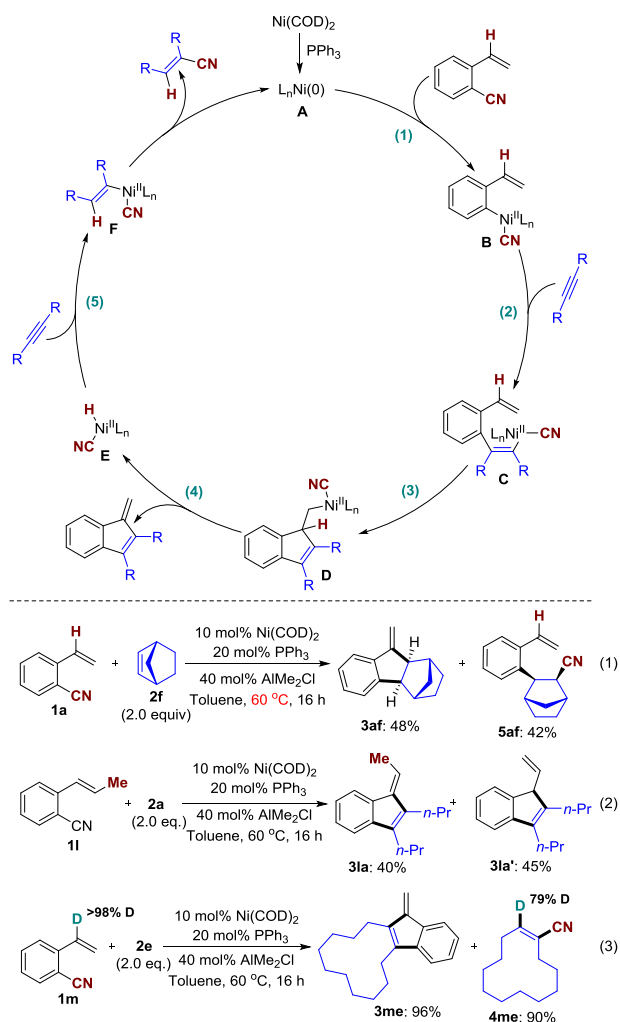
We could verify our hypothesis experimentally through the use of 2-cyanostyrene (**1a**) in the presence of 4-octyne (**2a**). Under optimized conditions (substrate **1a**, 2.0 equiv. alkyne **2a**, 10 mol% Ni(COD)₂, 20 mol% PPh₃, 40 mol% AlMe₂Cl in toluene at 60 °C for 16 h) the desired benzofulvene product **3aa** was obtained in good yield. Importantly, the transfer hydrocyanation product **4a** was also obtained in good yield, a result that clearly supports the proposed transfer mechanism. Control reactions revealed the importance of all the components and confirmed that the addition of base was detrimental to the reaction (Table S2). Importantly, the use of 2-bromostyrene in place of **1a** led to rapid, undesired cyclotrimerization of **2a** under a range of conditions, with no formation of desired product **3aa**. These results demonstrate the divergent reactivity and thus, utility, of the cyano electrophile in this transformation.

We next studied the scope of the reaction (Scheme 3). Halogens and ethers on substrate **1** were tolerated and afforded the products in high yields (**3ca–3fa**). An alkene and an alkyne were also tolerated as substituents and the desired benzofulvene products were obtained in good yields (**3ga** and **3ha**). Heterocycles were also tolerated and afforded the products both when used as substituents or as part of the final heterocyclic product (**3ia** and **3ja**). Both aliphatic and cyclic alkynes were efficient partners in the transformation (**3ab–3ae**, **3ag**). Finally, strained alkenes such as norbornene can also be used in the transformation (**3af**). Importantly, all the experiments provided moderate to good yields of the corresponding transfer hydrocyanation products **4** (see SI for details). The method provides a practical access to benzofulvene derivatives that are widely used in polymer chemistry and organic electronics.¹⁷



Scheme 4. Synthesis of polysubstituted naphthalene compounds.

When using 2-(2-vinylphenyl)acetonitrile (**1k**) as a substrate (Scheme 4), the transformation generated conjugated aromatic products. This reaction likely proceeds through a similar mechanism, although in this case the initially formed product undergoes rapid isomerization and aromatization leading to the thermodynamically more stable product **3ka** and **3ke** in good yield.

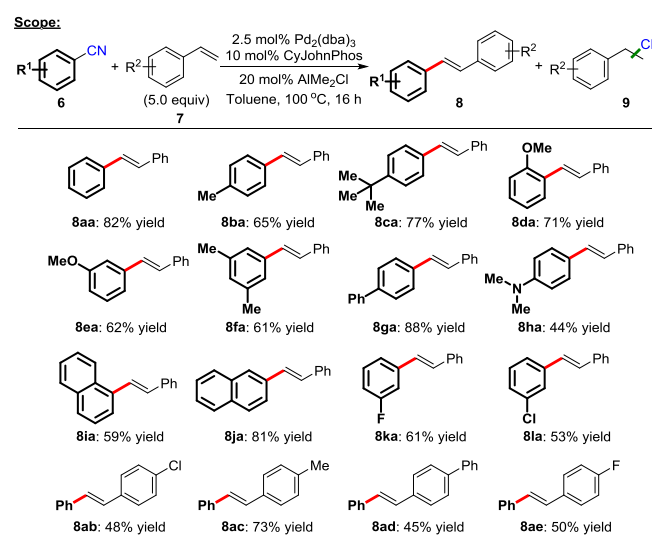


Scheme 5. Proposed catalytic cycle and mechanistic experiments.

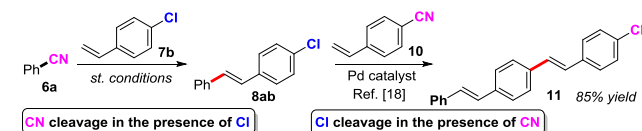
We propose a catalytic cycle for the transformation in Scheme 5. Several control reactions were performed to support this mechanistic picture. Step (2) was confirmed by the isolation, at lower temperature, of reductive elimination product **5af** (Scheme 5, eq 1). The intermediacy of alkyl-Ni complex **D** is supported by an experiment using a *trans*- β methyl styrene derivative **1l** as substrate that resulted in the isolation of two alkene regioisomers (**3la** and **3la'**) derived from the non-regioselective β -hydride elimination of intermediate **D** (Scheme 5, eq 2). Most importantly, the key transfer hydrocyanation of the HCN molecule generated from the MH cyclization is attested by a labelling experiment showing the transfer of DCN to the alkyne

when using labelled substrate **1m** (Scheme 5, eq 3). Collectively, these experiments provide strong support for the proposed mechanism and clearly establish the transfer hydrocyanation as the turnover-enabling step in the process.

After having established that transfer hydrocyanation of an alkyne acceptor is a viable approach to catalyst turnover in MH-type cyclization reactions, we turned our attention to the use of less reactive alkene acceptors in intermolecular MH-type reactions of aryl cyanides. Initial reactions between benzonitrile (**6a**) and styrene (**7a**) under Ni-catalysis proved challenging and led to low yields of the products. However, after some additional optimization (Table S3), we identified a Pd-based system (Scheme 6) that gave 82% yield of the MH product **8aa**. The corresponding hydrocyanation product **9aa** was also obtained in good yield as a mixture of regioisomers. The scope of this reaction is presented in Scheme 6. A range of benzonitrile **6** and styrene substrates **7** were successfully employed in the transformation and led to the formation of the corresponding stilbenes. The transformation tolerates several functional groups, including electrophiles (Cl, OMe) that can be used as substrates for other cross-coupling reactions. The two-step iterative synthesis of π -conjugated molecule **11** using two fully orthogonal MH protocols further demonstrates the synthetic potential of our transformation.



2-step synthesis of a π -conjugated molecule using two fully orthogonal Heck reactions:



Scheme 6. Scope of the intermolecular Heck-type reaction and application in chemoselective iterative coupling reactions.

In conclusion, we have presented a new transfer hydrofunctionalization approach to catalyst turnover in MH reactions that has enabled, first the time, a broad range of aryl cyanides and alkenes to be utilized as substrates. A cascade

intramolecular MH-type cyclization under Ni-catalysis, using an alkyne acceptor, and an intermolecular coupling under Pd-catalysis, using an alkene acceptor, were realized using this novel concept, a result that demonstrates the very broad potential of this mechanistically distinct approach in MH reactions.

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Keywords: Mizoroki-Heck • Alkene • Cyanide • Alkyne • Transfer Hydrofunctionalization

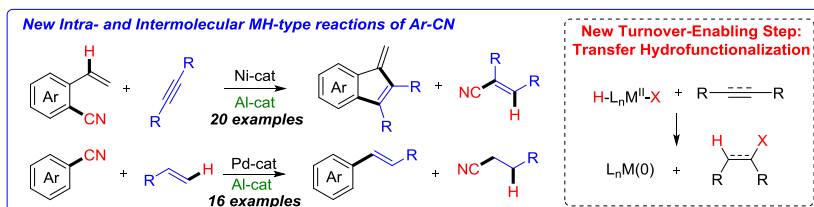
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Mizoroki-Heck
Type Reactions of
Aryl Cyanides
Using Transfer
Hydrocyanation

Layout 2:

COMMUNICATION

A new transfer hydrofunctionalization strategy to turnover H–M(II)–X complexes has enabled elusive intramolecular and intermolecular Mizoroki-Heck (MH) type reactions of aryl cyanides. A cascade intramolecular MH-type cyclization under Ni-catalysis, using an alkyne acceptor, and an intermolecular coupling under Pd-catalysis, using an alkene acceptor, were realized using this novel concept.

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Title