

Communication

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# Overcoming Selectivity Issues in Reversible Catalysis – A Transfer Hydrocyanation Exhibiting High Kinetic Control

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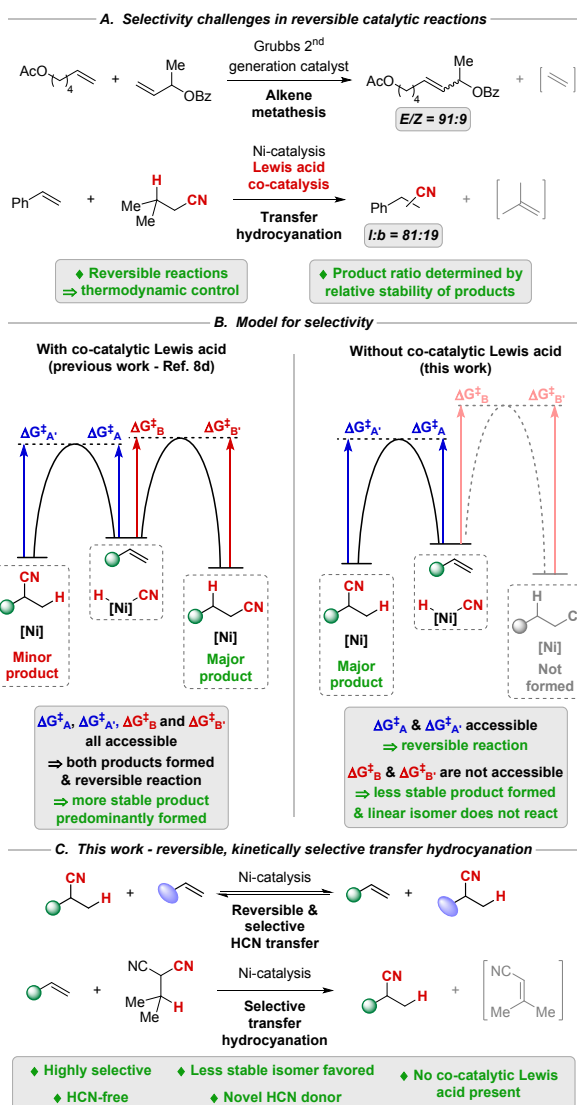
*Supporting Information. Detailed experimental procedures and characterization data.*

**ABSTRACT:** Reversible catalytic reactions operate under thermodynamic control and thus establishing a selective catalytic system poses a considerable challenge. Herein, we report a reversible transfer hydrocyanation protocol that exhibits high selectivity for the thermodynamically less favorable branched isomer. Selectivity is achieved by exploiting the lower barrier for C–CN oxidative addition and reductive elimination at benzylic positions in the absence of co-catalytic Lewis acid. Through the design of a novel type of HCN donor, a practical, branched-selective, HCN-free transfer hydrocyanation was realized. The synthetically useful resolution of a mixture of branched and linear nitrile isomers was also demonstrated to underline the value of reversible and selective transfer reactions. In a broader context, this work demonstrates that high kinetic selectivity can be achieved in reversible transfer reactions, thus opening new horizons for their synthetic applications.

One fundamental drawback of metathesis and shuttle catalysis reactions is that, due to their inherent reversibility, they operate under thermodynamic control. This often leads to mixtures of products being formed such as in the case for alkene metathesis wherein the ratio of *E:Z* products is determined by their relative stability (Scheme 1A).<sup>1</sup> In a similar manner, the transfer hydrocyanation reported by our group also leads to mixtures of products, with the reaction of styrene affording an 81:19 mixture of linear and branched products, respectively.<sup>8d</sup> Again, this ratio reflects the relative thermodynamic stability of the two regioisomers.<sup>12</sup>

**Scheme 1. Context of the work.**

Reversible catalytic reactions such as alkene metathesis<sup>1</sup> and transfer hydrogenation<sup>2</sup> have found a plethora of applications in diverse fields of chemistry.<sup>3,4,5</sup> Given their value to the synthetic practitioner, our group and others have investigated expanding these transformations to include the metathesis of other bonds and the transfer of functionality other than H<sub>2</sub>.<sup>6,7,8</sup> These reaction paradigms offer numerous advantages such as implementing safer protocols avoiding the use of highly toxic reagents or unlocking previously unknown transformations. Our group applied a shuttle catalysis strategy to achieve transfer hydrocyanation whilst avoiding the use of highly toxic and volatile HCN.<sup>8d</sup> Notably, this strategy also enabled the first example of dehydrocyanation of aliphatic nitriles. These results have subsequently spurred the development of other transfer hydrocyanation protocols that circumvent the use of HCN<sup>9</sup> as well as opening new approaches for other cyanation reactions using relatively non-toxic cyanide sources.<sup>10,11</sup>



These reactions are reversible because the products possess the same functionality as the starting materials and thus are roughly ergoneutral (Scheme 1B). Hence, in most cases, the barrier for both the forward and reverse reaction is similar. In reactions where the formation of more than one isomer is kinetically accessible, the selectivity is determined by their relative stability. To override this thermodynamic bias in selectivity, the barrier for one of the isomers must be kinetically inaccessible. In this scenario, the reaction will remain reversible but restricted to a smaller subset of isomers. This is the case in Z-selective alkene metathesis, wherein the intricate design of the catalysts lead to a significantly higher activation barrier for the formation and reaction of E-alkenes.<sup>13</sup> As a result, Z-alkenes are exclusively formed and, conversely, if a mixture of Z- and E-alkenes are present, then only the Z-alkenes will react. To date, there are no analogous examples of a transfer reaction that has been demonstrated to be reversible and kinetically selective.

Instead, most reversible transfer reactions proceed to form the more thermodynamically stable products.

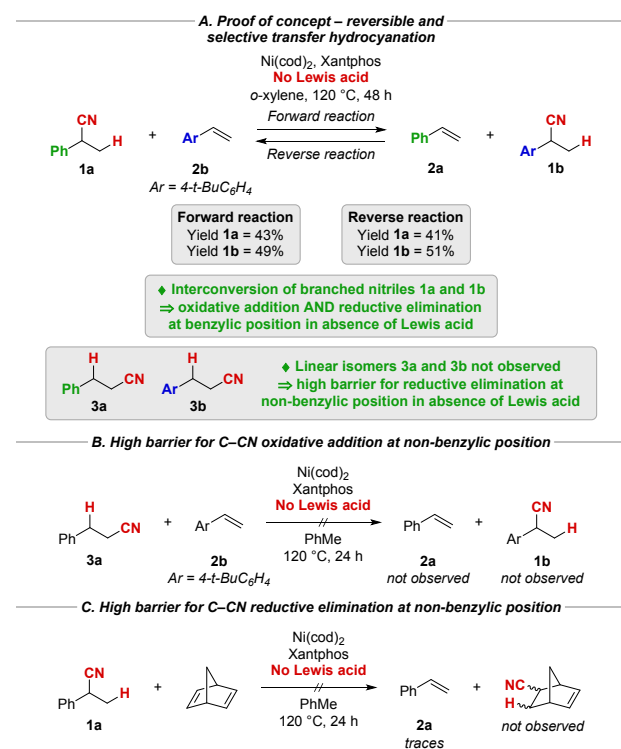
Inspired by the precedent set by Z-selective alkene metathesis to obtain a selective and reversible metathesis manifold,<sup>13</sup> we sought to develop a protocol that would enable a selective and reversible transfer hydrocyanation of styrenes by manipulating the difference in the barrier for the formation of the branched and linear nitrile isomers to selectively form the less stable branched isomer (Scheme 1C). This would be complementary to the linear selectivity obtained in previous transfer hydrocyanation reactions.<sup>8d,9a</sup> Several groups have demonstrated that co-catalytic Lewis acids help facilitate both C–CN oxidative addition and reductive elimination,<sup>14,15</sup> resulting in a thermodynamic mixture of products in transfer hydrocyanation because both the linear and branched isomers are accessible. We surmised that in the absence of a Lewis acid co-catalyst a benzylic stabilization effect could lead to a markedly lower barrier for both the cleavage and formation of the branched nitrile product compared to the linear isomer, unlocking a branched selective transfer hydrocyanation of styrenes.

We verified this hypothesis experimentally through the reaction of 2-phenylpropionitrile **1a** with 4-*tert*-butylstyrene **2b** and found that a mixture of the starting materials with styrene **2a** and branched nitrile **1b** was obtained while the linear isomers (**3a** and **3b**) were not observed (Scheme 2a). This confirms that both the oxidative addition and reductive elimination can occur at the benzylic position in the absence of co-catalytic Lewis acid, whereas the formation of the linear product is considerably more challenging. Performing the reaction in reverse, gave an identical ratio of the two branched nitriles, a strong indicator that the reaction has reached equilibrium. The high barrier to oxidative addition of non-benzylic nitriles with the Lewis acid free system is also implicated by the lack of reactivity observed between 3-phenylpropionitrile **3a** and 4-*tert*-butylstyrene **2b** (Scheme 2b). Furthermore, hydrocyanation of norbornadiene was not observed upon reaction with 2-phenylpropionitrile **1a** (Scheme 2c). This truly underlines the challenging C–CN reductive elimination at non-benzylic positions with this transfer hydrocyanation manifold, as norbornadiene is typically a potent acceptor for transfer reactions.<sup>6d,8c-e</sup> Collectively, these results show that, in the absence of co-catalytic Lewis acid, the reaction is still reversible and kinetically controlled toward selective formation and cleavage of the branched isomer, leaving other positions unreacted.

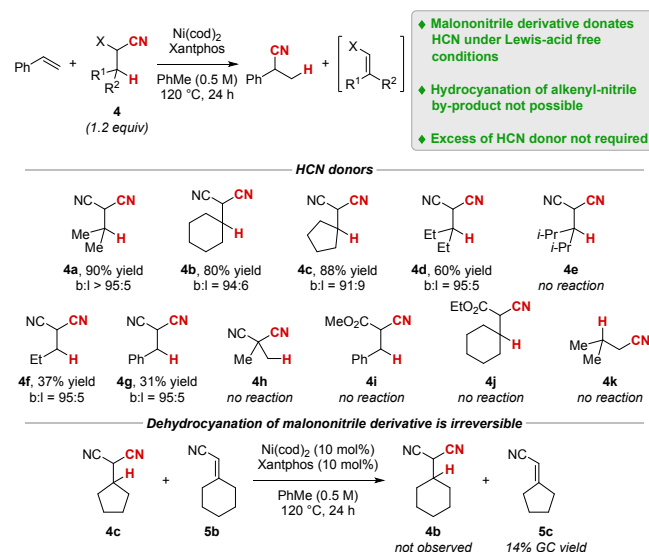
Next, we considered how to develop a practical, HCN-free transfer hydrocyanation process exhibiting such selectivity. While 2-phenylpropionitrile **1a** is a competent HCN donor under the reaction conditions, it is not ideal for use in transfer hydrocyanation as an excess would be required to ensure good conversion of the substrate. Aside from being highly wasteful, this would also present problems with regards to purification and, therefore, an alternative HCN donor was devised. Desirable features include being able to donate

HCN in the absence of a Lewis acid and it should also ideally form a stable alkene by-product that would be unsusceptible to hydrocyanation itself. We reasoned that malononitrile derivatives bearing an aliphatic group could fulfill these criteria while also being simply synthesized from inexpensive starting materials.<sup>16,17</sup> It was anticipated that these species should be activated toward donating HCN to the Ni-catalyst<sup>18,19</sup> and the conjugated alkenyl nitrile by-product should be recalcitrant to undergoing hydrocyanation. Gratifyingly, we discovered that malononitriles bearing a secondary aliphatic substituent (**4a–4d**) afforded high yields of product, although those bearing bulkier substituents (**4e**) failed in the reaction (Scheme 3). A simple isofunctional experiment confirmed that the dehydrocyanation of the reagent is irreversible under the reaction conditions. These results are also supported by comparison of the ground state free energies of reactants and products in the hydrocyanation of styrene **2a** with malononitrile **4a**, which suggests that the reaction is distinctly exergonic ( $\Delta G = -12.9$  kcal/mol at 298 K, see SI for details).

**Scheme 2. Experiments to compare relative ease of C–CN oxidative addition and reductive elimination at benzylic and non-benzylic positions.**



### Scheme 3. Development of novel HCN donors for regioselective transfer hydrocyanation.

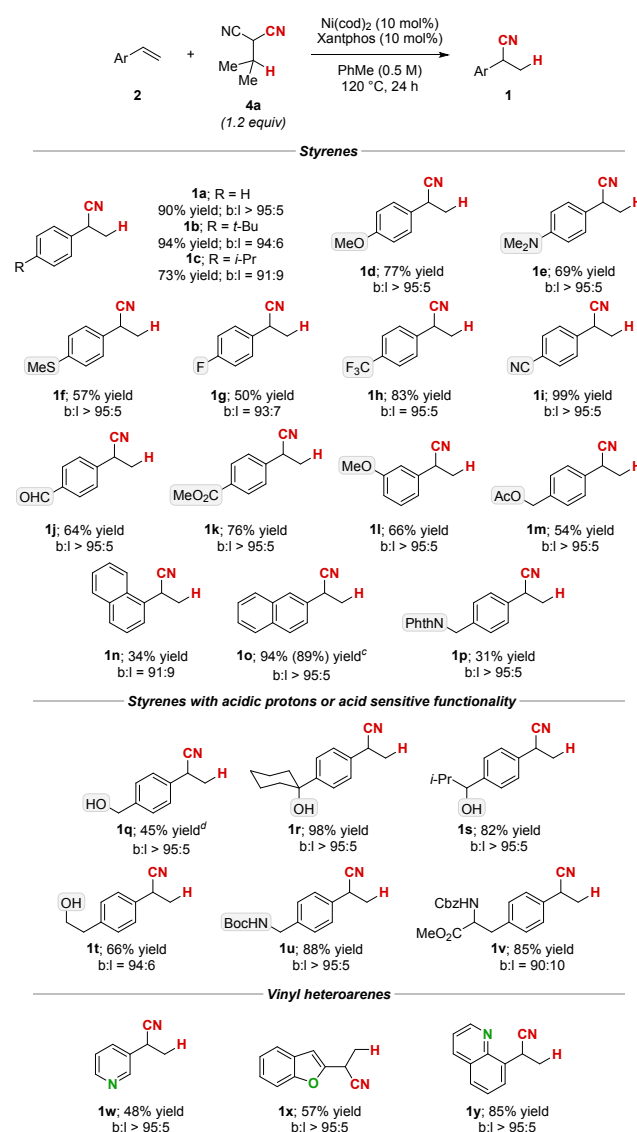


Following further optimization of the reaction conditions, the applicability of this HCN-free, branched-selective transfer hydrocyanation was examined (Scheme 4). A variety of functional groups were well tolerated in the reaction including both electron donating and electron withdrawing moieties. The reaction also affords high yields and selectivities when performed with lower catalyst loadings (10). Besides the high branched selectivity of this new reaction, which is complementary to previous protocols, we were also interested to see if it exhibits greater functional group tolerance, given that the current reaction conditions do not require co-catalytic Lewis acid. Indeed, substrates possessing acidic protons (1q–1v) or a Boc-protected amine (1u) were well tolerated. Finally, common heterocyclic cores (1w–1y) were found to successfully undergo transfer hydrocyanation with high selectivity. In cases with reduced yields, this was primarily due to low conversion.

Interestingly, while studying vinylheteroarenes as substrates in the reaction, a complete switch in regioselectivity was observed with 2-vinylpyridine 6 (Scheme 5). In this case, exquisite selectivity for the linear isomer 7 was observed. This is most likely due to a directing group effect, by the N atom of the pyridine, lowering the otherwise inaccessible energy barrier for C–CN reductive elimination at non-benzylic positions.<sup>20</sup> To further probe this coordinating effect, reaction of 6-methyl-2-vinylpyridine 8 was attempted and this was found to afford a mixture of both the linear (9) and branched (10) isomers, with the latter preferred. This lack of selectivity likely arises from the methyl group interfering with the ligation of the pyridine ring to the metal catalyst, allowing for the normal benzylic stabilization-controlled selectivity to compete with the directing group effect. In addition, linear isomer 7 could act as a HCN donor for hydrocyanation of simple styrenes (see SI for details), suggesting that the pyridine directing group also facilitates C–CN oxidative addition at the non-benzylic

position. Excitingly, even simple, unprotected alcohols (e.g. 11) afforded the linear product 12, suggesting that alcohols can also act as directing groups.

### Scheme 4. Substrate scope for the regioselective, HCN-free transfer hydrocyanation.<sup>a,b</sup>



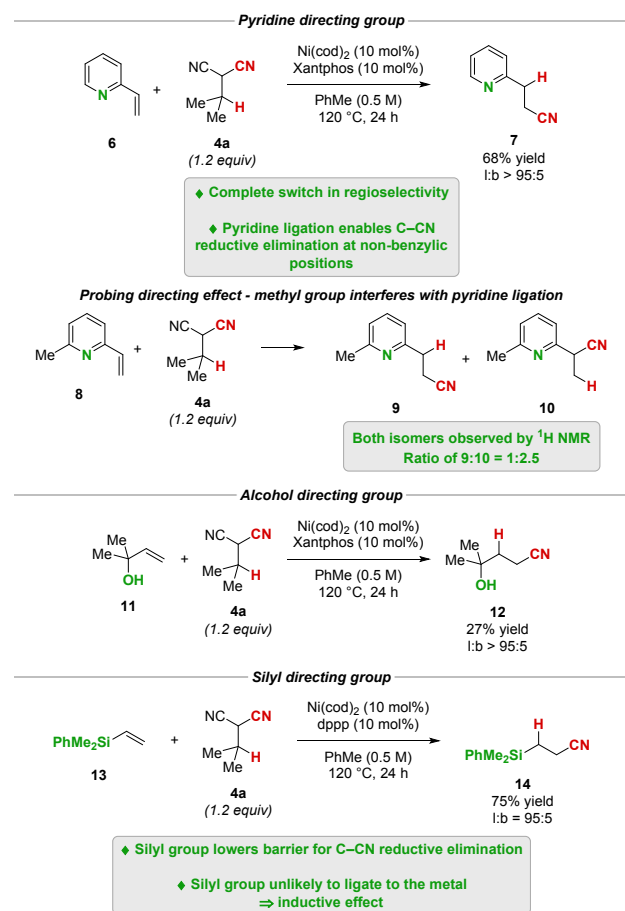
<sup>a</sup>Yields are given for isolated and purified material.

Reactions were conducted on a 0.5 mmol scale.

<sup>b</sup>Regioselectivity was determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>c</sup>Yield in parentheses for reaction performed on 2.0 mmol scale with 2.5 mol% Ni(cod)<sub>2</sub> and Xantphos. <sup>d</sup>Aldehyde 1j was also isolated in 33% yield.

1        Having found that directing groups could be used to  
2        control the selectivity of the reaction, we recognized that this  
3        provided an opportunity to explore less well-documented  
4        directing group effects.<sup>21</sup> In particular, we were attracted to  
5        vinylsilanes as we reasoned that the silyl groups ability to  
6        stabilize both  $\alpha$ -anions and  $\beta$ -cations could provide another  
7        mechanism to lower the energy barrier for reductive  
8        elimination through inductive effects (Scheme 5).  
9        Accordingly, phenyldimethylvinylsilane **13** afforded the  
10       linear nitrile product **14** in high yields and selectivity,  
11       possibly hinting at the build-up of a positive charge at the  $\beta$ -  
12       position to the silicon during the C–CN reductive  
13       elimination.  
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# Scheme 5. Control of regioselectivity by directing groups.<sup>a,b</sup>



<sup>a</sup>Yields are given for isolated and purified material. Reactions were conducted on a 0.5 mmol scale.  
<sup>b</sup>Regioselectivity was determined by <sup>1</sup>H NMR analysis of the crude reaction mixture.

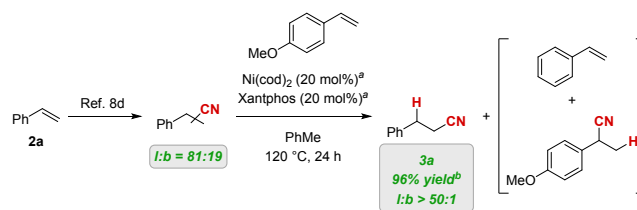
Finally, to further illustrate the value of this reversible and selective reaction, we used this new protocol to resolve the mixture of linear and branched isomers (l:b = 81:19) obtained upon transfer hydrocyanation of styrene **2a** using our previous, thermodynamically controlled protocol (Scheme 6).<sup>8d</sup> By using an excess of commercially available 4-methoxystyrene, selective dehydrocyanation of the branched isomer was achieved while the linear isomer **3a** could be recovered quantitatively with exquisite linear purity. In this manner, the linear nitrile can be obtained in high regiopurity through successive transfer hydrocyanations. This process is analogous to the resolution of a mixture of *E*- and *Z*-alkenes by *Z*-selective ethenolysis to afford enrichment of the *E*-alkene content.<sup>22</sup>

Preliminary deuterium labeling studies resulted in a statistical distribution of deuterium at both the branched and linear positions (Scheme 7). This suggests that a rapid pre-equilibrium has been reached and that the barrier for hydride insertion and  $\beta$ -hydride elimination is likely to be

insignificant compared to the barrier for C–CN reductive elimination. Thus, a rapid scrambling of the hydrogens at the branched and linear positions can occur. This result further verifies that selectivity in our reaction arises from the insurmountable barrier for C–CN reductive elimination at the linear position in the absence of co-catalytic Lewis acid.

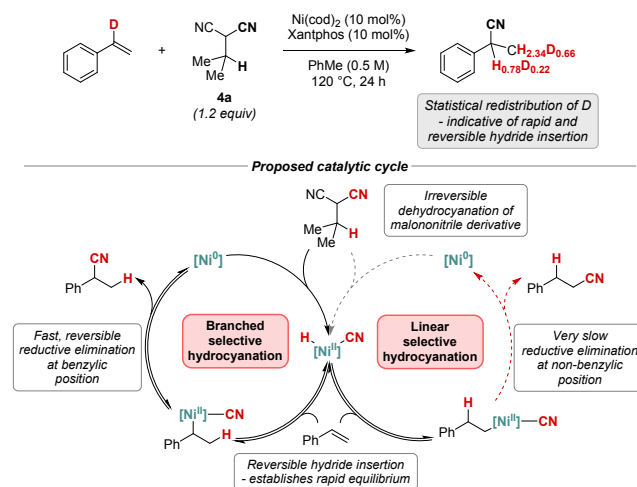
This observation, combined with the results shown in Schemes 2 and 3, allows us to understand the origins of the branched selectivity (Scheme 7). Irreversible dehydrocyanation of the malononitrile generates the corresponding H–Ni–CN intermediate. Rapid and reversible alkene insertion into the Ni–H bond allows for an equilibrium to be established between the branched and the linear alkyl nickel intermediates. Finally, reversible reductive elimination to form the desired branched isomer occurs with high kinetic control over formation of the linear isomer.

## Scheme 6. Resolution of a regioisomeric mixture by selective dehydrocyanation.



<sup>a</sup>Catalyst loadings are reported with respect to the amount of the branched isomer in the regioisomeric mixture. <sup>b</sup>The yield was calculated by reference to an internal standard by GC-FID analysis and is given with respect to the amount of the linear isomer in the regioisomeric mixture.

## Scheme 7. Labeling studies and proposed catalytic cycle.



In conclusion, we have discovered a HCN-free transfer hydrocyanation manifold that exhibits high kinetic selectivity for the thermodynamically less stable, branched

1 isomer but, significantly, also remains reversible. Key to this  
2 selectivity is the lower barrier for C–CN oxidative addition  
3 and reductive elimination at the benzylic position in the  
4 absence of co-catalytic Lewis acid. This manifold was  
5 exploited to achieve a highly selective transfer  
6 hydrocyanation of styrenes by using a novel design of HCN  
7 donor. To date, no other transfer reactions have been  
8 demonstrated to be both kinetically selective and reversible.  
9 Extending this concept could have enormous potential in  
10 organic synthesis, opening new strategies to both selectively  
11 functionalize multiple bonds and, through the reverse  
12 reaction, selectively defunctionalize complex molecules.  
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## ASSOCIATED CONTENT

### Supporting Information

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

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### Notes

A patent application for transfer hydrocyanation has been filed (US2019031602 (A1)).

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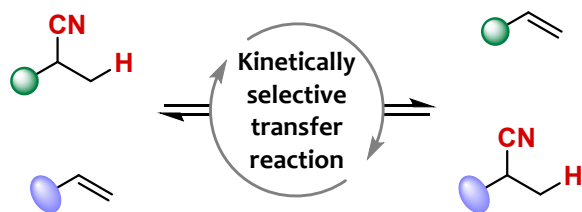
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- ♦ *HCN-free transfer hydrocyanation*
- ♦ *reversible reaction*
- ♦ *selective for thermodynamically less stable isomer*
- ♦ *new HCN donor*
- ♦ *resolution of regioisomeric mixture*