Late-Stage Carbon Isotope Exchange of Aryl Nitriles through Ni-Catalyzed C−CN Bond Activation

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ABSTRACT: A facile one-pot strategy for ^{13}CN and ^{14}CN exchange with aryl, heteroaryl, and vinyl nitriles using a Ni phosphine catalyst and BPh_3 is described. This late-stage carbon isotope exchange (CIE) strategy employs labeled $Zn(CN)_2$ to facilitate enrichment using the non-labeled parent compound as the starting material, eliminating *de novo* synthesis for precursor development. A broad substrate scope encompassing multiple pharmaceuticals is disclosed, including the preparation of [^{14}C]belzutifan to illustrate the exceptional functional group tolerance and utility of this labeling approach. Preliminary experimental and computational studies suggest the Lewis acid BPh_3 is not critical for the oxidative addition step and instead plays a role in facilitating CN exchange on Ni. This CIE method dramatically reduces the synthetic steps and radioactive waste involved in preparation of ^{14}C labeled tracers for clinical development.

Radiolabeled pharmaceuticals play a critical role in the discovery and development of drug candidates.[1-2] These tracers assist in determining the fates of active pharmaceutical ingredients (APIs) and their metabolites, including (pre)clinical absorption, distribution, metabolism, and excretion (ADME), and pharmacokinetics.[3-4] Generally, carbon-14 (^{14}C, $t_{1/2}$ = 5730 years) is the radionuclide of choice for tracer synthesis to support drug disposition studies during late phase development as ^{14}C can be embedded directly into metabolically stable positions of the carbon framework of the target molecule, affording a robust radiolabeled species. This stability provides an advantage to that of ^{3}H ($t_{1/2}$ = 12.32 years) labeled tracers, which can lose the label under physiological conditions through ^{3}H/^{1}H exchange, hydroxylation, and other metabolic pathways.[5] However, a major limitation of ^{14}C-labeled compounds is the need for costly and time consuming *de novo* synthesis due to the limited selection of ^{14}C starting materials, which ultimately leads to the production of large amounts of radioactive waste and contamination.

A survey of pharmaceutical compound libraries, drug candidates, and FDA approved therapeutics reveals that ArCN moieties are pervasive throughout (Figure 1A), with the nitrile group serving as a common target for radiolabeling.[6-8] Previous methods for preparation of isotopically labeled nitrile moieties have relied upon multi-step syntheses of aryl halide precursors[9-10], followed by additional transformations to access radiolabeled APIs (Figure 1B). Frequently, these synthetic routes are significantly lengthier than those to the unlabeled APIs due to the need to incorporate ^{14}C late in the synthesis to minimize radioactive handling and the absence of commercial Ar-^{14}CN building blocks.[11] With these considerations in mind, we envisioned a single-step carbon isotope exchange (CIE) strategy whereby isotopically labeled cyanide could be incorporated into unlabeled ArCN APIs with complex molecular structures, *e.g.* belzutifan, a promising renal cell carcinoma (RCC) therapeutic[12-13] (Figure 1C).

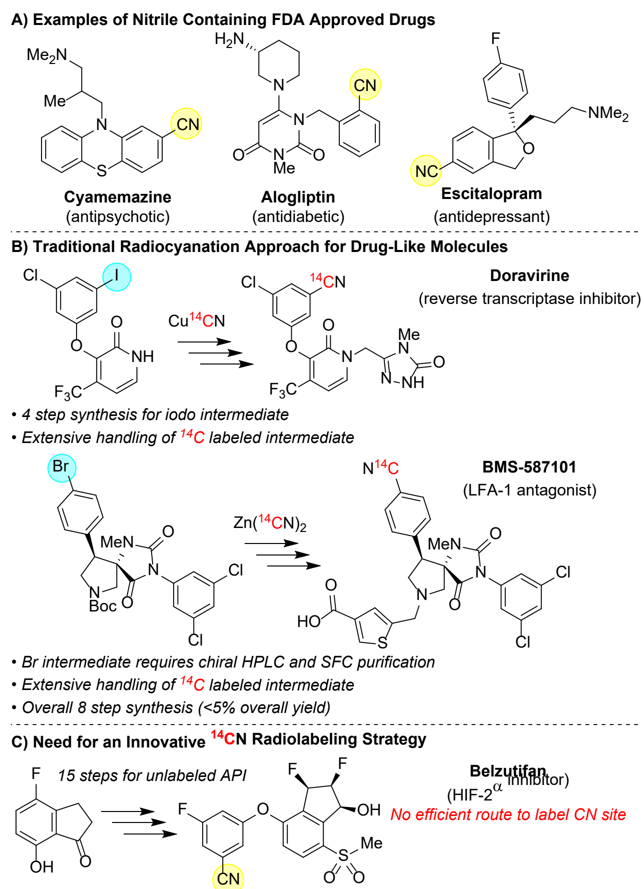


Figure 1. Examples of commercial pharmaceuticals containing nitriles and common radiolabeling strategies.

Late-stage CIE, akin to more common and facile hydrogen isotope exchange (HIE), allows for the streamlined production of the labeled compounds, and has become an emerging concept and an active area of research.[14] The pioneering methods from Gauthier,[15] Baran,[16] and Cantat/Audisio[17] using ^{13}CO or $^{13}CO_2$, to facilitate CIE showed the power of utilizing transition metal catalysts to achieve C–C bond activation, allowing for a sustainable late-stage carbon isotope enrichment strategy for pharmaceutically relevant small molecules. Despite added progress in this arena[18-22], CIE labeling approaches are limited to carboxylic acids, revealing the unmet need for new CIE methods to address the diverse functional groups present in pharmaceuticals and natural products, and ideally employing easily handleable solid labeling sources (Figure 2A).[23] Herein we report a novel CIE strategy which is the first to employ Ar-CN exchange and demonstrate its utility for incorporating ^{13}C or ^{14}C labels (Figure 2B). This one-step approach offers broad substrate scope (*vide infra*) and uses both a common, solid ^{13}C/^{14}C source and air-stable catalyst precursor. Taken together, this CIE method delivers a robust and practical radiolabeling strategy for nitrile-containing pharmaceuticals and intermediates in drug development, and addresses a critical gap in the assembly of carbon isotope labeling methods.

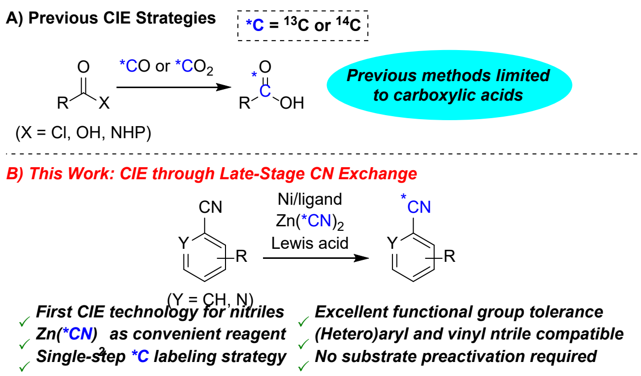
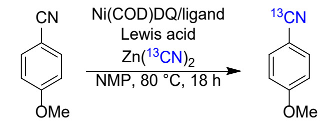


Figure 2. Reported CIE strategies compared to this work.

We focused our attention on Ni catalysis due to the literature precedent for oxidative addition of C–CN bonds.[24] We began our studies by examining multiple commercially available Ni(II) complexes as potential CIE precatalysts, using 4-methoxybenzonitrile (**1a**) as the substrate, $AlMe_3$ as the Lewis acid, and Zn $(^{13}CN)_2$ as the labeling source (a non-radioactive surrogate for $Zn(^{14}CN)_2$), along with an array of solvents (SI, Table S1). From these studies, we identified reaction conditions using $NiCl_2(PMe_3)_2$, $AlMe_3$, and 1.2 equiv $Zn(^{13}CN)_2$ in NMP[25] giving 73% ^{13}C enrichment and 60% isolated yield of the labeled product **2a** (Table 1, entry 1). Based on the equivalents of $Zn(^{13}CN)_2$ employed, the theoretical maximum incorporation was 71% (assuming no isotope effect), demonstrating that the reaction proceeded to equilibrium. It should also be noted that 100% incorporation is unnecessary as this level of ^{14}C enrichment is suitable for both clinical (~20 μCi/mg) and preclincal (≥20 μCi/mg) ADME related radiolabeling studies.[26] Interestingly, other than AlR_3 species, none of the other Lewis acids examined provided ^{13}C incorporation (SI, Table S1). Replacing $AlMe_3$ with the more air-stable solid alternative $(Me_3Al)_2$·DABCO[27] allowed this CIE method to be set-up on the bench top without the need for an inert atmosphere, giving the corresponding product with 54% enrichment (SI, Table S3).

Encouraged by these preliminary results, we sought to identify a Lewis acid that would be more functional group tolerant than the highly reactive $AlMe_3$. However, we suspected that $AlMe_3$ was serving the dual roles of reducing the Ni(II) precursors to the necessary Ni(0) oxidation state, and promoting oxidative addition of the Ar-CN bond.[28-32] By changing to the air-stable, commercially available Ni(0) precursor Ni(COD)DQ,[33] a reductant was no longer necessary, allowing for the evaluation of milder Lewis acids (Table 1, entries 2-8).

Table 1. Optimization of CIE with 1a[a]



1a 2a

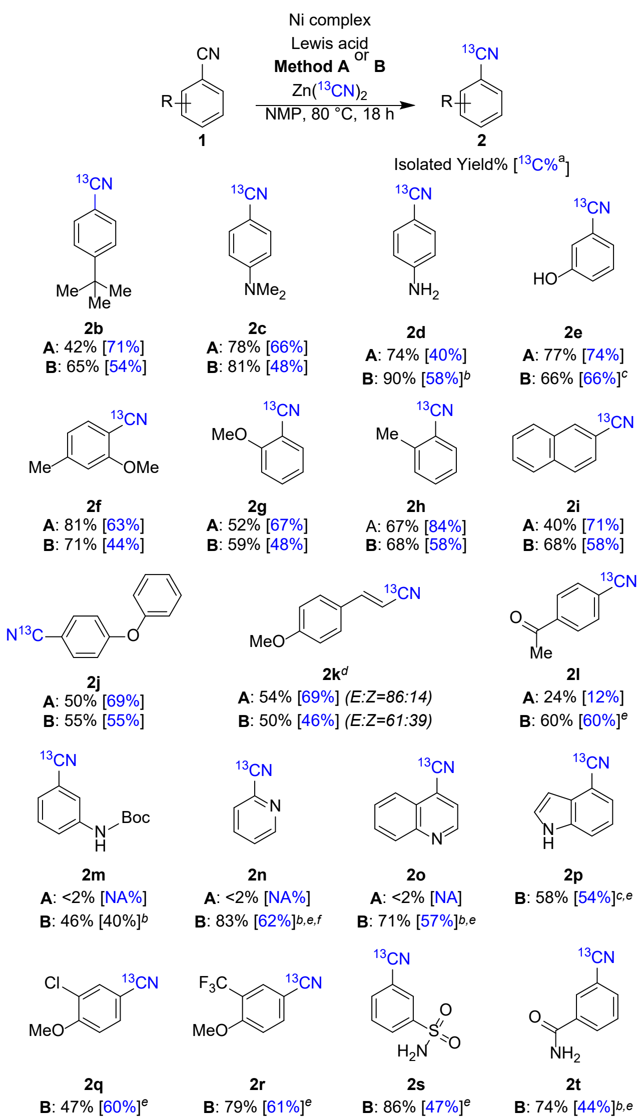
Entry	Ligand	Lewis acid	$Zn(^{13}CN)_2$ (equiv)	Yield %[b]	%^{13}C[c]
1[d]	PMe_3	$AlMe_3$	1.2	60	73
2	PPh_3	$AlCl_3$	0.5	47	0
3	PPh_3	BPh_3	0.5	35	17
4	PPh_3	BF_3·OEt_2	0.5	20	0
5	PPh_3	$Ho(OTf)_2$	0.5	15	0
6	PPh_3	$Zn(OTf)_2$	0.5	20	0
7	PPh_3	TMSOTf	0.5	26	0
8	PPh_3	TFAA	0.5	32	0
9	**PMe_3**	**BPh_3**	**1.2**	**91**[e]	**58**
10	PMe_3	none	1.2	93	0
11[f]	PMe_3 (No Ni)	BPh_3	1.2	>95	0
12	PMe_3	$B(Mes)_3$	1.2	94	0
13	PMe_3	$B(C_6F_5)_3$	1.2	94	0
14	$PPhMe_2$	BPh_3	1.2	58	38
15	PPh_2Me	BPh_3	1.2	>95	14

[a]Reaction conditions: **1a** (0.5 mmol), 15-20 mol% Ni(COD)DQ, 2:1 ratio of Ligand:Ni, $Zn(^{13}CN)_2$, 60-80 mol% Lewis acid, and NMP (2 mL) at 80 ºC for 18 hours. [b]HPLC yield. [c]Percent incorporation of ^{13}C isotope. [d]$NiCl_2(PMe_3)_2$ used instead of Ni(COD)DQ. [e]Isolated yield. [f]No Ni(COD)DQ.

From the Lewis acids examined, BPh_3 was the only one to afford any meaningful ^{13}C enrichment for product **2a** (entry 3). By employing this Ni(0) source with the optimal ligand (PMe_3) and $Zn(^{13}CN)_2$ loadings (1.2 equiv) – conditions obtained from our preliminary studies – we obtained the labeled compound **2a** with 58% ^{13}C enrichment in 91% yield (entry 9). No exchange was observed without the use of BPh_3 (entry 10) or in the absence of Ni(COD)DQ (entry 11), inconsistent with an S_NAr pathway. Alternative triarylborane species and related phosphines were evaluated in combination with Ni(COD)DQ (entries 12-15); however, both BPh_3 and PMe_3 were found to be optimal for promoting the desired CN exchange.

We then deployed the optimized conditions with $AlMe_3$ and BPh_3 to assess the compatibility of these methods with a series of aryl nitriles (Figure 3). Overall, $AlMe_3$ (Method A) delivered good to excellent ^{13}C isotope enrichment and yield of aryl and vinyl nitriles **2b-k**, while BPh_3 (Method B) also afforded moderate to good ^{13}C incorporation with slightly higher isolated yields. Substrates with highly coordinating groups (**1d** and **1e**) required additional BPh_3 (2 equiv) and/or Ni catalyst loading to achieve high ^{13}C incorporation. This finding with excess BPh_3 is in contrast to what Jones and co-workers reported, where the rate of Ar-CN oxidative addition was much slower when >1 equiv of Lewis acid was utilized.[29]

Figure 3. Aryl Nitrile CIE Scope

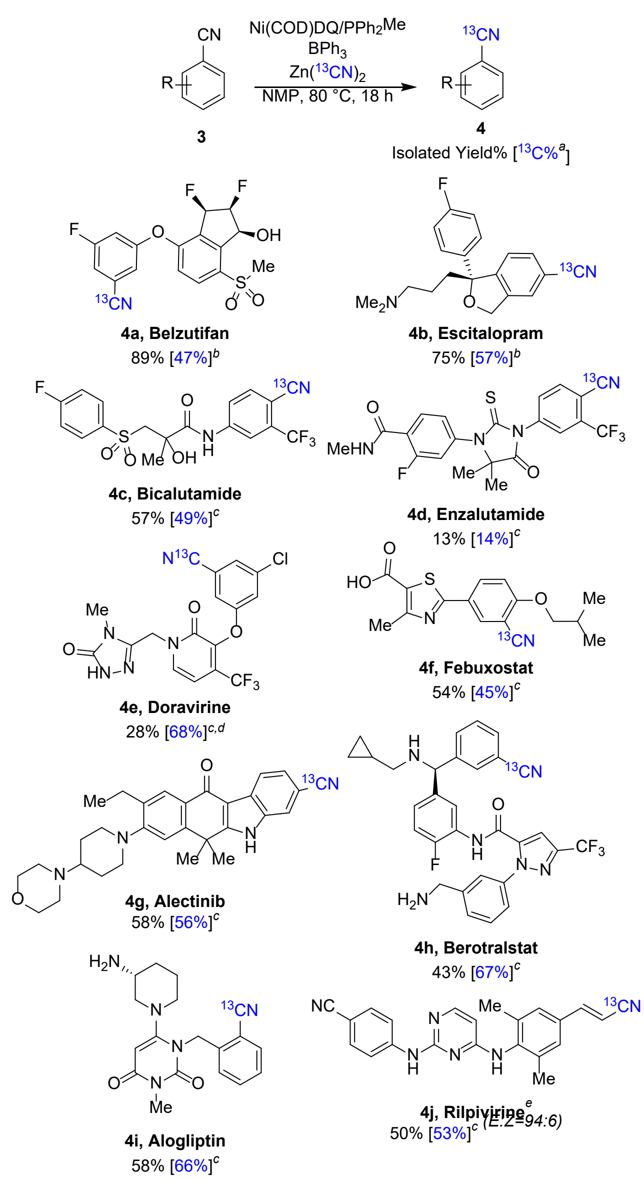


Method A: **1** (0.5 mmol), $NiCl_2(PMe_3)_2$ (0.2 equiv), $Zn(^{13}CN)_2$ (1.2 equiv), $AlMe_3$ (0.8 equiv) and NMP (2 mL); **Method B**: **1** (0.5 mmol), Ni(COD)DQ (0.2 equiv) PMe_3 (0.4 equiv) $Zn(^{13}CN)_2$ (1.2 equiv), BPh_3 (0.8 equiv) and NMP (2 mL). [a]Percent incorporation of ^{13}C isotope. [b]2 equiv of Lewis acid used. [c]Lewis acid (2 equiv), Ni complex (0.4 equiv), ligand (0.8 equiv) at 100 ºC. [d]**1k** used as a mixture (*E:Z*=44:56), ratios determined by ^{1}H-NMR spectroscopy. [e]PPh_2Me instead of PMe_3. [f]HPLC yield.

Method A was not compatible with base-sensitive substrates **1l** and **1m** and resulted in nearly complete compound decomposition and little to no exchange. Additionally, nitrogen-containing heterocycles **1n** and **1o** also performed poorly, leading to substrate decomposition. By contrast, Method B, with the milder Lewis acid BPh_3, proved to be effective for preparing base-sensitive species **2l** and **2m**. Furthermore, by switching from PMe_3 to PPh_2Me, and using excess BPh_3 in the presence of basic nitrogens, heterocyclic and electron deficient arenes **2n**-**t** were obtained in both high yields and ^{13}C-incorporations.[34] We were pleasantly surprised to find that chloroarene **1q** was compatible with Method B as well, affording 60% ^{13}C enrichment and 47% yield, despite competing Ar-Cl cyanation[35].

Given the low functional compatibility of Method A, we applied Method B to an array of pharmaceutically relevant therapeutics - many composed of complex molecular scaffolds - in order to assess the true functional group tolerance and utility of this CIE strategy (Figure 4). With these conditions, we observed good overall ^{13}C enrichments and yields for functionally diverse drugs (**3a**-**c**) compromising of aryl ether, alkyl alcohol, amide, and sulfone moieties. Low ^{13}C incorporation and product recovery were obtained with enzalutamide (**4d**), even with increased catalyst and temperature, presumably due to catalyst deactivation by the thiourea moiety.

Figure 4. Aryl Nitrile Pharmaceutical CIE Scope

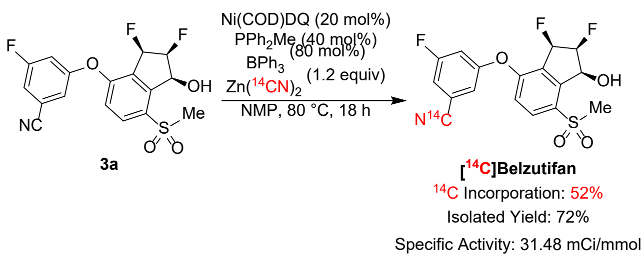


[a]Percent incorporation of ^{13}C isotope. [b]**3** (0.5 mmol), Ni(COD)DQ (0.2 equiv), PPh_2Me (0.4 equiv), $Zn(^{13}CN)_2$ (1.2 equiv), BPh_3 (0.8 equiv), and NMP (2.0 mL) at 80 ºC. [c]**3** (0.5 mmol), Ni(COD)DQ (0.4 equiv), PPh_2Me (0.8 equiv), $Zn(^{13}CN)_2$ (1.2 equiv), BPh_3 (2.0 equiv), and NMP (2.0 mL) at 100 ºC. [d]Reaction conducted at 80 ºC. [e]**3j** standard contained 3% *cis* impurity (*E:Z*=97:3), ratios determined by ^{1}H-NMR spectroscopy.

This methodology was successfully applied to doravirine (**3e**) despite the presence of the Ar-Cl moiety, delivering **4e** with an excellent ^{13}C enrichment of 68%. Pharmaceuticals bearing potentially reactive thiazole, carboxylic acid, indole N-H, 1º and 2º amines moieties (**3f-i**) were also found to be compatible with our labeling strategy, with over 60% ^{13}C enrichment obtained for drugs **4h-i**. Finally, we examined the HIV therapeutic rilpivirine (**3j**) to determine if this CIE approach would exhibit any preference for vinyl or aryl CN exchange. Interestingly, we found **4j** to be exclusively labeled at the vinyl-nitrile position (53% enrichment), showing minimal impact on the *E/Z* ratio (97:3 to 94:6).[36]

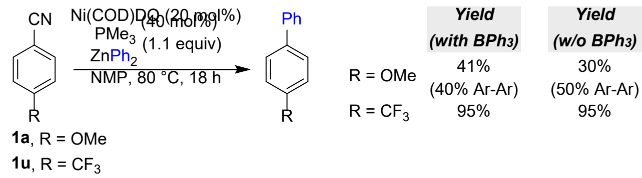
To demonstrate the utility of this CIE strategy for radiosynthesis, we switched to $Zn(^{14}CN)_2$ and examined the labeling of compound **3a**. Employing this late-stage CIE method afforded [^{14}C]belzutifan with a specific activity of 31.48 mCi/mmol (^{14}C incorporation = 51%) and a 72% isolated yield. This high level of specific activity is more than sufficient to satisfy the requirements of a ^{14}C-labeled radiotracer for all preclinical and clinical ADME studies.[3-4, 37] Given the complex 15-step synthesis required for the unlabeled belzutifan, our strategy avoids the need for a time-consuming *de novo* synthesis of a suitable halide precursor for [^{14}C]cyanation. Moreover, this example highlights the unparalleled convenience and efficiency of CIE radiolabeling approach compared to other ^{14}C labeling methods.

Scheme 1. Late-Stage ^{14}CN Exchange on Belzutifan



It is clear that a Lewis acid is critical for this exchange reaction to proceed. To better understand the role of BPh_3, we performed additional experimental and computational investigations. The necessity of Lewis acids in Ni-catalyzed oxidative addition to aryl nitriles remains ambiguous as some studies have suggested that Lewis acids facilitates this process,[30-31, 38] while others have reported they are not required for Ni insertion into C–CN bonds.[39-41] We first investigated if BPh_3 is necessary for oxidative addition to occur by attempting cross-coupling of diphenyl zinc with electron rich and electron poor substrates **1a** and **1u** (Scheme 2). For the electron deficient substrate **1u**, identical results were obtained with or without BPh_3. The reaction with electron-rich substrate **1a** was lower yielding due to the formation of Ar-Ar homocoupling by-products, but still showed significant desired cross coupling both in the presence and absence of BPh_3 (41% vs 30%, respectively). Given that no ^{13}CN exchange was observed in the presence of $Zn(OTf)_2$ during our optimization trials (Table 1, entry 6), the possibility of $ZnPh_2$ acting as a Lewis acid seemed unlikely. As such, these results indicate that inclusion of a Lewis acid (i.e. BPh_3) is not required for the oxidative addition step in this CN exchange process.

Scheme 2. Dependence of BPh_3 on Oxidative Addition and Cross Coupling of Ar-CN



The mechanism of Ni-catalyzed oxidative addition has been previously studied both experimentally and computationally. Jones and coworkers reported that the Ni(0) fragment [(dippe)Ni] forms an η^2-CN adduct with benzonitrile, which undergoes reversible oxidative addition upon heating without a Lewis acid.[41] Low-energy η^2-arene species could be identified for some substrates prior to Ni insertion into the C–CN bond, which has been computationally reported to be, in general, the energetically most demanding step for the overall oxidative addition process.[42] A BPh_3 complex of the benzonitrile η^2-CN adduct has also been isolated and characterized.[29]

In light of these studies on a related Ni-phosphine system, we modeled the thermodynamics for the oxidative addition step for our system, as well as the nickel insertion transition state, with or without BPh_3 (Figure 5). The oxidative addition step is roughly thermoneutral ($\Delta G = -0.3$ kcal/mol) without BPh_3 and endergonic by 4.5 kcal/mol with BPh_3. Importantly, the barriers with or without BPh_3 were found to be similar, differing by only 0.6 kcal/mol. These results, taken together with our experimental studies (Scheme 2), suggest that the Lewis acid is not critical in facilitating oxidative addition.

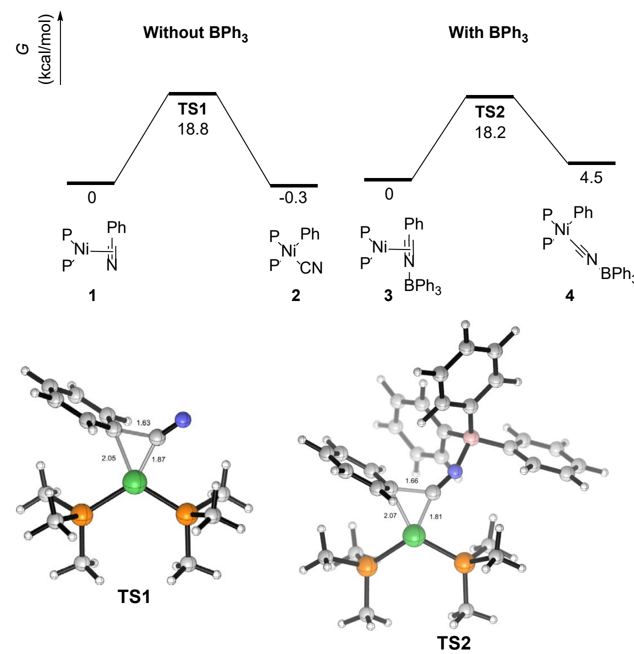


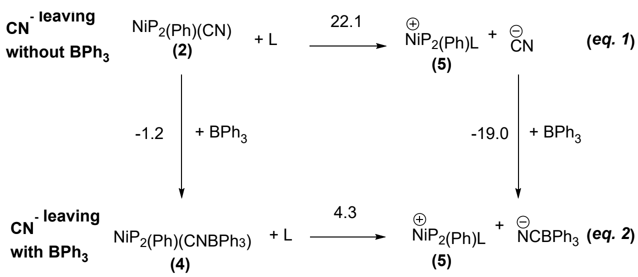
Figure 5. Schematic reaction energy diagrams and computed transition structures for the oxidative addition/reductive elimination without or with BPh_3 (P = PMe_3; M06/def2-TZVPD//B3LYP-D3/6-31+G*,LANL2DZ, PCM(ε = 32.0).

The reductive elimination follows the microscopic reverse of the oxidative addition process (save for the isotopic label). As shown in Fig. 5, the catalyzed barrier for reductive elimination is 18.2 − 4.5 = 13.7 kcal/mol and represents a 5.4 kcal/mol decrease relative to the uncatalyzed pathway (18.8 − (−0.3) =

19.1 kcal/mol). Therefore, the importance of the Lewis acid in promoting reductive elimination cannot be ruled out.

To the best of our knowledge, the mechanism of transmetallation of cyanide groups has not been studied in detail either experimentally or computationally. Indeed, DFT modeling of transition states for the CN-exchange step is not tractable due to the uncertain and likely fluctuating number of NMP molecules bound to Ni and Zn during the cyanide transfer. Nevertheless, to understand the role of BPh_3 here, we explored the energies of the putative ionic intermediates formed upon cyanide departure as shown in Scheme 3[43]. The leaving of cyanide is highly unfavorable in the absence of Lewis acid (**2** → **5** ΔG = 22.1 kcal/mol, eq 1) but is only 4.3 kcal/mol uphill in the presence of BPh_3 (**4** → **5**, eq 2). BPh_3 binds only weakly to the oxidative adduct but is a strong binder of cyanide (ΔG = −19.0 kcal/mol)[44], effectively stabilizing the leaving group. Congruent with these results, Jones and coworkers have reported that BPh_3 could abstract a cyanide ion from the oxidative addition adduct of (dippe)Ni and allyl cyanide, forming the Ni(II) cation [(dippe)Ni(π-allyl)]$^+$ which has been characterized in solution[45], lending further credence to the low reaction energy that we computed for eq 2. As an aprotic solvent, NMP is expected to be a poor solvator for cyanide. Thus, we propose that the main role of the BPh_3 is to facilitate the CN-exchange step by sequestering the cyanide from Ni in the dissociative pathway.

Scheme 3. Thermodynamic cycle illustrating how strong binding of cyanide by BPh_3 promotes departure of cyanide (P = PMe_3, L = NMP; Gibbs energies in kcal/mol).



In summary, we have developed the first CIE method operating on aryl, heteroaryl, and vinyl nitriles allowing for late-stage incorporation of isotopic labels. Our conditions tolerate a wide range of functional groups and use a stable, commercially available Ni(0) source as well as readily available labeled $Zn(CN)_2$. Employing this strategy avoids the need for *de novo* synthesis of isotopically labeled Ar-CN precursors (Ar-X) and instead allows complex APIs or intermediates to be used as the starting material. This was exemplified by employing the non-labeled belzutifan, an API that requires a complex 15-step synthesis, as the starting materials to afford the ^{14}C labeled tracer in just a single-step. Preliminary mechanistic investigations indicate that the Lewis acid employed may play a key role in a dissociative CN-exchange process on Ni, rather than in the oxidative addition step. This method expands the CIE concept beyond carboxylic acid exchange and will become an invaluable radiolabeling strategy for drug development.

ASSOCIATED CONTENT

Supporting Information is available free of charge via the Internet at http://pubs.acs.org."

Experimental and computational details, along with characterization data for ^{13}C-labeled compounds and [^{14}C]belzutifan

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