Electrophilic C(sp^2)–H Cyanation with Inorganic Cyanate (OCN^-) by P^{III}/P^{V}=O-Catalyzed Phase Transfer Activation

by

Shicheng Hu

Submitted to the Department of Chemistry in Partial Fulfillment of the Requirement for the Degree of

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Author_____

Department of Chemistry

May 10th, 2024

Certified by_____

Alexander T. Radosevich

Professor of Chemistry

Thesis Supervisor

Accepted by_____

Elizabeth M. Nolan

Ivan R. Cottrell Professor of Immunology

Associate Department Head, Department of Chemistry

Wir wollen nicht nur wissen wie die Natur ist (und wie ihre Vorgänge ablaufen), sondern wir wollen auch nach Möglichkeit das vielleicht utopisch und anmaßend erscheinenden Ziel erreichen, zu wissen, warum die Natur so und nicht anders ist.

~Albert Einstein, 1929

For mom and dad

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ABSTRACT

A catalytic method for the direct electrophilic cyanation of C(sp^2)–H nucleophiles with sodium cyanate (NaOCN) is reported. Mechanistic experiments show that under solid-liquid phase transfer, an inorganic cyanate is activated by halide displacement on a halophosphonium. Redox catalysis is enabled by the usage of a strained phosphine (phosphetane) so that catalyst turnover from phosphine oxide to phosphine can be easily achieved by the usage of a terminal hydrosilane reductant. These results demonstrate the feasibility of deoxyfunctionalization of insoluble inorganic salts by P^{III}/P^V=O catalyzed phase transfer activation, as exemplified by C(sp^2)–H cyanation with NaOCN as the "CN^+" source.

Thesis Supervisor: Alexander T. Radosevich

Title: Professor of Chemistry

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I have been incredibly fortunate to pursue my undergraduate degree in chemistry at MIT. Over these four years, I have had the complete freedom and support to explore my interests through classes and research. Throughout this journey, I am grateful to many incredible individuals who have supported me, and I would like to take this opportunity to express my heartfelt gratitude to them.

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you and your groups. I would like to extend my gratitude to my high school research advisor, Prof. Gengfeng Zheng (Fudan University). Thank you for introducing me to scientific research, a career I aim to pursue for the rest of my life.

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To my friends and family outside the RadLab: I am immensely grateful for your help and support over the past four years. To the members of the Van Voorhis group, thank you for being fantastic lab mates and always being there to answer my questions! To the members of the Wendlandt group, thank you for welcoming me to group meetings and events and for being

wonderful friends. A special shout-out to Dr. Xin Gu, who has been a “real force of positivity” and an incredibly supportive upperclassman in both high school (despite our non-overlapping times) and at MIT. Thank you for introducing me to MIT and Cambridge/Boston, and for always being a reliable friend. I would like to extend my gratitude to my friends in the Class of 2024, Ana Florescu-Ciobotaru and Cholapat (Turbo) Varongchayakul. Completing the highest-level undergraduate courses as freshman/sophomore was beyond my imagination, and I am glad we tackled them together. Thank you for challenging me to achieve my best and supporting each other through the journey.

To Mom and Dad, my deepest gratitude. Thank you for encouraging me to explore various fields since kindergarten and for providing unwavering support whenever I discover a passion. I am especially thankful for your support during my high school years, when my fascination with chemistry took root. Thank you for nurturing that passion by supporting my chemistry research at Fudan University as a high school student. Your support was instrumental in my application to MIT to further pursue my studies in chemistry – a dream that seemed unimaginable at the time. I am grateful that this dream not only came true but also led to accomplishments beyond what I had planned.

Finally, as my time at MIT draws to a close, I want to express my heartfelt gratitude to MIT. IHTFP (I Have Truly Found Paradise).

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Electrophilic C(sp^2)–H Cyanation with Inorganic Cyanate (OCN^-) by P^{III}/P^{V}=O-Catalyzed Phase Transfer Activation

1. Introduction and Background

Nitriles are prevalent moieties in natural products and pharmaceutical compounds[1] and versatile synthetic precursors for further functionalization.[2] In terms of nitrile synthesis, methods for nucleophilic cyanation are legion[3,4] but require the use of cyanide (CN^-) sources with documented safety hazards.[5] By way of complement, electrophilic cyanation presents alternative options for the preparation of nitriles,[6] but synthetic equivalents of the "CN^+" synthon[7,8,9,10] are themselves prepared in (multistep) sequences either from cyanide itself or from volatile and toxic cyanogen halides (Figure 1A).

Sodium cyanate (NaOCN) is an accessible and readily-employed reagent with an established profile in organic synthesis: [11] it is commonly encountered as a C-centred electrophile in condensation reactions[12]and as an ambident nucleophile in substitution reactions.[13] Notably, though, NaOCN has not previously been employed as an electrophilic cyanation reagent (i.e. a source of "CN^+" equivalents). Much like the neutral CO_2 molecule with which it is isoelectronic, OCN^- features a robust and persistent carbon–oxygen bond that poses a thermodynamic challenge to deoxyfunctionalization.[14]

Halophosphonium ions **P•**X^+ are known reactive intermediates for a range of deoxyfunctionalization transformations, and prior work has established that small-ring phosphine oxides such as phosphetane(V) oxides **P•**[O] (Figure 1B) are readily deoxygenated to the corresponding P(III) oxidation state by hydrosilanes, and that the inclusion of a mild halenium (X^+)

donor permits generation of **P•X**$^{+}$ under conditions of P^{III}/P^{V}=O redox catalysis. [15] Here, to overcome the limited solubility of NaOCN in common organic media, the further application of **P•X**$^{+}$ in solid-liquid phase transfer processes, [16] alongside its established role in deoxyfunctionalization, was explored. Realization of this work establishes the feasibility of inorganic salt deoxygenation by P^{III}/P^{V}=O catalyzed phase transfer activation and enables the direct electrophilic cyanation of C(sp^2)–H nucleophiles[17,18,19] under such mechanistic guidelines with NaOCN as the "CN^{+}" source.

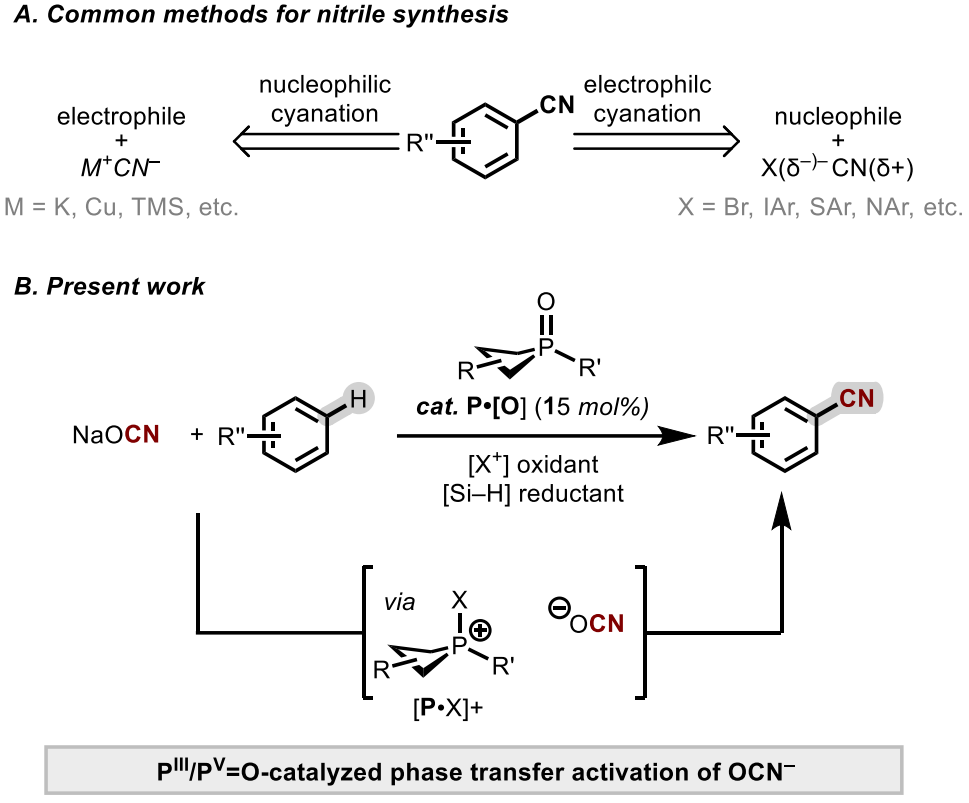
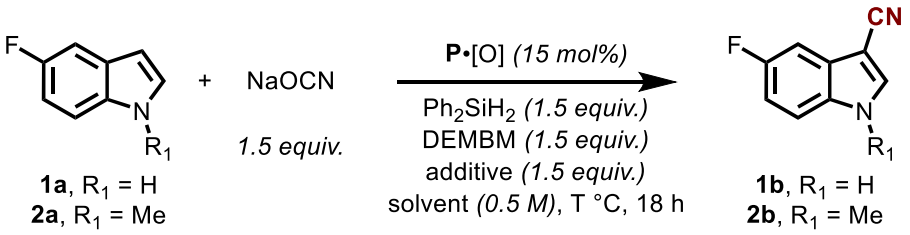
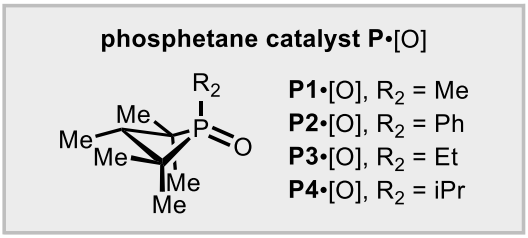


Figure 1. (A) common methods for nitrile synthesis; (B) present work: electrophilic cyanation of C(sp^2)–H nucleophiles with inorganic cyanate (OCN^{-}) by P^{III}/P^{V}=O-catalyzed phase transfer activation.

2. Results and Discussion

5-Fluoro-1H-indole **1a** was selected as a suitable test substrate for discovery and optimization experiments. As seen in Table 1 entry 1, conditions using 15% 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**P1**•[O])[20] as catalyst, in combination with 1.5 equivalents of diphenylsilane (Ph_2SiH_2) as terminal reductant and diethyl 2-bromo-2-methylmalonate (DEMBM) as oxidant did indeed provide the target nitrile product **1b** albeit in low (8%) yield. While this entry serves as an exciting proof of concept, the yield was suboptimal, potentially due to the quenching of the active electrophilic cyanation reagent by the highly nucleophilic dehalogenated methylmalonate anion. The protonates the malonate and suppresses its nucleophilicity, resulting in a significantly improved yield of 72% (entry 2). Other degradation pathways of the halenium oxidant, such as nucleophilic substitution with cyanate, were prevented with the usage of the less soluble NaOCN: diminished yields were obtained with the more soluble potassium (KOCN, 48%) and tetrabutylammonium cyanates (TBAOCN, 26%). With less nucleophilic substrates, the competing reactivity of phosphetane catalyst as nucleophile starts to dominate, resulting in catalyst death and decreased yields. For instance, under otherwise identical conditions, the cyanation of 5-fluoro-1-methyl-1H-indole **2a** resulted in a 49% yield (entry 3, cf. entry 2 with **1a**). Tailoring R_2 on the phosphetane catalyst **P1**•[O] either electronically (entry 4, 55% with **P2**•[O]) or sterically (62% with **P3**•[O] in entry 5 and 77% with **P4**•[O] in entry 6) led to increased yields. Further increase in yield was achieved by a temperature rise and a solvent switch to benzonitrile (entry 7, 84%) or mixed benzonitrile/dichloroethane (entry 8, 91%). The omission of phosphetane catalyst, hydrosilane reductant, or halenium oxidant resulted in no target product formation.





entry	solvent	T °C	additive	R_1	P•[O]	yield
1	DCE	100	-	H	**P1**•[O]	**1b:** *8%*
2	DCE	100	PyHBr	H	**P1**•[O]	**1b:** *72%*
3	DCE	100	PyHBr	Me	**P1**•[O]	**2b:** *49%*
4	DCE	100	PyHBr	Me	**P2**•[O]	**2b:** *55%*
5	DCE	100	PyHBr	Me	**P3**•[O]	**2b:** *62%*
6	DCE	100	PyHBr	Me	**P4**•[O]	**2b:** *77%*
7	PhCN	120	PyHBr	Me	**P4**•[O]	**2b:** *84%*
8	PhCN:DCE 3:1	120	PyHBr	Me	**P4**•[O]	**2b:** *91%*

Table 1. Discovery and optimization of electrophilic cyanation with inorganic cyanate (OCN^-) by P^{III}/P^{V}=O-catalyzed phase transfer activation. Yields were determined by ^{19}F NMR against internal standard fluorobenzene on 0.2 mmol reaction.

With the optimal catalyst **P4**•[O], the scope extended to a wide range of C(sp^2)–H nucleophiles (Figure 2). Indoles substituted with strong electron-donating (e.g., OMe in **6b**) and electron-withdrawing groups (e.g., CF_3 in **8b**) were transformed successfully. Halide (**3b** and **4b**) and boron pinacolato substituents (**5b**) were tolerated, allowing further functionalization with

transition metal cross-coupling reactions. Functional groups otherwise prone to activation by phosphorus-mediated chemistry, such as ester (**7b**), nitro (**9b**), sulfonyl (probenecid derivative, **10b**), and amide (paroxetine derivative, **11b**), were preserved. Steric hindrance on the ortho position was well tolerated despite the isopropyl substituent on **P4•**[O] (**12b-14b**). The strategy proved effective for pyrroles (**15b-17b**) and demonstrated selectivity for cyanation at the 2-position (**16b**). A noteworthy advantage of this approach was its capability to functionalize several heterocycles containing basic nitrogen or sulphur, which would be difficult with strategies that employ Lewis acid activators (**18b-22b**). Furthermore, the versatility of this method was evident as various carbocycles, such as benzene and naphthalene substituted with pyrrolidine groups, were successfully cyanated with good yields (**23b-35b**). Moreover, this general method extended its applicability to electron-rich alkenes (**26b-28b**), providing a broad and effective approach for direct cyanation of $C(sp^2)$–H nucleophiles.

To gain insight into the reaction mechanism, single turnover experiments and computational studies were performed. As depicted in Figure 3A, cyanate activation by bromide displacement on bromophosphetanium **[P1•Br]Br**[21] occurred at room temperature within thirty minutes, showcasing the versatility of **[P1•Br]**$^+$ as a phase transfer reagent. The two peaks belonging to the two isomers of **[P1•Br]**$^+$ gradually disappeared on ^{31}P NMR, with the emergence of new peaks at δ 82 and 92 ppm. Consistent with the formation of a cationic adduct between phosphetane and cyanate, the corresponding mass M/Z = 200.12 was detected by Direct Analysis in Real Time Mass Spectrometry (DART-MS), and new peaks at δ 126 and 127 ppm emerged on ^{13}C NMR.

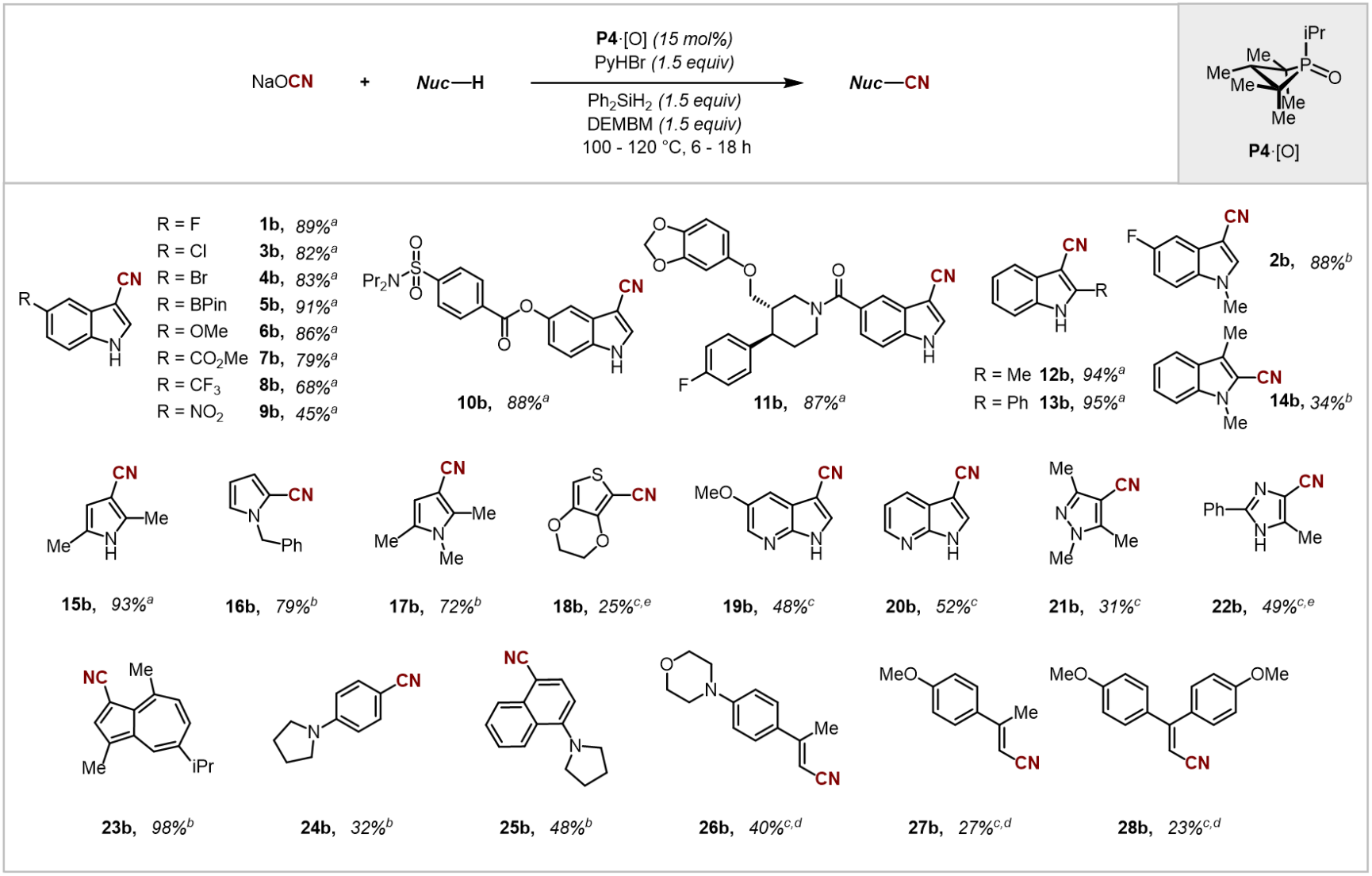
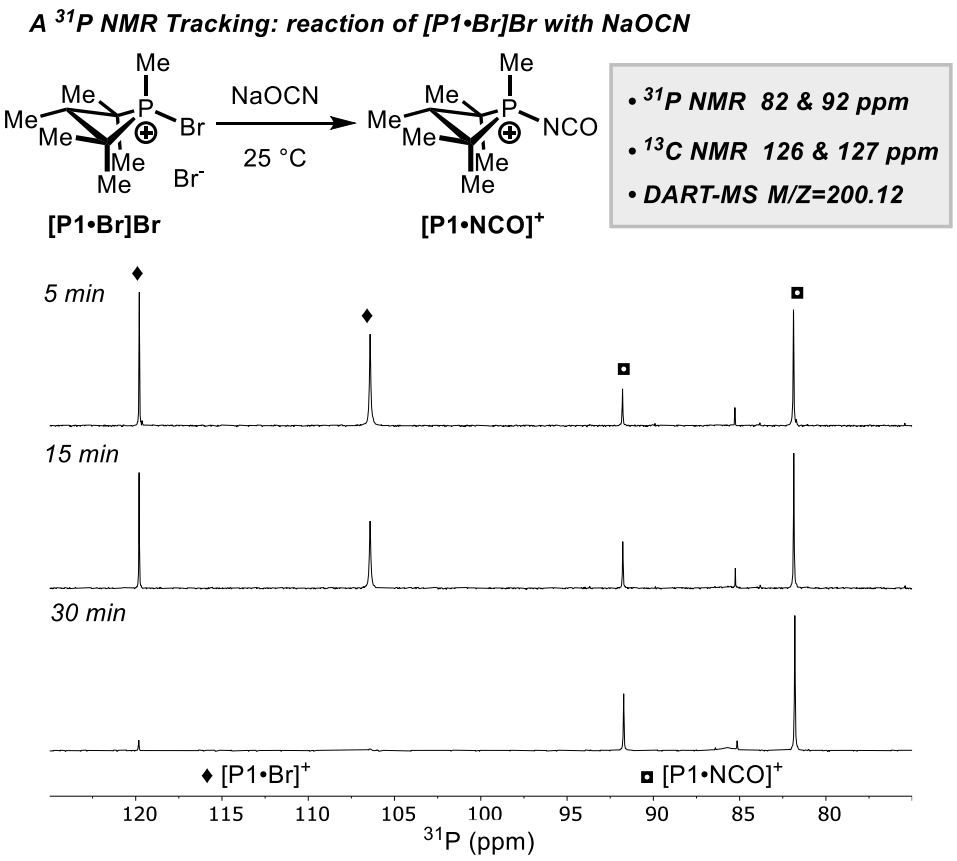

NaOCN
+
Nuc—H
P4·[O] (15 mol%)
PyHBr (1.5 equiv)
Ph2SiH2 (1.5 equiv)
DEMBM (1.5 equiv)
100 - 120 °C, 6 - 18 h
Nuc—CN
P4·[O]
R = F 1b, 89%a
R = Cl 3b, 82%a
R = Br 4b, 83%a
R = BPin 5b, 91%a
R = OMe 6b, 86%a
R = CO2Me 7b, 79%a
R = CF3 8b, 68%a
R = NO2 9b, 45%a
10b, 88%a
11b, 87%a
R = Me 12b, 94%a
R = Ph 13b, 95%a
2b, 88%b
14b, 34%b
15b, 93%a
16b, 79%b
17b, 72%b
18b, 25%c,e
19b, 48%c
20b, 52%c
21b, 31%c
22b, 49%c,e
23b, 98%b
24b, 32%b
25b, 48%b
26b, 40%c,d
27b, 27%c,d
28b, 23%c,d

Figure 2. Synthetic scope of electrophilic cyanation of C(sp^2)–H nucleophiles with inorganic cyanate (OCN^-) by P^{III}/P^V=O-catalyzed phase transfer activation. All yields were isolated from 0.5 mmol reactions. See SI for full synthetic details. [a] DCE (0.5 M), 100 °C (Table 1, entry 6). [b] PhCN:DCE 3:1 (0.5 M), 120 °C (Table 1, entry 8). [c] PhCN (0.5 M), 120 °C (Table 1, entry 7). [d] 20% P4•[O] used. [e] Two equivalents of nucleophilic substrate were used (yield calculated with NaOCN as the limiting reagent).

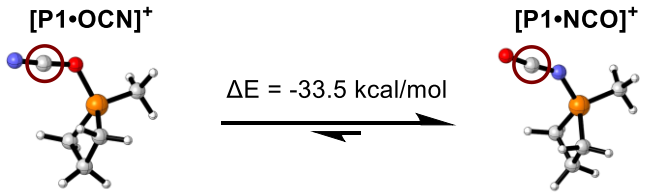
Given the ambident nature of the cyanate anion, two linkage isomers are possible: the N-bound isocyanatophosphonium **[P1•NCO]**$^+$ and the O-bound cyanatophosphonium **[P1•OCN]**$^+$. As shown in Figure 3B, density functional theory (DFT) calculation with various functionals, as benchmarked with experimental δ(**C**N) ppm in literature reports (difference < 5 ppm), predicted the δ(N**C**O) of **[P1•NCO]**$^+$ to be δ 126 – 131 ppm, more consistent with the experimentally observed value of δ 126 and 127 ppm, compared with **[P1•OCN]**$^+$ ($\Delta\delta_{\text{theory-experimental}} > 20$ ppm). In further support of the formation of a P–N bond, **[P1•NCO]**$^+$ was predicted to be 33.5 kcal/mol lower in energy compared with **[P1•OCN]**$^+$ at the level of theory SMD(CH_3CN)-pw6b95-d4/def2-TZVPP.[22] Literature precedents in which phosphorus halides, such as phosphinic chlorides, react with cyanates to form P–N bonds further support cyanate activation via the formation of the isocyanatophosphonium **[P1•NCO]**$^+$.[23]

Upon the addition of 6-fluoro-1-methyl-1H-indole **29a** to in situ generated **[P1•NCO]**$^+$ (Figure 4A), the only observable species on ^{19}F NMR after six hours at 100 °C was the cyanated product **29b** (85% yield). In contrast, at 20 °C, a signal at δ -119.5 ppm **29c**, different from the starting material or the cyanated product, existed as the dominant species (summed yield 79%). At 60 °C, the dominant species were **29b** (51%) and **29c** (32%). The detection of a mass signal M/Z

= 333.1687 by high-resolution mass spectrometry (HRMS) at temperatures below 60 °C suggested **29c** to be an adduct of the isocyanatophosphonium **[P1•NCO]**$^+$ and indole nucleophile **29a** (mass difference ppm = 1.08), which was confirmed by ^{13}C NMR and ^{1}H NMR upon successful isolation. In particular, the observation of a doublet ($^2J_{C–P}$ = 3.2 Hz) at δ 167.80 ppm on ^{13}C NMR indicated the formation of an amide and demonstrated the incorporation of inorganic cyanate into an organophosphorus moiety, showcasing merged organophosphorus redox and phase-transfer catalysis. ^{1}H NMR confirmed C–H rather than N–H activation of substrate **29a**. Finally, X-ray diffraction on a single crystal confirmed P–N instead of P–O activation (Figure 4B).

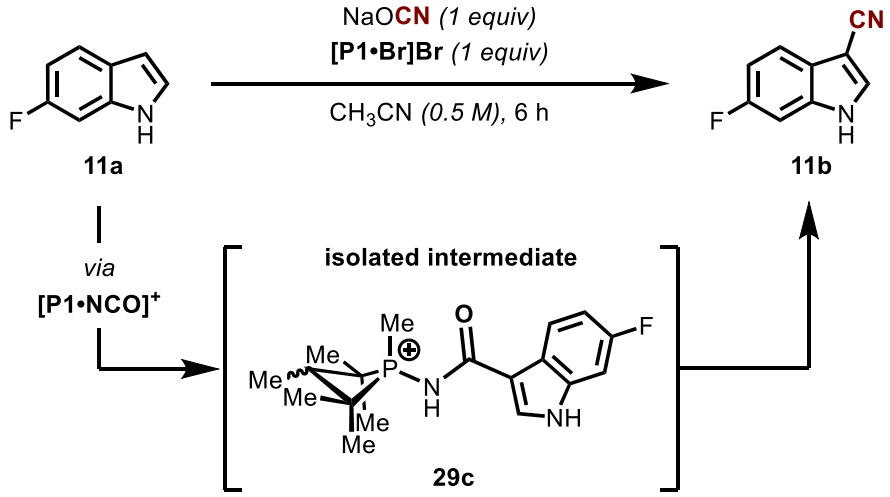


B Computed ^{13}C NMR in support of P–N activation

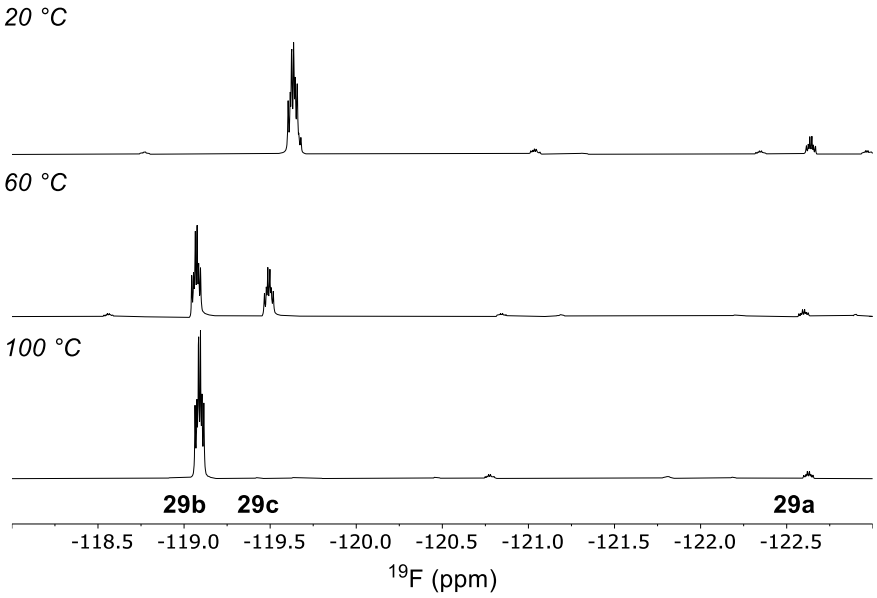


	δ(O**C**N) ppm	δ(N**C**O) ppm
B3LYP-D3	δ 103.44	δ 129.63
BP86	δ 100.55	δ 125.65
PBE0	δ 104.84	δ 131.38
Expt.		***δ 126 & 127***

Figure 3. Cyanate activation by bromide displacement on bromophosphetanium. (A) ^{31}P NMR tracking and spectroscopic data. (B) computed δ(**C**N) ppm on ^{13}C NMR in support of the formation of [P1•NCO]$^{+}$.



A ^{19}F NMR after heating at various temperatures for six hours



B Crystal structure of isolated intermediate

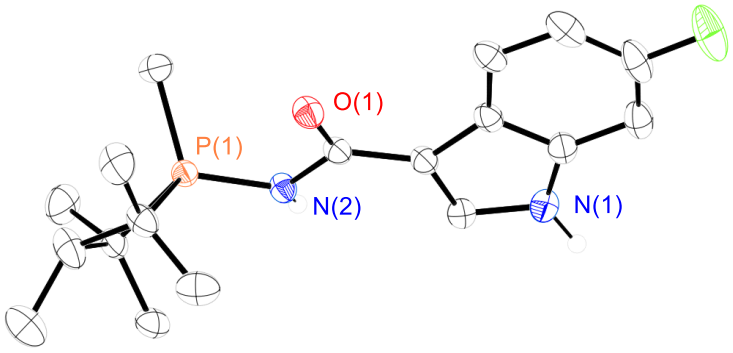


Figure 4. Formation of the cyanated product via attack on the isocyanatophosnonium $[P1•NCO]^+$. (A) ^{19}F NMR after heating at 20, 60, or 100 °C for six hours. (B) crystal structure of isolated intermediate **29c**.

A plausible catalytic cycle consistent with the foregoing experimental data is proposed in Figure 5A. Firstly, a strained phosphetane oxide catalyst **P•**[O] is reduced by a terminal hydrosilane reductant to form σ^3•**P**, which is then oxidized by a halenium oxidant to form $[\mathbf{P}•X]^+$.[15] As a phase transfer reagent, $[\mathbf{P}•X]^+$ brings the inorganic cyanate from the solid to the liquid phase. In solution, the cyanate is activated via halide displacement on $[\mathbf{P}•X]^+$. Computation predicts a strong preference for initial P–N binding over P–O binding (33.5 kcal/mol, SMD(CH_3CN)-pw6b95-d4/def2-TZVPP) due to favorable molecular orbital interaction between cyanate and phosphine moieties, and thus the alternative activation mode initiated by P–O binding should not be operative under reaction conditions. A nucleophile attacks the electrophilic carbon after the generation of $[\mathbf{P}•NCO]^+$, forming $[\mathbf{P}–N•INT]^+$. As illustrated in Figure 5B, $[\mathbf{P}–N•INT]^+$ then isomerizes to $[\mathbf{P}–O•INT]^+$ (ΔE = 15.8 kcal/mol) via a Wittig-type four-membered ring transition state $\mathbf{TS1}^+$ ($\Delta E^‡$ = 21.3 kcal/mol). After deprotonation, $[\mathbf{P}–O•INT]^+$ irreversibly converts to the cyanated product and **P•**[O],[24] completing the catalytic cycle. Notably, in the proposed catalytic cycle, organophosphorus species not only act as oxygen atom extractors in the net dehydration reaction but also as phase transfer reagents that enable the incorporation of the cyano group into an organic moiety from an inorganic cyanate salt.

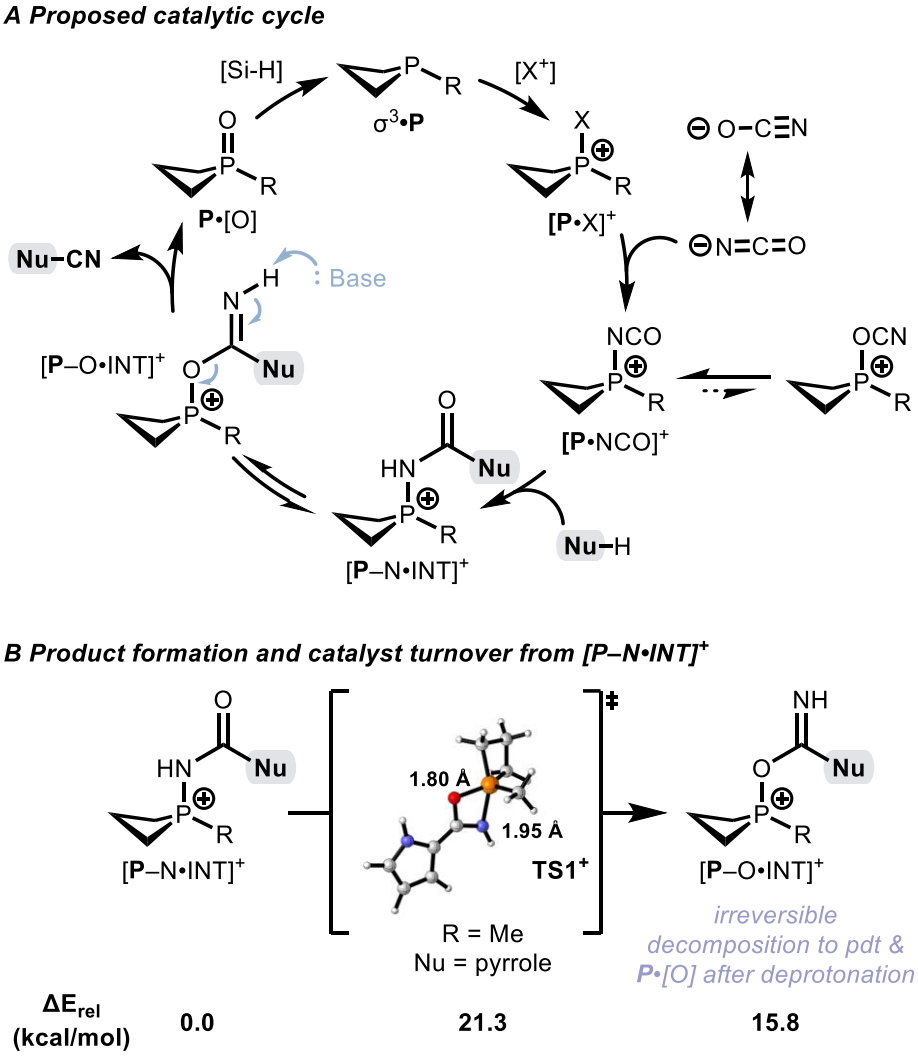


Figure 5. (A) Proposed catalytic cycle. (B) product formation and catalyst turnover from [P–N•INT]$^{+}$.

3. Conclusions

In summary, the results described above constitute a new method of electrophilic cyanation by activation of NaOCN under merged organophosphorus phase transfer and redox catalysis. Mechanistic studies indicate robust room-temperature activation of inorganic cyanate on

halophosphonium [**P**•X]$^+$ by P–N bonding (excluding the potential formation of hazardous BrCN) and nucleophilic attack on the isocyanatophosphonium [**P**•NCO]$^+$ to yield [**P**–N•INT]$^+$. Upon heating, the cyanated product is formed alongside one equivalent of **P**•[O], which enters the next catalytic cycle. The strategy enables direct cyanation of C(sp^2)–H nucleophiles in the absence of Lewis acid activators, providing an expedient route for the synthesis of electron-rich aryl nitriles, with several pharmaceutically relevant examples illustrated. Efforts to broaden the cyanation strategy to encompass a wider range of substrates, as well as to generalize merged organophosphorus phase transfer and redox catalysis, are undergoing in our laboratory, and the results will be shared in due course.

4. Supplementary Information

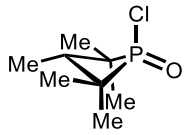
4.1 General Materials and Methods

All reagents were purchased from commercial vendors (Ambeed, Alfa Aesar, Combi-Blocks, MilliporeSigma, TCI, or Oakwood Chemical) and used without further purification unless otherwise indicated. Acetonitrile, dichloromethane, diethyl ether, dimethylformamide, toluene, and tetrahydrofuran were purified and collected under argon using a Glass Contour Solvent Purification System. Anhydrous dichloroethane and benzonitrile were obtained from MilliporeSigma (sure-seal® bottle) and used as received. All other solvents were ACS grade or better and were used without further purification unless otherwise noted. Reactions were conducted under an atmosphere of dry N_2 gas unless otherwise noted. Electrophilic cyanation reactions were carried out in glass culture tubes with a threaded end (13 x 100 mm; Fisher Scientific part # 14-959-35C), outfitted with a phenolic screw-thread open-top cap with red

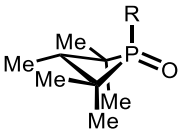
PTFE/white silicone (VWR part #82028-444). Column chromatography was carried out on silica gel (SiliFlash® Irregular Silica Gel, P60 40-63μm) or aluminum oxide (activated, neutral, Brockmann I) as noted. Preparative TLC was performed on Silicyle silica plates (TLG-R10011B-341). ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR were collected with Bruker Neo 600 (QCI-F helium cryoprobe), Bruker Neo 500 (BBO Prodigy nitrogen cryoprobe or BBFO SmartProbe), or Bruker AVANCE III HD 400 (BBO Prodigy nitrogen cryoprobe) spectrometers and processed using MestReNova. ^{1}H NMR chemical shifts are given in ppm with respect to solvent residual peak (acetone-d_6 δ 2.05 ppm; $CDCl_3$, δ 7.26 ppm; DMSO-d_6, δ 2.50 ppm). $^{13}C\{^{1}H\}$ NMR shifts are given in ppm with respect to (acetone-d_6 δ 29.84, 206.26 ppm; $CDCl_3$ δ 77.16 ppm, DMSO-d_6, δ 39.52 ppm). ^{31}P NMR shifts are given in ppm with respect to 85% H_3PO_4 (δ 0.0 ppm) as an external standard. Multiplicities are described as s = singlet, br = broad, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, m = multiplet. Coupling constants are reported in Hertz (Hz). High-resolution mass spectrometry (HRMS) was performed at the Mass Spectrometry Laboratory within the MIT Department of Chemistry Instrument Facilities using an Agilent QTOF 6545 with an ESI ionization source or a JEOL S4 AccuTOF 4G LC-plus equipped with a DART source.

4.2 Preparation of Organophosphorus Compounds

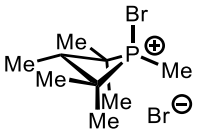
1-chloro-2,2,3,4,4-pentamethylphosphetane 1-oxide, 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**P1•[O]**), 2,2,3,4,4-pentamethyl-1-phenylphosphetane 1-oxide (**P2•[O]**), and 1-bromo-1,2,2,3,4,4-hexamethylphosphetan-1-ium bromide (**[P1•Br]Br**) were prepared according to literature procedures. NMR spectra matched those reported in the literature.[15]



1-chloro-2,2,3,4,4-pentamethylphosphetane 1-oxide

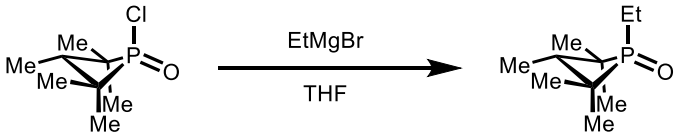


R = Me, **P1•[O]**
R = Ph, **P2•[O]**



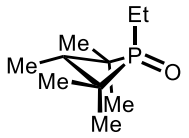
1-bromo-1,2,2,3,4,4-hexamethylphosphetan-1-ium bromide **[P1•Br]Br**

Preparation of 1-ethyl-2,2,3,4,4-pentamethylphosphetane 1-oxide (P3•[O]):



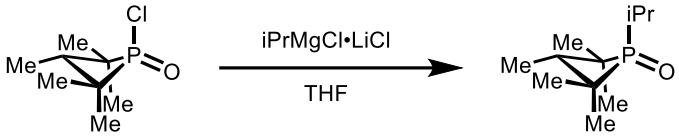
An oven-dried round-bottom flask was charged with 1-chloro-2,2,3,4,4-pentamethylphosphetane 1-oxide (10 mmol, 1.9 g) and sealed with a rubber septum. After evacuation and backfilling with nitrogen three times, 10 mL THF was added via syringe, and the mixture was stirred at 0 °C for ten minutes, following which 3.6 mL EtMgBr (3.0 M in THF, 1.1 equiv) was gradually added via syringe over ten minutes. Upon completion of the addition, the reaction mixture was transferred to a 35 °C oil bath. After overnight heating, the reaction was cooled to 0 °C and quenched with saturated aqueous ammonium chloride. The mixture was transferred to a separatory funnel: the aqueous layer was extracted with DCM, and the combined organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude was purified by recrystallization in hexane/toluene.

1-ethyl-2,2,3,4,4-pentamethylphosphetane 1-oxide (P3•[O]):



White solid (37%, 697 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.88 (m, 2H), 1.60 (qd, *J* = 7.2, 3.6 Hz, 1H), 1.36 – 1.26 (overlapping, 9H), 1.20 (d, *J* = 17.4 Hz, 6H), 0.91 (dd, *J* = 7.1, 1.7 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 45.57 (d, *J* = 57.6 Hz), 42.75 (d, *J* = 5.9 Hz), 24.77 (d, *J* = 3.4 Hz), 17.79 (d, *J* = 4.7 Hz), 17.23 (d, *J* = 41.8 Hz), 6.92 (d, *J* = 22.6 Hz), 5.64 (d, *J* = 5.4 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 61.28. **HRMS (ESI)** m/z calculated $C_{10}H_{22}OP$ $[M+H]^+$ 189.1403, found: 189.1408.

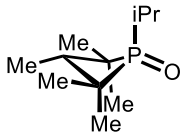
Preparation of 1-isopropyl-2,2,3,4,4-pentamethylphosphetane 1-oxide (P4•[O]):



An oven-dried round-bottom flask was charged with 1-chloro-2,2,3,4,4-pentamethylphosphetane 1-oxide (27 mmol, 5.3 g) and sealed with a rubber septum. After evacuation and backfilling with nitrogen three times, 15 mL THF was added via syringe, and the mixture was stirred at 0 °C for ten minutes, following which 23 mL iPrMgCl•LiCl (1.3 M in THF, 1.1 equiv) was gradually added via syringe over ten minutes. Upon completion of the addition, the reaction mixture was transferred to a 35 °C oil bath. After overnight heating, the reaction was cooled to 0 °C and quenched with saturated aqueous ammonium chloride. The mixture was transferred to a separatory funnel: the aqueous layer was extracted with DCM, and the combined organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude was

purified with flash column chromatography on silica gel (hexane/acetone 5:1 → 1:1). Minor impurities were removed by recrystallization in hexane/toluene.

1-isopropyl-2,2,3,4,4-pentamethylphosphetane 1-oxide (P4•[O]):



White solid (41%, 2.2 g). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.20 – 2.09 (sptd, 1H), 1.65 (qd, *J* = 7.1, 2.2 Hz, 1H), 1.34 – 1.21 (overlapping, 18H), 0.89 (dd, *J* = 7.1, 1.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 45.83 (d, *J* = 55.1 Hz), 43.05 (d, *J* = 5.4 Hz), 25.82 (d, *J* = 3.3 Hz), 24.30 (d, *J* = 41.3 Hz), 18.31 (d, *J* = 4.3 Hz), 16.05 (d, *J* = 3.9 Hz), 6.78 (d, *J* = 21.3 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 66.06. **HRMS (ESI)** m/z calculated $C_{11}H_{24}OP$ $[M+H]^+$ 203.1559, found: 203.1569.

4.3 General Procedure for Optimization of Reaction Conditions

To a 13*100 vial was added a small stir bar, fluoroindole substrate (0.2 mmol, 1 equiv), inorganic cyanate (0.3 mmol, 1.5 equiv), phosphine oxide catalyst (0.03 mmol, 15 mol%), additive (0.3 mmol, 1.5 equiv, if solid), and the halenium oxidant (0.3 mmol, 1.5 equiv, if solid). The vial was capped with a septum cap and put under N_2. Solvent (0.4 mL, 0.5 M) was added, followed by the halenium oxidant (0.3 mmol, 1.5 equiv, if liquid), the hydrosilane reductant (0.3 mmol, 1.5 equiv), and additive (if liquid). After sealing with parafilm, the vial was then heated at 100°C and stirred at 750 rpm for 18 h. After cooling to room temperature and dilution with 1 mL of $CDCl_3$, the crude

yield was analyzed with fluorobenzene as the internal standard with ^{19}F NMR spectroscopy (number of scans = 8 and relaxation delay = 8 s).

4.4 General Procedures for Electrophilic Cyanation

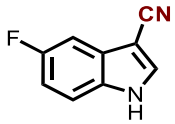
A. General Procedure

To a 13*100 glass culture tube was added a small stir bar, the nucleophilic substrate (0.5 mmol, 1.0 equiv, if solid), sodium cyanate (49 mg, 0.75 mmol, 1.5 equiv), pyridine hydrobromide (120 mg, 0.75 mmol, 1.5 equiv) and the precatalyst 1-isopropyl-2,2,3,4,4-pentamethylphosphetane 1-oxide **P4•[O]** (15 mg, 0.075 mmol, 0.15 equiv unless otherwise noted). The vial was capped with a septum cap and put under N_2. Then, DCE (1.0 mL, 0.5 M) was added, followed by the nucleophilic substrate (0.5 mmol, 1.0 equiv, if liquid), DEMBM (144 μL, 0.75 mmol, 1.5 equiv), and Ph_2SiH_2 (139 μL, 0.75 mmol, 1.5 equiv). The mixture was heated to 100°C and stirred at 750 rpm for 18 h. After completion, the mixture was cooled to room temperature, concentrated using rotary evaporation, and subjected to column chromatography with the indicated solvent for purification. Additional purification was carried out if required, using flash column chromatography or preparatory TLC with the indicated solvent.

DCE = dichloroethane; DEMBM = diethyl 2-bromo-2-methylmalonate; Ph_2SiH_2 = diphenylsilane.

B. Analytical Data for Cyanated Products

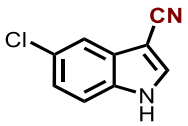
5-fluoro-1H-indole-3-carbonitrile (1b)



Following the general procedure using 5-fluoro-1H-indole (68 mg, 0.5 mmol), the product was obtained in 89% yield (71 mg) after purification by column chromatography on silica gel (hexane/EtOAc 5:1 → 3:1). Using **P1•[O]** (13 mg, 0.075 mmol) under otherwise identical conditions, the product was obtained in 71% yield (57 mg).

^{1}H NMR (500 MHz, Acetone) δ 11.65 – 11.19 (br, 1H), 8.17 (d, *J* = 2.9 Hz, 1H), 7.63 (dd, *J* = 9.0, 4.4 Hz, 1H), 7.40 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.12 (td, *J* = 9.2, 2.5 Hz, 1H). **^{13}C NMR** (126 MHz, Acetone) δ 159.33 (d, J = 237 Hz), 135.05, 132.17, 127.78 (d, *J* = 10.9 Hz), 115.06, 114.14 (d, *J* = 9.8 Hz), 112.06 (d, *J* = 26.4 Hz), 103.69 (d, *J* = 25.0 Hz), 86.15 (d, *J* = 4.6 Hz). **^{19}F NMR** (471 MHz, Acetone) δ -122.73 (td, *J* = 9.1, 4.3 Hz). **IR** (N–H, CN): 3252, 2229 cm^{-1}. **HRMS (ESI)** m/z calculated $C_9H_6FN_2$ $[M+H]^+$ 161.0510, found: 161.0510.

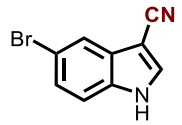
5-chloro-1H-indole-3-carbonitrile (3b)



Following the general procedure using 5-chloro-1H-indole (76 mg, 0.5 mmol), the product was obtained in 82% yield (72 mg) after purification by column chromatography on silica gel (hexane/EtOAc 4:1 → 3:1).

^{1}H NMR (500 MHz, Acetone) δ 11.39 (br, 1H), 8.18 (s, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.62 (dd, *J* = 8.8, 0.6 Hz, 1H), 7.30 (dd, *J* = 8.7, 2.0 Hz, 1H). **^{13}C NMR** (101 MHz, Acetone) δ 134.83, 133.97, 128.24, 127.33, 123.92, 118.05, 114.87, 114.27, 85.72. **IR** (N–H, CN): 3287, 2218 cm^{-1}. **HRMS (ESI)** m/z calculated $C_9H_6ClN_2$ $[M+H]^+$ 177.0215, found: 177.0217.

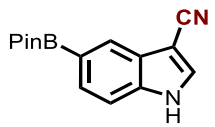
5-bromo-1H-indole-3-carbonitrile (4b)



Following the general procedure using 5-bromo-1H-indole (98 mg, 0.5 mmol), the product was obtained in 83% yield (92 mg) after purification by column chromatography on silica gel (hexane/EtOAc 4:1 → 3:1).

^{1}H NMR (500 MHz, Acetone) δ 11.40 (br, 1H), 8.16 (s, 1H), 7.84 (d, *J* = 1.9 Hz, 1H), 7.59 – 7.56 (m, 1H), 7.42 (dd, *J* = 8.7, 1.9 Hz, 1H). **^{13}C NMR** (101 MHz, Acetone) δ 134.75, 134.31, 128.83, 126.54, 121.16, 114.87, 114.82, 114.65, 85.61. **IR** (N–H, CN): 3289, 2217 cm^{-1}. **HRMS (ESI)** m/z calculated $C_9H_6BrN_2$ $[M+H]^+$ 220.9709, found: 220.9705.

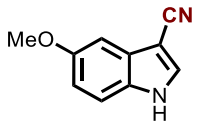
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-3-carbonitrile (5b)



Following the general procedure using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (122 mg, 0.5 mmol), the product was obtained in 91% yield (122 mg) after purification by column chromatography on silica gel (hexane/EtOAc 4:1 → 3:1). Using **P1•[O]** (13 mg, 0.075 mmol) under otherwise identical conditions, the product was obtained in 89% yield (119 mg).

^{1}H NMR (400 MHz, Acetone) δ 11.30 (br, 1H), 8.20 – 8.12 (m, 2H), 7.70 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.62 (dd, *J* = 8.2, 0.9 Hz, 1H), 1.38 (s, 12H).**^{13}C NMR** (101 MHz, Acetone) δ 137.50, 133.64, 133.48, 129.43, 126.85, 126.05, 115.33, 112.11, 86.34, 83.60, 24.35. **IR** (N–H, CN): 3271, 2219 cm^{-1}. **HRMS (ESI)** m/z calculated $C_{15}H_{18}BN_2O_2$ $[M+H]^+$ 269.1456, found: 269.1484.

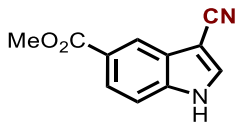
5-methoxy-1H-indole-3-carbonitrile (6b)



Following the general procedure using 5-methoxy-1H-indole (74 mg, 0.5 mmol), the product was obtained in 86% yield (74 mg) after purification by column chromatography on silica gel (hexane/EtOAc 4:1 → 3:1). Using **P1•[O]** (13 mg, 0.075 mmol) under otherwise identical conditions, the product was obtained in 65% yield (56 mg).

^{1}H NMR (400 MHz, Acetone) δ 11.09 (br, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.89 (s, 3H). **^{13}C NMR** (101 MHz, Acetone) δ 156.01, 133.27, 130.38, 128.01, 115.73, 114.22, 113.54, 99.87, 85.61, 55.05. **IR** (N–H, CN): 3250, 2216 cm^{-1}. **HRMS (ESI)** m/z calculated $C_{10}H_9N_2O$ $[M+H]^+$ 173.0710, found: 173.0734.

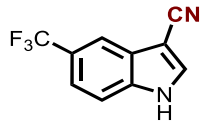
methyl 3-cyano-1H-indole-5-carboxylate (7b)



Following the general procedure using methyl 1H-indole-5-carboxylate (88 mg, 0.5 mmol), the product was obtained in 79% yield (79 mg) after purification by column chromatography on silica gel (hexane/EtOAc 10:1 → 1:1).

^{1}H NMR (600 MHz, Acetone) δ 11.52 (br, 1H), 8.39 (dd, *J* = 1.6, 0.8 Hz, 1H), 8.26 (s, 1H), 7.97 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.70 (dd, *J* = 8.6, 0.7 Hz, 1H), 3.94 (s, 3H). **^{13}C NMR** (151 MHz, Acetone) δ 166.61, 137.99, 135.21, 126.77, 124.58, 124.08, 120.95, 114.81, 112.77, 87.24, 51.43. **IR** (N–H, CN): 3251, 2224 cm^{-1}. **HRMS (ESI)** m/z calculated $C_{11}H_9N_2O_2$ $[M+H]^+$ 201.0659, found: 201.0676.

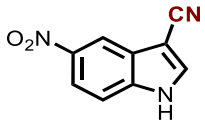
5-(trifluoromethyl)-1H-indole-3-carbonitrile (8b)



Following the general procedure using 5-(trifluoromethyl)-1H-indole (93 mg, 0.5 mmol), the product was obtained in 68% yield (71 mg) after purification by column chromatography on silica gel (hexane/EtOAc 5:1 → 2:1). Using **P1•[O]** (13 mg, 0.075 mmol) under otherwise identical conditions, the product was obtained in 44% yield (46 mg).

^{1}H NMR (600 MHz, Acetone) δ 11.60 (br, 1H), 8.31 (s, 1H), 8.04 (dt, *J* = 1.9, 0.9 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.61 (dd, *J* = 8.7, 1.8 Hz, 1H). **^{13}C NMR** (151 MHz, Acetone) δ 137.10, 135.71, 126.59, 125.11 (q, *J* = 270.8 Hz), 123.72 (q, *J* = 31.9 Hz), 120.17 (q, *J* = 3.4 Hz), 116.32 (q, *J* = 4.5 Hz), 114.58, 113.75, 87.10. **^{19}F NMR** (565 MHz, Acetone) δ -61.22. **IR** (N–H, CN): 3261, 2225 cm^{-1}. **HRMS (ESI)** m/z calculated $C_{10}H_6F_3N_2$ $[M+H]^+$ 211.0478, found: 211.0525.

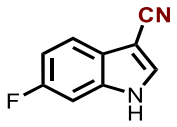
5-nitro-1H-indole-3-carbonitrile (9b)



Following the general procedure using methyl 5-nitro-1H-indole (81 mg, 0.5 mmol), the product was obtained in 45% yield (42 mg) after purification by column chromatography on silica gel (hexane/EtOAc 5:1 → 1:1).

^{1}H NMR (600 MHz, Acetone) δ 8.62 – 8.55 (m, 1H), 8.39 (s, 1H), 8.20 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.94 – 7.76 (m, 1H). **^{13}C NMR** (151 MHz, Acetone) δ 143.31, 138.45, 137.17, 126.50, 118.80, 115.30, 114.09, 113.52, 88.35. **IR** (N–H, CN): 3280, 2225 cm^{-1}. **HRMS (ESI)** m/z calculated $C_9H_6N_3O_2$ $[M+H]^+$ 188.0455, found: 188.0508.

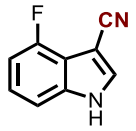
6-fluoro-1H-indole-3-carbonitrile (29b)



Following the general procedure using 6-fluoro-1H-indole (68 mg, 0.5 mmol), the product was obtained in 91% yield (73 mg) after purification by column chromatography on silica gel (hexane/EtOAc 5:1 → 3:1). Using **P1•[O]** (13 mg, 0.075 mmol) under otherwise identical conditions, the product was obtained in 76% yield (61 mg).

^{1}H NMR (500 MHz, Acetone) δ 11.29 (br, 1H), 8.13 (s, 1H), 7.70 (dd, *J* = 8.8, 5.1 Hz, 1H), 7.37 (dd, *J* = 9.5, 2.4 Hz, 1H), 7.12 (ddd, *J* = 9.5, 8.7, 2.3 Hz, 1H). **^{13}C NMR** (126 MHz, Acetone) δ 160.45 (d, *J* = 238.4 Hz), 135.65 (d, *J* = 13.2 Hz), 134.24, 123.67, 119.95 (d, *J* = 10.2 Hz), 115.13, 110.48 (d, *J* = 25.3 Hz), 98.97 (d, *J* = 26.6 Hz), 86.17. **^{19}F NMR** (471 MHz, Acetone) δ -120.22 (td, *J* = 9.8, 5.2 Hz). **IR** (N–H, CN): 3237, 2228 cm^{-1}. **HRMS (ESI)** m/z calculated $C_9H_6FN_2$ $[M+H]^+$ 161.0510, found: 161.0527.

4-fluoro-1H-indole-3-carbonitrile (30b)

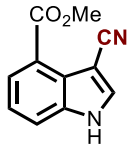


Following the general procedure using 4-fluoro-1H-indole (68 mg, 0.5 mmol), the product was obtained in 83% yield (67 mg) after purification by column chromatography on silica gel (hexane/EtOAc 5:1 → 1.5:1). Using **P1•[O]** (13 mg, 0.075 mmol) under otherwise identical conditions, the product was obtained in 58% yield (47 mg).

^{1}H NMR (600 MHz, Acetone) δ 11.46 (br, 1H), 8.16 (s, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.29 (td, *J* = 8.1, 5.0 Hz, 1H), 6.98 (ddd, *J* = 10.7, 7.9, 0.7 Hz, 1H). **^{13}C NMR** (151 MHz, Acetone) δ 155.67 (d, *J* = 246.8 Hz), 138.22 (d, *J* = 9.4 Hz), 134.42, 124.45 (d, *J* = 7.2 Hz), 115.57 (d, *J* = 19.9 Hz),

115.31, 109.14 (d, J = 3.9 Hz), 106.51 (d, J = 17.9 Hz), 83.00. **^{19}F NMR** (565 MHz, Acetone) δ -125.29 (dd, J = 10.7, 5.0 Hz). **IR** (N–H, CN): 3243, 2223 cm^{-1}. **HRMS (ESI)** m/z calculated $C_9H_5FN_2$ $[M+H]^+$: 161.0510, found: 161.0502.

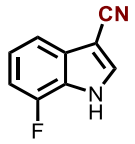
methyl 3-cyano-1H-indole-4-carboxylate (35b)



Following the general procedure using methyl 1H-indole-4-carboxylate (88 mg, 0.5 mmol), the product was obtained in 69% yield (69 mg) after purification by column chromatography on silica gel (hexane/EtOAc 10:1 → 1:1)

^{1}H NMR (400 MHz, Acetone) δ 11.55 (br, 1H), 8.31 (s, 1H), 7.91 (dd, J = 7.5, 1.1 Hz, 1H), 7.88 (dd, J = 8.2, 1.1 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 4.00 (s, 3H). **^{13}C NMR** (101 MHz, Acetone) δ 166.73, 137.33, 136.81, 124.95, 123.54, 122.84, 122.70, 117.55, 116.39, 87.49, 50.36. **IR** (N–H, CN): 3269, 2226 cm^{-1}. **HRMS (ESI)** m/z calculated $C_{11}H_9N_2O_2$ $[M+H]^+$ 201.0659, found: 201.0684.

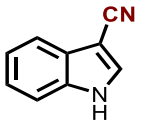
7-fluoro-1H-indole-3-carbonitrile (31b)



Following the general procedure using 4-fluoro-1H-indole (68 mg, 0.5 mmol), the product was obtained in 81% yield (65 mg) after purification by column chromatography on silica gel (hexane/EtOAc 10:1 → 4:1). Using **P1•[O]** (13 mg, 0.075 mmol) under otherwise identical conditions, the product was obtained in 41% yield (33 mg).

^{1}H NMR (400 MHz, Acetone) δ 11.72 (br, 1H), 8.21 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.27 (td, *J* = 8.0, 4.7 Hz, 1H), 7.11 (dd, *J* = 11.3, 7.9 Hz, 1H). **^{13}C NMR** (126 MHz, Acetone) δ 149.83 (d, *J* = 245.4 Hz), 134.22, 130.67 (d, *J* = 5.1 Hz), 129.68, 127.52, 122.50 (d, *J* = 6.3 Hz), 114.79 (d, *J* = 3.9 Hz), 108.40 (d, *J* = 16.1 Hz), 87.08 (d, *J* = 3.2 Hz). **^{19}F NMR** (471 MHz, Acetone) δ -134.14 (dd, *J* = 11.2, 4.7 Hz). **IR** (N–H, CN): 3243, 2223 cm^{-1}. **HRMS (ESI)** m/z calculated $C_9H_6FN_2$ $[M+H]^+$ 161.0510, found: 161.0524.

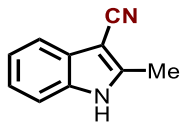
1H-indole-3-carbonitrile (32b)



Following the general procedure using 1H-indole (59 mg, 0.5 mmol), the product was obtained in 95% yield (68 mg) after purification by column chromatography on silica gel (hexane/EtOAc 4:1 → 3:1).

^{1}H NMR (400 MHz, Acetone) δ 11.22 (br, 1H), 8.12 (s, 1H), 7.76 – 7.66 (m, 1H), 7.62 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.31 (m, 2H). **^{13}C NMR** (101 MHz, Acetone) δ 135.57, 133.36, 127.17, 123.61, 121.80, 118.67, 115.52, 112.72, 85.89. **IR** (N–H, CN): 3254, 2221 cm^{-1}. **HRMS (ESI)** m/z calculated $C_9H_7N_2$ $[M+H]^+$ 143.0604, found: 143.0634.

2-methyl-1H-indole-3-carbonitrile (12b)

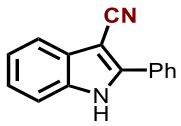


Following the general procedure using 2-methyl-1H-indole (59 mg, 0.5 mmol), the product was obtained in 94% yield (73 mg) after purification by column chromatography on silica gel (hexane/EtOAc 8:1 → 2:1).

^{1}H NMR (500 MHz, Acetone) δ 11.02 (br, 1H), 7.59 – 7.55 (m, 1H), 7.51 – 7.43 (m, 1H), 7.26 – 7.19 (m, 2H), 2.62 (s, 3H). **^{13}C NMR** (126 MHz, Acetone) δ 145.31, 135.25, 127.73, 122.84, 121.49, 117.97, 115.68, 111.79, 84.42, 11.88.

NMR spectroscopic signatures matched with previously reported ones.[25]

2-phenyl-1H-indole-3-carbonitrile (13b)

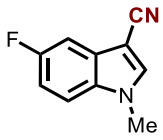


Following the general procedure using 2-phenyl-1H-indole (97 mg, 0.5 mmol), the product was obtained in 95% yield (104 mg) after purification by column chromatography on silica gel (hexane/EtOAc 8:1 → 3:1).

^{1}H NMR (400 MHz, Acetone) δ 11.57 (br, 1H), 8.09 – 8.03 (m, 2H), 7.77 – 7.68 (m, 1H), 7.66 – 7.51 (m, 4H), 7.32 (m, 2H). **^{13}C NMR** (101 MHz, Acetone) δ 144.69, 135.82, 129.89, 129.30, 128.86, 127.52, 127.01, 124.06, 122.11, 118.66, 116.34, 112.39, 82.86.

NMR spectroscopic signatures matched with previously reported ones.[26]

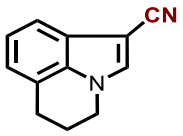
5-fluoro-1-methyl-1H-indole-3-carbonitrile (2b)



The title compound was prepared by a modification of the general procedure using 5-fluoro-1-methyl-1H-indole (75 mg, 0.5 mmol). A solvent mixture of DCE/PhCN (1 mL, 1:3 v:v) was used in place of pure DCE, and the reaction was heated at 120 °C for 18 h. Following purification by column chromatography on silica gel (hexane/EtOAc 10:1 → 2:1), the product was obtained in 88% yield (77 mg).

^{1}H NMR (500 MHz, Acetone) δ 8.05 (s, 1H), 7.59 (dd, *J* = 9.0, 4.3 Hz, 1H), 7.36 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.16 (td, *J* = 9.2, 2.5 Hz, 1H), 3.96 (s, 3H). **^{13}C NMR** (126 MHz, Acetone) δ 159.15 (d, *J* = 237.1 Hz), 138.16, 132.98, 128.21 (d, *J* = 10.9 Hz), 114.86, 112.48 (d, *J* = 10.0 Hz), 111.83 (d, *J* = 26.4 Hz), 103.91 (d, *J* = 25.0 Hz), 84.59 (d, *J* = 4.5 Hz), 33.26. ^{19}F NMR (471 MHz, Acetone) δ -122.72 (td, *J* = 9.1, 4.2 Hz). **IR** (CN): 2218 cm^{-1}. **HRMS (ESI)** m/z calculated $C_{10}H_8FN_2$ $[M+H]^+$ 175.0666, found: 175.0653.

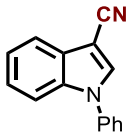
5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1-carbonitrile (33b)



The title compound was prepared by a modification of the general procedure using 5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline (79 mg, 0.5 mmol). A solvent mixture of DCE/PhCN (1 mL, 1:3 v:v) was used in place of pure DCE, and the reaction was heated at 120 °C for 18 h. Following purification by column chromatography on silica gel (hexane/EtOAc 10:1 → 3:1), the product was obtained in 97% yield (88 mg).

^{1}H NMR (600 MHz, Acetone) δ 7.95 (s, 1H), 7.47 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.19 (dd, *J* = 8.1, 7.1 Hz, 1H), 7.05 (dd, *J* = 7.2, 1.1 Hz, 1H), 4.36 – 4.18 (m, 2H), 3.00 (tt, *J* = 6.1, 1.0 Hz, 2H), 2.27 – 2.21 (m, 2H). **^{13}C NMR** (151 MHz, Acetone) δ 133.91, 127.53, 125.69, 123.66, 122.32, 120.46, 116.22, 115.83, 84.03, 44.66, 23.91, 22.47. **IR** (CN): 2207 cm^{-1}. **HRMS (ESI)** m/z calculated $C_{12}H_{11}N_2$ $[M+H]^+$ 183.0917, found: 183.0902.

1-phenyl-1H-indole-3-carbonitrile (34b)

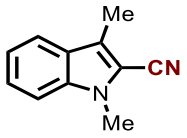


The title compound was prepared by a modification of the general procedure using 1-phenyl-1H-indole (97 mg, 0.5 mmol). A solvent mixture of DCE/PhCN (1 mL, 1:3 v:v) was used in place of pure DCE, and the reaction was heated at 120 °C for 18 h. Following purification by column chromatography on silica gel (hexane/EtOAc 20:1 → 8:1), the product was obtained in 40% yield (44 mg).

^{1}H NMR (500 MHz, Acetone) δ 8.32 (s, 1H), 7.84 – 7.77 (m, 1H), 7.71 – 7.66 (m, 4H), 7.64 – 7.54 (m, 2H), 7.43 – 7.36 (m, 2H). **^{13}C NMR** (101 MHz, Acetone) δ 137.91, 135.75, 135.58, 130.04, 128.30, 127.94, 124.94, 124.49, 122.77, 119.33, 114.84, 111.70, 87.52.

NMR spectroscopic signatures matched with previously reported ones.[27]

1,3-dimethyl-1H-indole-2-carbonitrile (14b)

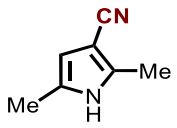


The title compound was prepared by a modification of the general procedure using 1,3-dimethyl-1H-indole (73 mg, 0.5 mmol). A solvent mixture of DCE/PhCN (1 mL, 1:3 v:v) was used in place of pure DCE, and the reaction was heated at 120 °C for 18 h. The product was purified by column chromatography on silica gel (hexane/EtOAc 10:1 → 2:1). Impure fractions were further purified by a second column (hexane/DCM 50:1 → 1:1) to afford the product as a white solid (29 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.43 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.33 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.22 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 3.86 (s, 3H), 2.52 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.06, 126.41, 125.93, 123.72, 120.57, 120.50, 113.67, 109.96, 109.02, 31.38, 9.74.

NMR spectroscopic signatures matched with previously reported ones.[28]

2,5-dimethyl-1H-pyrrole-3-carbonitrile (15b)

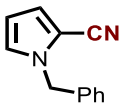


Following the general procedure using 2,5-dimethyl-1H-pyrrole (48 mg, 0.5 mmol), the product was obtained in 93% yield (56 mg) after purification by column chromatography on silica gel (hexane/EtOAc 8:1 → 3:1).

^{1}H NMR (400 MHz, Acetone) δ 10.32 (br, 1H), 5.95 (d, *J* = 1.1 Hz, 1H), 2.32 (s, 3H), 2.18 (d, *J* = 1.1 Hz, 3H). **^{13}C NMR** (151 MHz, Acetone) δ 135.91, 127.65, 116.98, 107.24, 90.04, 11.53, 10.96.

NMR spectroscopic signatures matched with previously reported ones.[29]

1-benzyl-1H-pyrrole-2-carbonitrile (16b)

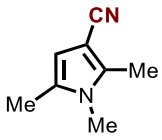


The title compound was prepared by a modification of the general procedure using 1-benzyl-1H-pyrrole (79 mg, 0.5 mmol). A solvent mixture of DCE/PhCN (1 mL, 1:3 v:v) was used in place of pure DCE, and the reaction was heated at 120 °C for 18 h. The product was purified by column chromatography on silica gel (hexane/EtOAc 50:1 → 10:1). Impure fractions were further purified by a second column (hexane/DCM 50:1 → 1:1) to afford the product as a white solid (72 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 3H), 7.24 – 7.19 (m, 2H), 6.90 – 6.83 (m, 2H), 6.23 (dd, *J* = 4.0, 2.7 Hz, 1H), 5.23 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.99, 129.03, 128.39, 127.44, 126.67, 120.33, 113.82, 109.96, 104.20, 52.44.

NMR spectroscopic signatures matched with previously reported ones.[30]

1,2,5-trimethyl-1H-pyrrole-3-carbonitrile (17b)

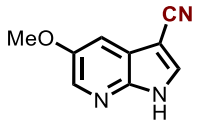


The title compound was prepared by a modification of the general procedure using 1,2,5-trimethyl-1H-pyrrole (55 mg, 0.5 mmol). A solvent mixture of DCE/PhCN (1 mL, 1:3 v:v) was used in place of pure DCE, and the reaction was heated at 120 °C for 18 h. The product was purified by column chromatography on silica gel (hexane/EtOAc 20:1 → 5:1). Impure fractions were further purified by a second column (hexane/EtOAc 20:1 → 5:1) to afford the product as a white solid (48 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (s, 1H), 3.41 (s, 3H), 2.34 (s, 3H), 2.19 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.31, 129.24, 117.85, 107.53, 89.55, 30.78, 12.22, 11.66.

NMR spectroscopic signatures matched with previously reported ones.[31]

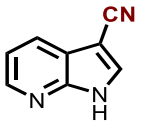
5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (19b)



The title compound was prepared by a modification of the general procedure using 5-methoxy-1H-pyrrolo[2,3-b]pyridine (74 mg, 0.5 mmol). PhCN (1 mL) was used in place of DCE, and the reaction was heated at 120 °C for 6 h. Following purification by column chromatography on silica gel (hexane/EtOAc 8:1 → 2:3), the product was obtained in 48% yield (42 mg).

^{1}H NMR (400 MHz, Acetone) δ 11.58 (br, 1H), 8.22 (s, 1H), 8.15 (d, *J* = 2.7 Hz, 1H), 7.65 (d, *J* = 2.7 Hz, 1H). **^{13}C NMR** (101 MHz, Acetone) δ 152.97, 136.50, 134.16, 134.01, 119.42, 114.86, 108.69, 84.46, 55.62. **IR** (CN): 2217 cm^{-1}. **HRMS (ESI)** m/z calculated $C_9H_8N_3O$ $[M+H]^+$ 174.0662, found: 174.0680.

1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (20b)

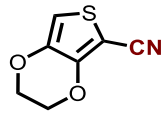


The title compound was prepared by a modification of the general procedure using 1H-pyrrolo[2,3-b]pyridine (59 mg, 0.5 mmol). PhCN (1 mL) was used in place of DCE, and the reaction was heated at 120 °C for 6 h. Following purification by column chromatography on silica gel (hexane/EtOAc 8:1 → 2:3), the product was obtained in 52% yield (37 mg).

^{1}H NMR (500 MHz, DMSO) δ 8.45 (s, 1H), 8.41 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.13 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.30 (dd, *J* = 8.0, 4.7 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO) δ 147.89, 145.53, 136.04,

127.83, 119.39, 118.38, 116.08, 83.73. **IR** (CN): 2221 cm^{-1}. **HRMS (ESI)** m/z calculated $C_8H_6N_3$ $[M+H]^+$ 144.0557, found: 144.0554.

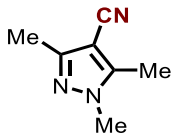
2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carbonitrile (18b)



The title compound was prepared by a modification of the general procedure using 2,3-dihydrothieno[3,4-b][1,4]dioxine (142 mg, 1.0 mmol). PhCN (1 mL) was used in place of DCE, and the reaction was heated at 120 °C for 18 h. The product was purified by column chromatography on silica gel (hexane/EtOAc 50:1 → 10:1). Impure fractions were further purified by a second column (hexane/EtOAc 50:1 → 9:1) to afford the product as a white solid (31 mg, 25%, with NaOCN as limiting reagent).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 1H), 4.40 – 4.34 (m, 2H), 4.31 – 4.23 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.52, 140.75, 112.71, 107.20, 85.47, 65.38, 64.26. **IR** (CN): 2213 cm^{-1}. **HRMS (ESI)** m/z calculated $C_7H_6NO_2S$ $[M+H]^+$ 168.0114, found: 168.0118.

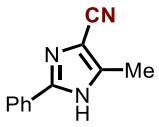
1,3,5-trimethyl-1H-pyrazole-4-carbonitrile (21b)



The title compound was prepared by a modification of the general procedure using 1,3,5-trimethyl-1H-pyrazole (55 mg, 0.5 mmol). PhCN (1 mL) was used in place of DCE, and the reaction was heated at 120 °C for 18 h. The product was purified by column chromatography on silica gel (hexane/EtOAc 5:1 → 1:1). Impure fractions were further purified by a second column (hexane/EtOAc 50:1 → 1:1) to afford the product as a white solid (21 mg, 31%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 1H), 2.39 (s, 1H), 2.33 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.80, 145.25, 114.50, 91.80, 36.39, 12.48, 10.65. **IR** (CN): 2226 cm^{-1}. **HRMS (ESI)** m/z calculated $C_7H_{10}N_3$ $[M+H]^+$ 136.0870, found: 136.0889.

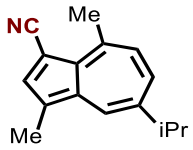
5-methyl-2-phenyl-1H-imidazole-4-carbonitrile (22b)



The title compound was prepared by a modification of the general procedure using 5-methyl-2-phenyl-1H-imidazole (158 mg, 1.0 mmol), DEMBM (192 µL, 1.0 mmol) and Ph_2SiH_2 (186 µL, 1.0 mmol). PhCN (1 mL) was used in place of DCE, and the reaction was heated at 120 °C for 18 h. Following purification by column chromatography on silica gel (hexane/EtOAc 8:1 → 1:1), 59 mg pure product was obtained (48%, with NaOCN as the limiting reagent).

^{1}H NMR (400 MHz, DMSO) δ 13.19 (s, 1H), 7.94 – 7.89 (m, 2H), 7.52 – 7.38 (m, 3H), 2.41 (s, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 146.98, 140.01, 129.67, 129.55, 129.40, 125.65, 116.41, 111.04, 10.36. **IR** (N–H, CN): 3439, 2252 cm^{-1}. **HRMS (ESI)** m/z calculated $C_{11}H_{10}N_3$ $[M+H]^+$ 184.0870, found: 184.0888.

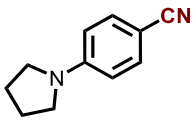
5-isopropyl-3,8-dimethylazulene-1-carbonitrile (23b)



The title compound was prepared by a modification of the general procedure using 7-isopropyl-1,4-dimethylazulene (99 mg, 0.5 mmol). A solvent mixture of DCE/PhCN (1 mL, 3:1 v:v) was used in place of pure DCE, and the reaction was heated at 120 °C for 18 h. The product was purified by column chromatography on silica gel (hexane/EtOAc 50:1 → 15:1). Impure fractions were further purified by a second column (hexane/EtOAc 50:1 → 20:1) to afford the product as a blue solid (94 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 2.1 Hz, 1H), 7.82 (s, 1H), 7.62 (dd, *J* = 10.8, 2.1 Hz, 1H), 7.41 – 7.26 (m, 1H), 3.25 (s, 3H), 3.16 (hept, *J* = 6.9 Hz, 1H), 2.61 (d, *J* = 0.8 Hz, 3H), 1.40 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.62, 145.21, 140.42, 139.71, 139.44, 137.39, 135.73, 130.77, 125.87, 121.04, 92.36, 38.19, 25.85, 24.58, 12.80. **IR** (CN): 2196 cm^{-1}. **HRMS (ESI)** m/z calculated $C_{16}H_{18}N$ $[M+H]^+$ 224.1434, found: 224.1445.

4-(pyrrolidin-1-yl)benzonitrile (24b)

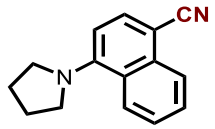


The title compound was prepared by a modification of the general procedure using 1-phenylpyrrolidine (74 mg, 0.5 mmol). A solvent mixture of DCE/PhCN (1 mL, 1:3 v:v) was used in place of pure DCE, and the reaction was heated at 120 °C for 18 h. The product was purified by column chromatography on silica gel (hexane/EtOAc 100:1 → 10:1). Impure fractions were further purified by a second column (hexane/EtOAc 50:1 → 10:1) to afford the product as a white solid (27 mg, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.9 Hz, 2H), 6.52 (d, *J* = 8.9 Hz, 2H), 3.39 – 3.31 (m, 4H), 2.11 – 2.02 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.04, 133.45, 121.06, 111.48, 96.51, 47.50, 25.44.

NMR spectroscopic signatures matched with previously reported ones.[32]

4-(pyrrolidin-1-yl)-1-naphthonitrile (25b)



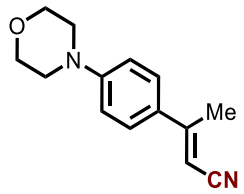
The title compound was prepared by a modification of the general procedure using 1-(naphthalen-1-yl)pyrrolidine (99 mg, 0.5 mmol). A solvent mixture of DCE/PhCN (1 mL, 1:3 v:v) was used in place of pure DCE, and the reaction was heated at 120 °C for 18 h. Following purification by column chromatography on silica gel (hexane/EtOAc 50:1 → 10:1), the product was obtained in 48% yield (54 mg).

^{1}H NMR (400 MHz, Acetone) δ 8.40 (d, *J* = 8.7 Hz, 1H), 8.10 – 8.03 (m, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.67 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.51 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 6.80 (d, *J* = 8.3 Hz,

1H), 3.68 – 3.62 (m, 4H), 2.08 – 2.01 (m, 4H). **^{13}C NMR** (101 MHz, Acetone) δ 151.76, 134.69, 133.58, 127.96, 126.37, 125.17, 124.78, 124.33, 118.91, 107.68, 97.47, 52.65, 25.56.

NMR spectroscopic signatures matched with previously reported ones.[33]

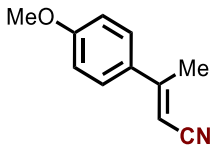
(E)-3-(4-morpholinophenyl)but-2-enenitrile (26b)



The title compound was prepared by a modification of the general procedure using 4-(4-(prop-1-en-2-yl)phenyl)morpholine (102 mg, 0.5 mmol) and **P4•[O]** (20 mg, 0.1 mmol, 20%). PhCN (1 mL) was used in place of DCE, and the reaction was heated at 120 °C for 18 h. Following purification by column chromatography on silica gel (hexane/EtOAc 50:1 → 2:1), the product was obtained in 40% yield (46 mg) as a mixture of E and Z isomers (Z/E = 0.38).

^{1}H NMR (400 MHz, $CDCl_3$) E isomer δ 7.44 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 5.56 (d, *J* = 1.1 Hz, 1H), 3.97 – 3.82 (m, 3H), 3.35 – 3.18 (m, 3H), 2.45 (d, *J* = 1.0 Hz, 3H). Z isomer δ 7.61 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 5.27 (d, *J* = 1.4 Hz, 1H), 4.05 – 3.75 (m, 3H), 3.48 – 3.12 (m, 3H), 2.27 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) E isomer δ 158.58, 152.49, 128.53, 127.09, 118.49, 114.49, 91.99, 66.65, 48.10, 19.77. **IR** (CN): 2206 cm^{-1}. **HRMS (ESI)** m/z calculated $C_{14}H_{17}N_2O$ $[M+H]^+$ 229.1336, found: 229.1354.

(E)-3-(4-methoxyphenyl)but-2-enenitrile (27b)

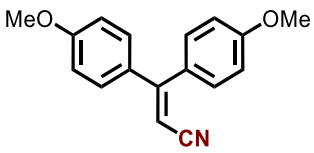


The title compound was prepared by a modification of the general procedure using 1-methoxy-4-(prop-1-en-2-yl)benzene (148 mg, 1.0 mmol) and **P4•[O]** (20 mg, 0.1 mmol, 20%). PhCN (1 mL) was used in place of DCE, and the reaction was heated at 120 °C for 18 h. The product was purified by column chromatography on silica gel (hexane/EtOAc 200:1 → 10:1). Impure fractions were further purified by a second column (hexane/DCM 50:1 → 11:1) to afford the product as a mixture of E and Z isomers (Z/E = 0.17) in 27% yield (23 mg).

^{1}H NMR (400 MHz, $CDCl_3$) E isomer δ 7.46 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 5.57 (d, *J* = 1.1 Hz, 1H), 3.86 (s, 3H), 2.46 (d, *J* = 1.0 Hz, 3H). Z isomer δ 7.59 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 5.33 (d, *J* = 1.5 Hz, 1H), 3.86 (s, 3H), 2.28 (d, *J* = 1.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) E isomer δ 161.36, 158.81, 130.44, 127.38, 118.12, 114.15, 93.25, 55.43, 20.02.

NMR spectroscopic signatures matched with previously reported ones.[34]

3,3-bis(4-methoxyphenyl)acrylonitrile (28b)

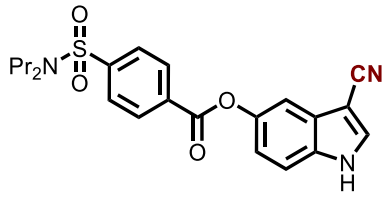


The title compound was prepared by a modification of the general procedure using 4,4'-(ethene-1,1-diyl)bis(methoxybenzene) (120 mg, 0.5 mmol). PhCN (1 mL) was used in place of DCE, and the reaction was heated at 120 °C for 18 h. Following purification by column chromatography on silica gel (hexane/EtOAc 50:1 → 2:1), the product was obtained in 23% yield (31 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 5.57 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.36, 161.48, 161.00, 131.71, 131.32, 130.19, 129.56, 118.80, 113.99, 113.87, 91.55, 55.44, 55.38.

NMR spectroscopic signatures matched with previously reported ones.[35]

3-cyano-1H-indol-5-yl 4-(N,N-dipropylsulfamoyl)benzoate (10b)

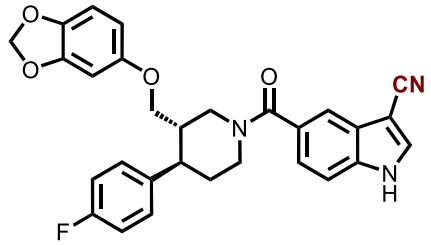


Following the general procedure using **10a** (80 mg) on 0.2 mmol scale. Following purification by column chromatography on silica gel (hexane/EtOAc 10:1 → 1:1), the product was obtained in 88% yield (75 mg).

^{1}H NMR (400 MHz, Acetone) δ 11.39 (s, 1H), 8.42 (d, *J* = 8.5 Hz, 2H), 8.21 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 2.2 Hz, 1H), 7.30 (dd, *J* = 8.8, 2.3 Hz, 1H), 3.27 – 3.15 (m, 4H), 1.61 (m, 4H), 0.90 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR** (126 MHz, Acetone) δ 164.13,

146.33, 144.96, 134.80, 133.50, 133.16, 130.72, 127.55, 127.36, 118.24, 115.09, 113.52, 111.30, 86.29, 50.01, 21.91, 10.50. **IR** (CN): 2221 cm^{-1}. **HRMS (ESI)** calculated for $C_{22}H_{24}N_3O_4S$ $[M+H]^+$ 426.1482, found: 426.1465.

5-((3S,4R)-3-((benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine-1-carbonyl)-1H-indole-3-carbonitrile (11b)



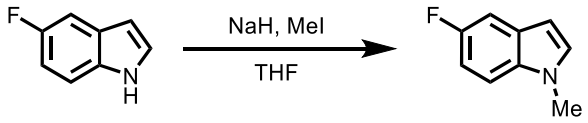
Following the general procedure using **11a** (95 mg) on 0.2 mmol scale. Following purification by column chromatography on silica gel (hexane/EtOAc 10:1 → 1:4), the product was obtained in 87% yield (87 mg).

^{1}H NMR (400 MHz, Acetone) δ 11.43 (s, 1H), 8.19 (d, *J* = 2.8 Hz, 1H), 7.84 (d, *J* = 1.5 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.13 – 7.02 (m, 2H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.32 (s, 1H), 6.13 (s, 1H), 5.88 (s, 2H), 3.61 (d, *J* = 25.1 Hz, 2H), 3.04 (s, 2H), 2.91 (dt, *J* = 11.6, 5.8 Hz, 1H), 2.87 (s, 2H), 2.31 (tdt, *J* = 11.1, 7.1, 3.7 Hz, 1H), 1.99 – 1.84 (m, 2H). **^{13}C NMR** (151 MHz, Acetone) δ 170.78, 162.42 (d, *J* = 242.5 Hz), 155.18, 149.10, 142.57, 140.61 (d, *J* = 3.1 Hz), 136.76, 135.48, 131.38, 130.15 (d, *J* = 8.0 Hz), 127.56, 123.86, 118.81, 116.02 (d, *J* = 21.1 Hz), 113.52, 108.54, 106.49, 101.99, 98.62, 87.40, 69.77, 43.02, 45.06, 34.95.

IR (CN): 2220 cm^{-1}. **HRMS (ESI)** calculated for $C_{29}H_{25}FN_3O_4$ $[M+H]^+$ 498.1824, found: 498.1818.

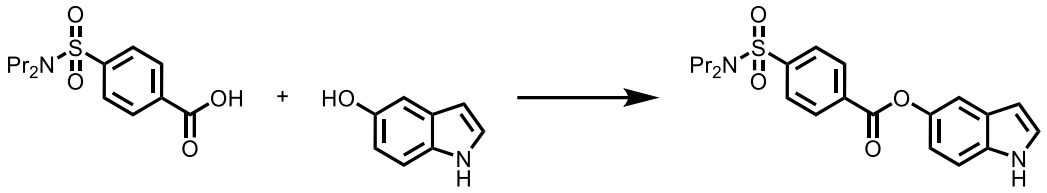
C. Preparation of Starting Materials

Preparation of 5-fluoro-1-methyl-1H-indole (2a):



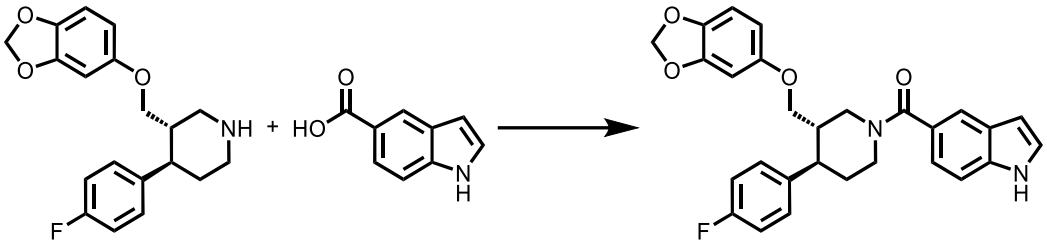
5-fluoro-1H-indole (4.1 g, 30 mmol, 1.0 equiv) was dissolved in 100 mL of dry THF (0.3 M). Sodium hydride (60% suspension in mineral oil, 1.50 equiv) was slowly added under N_2 flow at 0 °C. The reaction was stirred at 0 °C for 15 min, warmed to room temperature and stirred for 1.5 h, then cooled to 0 °C. Following the dropwise addition of MeI (2.4 mL, 39 mmol, 1.3 equiv), the reaction was warmed to room temperature and stirred overnight. Upon the completion of the reaction, the reaction was quenched with water, extracted with Et_2O, the combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting crude product was purified via flash column chromatography (hexane:EtOAc 10:1 → 5:1), to give the desired 5-fluoro-1-methyl-1H-indole. NMR spectra matched those reported in the literature.[36]

1H-indol-5-yl 4-(N,N-dipropylsulfamoyl)benzoate (10b)



Prepared according to literature procedure. NMR spectra matched those reported in the literature.[37]

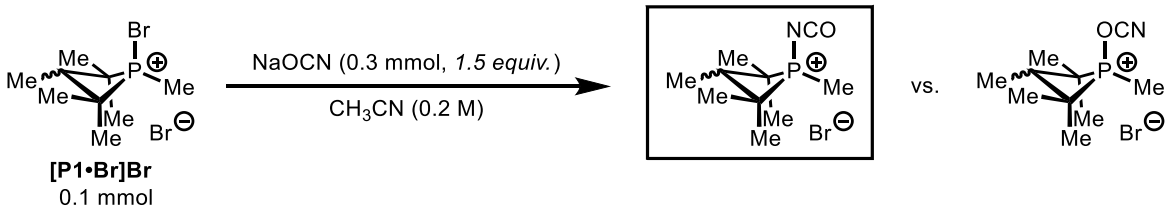
((3S,4R)-3-((benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidin-1-yl)(1H-indol-5-yl)methanone (11b)



Prepared according to literature procedure. NMR spectra matched those reported in the literature.[26]

4.5 Mechanistic Investigation

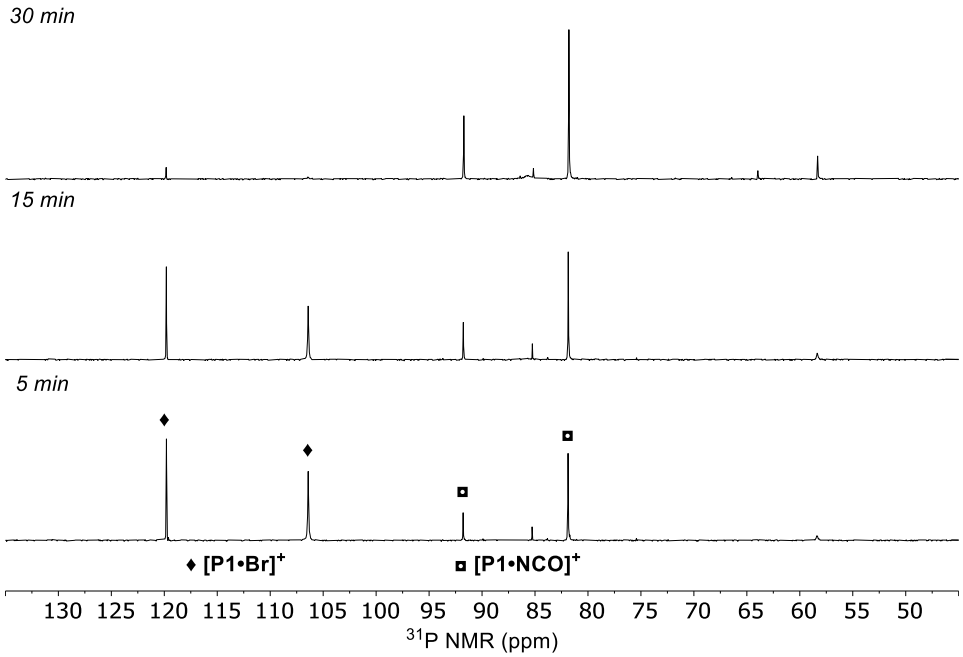
A. Activation of Inorganic Cyanate on Halophosphonium



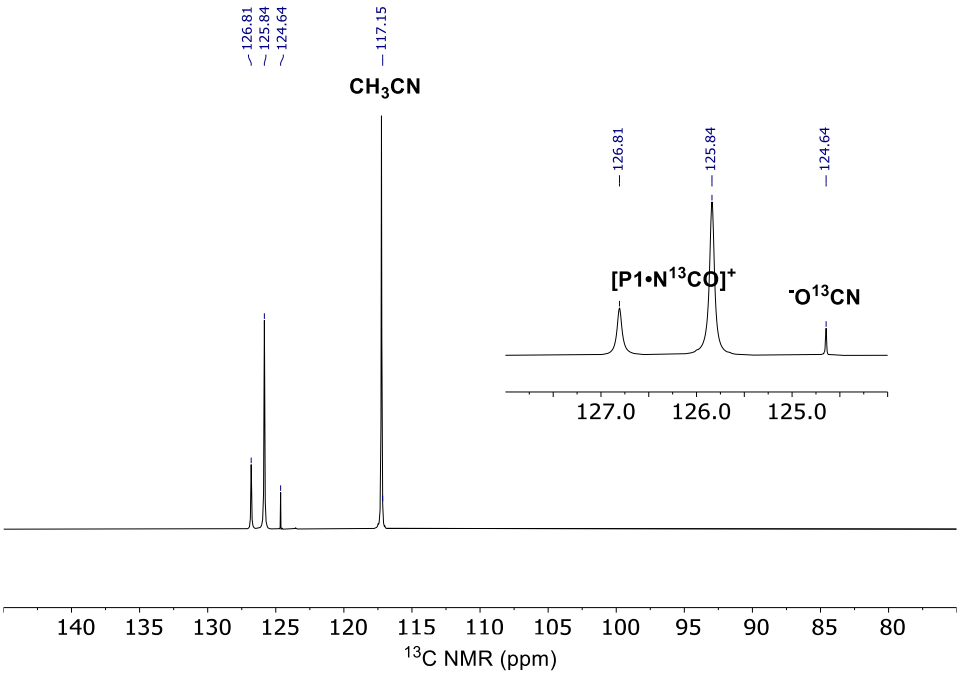
In a nitrogen-filled glovebox, **[P1•Br]Br** (0.4 mmol, 127.2 mg) was dissolved in CH_3CN to create an approximately saturated solution (0.2 M). Subsequently, an NMR tube was charged with NaOCN (0.3 mmol, 1.5 equiv), followed by 0.5 mL solution of **[P1•Br]Br** (0.2 M in CH_3CN, 0.1 mmol). The NMR tube was then capped, sealed with tape, and brought out of the glovebox for DART-MS and NMR analysis.

DART-MS m/z calculated $C_{10}H_{19}NOP^+$: 200.1199, found 200.1221.

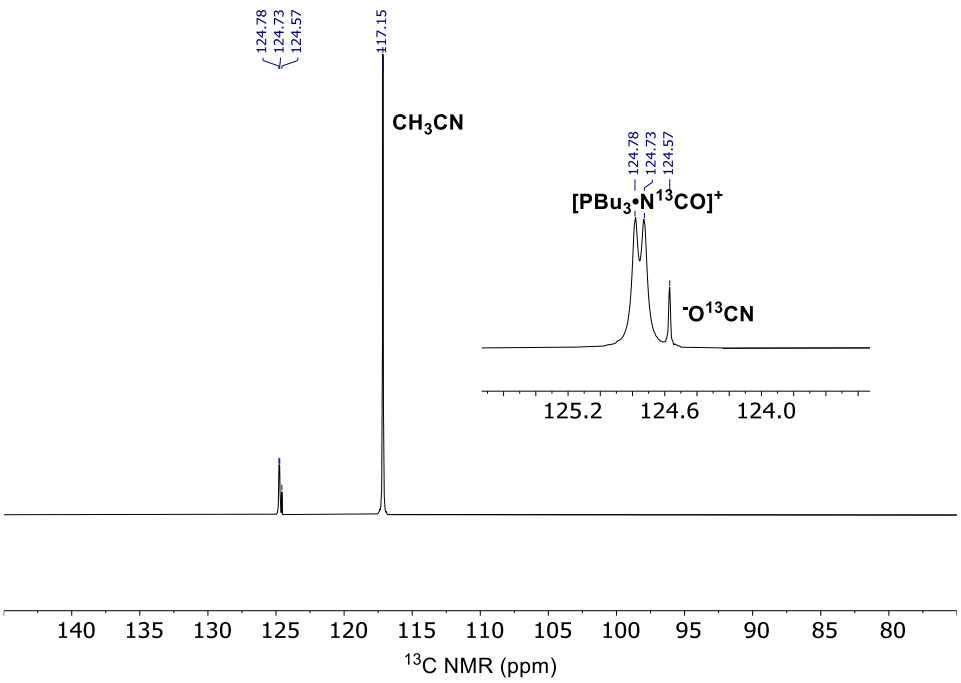
^{31}P NMR: Between each time point measurement, the NMR tube was vigorously shaken. Peaks corresponding to **[P1•Br]$^+$** at 119.80 and 106.41 ppm gradually disappeared within 30 min, with the emergence of new peaks at 91.78 and 81.88 ppm (assigned to **[P1•NCO]$^+$**). Minor peaks at 63.96 and 58.32 ppm corresponding to decomposition to phosphetane oxide **P1•[O]** were observed. No other peaks were observed outside the spectroscopic window provided.



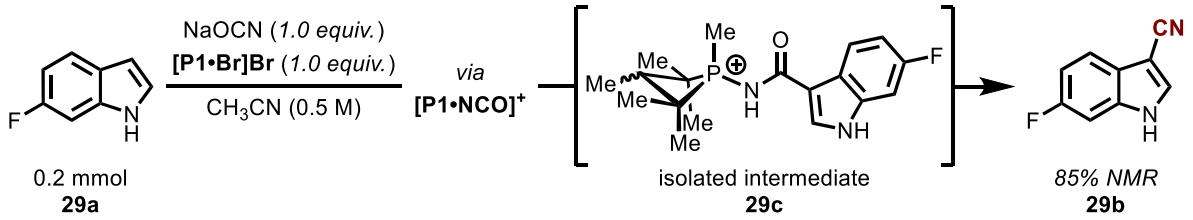
^{13}C NMR: when ^{13}C labeled KO^{13}CN was used in place of NaOCN, new peaks at 126.81 and 125.84 ppm were observed in the cyano region on ^{13}C NMR. These chemical shifts were more consistent with the formation of **[P1•NCO]$^{+}$** via P–N binding (see computational results in section 4.6).



$^{2}J_{C–P}$ = 7.2 Hz coupling (124.7 ppm) was observed when **[PBu3•Br]Br** (a less efficient, but still viable stoichiometric cyanate activator for electrophilic cyanation, vide infra) was used in place of **[P1•Br]Br**.



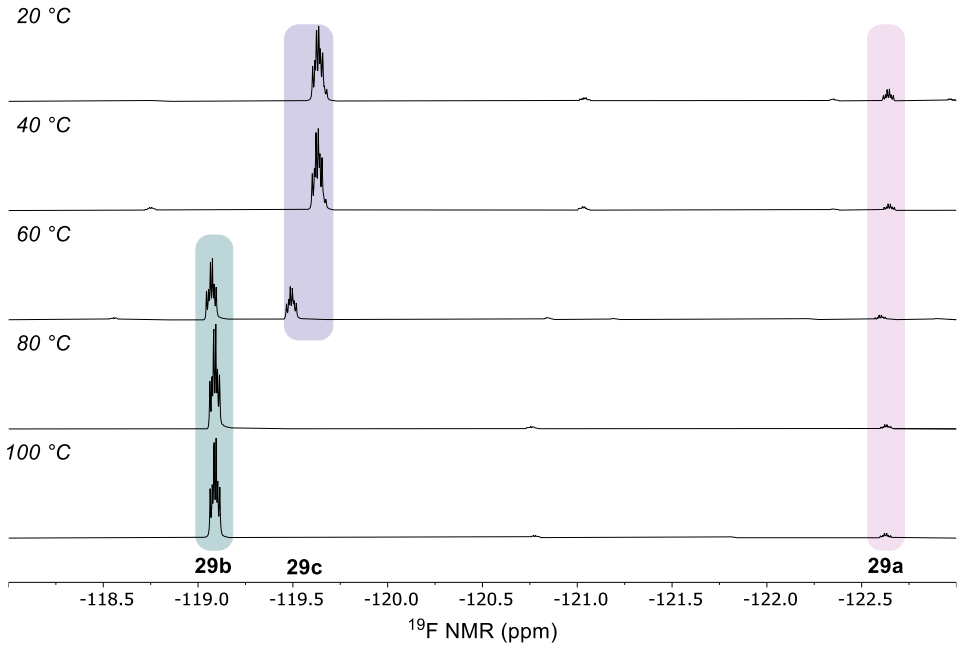
B. Nucleophilic Attack on Activated Cyanate



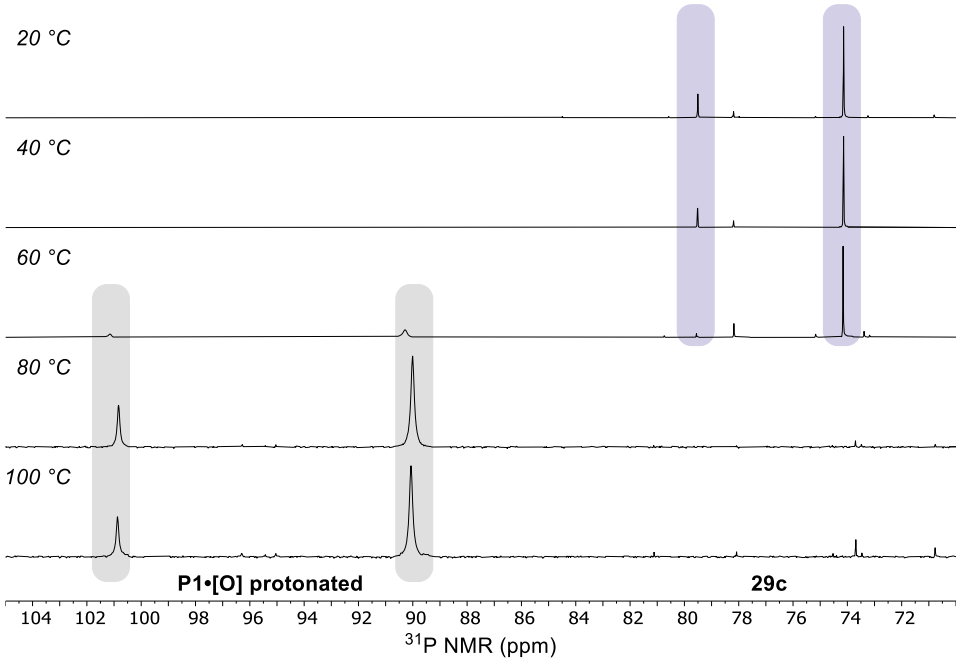
In a nitrogen-filled glovebox, NaOCN (13 mg, 0.2 mmol, 1 equiv) and **[P1•Br]Br** (64 mg, 0.2 mmol, 1 equiv) were weighed into a 13*100 vial, following which a 0.4 mL solution of **29a** in CH_3CN (0.5 M, 0.2 mmol, 1 equiv) was added. Five such reactions were prepared in parallel. The vials were capped, sealed with tape, brought out of the glovebox, and heated at 20, 40, 60, 80, 100 °C respectively. After 6 h, the reactions were cooled to room temperature, diluted with 1 mL of $CDCl_3$, and submitted for MS and NMR analysis.

Analysis of the crude

^{19}F NMR: Yields were quantified against an internal standard of fluorobenzene (number of scans = 8, relaxation delay = 8s). Compound **29c** formed readily at room temperature and decomposed to cyanated product **29b** at temperatures above 60 °C.



^{31}P NMR: In accordance with ^{19}F NMR, compound **29c** formed readily at room temperature and decomposed to phosphetane oxide **P1•[O]** at temperatures above 60 °C. Note: Signals corresponding to **P1•[O]** are shifted downfield in the ^{31}P NMR spectra due to protonation.[15]



LCMS: At 80 and 100 °C, masses corresponding to **P1•[O]** were the only species detected by LCMS, consistent with deoxygenation of inorganic cyanate. In contrast, mass corresponding to compound **29c** (m/z = 335.1) was detected by LCMS at temperatures below 60 °C.

*Under otherwise identical conditions, when **[PBu$_3$•Br]Br** was used in place of **[P1•Br]Br**, the yield of **29b** at 100 °C was 53% (cf. 84%) and the yield of amidophosphonium analog **29c'** was 19% at 20°C (cf. 79%). No conversion of **29c'** to **29b** was observed below 80°C (cf. 60 °C).

Isolation & characterization of intermediate 29c

Intermediate **29c** was purified by concentration of the reaction mixture at 40 °C under reduced pressure, followed by trituration in cold (0 ºC) DCM. A single crystal of the major isomer of **29c** was obtained by vapor diffusion of pentane into a DCM solution in the glovebox. Note: Compound

29c can be handled outside the glovebox for a short period of time, but slowly hydrolyzes to phosphine oxide and amide over the period of a week.

^{19}F NMR (565 MHz, DMSO) major diastereomer δ -119.17.

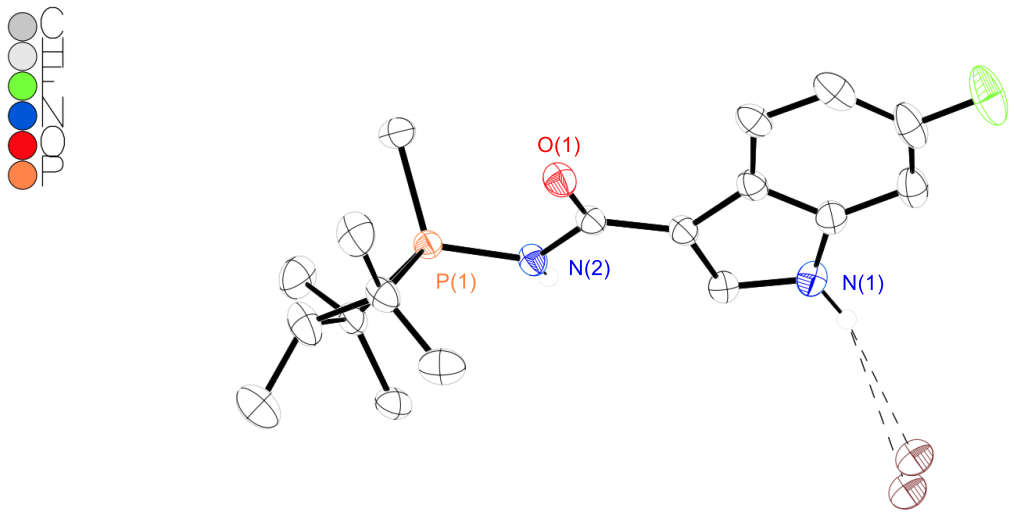
^{31}P NMR (203 MHz, DMSO) major diastereomer δ 74.57.

^{1}H NMR (500 MHz, DMSO) major diastereomer δ 12.33 – 12.26 (br, 1H), 10.27 (d, J = 9.6 Hz, 1H), 8.62 (d, J = 3.1 Hz, 1H), 8.04 (dd, J = 8.7, 5.5 Hz, 1H), 7.38 (dd, J = 9.6, 2.5 Hz, 1H), 7.19 – 7.02 (m, 1H), 2.72 (qd, J = 7.0, 1.8 Hz, 1H), 2.39 (d, J = 13.2 Hz, 3H), 1.42 (m, 12H), 1.00 (dd, J = 7.1, 1.6 Hz, 3H).

^{13}C NMR (151 MHz, DMSO) major diastereomer δ 167.82 (d, J = 3.2 Hz), 159.84 (d, J = 237.1 Hz), 150.39, 136.84 (d, J = 12.6 Hz), 134.99, 122.87, 122.22 (d, J = 10.0 Hz), 110.94 (d, J = 24.3 Hz), 99.40 (d, J = 26.0 Hz), 47.19 (d, J = 5.3 Hz), 41.77 (d, J = 55.0 Hz), 23.43 (d, J = 3.3 Hz), 18.23 (d, J = 5.0 Hz), 8.36 (d, J = 25.2 Hz), 6.08 (d, J = 35.9 Hz).

HRMS (ESI) m/z calculated $C_{18}H_{25}FN_2OP^+$: 335.1683, found 335.1687.

X-ray diffraction on single crystal of 29c:



Crystal data and structure refinement for **29c**.

Identification code **29c**

Empirical formula C18 H25 Br F N2 O P

Formula weight 415.28

Temperature 100(2) K

Wavelength 0.71073 Å

Crystal system Orthorhombic

Space group Pbca

Unit cell dimensions a = 13.7406(4) Å a= 90°.

b = 13.8904(4) Å b= 90°.

c = 20.4578(6) Å g = 90°.

Volume 3904.6(2) Å3

Z 8

Density (calculated) 1.413 Mg/m3

Absorption coefficient 2.204 mm-1

F(000) 1712

Crystal size 0.480 x 0.080 x 0.055 mm3

Theta range for data collection 1.991 to 31.008°.

Index ranges -19<=h<=19, -20<=k<=20, -29<=l<=29

Reflections collected 161422

Independent reflections 6220 [R(int) = 0.0531]

Completeness to theta = 25.242° 99.9 %

Absorption correction Semi-empirical from equivalents

Refinement method Full-matrix least-squares on F2

Data / restraints / parameters 6220 / 2 / 233

Goodness-of-fit on F2 1.046

Final R indices [I>2sigma(I)] R1 = 0.0395, wR2 = 0.1052

R indices (all data) R1 = 0.0501, wR2 = 0.1124

Extinction coefficient n/a

Largest diff. peak and hole 1.588 and -0.691 e.Å-3

4.6 Computational Studies

A. General Computational Information

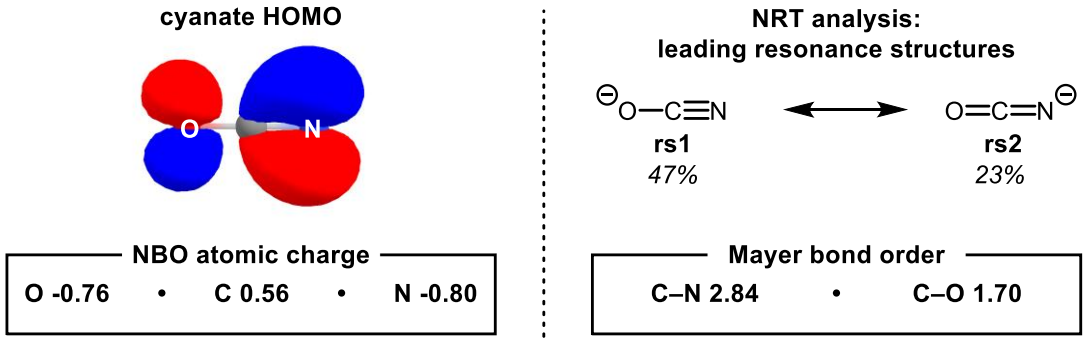
Calculations were performed using density functional[38] and coupled-cluster theory[39] implemented in Orca 5.0[40] and NBO 6.0.[41] Geometry optimizations were carried out in the gas phase with B3LYP functional[42] with Grimme's D3 correction[43] and def2-TZVP basis set. In cases where multiple conformers were possible, the lowest energy conformer was identified with the CREST

and CENSO programs.[22] With the optimized geometries, single point energies were re-evaluated at the level of theory SMD(CH_3CN)-pw6b95-d4/def2-TZVPP. Stationary points were characterized by frequency calculations to verify their identity as either local minima (zero imaginary frequencies) or first-order saddle points (one imaginary frequency). The three-dimensional molecular structures were visualized using Chemcraft and CYL-view.

B. Activation of Inorganic Cyanate on Halophosphonium

Ambident nature of inorganic cyanates

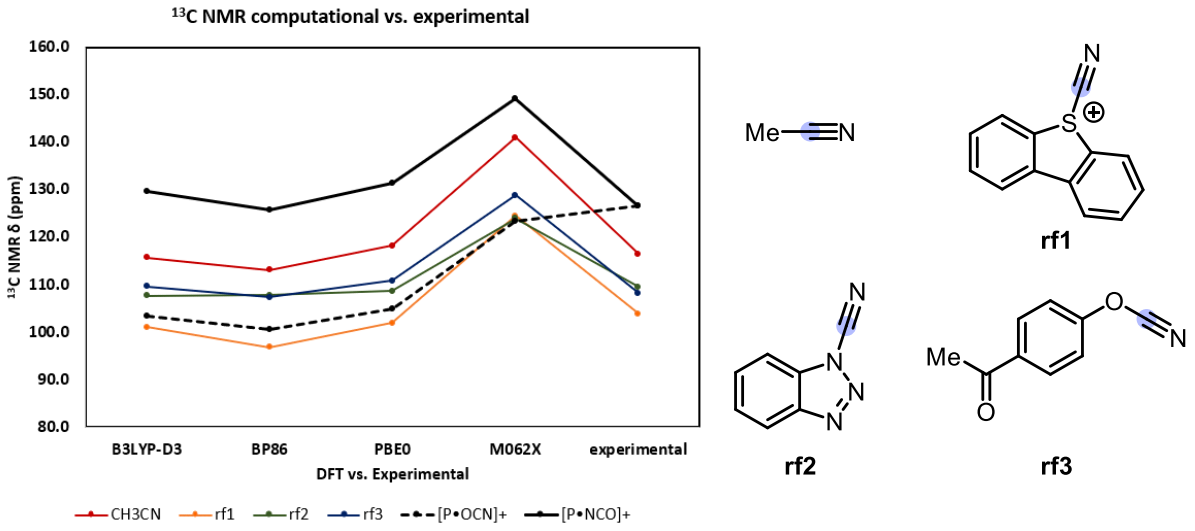
While there is comparable negative charge on the nitrogen (-0.80) and oxygen (-0.76) end of a cyanate anion, visualization of the HOMO showed greater orbital density on the nitrogen end. Natural resonance theory (NRT) analysis [44] predicted two dominant contributing resonance structures **rs1** (47%) and **rs2** (23%). Consistent with significant contribution from **rs2**, the computed C–O Mayer bond order[45] is 1.70.



Cyanate activation via P–N vs. P–O binding

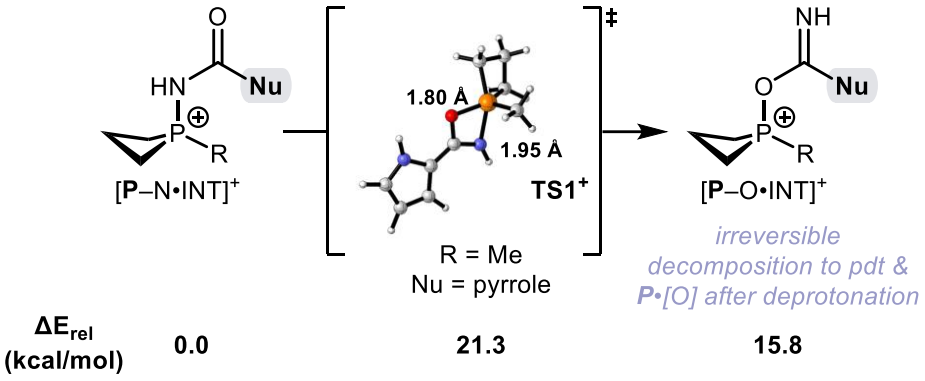
Energy evaluation of cyanate linkage isomers: Cyanate binding to give P–N binding was predicted to be 33.5 kcal/mol lower in energy compared with P–O binding. Mayer bond order analysis predicted stronger P–N bond in $[P•NCO]^+$ (bond order = 1.03) compared with P–O bond in $[P•OCN]^+$ (bond order = 0.93).

^{13}C NMR Chemical Shift Prediction: Several functionals (B3LYP-D3, BP86, PBE0, and M06-2X) were evaluated for their accuracy in predicting chemical shift of the cyano group on ^{13}C NMR with def2-TZVP basis set. Literature examples selected for benchmarking include acetonitrile, 5-cyano-5H-dibenzothiophen-5-ium (**rf1**),[46] 1H-benzo[d][1,2,3]triazole-1-carbonitrile (**rf2**),[47] and 1-(4-cyanatophenyl)ethan-1-one (**rf3**).[48] As shown below, B3LYP, BP86 and PBE0 accurately predicted the δ(CN) ppm of acetonitrile, **rf1**, **rf2**, and **rf3** (±5 ppm cf. experimental). These functionals predicted the δ(N**C**O) of **[P•NCO]$^+$** to be δ 126 – 131 ppm, more consistent with the experimentally observed value of δ 126.8 and 125.8 ppm, compared with **[P•OCN]$^+$** ($\Delta\delta_{theory\text{-}experimental}$ > 20 ppm).

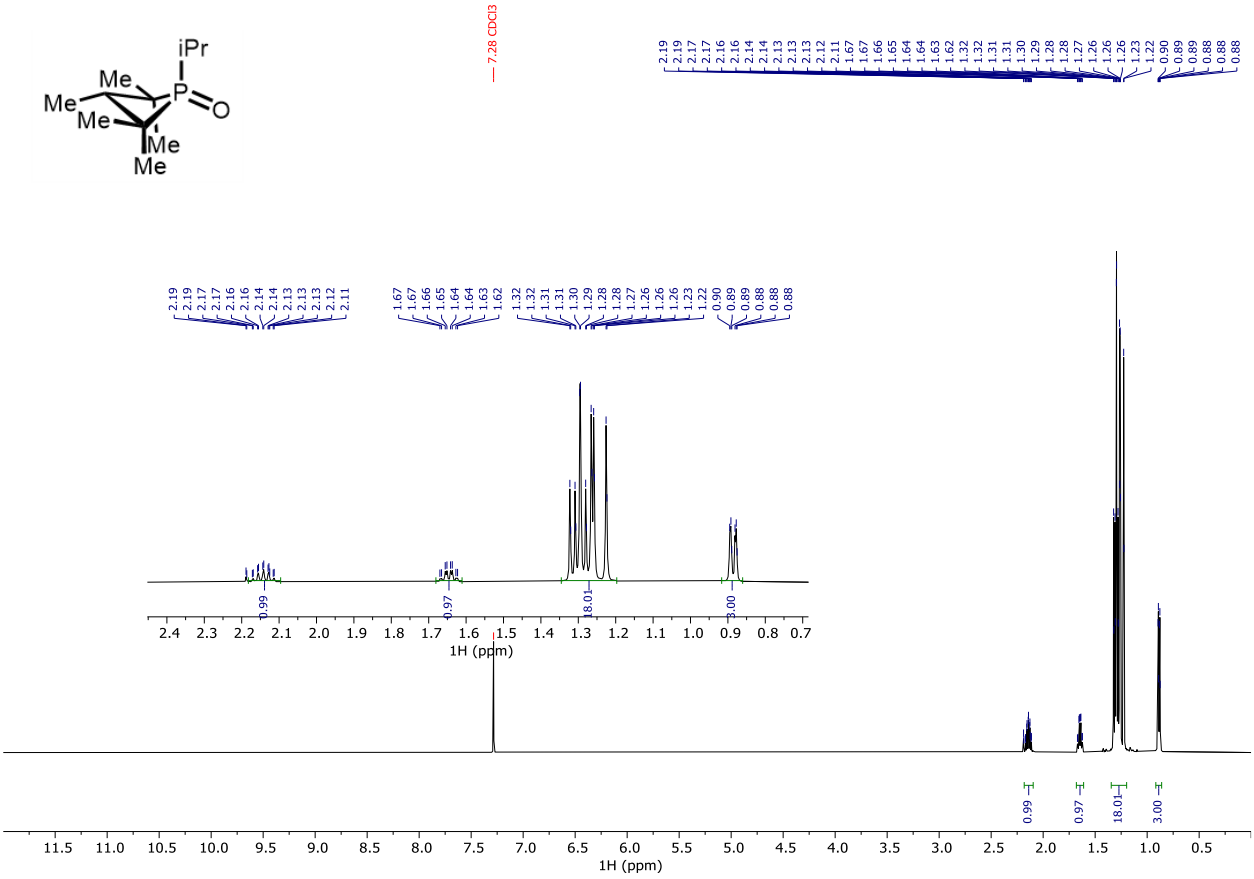


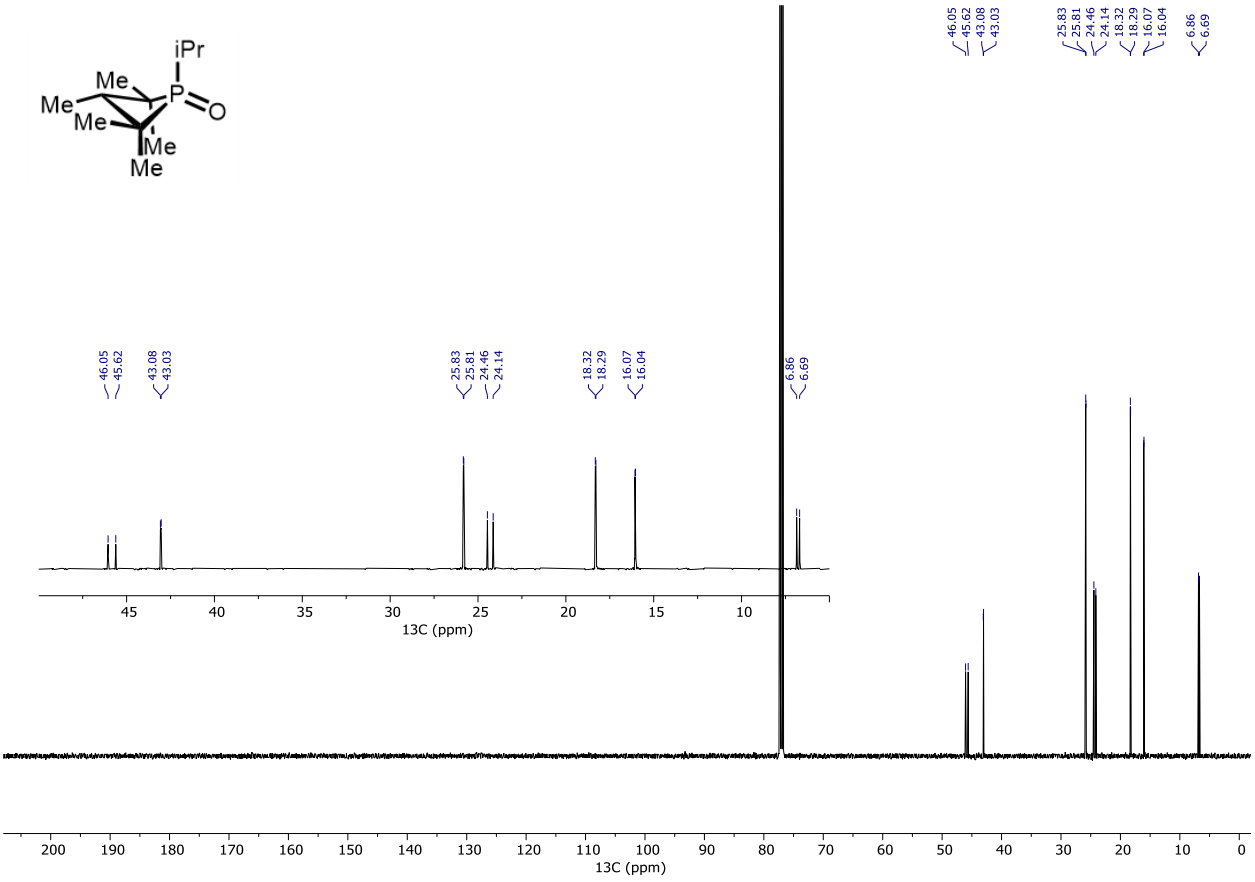
C. Turnover of Amidophosphonium to Phosphine Oxide and Cyanated Product

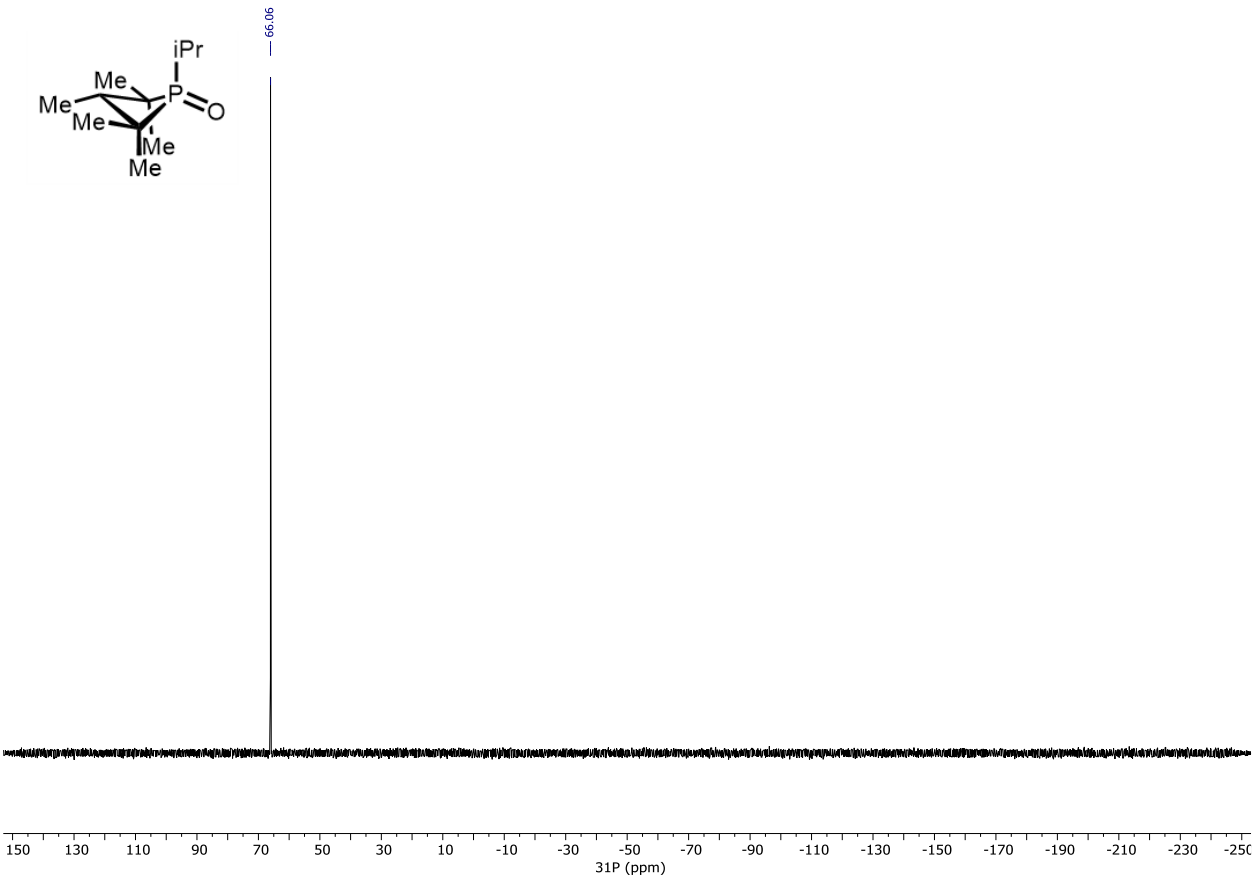
The conversion of the experimentally characterized N-bound intermediate **[P–N•INT]**$^+$ (ΔE_{rel} = 0 kcal/mol) to cyanated product and phosphine oxide via a four-membered Wittig-type transition state **TS1**$^+$ ($\Delta E^{‡}$ = 21.3 kcal/mol) and the O-bound intermediate **[P–O•INT]**$^+$ (ΔE_{rel} = 15.8 kcal/mol) is energetically feasible. Upon deprotonation, **[P–O•INT]**$^+$ irreversibly converts to cyanated product and phosphine oxide.



5. Selected Relevant Spectra




iPr
Me
Me
Me
P
O
Me
Me
46.05
45.62
43.08
43.03
25.83
25.81
24.46
24.14
18.32
18.29
16.07
16.04
6.86
6.69
13C (ppm)
13C (ppm)


66.06
iPr
Me
Me
Me
P
O
Me
Me
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
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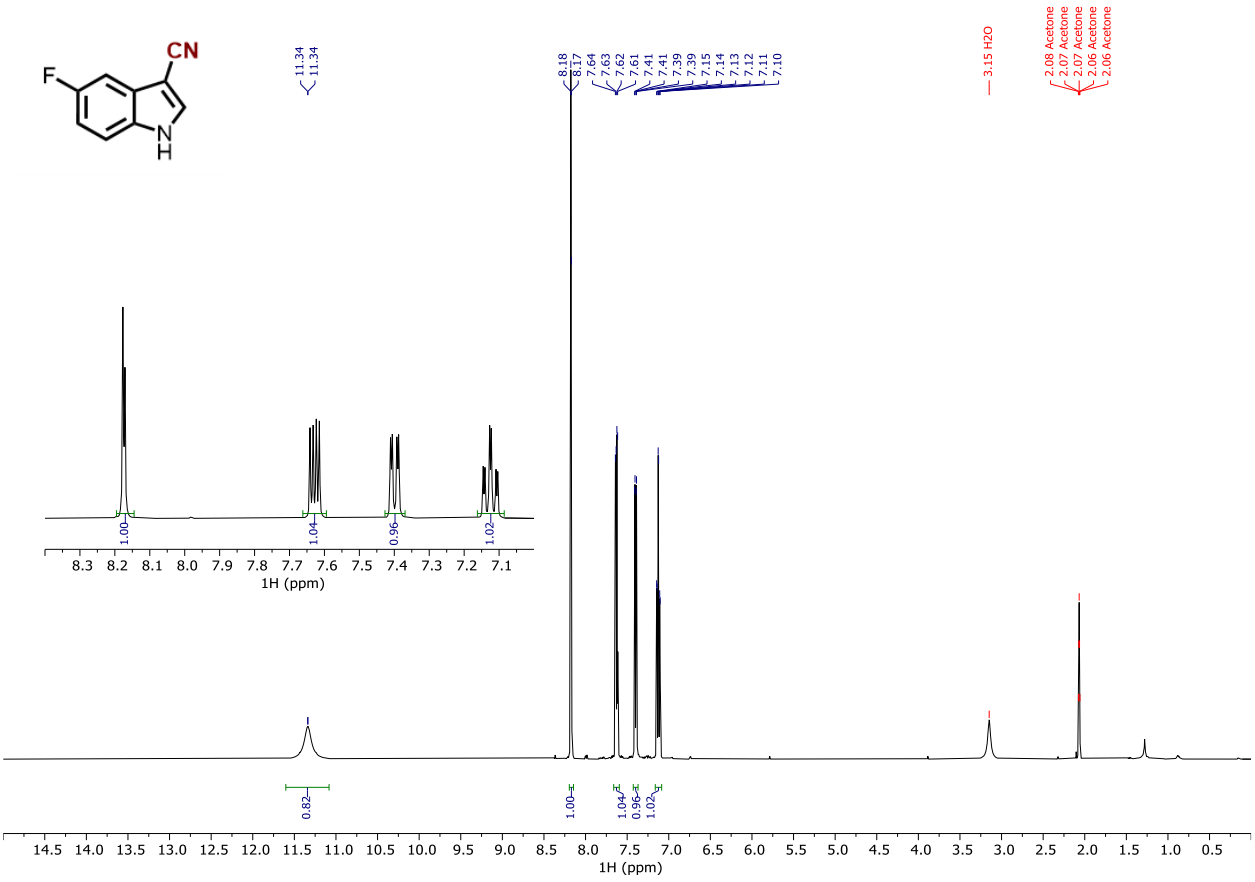
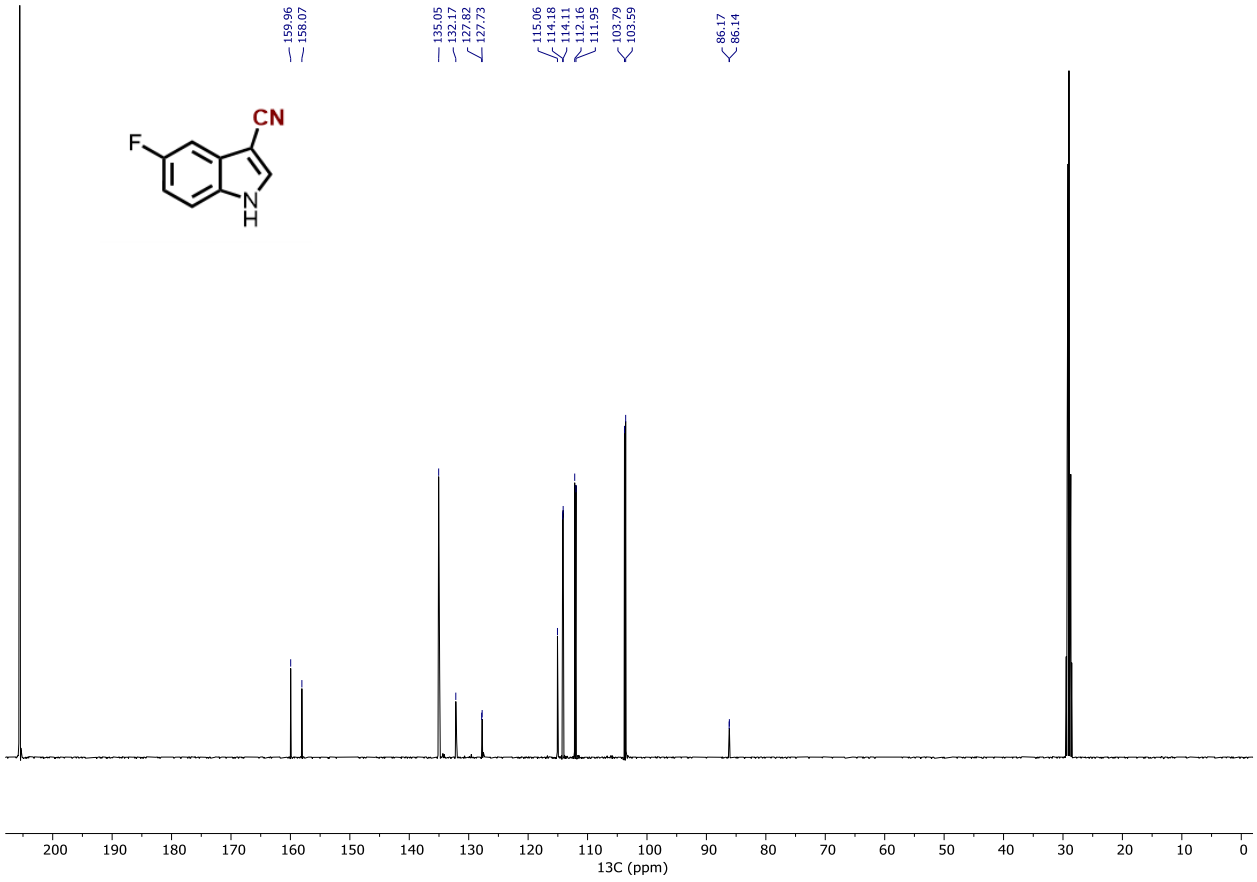
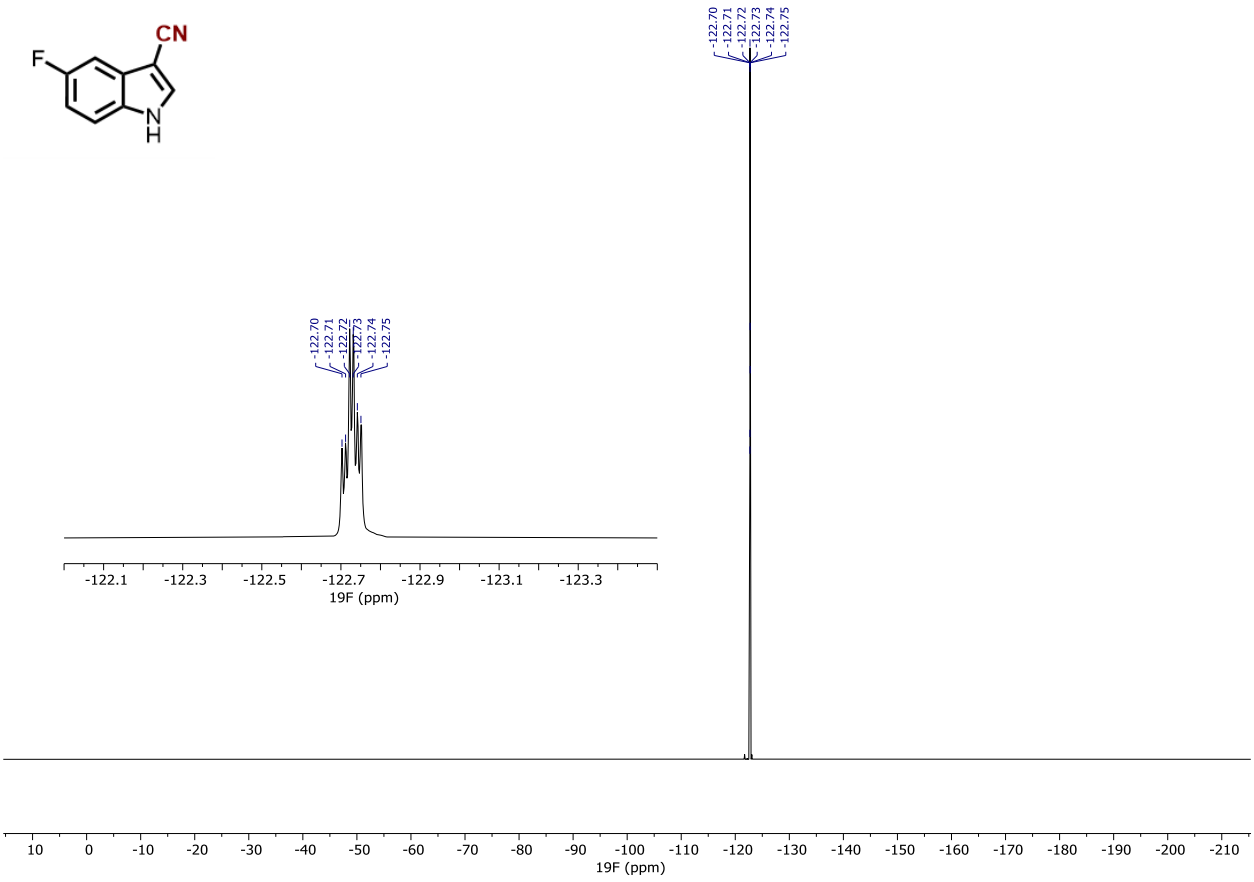
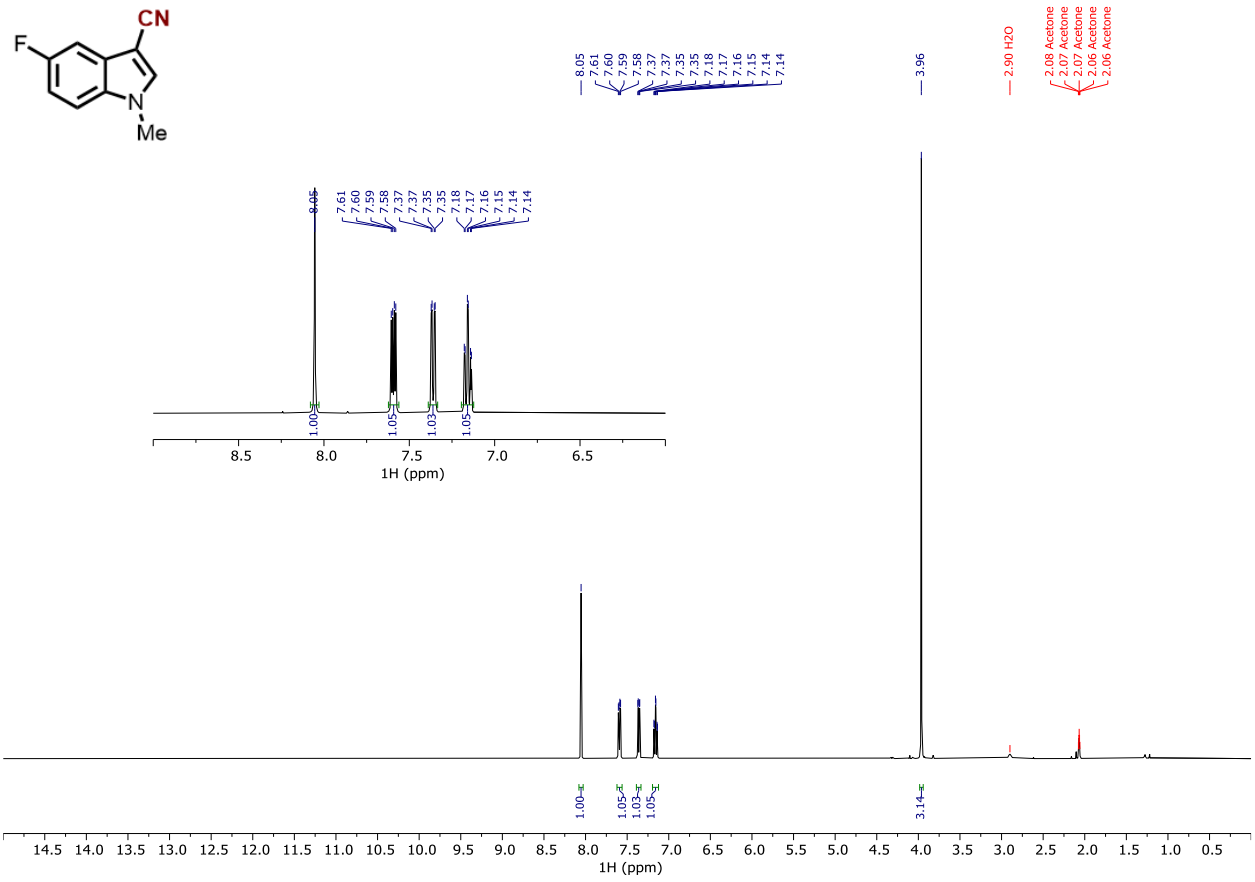
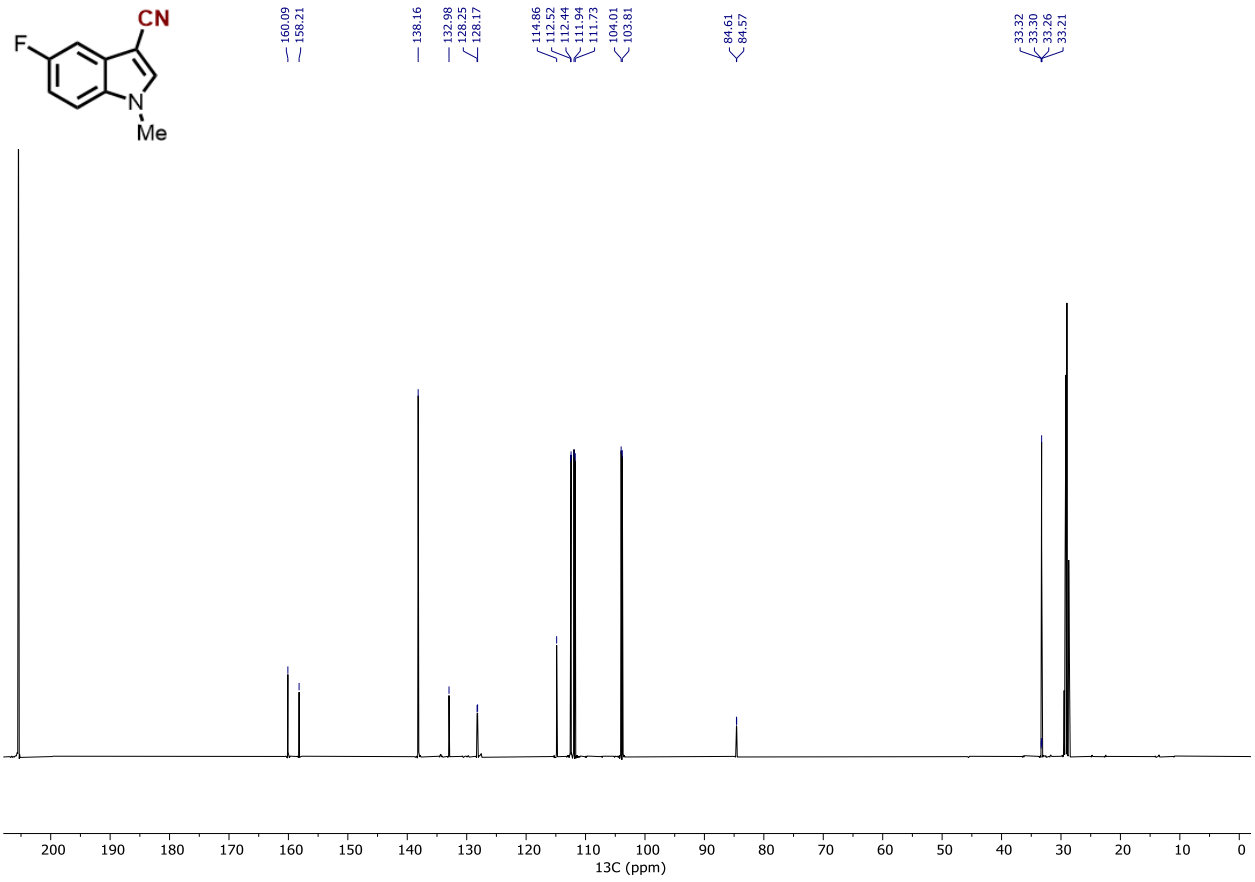
-130
-150
-170
-190
-210
-230
31P (ppm)

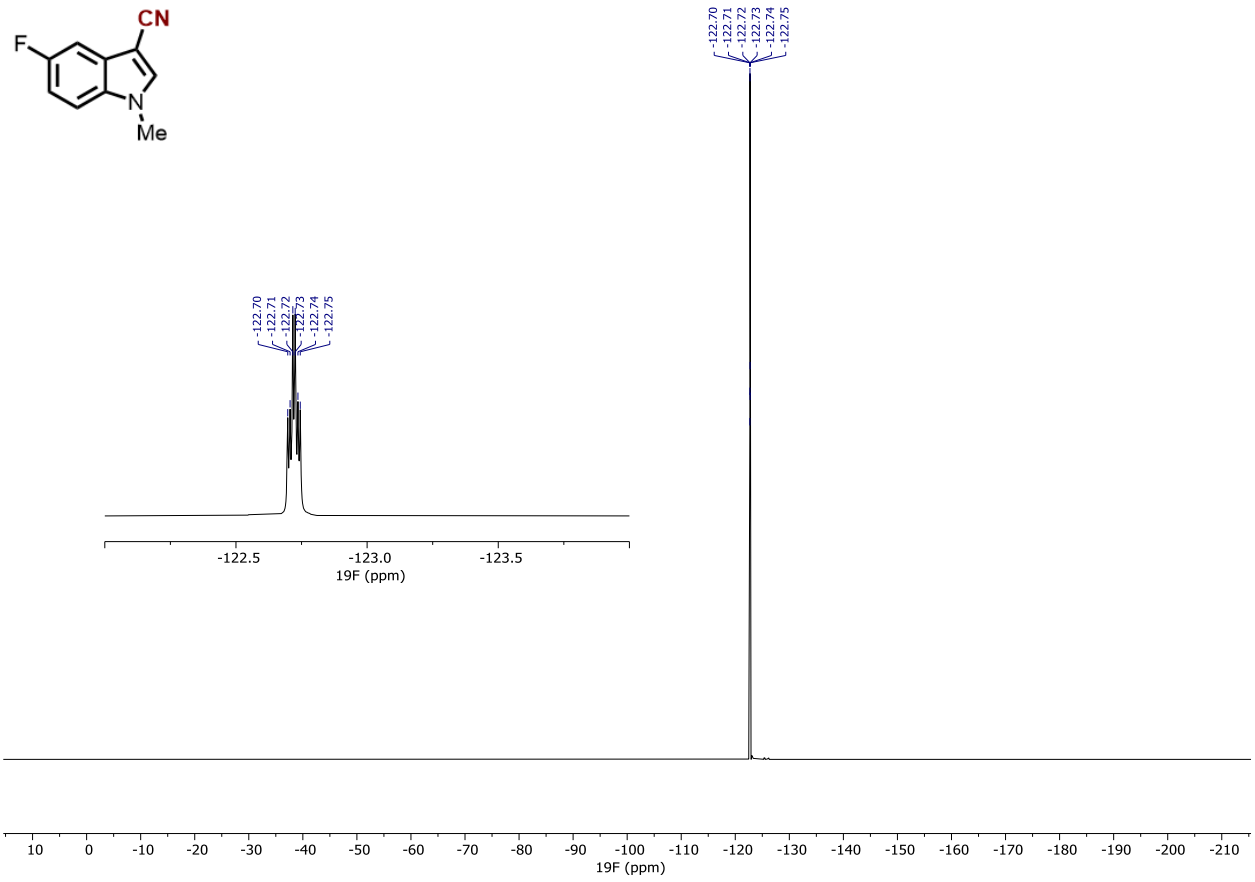

F
CN
N
H
11.34
11.34
8.18
8.17
7.64
7.63
7.62
7.61
7.41
7.41
7.39
7.39
7.15
7.14
7.13
7.12
7.11
7.10
3.15 H2O
2.08 Acetone
2.07 Acetone
2.07 Acetone
2.06 Acetone
2.06 Acetone
1.00
1.04
0.96
1.02
8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1
1H (ppm)
0.82
1.00
1.04
0.96
1.02
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
1H (ppm)

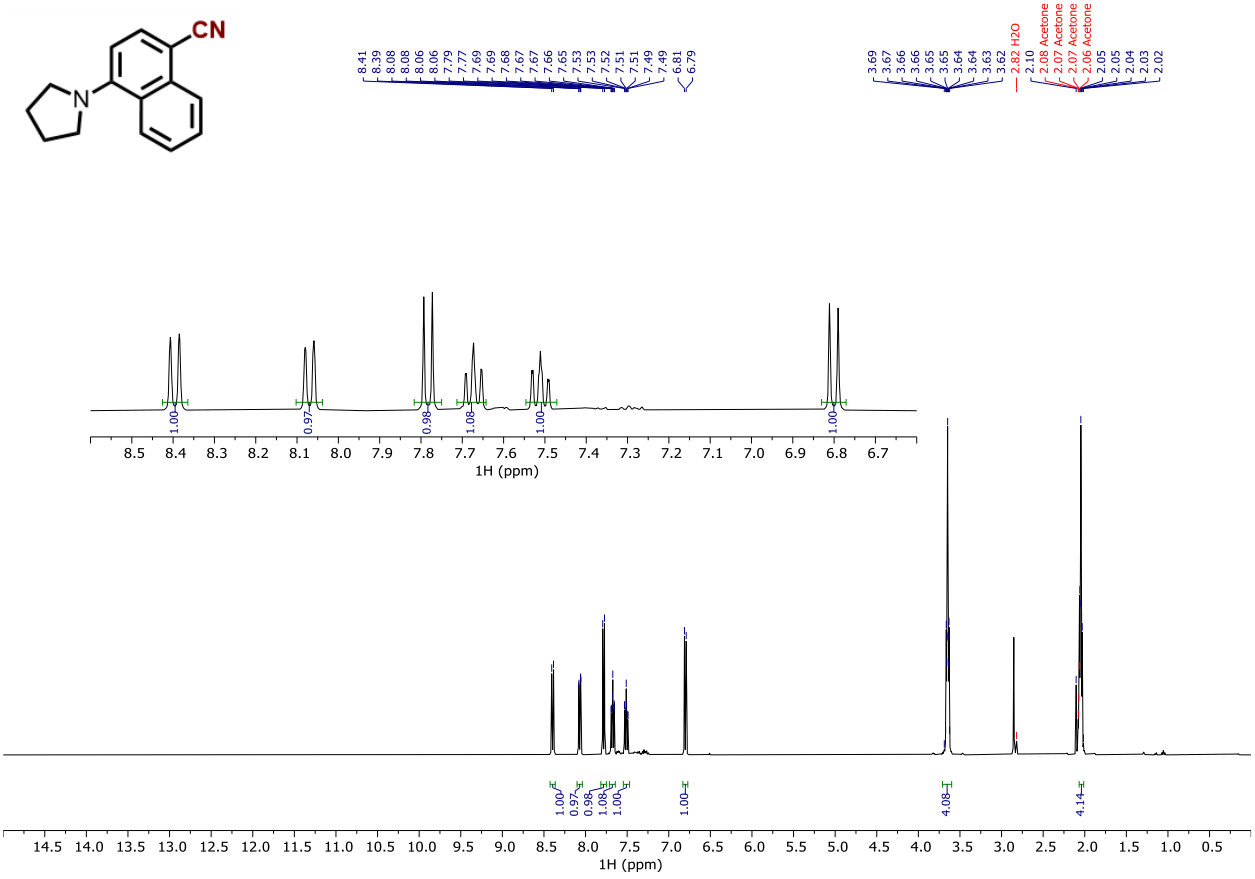

159.96
158.07
135.05
132.17
127.82
127.73
115.06
114.18
114.11
112.16
111.95
103.79
103.59
86.17
86.14
CN
F
N
H
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
13C (ppm)

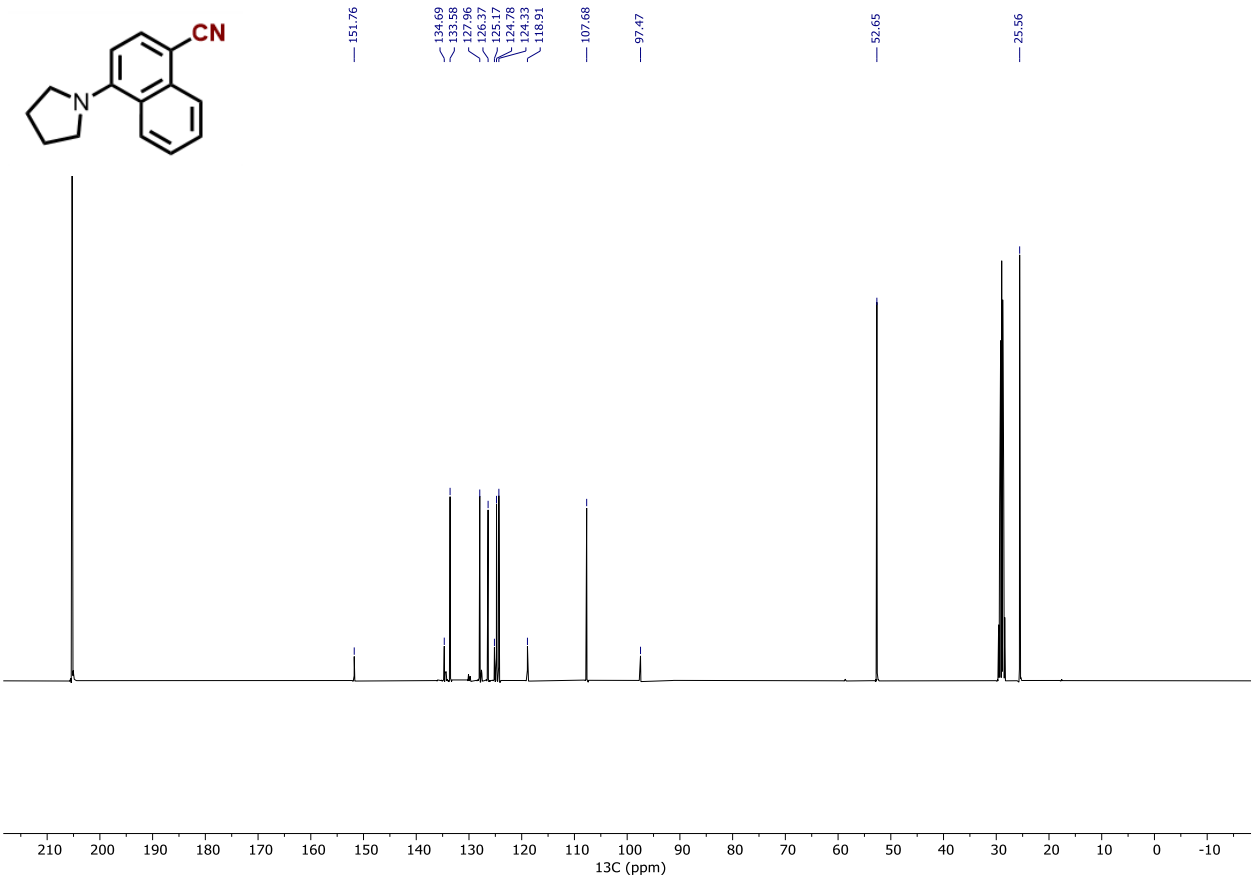

CN
F
N
H
-122.70
-122.71
-122.72
-122.73
-122.74
-122.75
-122.1
-122.3
-122.5
-122.7
-122.9
-123.1
-123.3
19F (ppm)
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
19F (ppm)

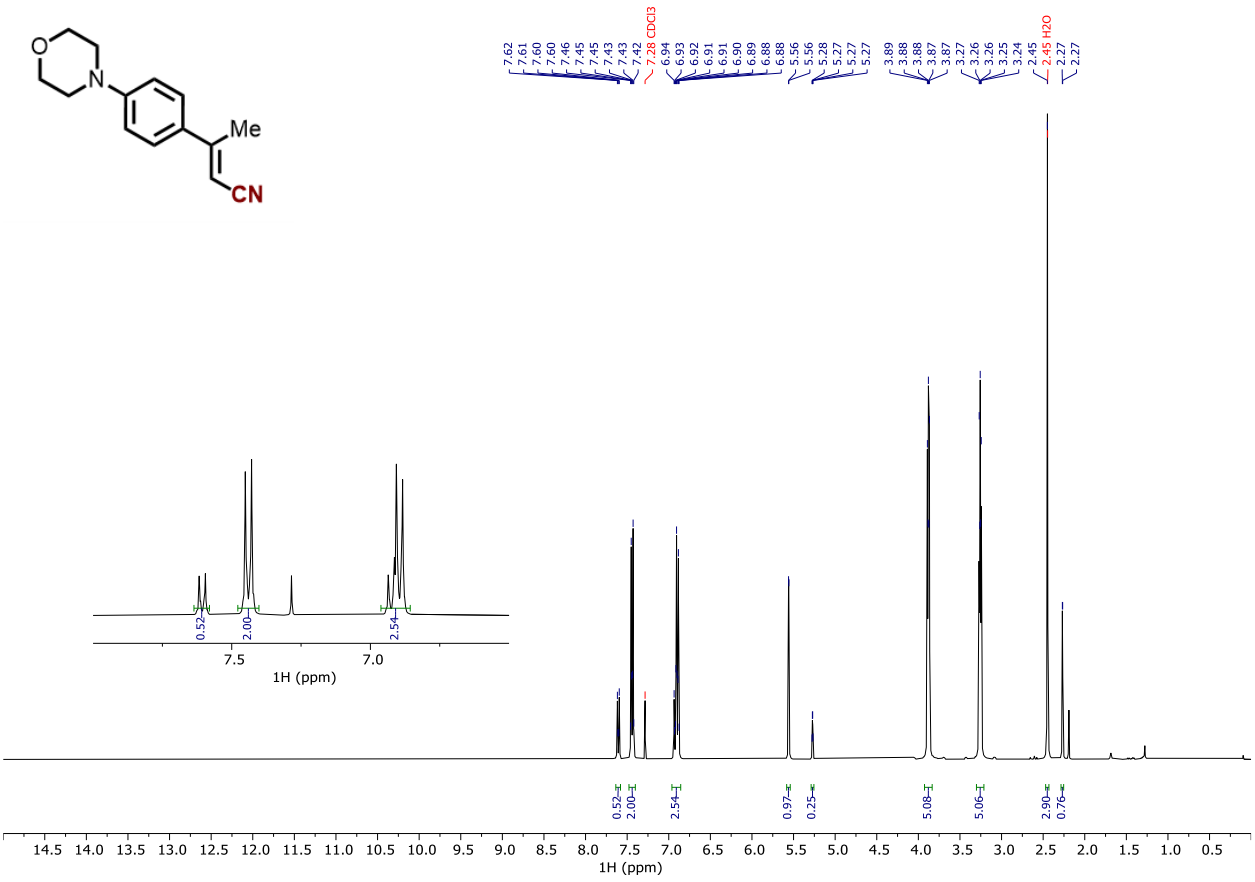

CN
F
N
Me
8.05
7.61
7.60
7.59
7.58
7.37
7.37
7.35
7.35
7.18
7.17
7.16
7.15
7.14
7.14
3.96
2.90 H2O
2.08 Acetone
2.07 Acetone
2.07 Acetone
2.06 Acetone
2.06 Acetone
1.00
1.05
1.03
1.05
3.14
1H (ppm)

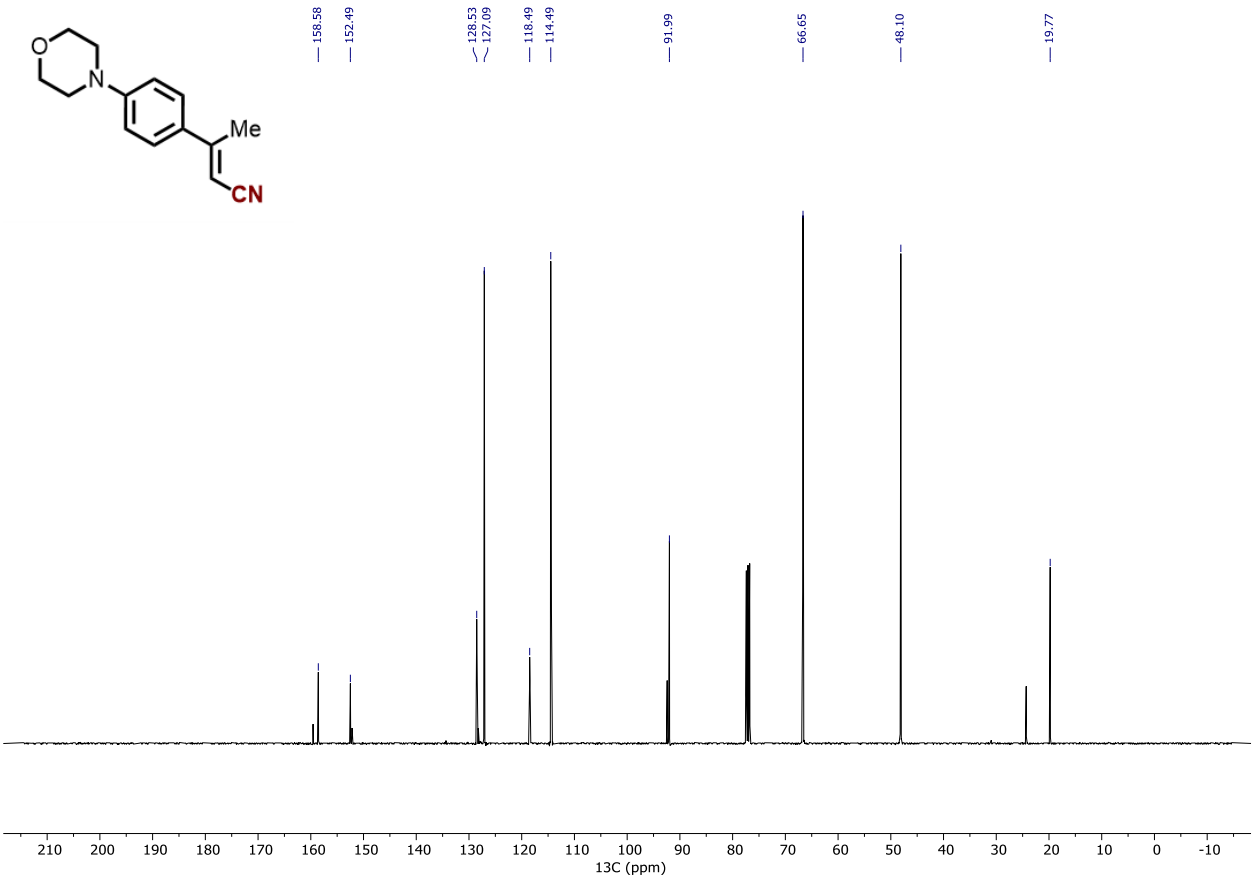

CN
F
N
Me
160.09
158.21
138.16
132.98
128.25
128.17
114.86
112.52
112.44
111.94
111.73
104.01
103.81
84.61
84.57
33.32
33.30
33.26
33.21
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
13C (ppm)


CN
F
N
Me
-122.70
-122.71
-122.72
-122.73
-122.74
-122.75
-122.5
-123.0
-123.5
19F (ppm)
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
19F (ppm)


CN
N
8.41
8.39
8.08
8.08
8.06
8.06
7.79
7.77
7.69
7.69
7.68
7.67
7.67
7.66
7.65
7.53
7.53
7.52
7.51
7.51
7.49
7.49
6.81
6.79
3.69
3.67
3.66
3.66
3.65
3.65
3.64
3.64
3.63
3.62
2.82 H2O
2.10
2.08 Acetone
2.07 Acetone
2.07 Acetone
2.06 Acetone
2.05
2.05
2.04
2.03
2.02
1.00
0.97
0.98
1.08
1.00
1.00
8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7
1H (ppm)
1.00
0.97
0.98
1.08
1.00
1.00
4.08
4.14
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
1H (ppm)


CN
N
151.76
134.69
133.58
127.96
126.37
125.17
124.78
124.33
118.91
107.68
97.47
52.65
25.56
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C (ppm)


O
N
Me
CN
7.62
7.61
7.60
7.60
7.46
7.45
7.45
7.43
7.43
7.42
7.28 CDCl3
6.94
6.93
6.92
6.91
6.91
6.90
6.89
6.88
6.88
5.56
5.56
5.28
5.27
5.27
5.27
3.89
3.88
3.88
3.87
3.87
3.27
3.26
3.26
3.25
3.24
2.45
2.45 H2O
2.27
2.27
0.52
2.00
2.54
7.5
7.0
1H (ppm)
0.52
2.00
2.54
0.97
0.25
5.08
5.06
2.90
0.76
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
1H (ppm)


158.58
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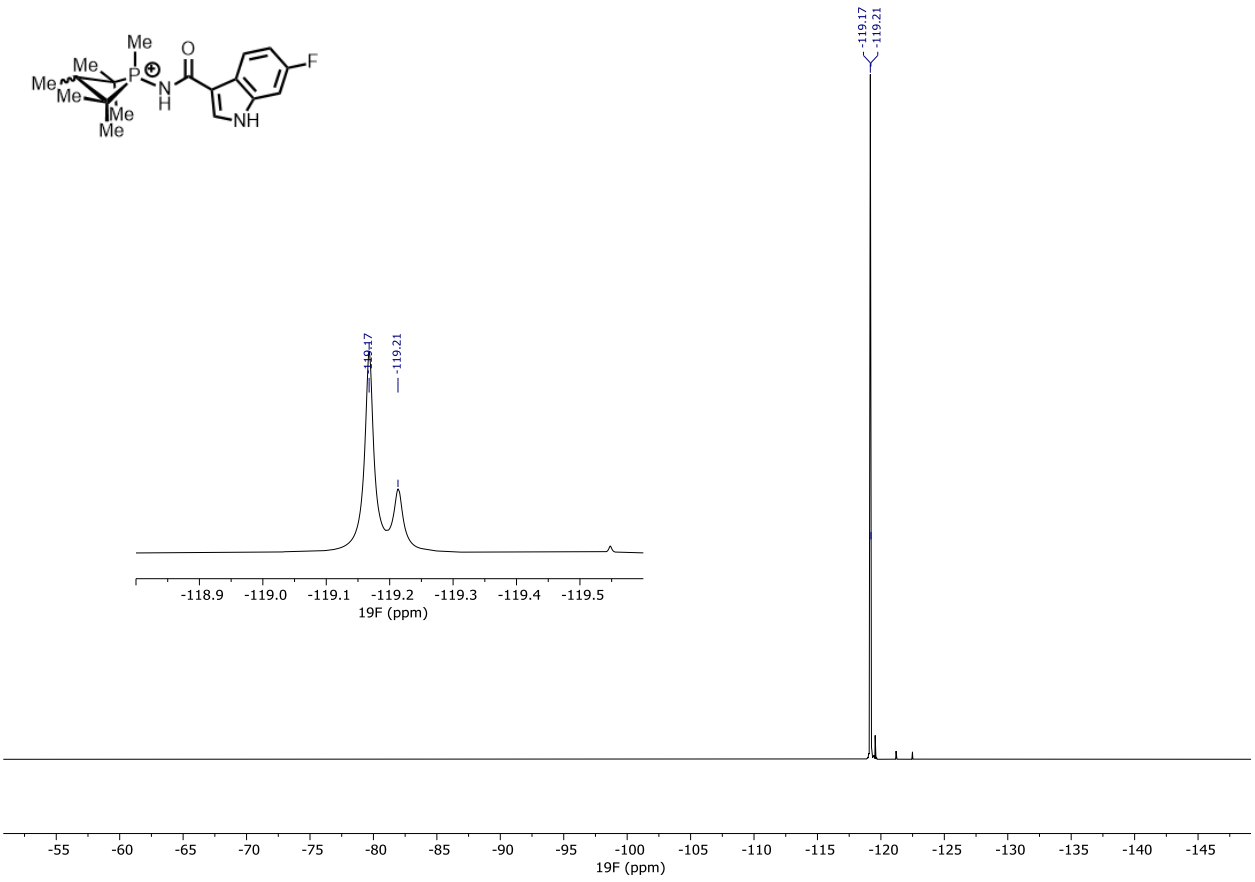
127.09
118.49
114.49
91.99
66.65
48.10
19.77
O
N
Me
CN
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C (ppm)


Me
Me
Me
Me
Me
P
N
H
O
F
NH
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-119.21
-118.9
-119.0
-119.1
-119.2
-119.3
-119.4
-119.5
19F (ppm)
-55
-60
-65
-70
-75
-80
-85
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-100
-105
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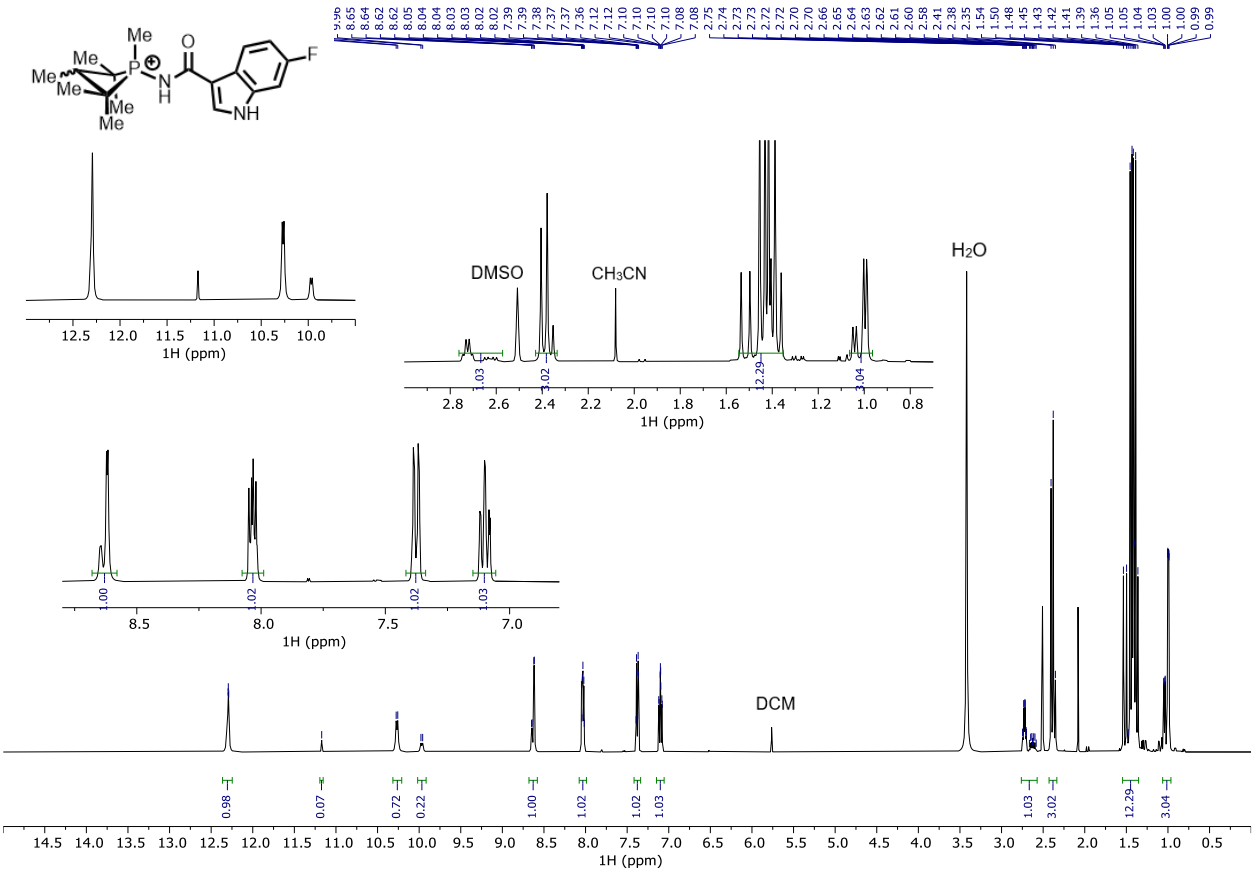
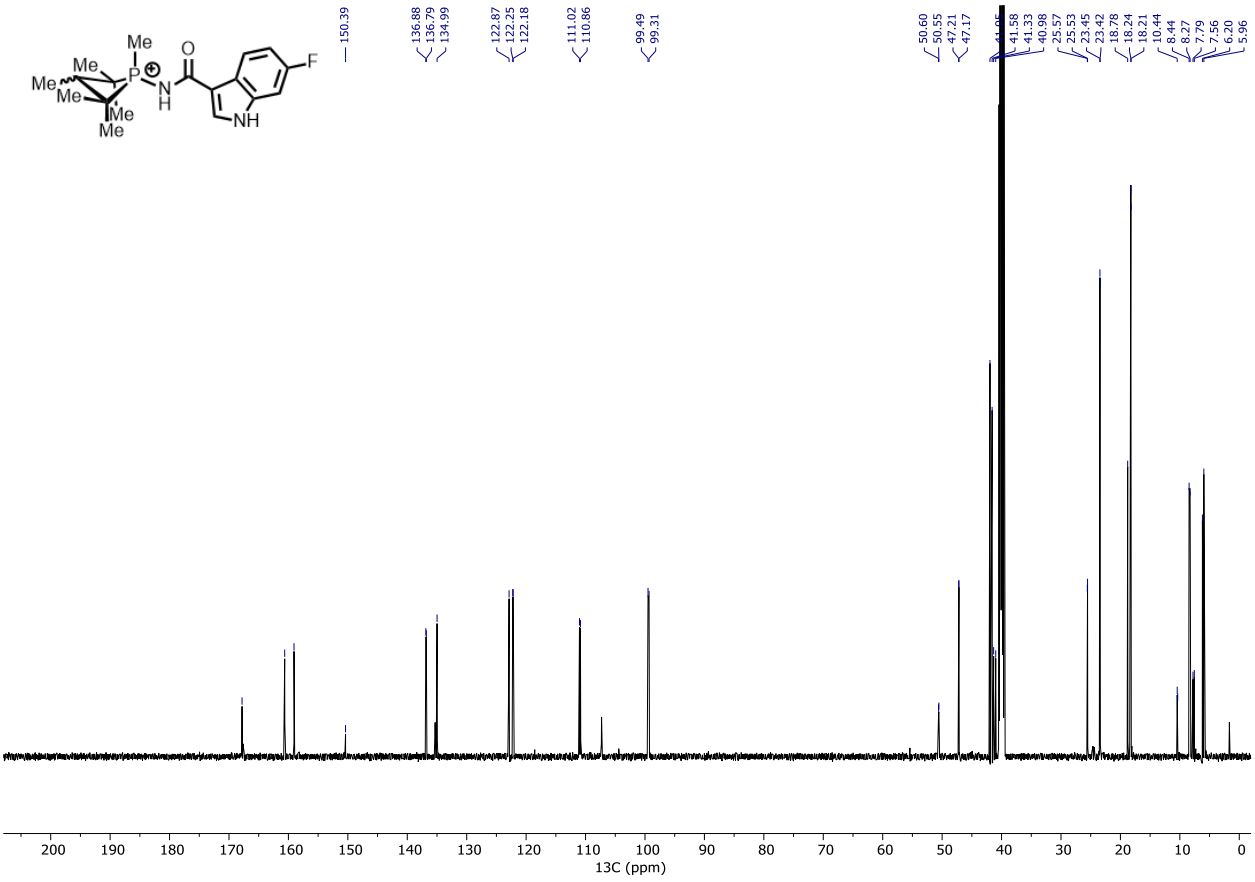
-115
-120
-125
-130
-135
-140
-145
19F (ppm)


Me
Me
Me
Me
Me
P
N
H
O
F
NH
DMSO
CH3CN
H2O
DCM
1H (ppm)


Me
Me
Me
Me
Me
P
N
H
O
F
NH
150.39
136.88
136.79
134.99
122.87
122.25
122.18
111.02
110.86
99.49
99.31
50.60
50.55
47.21
47.17
41.58
41.33
40.98
25.57
25.53
23.45
23.42
18.78
18.24
18.21
10.44
8.44
8.27
7.79
7.56
6.20
5.96
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
13C (ppm)

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[1] a) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902–7917; b) T. G. M. Dhar *et al.*, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3557–3560; c) P. Rhoennstad, E. Kallin, T. Apelqvist, M. Wennerstaal, A. Cheng, WO 2009127686, **2009**; d) L.-H. Zhang, L. Wu, H. K. Raymon, R. S. Chen, L. Corral, M. A. Shirley, R. K. Narla, J. Gamez, G. W. Muller, D. I. Stirling, J. B. Bartlett, P. H. Schafer, F. Payvandi, *Cancer Res.* **2006**, *66*, 951–959; e) H. H. Bailey, D. B. Alberti, J. P. Thomas, D. L. Mulkerin, K. A. Binger, M. M. Gottardis, R. E. Martell, and G. Wilding, Clin. *Cancer Res.* **2007**, *13*, 3623–3629; f) T. C. Reid and L. S. Beese, *Biochemistry* **2004**, *43*, 6877-6884.

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