Chemical Science

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Cite this: *Chem. Sci.*, 2025, **16**, 16145

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 14th July 2025
Accepted 4th August 2025

DOI: 10.1039/d5sc05216e

rsc.li/chemical-science

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Nitrilation of carboxylic acids by P^{III}/P^{V}-catalysis

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A mild and catalytic method for the direct conversion of carboxylic acids into their corresponding nitriles is reported. In contrast to common nitrile preparations that rely on hazardous cyanide and cyanogen precursors, the present protocol employs a P^{III}/P^{V}-catalyzed 'oxidation–reduction condensation' approach to effect iterative amidation/retro-Ritter reaction of carboxylic acids with 1-phenethylamine. Primary, secondary, tertiary, and aromatic carboxylic acids all undergo nitrilation in synthetically viable yields, including several pharmaceuticals and natural products. Using homochiral 1-phenethylamine, both resolution and nitrilation of racemic carboxylic acids can be achieved, allowing synthetic access to chiral nitriles.

Introduction

Nitriles are an important functional group in a variety of natural products, materials, and pharmaceutically active compounds.[1,2] Commonly, nitrile syntheses involve installation of the diatomic "—CN" unit through a C–C bond forming cyanation of a suitable organic precursor. The versatility of this approach is only offset by the handling and disposal hazards associated with the requisite nucleophilic (cyanide) or electrophilic (cyanogen) cyanation reagents,[3] with few notable exceptions (Fig. 1A).[4] An alternative approach to nitrile synthesis that builds up the nitrile functional group by formation of the C≡N triple bond presents an appealing complement. Specifically the isohypsic[5] transformation of carboxylic acids to nitriles (—CO_2H → –CN) transformation might represent a useful entry to nitriles that leverages abundant carboxylic acid substrates. Indeed, carboxylic acids[6,7]—readily accessible and structurally diverse—have been noted as desirable building blocks in organic synthesis, especially in drug development.[8–10] But whereas the conversion of nitriles into carboxylic acids (*i.e.* nitrile hydrolysis) is prosaic, the inverse transformation of carboxylic acids into nitriles (*i.e.* carboxylate nitrilation) remains synthetically underdeveloped. Multistep amidation/dehydration synthetic sequences can achieve the conversion,[11–13] albeit with significant waste and process inefficiencies. Catalytic approaches for the direct conversion of carboxylic acids to nitriles are few; these methods either employ bespoke reagents or high temperatures, and are usually limited to benzylic or aromatic carboxylic acids (Fig. 1B).[14–21] A mild, catalytic method that allows for the direct nitrilation of both aryl and alkyl carboxylic acids under operationally simple and cyanide-free conditions could represent a useful addition to existing methods.

Recently, organophosphorus catalysis based on P^{III}/P^{V} redox cycling[22–24] has emerged as a powerful platform for catalytic "oxidation–reduction condensation"[25–27] reactions, in which the phosphorus center cycles between +3 and +5 oxidation states to orchestrate sequential bond-forming and dehydrative steps. Specifically, a phosphetane-based catalyst in conjunction with

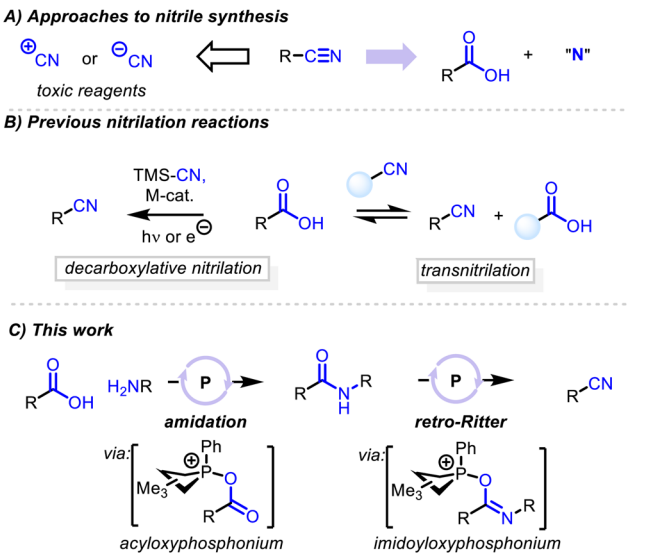

Fig. 1 A summary of approaches to nitrile synthesis. (A) General strategies in nitrile synthesis. (B) Previous direct nitrilation reactions. (C) Summary of the reported work.

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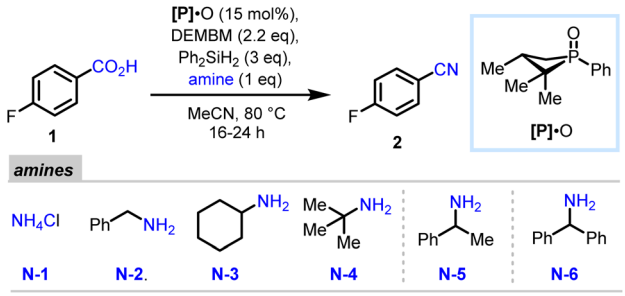
a mild halenium-based oxidant and hydrosilane reductant has been shown to functionalize carboxylic acids by sequential dehydrative amidation and amide functionalization through recursive generation of electrophilic quasiphosphonium intermediates—such as acyloxyphosphonium and imidoyloxyphosphonium ions.[28,29] Having previously intercepted the imidoyloxyphosphonium ions for C–C and C–N bond-forming reactions with nucleophilic coupling partners, we questioned whether they might be induced to dissociate a phosphine oxide and thereby generate a nitrilium cation,[30,31] from which a retro-Ritter reaction[32] might afford a nitrile product (Fig. 1C). In so doing, an approach to the valuable direct conversion of carboxylic acids to nitriles might be realized.

Herein we disclose such a direct nitrilation of primary, secondary, tertiary, and aromatic carboxylic acids under auto-tandem P^{III}/P^{V} redox cycling conditions. This mild and cyanide-free approach to the $-CO_2H \rightarrow -CN$ transformation not only extends the utility of organophosphorus redox catalysis but also highlights P^{III}/P^{V}-catalyzed oxidation–reduction condensation as a versatile strategy for constructing synthetically valuable functionalities. By expanding the scope of P^{III}/P^{V} catalysis to include direct nitrilation, this work establishes a new organophosphorus-enabled synthesis that enhances molecular diversity from abundant carboxylic acid feedstocks.

Results

The conversion of 4-fluorobenzoic acid (**1**) to 4-fluorobenzonitrile (**2**) was investigated for discovery and development experiments. Employing diethylmethylbromomalonate (DEMBM) and diphenylsilane as a compatible oxidant and reductant pair to enable redox cycling of catalyst 1-phenyl-2,2,3-trimethylphosphetane oxide ([**P**]·O),[28] the reaction outcome was found to be highly dependent on the identity of the amination reagent (Table 1). Whereas ammonium chloride (**N-1**) and primary amine additives (**N-2**) formed minimal desired product **2** (entries 1,2), cyclohexylamine (**N-3**) and *t*-butylamine (**N-4**) provided **2** in promising yields (entries 3,4). The higher yield of nitrile with increasing α-branching of the amination reagent implied significant dissociative and heterolytic character in the *N*-dealkylation event. Accordingly, the use of secondary benzylic (±)-1-phenethylamine (**N-5**), which is widely available and inexpensive,[33] resulted in formation of the corresponding nitrile product **2** in 89% yield (entry 5). Interestingly, benzhydrylamine (**N-6**, entry 6) proved less effective, perhaps as a function of steric hindrance to imidoyloxyphosphonium formation. Alternative halenium/hydrosilane pairs are also functional (*viz.* entry 7, dibromodiethylmalonate (DBDEM) and phenylsilane) albeit with somewhat lower efficiency. Control experiments omitting the phosphetane catalyst resulted in no nitrile product, indicating that the DEMBM and diphenylsilane pair are not sufficient in themselves for acid and amide activation (entry 8). Notably, the optimal catalytic conditions in entry 5 outperform a stoichiometric counterpart (employing PPh_3 along with DEMBM oxidant), which resulted in poorer efficiency and selectivity for the desired nitrile product (entry 9).

Table 1 Reaction discovery and optimization



Entry	Amine	Cat.	[Si]-H	Yield[a] (%)
1	**N-1**	[**P**]·O (15 mol%)	Ph_2SiH_2	10%
2	**N-2**	[**P**]·O (15 mol%)	Ph_2SiH_2	n.d.
3	**N-3**	[**P**]·O (15 mol%)	Ph_2SiH_2	68%
4	**N-4**	[**P**]·O (15 mol%)	Ph_2SiH_2	53%
5	**N-5**	[**P**]·O (15 mol%)	Ph_2SiH_2	89%
6	**N-6**	[**P**]·O (15 mol%)	Ph_2SiH_2	49%
7[b]	**N-5**	[**P**]·O (15 mol%)	$PhSiH_3$	80%
8	**N-5**	—	Ph_2SiH_2	n.d.
9	**N-5**	PPh_3 (2 equiv.)	—	58%

[a] Yields determined by ^{19}F NMR spectroscopy. [b] Dibromodimethylmalonate used as oxidant.

With effective nitrilation conditions established, multinuclear NMR and mass spectrometry experiments were undertaken to provide a working mechanistic framework (Fig. 2). The treatment of phosphetane oxide [**P**]·O with DEMBM and diphenylsilane in the absence of carboxylic acid **1** or amine results in clean conversion to bromophosphonium **I** (^{31}P $\delta = 46.5$ ppm), which is consistent with previous reports on halophosphonium generation.[28,29] However, inspection of the operative catalytic nitrilation of carboxylic acid **1** by ^{31}P and ^{19}F NMR spectroscopy identified a distinct species at ^{31}P $\delta = 86.3$ ppm and ^{19}F $\delta = -102.4$ ppm as the major catalytic resting state. The same species is observed when amide **A** is mixed with phosphetane oxide [**P**]·O, DEMBM, and diphenylsilane, which is consistent with imidoyloxyphosphonium **III** (formed from amide **A** interception of bromophosphonium **I**) as the major catalytic resting state. Finally, mass spectrograms of the crude reaction mixture indicated the presence of (1-bromoethyl)benzene, which could be formed from the retro-Ritter rection of imidoyloxyphosphonium **III**, followed by interception of the resultant carbocation by a bromide anion.

Taken together, the experimental observations are consistent with the following mechanistic sequence (Fig. 2). First, reduction of phosphetane oxide [**P**]·O by diphenylsilane generates P^{III}-phosphetane **P**, which reacts with DEMBM to afford the electrophilic bromophosphonium species **I** by halophilic substitution.[34–36] Carboxylic acid **1** attacks electrophilic bromophosphonium **I** to form acyloxyphosphonium **II**, which can be intercepted by amine **N-5** to form the amide **A**. Subsequent interaction of amide **A** with another equivalent of bromophosphonium **I** affords the imidoyloxyphosphonium **III**, which is the experimentally observed catalytic resting state.

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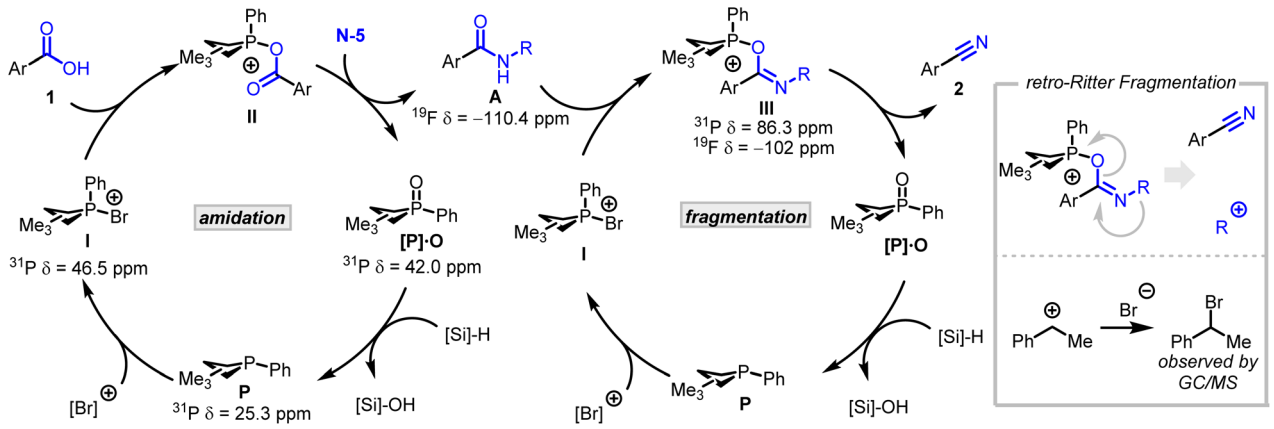

Fig. 2 Proposed P^{III}/P^{V}-catalyzed nitrilation mechanism. Ar = 4-fluorophenyl, R = 1-methylphenyl.

Finally, imidoyloxyphosphonium **III** fragments to dissociate the phosphetane oxide [**P**]·O, generating an incipient nitrilium ion, which undergoes a retro-Ritter rection, liberating nitrile product **2**. In both the carboxylic and amide activation processes, phosphetane oxide [**P**]·O is generated as a byproduct, which can be reduced easily by silane reductants, affording phosphetane **P** and closing the catalytic cycles.

The synthetic scope of the catalytic nitrilation is outlined in Fig. 3. Electron-neutral and electron-deficient benzoic acids undergo efficient conversion to the corresponding nitriles (**2**–**5**).

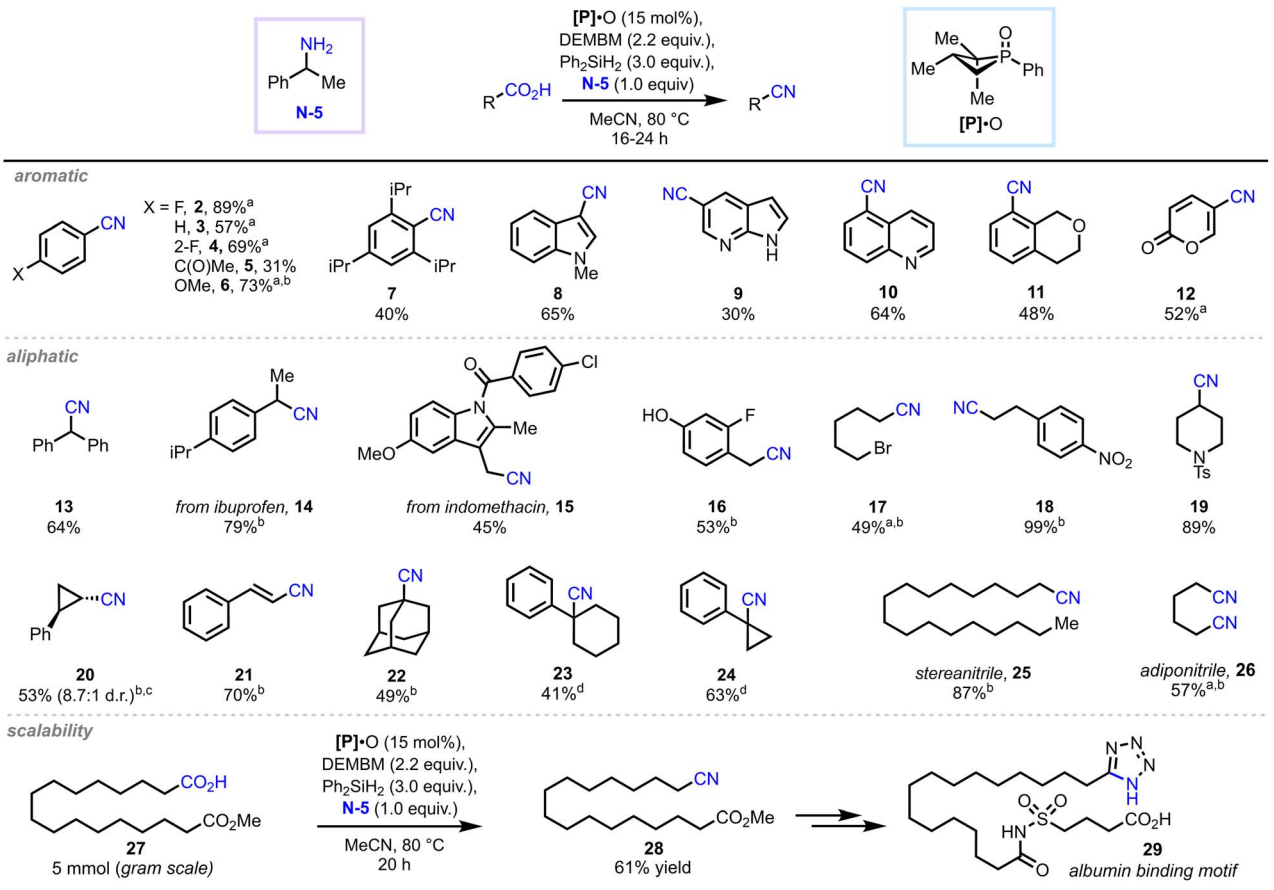

Fig. 3 Exploration of nitrile reaction scope. All yields are of isolated products unless otherwise indicated. [a]Yields determined by ^{1}H NMR spectroscopy, ^{19}F NMR spectroscopy, or GC/MS. [b]Dibromodiethylmalonate (2.2 equiv.) used instead of DEMBM and $PhSiH_3$ used instead of Ph_2SiH_2. [c]Crude d.r. reported using GC/MS; isolated product >20 : 1 d.r. [d]Dibromodiethylmalonate (2.2 equiv.) used instead of DEMBM and $PhSiH_3$ used instead of Ph_2SiH_2; toluene used as solvent and reaction heated to 110 °C. See SI for full experimental details.

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In contrast, electron-rich substrates required the use of an alternative redox pair—dibromodiethylmalonate and phenylsilane—to overcome poor conversion under standard conditions, as exemplified by substrate **6**. Despite the steric demands of the imidoyloxyphosphonium intermediate, *ortho*-substituted benzoic acid **7** is transformed in synthetically useful yield. Heteroaromatic acids bearing indole, azaindole, pyridine, isochroman, and pyrone motifs (**8–12**) are also compatible.

Aliphatic acids are viable substrates, demonstrating the reaction's tolerance for saturated frameworks and polar functional groups. (Hetero)arylacetic acids (**13–16**), including ibuprofen (**14**) and indomethacin (**15**), afford the corresponding nitriles in good yield. Notably, the tertiary amide in indomethacin remains intact, highlighting the selectivity of the catalytic system for reactive secondary amides. Free alcohol (**16**) and alkyl bromide (**17**) substituents are preserved, offering handles for further elaboration. This level of chemoselectivity contrasts with cyanide-based methods of nitrile synthesis, which often suffer from poor compatibility with electrophilic or protic functionalities.[37]

The method tolerates additional functional groups that are typically reactive under P^{III}/P^{V} catalysis. Nitroarene-[38–40] and sulfonamide[41]-bearing substrates (**18**, **19**) are smoothly converted without reduction, indicating orthogonal functional group tolerance under the catalytic oxidation–reduction condensation conditions.

Aliphatic acids bearing α-substitution (**20** (ref. 42)) and α,β-unsaturation (**21**) are amenable to nitrilation. Tertiary acids, while more challenging, can be converted under modified conditions. For example, 1-adamantylcarboxylic acid affords the nitrile product (**22**) in moderate yield under standard conditions. However, for more sterically hindered substrates such as 1-phenylcyclohexyl- (**23**) and 1-phenylcyclopropylcarboxylic acids (**24**), a solvent modification (PhMe) and increased temperature (110 °C) were essential to facilitate nitrile synthesis.

Finally, the reaction is scalable and suitable for the synthesis of relevant nitriles from renewable feedstocks. Stearic acid, adipic acid, and carboxylic acid **27** are converted to nitriles **25**, **26**, and **28**, respectively. Nitrile **28** was prepared on a 5 mmol scale in 61% yield, comparable to small-scale reactions. Nitrile **28** can be further elaborated to tetrazole **29**, a motif of interest as an albumin-binding handle for intracellular delivery of large molecules.[43,44]

A direct synthesis of enantioenriched nitriles was achieved through a telescoped resolution/nitrilation sequence using enantiopure (*S*)-1-phenylethylamine ((*S*)-**N-5**, Fig. 4). This inexpensive amine—which is readily available as either enantiomer—serves a dual role: first, as a resolving agent *via* selective crystallization of diastereomeric ammonium carboxylate salts formed from racemic carboxylic acids; second, as the aminating component in the P^{III}/P^{V}-catalyzed nitrilation. Such ammonium salts are commonly employed as checkpoints in process chemistry due to their ability to reject impurities upon crystallization. Direct exposure of the isolated homochiral salts to the phosphetane oxide precatalyst, dibromodiethylmalonate, and phenylsilane effected nitrile formation with retention of enantiomeric purity. Indeed, using (*S*)- or (*R*)-1-phenylethan-1-amine, respectively, racemic 1-indanylmethyl and 3-phenylbutanoic carboxylic acids were thus transformed into optically enriched nitriles (**30**, **31**) under standard catalytic conditions.

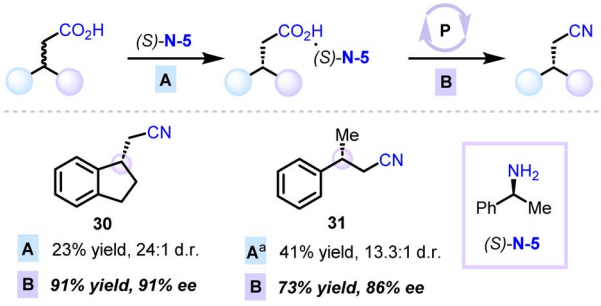

Fig. 4 Synthesis of chiral nitriles through two-step one-pot protocol. Conditions: (A) (*S*)-**N-5** (1.0 equiv.) in acetone (2.0 M) or THF (0.19 M), rt; (B) [P]·O (0.15 equiv.), diethyldibromomalonate (2.2 equiv.), phenylsilane (3.0 equiv.), in acetonitrile (0.25 M) at 80 °C. [a](*R*)-**N-5** used. Enantiomeric excesses were determined by either chiral SFC or chiral HPLC.

Conclusions

In conclusion, we have developed a general, catalytic method for the direct conversion of carboxylic acids to nitriles under mild, autotandem on P^{III}/P^{V} catalysis. This transformation proceeds *via* an organophosphonium-driven amidation/activation/elimination sequence, wherein imidoyloxyphosphonium intermediates undergo retro-Ritter rection to furnish the corresponding nitriles. The method is effective across a broad range of primary, secondary, tertiary, aromatic, and heteroaromatic carboxylic acids and exhibits good functional group tolerance. The use of bench-stable and inexpensive 1-phenethylamine as the nitrilation reagent enables operational simplicity and scalability, and allows for a straightforward route to enantioenriched nitriles from racemic carboxylic acids. Taken together, these findings expand the synthetic utility of P^{III}/P^{V} catalysis beyond nucleophilic coupling and establish a broadly applicable, cyanide-free platform for accessing structurally diverse nitriles from readily available carboxylic acid feedstocks.

Author contributions

S. Z. A., J. M. L., N. A. W., and A. T. R. conceptualized this work and designed the experiments. S. Z. A., N. A. M., J. S.; A. S., and N. A. W. performed the experiments. S. Z. A., A. T. R., N. A. W., J. S., and J. M. L. contributed to preparation of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Data availability

The data supporting this article have been included as part of the ESI. Crystallographic data for all compounds have been deposited at the CCDC under 2323130.

CCDC 2323130 contains the supplementary crystallographic data for this paper.[45]

Synthetic procedures, analytical and characterization data, and crystallographic details. See DOI: **https://doi.org/10.1039/d5sc05216e**.

Acknowledgements

Financial support was provided by NIGMS of the National Institutes of Health (NIH) under Award Number GM114547. S. Z. A. acknowledges the NIH for support through the Ruth L. Kirschstein Postdoctoral Fellowship (F32GM13091). All authors are grateful to Dr G. Li and Z. Qin for preliminary experiments, Dr P. Müller for assistance with crystallographic data collection and refinement, and Dr J. G. Napolitano for assistance with NMR acquisition and interpretation.

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