OL Organic Letters

pubs.acs.org/OrgLett

Letter

Unveiling the Phosphine-Mediated *N*-Transfer from Azide to Isocyanide en Route to Carbodiimides and 4-Imino-1,3,2-diazaphosphetidines

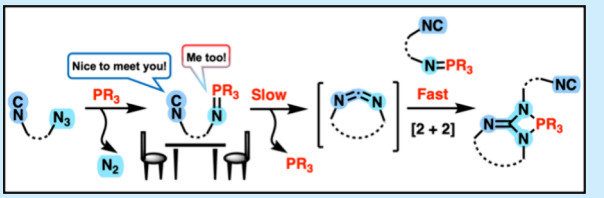
Aurelia Pastor,* Carmen Lopez-Leonardo,* Guillermo Cutillas-Font, Alberto Martinez-Cuezva, Marta Marin-Luna, Jose-Antonio Garcia-Lopez, Isabel Saura-Llamas, and Mateo Alajarin*

Cite This: *Org. Lett.* 2025, 27, 73−79

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Intramolecular reactions between isocyano and iminophosphorane functions yield species containing an embedded 1,3,2-diazaphosphetidine ring, as result of the [2 + 2] cycloaddition of the primary reactive product, the cyclic carbodiimide, with a second unit of reactant. DFT studies reveal a first rate-determining step entailing a [2 + 1] cycloaddition involving the isocyanide carbon atom and the P═N double bond, with the further intervention of a dipolar precursor of the intermediate carbodiimide. The 1,3,2-diazaphosphetidine ring of the final products is shown to be hydrolytically and thermally labile.

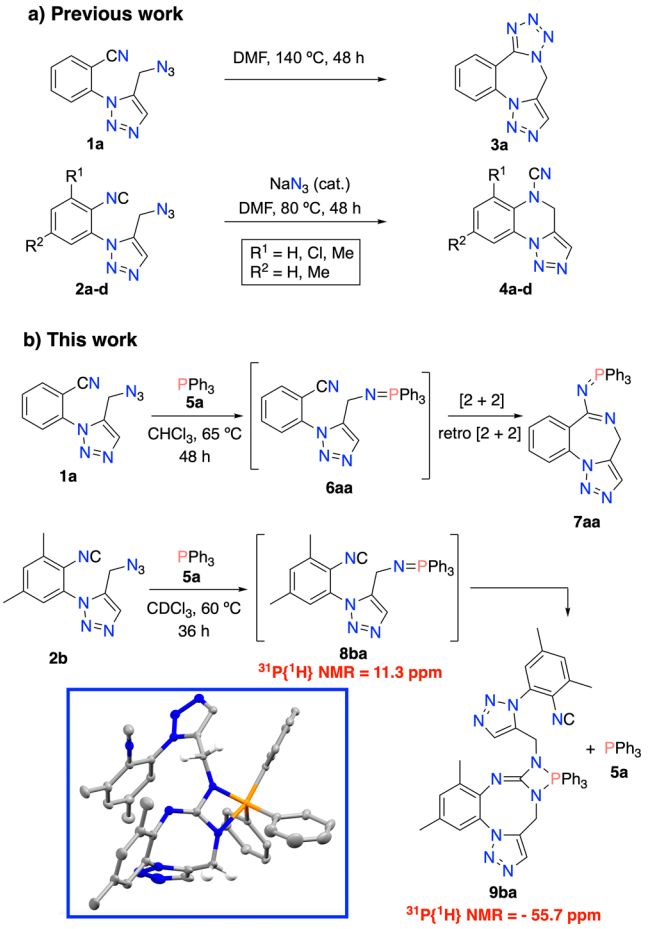


Isocyanides, with its peculiar divalent carbon atom, have captured the attention of chemists since ancient times.[1] This carbon enables its chameleonic reactivity, the simultaneous α-addition of a strong electrophile and a nucleophile.[2] The best-known chemical behavior of isocyanides relies in its participation in multicomponent reactions.[3] Some of us have recently reported the synthesis of a series of functionalized cyanides and isocyanides bearing an azido group at a six-bond distance of the (iso)cyano group, compounds **1a** and **2a−d** (Scheme 1a), and studied their cyclization by the interaction between both functions.[4] Whereas the thermally activated reaction of the azido-cyanide **1a** occurred as expected, yielding a new fused tetrazole ring, compound **3a**, the analogous isocyanides **2a−d** only cyclized under the activation of the azide anion as a catalyst, unexpectedly giving rise to the fused cyanamides **4a−d**. With compounds **2** in hand, we next studied the reaction of isocyanides with a nearby iminophosphorane function, a process not previously disclosed neither in intramolecular nor intermolecular versions (Scheme 1b).[5] Herein we reveal the results of such a study showing a novel reactivity mode of the isocyanide function, inserting into the N═P double bond of iminophosphoranes in a formal [2 + 1] cycloaddition. Although the putative products, CNP three-membered rings, are acquainted by computational methods as shown below, these species do not survive under the reaction conditions, leading to heterotetracycles containing a CN_2P four-membered ring as the final products of such processes.

We first checked the reaction between the *cyanide* and iminophosphorane functional groups, a known process leading to the (*N*-imidoyl)iminophosphoranes through a [2 + 2]-retro [2 + 2] cycloaddition protocol (Scheme 1b).[6] As desired, in situ cyano-iminophosphorane **6aa** prepared from the reaction of **1a** with triphenylphosphine (**5a**), was converted by heating at 65 °C in $CHCl_3$ solution under N_2 into the new imidoyl-phosphazene **7aa** in moderate yield (60%) (Figure S1, Supporting Information). By contrast, the thermal activation at 60 °C of *isocyano*-iminophosphorane **8ba** prepared from **2b** unexpectedly resulted in the recovery of PPh_3 and the formation of **9ba**, a species containing a fused 1,3,2-diazaphosphetidine ring, a scarcely reported organophosphorus small cycle (Scheme 1b). Next, we monitored the reaction of an equimolecular mixture of azidoisocyanide **2b** and PPh_3 in dry $CDCl_3$ at −40 °C by ^1H and ^{31}P NMR spectroscopy (Figures S2 and S3, Supporting Information). Reaching −10 °C, we detected the first reaction product, the PN_3 adduct[7] (^{31}P signal at +19.4 ppm), which rapidly decays by increasing the temperature to 25 °C, converting into the expected iminophosphorane (λ^5-phosphazene) by N_2 extrusion (^{31}P at +11.3 ppm, $C\underline{H}_2$ ^1H at 4.36 ppm, $^3J_{HP}$ = 17.9 Hz). By increasing the temperature to 60 °C, we observed the slow decrease with time of the iminophosphorane signal in the ^{31}P spectra and the progressive appearance of two others, one at −55.7 ppm,[8] which we initially attributed to a three-membered CNP ring[9] but finally identified as **9ba**, and a second one at −7.8 ppm corresponding to PPh_3. After 36 h at 60 °C, only these two latter signals remained in the ^{31}P NMR spectrum of

Received: October 17, 2024
Revised: December 13, 2024
Accepted: December 18, 2024
Published: December 21, 2024

Scheme 1. (a) Cyclization of (Iso)cyano Compounds 1a and 2a–d Previously Reported by Some of Us;[4] (b) Reaction of (Iso)cyano Compounds 1a and 2b with Triphenylphosphine

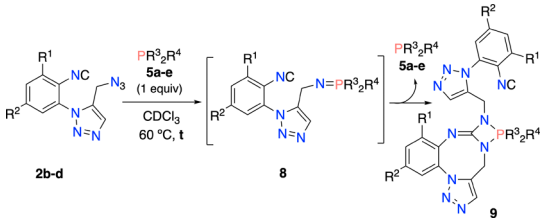


the final reaction mixture in a 1:1 ratio. The identity of **9ba** was corroborated by an X-ray determination (Scheme 1b).

To verify the general scope of the reaction, we next checked the reactions of a range of azido isocyanides **2b–d** with phosphines **5a–e** (Table 1). We first studied these processes under the reaction conditions used in our successful preparation of **9ba**. In this way, we could prepare only a new additional sample of our target compounds (**9be**, entry 4). However, other reactions yielded complex mixtures of products, most probably due to further degradation of the expected products (see below). Taking this into account, we next carried out the reactions into the NMR probe for controlling the optimal reaction time of each process by ^{1}H and ^{31}P spectroscopy. In this manner, we successfully prepared up to 12 examples of compounds **9** in yields ranging 40–95% (Table 1). The notable influence of the substituents at the phenyl ring bearing the isocyano group in the speed of these reactions is shown in this table (reaction times ranging 1–36 h). Note that the processes with the *o*-Cl substrate (**2d**) were rather rapid (entries 8–12), whereas *o*- and *p*-CH_3 groups slow these reactions (entries 1–4).

At this point, we should remark that several unsuccessful experiments were run with other phosphines, for instance $P(C_6H_4\text{-Me-}o)_3$, not reacting with the azido group due to steric reasons, and PBu^n_3 yielding a stable PN_3 phosphazide not converting into the iminophosphorane under the general reaction conditions. In other cases, the expected products **9** were detected by ^{1}H (four characteristic multiplets in the CH_2 region) and ^{31}P NMR but apparently degraded very rapidly, precluding their isolation in pure form (Table S1, Supporting Information). Such decomposition processes resulted in very complex aliphatic regions at the ^{1}H NMR spectra (appearing signals attributable to at least two new species, besides those of **9**) and in the rising of the signals corresponding to the respective phosphine and its oxide in their ^{31}P NMR spectra, both increasing at the expense of the resonance attributed to **9**. These were the cases of iminophosphoranes derived from

Table 1. Scope of the Reaction of Azidoisocyanides 2b–d with Phosphines 5a–e To Give Compounds 9 (DAP)[a]



Entry	DAP (9)	R^1	R^2	R^3	R^4	Yield (9) (reaction time)
1	**9ba**	Me	Me	C_6H_5	C_6H_5	94% (**36 h**)
2	**9bb**	Me	Me	*m*-Me-C_6H_4	*m*-Me-C_6H_4	74% (32 h)
3	**9bd**	Me	Me	3,5-Me_2-C_6H_3	3,5-Me_2-C_6H_3	78% (28 h)
4	**9be**	Me	Me	C_6H_5	*p*-Me-C_6H_4	86% (36 h)
5	**9ca**	Me	H	C_6H_5	C_6H_5	80% (20 h)
6	**9cb**	Me	H	*m*-Me-C_6H_4	*m*-Me-C_6H_4	65% (12 h)
7	**9cd**	Me	H	3,5-Me_2-C_6H_3	3,5-Me_2-C_6H_3	93% (15 h)
8	**9da**	Cl	Me	C_6H_5	C_6H_5	85% (1.75 h)
9	**9db**	Cl	Me	*m*-Me-C_6H_4	*m*-Me-C_6H_4	72% (1.5 h)
10	**9dc**	Cl	Me	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	40% (4 h)
11	**9dd**	Cl	Me	3,5-Me_2-C_6H_3	3,5-Me_2-C_6H_3	95% (1 h)
12	**9de**	Cl	Me	C_6H_5	*p*-Me-C_6H_4	89% (**1.75 h**)

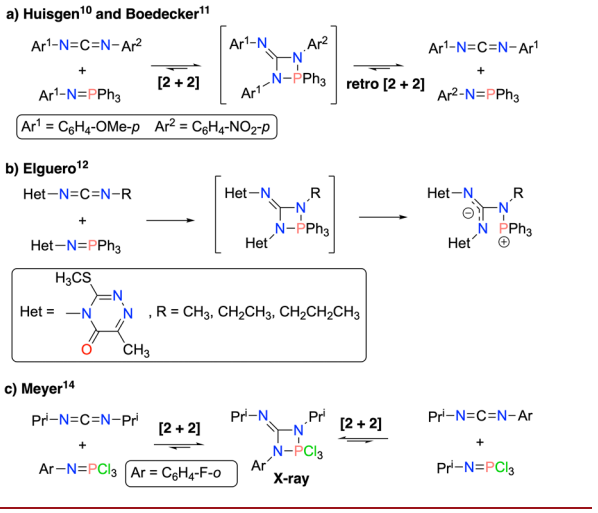
[a]Reaction times (*t*) are given in each entry.

https://doi.org/10.1021/acs.orglett.4c03902
Org. Lett. 2025, 27, 73–79

electron-rich phosphines such as $P(C_6H_4\text{-}OMe\text{-}p)_3$, $P(C_6H_4\text{-}Me\text{-}p)_3$ and PPh_2Me, resulting in rapid reactions and subsequent degradations, but also of some attempts with less nucleophilic phosphines as $P(C_6H_4\text{-}Cl\text{-}p)_3$ reacting slowly but showing rapid degradation of the putative species **9**. As summarized in Table 1, triphenylphosphine and other triaryl partners with similar electronic characteristics, such as $P(C_6H_4\text{-}Me\text{-}m)_3$, $P(C_6H_3\text{-}Me_2\text{-}3,5)_3$ and $PPh_2(C_6H_4\text{-}Me\text{-}p)$, gave the best results in terms of yield and stability of the reaction products **9**.

Species with the key 4-imino-1,3,2-diazaphosphetidine fragment, present in compounds **9**, have been scarcely documented (Scheme 2). They were first proposed as

Scheme 2. Previous Examples of Reactions between Carbodiimides and Iminophosphoranes Affording 4-Imino-1,3,2-diazaphosphetidines as Either Proposed Intermediates or Isolated Products



nonisolable reactive intermediates by R. Huisgen[10] and later on by Boedeker,[11] in a reaction between a carbodiimide and an iminophosphorane leading to another pair of similar species via a [2 + 2]-retro[2 + 2] cycloaddition sequence.

Some of us also proposed 4-imino-1,3,2-diazaphosphetidines as necessary, nonisolable intermediates for explaining the formation of phosphonium betaines by reaction of heterocyclic *N*-iminophosphoranes with some alkyl isocyanates.[12,13] Finally, Meyer could isolate the first example of these small rings by reaction of diisopropylcarbodiimide with $o\text{-F}-C_6H_4-N{=}PCl_3$ and determined its crystal structure by X-ray diffraction.[14]

Consistent with those precedents, the more reasonable explanation for the formation of compounds **9** is the reaction of iminophosphoranes **8** with the cyclic carbodiimide intermediates **12** in a regioselective [2 + 2] cycloaddition manner, involving the most nucleophilic nitrogen atom (*N*-CH_2) of the heterocumulene function (Figure 1, upper box). In a previous step, the key intramolecular reaction between the isocyano and $R^3{}_2R^4P{=}N$ functionalities of the starting materials should yield the cyclic carbodiimides **12** and the corresponding phosphine.[15] This step should occur at such low rate that the reactive carbodiimides **12** always find, in the reaction medium, a high molar ratio of its precursory isocyano-iminophosphorane, thus leading to the fused 4-imino-1,3,2-diazaphosphetidines **9** through a formal intermolecular [2 + 2] cycloaddition (Figure 1, upper box). [2 + 2] Cycloaddition reactions of carbodiimides are well-known and common processes,[16] especially when confronted with heterocumulenes such as (thio)ketenes, iso(thio, seleno)cyanates and ketenimines. Carbodiimides have been also shown to undergo [2 + 2] cyclodimerizations yielding 1,3-diazetidine-2,4-diimines.[17]

To explore the above mechanistic proposal, we carried out a computational DFT study of the reaction path leading from the isocyano-iminophosphorane **8ca** to the cyclic carbodiimide and then to the [2 + 2] cycloadduct **9ca** (Figure 1). As shown, the reaction between the isocyano- and iminophosphorane functions is rate-determining (RDS), with an energy barrier of 114.6 kJ mol^{-1}.

To reach its transition state **TS1**, the nucleophilic N atom of the $N{=}PPh_3$ fragment approaches the carbon atom of the isocyanide function, therefore playing an electrophilic role. The IRC analysis of **TS1** reveals its progress toward the three-membered azaphosphiridine **10ca**, thus completing the insertion of the isocyanide carbon into the N=P bond for a formal, highly asynchronous [2 + 1] cycloaddition step.[18] Intermediate **10ca** quickly converts into stabilized *N*,*P*-betaine **11ca** overcoming an energy barrier of 10.5 kJ mol^{-1}. Next, the cyclic carbodiimide **12c** is formed by extrusion of a PPh_3 molecule through **TS3**. The final stage of the process is the nucleophilic addition of **8ca**, through the N atom of its $N{=}PPh_3$ fragment, into the electrophilic central carbon of the cyclic carbodiimide, whereas the more nucleophilic nitrogen of the heterocumulene *N*-CH_2 binds to the phosphorus atom of that fragment for completing a formal [2 + 2] cycloaddition, by surpassing a small energy barrier.[19] The computed ^{31}P NMR shift of **9ca** is −54.3 ppm, which is in agreement with the experimental value.

To the best of our knowledge, not even in any other formulation the isocyanide plus iminophosphorane reaction has been previously reported.[20] Note that even for the entropically favored intramolecular cyclization of **8ca**, our calculations show a high energy barrier justifying its low rate under the experimental conditions.[21] As our DFT results revealed that the isocyanide function behaves as the electrophile in the rate-determining step, electron-withdrawing groups at the phenyl ring supporting the isocyano group should contribute to accelerating the whole process (as is the case, see entries 8−12 of Table 1).[22] The computed rate-determining insertion of the isocyanide carbon into the N=P double bond adds to the rarely reported [2 + 1] cycloaddition reactions of isocyanides.[23] In its general formulation, the isocyanide plus iminophosphorane reaction could be also labeled as the cross-coupling of two 1,1-dipolar synthons,[24] residing one at the isocyanide carbon and the second at the iminophosphorane nitrogen, yielding a new C=N double bond.[25]

Finally, to further demonstrate the application potential of this reaction, we conducted a 1 mmol-scale reaction of **2b** with triphenylphosphine (**5a**). In this case, 0.331 g of 4-imino-1,3,2-diazaphosphetidine **9ba** was obtained, which corresponds to a yield of 93% (Scheme 3).

The degradation processes of compounds **9** observed in the NMR scale experiments prompted us to assay: (*i*) the hydrolysis of **9ba**, perhaps justifying the formation of $OPPh_3$; and (*ii*) its degradation by heating in solution (Scheme 4). Thus, when **9ba** was submitted to a hydrolytic treatment with silica gel in $CHCl_3$-ethanolic solution, it cleanly converted into the guanidine derivative **13b** and triphenylphosphine oxide in practically quantitative yield. On the other hand, prolonged

https://doi.org/10.1021/acs.orglett.4c03902
Org. Lett. 2025, 27, 73−79

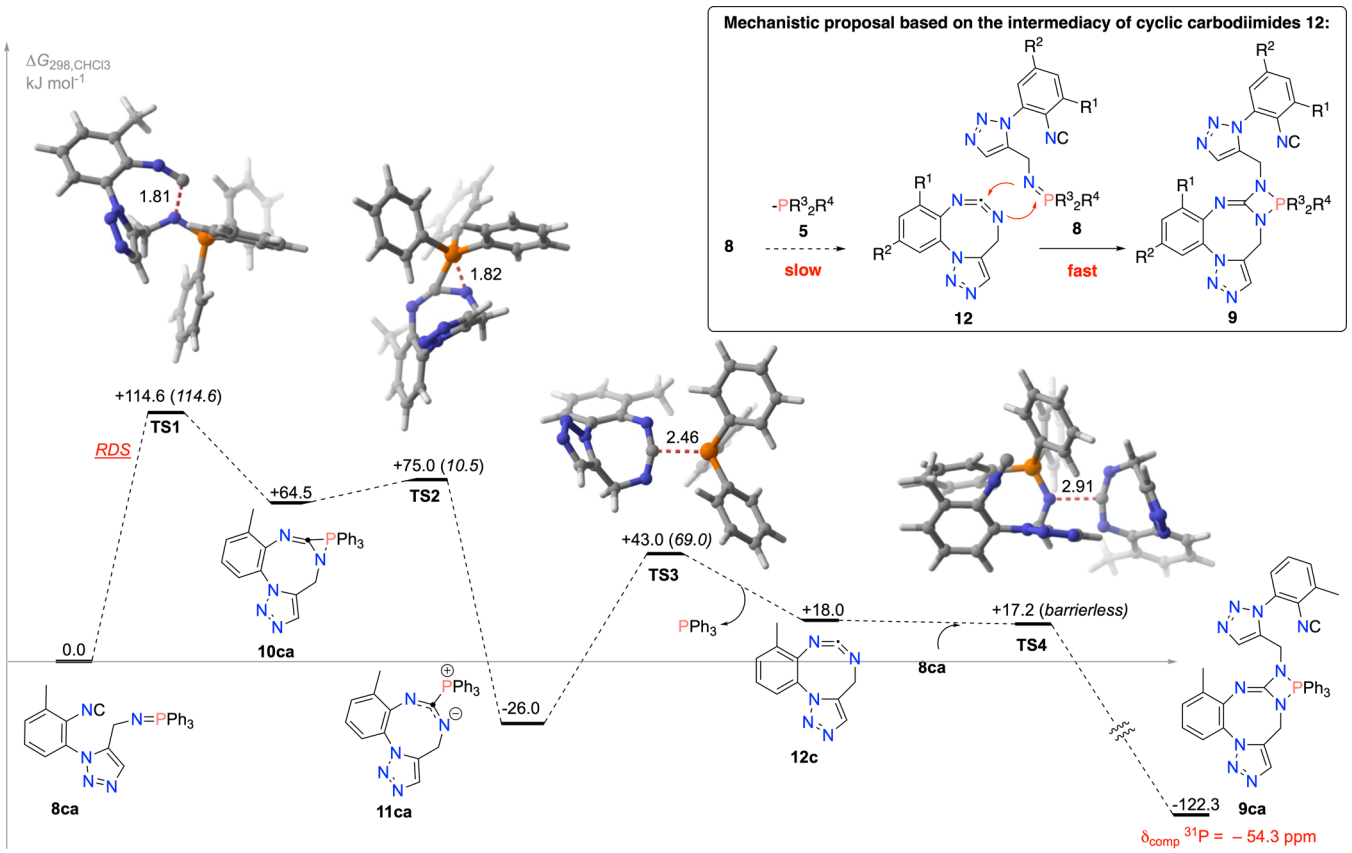
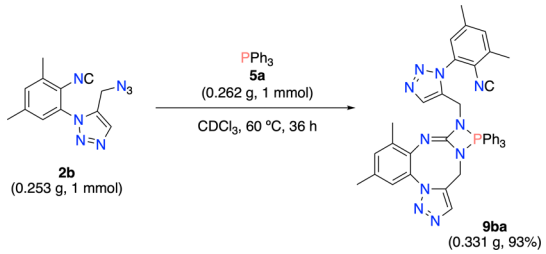
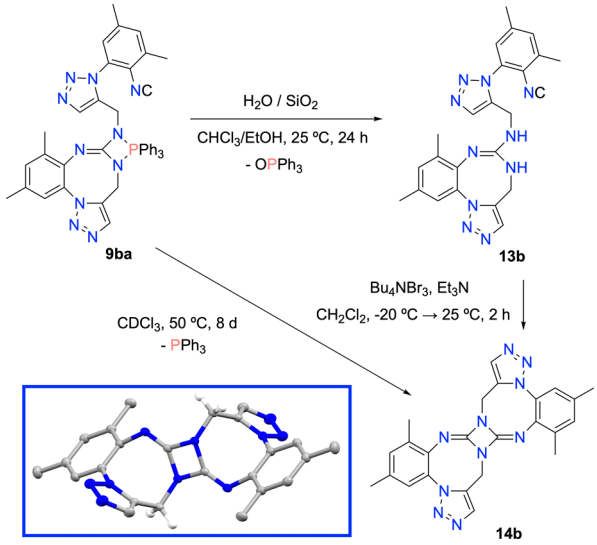


Figure 1. Computed mechanism for the conversion of isocyano-iminophosphorane **8ca** into the fused 4-imino-1,3,2-diazaphosphetidine **9ca**. Energy barriers (kJ mol $^{-1}$) are shown in parentheses. Upper box: Mechanistic proposal based on previous knowledge.

Scheme 3. Scale-up Synthesis of 9ba



Scheme 4. Hydrolysis and Thermal Treatment of 9ba To Give 13b and 14b[a]



[a]Conversion of **13b** into **14b** by treatment with tetrabutylammonium tribromide.

heating of **9ba** in $CDCl_3$ solution at 50 °C led to the formation of PPh_3 and a non-P-containing compound.

After its separation and purification, this new species was identified as centrosymmetric, fused 2,4-diimino-1,3-diazetidine **14b** as confirmed by its X-ray structure determination. Finally, we envisioned an innovative route potentially leading also to diazetidine **14b** starting from guanidine **13b**. In fact, we successfully converted **13b** into **14b** by treatment with tetrabutylammonium tribromide in the presence of triethylamine, presumably through the respective isocyanide dibromide ($-N{=}CBr_2$) intermediate.

In conclusion, the first examples of the reaction between the isocyanide and iminophosphorane functional groups are herein shown, occurring in an entropically favored intramolecular way. The gradual release of the phosphine fragment during the reaction was acquainted for the formation of a carbodiimide as the primary reaction product. This reaction can be regarded as a phosphine-mediated transfer of a nitrene from the azide to the isocyanide carbon atom resulting in the formation of a new N=C bond, a chemical transformation that is usually achieved by transition-metal catalysis.[26] As soon as formed, the reactive carbodiimide couples with the starting organophosphorus compound to yield [2 + 2] cycloadducts containing the scarcely reported 1,3,2-diazaphosphetidine ring, and the reaction products were actually isolated. This stepwise

https://doi.org/10.1021/acs.orglett.4c03902
Org. Lett. 2025, 27, 73−79

mechanism is supported by DFT calculations, revealing also the [2 + 1] coupling of the two reactive fragments in the computed rate-determining first step. The global process, a tandem intramolecular−intermolecular sequence, allows the preparation of complex structures containing two units of the starting bifunctional reactant, from which isocyanoguanidines and 2,4-dimino-1,3-diazetidines are easily derived. The scope of the novel primary reaction, isocyanide plus λ^5-phosphazene, is being currently more widely studied in our laboratories.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c03902.

Synthetic procedures, experimental data, ^{1}H and ^{31}P NMR monitoring of the reaction of **1a** and **2b** with triphenylphosphine, ^{31}P NMR data of other reactions where diazaphosphetidines were detected, crystal data and structure refinement for **9ba** (CCDC 2387940) and **14b** (CCDC 2387939), copies of the NMR spectra compounds, computational methods, computational data and Cartesian coordinates (PDF)

Accession Codes

Deposition Numbers 2387939−2387940 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

■ AUTHOR INFORMATION

Corresponding Authors

Aurelia Pastor − *Departamento de Química Orgánica, Facultad de Química, Regional Campus of International Excellence "Campus Mare Nostrum", Universidad de Murcia, E-30100 Murcia, Spain;* orcid.org/0000-0003-0437-2605; Email: aureliap@um.es

Carmen Lopez-Leonardo − *Departamento de Química Orgánica, Facultad de Química, Regional Campus of International Excellence "Campus Mare Nostrum", Universidad de Murcia, E-30100 Murcia, Spain;* orcid.org/0000-0001-8737-4280; Email: melill@um.es

Mateo Alajarin − *Departamento de Química Orgánica, Facultad de Química, Regional Campus of International Excellence "Campus Mare Nostrum", Universidad de Murcia, E-30100 Murcia, Spain;* orcid.org/0000-0002-7112-5578; Email: alajarin@um.es

Authors

Guillermo Cutillas-Font − *Departamento de Química Orgánica, Facultad de Química, Regional Campus of International Excellence "Campus Mare Nostrum", Universidad de Murcia, E-30100 Murcia, Spain*

Alberto Martinez-Cuezva − *Departamento de Química Orgánica, Facultad de Química, Regional Campus of International Excellence "Campus Mare Nostrum", Universidad de Murcia, E-30100 Murcia, Spain;* orcid.org/0000-0001-8093-7888

Marta Marin-Luna − *Departamento de Química Orgánica, Facultad de Química, Regional Campus of International Excellence "Campus Mare Nostrum", Universidad de Murcia, E-30100 Murcia, Spain;* orcid.org/0000-0003-3531-6622

Jose-Antonio Garcia-Lopez − *Departamento de Química Inorgánica, Facultad de Química, Regional Campus of International Excellence "Campus Mare Nostrum", Universidad de Murcia, E-30100 Murcia, Spain;* orcid.org/0000-0002-8143-7081

Isabel Saura-Llamas − *Departamento de Química Inorgánica, Facultad de Química, Regional Campus of International Excellence "Campus Mare Nostrum", Universidad de Murcia, E-30100 Murcia, Spain;* orcid.org/0000-0001-8335-6747

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.4c03902

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Dedicated to Professor José Elguero, a highly valued scientist, person and friend. This work was supported by the MICINN (PID2020-113686GB-I00/MCIN/AEI/10.13039/501100011033) and Fundacion Seneca-CARM (Project 21907/PI/22). G. Cutillas-Font thanks Fundacion Seneca-CARM for his contract (21442/FPI/20). J.-A. Garcia-Lopez and I. M. Saura Llamas acknowledge the grant PID2021-122966NB-I00 funded by MCIN/AEI/10.13039/501100011033 and "ERDF A way of making Europe".

■ REFERENCES

(1) For the first years of isocyanide chemistry, see: Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. Isonitrile Syntheses. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 472−484.

(2) (a) *Isocyanide Chemistry: Applications in Synthesis and Material Science*; Nenajdenko, V. G., Ed.; Wiley-VCH Verlag, Weimheim (Germany), 2012. (b) Kornfeind, J.; Fleming, F. F. Multiple Isocyanide Insertions Promoted by Protic and Lewis Acids. *Tetrahedron Chem.* **2024**, *9*, No. 100056. (c) Wang, Y.; Zhang, C.; Li, S.; Liu, L.; Feng, X.; Liu, G. Silver-Catalyzed and Silver-Promoted Reactions of Isocyanides. *Eur. J. Org. Chem.* **2023**, *26*, No. e202300323. (d) Tashrifi, Z.; Mohammadi Khanaposhtani, M.; Gholami, F.; Larijani, B.; Mahdavi, M. Reactions Involving Multiple Isocyanide Insertions. *Adv. Synth. Catal.* **2023**, *365*, 926−947. (e) Chen, D.; Li, J.; Wang, X.; Shan, Y.; Huang, K.; Yan, X.; Qiu, G. Catalytic Metal-enabled Story of Isocyanides for Use as "C1N1" Synthons in Cyclization: Beyond Radical Chemistry. *Org. Chem. Front.* **2022**, *9*, 4209−4220. (f) Zhang, Z.; Tan, P.; Chang, W.; Zhang, Z. Transition-Metal-Catalyzed Cross-Coupling and Sequential Reactions of Azides with Isocyanides. *Adv. Synth. Catal.* **2021**, *363*, 5344−5359. (g) Massarotti, A.; Brunelli, F.; Aprile, S.; Giustiniano, M.; Tron, G. C. Medicinal Chemistry of Isocyanides. *Chem. Rev.* **2021**, *121*, 10742−10788. (h) Luo, J.; Chen, G.-S.; Chen, S.-J.; Li, Z.-D.; Liu, Y.-L. Catalytic Enantioselective Isocyanide-Based Reactions: Beyond Passerini and Ugi Multicomponent Reactions. *Chem.—Eur. J.* **2021**, *27*, 6598−6619. (i) Pharande, S. G. Synthesis of Lactams via Isocyanide-Based Multicomponent Reactions. *Synthesis* **2021**, *53*, 418−446. (j) Wang, W.; Liu, T.; Ding, C.-H.; Xu, B. C(sp3)−H Functionalization with Isocyanides. Org. *Chem. Front.* **2021**, *8*, 3525−3542. (k) Wang, J.; Li, D.; Li, J.; Zhu, Q. Advances in Palladium-Catalysed Imidoylative Cyclization of Functionalized Isocyanides for the Construction of *N*-Heterocycles. *Org. Biomol. Chem.* **2021**, *19*, 6730−6745. (l) Cai, Z.; Ren, Y.; Li, X.; Shi, J.; Tong, B.; Dong, Y.

Functional Isocyanide-Based Polymers. Acc. *Chem. Res.* **2020**, *53*, 2879−2891. (m) Méndez, Y.; Vasco, A. V.; Humpierre, A. R.; Westermann, B. Isonitriles: Versatile Handles for the Bioorthogonal Functionalization of Proteins. *ACS Omega* **2020**, *5*, 25505−25510. (n) Deb, T.; Franzini, R. M. The Unique Bioorthogonal Chemistry of Isonitriles. *Synlett* **2020**, *31*, 938−944. (o) Yurino, T.; Ohkuma, T. Nucleophilic Isocyanation. *ACS Omega* **2020**, *5*, 4719−4724. (p) Collet, J. W.; Roose, T. R.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. Base Metal Catalyzed Isocyanide Insertions. *Angew. Chem., Int. Ed.* **2020**, *59*, 540−558. (q) Altundas, B.; Marrazzo, J.-P. R.; Fleming, F. F. Metalated Isocyanides: Formation, Structure, and Reactivity. *Org. Biomol. Chem.* **2020**, *18*, 6467−6482. (r) Knorn, M.; Lutsker, E.; Reiser, O. Isonitriles as Supporting and Non-innocent Ligands in Metal Catalysis. *Chem. Soc. Rev.* **2020**, *49*, 7730−7752.

(3) (a) Divyavani, C.; Padmaja, P.; Reddy, P. N. Isocyanide-based Multicomponent Reactions (IMCRs) in Water or Aqueous Biphasic Systems. *Curr. Org. Synth.* **2024**, *21*, 140−165. (b) Russo, C.; Brunelli, F.; Cesare Tron, G.; Giustiniano, M. Isocyanide-Based Multicomponent Reactions Promoted by Visible Light Photoredox Catalysis. *Chem.—Eur. J.* **2023**, *29*, No. e202203150. (c) Flores-Reyes, J. C.; Islas-Jácome, A.; González-Zamora, E. The Ugi Three-Component Reaction and Its Variants. *Org. Chem. Front.* **2021**, *8*, 5460−5515. (d) Lambruschini, C.; Moni, L.; Banfi, L. Diastereoselectivity in Passerini Reactions of Chiral Aldehydes and in Ugi Reactions of Chiral Cyclic Imines. *Eur. J. Org. Chem.* **2020**, *2020*, 3766−3778.

(4) Alajarin, M.; Cutillas-Font, G.; Lopez-Leonardo, C.; Orenes, R.-A.; Marin-Luna, M.; Pastor, A. Intramolecular Cyclization of Azido-Isocyanides Triggered by the Azide Anion: An Experimental and Computational Study. *J. Org. Chem.* **2023**, *88*, 8658−8668.

(5) For intramolecular reactions between iminophosphoranes and metal-coordinated isocyanide functions, see: (a) Tamm, M.; Hahn, F. E. Reactions of *β*-Functional Phenyl Isocyanides. *Coord. Chem. Rev.* **1999**, *182*, 175−209. (b) Michelin, R. A.; Pombeiro, A. J. L.; Guedes da Silva, M. F. C. Aminocarbene Complexes Derived from Nucleophilic Addition to Isocyanide Ligands. *Coord. Chem. Rev.* **2001**, *218*, 75−112.

(6) (a) Tukhtaev, H. B.; Sorokin, I. D.; Melnikov, M. Y.; Budynina, E. M. Acetylenes and Nitriles as Unconventional Reactants for Aza-Wittig Reactions. *Mendeleev Commun.* **2020**, *30*, 687−696. (b) Tukhtaev, H. B.; Ivanov, K. L.; Bezzubov, S. I.; Cheshkov, D. A.; Melnikov, M. Y.; Budynina, E. M. Aza-Wittig Reaction with Nitriles: How Carbonyl Function Switches from Reacting to Activating. *Org. Lett.* **2019**, *21*, 1087−1092. (c) Uchiyama, T.; Fujimoto, T.; Kakehi, A.; Yamamoto, I. [2 + 2] Cycloaddition and Ring Expansion Reactions of Cyclic Phosphonium and Aminophosphonium Salts: Synthesis and Structure of the First Eight-membered Ylide-Type Heterocycles. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1577−1580. (d) Ciganek, E. Iminophosphoranes from the Reaction of Ylides with Nitriles. *J. Org. Chem.* **1970**, *35*, 3631−3636.

(7) (a) Tian, W. Q.; Wang, Y. A. Mechanisms of Staudinger Reactions within Density Functional Theory. *J. Org. Chem.* **2004**, *69*, 4299−4308. (b) Alajarin, M.; Conesa, C.; Rzepa, H. S. *Ab Initio* SCF-MO Study of the Staudinger Phosphorylation Reaction between a Phosphane and an Azide to Form a Phosphazene. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1811−1814. (c) Leffler, J. E.; Temple, R. D. Staudinger Reaction between Triarylphosphines and Azides. Mechanism. *J. Am. Chem. Soc.* **1967**, *89*, 5235−5246.

(8) *CRC Handbook of Phosphorus-31 Nuclear Magnetic Resonance Data*; Tebby, J. C., Ed.; CRC Press, Boca Raton (US), 1991.

(9) Rassukana, Y. V.; Onys'ko, P. P.; Davydova, K. O.; Sinitsa, A. D. *C*-Phosphorylated *N*-(Trichloroethylidene)sulfonamides: A New Type of Highly Electrophilic Imines. *Eur. J. Org. Chem.* **2004**, *2004*, 3643−3649.

(10) Huisgen, R.; Wulff, J. 1.3-Dipolare Cycloadditionen, LII. Umsetzungen von 1.3-Dipolen mit Iminophosphoranen. *Chem. Ber.* **1969**, *102*, 1848−1858.

(11) Boedeker, J.; Köckritz, P.; Courault, K. 4 + 2-Cycloaddition Heteroarylsubstituierter Carbodiimide: Reaktion *N*-*α*-heteroaryl-substituierter Iminophosphorane mit Diphenylcarbodiimid. *Z. Chem.* **1979**, *19*, 59−59.

(12) Molina, P.; Alajarin, M.; Lopez Leonardo, C.; Claramunt, R. M.; Foces-Foces, M. C.; Hernandez Cano, F.; Catalan, J.; De Paz, J. L. G.; Elguero, J. Experimental and Theoretical Study of the R_3P^+-X^- bond. Case of Betaines Derived from *N*-Iminophosphoranes and Alkyl Isocyanates. *J. Am. Chem. Soc.* **1989**, *111*, 355−363.

(13) The ^{31}P NMR shifts of betaines were in the range of +34−35 ppm, typical of σ^4, λ^4 phosphonium species. Thus, we consider that the ^{31}P NMR shift of compounds **9**, around −50 ppm, and that of the betaines, around +35 ppm, is a clear criterium to discriminate neatly between the ring-chain tautomers 1,3,2-diazaphosphetidines (ring) and amido-phosphonium betaines (chain).

(14) Bell, S. A.; Geib, S. J.; Meyer, T. Y. Iminophosphorane-mediated Carbodiimide Metathesis. *Chem. Commun.* **2000**, 1375−1376.

(15) In accordance with this mechanistic interpretation, treatment of azido-isocyanide **2b** with only half equivalent of triphenylphosphine (**5a**) and further heating in solution led also to **9ba** in comparable yield to the reaction starting from the isocyano-iminophosphorane **8ba**.

(16) (a) Ulrich, H. *Chemistry and Technology of* Carbodiimides; Ed.; John Wiley & Sons, West Sussex, England, 2007. (b) Wang, Y.; Zhang, W.-X.; Xi, Z. Carbodiimide-Based Synthesis of *N*-heterocycles: Moving from Two Classical Reactive Sites to Chemical Bond Breaking/Forming Reaction. *Chem. Soc. Rev.* **2020**, *49*, 5810−5849.

(17) Alajarin, M.; Molina, P.; Sanchez-Andrada, P.; Foces-Foces, M. C. Preparation and Intramolecular Cyclization of Bis(carbodiimides). Synthesis and X-ray Structure of 1,3-Diazetidine-2,4-diimine Derivatives. *J. Org. Chem.* **1999**, *64*, 1121−1130 and references therein.

(18) For a recent computational study on an intramolecular [2 + 1] cycloaddition involving an isocyano carbon atom as the one-atom component, see: Fei, Y.; Zhou, Z.; Ni, Z.; Peng, X.; Cui, L.; Zhou, Z.; Li, X.; Li, C.; Jia, X.; li, j. Chemoselective Construction of Polycyclic Heterocycles Containing a [6−6−5] or [7−6−5] Tricyclic Core Skeleton from a 2-Isocyanophenyl Propargylic Ester. *Angew. Chem., Int. Ed.* **2024**, No. e202414726.

(19) In accordance with the experimental result, the alternative [2 + 2] regioisomeric cycloadduct **9ca′** (the 1,3,2-diazaphosphetidine integrating the aryl-N═C double bond of CC into the new 4-membered ring instead of the alkyl-N═C) is computed (computational level: PCM($CHCl_3$)/wB97XD/def2-TZVPD//PCM($CHCl_3$)/wB97XD/def2-SVP) to have an energy 34 kJ mol^{-1} higher than **9ca**.

(20) In contrast, intramolecular reactions between isocyanide and alkylidenephosphorane functions are known; see: (a) Zhang, L.; Yu, W.; Liu, C.; Xu, Y.; Duan, Z.; Mathey, F. The Chemistry of *ortho*-(Diarylphosphino)aryl Isocyanides. *Organometallics* **2015**, *34*, 5697−5702. (b) Michelin, R. A.; Facchin, G.; Braga, D.; Sabatino, P. Functionalized Isocyanides as Ligands. 4. Base-promoted Cyclization Reactions of Free and Platinum(II)-coordinated *o*-(Phosphoniomethyl)phenyl Isocyanide Tetrafluoroborates, *o*-($BF_4^-R_3P^+$-CH_2)C_6H_4NC. Synthesis and Spectroscopic Characterization of 1- and 2-Platinum(II)-Substituted Indole Derivatives and X-ray Structure of *trans*-[$(PPh_3)_2$Pt[CN(H)-*o*-C_6H_4C(PMe_3)]Cl]-BF_4•$C_2H_4Cl_2$. *Organometallics* **1986**, *5*, 2265−2274.

(21) In fact, at the start of this research we doubted the feasibility of the isocyanide plus iminophosphorane reaction, as we were aware of the common use in synthesis of the CN−N═PPh_3 reagent bearing both functional groups. For reviews, see: (a) Ojeda-Carralero, G. M.; Ceballos, L. G.; Coro, J.; Rivera, D. G. One Reacts as Two: Applications of *N*-Isocyaniminotriphenylphosphorane in Diversity-Oriented Synthesis. *ACS Comb. Sci.* **2020**, *22*, 475−494. (b) Wang, Y.; Zhang, C. Progress in Reactions of *N*-Isocyanoiminotriphenylphosphorane. *ChemistrySelect* **2020**, *5*, 171−177.

(22) A screening of several aryl isocyanides made by P. Knochel et al. showed that 2,4,6-Cl_3-C_6H_2-NC was an excellent acceptor for arylmagnesium halide additions, due to the strong inductive electron-withdrawing effect of the chloride substituents; see: Schwärzer, K.; Bellan, A.; Zöschg, M.; Karaghiosoff, K.; Knochel, P. Magnesium

https://doi.org/10.1021/acs.orglett.4c03902
Org. Lett. 2025, 27, 73−79

Aldimines Prepared by Addition of Organomagnesium Halides to 2,4,6-Trichlorophenyl Isocyanide: Synthesis of 1,2-Dicarbonyl Derivatives. *Chem.—Eur. J.* **2019**, *25*, 9415−9418.

(23) (a) Nguyen, L. T.; Le, T. N.; De Proft, F.; Chandra, A. K.; Langenaeker, W.; Nguyen, M. T.; Geerlings, P. Mechanism of [2 + 1] Cycloadditions of Hydrogen Isocyanide to Alkynes: Molecular Orbital and Density Functional Theory Study. *J. Am. Chem. Soc.* **1999**, *121*, 5992−6001. (b) Nguyen, M. T.; Keer, A. V.; Pierloot, K.; Vanquickenborne, L. G. Reaction of Phosphaethene with Hydrogen Isocyanide: [2 + 1] versus [2 + 2] Cycloaddition. *J. Am. Chem. Soc.* **1995**, *117*, 7535−7543.

(24) For other relevant classes of 1,1-dipolar equivalents see, for instance: (a) Trost, B. M.; Chadiri, M. R. Sulfones as Chemical Chameleons. Cyclization via 1,1-Dipole Synthons. *J. Am. Chem. Soc.* **1984**, *106*, 7260−7261. (b) Trost, B. M.; Quayle, P. 2-Alkoxybenzo-1,3-dithiole 1,1,3,3-tetraoxide. A Carbonyl 1,1-Dipole Synthon. *J. Am. Chem. Soc.* **1984**, *106*, 2469−2471. (c) Wasserman, H. H.; Ho, W.-B. (Cyanomethylene)phosphoranes as Novel Carbonyl 1,1-Dipole Synthons: An Efficient Synthesis of α-Keto Acids, Esters, and Amides. *J. Org. Chem.* **1994**, *59*, 4364−4366. (d) Deng, Y.-H.; Chu, W.-D.; Shang, Y.-H.; Yu, K.-Y.; Jia, Z.-L.; Fan, C.-A. $P(NMe_2)_3$-Mediated Umpolung Spirocyclopropanation Reaction of *p*-Quinone Methides: Diastereoselective Synthesis of Spirocyclopropane-Cyclohexadienones. *Org. Lett.* **2020**, *22*, 8376−8381.

(25) In this sense, we find our reaction reminiscent of the old preparation of carbodiimides by treatment of isocyanides with chloramine T, another nitrogenated 1,1-dipolar reagent; see: Aumüller, W. Experiments with Chloramine T in the Toluenesulfonylurea Series. *Angew. Chem., Int. Ed.* **1963**, *2*, 616−616.

(26) For a recent review, see: Sawant, D. M.; Joshi, G.; Ansari, A. J. Nitrene-Transfer from Azides to Isocyanides: Unveiling Its Versatility as a Promising Building Block for the Synthesis of Bioactive Heterocycles. *iScience* **2024**, *27*, No. 109311.

https://doi.org/10.1021/acs.orglett.4c03902
Org. Lett. 2025, 27, 73−79