A Three-Component Ugi-Type Reaction of *N*-Carbamoyl Imines Enables A Broad Scope Primary α-Amino 1,3,4-Oxadiazole Synthesis

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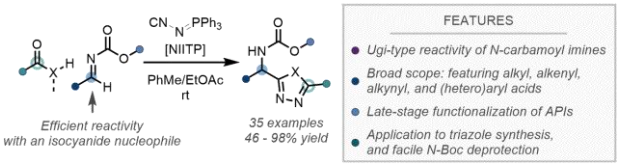
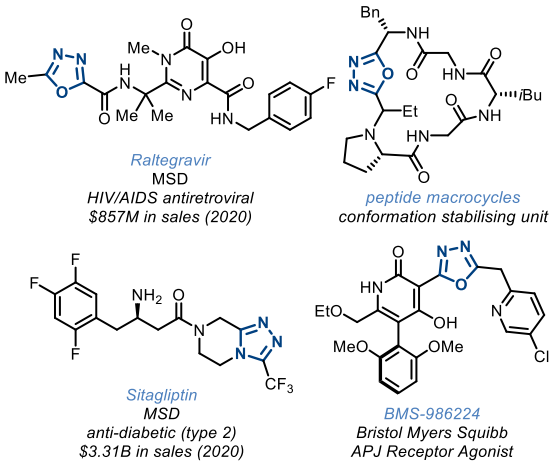
Supporting Information Placeholder



ABSTRACT: A general synthesis of *N*-protected primary α-amino 1,3,4-oxadiazoles from *N*-carbamoyl imines, *N*-isocyaniminotriphenylphosphorane (NIITP), and carboxylic acids, is described. Featuring an isocyanide addition reaction with *N*-carbamoyl imines, this efficient three-component Ugi-type reaction was found to be broad in scope with respect to imine, and carboxylic acid coupling partners. Furthermore, the versatility of this method was demonstrated by α-amino 1,2,4-triazole synthesis, the late-stage functionalization of 7 drug molecules, and five divergent derivatizations of a primary α-amino 1,3,4-oxadiazole.

1,3,4-Oxadiazoles, and 1,2,4-triazoles, are privileged heterocyclic motifs in the pharmaceutical industry. They feature in the best-selling drugs Raltegravir, and Sitagliptin whose combined revenue exceeded $4.1 billion in 2020 (Scheme 1).[1] The biological activities of these heterocycles are broad ranging and investigations of their function as antiviral, anti-inflammatory, and antiparasitic agents demonstrate their prominence within medicinal chemistry.[2] Furthermore, α-amino 1,3,4-oxadiazoles have been shown to be excellent structural bioisosteres for peptide (and ester) bonds, providing increased hydrolytic stability, and have been utilized as a conformation stabilizing peptidomimetic within peptide macrocycles.[3]

Scheme 1. 1,3,4-Oxadiazoles and 1,2,4-triazoles in pharmaceuticals, and peptide macrocycles.

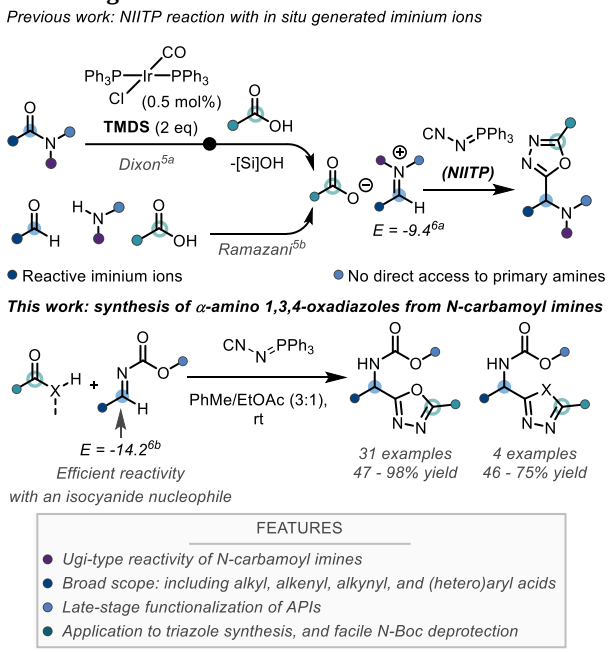


Classical syntheses of α-amino 1,3,4-oxadiazoles have relied on the dehydration of 1,2-diacylhydrazines, or oxidative cyclisation of *N*-acyl hydrazones, often requiring harsh dehydrative (or oxidative) conditions that limit the range of tolerated functional groups.[4] Additionally, these approaches necessitate multistep synthesis of the reaction precursors before construction of the oxadiazole ring. In recent years, however, the functionalized isocyanide *N*-isocyaniminotriphenylphosphorane (NIITP) has significantly improved the synthetic access of α-amino 1,3,4-oxadiazoles by facilitating their direct synthesis from *in situ* generated iminium ions, NIITP, and a carboxylic acid partner *via* an Ugi-type reaction.[5] These reactive iminium ions (typically E = -9.4, on Mayr's electrophilicity scale)[6] allow for efficient engagement with NIITP, however analogous couplings employing usefully protected neutral imine electrophiles are underexplored.

Building upon our recent work using NIITP for the late-stage functionalization (LSF) of tertiary amides and lactams,[5a] we were eager to expand the range of accessible α-amino 1,3,4-oxadiazoles. As our previous strategy was limited to tertiary amines, preventing direct synthesis of secondary and primary α-amino 1,3,4-oxadiazoles, we posited that a new method enabling access to usefully *N*-protected primary α-amino 1,3,4-oxadiazoles would be synthetically valuable (Scheme 2). To this end, *N*-carbamoyl imines presented an attractive class of electrophiles for *N*-protected α-amino 1,3,4-oxadiazole synthesis, having been shown to be readily amenable, and broadly exploited, for the formation of protected amines in numerous C-C bond forming methodologies.[7] Surprisingly, however, *N*-carbamoyl imines have to date not been productively engaged by isocyanide nucleophiles in an Ugi-type reaction, possibly due to their low electrophilicity (E = -14.2).[6b] As such, and looking

to the build upon the broad scope of reactivity of this important class of electrophiles, the synthesis of *N*-Boc α-amino 1,3,4-oxadiazoles from readily accessible *N*-Boc aldimines was targeted, due to their potential ability to yield high-value primary α-amino 1,3,4-oxadiazoles after facile *N*-Boc deprotection. Herein we wish to report our findings.

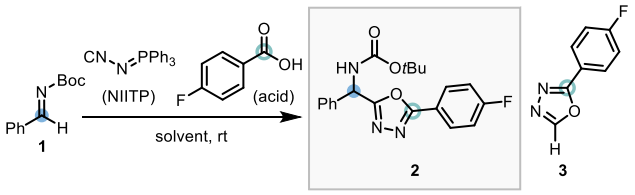
Scheme 2. Previous approaches to α-amino 1,3,4-oxadiazoles using NIITP and this work.



Our investigation began by exploring the reactivity of benzaldehyde-derived *N*-Boc imine **1** with NIITP and 4-fluorobenzoic acid (allowing for ready reaction monitoring by ^{19}F NMR) as a model system. Imine **1** was initially chosen as the limiting reagent and gratifyingly, using 3 equivalents of carboxylic acid and NIITP, formation of the desired product **2** from **1** occurred in 45% yield (Scheme 3, entry 1).[8] A solvent screen (entries 2-5) revealed toluene as an effective reaction solvent giving an 86% yield of **2**. Nevertheless, a significant amount of the undesired side product **3** — formed from the reaction of excess carboxylic acid and NIITP[9] — was also produced and complicated purification attempts. Therefore, inverting the stoichiometry so that the carboxylic acid was the limiting reagent, was investigated, and we were pleased to find a significantly cleaner reaction profile (entry 6) with a concomitant improvement in reaction yield. Subsequently, it was found that increasing the equivalents of NIITP (entry 7) or reducing the equivalents of imine to 1.2 (entry 8) lowered the reaction yield. Finally, optimal conditions were achieved using 1.5 equivalents of imine **1** in conjunction with 2 equivalents of NIITP and 1 equivalent of the carboxylic acid; the desired 1,3,4-oxadiazole **2** was afforded in an excellent 79% isolated yield (entry 9), with only limited formation of by-product **3**. Notably, attempts to form *N*-Boc imine **1** *in situ*, from benzaldehyde and *tert*-butyl carbamate, under the reaction conditions proved unsuccessful affording only an alcohol product derived from NIITP addition into benzaldehyde.[10]

With optimal conditions established, the scope of the reaction with respect to the carboxylic acid component was explored (Scheme 4). A range of halogen-containing benzoic acids (**2** – **5**), including 2-chlorobenzoic acid (**5**) gave good yields of the α-amino 1,3,4-oxadiazoles. Electron-rich benzoic acids (**6** & **7**) both gave 67% yield of their respective 1,3,4-oxadiazole products. Heterocyclic acids, 1H-indazole-7-carboxylic acid (**8**) and 5-chloro-2-(methylthio)pyrimidine-4-carboxylic acid (**9**) reacted productively demonstrating the reaction's tolerance to potentially-disruptive Lewis-basic functionalities. An expansion of the scope to include simple alkynyl (**10**), alkenyl (**11**), and alkyl carboxylic acids (**12**) proved fruitful. *N*-Cbz glycine (**13**) was successfully incorporated to provide a bis-α-amino 1,3,4-oxadiazole bearing two orthogonally protected amines. Pursuing a divergent synthesis of valuable peptidomimetic compounds, a range of functionally, and structurally, diverse amino acids (**14** – **19**) were subjected to our optimal conditions, and pleasingly gave products in yields ranging from 58% - 76%.[3a,b] Importantly, chiral HPLC analysis showed that no epimerization of the amino acid stereocenter was occurring during the synthesis of **14** (and by analogy **15** – **19**),[11] and that the diastereomeric ratios observed arose solely from the newly-formed stereocenter in the products. The application of the reaction to the late-stage functionalization (LSF) of four carboxylic acid-containing drug compounds (**20** – **23**) demonstrated the applicability of this method for the synthesis of structurally-complex α-amino 1,3,4-oxadiazoles.

Scheme 3. Reaction discovery and optimization.

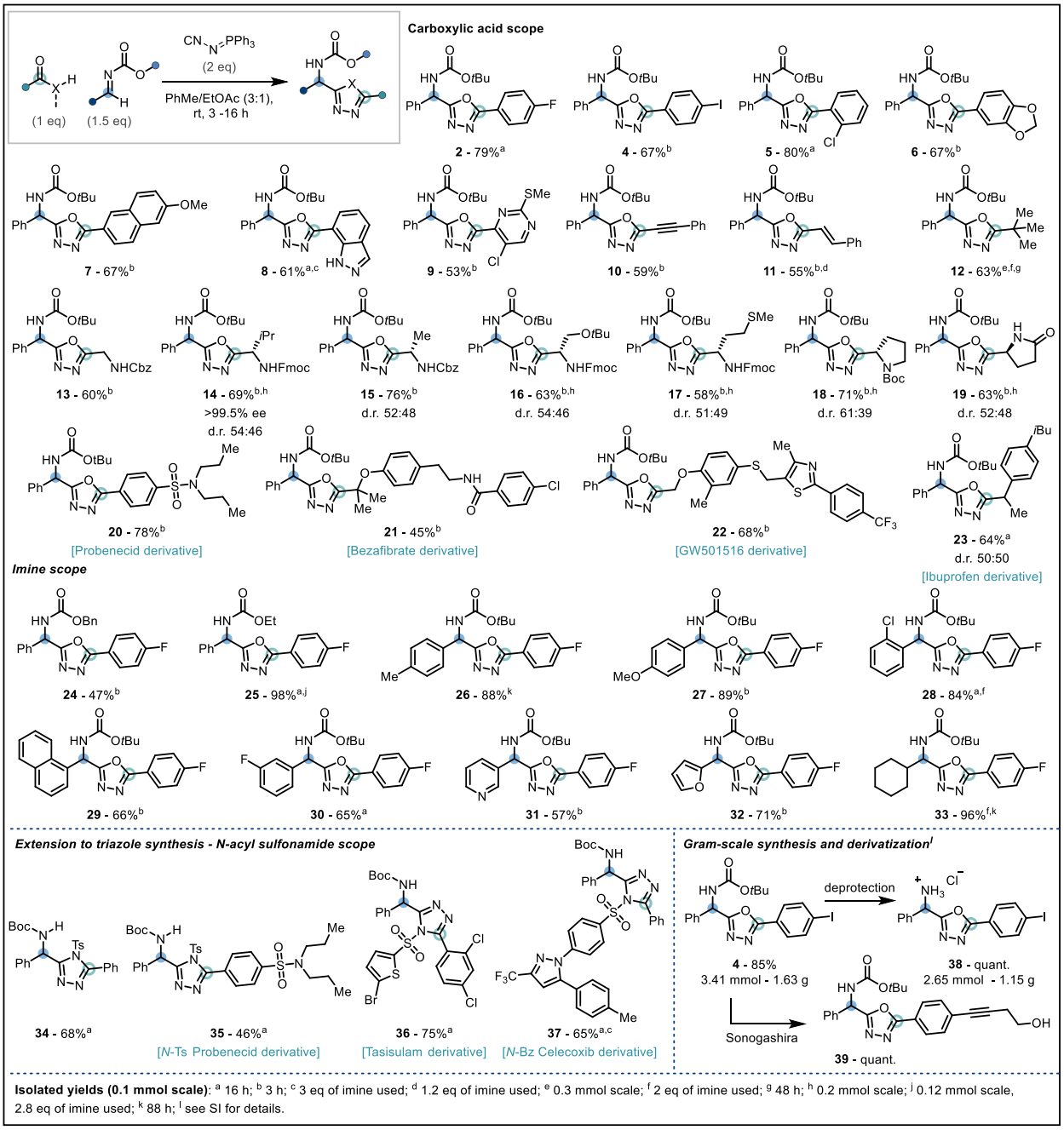


entry	solvent	1 (eq)	NIITP (eq)	acid (eq)	2 (%)[a]	2:3[b]
1	CH_2Cl_2	1	3	3	45	1:2.3
2	THF	"	"	"	63	1:3.2
3	MeCN	"	"	"	41	1:1.6
4	EtOAc	"	"	"	75	1:2.7
5	**PhMe**	"	"	"	86	1:2.2
6	"	2	2	**1**	91	9:1
7	"	2	3	"	85	7.3:1
8	"	1.2	2	"	69	2.5:1
9[c]	**PhMe**	**1.5**	**2**	**1**	**(79)**	**4.6:1**

***N*-protected primary α-amino 1,3,4-oxadiazole synthesis.** General conditions (0.1 mmol scale): **1** (x eq), NIITP (y eq), carboxylic acid (z eq), solvent (0.1 M), time (3 h (entries 6, 7, & 8), otherwise 16 h). [a] ^{19}F NMR yield using α,α,α-trifluorotoluene as an internal standard, isolated yield in parentheses. [b] Ratio of **2**:**3** determined by ^{19}F NMR. [c] Imine added as PhMe solution, acid added as EtOAc solution, 0.05 M reaction concentration.

Next, the scope of the *N*-carbamoyl imine component was explored. Varying the protecting group on the imine, we found that, in addition to the *N*-Boc protected imine model substrate, Cbz (**24**) and ethyl carbamate (**25**) groups were well tolerated thus giving access to differentially protected α-amino 1,3,4-oxadiazoles. Electron-rich para-methyl (**26**) and para-methoxy (**27**) *N*-Boc imines gave products in excellent yields of 88% and 89%, respectively. Ortho-substituted (**28** & **29**) and meta- substituted (**30**) imines could be successfully employed giving

Scheme 4. Reaction scope.



Isolated yields (0.1 mmol scale): [a] 16 h; [b] 3 h; [c] 3 eq of imine used; [d] 1.2 eq of imine used; [e] 0.3 mmol scale; [f] 2 eq of imine used; [g] 48 h; [h] 0.2 mmol scale; [j] 0.12 mmol scale, 2.8 eq of imine used; [k] 88 h; [l] see SI for details.

products with distinctive substitution patterns. Pleasingly, heteroaromatic imines bearing 3-pyridyl (**31**), or 2-furyl (**32**) groups afforded the desired products. Furthermore, the reaction was tolerant of cyclohexyl *N*-Boc imine (**33**), permitting access to an β-branched α-amino 1,3,4-oxadiazole in 96% yield.

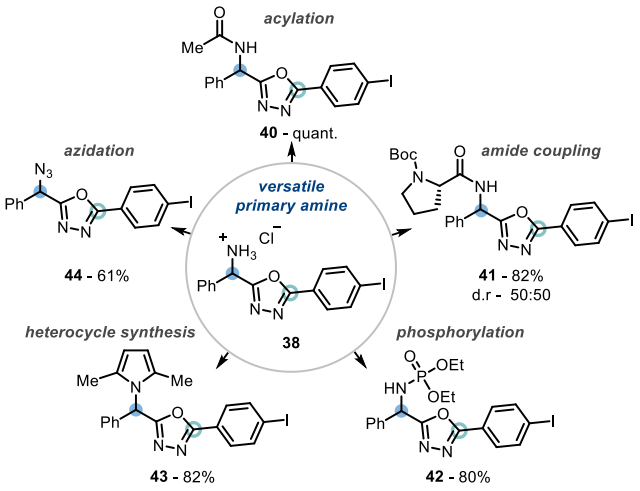
Heterodiazoles are also an important heterocyclic motif with properties ranging from in-vitro antitumor activity, to electron transport; thus the reaction scope was expanded to include the synthesis of α-amino 1,2,4-triazoles.[12] This was achieved by exchanging the carboxylic acid coupling partner for *N*-centered Brønsted acids, having previously found them to be suitably acidic replacements.[5a] This adjustment enabled the synthesis of four distinct triazoles (**34** – **37**), synthesized using *N*-acylsulfonamides as the Brønsted acidic partner. Compounds **35** – **37** demonstrated 1,2,4-triazole synthesis *via* LSF of three drug molecules, a carboxylic acid-containing drug (Probenecid, **35**), an *N*-Acyl sulfonamide drug (Tasisulam, **36**), and a sulfonamide-containing drug (Celecoxib, **37**).[13] Notably, attempted use of *S*-H Brønsted acids, such as thioacids, did not afford the desired 1,3,4-thiadiazole presumably due to competitive and deleterious reactivity with the imine electrophile

The potential for industrial applicability of the method was demonstrated by gram-scale synthesis of **4** in 85% yield. Furthermore, the subsequent facile and quantitative *N*-Boc deprotection was achieved using 4 M HCl in dioxane, and afforded primary α-amino 1,3,4-oxadiazole **38** as the hydrochloride salt on gram-scale. A Sonogashira coupling was used to install further functionality from the aryl-iodide giving **39** in quantitative

yield, thus showcasing the utility of the reaction products as complex building blocks, with functional handles being readily incorporated using either coupling partner.

Primary amines provide plentiful opportunity for functional group transformations, and downstream synthetic opportunities. To exemplify this versatility and synthetic utility, the primary amine group of **38** was exploited for the synthesis of five distinct compounds (Scheme 5). Firstly, acylation afforded the *N*-acyl α-amino 1,3,4-oxadiazole **40** in quantitative yield. A dipeptide (**41**) was readily synthesized by an amide coupling with *N*-Boc proline. Phosphorous(V) compounds, such as phosphoramidates, are of increasing importance in medicinal chemistry and feature in antiviral drugs such as remdesivir and Tenofovir alafenamide.[14] As phosphorylation of primary amines is a common method for the synthesis of phosphoramidates **38** was reacted with diethyl phosphorochloridate to successfully afford **42** in 80% yield. Moreover, nitrogen heterocycles are ubiquitous within pharmaceuticals,[15] and primary amines provide an effective handle for their synthesis, as exemplified by the production of pyrrole **43** from **38** in excellent yield *via* a Paal-Knorr reaction.[16] Finally, **38** was converted into the α-azido 1,3,4-oxadiazole **44** in 61% yield, using imidazole-1-sulfonyl azide as an diazo-transfer reagent, thus providing a synthetically powerful functional group for click-chemistry and further *N*-containing compound synthesis.[17]

Scheme 5. Divergent derivatization of 38, see SI for experimental details.



In conclusion, a robust method for the synthesis of primary α-amino 1,3,4-oxadiazoles taking advantage of an efficient isocyanide addition reaction with *N*-carbamoyl imines, and utilizing carboxylic acids as feedstock coupling partners, has been developed. The reaction was tolerant of (hetero)aryl-, alkynyl-, alkenyl-, and alkyl-carboxylic acids, and use of amino acids afforded enantiopure peptidomimetic products. The scope with respect to *N*-carbamoyl imines was found to be broad, tolerating (hetero)aryl and alkyl groups as well as useful *N*-Boc and *N*-Cbz protecting groups. The potential for LSF was demonstrated with 7 drug compounds, including three *N*-acyl sulfonamides which were converted into the corresponding α-amino 1,2,4-triazoles without changing the optimized reaction conditions. Gram-scale synthesis, and subsequent deprotection of a *N*-Boc α-amino 1,3,4-oxadiazole was exemplified and allowed five divergent derivatizations to be carried out. Further work to uncover new broad scope access to 1,3,4-oxadiazole motifs is ongoing in our laboratory and the results will be disclosed in due course.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures and characterization for novel compounds (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* **2010**, *87*, 1348-1349.
(2) (a) Somani, R. R.; Shirodkar, P. Y. Oxadiazole: A biologically important heterocycle. *Pharma Chem*. **2009**, *1*, 130-140. (b) Li, Z.; Zhan, P.; Liu, X. 1,3,4-Oxadiazole: A Privileged Structure in Antiviral Agents. *Mini-Rev. Med. Chem.* **2011**, *11*, 1130-1142. (c) De Oliveria, C. S.; Lira, B. F.; Barbosa-Filho, J. M.; Lorenzo, J. G. F.; De Athayde-Filho, P. F. Synthetic Approaches and Pharmacological Activity of 1,3,4-Oxadiazoles: A Review of the Literature from 2000–2012. *Molecules*. **2012**, *17*, 10192-10231. (d) Boström, J.; Hogner, A.; Llinàs, A.; Wellner, E.; Plowright, A. T. Oxadiazoles in Medicinal Chemistry. *J. Med. Chem*. **2012**, *55*, 1817-1830. (e) Sun, J.; Makawana, J. A.; Zhu, H.-L. 1,3,4-oxadiazole derivatives as potential biological agents. *Mini-Rev. Med. Chem.* **2013**, *13*, 1725-1743. (f) Bajaj, S.; Asati, V.; Singh, J.; Roy, P. P. 1,3,4-Oxadiazoles: An emerging scaffold to target growth factors, enzymes and kinases as anticancer agents. *Eur. J. Med. Chem.* **2015**, *97*, 121-141. (g) Salahuddin.; Mazumder, A.; Yar, M. S.; Mazumder, R.; Chakraborth, G. S.; Ahsan, M. J.; Rahman, M. U. Updates on synthesis and biological activities of 1,3,4-oxadiazole: A review. *Synth. Commun.* **2017**, *47*, 1805-1847. (h) Bajaj, S.; Roy, P. P.; Singh, J. 1,3,4-Oxadiazoles as Telomerase Inhibitor: Potential Anticancer

Agents. *Anti-Cancer Agents Med. Chem*. **2017**, *17*, 1869-1883. (i) Chawla, G.; Naaz, B.; Siddiqui, A. A. Exploring 1,3,4-Oxadiazole Scaffold for Anti-inflammatory and Analgesic Activities: A Review of Literature From 2005-2016. *Mini-Rev. Med. Chem*. **2018**, *18*, 216-233. (j) Pitasse-Santos, P.; Sueth-Santiago, V.; Lima, M. E. F. 1,2,4- and 1,3,4-Oxadiazoles as Scaffolds in the Development of Antiparasitic Agents. *J. Braz. Chem. Soc*. **2018**, *29*, 435-456. (k) Nayak, S. G.; Poojary, B. A Review on the Preparation of 1,3,4-Oxadiazoles From the Dehydration of Hydrazines and Study of Their Biological Roles. *Chem. Afr*. **2019**, *2*, 551-571. (l) Verma, G.; Khan, M. F.; Akhtar, W.; Alam, M. M.; Akhter, M.; Shaquiquzzaman, M. A Review Exploring Therapeutic Worth of 1,3,4-Oxadiazole Tailored Compounds. *Mini-Rev. Med. Chem*. **2019**, *19*, 477-509.

(3) (a) Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Csoeregh, I.; Hesselink, W.; Hacksell, U. Synthesis of 1,2,4-Oxadiazole-, 1,3,4-Oxadiazole-, and 1,2,4-Triazole-Derived Dipeptidomimetics. *J. Org. Chem*. **1995**, *60*, 3112-3120. (b) Ko, E.; Liu, J.; Perez, L. M.; Lu, G.; Schaefer, A.; Burgess, K. Universal Peptidomimetics. *J. Am. Chem. Soc*. **2011**, *133*, 462-477. (c) Frost, J. R.; Scully, C. C. G.; Yudin, A. K. Oxadiazole grafts in peptide macrocycles. *Nature Chemistry*. **2016**, *8*, 1105-1111. (d) Appavoo, S. D.; Kaji, T.; Frost, J. R.; Scully, C. C. G.; Yudin, A. K. Development of Endocyclic Control Elements for Peptide Macrocycles. *J. Am. Chem. Soc*. **2018**, *140*, 8763-8770.

(4) For reviews discussing oxadiazole synthesis see: (a) Jakopin, Z.; Dolenc, M. S. Recent Advances in the Synthesis of 1,2,4- and 1,3,4-Oxadiazoles. *Curr. Org. Chem.* **2008**, *12*, 850-898. (b) Patel, K. D.; Prajapati, S. M.; Panchal, S. N.; Patel, H. D. Review of Synthesis of 1,3,4-Oxadiazole Derivatives. *Synth. Commun.* **2014**, *44*, 1859-1875; and reviews cited in reference 2. For an alterntative desulfuritive approach see: (c) Guin, S.; Rout, S. K.; Gogoi, A.; Nandi, S.; Ghara, K. K.; Patel, B. K. Desulfurization Strategy in the Construction of Azoles Possessing Additional Nitrogen, Oxygen or Sulfur using a Copper(I) Catalyst. *Adv. Synth. Catal*. **2012**. *354*, 2757-2770.

(5) Matheau-Raven, D.; Dixon, D. J. General α-Amino 1,3,4-Oxadiazole Synthesis via Late-Stage Reductive Functionalization of Tertiary Amides and Lactams. *Angew. Chem., Int. Ed*. **2021**, *60*, 19725-19729. (b) Ramazani, A.; Rezaei, A. Novel One-Pot, Four-Component Condensation Reaction: An Efficient Approach for the Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazole Derivatives by a Ugi-4CR/*aza*-Wittig Sequence. *Org. Lett*. **2010**, *12*, 2852-2855. (c) Jethava, K. P.; Fine, J.; Chen, Y.; Hossain, A.; Chopra, G. Accelerated Reactivity Mechanism and Interpretable Machine Learning Model of *N*-Sulfonylimines toward Fast Multicomponent Reactions. *Org. Lett.* **2020**, *22*, 8480-8486. For reviews on the chemistry of NIITP see: (d) 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. (e) Wang, Y.; Zhang, C. Progress in Reactions of *N*-Isocyanoiminotriphenylphosphorane. *ChemistrySelect.* **2020**, *5*, 171-177. (f) Giustiniano, M.; Basso, A.; Mercalli, V.; Massarotti, A.; Novellino, E.; Tron, G. C.; Zhu, J. To each his own: isonitriles for all flavors. Functionalized isocyanides as valuable tools in organic synthesis. *Chem. Soc. Rev*. **2017**, *46*, 1295-1357.

(6) (a) Appel, R.; Chelli, S.; Tokuyasu, T.; Troshin, K.; Mayr, H. Electrophilicities of Benzaldehyde-Derived Iminium Ions: Quantification of the Electrophilic Activation of Aldehydes by Iminium Formation. *J. Am. Chem. Soc.* **2013**, *135*, 6579-6587. (b) Appel, R.; Mayr, H. Quantification of the Electrophilic Reactivities of Aldehydes, Imines, and Enones. *J. Am. Chem. Soc*. **2011**, *133*, 8240-8250. (c) Mayr, H.; Patz, M. Scales of Nucleophilicity and Electrophilicity: A System for Ordering Polar Organic and Organometallic Reactions. *Angew. Chem., Int. Ed*. **1994**, *33*, 938-957. (d) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. Reference Scales for the Characterization of Cationic Electrophiles and Neutral Nucleophiles. *J. Am. Chem. Soc*, **2001**, *123*, 9500-9512.

(7) (a) Vesely, J.; Rios, R. Enantioselective methodologies using *N*-carbamoyl-imines. *Chem. Soc. Rev*. **2014**, *43*, 611-630. (b) Marcantoni, E.; Petrini, M. Recent Developments in the Stereoselective Synthesis of Nitrogen-Containing Heterocycles using *N*-Acylimines as Reactive Substrates. *Adv. Synth. Catal.* **2016**, *358*, 3657-3682.

(8) For a plausible reaction mechanism see SI.

(9) (a) Souldozi, A.; Ramazani, A. The reaction of (*N*-isocyanimino)triphenylphosphorane with benzoic acid derivatives: a novel synthesis of 2-aryl-1,3,4-oxadiazole derivatives. *Tetrahedron Lett*. **2007**, *48*, 1549-1551.

(10) Adib, M.; Kesheh, M. R.; Ansari, S.; Bijanzadeh, H. R. Reaction between *N*-Isocyaniminotriphenylphosphorane, Aldehydes, and Carboxylic Acids: A One-Pot and Three-Component Synthesis of 2-Aryl-5-hydroxyalkyl-1,3,4-oxadiazoles. *Synlett*. **2009**, *2009*, 1575-1578.

(11) See SI for details.

(12) (a) Janietz, S.; Barche, J.; Wedel, A.; Sainova, D. n-Type Copolymers with Fluorene and 1,3,4-Heterodiazole Moieties. *Macromol. Chem. Phys.* **2004**, *205*, 187-198. (b) Taher, A. T.; Georgey, H. H.; El-Subbagh, H. I. Novel 1,3,4-heterodiazole analogues: Synthesis and *in-vitro* antitumor activity. *Eur. J. Med. Chem*. **2012**, *47*, 445-451.

(13) Mader, M. M.; Shih, C.; Considine, E.; Dios, A. D.; Grossman, C. S.; Hipskind, P. A.; Lin, H.-S.; Lobb, K. L.; Lopez, B.; Lopez, J. E.; Cabrejas, L. M. M.; Richett, M. E.; White, W. T.; Cheung, Y.-Y.; Huang, Z.; Reilly, J. E.; Dinn, S. R. Acyl sulfonamide anti-proliferatives. Part 2: Activity of heterocyclic sulfonamide derivatives. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 617-620.

(14) Rodriguez, J. B.; Gallo-Rodriguez, C. The Role of the Phosphorus Atom in Drug Design. *ChemMedChem*. **2018**, *14*, 190-216.

(15) (a) Baumann, N.; Baxendale, I. R. An overview of the synthetic routes to the best selling drugs containing 6-membered heterocycles. *Beilstein. J. Org. Chem.* **2013**, *9*, 2265-2319. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257-10274.

(16) (a) Paal, C. Ueber die Derivate des Acetophenonacetessigesters und des Acetonylacetessigesters. *Ber. Dtsch. Chem. Ges*. **1884**, *17*, 2756-2767. (b) Knorr, L. Synthese von Furfuranderivaten aus dem Diacetbernsteinsäureester. *Ber. Dtsch. Chem. Ges*. **1884**, *17*, 2863-2870.

(17) (a) Ye, H.; Liu, R.; Li, D.; Liu, Y.; Yuan, H.; Guo, W.; Zhou, L.; Cao, X.; Tian, H.; Shen, J.; Wang, P. G. A Safe and Facile Route to Imidazole-1-sulfonyl Azide as a Diazotransfer Reagent. *Org. Lett*. **2013**, *15*, 18-21. (b) Goddard-Borger, E. D.; Stick, R. V. An Efficient, Inexpensive, and Shelf-Stable Diazotransfer Reagent: Imidazole-1-sulfonyl Azide Hydrochloride. *Org. Lett.* **2007**, *9*, 3797-3800. (c) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. Organic azides: an exploding diversity of a unique class of compounds. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188-5240. (d) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem. Int. Ed*. **2001**, *40*, 2004-2021.