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Gopakumar, K., Gallagher, S., Benoit, G. et al. (2026) Development of a Cu-catalyzed regioselective hydrazidation of 1,2-diborylalkenes. Advanced Synthesis & Catalysis, 368 (10). e70529. ISSN: 1615-4150

https://doi.org/10.1002/adsc.70529

Advanced Synthesis & Catalysis

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RESEARCH ARTICLE OPEN ACCESS

Development of a Cu-Catalyzed Regioselective Hydrazidation of 1,2-Diborylalkenes

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Received: 18 December 2025 | **Revised:** 30 April 2026 | **Accepted:** 4 May 2026

Keywords: boronic ester | catalysis | hydrazidation

ABSTRACT

We report a Cu-catalyzed hydrazidation of 1,2-diborylalkenes that generates densely functionalized intermediates with control of regiochemistry (29%–71%; >98:2). The products undergo a surprisingly facile second hydrazidation step, an observation that we attribute to a substrate directed transmetallation of the remaining boronate ester to Cu(II).

1 | Introduction

The transition metal catalyzed addition of diboron compounds to alkynes offers a direct and efficient means for the synthesis of 1,2-diborylalkenes [1]. Given the established versatility of organoboronates in organic synthesis, 1,2-diborylalkenes represent valuable functionalized intermediates for further elaboration to new molecular entities. However, in order to implement this in an efficient way, it is essential that the boronate moieties can be derivatized selectively and independently. In this context, selective Suzuki coupling reactions have been reported [2, 3], although careful optimization can be required to avoid over-coupling and/or protodeborylation leading to challenging product separation issues [4–7]. This problem has been elegantly circumvented by the design of intramolecular cross-coupling reactions leading to dibenzoxapines [8]. In addition, selective borono-Mannich reactions [9] and azide coupling [2] have been demonstrated, while our group has devised a 6π-electrocyclization-elimination sequence for the synthesis of *N*-heteroaromatic systems [10–12]. We were attracted to the potential of 1,2-diborylalkenes to produce borylated enamine derivatives via their addition to azo dicarboxylate esters. Although the addition of aromatic boronic acids to azo dicarboxylates has been established [13, 14], there is only a single report of this transformation using boronic esters, to the best of our knowledge [15]. We report herein the first example of the addition of alkene 1,2-diboronate esters to azodicarboxylates, together with challenges associated with selective monocoupling reactions and their possible origins (Figure 1).

2 | Results and Discussion

The addition of 1,2-diborylalkenes to azo dicarboxylate esters can lead to a number of products, including regioisomeric hydrazides and double addition products. Accordingly, we began our investigations by exploring the reactivity of diboryl olefin **1a** [16] with di-*tert*-butyl azodicarboxylate (DBAD) and our results are shown in Table 1. The use of catalytic $Cu(OAc)_2$ at 50°C provided hydrazide **2** in low yield but as a single regioisomer as judged by LC-MS analysis (a discussion of regiochemical assignment is provided later). We also detected dihydrazide **3** at this stage (not isolated) and set about trying to avoid formation of this by-product. There was an evident change of color from green to yellow, which we surmised to indicate the reduction of Cu(II) to Cu(I), and so we repeated the reaction at 0°C. Indeed, a high conversion of **1a** was observed along with an improvement in the yield of **2**. However, dihydrazide **3** was also isolated in significant yield under these conditions. We next screened available ligands in an effort to minimize over-hydrazidation and found that the presence of a

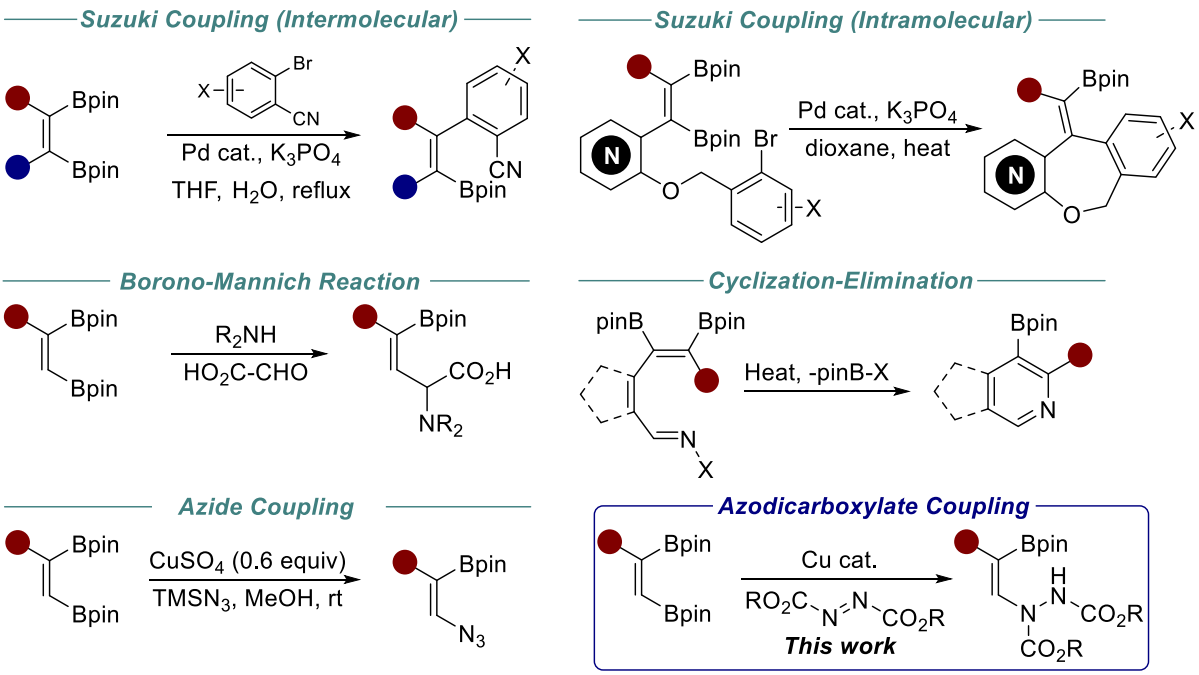
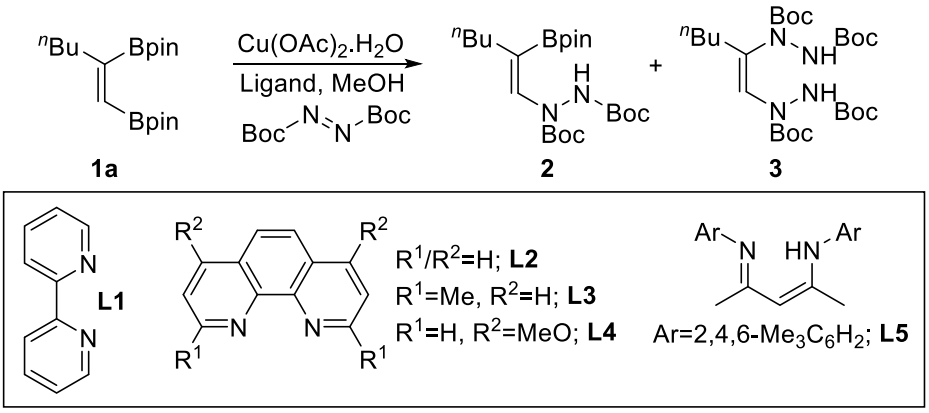


FIGURE 1 | Selective monofunctionalization of 1,2-diborylalkenes.

TABLE 1 | Optimization of the Cu-catalyzed addition of 1a to DBAD.



Entry[a]	L	Catalyst loading	*T*,C	Yield 2	Yield 3
1	—	10%, $Cu(OAc)_2$	50	30%	ND
2	—	10%, $Cu(OAc)_2$	0	51%	44%
3	**L1**	10%, $Cu(OAc)_2$	0	22%	11%
4	**L2**	10%, $Cu(OAc)_2$	0	33%	ND
5	**L3**	10%, $Cu(OAc)_2$	0	19%	18%
6	**L4**	10%, $Cu(OAc)_2$	0	40%	21%
7	**L2**	10%, $Cu(OAc)_2$	21	**59%**	12%
8	**L3**	10%, $Cu(OAc)_2$	21	53%	15%
9	**L4**	10%, $Cu(OAc)_2$	21	41%	28%
10	**L5**	10%, $Cu(OAc)_2$	21	49%	29%
11	**L2**	10% $Cu(OTf)_2$	21	**63%**	34%

[a]Reaction conditions: 1,2-diborylolefin (1 equiv), di-*tert*-butyl azodicarboxylate, Cu catalyst (10 mol%) and ligand (10 mol%) stirred under a nitrogen atmosphere in MeOH (0.25 M). ND, Not determined.

ligand generally resulted in a slower reaction overall. Therefore, we rescreened these ligands in the reaction at room temperature and found **L2** to offer the best overall conversion and selectivity for hydrazide **2**. Finally, we also found $Cu(OTf)_2$ to function well in combination with **L2**.

Assigning product regio-chemistry and -selectivity was challenging in these products due to the presence of rotamers [13, 17, 18]. However, a combination of DEPTQ $^{13}C\{^1H\}$ NMR spectroscopy and the inability to detect carbon signals directly attached to Bpin (due to the quadrupolar relaxation of the boron nuclei) offered a convenient way to assign product regiochemistry. Specifically, the ^{13}C NMR spectrum of **2** showed the presence of three CH-signals in the region 134–138 ppm and six signals in the region 152–155 ppm corresponding to Boc carbonyl signals, suggesting the regioisomer shown in Table 1. The corresponding quaternary ^{13}C signal could not be detected (Figure 2).

We next undertook a brief study of the scope of the azodicarboxylate ester addition reaction, and our results are summarized in Figure 3. Applying our optimized conditions to diborylalkenes bearing cyclopropyl **4**, 1-chlorobutyl **5**, benzyl group **6**, and a THP ether **7** proceeded as expected, albeit with diminished product yields. The method could be extended to a series of aryl- and alkenyl-substituted 1,2-diborylolefins, and again the products were delivered in modest yields, with the *para*-methyl ester **11** and *ortho*-chloroarene **12** proving to be surprisingly more efficient. In addition, we were able to employ the CBz-based diazo substrate, allowing hydrazidoboronates **14**-**20** to be generated in similar overall yields.

In most cases, modest yields arose due to: (1) consumption of the azo dicarboxylates by reduction to hydrazide by-products and (2) the conversion of 1,2-diborylalkene to the corresponding 1,2-dihydrazide (c.f. **3** in Table 1). Despite extensive efforts to obviate the second hydrazidation reaction, including varying substrate stoichiometries and slow addition of azodicarboxylate ester, we were unable to significantly retard this side-reaction. We were surprised to find that the second hydrazidation proceeded so readily and undertook further investigation of this process. In this regard, subjecting commercially available **21** to the reaction conditions resulted in complete consumption of DBAD after 5 h, with ~60% conversion of starting material, from which the corresponding hydrazide **22** could only be isolated in low yield [19]. By comparison, DBAD was consumed much more quickly in the case of **8**, resulting in a higher conversion to the amidated product **23** within 2 h (as judged by 400 MHz ^1H NMR spectroscopy of the crude reaction mixture). These results led us to speculate that transmetallation of the more hindered boronate is directed by the hydrazide, thereby explaining why preventing the formation of unwanted dihydrazide has proven to be so challenging [20]. Figure 4 provides a proposed mechanism for the formation of hydrazide products. Monohydrazidation follows an established paradigm [13], but we believe that **I** can either undergo reversible protonation to deliver hydrazidoboronates or undergo intramolecular transmetallation to generate **II**, which then delivers the observed dihydrazide by-products. Alternative mechanisms that promote the second hydrazidation step such as Lewis base activation of the boronate by adjacent carbamate carbonyl, are also feasible and cannot be ruled out at this stage.

Finally, we also undertook preliminary studies on the synthetic potential of the borylated hydrazides, and our results are shown in Scheme 1. Alkyl hydrazide **24** could be isolated in modest yield after Pt-catalyzed hydrogenation. In addition, oxidation of **2** proceeded smoothly to generate the corresponding ketone **25** [21]. Furthermore, Pd-catalyzed hydrogenation of the olefin **2**, followed by removal of the Boc-groups, allowed the intermediate hydrazide to condense with acetylacetone to generate borylated pyrazole **26**. Although this compound was generated with only minor impurities, it could not be obtained in analytically pure form due to its instability on column chromatography [22]. However, we were able to purify and isolate the corresponding alcohol **27** after perborate oxidation.

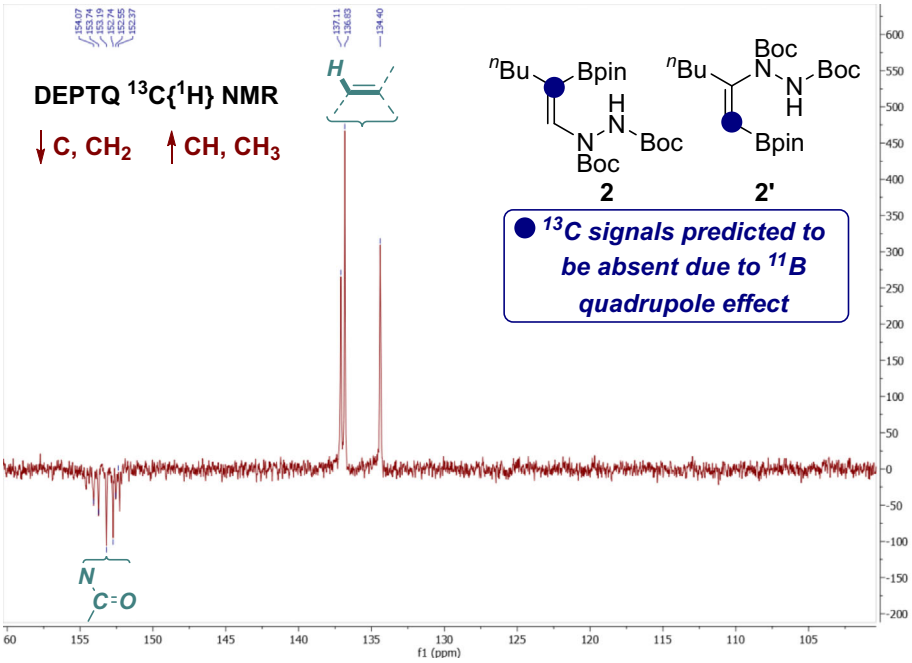


FIGURE 2 | Characterization of hydrazide regiochemistry.

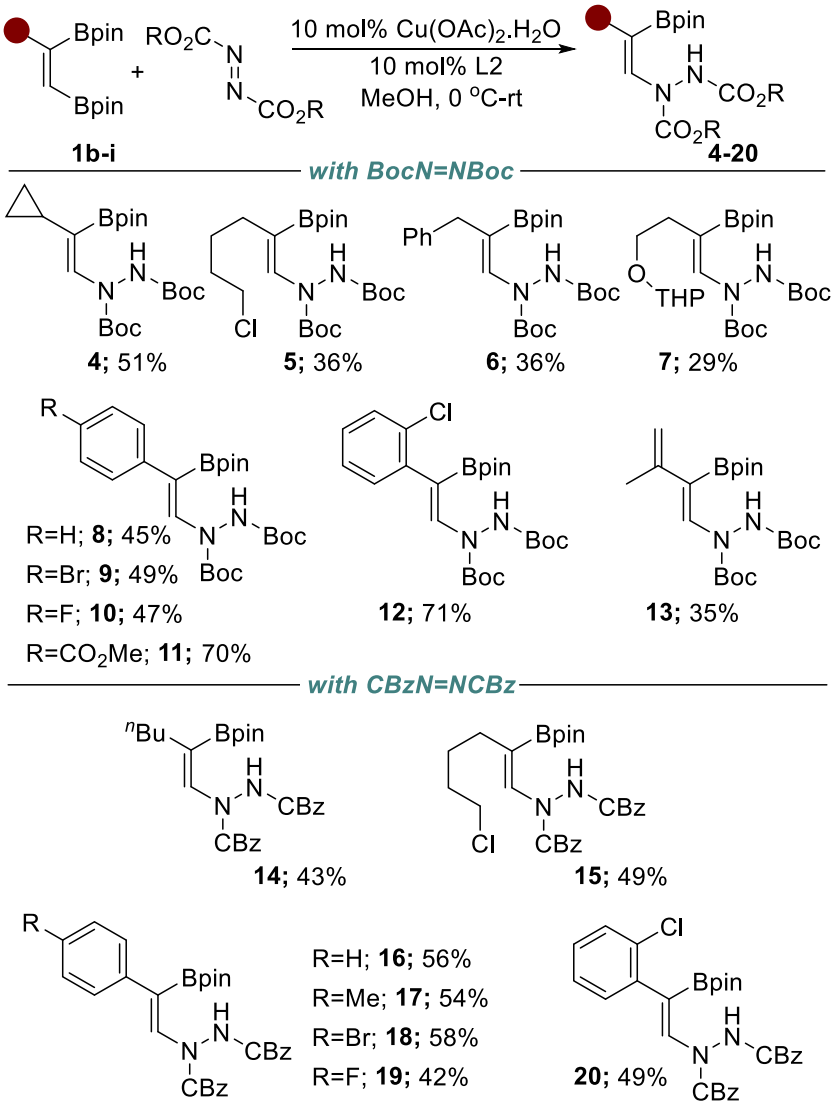


FIGURE 3 | Scope of the Cu-catalyzed addition to azodicarboxylate esters. THP: tetrahydropyranyl.

3 | Conclusion

1,2-Diborylalkenes undergo Cu-catalyzed hydrazidation to generate densely functionalized intermediates that can be further exploited in the synthesis of small molecule building blocks. This method is highly regioselective for C—N bond coupling at the less hindered boronate ester moiety. Surprisingly, selective monofunctionalization of the 1,2-diborylalkenes is challenging as these compounds undergo a facile second hydrazidation, which we propose takes place through a substrate directed transmetallation step.

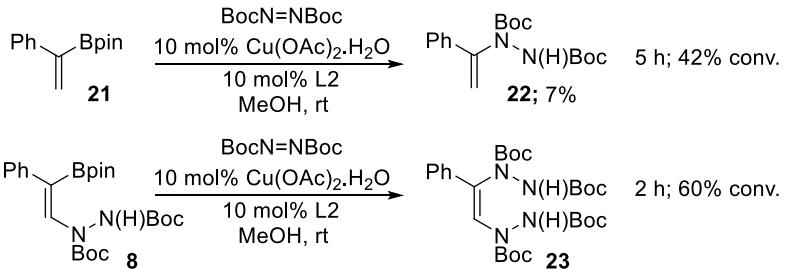
4 | Experimental Section/Methods

4.1 | General Procedure for the Cu-Catalyzed Hydrazidation Reaction With Di-*Tert*-Butyl Azodicarboxylate

To a flame-dried round-bottom flask was added 1,2-diborylolefin (1 equiv), DBAD, $Cu(OAc)_2{\cdot}H_2O$ (10 mol%) and ligand (10 mol%), along with methanol (0.25 M). After stirring for the stated time and temperature, the reaction mixture was quenched with water, and the product was extracted with EtOAc and dried over $MgSO_4$. The resulting crude extract was then concentrated under vacuum and purified by column chromatography using a 9:1 hexane/ethyl acetate eluent system, obtaining the desired product. In all cases, the products were isolated as a mixture of rotamers and/or E/Z isomers.

4.2 | General Procedure for the Cu-Catalyzed Hydrazidation Reaction With Dibenzyl Azodicarboxylate

To a flame-dried round-bottom flask was added 1,2-diborylolefin (1 equiv), dibenzyl azodicarboxylate (0.5 equiv), $Cu(OTf)_2$ (10 mol%), and ligand (10 mol%), along with methanol (0.5 M). Dibenzyl azodicarboxylate was added in 0.5 equiv portions at 30 min. intervals until the 1,2-diborylolefin was completely consumed (as judged by TLC analysis). The reaction mixture was quenched with water, and the product was extracted with



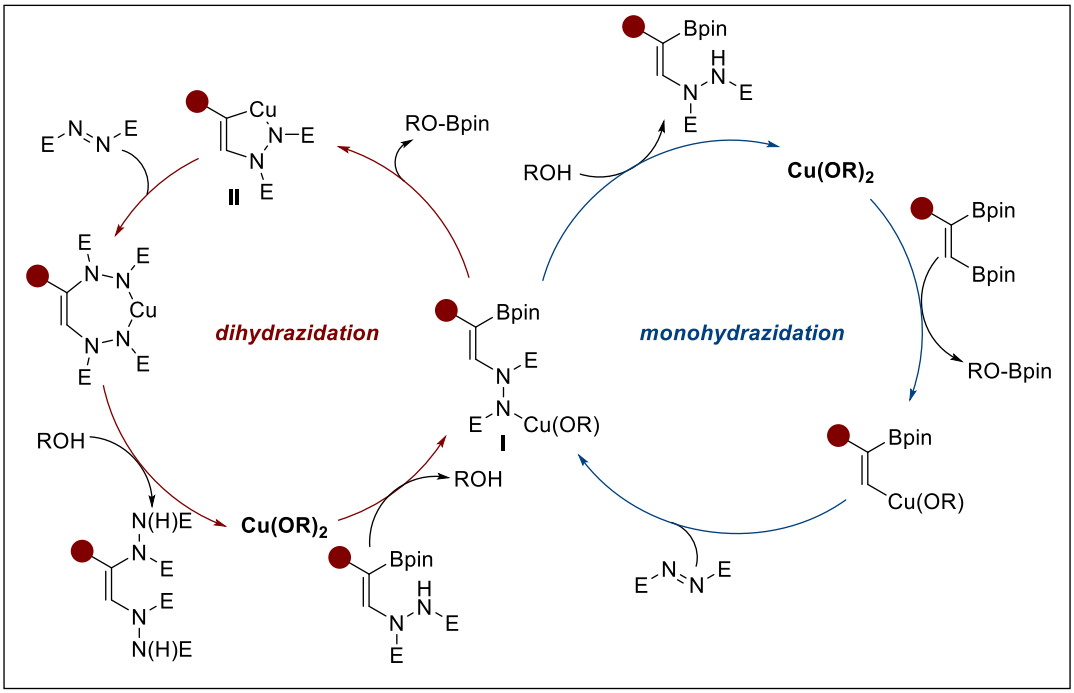
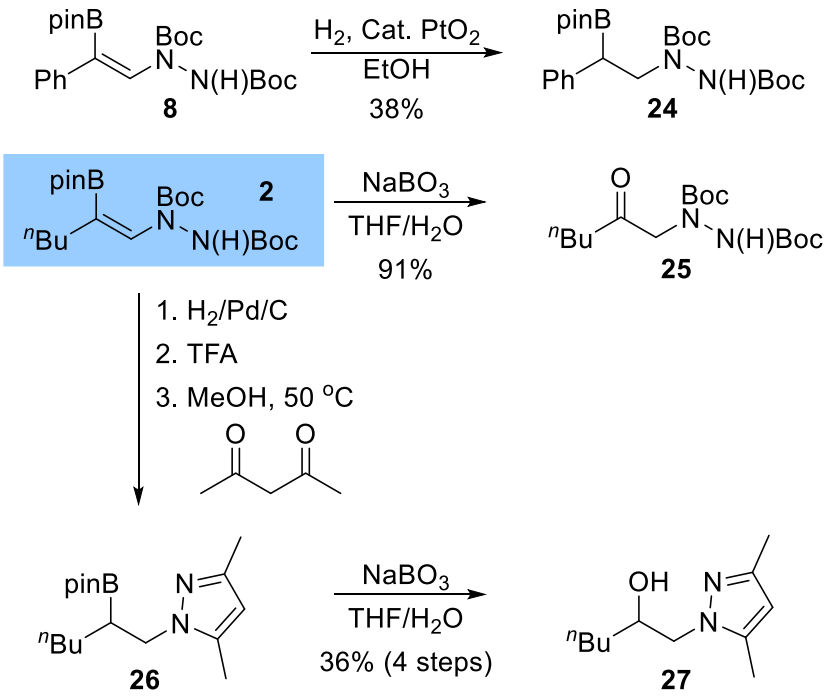


FIGURE 4 | Proposed mechanism of mono- and di-hydrazidation.



SCHEME 1 | Functionalization reactions.

EtOAc and dried over $MgSO_4$. The resulting crude extract was then concentrated under vacuum and purified by column chromatography using a 9:1 hexane/ethyl acetate eluent system, obtaining the desired product. In all cases, the products were isolated as a mixture of rotamers and/or E/Z isomers.

Acknowledgements

This project was funded by the European Union under AiRPaDD Project (grant agreement no. 101069949, https://doi.org/10.3030/101069949).

Funding

Funded by the European Union under AiRPaDD Project (grant agreement no. 101069949, https://doi.org/10.3030/101069949).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.