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Long He, Gregory Laurent, Pascal Retailleau, Benoît Folléas, Jean-Louis Brayer, et al.. Highly Enantioselective Aza-Diels-Alder Reaction of 1-Azadienes with Enecarbamates Catalyzed by Chiral Phosphoric Acids. *Angewandte Chemie*, 2013, 125 (42), pp.11294-11297. <10.1002/ange.201304969>. <hal-04047851>

HAL Id: hal-04047851

<https://hal.science/hal-04047851v1>

Submitted on 27 Mar 2023

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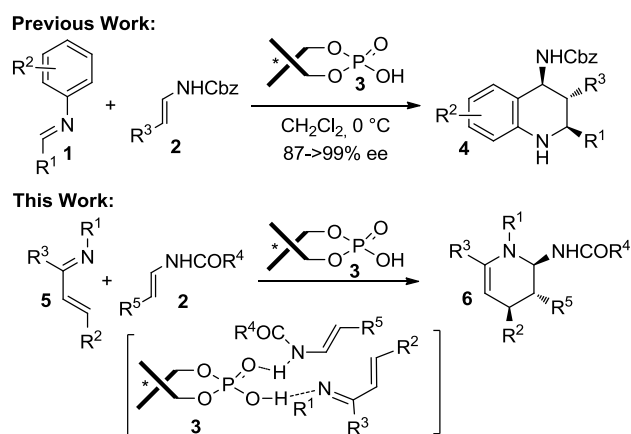
Highly Enantioselective Aza-Diels–Alder Reaction of 1-Azadienes with Encarbamates Catalyzed by Chiral Phosphoric Acids

Long He, Gregory Laurent, Pascal Retailleau, Benoît Folléas, Jean-Louis Brayer and Géraldine Masson*

Chiral tetrahydropyridine framework represents a privileged six-membered azacycle commonly found within a wide variety of biologically active natural products and synthetic compounds of medicinal interest.^[1] Among the synthetic approaches to access these valuable heterocycles, the inverse electron-demand aza-Diels–Alder (IEDADA) reaction of 1-azadienes with electron-rich alkenes is one of the most convergent methods, resulting in the one pot formation of a C–C and C–N bond and up to three new stereocenters.^[2] Nevertheless, this IEDADA reaction suffers from drawbacks such as a low reactivity and stability of 1-azadienes, which could be responsible for the slow development of its corresponding enantioselective version.^[3] The introduction of strong electron-withdrawing groups (*N*-acyl, *N*-sulfonyl)^[4,5] on the 1-aza-1,3-butadiene, enhancing its inherent electron-deficient character as well as its stability, have paved the way towards success in catalytic enantioselective IEDADA reaction.^[3] The first example was disclosed by Bode et al.,^[6] who reacted *N*-sulfonyl-1-aza-butadienes with β -activated aldehydes in the presence of catalytic amounts of a chiral *N*-heterocarbene catalyst. One year later, Arrayás and Carretero et al.^[7] reported that a DBFOX–Ph/Ni(II) complex was able to catalyze the asymmetric IEDADA reaction of *N*-heteroarylsulfonyl α,β -unsaturated imines with vinyl ethers. Afterward, other examples of organocatalysis relying on covalent attachment of the catalyst have been used, leading to significant advances in the enantioselective IEDADA reaction of *N*-sulfonyl-1-azadienes.^[8] To the best of our knowledge, no example of Brønsted acid-catalyzed^[9] IEDADA reaction of 1-azadienes has been reported, although Brønsted acids have been used successfully as catalysts in the cycloaddition of 2-azadienes.^[10]

Recently, we described that chiral phosphoric acids were efficient catalysts for the asymmetric IEDADA reaction of *N*-arylimines **1** and encarbamates **2** as dienophiles in a highly diastereo- and enantioselective manner.^[10b,f,g] A study of the mechanism indicated that the simultaneous dual activation through

hydrogen-bonding interactions of the bifunctional phosphoric acid with both *N*-arylimine **1** and the NH donor group **2** was critical for achieving high enantioselectivity.^[11–13] Based on these results, we reasoned that the encarbamate **2** and the *N*-aryl-1-azadiene **5** could be well adapted as dienophile and diene, respectively, to develop an enantioselective IEDADA reaction catalysed by chiral phosphoric acid. Indeed, the simultaneous dual activation of the two reacting partners by the phosphoric acid catalyst might ensure high reactivity and stereoselectivity (Scheme 1). As shown in our previous work, the cycloaddition with non- α -substituted *N*-aryl-azadiene ($R^3 = H$), solely giving the Povarov products **4**.^[10b,f] We speculated that the use of α,β -unsaturated ketoimines **5** might change the regioselectivity of the IEDADA reaction to lead to valuable 6-amino-1,4,5,6-tetrahydropyridine derivatives **6**. This latter structural motif is found in natural products such as Siastatin B, a potent neuraminidase inhibitor,^[1c,e,f] or in synthetic compounds exhibiting significant *in vitro* antimicrobial activities.^[1m]



Scheme 1. Bifunctional catalyst for the enantioselective IEDADA reaction.^[10b,f]

In our initial study, we chose the *N*-aryl β,γ -unsaturated α -iminoesters **5a**^[14] and benzylprop-1-enylcarbamate (*E*)-**2a** with chiral phosphoric acid catalyst as the model reaction. To our delight, *syn*- and *anti*-methyl (*E*)-4-(*p*-methoxyphenyl)-2-*p*-phenyliminobut-3-enoate^[1b,15] led to desired 6-amino-1,4,5,6-tetrahydropyridine **6a** with an excellent all *trans* diastereoselectivity (Scheme 2). After a brief survey of reaction conditions (catalysts, the solvents, the temperatures and the stoichiometries) we found that the reaction performed at room temperature in dichloromethane with 10 mol % of (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-BINOL (TRIP) phosphoric acid (**3**) (cf. Supporting information) furnished the desired product in 71% yield with 93% *ee*.

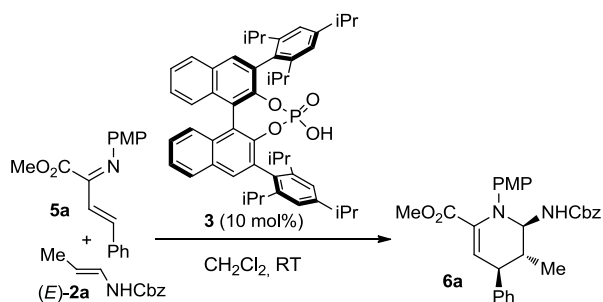
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[**] We wish to thank the ICSN and CNRS for financial supports and Pascal Retailleau in ICSN for the X-ray crystallographic analysis. H.L. also acknowledges ANR for post-doctoral fellowships. G.L. thanks Diverchim for a CIFRE grant

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Scheme 2. Chiral phosphoric acid (**3**)-catalyzed enantioselective IEDADA reaction of 1-azadienes.

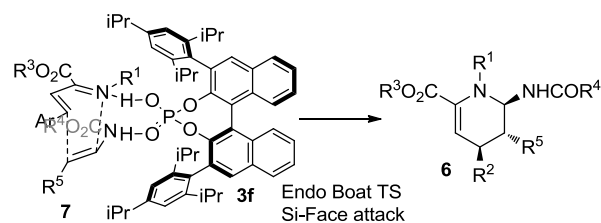
With the optimal conditions outlined above, a range of *N*-aryl-1-azabutadiene **5** was subjected to the enantioselective IEDADA cycloaddition. As summarized in table 1, various β,γ -unsaturated α -iminoesters bearing electron-donating and -withdrawing groups at γ position reacted smoothly to afford 4,5,6-trisubstituted 1,4,5,6-tetrahydropyridines **6c-6j** in good yields with excellent diastereo- and enantioselectivities (entries 1 to 8). The presence of heteroaromatic rings such as furyl (entry 7) and thiophenyl (entry 8) is well tolerated in the cycloaddition as well. Additionally, enantioselectivities of products resulting from the reaction of *N*-substituted arylimines were generally high, independently of the electronic character of the aromatic ring (entry 13 to 17). Several 1-azadienes bearing various ester moieties such as ethyl, isopropyl, propyl, and *tert*-butyl ester were investigated. In all the cases, chiral tetrahydropyridines were obtained with the same order of yields and *ees* (entries 9 to 12). The catalytic system also proved to be efficient for various carbamates affording the highly substituted tetrahydropyridines **6t-6y** with excellent diastereomeric (all *trans*) and *ees* (entries 18 to 22). The enecarbamate **2g** participated smoothly in the cycloaddition but with lower *ee* (entry 24). Finally, the current cycloaddition was extended to other 1-azadienes bearing phenyl group at the α -position of the β,γ -unsaturated imines and the cycloadditions with (*E*)-**2a** proceeded with complete regioselectivity, affording the desired products **6z** and **6aa** in high enantioselectivities, albeit with slightly moderate yields (entries 24-25). The absolute configuration of **6c** was unambiguously determined to be 4*S*, 5*R* and 6*R* by single crystal X-ray analysis (cf. Supporting information).

On the basis of previous works,^[2,16] we proposed two mechanism pathways that could be followed for the subsequent IEDADA cycloaddition: (a) a concerted mechanism between the 1-azadiene and the enecarbamate or (b) a two-step mechanism consisting first of the enecarbamate attacking the β,γ -unsaturated α -iminoester *via* a Michael reaction followed by an intramolecular amination of the formed anion to iminium ion.^[2g,17] To distinguish between the two mechanisms, we evaluated the influence of the substitution at *N*- and $C\gamma$ -positions in β,γ -unsaturated α -iminoesters. Here, we observed that the presence of an electron-donating or -withdrawing group on the nitrogen has an influence on reaction times (cf. Supporting information). Likewise, reaction rates are influenced by the electronic nature of aryl substituents in γ -position. These findings seem consistent with a concerted mechanism. In addition, when EtOH (3 to 10 equivalents or as solvent) was added to the reaction to trap the iminium intermediate **7**, neither the expected adduct nor the tetrahydropyridine were detected.^[18] Even though we cannot definitely rule out a possible stepwise mechanism, this supports a highly asynchronous concerted mechanism. Based on these

Table 1. Substrate scope of the enantioselective synthesis of 4,5,6-trisubstituted-1,4,5,6-tetrahydropyridines.^[a]

Entry	R ¹ /R ² /R ³	R ⁴ /R ⁵	6	Yield/ <i>ee</i> [%] ^[b,c]
1	PMP/4-ClC ₆ H ₄ /CO ₂ Me	Bn/Me	6c	75/95 ^[d]
2	PMP/4-MeC ₆ H ₄ /CO ₂ Me	Bn/Me	6d	72/90 ^[d]
3	PMP/4-OMeC ₆ H ₄ /CO ₂ Me	Bn/Me	6e	63/86
4	PMP/4-NO ₂ C ₆ H ₄ /CO ₂ Me	Bn/Me	6f	63/86
5	PMP/3-ClC ₆ H ₄ /CO ₂ Me	Bn/Me	6g	74/91
6	PMP/3-BrC ₆ H ₄ /CO ₂ Me	Bn/Me	6h	76/91
7	PMP//CO ₂ Me	Bn/Me	6i	72/94 ^[e]
8	PMP//CO ₂ Me	Bn/Me	6j	63/91
9	PMP/Ph/CO ₂ Et	Bn/Me	6k	76/93 ^[d]
10	PMP/Ph/CO ₂ <i>n</i> -Pr	Bn/Me	6l	62/91
11	PMP/Ph/CO ₂ <i>i</i> -Pr	Bn/Me	6m	72/92
12	PMP/Ph/CO ₂ <i>t</i> -Bu	Bn/Me	6n	61/94
13	4-ClC ₆ H ₄ /Ph/CO ₂ Me	Bn/Me	6o	72/94 ^[e]
14	4-MeC ₆ H ₄ /Ph/CO ₂ Me	Bn/Me	6p	82/92
15	2-MeOC ₆ H ₄ /Ph/CO ₂ Me	Bn/Me	6q	68/92 ^[d]
16	Ph/Ph/CO ₂ Me	Bn/Me	6r	75/92
17	4-BrC ₆ H ₄ /Ph/CO ₂ Me	Bn/Me	6s	74/92
18	PMP/Ph/CO ₂ Me	Et/Me	6t	78/90 ^[d]
19	PMP/Ph/CO ₂ <i>t</i> -Bu	/Me	6u	66/94
20	Ph/Ph/CO ₂ Me	4-CF ₃ C ₆ H ₄ CH ₂ /Me	6v	84/91 ^[f]
21	Ph/Ph/CO ₂ Me	4-BrC ₆ H ₄ CH ₂ /Me	6w	73/92 ^[g]
22	Ph/Ph/CO ₂ Me	C ₆ F ₅ CH ₂ /Me	6x	68/93 ^[f]
23	PMP/Ph/CO ₂ <i>i</i> -Pr	<i>t</i> -Bu/ <i>n</i> -C ₃ H ₇	6y	61/70 ^[e]
24	PMP/Ph/Ph	Bn/Me	6z	59/93
25	PMP/Ph/4-BrC ₆ H ₄	Bn/Me	6aa	57/88

[a] Reaction conditions: 1-azadiene **5** (0.1 mmol), enecarbamate (*E*)-**2** (0.2 mmol), **3f** (0.01 mmol) in CH₂Cl₂ (1.0 mL) at RT. [b] Yield of chromatographically pure product, all *trans* isomer (d.r.=95:5). [c] Determined by chiral HPLC analysis. [d] Reaction at 0 °C. [e] d.r.=7:1. [f] d.r.=9:1. [g] d.r.=12:1.

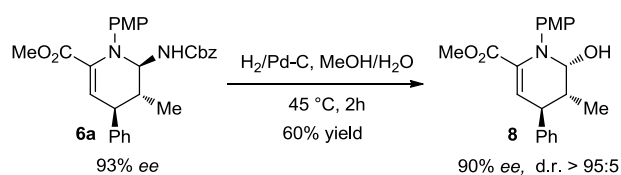


Scheme 3. Activation model *via* a putative transition state.

observations, we propose a transition state to explain the observed (absolute) stereochemical outcome of the enantioselective IEDDA reaction (Scheme 3). In this system, the chiral phosphoric acid may serve as a bifunctional catalyst: the OH group activates the 1-azadiene as a Brønsted acid and the phosphoryl oxygen activates the

enecarbamates as a Lewis base. IEDADA Reaction might take place with *endo* selectivity, *via* a transition state in which the Si face of the azadiene would be attacked, affording (4*S*,5*R*,6*R*)-cycloadduct **6**. The importance of the hydrogen atom on enecarbamate **2** was supported by the moderate yield and enantioselectivity of the reaction with tertiary endocyclic enecarbamate (cf. Supporting information). This indicates that the presence of the NH group is crucial for both reactivity and enantioselectivity.

With the successful construction of tetrahydropyridines, we turned our attention to perform further transformations of cycloadduct **6** into valuable compounds. As illustrated in scheme 4, removal of the Cbz group in **6a** by a Pd/C-catalyzed hydrogenolysis produced hemiaminal adduct **8** (a key precursor of a variety of chiral piperidines as described by other authors)^[8a-b] in 60% yield with a very subtle erosion of enantioselectivity (Scheme 4).



Scheme 4. Synthetic transformation of the tetrahydropyridine.

In summary, we have developed the first catalytic enantioselective IEDADA reaction of N-aryl α,β -unsaturated ketimines **5** and β -substituted enecarbamates **2** using a chiral bifunctional phosphoric acid catalyst. This cycloaddition employs easily accessible starting materials to construct densely functionalized 4,5,6-trisubstituted 1,4,5,6-tetrahydropyridines **6** with three contiguous stereogenic centers (with up to 84% yield, 95:5 dr and 95% *ee*). Early mechanistic studies seem to indicate that the reaction proceeds *via* an asynchronous concerted mechanism. Further studies regarding the applications of this IEDADA reaction are ongoing and will be reported in due course.

Received: ((will be filled in by the editorial staff))

Published online on ((will be filled in by the editorial staff))

Keywords: Chiral phosphoric acid · cycloaddition reaction · *aza*-Diels-Alder reaction · organocatalysis · tetrahydropyridines.

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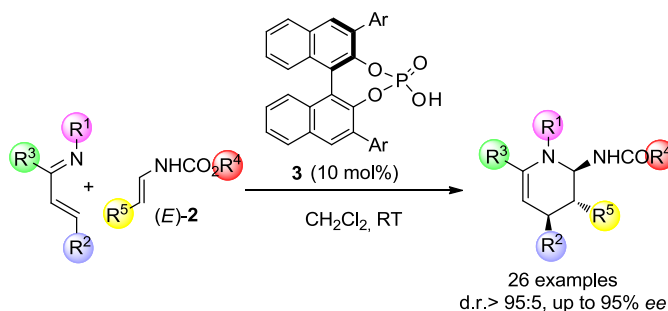
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Highly Enantioselective Aza-Diels–Alder
Reaction of 1-Azadienes with
Enecarbamates Catalyzed by Chiral
Phosphoric Acids



A highly enantio- and diastereoselective synthesis of 6-amino-trisubstituted tetrahydropyridine compounds has been developed through the inverse-electron-demand aza-Diels-Alder reaction of *N*-aryl α,β -unsaturated ketimines with enecarbamates. This cycloaddition is catalyzed by a chiral bifunctional phosphoric acid that achieves simultaneous activation of both the 1-azadiene and dienophile partners.