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Desymmetrization of Oxabenzonorbornadienes through Brønsted Acid-Catalyzed Enantioselective (3+2) Cycloaddition with Hydrazones

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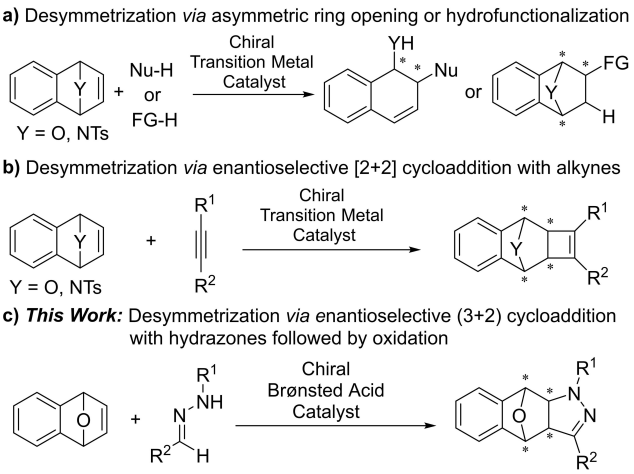
Dedicated to Prof. Dr. Keiji Maruoka on the occasion of his 70th birthday

Abstract: This work presents the desymmetrization of oxabenzonorbornadienes through the (3+2) cycloaddition reaction with hydrazones using a chiral Brønsted acid such as a BINOL-derived phosphoramide. This chiral acid catalyst appears as the most effective mediator for the activation of the hydrazone *via* hydrazonium cation that reacts in a (3+2) fashion with the oxabenzonorbornadiene as the olefinic counterpart. Under the optimized conditions, the reaction provided selectively *exo* cycloaddition products in satisfactory yields and moderate stereoselectivities. The scope of the reaction was explored displaying 21 examples of these highly functionalized tetrahydroepoxybenzoindazole compounds. A reaction mechanism is proposed to explain the outcome of the reaction.

Introduction

In the last decades, an extensive exploration of oxa(aza)benzonorbornadiene motifs in enantioselective transformations has been undertaken.[1] In particular, oxabenzonorbornadienes have proven to be suitable scaffolds to participate in desymmetrization reactions, and also as suitable starting materials for the synthesis of valuable compounds with interesting biological activities.[2] Among the enantioselective transformations carried out on these tricyclic systems, asymmetric ring opening reactions and hydrofunctionalizations prevail, which find the driving force on the strain that is released when either the C–O or the π C–C bond is cleaved (Scheme 1a).[3] On the other hand, the alternative desymmetrization of oxa(aza)benzonorbornadienes through a cycloaddition process in which the oxa- or aza-bicyclic scaffold is preserved has received much less attention, despite of the potential of this strategy for accessing interesting structures presenting up to four contiguous stereocenters.[4] It should be noted that these asymmetric cycloadditions in which oxa- or azanorbornenes have been involved are restricted to [2+2]-type cycloadditions with alkynes mediated by transition metal catalysts (Scheme 1b),[5] together with one example of a Rh-catalyzed cascade [2+2+2] cycloaddition reaction.[6] On the other hand, there are several examples in the literature showing the capacity of oxabenzonorbornadienes to undergo 1,3-dipolar cycloaddition with several dipoles such as nitrile oxides and azomethine ylides, in all cases in a non-enantioselective manner.[7]



Scheme 1. Desymmetrization of oxa(aza)norbornadienes through asymmetric catalysis.

In this context, we decided to survey the possibility for oxabenzonorbornadienes to undergo (3+2) cycloaddition with hydrazones to deliver the corresponding desymmetrized (3+2) cycloaddition adducts when carrying out the reaction in the presence of a chiral catalyst. Hydrazones are known to be suitable azomethine imine-type 1,3-dipoles that have the ability to engage in (3+2) cycloaddition reactions with olefins.[8] Remarkably, there are also several reports that have demonstrated that electron-rich alkenes undergo enantioselective (3+2) cycloaddition with hydrazone under catalysis by BINOL-derived chiral phosphoric acids or derivatives.[9] In view of this precedents, we envisioned that oxabenzonorbornadienes could

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be suitable substrates for a potential desymmetrization process enabled by the enantioselective (3+2) cycloaddition with hydrazones catalyzed by a chiral Brønsted acid (Scheme 1c). To the best of our knowledge, the desymmetrization of oxabenzonorbornadienes through (3+2) cycloaddition has not yet been reported in the literature. In this manuscript, we wish to present our recent results regarding such a desymmetrization process enabled by a chiral BINOL-based phosphoric acid catalyst that comprises a (3+2) cycloaddition followed by oxidation.

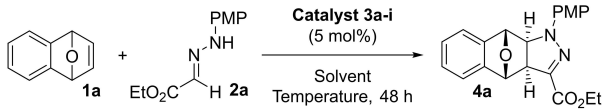
Results and Discussion

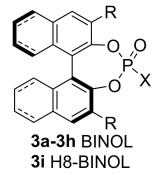
At the outset of our investigation, it was decided to explore the reactivity of oxabenzonorbornadiene **1a** with hydrazone **2a** as the model system using toluene as solvent and in the presence of different Brønsted acids as catalysts (Table 1). The first experiment using BINOL-phosphoric acid **3a** as catalyst resulted in a sluggish reaction that only provided product **4a** in a very low yield (entry 1). The formation of this compound can be explained considering that, after the expected (3+2) cycloaddition reaction, an oxidation has taken place. Remarkably, the more acidic *N*-trifluoromethanesulfonamide **3b** provided cycloadduct **4a** in a good yield, as a single diastereoisomer and as a racemic material (entry 2). Next, more elaborated versions of this catalyst **3b** that incorporated aryl substituents of different nature at the 3 and 3′-positions of the BINOL core were evaluated in order to achieve enantioselectivity in this transformation (entries 3–8).

We initially surveyed catalyst **3c** with a π-extended 9-anthryl substituent (entry 3) but this only led to minor improvement on the enantioselectivity. We next moved to the use of catalysts **3d-e** that incorporate 3,5-disubstituted aryl moieties as substituents of the BINOL core (entries 4–5) without any positive effect on enantioselectivity. Alternatively, a remarkable improvement in the e.r. was obtained when TRIP phosphoramide **3f** was used, although isolating adduct **4a** in a moderate yield (entry 6). Trying to improve the enantioselectivity, other related phosphoramide catalysts with bulkier substituents **3g** and **3h** were tested (entries 7 and 8), together with the partially hydrogenated version of TRIP phosphoramide **3i** (entry 9) but without being able to obtain better results. Adopting the use of catalyst **3f** as the best performing one, solvent effects were evaluated, observing little difference in the outcome of the reaction regardless whether chlorinated (entries 10–11), more polar (entry 12) or other aromatic solvents (entry 13) were employed. The reaction was also carried out at a lower temperature using toluene as solvent, but without any significant improvement (entry 14). Finally, the yield of the reaction increased when two equivalents of the oxabenzonorbornadiene were used, with no negative effect on the enantioselectivity (entry 15). These were adopted as the optimal conditions for the reaction. In all cases tested, the reaction was found to be fully diastereoselective.

With these conditions in hand, the scope of the reaction was explored, examining first the influence of the alkoxy substituent on the azomethine carbon of the hydrazone (Scheme 2). Both ethyl (**4a**) and isopropyl (**4b**) substituted esters were well tolerated in the reaction, although better enantioselectivity was obtained in the case of ethoxycarbonyl hydrazone **4a**. Then, the effect of the *N*-substituent at the hydrazone reagent was evaluated. We observed that the nature of the *N*-substituent had a striking influence, observing that *N*-phenyl hydrazone **2c** (R^1 = Et, R^2 = Ph) led to cycloaddition product **4c** with excellent yield and improved enantioselectiv-

Table 1. Screening of the Reaction Conditions.[a]



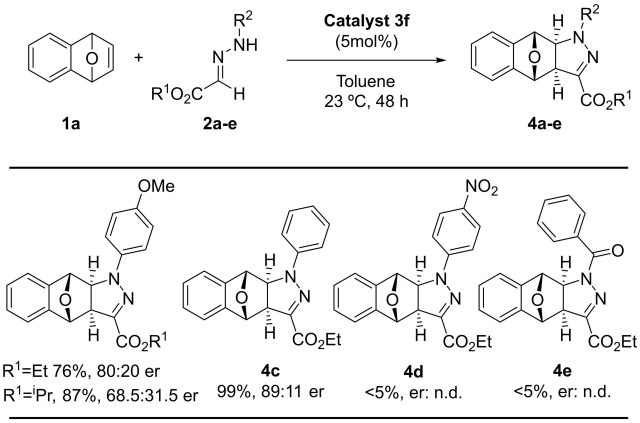


3a-3h BINOL
3i H8-BINOL

3a: X = OH; R = H
3b: X = NHTf; R = H
3c: X = NHTf; R = 9-anthryl
3d: X = NHTf; R = 3,5-$(SiPh_3)_2C_6H_3$
3e: X = NHTf; R = 3,5-$(CF_3)_2C_6H_3$
3f: X = NHTf; R = 2,4,6-$(^iPr)_3C_6H_2$
3g: X = NHTf; R = 2,4,6-$(Cy)_3C_6H_2$
3h: X = NHTf; R = 2,4,6-(c-Pentyl)$_3C_6H_2$
3i: X = NHTf; R = 2,4,6-$(^iPr)_3C_6H_2$

Entry	Catalyst **3a–h**	Solvent	Yield (%)	er[b]
1	**3a**	Toluene	8	n.d.
2	**3b**	Toluene	70	50:50
3	**3c**	Toluene	60	59:41
4	**3d**	Toluene	51	60:40
5	**3e**	Toluene	31	61:39
6	**3f**	Toluene	57	80:20
7	**3g**	Toluene	57	65:35
8	**3h**	Toluene	66	77:23
9	**3i**	Toluene	24	58:42
10	**3f**	CH_2Cl_2	35	79:21
11	**3f**	$CHCl_3$	42	72:28
12	**3f**	EtOAc	52	80:20
13	**3f**	*o*-Xylene	44	76:24
14[c]	**3f**	Toluene	27	70:30
15[d]	**3f**	Toluene	76	80:20

[a] Reactions conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), **3** (0.01 mmol), in 1 mL of solvent at 23 °C for 48 h. PMP = 4-MeOC_6H_4. All reactions delivered products as single diastereomer (dr > 20:1) determined by ^{1}H NMR analysis of crude reaction mixture. [b] Determined by chiral HPLC analysis (see SI for details). [c] Reaction carried out at 0 °C. [d] 0.4 mmol of **1a** were used.



4a R^1=Et 76%, 80:20 er
4b R^1=^{i}Pr, 87%, 68.5:31.5 er
4c 99%, 89:11 er
4d <5%, er: n.d.
4e <5%, er: n.d.

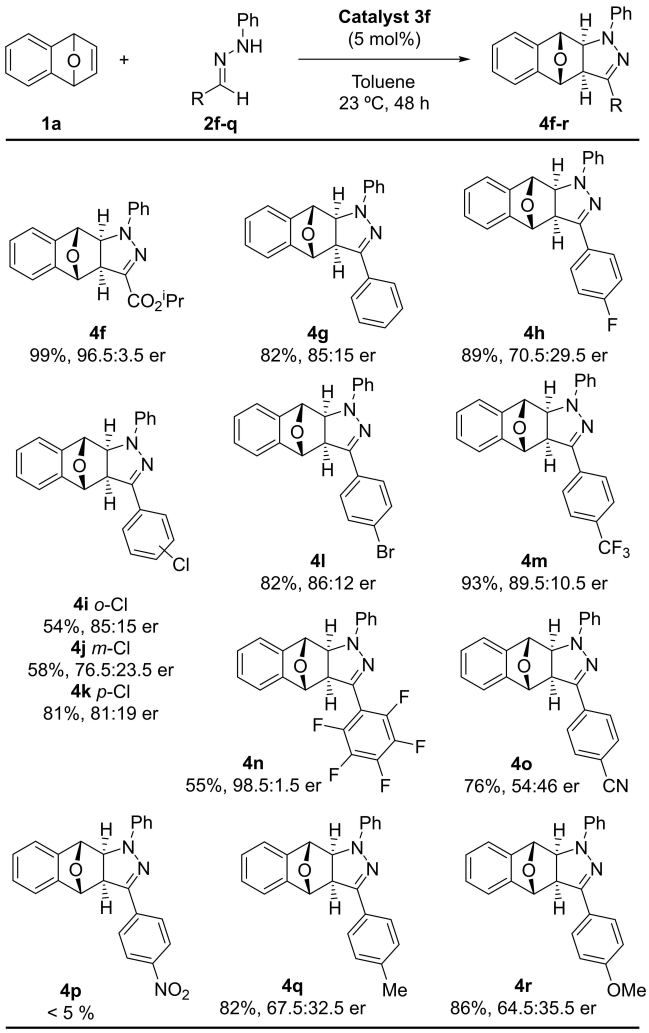
Scheme 2. Influence of the hydrazine N-substituent on the reaction.

ity. On the other hand, hydrazones with electron-releasing *N*-substituents such as *N*-*para*-nitrophenyl hydrazone **2d** or *N*-benzoyl hydrazone **2d** were found to be completely unreactive under the optimized conditions, isolating the starting oxabenzonorbornene unchanged after prolonged reaction times. The absolute configuration of these adducts was assigned by single crystal X-Ray analysis of compound **4b** and extending this configuration to all other adducts prepared based on mechanistic analogy.[10]

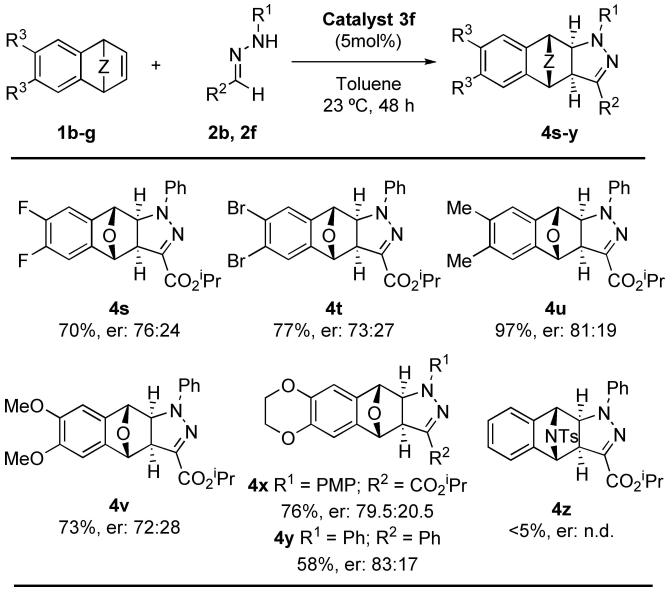
We next evaluated the influence of the substitution pattern at the azomethine carbon of the *N*-phenyl substituted hydrazone reagent (Scheme 3). Our first modification implied increasing the size of the alkoxycarbonyl substituent of the glyoxylate hydrazone reagent, obtaining compound **4f** with an excellent yield and enantioselectivity. We next moved to evaluate aryl hydrazones with different substitution patterns at the aryl moiety. In particular, phenyl hydrazone **2g** (R^2 = Ph) provided good yield and enantioselectivity (adduct **4g**) and similar results were observed using a variety of aryl hydrazones with electron withdrawing substituents (compounds **4h**–**m**). Remarkably, *ortho* and *meta* substituted hydrazones took part in the reaction albeit in a lower yield compared to their *para* substituted analog (**4i**–**k**); and the enantioselectivity was importantly increased when a hydrazone incorporating a bulkier electron-poor aryl substituent, such as in the case of the perfluorophenyl hydrazone **2n**, was tested despite of the lower yield in which this cycloadduct **4n** was isolated. Hydrazones with different electron withdrawing groups were evaluated, such as cyano **4o**, which showed diminished enantioselectivity or nitro **4p**, that did not enable product formation. In comparison, electron rich aryl substituents on the azometine carbon negatively affected the enantioselectivity of the process, although performing with high chemical yields (**4q**–**r**).

Regarding the performance of the reaction when other oxabenzonorbornadienes were used, 6,7-disubstituted substrates (**1b**–**g**) were tested in combination, with hydrazones **2b** and **2f** (Scheme 4). It was noticed that among these examples comparable results in terms of yield and enantioselectivity were obtained regardless the nature of the substituents on the oxabenzonorbornadiene. In particular, oxabenzonorbornadienes incorporating halogen (**4s**–**t**), alkyl (**4u**), or alkoxy substituents were surveyed (**4v**–**z**), obtaining in all these cases very similar yields and enantioselectivities. All these experiments demonstrated that the reaction is very tolerant to the use of oxabicyclic substrates with diverse electronic nature. The main limitation at this point was noticed when azabenzonorbornadiene **1g** was employed in this reaction, which resulted to be unreactive under these reaction conditions and failed to provide the corresponding cycloaddition adduct **4z**.

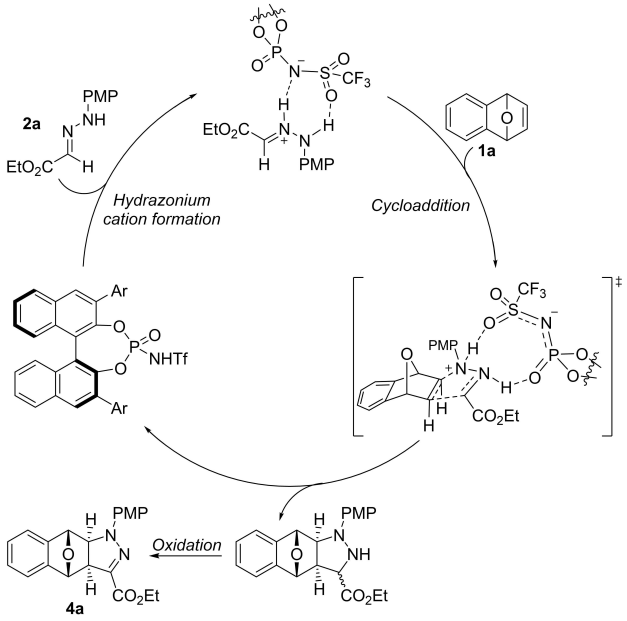
Based on literature precedents on BINOL-derived trifluoromethanesulfonyl phosphoramide catalyzed cycloaddition of hydrazones with alkenes, we propose the following reaction mechanism (Scheme 5).[9c] The reaction begins with the activation through protonation of the hydrazone substrate **2a** by the Brønsted acid catalyst, leading to the formation of an ion-pair



Scheme 3. Scope of the reaction: Influence of the substituent at the azomethine carbon of the hydrazone reagents.



Scheme 4. Scope of the reaction: oxa(aza)benzonorbornadiene component.



Scheme 5. Proposed reaction mechanism for the formation of cycloaddition adducts.

complex between an hydrazonium cation and the conjugated base of the catalyst. The chiral backbone of the BINOL-derived Brønsted acid provides the chiral environment to promote the stereoselective (3 + 2) cycloaddition between monopolar hydrazonium cation and oxabenzonorbornadiene **1 a**, delivering the adduct as *exo* diastereomer. The pyrazolidine intermediate is immediately oxidized in the reaction medium to the final pyrazone-ring,[11] thus providing the isolated tetrahydroepoxybenzoindazole product.

Conclusion

This work has demonstrated the feasibility of the (3 + 2) cycloaddition reaction between oxanorbornadienes and hydrazones under chiral Brønsted acid catalysis in an overall process that takes place together with the desymmetrization of the starting material. The reaction has resulted to be wide in scope for both oxabicycle and hydrazone partners. A wide variety of oxygen-bridged-tetracyclic adducts have been obtained in good yield and excellent *exo* diastereoselectivity. The enantioselectivity of the reaction was found to be highly substrate dependent regarding the hydrazone reagent, obtaining the highest enantiocontrol when electron-withdrawing substituents are placed on the azomethine carbon under the reported reaction conditions; while differences on electronic effects on the oxabenzonorbornadiene counterpart had little effect on the enantioselection.

Experimental Section

Cycloaddition of Oxabenzonorbornadienes with Hydrazones. Synhtesis of tetrahydroepoxybenzoindazole adducts 4 a. Into as oven-dried, screw-capped vial equipped with a magnetic stir bar, hydrazone **2 a** (44.5 mg, 0.20 mmol, 1.0 equiv), followed by oxabenzonorbornadiene **1 a** (57 mg, 0.40 mmol, 2.0 equiv) were weighed. Then, with the vial under positive argon pressure, toluene was added (1 mL) and the mixture was stirred for 5 min, followed by addition of the catalyst **3 f** (0.01 mmol, 0.05 equiv) as a solid. The mixture was stirred at 23 °C for 48 h monitoring by TLC. The crude reaction was dry loaded onto silica gel and subjected to column chromatography affording the corresponding adduct **4 a** (57.7 mg, 0.158 mmol) as a yellow solid. Yield: 76%. dr: > 20 : 1. er: 80 : 20. Rf (petroleum ether/EtOAc 7 : 3): 0.40. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.36 (m, 2 H), 7.27 (dd, J = 5.2, 3.1 Hz, 2 H), 7.24 (d, J = 2.1 Hz, 2 H), 6.94 (d, J = 9.0 Hz, 2 H), 5.75 (s, 1H), 5.71 (s, 1 H), 4.65 (d, J = 9.4 Hz, 1 H), 4.39 (q, J = 7.1 Hz, 2 H), 3.86 (d, J = 9.4 Hz, 1 H), 3.82 (s, 3 H), 1.42 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 155.1, 145.3, 142.2, 136.0, 135.7, 128.1, 127.6, 120.4, 115.5, 114.9, 83.6, 83.2, 69.8, 61.2, 55.7, 14.6. IR (ATR, cm^{-1}): 1685, 1508, 1261, 1164, 1105. MS (EI, 70 eV) m/z (%): 247 (27), 246 (100). HRMS (ESI$^+$): Calculated for $[C_{21}H_{21}N_2O_4]^+$: 365.1501 [(M + H)$^+$]; found: 365.1506. MP: 150–152 °C (petroleum ether/EtOAc). The er was determined by HPLC using a *Chiralpak OD-3* column [*n*-hexane/*i*-PrOH (90 : 10)]; flow rate 0.8 mL/min; τ_1 = 22.56 min, τ_2 = 33.98 min. $[\alpha]_D^{20}$ −25.6 (c = 1.0, $CHCl_3$).

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: cycloaddition · desymmetrization · enantioselective · hydrazone · oxabenzonorbornadiene

[1] a) P. Chiu, M. Lautens, *Top. Curr. Chem.* **1997**, *190*, 1–85; b) D. K. Rayabarapu, C.-H. Cheng, *Acc. Chem. Res.* **2007**, *40*, 971–983; c) R. Khan, J. Chen, B. Fan, *Adv. Synth. Catal.* **2020**, *362*, 1564–1601; d) S. V. Kumar, A. Yen, M. Lautens, P. J. Guiry, *Chem. Soc. Rev.* **2021**, *50*, 3013–3093; e) P. Sihag, M. Jeganmohan, *Synthesis* **2021**, *53*, 3249–3262; f) A. Punder, E. Neufeld, P. Myler, W. Tam, *Beilstein J. Org. Chem.* **2023**, *19*, 487–540.
[2] a) M. Lautens, T. Rovis, *J. Org. Chem.* **1997**, *62*, 5246–5247; b) M. Lautens, T. Rovis, N. D. Smith, D. Ostrovsky, *Pure Appl. Chem.* **1998**, *70*, 1059–1064; c) M. Lautens, T. Rovis, *Tetrahedron* **1999**, *55*, 8967–8976; d) G.-C Ge, C.-H. Ding, X.-L. Hou, *Org. Chem. Front.* **2014**, *1*, 382–385.
[3] a) M. Lautens, K. Fagnou, S. Hierbert, *Acc. Chem. Res.* **2003**, *36*, 48–58; b) R. Boutin, S. Koh, W. Tam, *Curr. Org. Synth.* **2019**, *16*, 460–484; c) M. Pineschi, *Eur. J. Org. Chem.* **2020**, *2020*, 2643–2649.
[4] a) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49–92; b) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2015**, *115*, 5366–5412.
[5] For selected examples of asymmetric [2 + 2] cycloadditions of oxa- and azabenzonorbornadienes and alkynes, see: a) D.-J. Huang, D. K. Rayabarapu, L.-P. Li, T. Sambaiah, C.-H. Cheng, *Chem. Eur. J.* **2000**, *6*, 3706–3713; b) B.-M. Fan, X.-J. Li, F.-Z. Peng, H.-B. Zhang, A. S. C. Chan, Z.-H. Shao, *Org. Lett.* **2010**, *12*, 304–306; c) D. Kossler, F. G. Perrin, A. A. Suleymanov,

G. Kiefer, R. Scopelliti, K. Severin, N. Cramer, *Angew. Chem. Int. Ed.* **2017**, *56*, 11490–11493; d) J. Chen, X. Xu, Z. He, H. Qin, W. Sun, B. Fan, *Adv. Synth. Catal.* **2018**, *360*, 427–431.

[6] J. Ni, J. Chen, Y. Zhou, G. Wang, S. Li, Z. He, W. Sun, B. Fan, *Adv. Synth. Catal.* **2019**, *361*, 3542–3547.

[7] For non-enantioselective 1,3-dipolar cycloadditions with oxa- and azabenzonorbornadienes, see: a) J. R. Nagireddy, E. Carlson, W. Tam, *Can. J. Chem.* **2014**, *92*, 1053–1058; b) S. Kumaran, R. Saritha, P. Gurumurthy, K. Parthasarathy, *Eur. J. Org. Chem.* **2020**, *2020*, 2725–2729.

[8] For some general reviews on 1,3-dipolar cycloadditions with azomethine imines, see: a) A. Padwa, S. Bur, *Chem. Heterocycl. Compd.* **2016**, *52*, 616–626; b) C. Nájera, J. M. Sansano, M. Yus, *Org. Biomol. Chem.* **2015**, *13*, 8596–8636; c) M. de Gracia Retamosa, E. Matador, D. Monge, J. M. Lassaletta, R. Fernández, *Chem. Eur. J.* **2016**, *22*, 13430–1344.; For some examples on (3 + 2) cycloadditions with hydrazones, see: d) S. Kobayashi, H. Shimizu, Y. Yamashita, H. Ishitani, J. Kobayashi, *J. Am. Chem. Soc.* **2002**, *124*, 13678–13679; e) Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 11279–11282; f) L. J. Rono, H. G. Yayla, D. Y. Wang, M. F. Armstrong, R. R. Knowles, *J. Am. Chem. Soc.* **2013**, *135*, 17735–17738; g) W. Dai, H. Lu, X.-L. Jiang, T.-T. Gao, F. Shi, *Tetrahedron* **2015**, *71*, 109–117; h) N. Zabaleta, U. Uria, E. Reyes, L. Carrillo, J. L. Vicario, *Chem. Commun.* **2018**, *54*, 8905–8908; i) B. Yang, J. Dai, Y. Luo, K. K. Lau, Y. Lan, Z. Shao, Y. Zhao, *J. Am. Chem. Soc.* **2021**, *143*, 4179–4186; j) J. Sendra, E. Reyes, L. Prieto, E. Fernández, J. L. Vicario, *Org. Lett.* **2021**, *23*, 8738–8743.

[9] a) O. V. Serdyuk, A. Zamfir, F. Hampel, S. B. Tsogoeva, *Adv. Synth. Catal.* **2012**, *354*, 3115–3121; b) M. Rueping, M. S. Maji, H. B. Küçük, I. Atodiresei, *Angew. Chem. Int. Ed.* **2012**, *51*, 12864–12868; c) X. Hong, H. B. Küçük, M. S. Maji, Y.-F. Yang, M. Rueping, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 13769–13780; d) F. E. Held, D. Grau, S. B. Tsogoeva, *Molecules* **2015**, *20*, 16103–16126; For selected reviews on the use of chiral Brønsted acid and chiral phosphoric acids, see: e) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *J. Am. Chem. Soc.* **2014**, *114*, 9047–9153; f) R. Maji, S. C. Mallojjala, S. E. Wheeler, *Chem. Soc. Rev.* **2018**, *47*, 1142–1158; g) E. I. Jiménez, *Org. Biomol. Chem.* **2023**, *21*, 3477–3502.

[10] Deposition number CCDC 2243297 contains the supplementary crystallographic data for compound **4 b**. See Supporting Information.

[11] For examples of spontaneous oxidation of pyrazolidines to pyrazolines, see: a) F. Jakob, E. Herdtweck, T. Bach, *Chem. Eur. J.* **2010**, *16*, 7537–7546; b) A. O. Chagarocskiy, V. V. Kuznetsov, O. A. Ivanova, A. S. Goloveshkin, I. I. Levina, N. N. Makhova, I. V. Trushkov, *Eur. J. Org. Chem.* **2019**, 5475–5485. For thermal or photochemical oxidations, see: c) N. C. Giampietro, J. P. Wolfe, *J. Am. Chem. Soc.* **2008**, *130*, 12907–12911; d) N. Petek, U. Grošelj, J. Svete, F. Požgan, D. Kočar, B. Štefane, *Catalysis* **2020**, *10*, 981–990.

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