JOC The Journal of Organic Chemistry

Brief Communication

pubs.acs.org/joc

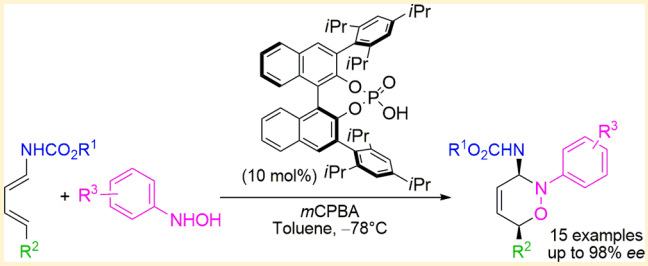
Asymmetric Oxidative Nitroso-Diels–Alder Reaction of *N*-Arylhydroxylamines Catalyzed by a Chiral Phosphoric Acid

Audrey Dumoulin and Géraldine Masson*,†

Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Sud, Université Paris-Saclay, 1, av de la Terrasse, 91198 Gif-sur-Yvette Cedex, France

Supporting Information

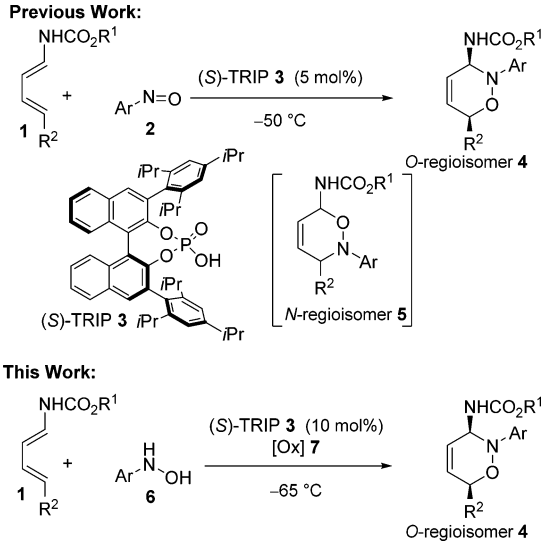
ABSTRACT: A highly stereoselective synthesis of *cis*-3,6-disubstituted dihydro-1,2-oxazines has been accomplished through the one-pot oxidative nitroso-Diels–Alder reaction of *N*-arylhydroxylamines with diene carbamates. The new system is based on a combination of chiral phosphoric acid and *m*-CPBA and gives various 3,6-disubstituted dihydro-1,2-oxazines in excellent regio-, diastereo-, and enantioselectivity.



3,6-Dihydro-1,2-oxazines are important motifs found in many biologically active compounds and can serve as key intermediates for the synthesis of naturals products.[1] While various methods may be envisaged, the nitroso Diels–Alder (NDA) reaction is without a doubt one of the most powerful methods to prepare such heterocycles.[2] Although efficient catalytic enantioselective versions using chiral Lewis[3] or Brønsted acid catalysts[4] have been recently reported, this NDA reaction suffers from drawbacks such as a low availability and stability of nitroso compounds.[1,2,5] Such problems can often be overcome using the procedure in which the nitroso compound is formed from a hydroxylamine derivative under oxidative conditions.[6] Despite numerous attempts to carry out an enantioselective oxidative NDA reaction,[3,4] only limited success has been achieved, thereby highlighting the difficulties of combining an oxidant and a chiral catalyst in the same reaction vessel. In 2005, Shea et al. reported that a catalytic amount of a chiral ruthenium salen complex catalyst was capable of promoting intramolecular tandem oxidative NDA reaction of an *N*-acylhydroxylamine to afford the cycloadduct in moderate enantioselectivity.[7a] This approach nevertheless has been found to be considerably less effective in the asymmetric intermolecular oxidative version, presumably due to the background (uncatalyzed) reaction.[5c,7b]

Recently, we described that (*S*)-TRIP (**3**)[8] was an efficient catalyst for the asymmetric NDA reaction of diene carbamates **1** and nitrosoarenes **2**, affording *cis*-3,6-disubstituted dihydro-1,2-oxazines **4** in high yields with excellent regio-, diastereo-, and enantioselectivities.[4a] Interestingly, the mechanism studies have shown that the catalyst **3** could control the stereoselectivity but also was able to reverse the regioselectivity of the uncatalyzed nitroso-Diels–Alder reaction, thus leading to the racemic 3,6-dihydro-2*H*-1,2-oxazin-6-amine **5** (Scheme 1, eq 1).[7,9] On the basis of our previous discoveries, we reasoned that the appropriate oxidant combined with chiral phosphoric acid may allow us to develop an enantioselective one-pot oxidative NDA reaction of diene carbamates **1** and *N*-arylhydroxylamines **6** (Scheme 1, eq 2). Indeed, the regioselective control by the phosphoric acid catalyst should ensure high enantioselectivity for 3,6-dihydro-2*H*-1,2-oxazin-3-amine **4**. We report herein the first asymmetric one-pot oxidative NDA reaction of *N*-aryl using catalytic amounts of chiral phosphoric in combination with a stoichiometric amount of oxidant **7** (Scheme 1, eq 2).

Scheme 1. TRIP-Catalyzed Enantioselective Synthesis of 1,6-dihydro-1,2-oxazines 4



The choice of oxidant is very crucial for the success of this one-pot enantioselective oxidative transformation. It has to

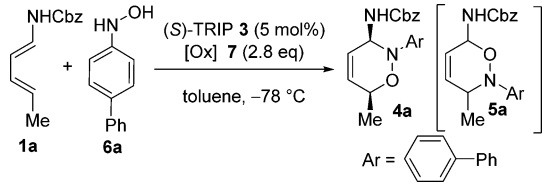
Special Issue: Heterocycles

Received: May 25, 2016
Published: June 23, 2016

DOI: 10.1021/acs.joc.6b01256
J. Org. Chem. 2016, 81, 10154–10159

satisfy the following criteria: (a) be compatible with the conditions of enantioselective NDA reaction, (b) be able to selectively oxidize the *N*-arylhydroxylamine **6** in the presence of the oxidizable diene carbamate **1**,[10] and (c) prevent the overoxidation and/or dimerization of *N*-arylhydroxylamine **6**.[5,6] For this purpose, a number of organic oxidizing agents were tested (see the Supporting Information). We initially examined the reaction of benzyl (penta-1,3-dien-1-yl)carbamate **1a** and *N*-biphenyl-4-ylhydroxylamine **6a** in the presence of 5 mol % of (*S*)-TRIP **3** and a stoichiometric amount of oxidant in toluene at −78 °C. Unfortunately, no reaction took place when oxidants such as $NaIO_4$, Bu_4NIO_4, IBX, and $PhI(OAc)_2$ were used (see the Supporting Information). To our delight, use of *m*-CPBA afforded the desired benzyl (6-methyl-3,6-dihydro-2*H*-1,2-oxazin-3-yl)carbamate (**4a**) with excellent diastereo- and enantioselectivity, although without regioselectivity (**4a**/**5a** = 1:1, Table 1, entry 1). Control experiments indicated that, the

Table 1. Survey of Reaction Conditions[a]



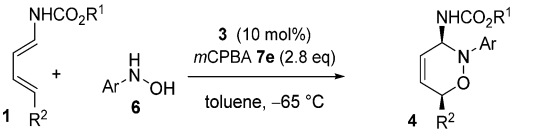
entry	7	time (d)	4a:5a rr[b]	4a yield[c] (%)	4a ee[d] (%)	5a yield[c] (%)
1	*m*-CPBA	1	1:1	36	93	39
2	*m*-CPBA	1	0:1	0		>95[e,f]
3	*m*-CPBA	3	1:0	56	96	0
4	*m*-CPBA	3	1:0	68[g,h]	96	0

[a]General conditions: **6a** (0.15 mmol) and *m*-CPBA **7** (0.14 mmol) for 10 min at rt, then **4** (0.0025 mmol) and **1a** (0.05 mmol) were added. [b]Regioisomer ratio determined by crude ^{1}H NMR. [c]Yields refer to chromatographically pure product. [d]Determined by HPLC analysis on chiral stationary phases. [e]Reaction performed without **3**. [f]No product was formed at −78 °C. [g]Reaction performed at −65 °C. [h]Reaction performed with 10 mol % of **3**.

phosphoric acid and the temperature were important factors for controlling the regioselectivity of this NDA reaction. In the absence of **3**, no cycloaddition occurred at −78 °C, and only the benzyl-(3,6-dihydro-2*H*-1,2-oxazin-6-yl)carbamate **5a** was isolated when the reaction was warmed at room temperature (entry 2). Therefore, the presence of remaining diene carbamate **1a** in the reaction mixture after 24 h suggested the possibility of improving the yield of **4a** by simply increasing the reaction time. Indeed, under the same conditions of entry 5, but after 3 days, the yield of 3,6-dihydro-1,2-oxazines **4a** was enhanced from 36 to 56% (entry 3). Under these conditions, we could avoid the formation of **5a**. Pleasingly, increasing the amount of (*S*)-TRIP catalyst **3** to 10 mol % and raising the temperature from −78 to −65 °C gave better results, leading to the desired NDA cycloadduct **4a** in 68% yield with 96% ee (entry 4).

The substrate scope and the generality of this enantioselective oxidative NDA reaction were then evaluated (Table 2). Pleasingly, all of the *N*-arylhydroxylamines **6**, regardless of their electronic properties, proceeded smoothly to afford the expected cis-1,6-dihydro-1,2-oxazines **4b**−**g** in moderate to good yields with excellent diastereo- and enantioselectivity (entries 1−6). Remarkably, when the reaction was scaled up to

Table 2. Substrate Scope of the Enantioselective Synthesis of 1,6-Dihydro-1,2-oxazines 4[a]



entry	R^1/ R^2	Ar	Product/ 4	yield (%)[b]	ee (%)[c]
1	Bn/Me		**4b**	68	94
2	Bn/Me		**4c**	69	93
3	Bn/Me		**4d**	57	93
4	Bn/Me		**4e**	65	94
5	Bn/Me		**4f**	60	96
6	Bn/Me		**4g**	47 (62)[d]	96 (94)[d]
7	Bn/Me		**4h**	47	96
8	Bn/Me		**4i**	43	96
9	Bn/Ph		**4j**	77	97
10	All/Me		**4k**	55	97
11	All/Me		**4l**	54	94
12			**4m**	52	99
13			**4n**	52	96
14			**4o**	51	94

[a]General conditions: **6a** (0.15 mmol) and *m*-CPBA **7** (0.14 mmol) for 10 min at rt, then **4** (0.0025 mmol) and **1a** (0.05 mmol) added at −65 °C. [b]Yields referred to chromatographically pure product. [c]Determined by HPLC analysis on chiral stationary phases. [d]Reaction performed on 1.0 mmol scale (c = 0.25 M).

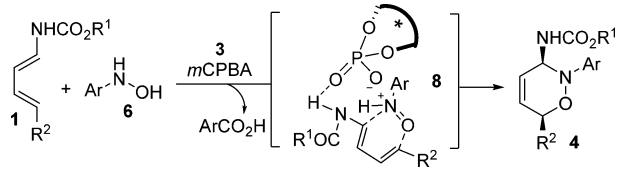
20 times, the product yield was higher (entry 6). The corresponding cycloadducts **4h**,**i** were also obtained in excellent enantiomeric excess with *N*-fluorenylhydroxylamine **6h** and *β*-naphthylhydroxylamine **6i** as the dienophile precursors. Unfortunately, the oxidative NDA reaction failed with hydroxylamine bearing a 5-memebered azacycle such as *N*-Boc-4-(hydroxyamino)-1*H*-pyrazole. A variety of selected enecarbamates **1b**−**e** reacted with excellent enantioselectivity to afford the desired 3,6-dihydro-2*H*-1,2-oxazin-3-amines **4j**−**o**. For instance, the diene carbamates with a phenyl substituent at the *δ*-position **1b** participated smoothly in this one-pot oxidative process, leading to **4j** in good yield and better enantiomeric excess than in the asymmetric NDA reaction of nitrosoarenes previously reported by our group (entry 9). We also found that various *N*-protecting groups **1c**−**e** were all compatible, leading to the respective 3,6-dihydro-1,2-oxazines **4k**−**o** in moderate to good yields with excellent enantiomeric excess values. The allyloxycarbonyl and 9-fluorenylmethyloxycarbonyl protecting groups on diene carbamates **1c** and **1d** were tolerated, affording the NDA cycloadducts **4k**−**o** whatever

DOI: 10.1021/acs.joc.6b01256
J. Org. Chem. 2016, 81, 10154−10159

the electronic properties of associated *N*-arylhydroxylamines, with moderate yields and high enantioselectivities (entries 10–14). Once again, the product **4m** was obtained in higher enantioselectivity than when the asymmetric NDA reaction starting from the corresponding nitrosoarene was used, showing the potential interest of this new strategy and the complementarity of these two methodologies. Finally, the high chemoselectivity of the present oxidation method is noteworthy; the olefinic double bonds of **1** and **4** are usually left intact.[11]

On the basis of our previous studies[4a] and other reports,[2,3,4b,c] a putative mechanism was postulated in Scheme 2. First, *m*-CPBA oxidizes the *N*-arylhydroxylamine **6** to form

Scheme 2. Activation Model via a Putative Transition State



nitrosoarene **2** and *m*-chlorobenzoic acid. Then, (*S*)-TRIP **3** protonates selectively the nitrogen atom to give ion **8**. Meanwhile, the secondary diene carbamate **1** forms a hydrogen bond with Lewis basic phosphoryl oxygen and is positioned close to the nitrosoarene **2**. Then the cycloaddition occurs to form (3*S*,6*S*)-dihydro-1,2-oxazines **4** exclusively. The excellent enantioselectivity and regioselectivity in this oxidative one-pot reaction observed under our optimized conditions deserve additional comments. Since the phosphoric acids are more acidic than *m*-chlorobenzoic acid,[8a,12] this could ensure the salt formation between nitroso compound **2** and phosphoric acid **3**, thereby controlling the enantioselectivity and regioselectivity of the reaction. In addition, it is worth noting that, despite the formation of a large excess of *m*-chlorobenzoic acid in the reaction media, excellent enantioselectivity was achieved in this oxidative process, thus demonstrating that this weak acid did not disturb the H-bonding interactions between substrates and the phosphoric acid catalyst.[13]

In conclusion, we have presented the first catalytic enantioselective one-pot oxidative NDA reaction of a wide range of *N*-arylhydroxylamines and diene carbamates by combining a chiral phosphoric acid and *m*-CPBA. The operational simplicity of this oxidative procedure makes it a practical protocol for synthesis of functionalized *cis*-3,6-disubstituted dihydro-1,2-oxazines in excellent regio-, diastereo-, and enantioselectivity.

EXPERIMENTAL SECTION

Materials and General Methods. All reactions were carried out under argon atmosphere in oven-dried glassware with magnetic stirring. Reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. All solvents used in the reactions were distilled from appropriate drying agents prior to use. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254. Visualization was accomplished by irradiation with a UV light at 254 nm. Chromatography was performed using silica gel 60 (0.040–0.063 mm). Proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$, δ 7.26 ppm). Some NMR measurements were performed in CD_3CN to minimize signal broadening due to rotamers mixture. Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, h = hexuplet, ht = heptuplet, m = multiplet), coupling constants (Hz), and integration. ^{13}C chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). The characteristic IR absorption frequencies were recorded for neat samples and are reported in cm^{-1}. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer. Enantiomeric excesses were determined by high-performance liquid chromatography (HPLC) equipped with diode array UV detectors using Chiralpak IA and AD-H columns. Arylhydroxylamine compounds and ene carbamates were synthesized according to reported literature procedures.[4a,12] Phosphoric acid catalysts were synthesized according to reported literature procedures.[14]

General Procedure. The aryl hydroxylamine **6** (0.15 mmol, 3.0 equiv) was dissolved in toluene (1.0 mL), and *m*-CPBA (0.14 mmol, 2.8 equiv) was added. The mixture was stirred at room temperature for 10 min, (*S*)-TRIP catalyst **3** (0.005 mmol, 10 mol %) was added, and the reaction mixture was cooled to −65 °C. After 5 min at −65 °C, the diene carbamate **1** (0.05 mmol, 1.0 equiv) was added, and the reaction was stirred at this temperature for 3 days. The mixture was quenched with a fresh solution of $Na_2S_2O_3$ and a solution of $NaHCO_3$ and allowed to reach room temperature. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (heptane/EtOAc = 8:2–5:5) to afford the desired products **4a–o**.

Compounds **4a–g,j,k,m** were synthesized and fully characterized in our previous report.[4a]

*Benzyl N-[(3S,6S)-6-Methyl-2-(4-phenylphenyl)-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4a**).* Reaction with 10.9 mg (0.050 mmol) of benzyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 13.6 mg of a colorless oil, 68% yield. $[\alpha]_D^{20}$ −137.5 (*c* 1.0 g/mL, $CHCl_3$). Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 95/5, flow rate 1.0 mL/min, 254 nm): t_{R1} = 14.80 min (major), t_{R2} = 16.07 min (minor). IR (cm^{-1}): 3320, 2968, 1723, 1521, 1209, 1050, 821, 704. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.60–7.51 (m, 4H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.36–7.15 (m, 8H), 5.97 (s, 2H), 5.93–5.83 (m, 0.8H, rot.1), 5.68–5.58 (m, 0.2H, rot.2), 5.44 (d, *J* = 9.9 Hz, 1H), 5.07–4.95 (m, 2H), 4.73 (q, *J* = 6.6 Hz, 1H), 1.33 (d, *J* = 6.8 Hz, 3H). ^1H NMR (CD_3CN, 300 MHz) δ (ppm): 7.69–7.06 (m, 14H), 6.24 (d, *J* = 9.9 Hz, 1H), 6.06–5.89 (m, 2H), 5.89–5.80 (m, 0.8H, rot.1), 5.80–5.70 (m, 0.2H, rot.2), 5.05 (d, AB syst, *J* = 12.6 Hz, 1H), 4.91 (d, AB syst, *J* = 12.6 Hz, 1H), 4.66 (q, *J* = 6.6 Hz, 1H), 1.31 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.7, 145.9, 140.8, 136.2, 135.0, 133.5, 128.7, 128.5, 128.3, 128.1, 127.8, 127.3, 126.7, 124.3, 116.7, 73.9, 66.8, 62.8, 18.5. ESI-HRMS (positive ion): $C_{25}H_{25}N_2O_3$ ($[M + H]^+$) requires 401.1860, found 401.1872.

*Benzyl N-[(3S,6S)-2-(4-Fluorophenyl)-6-methyl-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4b**).* Reaction with 10.9 mg (0.050 mmol) of benzyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 11.6 mg of a colorless oil, 68% yield. $[\alpha]_D^{20}$ −137.2 (*c* 0.5 g/mL, $CHCl_3$). Enantiomeric excess: 94%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 254 nm): t_{R1} = 6.13 min (major), t_{R2} = 13.38 min (minor). IR (cm^{-1}): 3318, 2966, 1705, 1509, 1217, 1037, 813, 694. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.40–7.27 (m, 3H), 7.21–7.07 (m, 4H), 6.96 (t, *J* = 8.7 Hz, 2H), 6.03–5.86 (m, 2H), 5.75–5.62 (m, 1H), 5.50–5.41 (m, 0.2H, rot.1), 5.35 (d, *J* = 10.0 Hz, 0.8H, rot.2), 5.01 (d, AB syst, *J* = 12.2 Hz, 1H), 4.91 (d, AB syst, *J* = 12.2 Hz, 1H), 4.68 (q, *J* = 6.8 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 3H). ^1H NMR (CD_3CN, 300 MHz) δ (ppm): 7.44–7.24 (m, 3H), 7.22–7.07 (m, 4H), 6.99 (t, *J* = 8.7 Hz, 2H), 6.19 (d, *J* = 9.0 Hz, 1H), 6.03–5.87 (m, 2H), 5.72–5.54 (m, 1H), 5.01 (d, AB syst, *J* = 12.9 Hz, 1H), 4.86 (d, AB syst, *J* = 12.9 Hz, 1H), 4.62 (q, *J* = 6.6 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.8 (d, *J* = 240.9 Hz), 155.6, 142.8, 136.2, 133.6, 128.5, 128.1, 127.8, 124.2, 118.6 (d, *J* = 7.8 Hz), 115.2

DOI: 10.1021/acs.joc.6b01256
J. Org. Chem. 2016, 81, 10154–10159

(d, J = 22.4 Hz), 74.0, 66.8, 63.8, 18.5. ESI-HRMS (positive ion): $C_{19}H_{20}FN_2O_3$ ($[M + H]^+$) requires 343.1452, found 343.1467.

*Benzyl N-[(3S,6S)-2-(4-Chlorophenyl)-6-methyl-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4c**).* Reaction with 10.9 mg (0.050 mmol) of benzyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 12.4 mg of a colorless oil, 69% yield. $[\alpha]_D^{20}$ −116.2 (*c* 0.5 g/mL, $CHCl_3$). Enantiomeric excess: 93%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 280 nm): t_{R1} = 6.51 min (major), t_{R2} = 13.06 min (minor). IR (cm^{-1}): 3311, 2974, 1716, 1509, 1222, 1038, 816, 698. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.45−7.00 (m, 9H), 6.11−5.84 (m, 2H), 5.84−5.64 (m, 0.8H, rot.1), 5.55−5.45 (m, 0.2H, rot.2), 5.37 (d, J = 10.0 Hz, 1H), 5.03 (d, AB syst, J = 12.3 Hz, 1H), 4.93 (d, AB syst, J = 12.3 Hz, 1H), 4.68 (q, J = 6.7 Hz, 1H), 1.29 (d, J = 6.8 Hz, 3H). ^{1}H NMR (CD_3CN, 300 MHz) δ (ppm): 7.44−7.00 (m, 9H), 6.22 (d, J = 9.3 Hz, 1H), 6.04−5.86 (m, 2H), 5.80−5.62 (m, 1H), 5.05 (d, AB syst, J = 12.9 Hz, 1H), 4.87 (d, AB syst, J = 12.9 Hz, 1H), 4.63 (q, J = 6.9 Hz, 1H), 1.28 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.6, 145.2, 136.1, 133.5, 128.6, 128.5, 128.1, 127.8, 127.4, 124.1, 117.9, 74.0, 66.8, 63.1, 18.4. ESI-HRMS (positive ion): $C_{19}H_{20}ClN_2O_3$ ($[M + H]^+$) requires 359.1157, found 359.1143.

*Benzyl N-[(3S,6S)-2-(4-Bromophenyl)-6-methyl-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4d**).* Reaction with 10.9 mg (0.050 mmol) of benzyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 11.5 mg of a colorless oil, 57% yield. $[\alpha]_D^{20}$ −77.1 (*c* 1.0 g/mL, $CHCl_3$). Enantiomeric excess: 93%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 254 nm): t_{R1} = 6.79 min (major), t_{R2} = 13.49 min (minor). IR (cm^{-1}): 3314, 2979, 1725, 1505, 1209, 1035, 825, 702. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.47−7.24 (m, 5H), 7.23−7.10 (m, 2H), 7.05 (d, J = 8.9 Hz, 2H), 6.04−5.85 (m, 2H), 5.81−5.74 (m, 0.8H, rot.1), 5.57−5.48 (m, 0.2H, rot.2), 5.37 (d, J = 10.0 Hz, 1H), 5.03 (d, AB syst, J = 12.0 Hz, 1H), 4.93 (d, AB syst, J = 12.0 Hz, 1H), 4.68 (q, J = 6.8 Hz, 1H), 1.29 (d, J = 6.8 Hz, 3H). ^{1}H NMR (CD_3CN, 300 MHz) δ (ppm): 7.44−7.98 (m, 9H), 6.23 (d, J = 9.0 Hz, 1H), 6.04−5.86 (m, 2H), 5.81−5.65 (m, 1H), 5.06 (d, AB syst, J = 12.9 Hz, 1H), 4.88 (d, AB syst, J = 12.9 Hz, 1H), 4.62 (q, J = 6.6 Hz, 1H), 1.28 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.7, 145.7, 136.1, 133.5, 131.5, 128.5, 128.2, 127.8, 124.1, 118.2, 115.0, 74.0, 66.9, 62.9, 18.4. ESI-HRMS (positive ion): $C_{19}H_{20}BrN_2O_3$ ($[M + H]^+$) requires 403.0652, found 403.0644.

*Benzyl N-[(3S,6S)-2-(4-Iodophenyl)-6-methyl-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4e**).* Reaction with 10.9 mg (0.050 mmol) of benzyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 14.6 mg of colorless oil, 65% yield. $[\alpha]_D^{20}$ −111.1 (*c* 1.0 g/mL, $CHCl_3$). Enantiomeric excess: 94%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 254 nm): t_{R1} = 7.16 min (major), t_{R2} = 13.45 min (minor). IR (cm^{-1}): 3313, 2966, 1715, 1512, 1217, 1037, 814, 693. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.57 (d, J = 8.8 Hz, 2H), 7.39−7.30 (m, 3H), 7.24−7.15 (m, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.04−5.90 (m, 2H), 5.84−5.75 (m, 0.8H, rot.1), 5.59−5.47 (m, 0.2H, rot.2), 5.37 (d, J = 10.0 Hz, 1H), 5.05 (d, AB syst, J = 12.3 Hz, 1H), 4.94 (d, AB syst, J = 12.3 Hz, 1H), 4.69 (q, J = 6.8 Hz, 1H), 1.30 (d, J = 6.8 Hz, 3H). ^{1}H NMR (CD_3CN, 300 MHz) δ (ppm): 7.56 (d, J = 8.4 Hz, 2H), 7.40−7.25 (m, 3H), 7.21−7.11 (m, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.22 (d, J = 9.3 Hz, 1H), 6.03−5.86 (m, 2H), 5.81−5.66 (m, 1H), 5.06 (d, AB syst, J = 12.6 Hz, 1H), 4.88 (d, AB syst, J = 12.6 Hz, 1H), 4.62 (q, J = 6.9 Hz, 1H), 1.28 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.7, 146.4, 137.4, 136.1, 133.5, 128.6, 128.2, 127.8, 124.1, 118.5, 85.2, 74.0, 66.9, 62.7, 18.4. ESI-HRMS (positive ion): $C_{19}H_{20}IN_2O_3$ ($[M + H]^+$) requires 451.0513, found 451.0521.

*Benzyl N-[(3S,6S)-6-Methyl-2-(4-methylphenyl)-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4f**).* Reaction with 10.9 mg (0.050 mmol) of benzyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 10.2 mg of a colorless oil, 60% yield. $[\alpha]_D^{20}$ − 83.6 (*c* 0.5 g/mL, $CHCl_3$). Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 254 nm): t_{R1} = 5.97 min (major), t_{R2} = 8.94 min (minor). IR (cm^{-1}): 3313, 2968, 1711, 1515, 1212, 1043, 808, 699. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.44−7.28 (m, 3H), 7.24−6.97 (m, 6H), 5.96 (s, 2H), 5.77 (d, J = 10.0 Hz, 0.8H, rot.1), 5.56−5.45 (m, 0.2H, rot.2), 5.38 (d, J = 9.8 Hz, 1H), 5.08−4.90 (m, 2H), 4.70 (q, J = 6.6 Hz, 1H), 2.32 (s, 3H), 1.31 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.6, 144.2, 136.3, 133.5, 131.8, 129.2, 128.4, 128.0, 127.8, 124.4, 116.7, 73.8, 66.7, 63.3, 20.7, 18.5. ESI-HRMS (positive ion): $C_{20}H_{23}N_2O_3$ ($[M + H]^+$) requires 339.1703, found 339.1713.

*Benzyl N-[(3S,6S)-6-Methyl-2-phenyl-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4g**).* Reaction with 10.9 mg (0.050 mmol) of benzyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 7.6 mg of a colorless oil, 47% yield. $[\alpha]_D^{20}$ −102.8 (*c* 0.5 g/mL, $CHCl_3$). Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 254 nm): t_{R1} = 6.03 min (major), t_{R2} = 13.91 min (minor). IR (cm^{-1}): 3314, 2976, 1717, 1511, 1217, 1036, 816, 696. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.34−7.24 (m, 5H), 7.22−7.12 (m, 4H), 6.99 (t, J = 7.2 Hz, 1H), 6.00−5.90 (m, 2H), 5.84−5.77 (m, 0.8H, rot.1), 5.64−5.55 (m, 0.2H, rot.2), 5.38 (d, J = 9.9 Hz, 1H), 5.07−4.89 (m, 2H), 4.75−4.85 (m, 1H), 1.30 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.7, 146.5, 136.3, 133.5, 128.7, 128.5, 128.0, 127.8, 124.3, 122.4, 116.5, 73.9, 66.7, 63.1, 18.5. ESI-HRMS (positive ion): $C_{19}H_{21}N_2O_3$ ($[M + H]^+$) requires 325.1547, found 325.1558.

*Benzyl N-[(3S,6S)-2-(9H-Fluoren-2-yl)-6-methyl-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4h**).* Reaction with 10.9 mg (0.050 mmol) of benzyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 12.2 mg of a colorless oil, 59% yield. $[\alpha]_D^{20}$ −96.1 (*c* 1.0 g/mL, $CHCl_3$). Enantiomeric excess: 93%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 254 nm): t_{R1} = 8.34 min (minor), t_{R2} = 9.49 min (major). IR (cm^{-1}): 3318, 2986, 1715, 1492, 1218, 1046, 762, 696. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.77−7.63 (m, 2H), 7.51 (d, J = 7.5 Hz, 1H), 7.42−7.03 (m, 9H), 5.98 (s, 2H), 5.85 (d, J = 10.2 Hz, 0.8H, rot.1), 5.60 (d, J = 9.9 Hz, 0.2H, rot.2), 5.41 (d, J = 9.9 Hz, 1H), 4.99 (d, AB syst, J = 12.3 Hz, 1H), 4.89 (d, AB syst, J = 12.3 Hz, 1H), 4.73 (q, J = 7.2 Hz, 1H), 3.82 (s, 2H), 1.33 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.8, 146.0, 144.2, 143.2, 141.9, 136.6, 136.3, 133.6, 128.7, 128.5, 128.3, 128.0, 127.8, 126.8, 125.9, 125.0, 124.5, 120.1, 119.0, 115.8, 113.6, 74.1, 66.8, 63.7, 37.2, 18.7. ESI-HRMS (positive ion): $C_{26}H_{25}N_2O_3$ ($[M + H]^+$) requires 413.1860, found 413.1872.

*Benzyl N-[(3S,6S)-6-Methyl-2-(naphthalen-2-yl)-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4i**).* Reaction with 10.9 mg (0.050 mmol) of benzyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 8.1 mg of a colorless oil, 43% yield. $[\alpha]_D^{20}$ −108.2 (*c* 0.5 g/mL, $CHCl_3$). Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 254 nm): t_{R1} = 6.99 min (major), t_{R2} = 7.63 min (minor). IR (cm^{-1}): 3316, 2976, 1714, 1496, 1218, 1036, 745, 697. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.84−7.70 (m, 3H), 7.62−7.50 (m, 1H), 7.49−7.30 (m, 4H), 7.22−6.96 (m, 4H), 6.05−5.91 (m, 2H), 5.72 (d, J = 9.3 Hz, 0.2H, rot.2), 5.43 (d, J = 9.3 Hz, 0.8H, rot.1), 4.95 (d, AB syst, J = 12.6 Hz, 1H), 4.86 (d, AB syst, J = 12.6 Hz, 1H), 4.75 (q, J = 6.9 Hz, 1H), 1.36 (d, J = 6.6 Hz, 2.8H, rot.1), 1.26 (br s, 0.8H, rot.2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.7, 144.3, 136.3, 134.1, 133.7, 130.0, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 126.3, 124.4, 124.3, 117.9, 112.5, 74.1, 66.8, 63.3, 18.7. ESI-HRMS (positive ion): $C_{23}H_{22}N_2O_3Na$ ($[M + Na]^+$) requires 397.1523, found 397.1523.

*Benzyl N-[(3S,6R)-2,6-Diphenyl-3,6-dihydro-2H-1,2-oxazin-3-yl]-carbamate (**4j**).* Reaction with 14.1 mg (0.050 mmol) of benzyl ((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)carbamate (**1b**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 14.8 mg of a colorless oil, 77% yield. $[\alpha]_D^{20}$ −20.2 (*c* 1.0 g/mL, $CHCl_3$). Enantiomeric excess: 97%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 95/5, flow rate 1.0 mL/min, 254 nm): t_{R1} = 12.96

DOI: 10.1021/acs.joc.6b01256
J. Org. Chem. 2016, 81, 10154−10159

min (major), t_{R2} = 16.56 min (minor). IR (cm^{-1}): 3316, 2978, 1719, 1523, 1215, 1042, 822, 699. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.43 (s, 6H), 7.37−7.27 (m, 4H), 7.23−7.14 (m, 4H), 7.02 (t, J = 7.1 Hz, 1H), 6.22−6.13 (m, 2H), 6.01−5.87 (m, 1H), 5.63 (s, 1H), 5.50 (d, J = 9.9 Hz, 1H), 5.11−4.92 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.7, 146.5, 137.4, 136.2, 131.7, 128.9, 128.7, 128.7, 128.5, 128.1, 128.0, 127.8, 125.4, 122.6, 116.7, 80.1, 66.8, 63.3. ESI-HRMS (positive ion): $C_{24}H_{23}N_2O_3$ ($[M + H]^+$) requires 387.1703, found 387.1702.

*Prop-2-en-1-yl N-[(3S,6S)-6-Methyl-2-phenyl-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4k**).* Reaction with 8.4 mg (0.050 mmol) of allyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1d**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 7.5 mg of a colorless oil, 55% yield. $[\alpha]_D^{20}$ −90.2 (*c* 0.5 g/mL, $CHCl_3$). Enantiomeric excess: 97%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 254 nm): t_{R1} = 4.79 min (major), t_{R2} = 6.83 min (minor). IR (cm^{-1}): 3323, 2974, 1723, 1521, 1247, 1049, 824, 712. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.32−7.25 (m, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.01−6.94 (m, 1H), 6.05−5.93 (m, 2H), 5.85−5.73 (m, 1.7H, rot.1), 5.61−5.50 (m, 0.3H, rot.2), 5.36−5.28 (m, 1H), 5.18−5.09 (m, 2H), 4.72 (q, J = 6.7 Hz, 0.8H, rot.1), 4.58−4.50 (m, 0.2H, rot.2), 4.46 (d, J = 5.4 Hz, 2H), 1.34 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.5, 146.5, 133.5, 132.5, 128.7, 124.4, 122.4, 117.5, 116.4, 73.9, 65.6, 62.9, 18.5. ESI-HRMS (positive ion): $C_{15}H_{19}N_2O_3$ ($[M + H]^+$) requires 275.1390, found 275.1385.

*Prop-2-en-1-yl N-[(3S,6S)-2-(4-Iodophenyl)-6-methyl-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4l**).* Reaction with 8.4 mg (0.050 mmol) of allyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1d**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 10.8 mg of colorless oil, 54% yield. $[\alpha]_D^{20}$ −90.4 (*c* 0.5 g/mL, $CHCl_3$). Enantiomeric excess: 94%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 254 nm): t_{R1} = 5.93 min (major), t_{R2} = 9.09 min (minor). IR (cm^{-1}): 3315, 1707, 1584, 1486, 1228, 1036, 821. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.56 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.02−5.85 (m, 2H), 5.85−5.68 (m, 1.7H, rot.1), 5.62−5.47 (m, 0.3H, rot.2), 5.40−5.27 (m, 1H), 5.19−5.05 (m, 1H), 4.67 (q, J = 6.6 Hz, 0.8H, rot.1), 4.62−4.54 (m, 0.2H, rot.2), 4.45 (d, J = 5.1 Hz, 2H), 1.30 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.6, 146.6, 137.6, 133.6, 132.4, 124.2, 118.6, 117.8, 85.4, 74.1, 65.9, 62.8, 18.5. ESI-HRMS (positive ion): $C_{15}H_{18}IN_2O_3$ ($[M + H]^+$) requires 401.0357, found 401.0353.

*9H-Fluoren-9-ylmethyl N-[(3S,6S)-6-Methyl-2-phenyl-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4m**).* Reaction with 15.2 mg (0.050 mmol) of (9*H*-fluoren-9-yl)methyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1e**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 10.7 mg of a colorless oil, 52% yield. $[\alpha]_D^{20}$ −108.0 (*c* 0.5 g/mL, $CHCl_3$). Enantiomeric excess: 99%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 254 nm): t_{R1} = 5.85 min (major), t_{R2} = 9.95 min (minor). IR (cm^{-1}): 3329, 2981, 1718, 1512, 1235, 1029, 817, 692. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.73 (d, J = 7.6 Hz, 2H), 7.52−7.16 (m, 10H), 6.94 (t, J = 7.1 Hz, 1H), 6.07−5.92 (m, 2H), 5.87−5.81 (m, 0.8H, rot.1), 5.74−5.62 (m, 0.2H, rot.2), 5.41 (d, J = 9.9 Hz, 0.8H, rot.1), 5.32−5.21 (m, 0.2H, rot.2), 4.73 (q, J = 6.6 Hz, 0.8H, rot.1), 4.67−4.57 (m, 0.2H, rot.2), 4.43−4.29 (m, 1H), 4.18−3.99 (m, 2H), 1.36 (d, J = 6.9 Hz, 2.7H, rot.1), 1.30−1.21 (m, 0.3H, rot.2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.7, 133.6, 128.7, 127.7, 127.6, 127.1, 127.0, 125.3, 125.0, 124.4, 122.5, 119.9, 116.5, 73.9, 67.1, 63.1, 47.0, 18.5. ESI-HRMS (positive ion): $C_{26}H_{25}N_2O_3$ ($[M + H]^+$) requires 413.1860, found 413.1873.

*9H-Fluoren-9-ylmethyl N-[(3S,6S)-2-(4-Bromophenyl)-6-methyl-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4n**).* Reaction with 15.2 mg (0.050 mmol) of (9*H*-fluoren-9-yl)methyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1e**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 12.9 mg of a colorless oil, 52% yield. $[\alpha]_D^{20}$ − 82.6 (*c* 0.5 g/mL, $CHCl_3$). Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 254 nm): t_{R1} = 7.11 min (major), t_{R2} = 14.99 min (minor). IR (cm^{-1}): 3315, 2983, 1712, 1518, 1243, 1487, 1229, 1034, 816, 696. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.74 (d, J = 7.5 Hz, 2H), 7.50−7.18 (m, 8H), 7.05 (d, J = 9.0 Hz, 2H), 6.04−5.87 (m, 2H), 5.79 (dd, J = 9.9 Hz and J = 3.9 Hz, 0.8H, rot.1), 5.64−5.49 (m, 0.2H, rot.2), 5.34 (d, J = 9.6 Hz, 0.8H, rot.1), 5.15−5.01 (m, 0.2H, rot.2), 4.70 (q, J = 6.9 Hz, 0.8H, rot.1), 4.64−4.52 (m, 0.2H, rot.2), 4.43−4.31 (m, 1H), 4.26−4.06 (m, 2H), 1.34 (d, J = 6.6 Hz, 2.7H, rot.1), 1.29−1.20 (m, 0.3H, rot.2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.9, 145.8, 143.8, 143.7, 141.4, 141.3, 133.7, 131.7, 127.9, 127.8, 127.2, 127.1, 125.1; 125.0, 124.2, 120.1, 120.0, 118.1, 115.1, 74.2, 67.2, 62.9, 47.1, 18.5. ESI-HRMS (positive ion): $C_{26}H_{24}BrN_2O_3$ ($[M + Na]^+$) requires 491.0965, found 491.0958.

*(Pentafluorophenyl)methyl N-[(3S,6S)-6-Methyl-2-phenyl-3,6-dihydro-2H-1,2-oxazin-3-yl]carbamate (**4o**).* Reaction with 15.2 mg (0.050 mmol) of (perfluorophenyl)methyl ((1*E*,3*E*)-penta-1,3-dien-1-yl)carbamate (**1f**). Eluent for the preparative TLC: heptane/ethyl acetate 8/2 to 5/5 to afford 10.6 mg of a colorless oil, 51% yield. $[\alpha]_D^{20}$ −68.6 (*c* 0.5 g/mL, $CHCl_3$). Enantiomeric excess: 94%, determined by HPLC (Daicel Chiralpak IA, heptane/EtOH = 80/20, flow rate 1.0 mL/min, 254 nm): t_{R1} = 5.10 min (minor), t_{R2} = 5.83 min (major). IR (cm^{-1}): 3319, 2983, 1714, 1523, 1224, 1038, 809, 701. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.30−7.21 (m, 2H), 7.14 (d, J = 7.8 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H), 6.03−5.90 (m, 2H), 5.79−5.71 (m, 0.8H, rot.1), 5.51−5.40 (m, 0.2H, rot.2), 5.36 (d, J = 9.8 Hz, 1H), 5.13−5.00 (m, 2H), 4.70 (q, J = 6.7 Hz, 1H), 1.32 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.7, 146.4, 133.8, 128.5, 124.0, 122.5, 116.7, 73.9, 63.5, 53.7, 18.4. ESI-HRMS (positive ion): $C_{19}H_{15}F_5N_2O_3$ ($[M + H]^+$) requires 415.1076, found 415.1069.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01256.

Characterization of new compounds and selected NMR and HPLC spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: geraldine.masson@cnrs.fr.

Notes

The authors declare no competing financial interest.

†ISHC member.

■ ACKNOWLEDGMENTS

A.D. thanks ICSN and CNRS for financial support and doctoral fellowships.

■ REFERENCES

(1) For selected reviews on the synthetic applications of nitroso Diels−Alder products, see: (a) Carosso, S.; Miller, M. J. *Org. Biomol. Chem.* **2014**, *12*, 7445. (b) Eschenbrenner-Lux, V.; Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 11146. (c) Bodnar, B. S.; Miller, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5630. (d) Streith, J.; Defoin, A. *Synthesis* **1994**, *1994*, 1107.

(2) For selected reviews of nitroso Diels−Alder reactions, see: (a) Yamamoto, H.; Kawasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595. (b) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, *2006*, 2031. (c) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317. (d) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514. (e) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317. (f) Waldmann, H. *Synthesis* **1994**, *1994*, 535.

(3) (a) Maji, B.; Yamamoto, H. *J. Am. Chem. Soc.* **2015**, *137*, 15957. (b) Jana, C. K.; Grimme, S.; Studer, A. *Chem. - Eur. J.* **2009**, *15*, 9078. (c) Jana, C. K.; Studer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6542. (d) Yamamoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*,

DOI: 10.1021/acs.joc.6b01256
J. Org. Chem. 2016, 81, 10154−10159

7082. (e) Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 4128.
(4) (a) Pous, J.; Courant, T.; Bernadat, G.; Iorga, B. I.; Blanchard, F.; Masson, G. *J. Am. Chem. Soc.* **2015**, *137*, 11950. (b) Momiyama, N.; Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 1190. (c) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962.
(5) (a) Lightfoot, A. P.; Pritchard, R. G.; Wan, H.; Warren, J. E.; Whiting, A. *Chem. Commun.* **2002**, 2072. (b) Quek, S. K.; Lyapkalo, I. M.; Huynh, H. V. *Synthesis* **2006**, *2006*, 1423. (c) Howard, J. A. K.; Ilyashenko, G.; Sparkes, H. A.; Whiting, A.; Wright, A. R. *Adv. Synth. Catal.* **2008**, *350*, 869.
(6) For a recent review, see: (a) Palmer, I. L.; Frazier, C. P.; Read de Alaniz, J. *Synthesis* **2014**, *46*, 269. For recent selected examples, see: (b) Nakashima, E.; Yamamoto, H. *Chem. Commun.* **2015**, *51*, 12309. (c) Frazier, C. P.; Palmer, L. I.; Samoshin, A. V.; Read de Alaniz, J. R. *Tetrahedron Lett.* **2015**, *56*, 3353. (d) Chen, J.-M.; Chang, C.-J.; Ke, Y.-J.; Liu, R.-S. *J. Org. Chem.* **2014**, *79*, 4306. (e) Frazier, C. P.; Bugarin, A.; Engelking, J. R.; Read de Alaniz, J. R. *Org. Lett.* **2012**, *14*, 3620. (f) Chaiyaveij, D.; Cleary, L.; Batsanov, A. S.; Marder, T. B.; Shea, K. J.; Whiting, A. *Org. Lett.* **2011**, *13*, 3442. (g) Frazier, C. P.; Engelking, J. R.; Read de Alaniz, J. *J. Am. Chem. Soc.* **2011**, *133*, 10430.
(7) (a) Chow, C. P.; Shea, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 3678. (b) Flower, K. R.; Lightfoot, A. P.; Wan, H.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2058.
(8) For a recent review on chiral phosphoric acid catalysis, see: (a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (b) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2009**, *291*, 395. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Terada, M. *Synthesis* **2010**, *2010*, 1929.
(9) For discussions on regioselectivity in NDA reaction, see: (a) Eberlin, L.; Carboni, B.; Whiting, A. *J. Org. Chem.* **2015**, *80*, 6574. (b) Galvani, G.; Lett, R.; Kouklovsky, C. *Chem. - Eur. J.* **2013**, *19*, 15604. (c) Tran, A. T.; Liu, P.; Houk, K. N.; Nicholas, K. M. *J. Org. Chem.* **2014**, *79*, 5617.
(10) Bekkaye, M.; Su, Y.; Masson, G. *Eur. J. Org. Chem.* **2013**, *2013*, 3978.
(11) A controlled experiments confirms that no oxidation of the endocyclic alkene of **4** by *m*-CPBA occurs in the presence of *N*-arylhydroxylamine at 78 °C.
(12) For recent examples, see: (a) Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 11569. (b) Yang, C.; Xue, X. S.; Jin, J. L.; Li, X.; Cheng, J. P. *J. Org. Chem.* **2013**, *78*, 7076.
(13) (a) Hojczyk, K. N.; Feng, P.; Zhan, C.; Ngai, M.-Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 14559. (b) Songis, O.; Didierjean, C.; Laurent, C.; Martinez, J.; Calmès, M. *Eur. J. Org. Chem.* **2007**, *2007*, 3166.
(14) Romanov-Michailidis, F.; Guénée, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9266.

DOI: 10.1021/acs.joc.6b01256
J. Org. Chem. 2016, 81, 10154−10159