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Emma Naulin, Marine Lombard, Vincent Gandon, Pascal Retailleau, Elsa Van Elslande, et al.. Enantioselective and Regiodivergent Synthesis of Dihydro-1,2-oxazines from Triene-Carbamates via Chiral Phosphoric Acid-Catalysis. *Journal of the American Chemical Society*, inPress, 10.1021/jacs.3c12015 . hal-04313016

HAL Id: hal-04313016

<https://hal.science/hal-04313016>

Submitted on 28 Nov 2023

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Enantioselective and Regiodivergent Synthesis of Dihydro-1,2-oxazines from Triene-Carbamates *via* Chiral Phosphoric Acid-Catalysis

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ABSTRACT: Conjugated trienes are fascinating building blocks for the rapid construction of complex polycyclic compounds. However, limited success has been achieved due to the challenging regioselectivity control. Herein, we report an enantio- and diastereoselective process allowing to regioselectively control the functionalization of NH-triene-carbamates. Synthesis of chiral *cis*-3,6-dihydro-2H-1,2-oxazines is achieved by a chiral phosphoric acid catalyzed Nitroso-Diels-Alder cycloaddition involving ((1*E*,3*E*,5*E*)-hexa-1,3,5-trien-1-yl)carbamates. Moreover, a modular access to three different regioisomers with excellent diastereoselectivities and high to excellent enantioselectivities is obtained by careful choice of the reaction conditions. Utility of each regioisomeric cycloadduct is highlighted by a variety of synthetic transformations.

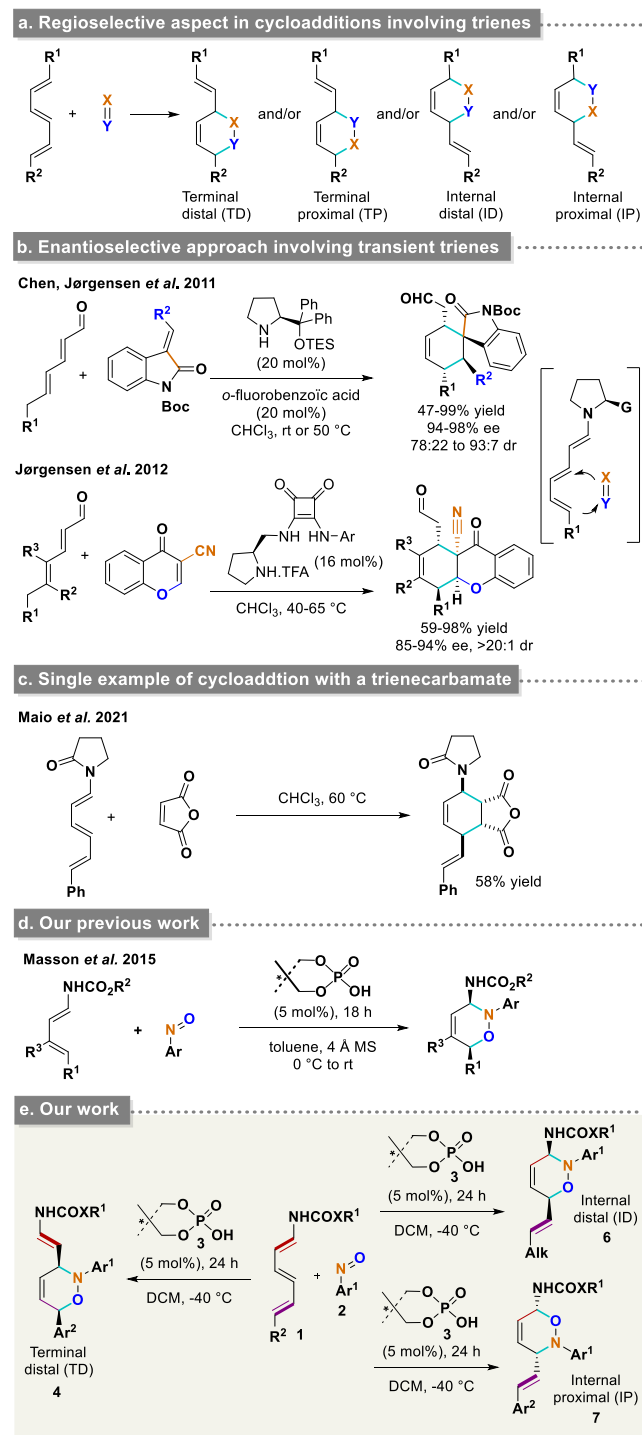
INTRODUCTION

Linear conjugated trienes are important structural motifs found in many natural products and biologically active compounds,¹ and they have many applications in materials science.² Consequently, the development of efficient protocols for their synthesis has attracted great attention over the recent decades.³ Moreover, the presence of three double bonds that can be individually functionalized makes them a unique platform for constructing complex molecules.⁴ For instance, linear conjugated trienes have successfully been employed in intramolecular Diels-Alder (DA) reactions⁵ for synthesizing natural products.⁶ By contrast, the use of such non-symmetrical polarized linear trienes in intermolecular and hetero-DA reactions has been rarely investigated, presumably owing to difficult regio-control stemming from the presence of two reactive dienes in the same molecule.⁷ Furthermore, an unsymmetrical dienophile can react from the distal or proximal mode.⁸ As a result, up to four regioisomers can be formed, rendering such DA reactions highly challenging (Scheme 1a). Therefore, specific trienes⁹ with a defined geometry (*E* vs *Z*), or steric or electronic bias have been mainly used for minimizing the problem of regioselectivity in these reactions.¹⁰ Additionally, only a few enantioselective DA reactions with trienes have been studied to date.¹¹ In 2011, Chen and Jørgensen *et al.* reported the first regioselective, diastereoselective, and enantioselective DA reaction of di-enals with dienophiles derived from oxindoles and cyanoacetate, catalyzed by a secondary amine through linear conjugated trienamine formation (Scheme 1b).¹² Later, Jørgensen *et al.* achieved an asymmetric DA reaction between α,β -unsaturated enals and activated chromones through a similar catalytic strategy, affording complex tetrahydroxanthenes with high enantioselectivity.^{13a} In both reports, only terminal dienes reacted in the cycloadditions. To the best of our knowledge, no example of enantioselective cycloaddition involving trienes with internal double bonds as reactants has been reported. In this context and despite the key achievements described above,¹⁴ there is still room for developing new enantioselective DA reactions with

linear trienes, paving the way for the production of regiodivergent¹⁵ cycloadducts.

In view of the aforementioned current state, coupled with our recent success in the development of various cycloaddition reactions with diene-carbamates¹⁶⁻¹⁸ we explored the feasibility of conducting challenging regioselective and enantioselective DA reactions using 1,3,5-triene-carbamates. Up to now, the linear NH-1,3,5-triene-1-carbamates (RNHCOOR') have found limited use despite their potential to undergo diverse cycloadditions around of each unsaturation for the synthesis of advanced compounds.¹⁹ A single example of a DA reaction involving a linear conjugated triene-tertiary-carbamate, namely, *N*-((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)pyrrolidin-2-one, was reported by Maio; the carbamate was found to undergo cycloaddition with maleic anhydride under thermal conditions.²⁰ Interestingly, an opposite regioselectivity was observed when compared with Jørgensen's works^{12,13a} and only the internal diene reacted to afford the racemic *endo*-product (Scheme 1c). Motivated from this precedent along with our previous work on diene-controlled regiodivergent (4+2) cycloaddition,²¹ we envisioned that the regioselectivity might be influenced by the nature of the substituent on the triene. Additionally, since the regio- and enantioselectivity can be also strongly influenced by the choice of the dienophile and chiral catalyst, they must be carefully chosen to develop regio- and enantioselective cycloaddition with triene-carbamates. In light of this and guided by our successful work in asymmetric nitroso-DA reaction (Scheme 1d),^{17a} the nitrosoarenes²² and chiral phosphoric acid²³ were selected as dienophiles and catalyst, respectively. Herein, we report our findings on a substrate/catalyst-controlled highly enantioselective chiral phosphoric acid-catalyzed nitroso-DA reaction that allows regioselective and regiodivergent production of three out of four possible dihydro-1,2-oxazines from simple linear NH-triene-carbamates (Scheme 1e).

Scheme 1. Trienes functionalization through cycloadditions.



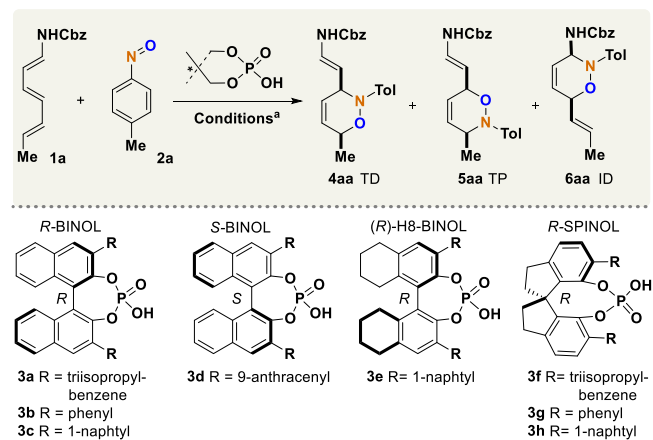
RESULTS AND DISCUSSION

Reaction Optimization and Scope

To begin our investigation, we choose to study the reaction between ((1*E*,3*E*,5*E*)-hepta-1,3,5-trien-1-yl)carbamate²⁴ (**1a**) and 1-methyl-4-nitrosobenzene (**2a**) in presence of chiral phosphoric acid catalyst (Table 1). Performing the reaction with 5 mol% of BINOL-derived phosphoric acid catalyst **3a** in dichloromethane (DCM) at room temperature led to the formation of three out of four regioisomeric adducts with an overall yield

of 56% in a 6:2:2 ratio (entry 2). Each regioisomer was isolated as a single *cis*-diastereomer. The major product was found to be the internal distal cycloadduct **6aa**, which exhibited an interesting enantiomeric excess of 65%. Terminal adduct **5aa** did not benefit of any enantio-enrichment (0% *ee*), while only residual induction was observed for compound **4aa** (<5% *ee*). Based on our previous work, we wondered whether the two racemic cycloadducts would arise from uncatalyzed process. Performing the reaction in absence of catalyst delivered isomers **5aa** and **6aa** in 19% and 37% yield, respectively (entry 1). This result supports our hypothesis that the thermal reaction competes with the catalyzed one. Fortunately, this uncatalyzed process could be significantly reduced by lowering the temperature

Table 1. Optimization of catalytic enantioselective nitroso-DA reaction involving triene-carbamate **1a.^a**



entry	Cat.	Solvent	Yield (%) (4+5+6) ^b	Ratio 4/5/6 ^c	6aa <i>ee</i> (%) ^d	4aa <i>ee</i> (%) ^d
1 ^e	None	DCM	56	0:7:3	-	-
2 ^e	(<i>R</i>)- 3a	DCM	55	2:2:6	65	<5
3 ^f	(<i>R</i>)- 3a	DCM	54	4:0:6	84	<5
4	(<i>R</i>)- 3a	DCM	55	4:0:6	92	39
5 ^g	(<i>R</i>)- 3a	DCM	60	1:4:5	85	10
6	(<i>R</i>)- 3a	Tol	50	7:1:2	60	15
7	(<i>R</i>)- 3a	EtOAc	50	2:2:6	60	ND
8 ^h	(<i>R</i>)- 3a	MeCN	45	4:1:5	84	24
9 ⁱ	(<i>R</i>)- 3a	PhCF ₃	50	7:0:2	75	<5
10	(<i>R</i>)- 3b	DCM	50	9:0:1	69	32
11	(<i>R</i>)- 3c	DCM	55	9:0:1	78	74
12	(<i>S</i>)- 3d	DCM	70	95:0:5	-	97
13	(<i>R</i>)- 3e	DCM	55	4:0:1	72	87
14 ^j	(<i>R</i>)- 3f	DCM	40	1:1:0	-	40
15	(<i>R</i>)- 3g	DCM	55	95:0:5	-	86
16	(<i>R</i>)- 3h	DCM	50	9:0:1	49	94

^aGeneral conditions: **1a** (0.05 mmol), **2a** (0.075 mmol) and **3** (5 mol%) in solvent (0.05 M), 24 h at -40 °C. ^bTotal yield of isolated pure product **5+6+7** after preparative TLC chromatography. ^cDetermined on the crude based on ¹H NMR. ^dDetermined by HPLC analysis on a chiral stationary phase vs racemic. ^ePerformed at rt. ^fPerformed at -15 °C. ^gPerformed at -60 °C. ^hPerformed at -25

°C. ⁱPerformed at -35 °C. ^j72 h. ND: not determined, DCM: dichloromethane; EtOAc: ethyl acetate; MeCN: acetonitrile; PhCF₃: (trifluoromethyl)-benzene. Tol: toluene.

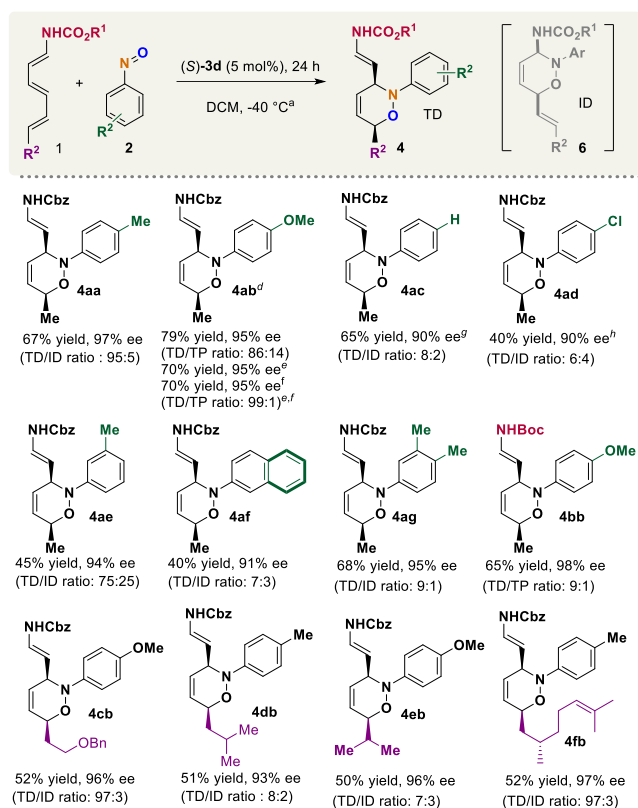
(-15, -40 °C, entries 3-4), thereby improving the regioisomeric distribution (6:0:4 ratio for **4aa**/**5aa**/**6aa**) but also the enantioselectivity of both compound **4aa** and **6aa**. A further drop in the temperature to -60 °C was not satisfactory as the reaction became slow and occurred presumably to a significant extent during the work up (entry 5). It is interesting to note that the regioisomers were found to be easily separable by column chromatography. Yields were essentially maintained over a range of solvents, but a strong impact on the regioselectivity was observed (entries 6-9); indeed, while DCM, ethyl acetate and acetonitrile furnished **6aa** as the dominating isomer, compound **4aa** was the main adduct when using aromatic solvents (toluene and trifluoromethylbenzene). DCM remained however the best choice when considering enantioselectivity for either **4aa** or **6aa**. Chiral phosphoric acid screening subsequently highlighted the importance of the 3,3' (or 6,6')-substituent of phosphoric acid scaffold (entries 10-16). While a bulky 2,4,6-triisopropylphenyl residue (catalyst **3a**) favored the formation of **6aa** over **4aa** (ratio of 6:4), using less sterically demanding 3,3' aromatic side chains (**3b-e** and **3g-h**), clearly favored compound **4aa** (entry 4 vs entries 10-13 and 15-16, ratio of **4aa** vs **6aa** up to 95:5). In addition, extended aromatic side arms (1-naphtyl or 9-anthracenyl) on BINOL, H8-BINOL or SPINOL backbones, substantially increased the enantioselectivity of **4aa** (entries 11-13 and 15-16). Overall catalyst **3d**, bearing 9-anthracenyl residues, furnished the best result taking into account yield, ratio and enantioselectivity (**4aa**: 70% yield, ratio of **6aa**/**4aa**: 5:95, 97% ee, entry 12).

With optimized conditions toward the enantioselective synthesis of regiodefined terminal distal *cis*-cycloadduct in hands (Table 1, entry 12), the scope of the transformation was examined with a set of diverse nitrosoarenes **2** (Scheme 2). Enantioenriched terminal distal (TD) cycloadduct could be isolated in each case (**4ab-4ag**) but the nature of the nitrosoarenes exerted a strong influence on results. Electro-rich *para*-substituted nitrosoarenes (OMe, Me) behaved well in the reaction furnishing terminal *cis*-cycloadducts with good yields and excellent enantioselectivities (**4aa**, **4ab**, >95% ee). Surprisingly, **2** with *p*-MeO group, the minor isomer formed is terminal distal instead of expected internal distal (ID). Increasing the catalyst loading to 10 mol% helped in reaching near perfect regioselectivity in the case of **4ab**. Overall, regioselectivity was less pronounced (ratio TD/ID between 8:2 and 6:4) for the neutral or electro-deficient nitrosobenzene, nevertheless furnishing high enantioselectivities (**4ac** and **4ad**, 90% ee for both). Use of *meta*-substituted or *para/meta*-doubly-substituted nitrosoarenes was also tolerated. In these cases, yield of isolated terminal *cis*-cycloadducts remained decent and enantioselectivity was high (**4ae-4ag**, 91% ee).²⁵ Robustness of the conditions was also demonstrated by performing a large-scale synthesis of compound **4ab** (0.5 mmol), thereby furnishing results in line with the optimization data.

Variation of the triene-carbamates was also investigated in the transformation. In addition to benzyl carbamate (NHCbz), tert-butyl carbamate protection (NHBoc) was well tolerated and the corresponding pure TD product **4bb** was obtained uneventfully in similar yield and enantioselectivity compared to the *N*-Cbz protected **4ab**. Pleasingly, 1,3,5-trien-1-yl carbamate with sterically demanding or functionalized ζ -substituted alkyl side

chains (isopropyl or 3-(benzyloxy)propyl) were also competent partners to build 3,6-dihydro-2H-1,2-oxazin-3-yl)vinyl)carbamates **4eb** and **4cb** with medium yields but excellent enantioselectivity (96% ee for both). The enantioenriched triene-carbamate **1f** (prepared from (*S*)-citronellal) participated in the reaction with equal efficiency. It is worth mentioning that the enantioselective process was hampered neither by a remote chiral center nor by the presence of an unsaturation in the side chain.

Scheme 2. Scope of enantioselective synthesis of TD cycloadducts **4**.^{a,b,c}

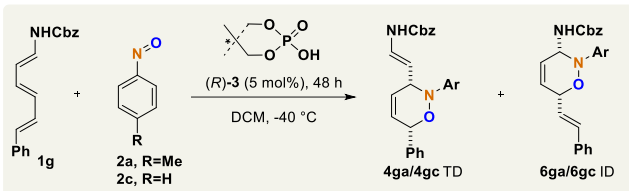


^aFor conditions see Table 1, entry 12 (0.05 mmol scale). ^bYield referred to pure TD adduct. ^cTD/ID Ratio was determined on the crude based on ¹H NMR. ^dThe absolute configuration of **4ab** was determined to be 3*S* and 6*S* by X-ray analysis (cf Supporting information). ^ePerformed with 10 mol% of **3d**. ^f0.5 mmol scale and performed with 10 mol% of **3d**. ^gFor 6 h of reaction time. ^hFor 2 h of reaction time.

The presence of an alkyl side chain at ζ position of the triene seems to be important to effectively building enantioenriched terminal distal cycloadduct under such conditions. Indeed, reaction performed with unsubstituted benzyl ((1*E*,3*E*)-hexa-1,3,5-trien-1-yl)carbamate²¹ or benzyl ((1*E*,3*E*,5*E*)-6-phenylhexa-1,3,5-trien-1-yl)carbamate (**1g**) led to poor results (not shown). Interestingly, inspection of the crude reaction performed with **1g**, revealed that the main isomer was not in favor of the terminal *cis*-cycloadduct but in favor of the internal one (albeit with low ee). From this, we hypothesized that alternative conditions could provide an entry to the selective formation of enantioenriched internal adducts. We rapidly turned our attention to catalyst **3a** that favored the internal *cis*-cycloadduct in our first set of screening (Table 1). Pleasingly, phenylhexatrienyl carbamates **1g** furnished a 4:1 ratio in favor of the internal distal vs terminal distal *cis*-cycloadduct when the reaction

was performed with such catalyst under otherwise identical conditions (Table 2, entry 1). As such, compound **6ga** was isolated in 42% yield and with 60% *ee*. The modest enantioselectivity arose probably from thermal background reaction found to deliver racemic **6ga** as the sole adduct (entry 2). Enantioselectivity could not be improved using either a higher loading of catalyst **3a**, a catalyst bearing less sterically hindered 3,3' substituent, nor by changing the solvent (entry 3 and 5-7). As previously observed, decreasing the temperature to -60 °C was also not possible because of solubility issues. Fortunately, conditions were found to furnish good results (67% yield of internal distal cycloadduct, 84% *ee*, 95:5 regioisomeric ratio) when using nitrosobenzene (**2c**) instead of nitrosotoluene (**2a**) in the reaction (entry 4).

Table 2. Optimization of catalytic enantioselective nitroso Diels-Alder involving triene-carbamate **1g.**^a



entry	Cat.	Solvent	Yield (%) (4+6) ^b	Ratio 4/6 ^c	6 <i>ee</i> (%) ^d
1	(<i>R</i>)- 3a	DCM	47	1:4	60
2 ^e	None	DCM	71	0:1	-
3	(<i>R</i>)- 3b	DCM	50	1:1	-
4 ^f	(<i>R</i>)- 3a	DCM	67	5:95	84
5 ^{f,g}	(<i>R</i>)- 3a	DCM	60	5:95	82
6 ^f	(<i>R</i>)- 3a	Toluene	30	1:9	46
7 ^f	(<i>R</i>)- 3a	CHCl ₃	33	1:4	38

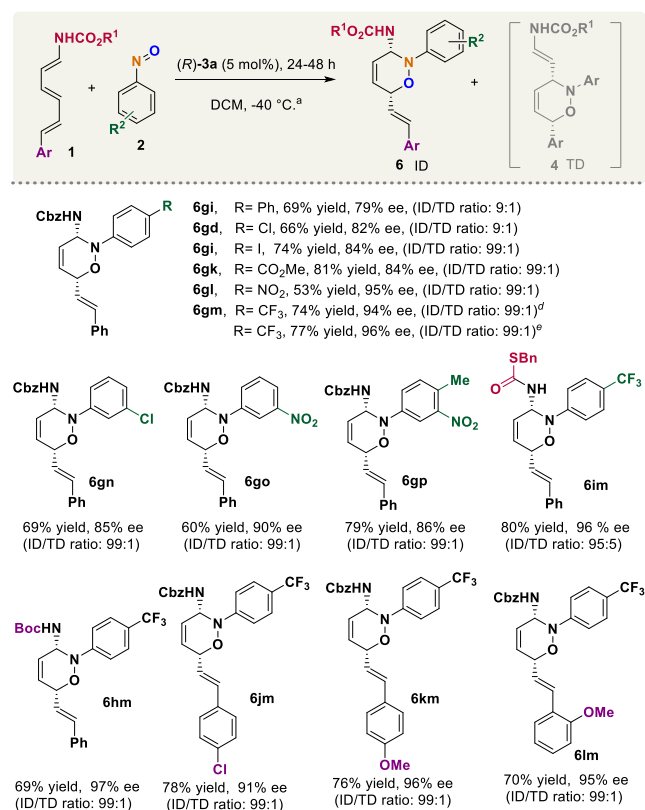
^aGeneral conditions: **1a** (0.05 mmol), **2a** (0.075 mmol) and **3** (5 mol%) in solvent (0.05 M). ^bTotal yield of isolated pure product **4+6**, after preparative TLC chromatography. ^cDetermined on the crude based on ¹H NMR. ^dDetermined by HPLC analysis on a chiral stationary phase *vs* racemic. ^ePerformed at rt. ^f**2c** (0.125 mmol). ^gWith 10 mol% of **3a**.

The influence of substitution on the nitrosobenzene was further investigated and engaging a set of diverse nitrosoarenes revealed that electronic properties exerted a strong effect on the outcome of the reaction (Scheme 3). Contrary to *p*-methyl-nitrosobenzene (**2a**), nitrosobenzene incorporating a phenyl, a chloro, an iodo or an ester group at the *para* position not only furnished the corresponding *cis*-3,6-dihydro-2H-1,2-oxazine **6gi-6gk** in good yield (62-74%), but pleasingly also with an appreciable enantioselective induction (79 to 84% *ee*) and excellent regioselectivity. Strong withdrawing groups such as nitro or trifluoromethyl group exerted a clear beneficial effect on the enantioselective process allowing to isolate pure *cis*-ID regioisomers **6gl** and **6gm** in 94% *ee*, each. In addition, results were maintained by scaling the synthesis on a 0.5 mmol scale (**6gm**, 80%, 9:1; 96% *ee*).

The reaction was not limited to the use of *para*-substituted nitrosobenzene and *meta*-substituted 1-chloro- or 1-nitro-3-nitrosobenzene proved themselves to be competent partners. In such cases, internal distal *cis*-cycloadduct **6gn** and **6go** were isolated

in good yield and high enantioselectivity (85 and 90% *ee*, respectively). Interestingly, while the reaction with *para*-nitrosotoluene (**2a**) was modest in terms of enantioselectivity (**6ga**, 60% *ee*, entry 1, Table 2), use of disubstituted nitrosobenzene bearing a *para* donating (methyl) and a *meta* withdrawing group (such as nitro) furnished a significantly higher enantioselective induction (**6gp**, 86% *ee*). 6-Phenylhexa-1,3,5-triene protected with benzylthiocarbamate or Boc group uneventfully delivered product **6im** and **6hm**, respectively, in high yield and enantioselectivity. Electronically or sterically biased 6-arylhexa-1,3,5-trien-1-yl) carbamates were also suitable partners in the reaction as exemplified with the synthesis of compound **6jm-6lm**, obtained in good yields (70 to 78% yield) and with excellent enantioselectivities (> 91% *ee*). It should be noted that under the described reaction conditions, 6-aryl hexa-1,3,5-trien-1-yl) carbamates led systematically to the internal distal cycloadduct with high regioselectivity ranging from 9:1 to 99:1.

Scheme 3. Scope of enantioselective synthesis of ID cycloadducts **6.**^{a,b,c}

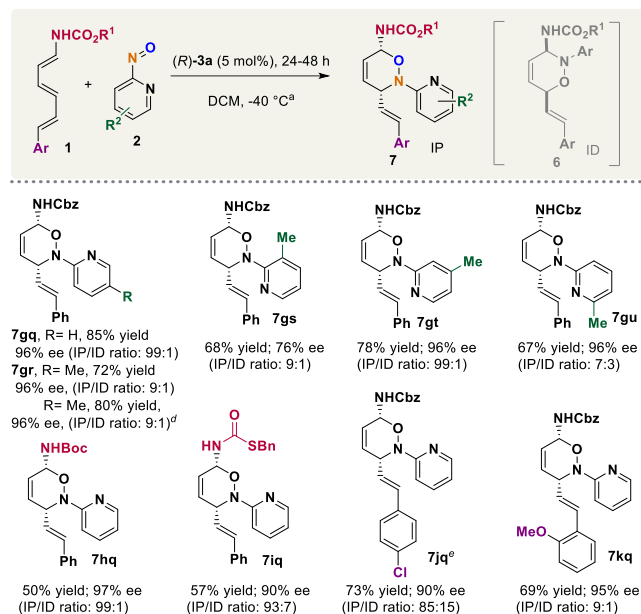


^aFor conditions see Table 2, entry 4 (0.05 mmol scale). ^bYield referred to pure ID adduct. ^cID/TD Ratio was determined on the crude based on ¹H NMR. ^dThe absolute configuration of **6gm** was determined to be 3*R* and 6*R* by X-ray analysis (cf Supporting information). ^e0.5 mmol scale.

Since electron poor nitrosoarenes were particularly effective in building the internal distal cycloadducts **6**, we reasoned that nitrosopyridines could be suitable partners too.²⁶ Gratifying when engaged under the same reaction conditions, a clean reaction took place allowing *cis*-compound **7gq** to be isolated in a good yield and high enantioselectivity (Scheme 4, 85% yield, 96% *ee*). Following a close inspection, the structure of compound **7gq** was established as the internal proximal cycloadd-

duct. A decisive role of the catalyst in this alternative regiochemical cyclisation mode was unveiled, since in the absence of catalysis, *i.e.*, under thermal conditions, only the internal distal adduct **6** was observed (Not Shown).

Scheme 4. Scope of enantioselective synthesis of IP cycloadducts **7**.^{a,b,c}



^aFor conditions see Table 2, entry 4 (0.05 mmol scale). ^bYield referred to pure IP adduct. ^cIP/ID Ratio was determined on the crude based on ¹H NMR. ^d0.5 mmol scale. ^eThe absolute configuration of **7jq** was determined to be *3R* and *6R* by X-ray analysis (cf Supporting information).

The complementary regiochemistry was further explored using various nitrosopyridines. Substitution at the 3, 4, 5 or 6-position of the nitrosopyridines was possible leading to *cis*-cycloadducts **7gr-7gu** in yields ranging between 67% and 78%. Enantioselectivities were generally high (96% *ee*) even if a slight decrease was observed when the substituent was at the 3-position (**7gs**, 76% *ee*). Position of the substituent also influenced the regioselectivity that was less pronounced when the substituent was positioned closer to the nitrogen (position 6, **7gu**, ratio **7/6**: 7:3) compared to remote substitutions (position 3–5, ratio **7/6**: up to 99:1). Effective synthesis of internal proximal *cis*-cycloadducts could also be achieved from diverse 6-arylhexa-1,3,5-trien-1-yl carbamate, incorporating donating or withdrawing groups (OMe, Cl) at their aryl unit or bearing various carbamates protection (*tert*-butoxy or thio-carbamate). A variable regioselectivity that however remained high in each case allowed isolating the pure regioisomer **4jq-4kq** in high yields and excellent enantioselectivity (>90% *ee*).

Mechanistic Studies

Control experiments were conducted to gain some mechanistic insights. A trapping experiment involving ethanol as an external nucleophile was performed (see the Supporting Information). In this experiment, intermediates could not be identified and the reaction uneventfully afforded the expected terminal distal 3,6-dihydro-2H-1,2-oxazine in 68% yield and 93% *ee* (Scheme 5a). Although not a definitive proof, this result suggests that this reaction follows the generally accepted one-step,

asynchronous concerted mechanism, which is characteristic of hetero-DA reactions.²⁷

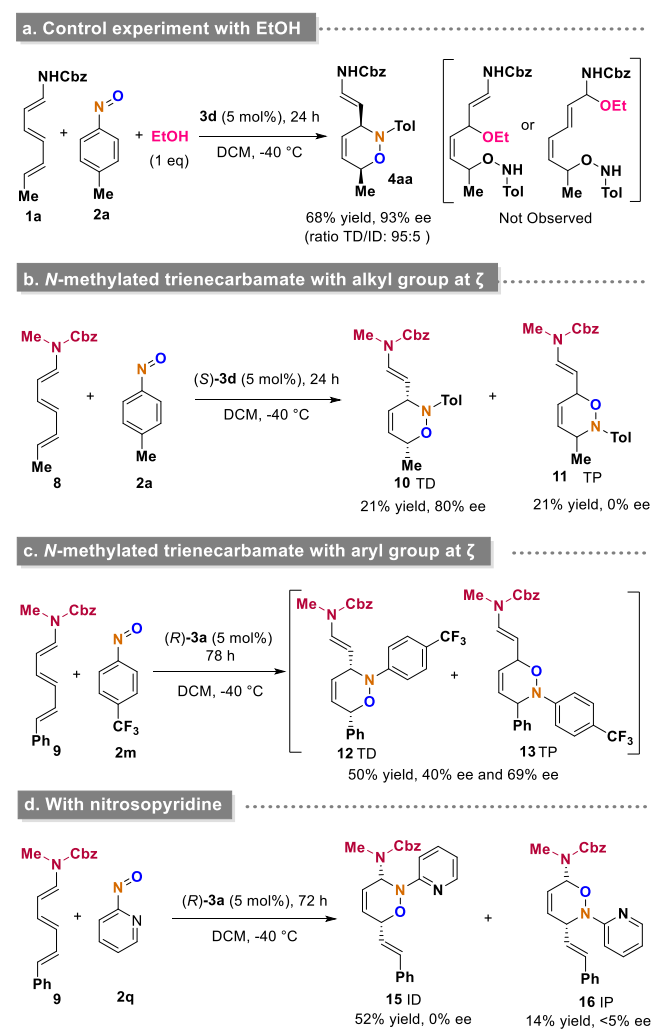
Uncatalyzed (thermal) and catalyzed reactions differ in enantioinduction and regiochemical outcomes, particularly when targeting terminal distal and internal proximal regions of the carbamate molecule. Involvement of the H-bond between the Lewis basic site of phosphoric acid and the Lewis acidic site of the triene-carbamate (RCO₂N–H) could be responsible for such differences in the regiochemistry. We therefore probed this further using *N*-methylated methyl- or phenyl-triene-carbamate (**8** and **9**, respectively) as a reactant under the three regiochemical conditions (Scheme 5). While oxazines did form in each case, we noticed that the *N*-methylated trienes were far less reactive compared to their parent NH trienes.²⁸ Moreover, regio-distribution of cycloadducts as well as enantioselectivities were profoundly affected. An enantioenriched terminal distal adduct **10** (21% yield, 80% *ee*) and a racemic terminal proximal adduct **11** (21% yield) were isolated from the reaction that involved *N*-methyl hepta-1,3,5-trien-1-yl carbamate **8** and 1-methyl-4-nitrosobenzene (**2a**) (Scheme 5b). Interestingly, the absolute configuration of compound **10** was found to be opposite to that observed for the one produced independently *via* a sequential reaction entailing first the cycloaddition of 1-methoxy-4-nitrosobenzene to the NH carbamate in the presence of the same (*S*)-**3d** catalyst and a subsequent methylation step (using NaH and MeI, see the Supporting Information). The reaction between *N*-methylated 6-phenylhexatrienyl carbamate **9** and 1-nitroso-4-(trifluoromethyl)benzene (**2m**) predominantly produced a mixture of modestly enantioenriched terminal regioisomers (**12** and **13**) and the expected internal adduct **14**, independently prepared (see the Supporting Information), was essentially absent from the crude mixture (Scheme 5c). Finally, the reaction involving nitrosopyridine **2q** led to the formation of a fully racemic mixture of compounds **15** and **16** (Scheme 5d). Given that the regioisomeric distribution and the enantio-induction observed in these cases are clearly different from those observed in the reaction involving the NH precursors, these three control experiments highlighted a strong involvement of the acidic NH function in the reaction mechanism.

The relative and absolute configuration of the internal distal adduct (**6**) and the internal proximal adduct (**7**) was unambiguously assigned to be (*3R,6R*) based on the results obtained from the X-ray single crystal structure analysis of enantioenriched **6gm** and **7jq** obtained using (*R*)-**3a** as the catalyst. While direct X-Ray analysis of the terminal distal adduct (**4**) was not achieved because of the lack of crystalline material, the configuration was determined via postreaction transformation (*vide infra*)—considering that the catalyst (*S*)-(**3d**) was used—and assigned to be (*3S,6S*).

Based on these results and considering that with complementary Lewis base/Brønsted acid properties,^{16b,17,21,23,29} as previously demonstrated, formation of a hydrogen bond or, in other words, protonation between the nitrosoarene and the acidic catalyst can be anticipated,^{17a} we can propose that each individual regioselective and enantioselective product formation reaction could involve the formation of a highly organized ternary complex containing the catalyst, NH-triene-carbamate, and nitrosoarene, which upon dual activation would form the product (Scheme 6). To facilitate the comprehensibility of proposed transition states (TS), catalyst derived from (*R*)-BINOL **3a** and **3d** was chosen. In the general case, interaction between the catalyst and nitrosoarene would occur at the basic nitrogen center of the nitroso

residue, as seen in the transition state (TS)-A and TS-B. However, nitrosopyridine could provide an alternative binding mode, in which the azaphilic phosphoric acid^{17,23} would interact with the nitrogen of the pyridine and be further stabilized by the lone pairs of oxygen (TS-C). Such a chelation has been proposed in the case of copper-catalyzed nitroso-DA reactions.²²ⁱ To add to this, the formation of an additional bond between the acidic NH of triene-carbamate and the Lewis-basic phosphoryl oxygen would result in a ternary complex in which the two consecutive double bonds in the triene need to adopt an *s-cis* conformation to allow the cycloaddition to proceed. On the one hand, in a narrow cavity, such as the one created as a result of catalyst **3a** bearing the sterically demanding triisopropylbenzene side arms, the nitrosoarene will be in close proximity with the internal reaction sites of the 1,4-*s-cis* triene-carbamate (TS-B and TS-C). On the other hand, the less crowded and π -extended anthracenyl group present in catalyst **3d** could favor a 3,6-*s-cis* conformation of the triene and allow the nitrosoarene to reach the terminal reaction site as seen in TS-A.

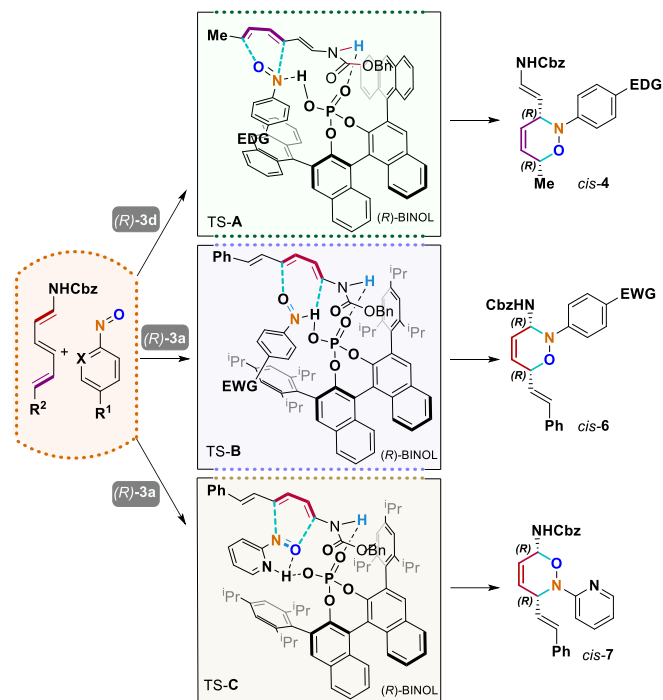
Scheme 5. Control experiments.



Further studies are required to identify the precise origin of the enantioselectivity in such reactions, but in close analogy to our computed results arrived in the context of the enantioselective nitroso-DA reaction with 1,3-diene-1-carbamates,²²ⁱ three plausible transition states TS-A, TS-B, and TS-C can be proposed. The (*R*)-catalyst would impose a fully defined arrangement of

the chiral faces, presenting the *Si* face of the triene-carbamate to the nitrosoarene. Following a dual activation of both reactants, an asynchronous concerted exo-cyclization³⁰ through these well-organized transition states would effectively lead to the formation of the product with observed (*3R,6R*) enantioselectivity and diastereoselectivity based on the (*R*) chirality in the catalyst.

Scheme 6. Proposed transition state models.

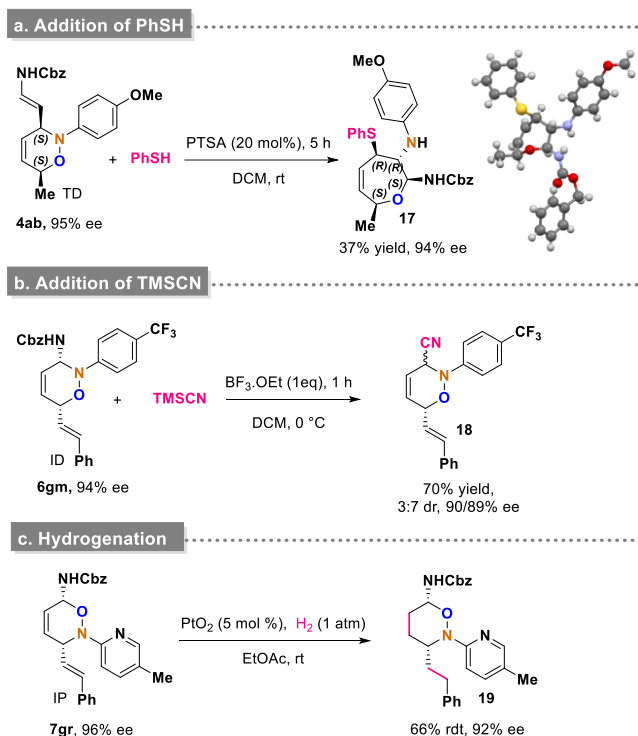


Applications and Derivatizations

To show the practicability of these protocols, 0.5 mmol-scale synthesis of **4ab**, **6gm** and **7gr** were carried out and they were isolated in similar yields with same level of regio- enantio- and diastereoselectivity (Scheme 2, 3 and 4). To further demonstrate the value of individual regioselective processes, post-transformations were conducted using a representative example of each type of adduct (Scheme 7). Selective manipulation of the enecarbamate residue present in terminal distal cycloadducts was investigated first. The initial plan was to convert the enecarbamate into an α -carbamoylsulfide derivative.³¹ However, surprisingly, when compound **4ab** was subjected to the catalytic action of *para*-toluenesulfonic acid in the presence of an excess of thiophenol in DCM, an interesting chiral 2,3,4,7-tetrahydrooxepine derivative (**17**) was produced in 34% yield (Scheme 7a).^{32,33} Enantioselectivity was nearly fully preserved during the transformation, as is evident from the 95% *ee* for **4ab** and the 94% *ee* measured for compound **17**. In addition, the (*2S,3R,4R,7S*) absolute configuration observed via X-ray analysis allowed the absolute stereochemistry of compound **4ab** to be tracked and assigned as (*3S,6S*). It was also possible to convert the internal distal adduct **6gm** into 3,6-dihydro-2H-1,2-oxazine-3-carbonitrile (**18**) using boron trifluoride diethyl etherate Lewis acid along with trimethylsilyl cyanide (Scheme 7b).³⁴ In this transformation, only marginal diastereocontrol was observed relative to the newly formed center (7:3 mixture of diastereoisomers); however, enantioselectivity was essentially pre-

served throughout the transformation and each enantiomer presented a high degree of enantioenrichment (90% *ee*). Hydrogenation of internal proximal styryl-substituted 3,6-dihydro-2H-1,2-oxazin-6-yl carbamate (**7gr**) was also investigated (Scheme 7c). A clean reduction of both unsaturated bonds occurred to afford 1,2-oxazinane (**19**) in 66% yield and 92% *ee* in the presence of a catalytic amount of PtO₂ (5 mol%) in EtOAc at room temperature under 1-atm hydrogen. Overall, these transformations demonstrate the value of the cycloadducts in building enantioenriched products with complex architectures.

Scheme 7. Stereospecific derivatizations of TD, ID and IP cycloadducts.



CONCLUSIONS

We have explored the regioselective and enantioselective phosphoric acid-catalyzed nitroso-DA reaction using linear conjugated triene-carbamates. We have discovered regioselective divergent cycloaddition pathways that are dependent on the conditions and the terminal substitution of the triene carbamate. Three out of four possible regioisomers can be conveniently constructed with excellent enantioselectivities and regioselectivities. Each regio-cycloadduct was amenable to further transformations and could be converted into enantioenriched products with complex architectures.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

X-ray crystallographic data (CIF), experimental procedures and additional optimizations studies, computational details, charts of ¹H- and ¹³C-NMR spectra, chiral and racemic HPLC traces (PDF).

Accession Codes

CCDC 2260833, CCDC 2260839 and CCDC 2285002 contains the supplementary crystallographic data for this paper. These data can

be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

ML and EN thank Paris-Saclay University for the doctoral fellowship. We thank the UPSaclay and CNRS for financial support of this work.

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