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Synthesis of Nitrogen-Containing Heterocycles and Cyclopentenone Derivatives via Phosphine-Catalyzed Michael Addition/Intramolecular Wittig Reaction

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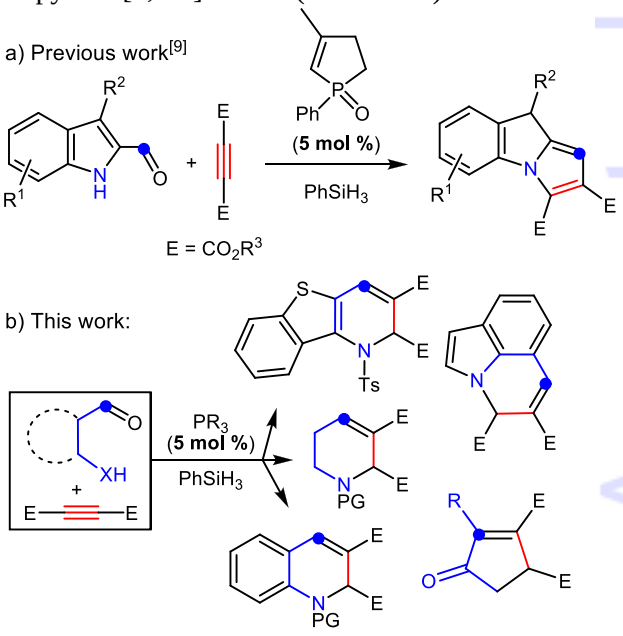
Abstract. The phosphine-catalyzed Michael addition/intramolecular Wittig reaction between dialkyl acetylenedicarboxylate and amino-carbaldehyde or amino-ester derivatives has been developped. This reaction can be rendered catalytic in phosphine by the in situ chemoselective reduction of the phosphine oxide with silane. This methodology enables rapid access to a variety of nitrogen-containing heterocycles, which are present in numerous natural products and/or bioactive compounds. Either classical heating or microwave conditions give access to the desired products in good yields (15 examples, 60-99% yields). This catalytic methodology is further applicable to the synthesis of enantioenriched 1*H*-pyrrole derivatives, with the use of chiral phosphines. Finally, we successfully extended the reaction to the synthesis of polysubstituted cyclopentenone, starting from butane-2,3-dione as substrate.

Keywords: Phosphine; Organocatalysis; In situ reduction; Cyclization; Wittig reaction

Introduction

Stoichiometric phosphine-promoted processes, such as the Wittig, Staudinger, and Mitsunobu reactions are widely used in organic synthesis.[1] In addition to these well-known transformations, some interesting phosphine-mediated annulation reactions have been recently described, giving access to a wide range of heterocycles.[2] Despite their usefulness, these reactions possess a major drawback, namely the concomitant formation of a stoichiometric quantity of phosphine oxide, which often complicates the purification of large-scale processes and globally decreases the atom economy.[3] With the aim of developing a more environmentally friendly chemistry, a substoichiometric amount of phosphine should be ideally employed. To reach this goal, different strategies have been undertaken, such as the activation of the phosphine oxide with isocyanates[4] or oxalyl chloride,[5] and the in situ chemoselective reduction of the phosphine oxide formed during the reaction. The latter strategy is the most popular,[6] and consequently many reactions were already rendered catalytic in phosphine (catalytic loading of 5-20 mol%) upon using a stoichiometric quantity of a reducing agent, such as silane.[7]

Relying on this strategy, we have developed the first catalytic cyclization reactions between the so-called Huisgen zwitterion and α–ketoester derivatives.[8] Recently, we also reported the first phosphine-catalyzed sequential addition/intramolecular Wittig reaction between dialkylacetylene-dicarboxylate (DAAD) and indole-2-carboxaldehyde derivatives, for the synthesis of highly functionalized 9*H*-pyrrolo[1,2-*a*]indoles (Scheme 1a).[9]



Scheme 1. Phosphine-catalyzed synthesis of nitrogen-containing heterocycles and cyclopentenone derivatives.

Herein, we propose to fully explore the scope of the catalytic addition/intramolecular Wittig reaction between DAAD, amino-carbaldehyde and amino-

ester derivatives, and therefore expand our methodology towards an easy access to plenty of *N*-containing condensed heterocycles (Scheme 1b).

Although few of these structures have already been obtained by using stoichiometric amounts of phosphine,[10] other products were directly synthesized with this catalytic methodology. The process proved to be very efficient for developing quickly a library of various heterocyclic scaffolds well known for their biological properties and their presence in many drugs.[11] For example, as shown in Figure 1, mitomycin A (**I**) based on a pyrrolo[1,2-*a*]indole core is an effective anti-tumor agent.[12] Licofelone (**II**) based on a pyrrolizine core is an analgesic, an anti-inflammatory agent, and considered as a treatment for osteoarthritis.[13] Vinpocetine (**III**), based on an indole-naphthyridine backbone, enhances the cerebral blood-flow, has neuroprotective effects and was used as a drug for the treatment of cerebrovascular disorders.[14]

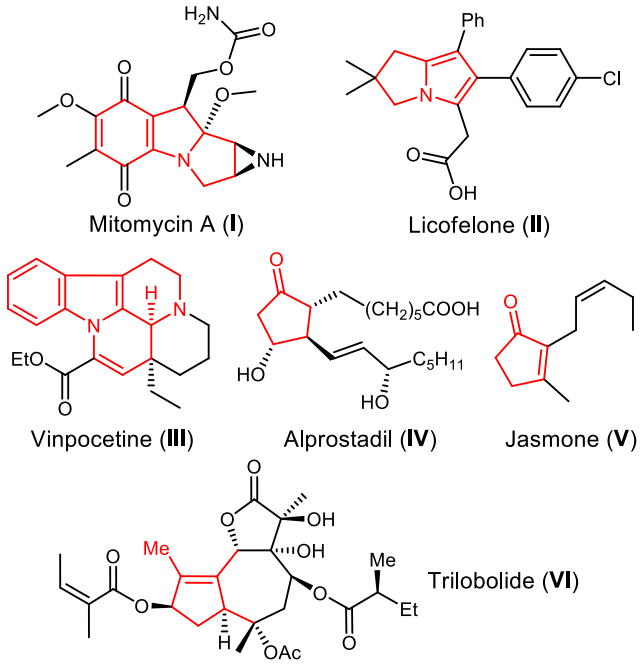


Figure 1. Some natural and bioactive products containing the targeted heterocycles and carbocycles.

In addition to *N*-containing heterocycles, the "catalytic addition/intramolecular Wittig reaction" methodology can be interestingly extended towards the synthesis of 4-oxocyclopent-2-ene-1,2-dicarboxylate derivatives. This skeleton was found in several drugs such as alprostadil[15] (**IV**) (Prostaglandin E1 (PGE1)), used in the continuous treatment of erectile dysfunction,[16] as well as in natural products such as Jasmone (**V**) which is a volatile portion of the oil from jasmine flowers. Trilobolide (**VI**), a bioactive compound possessing anticancer activities, could be synthesized also from this key builduing block.[17] In addition, our methodology gives access to products containing stereogenic centers, thus we were interested to assess the possibility of developing the first catalytic and asymmetric version of such tandem addition/intramolecular Wittig reaction. To further validate the synthetic flexibility of this methodology, we envisioned applying it to a wide range of substrates, and the main results of these studies are summarized hereafter.

Results and Discussion

I) Phosphine-catalyzed synthesis of diverse nitrogen-containing condensed heterocycles.

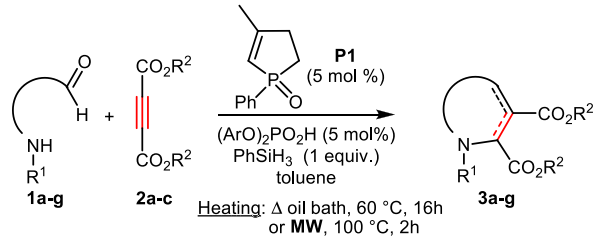
The major challenges to circumvent during the development of phosphine-catalyzed reactions are: i) the choice of an appropriate reducing agent to chemoselectively reduce *in situ* the phosphine oxide without altering the starting materials, intermediates, and/or products; ii) the phosphine oxide should be easily reduced and iii) the trivalent phosphine should exhibit a good nucleophilicity. It is well known nowadays that the 5-membered ring cyclic phosphines possess these features and that [R_3SiH/Brønsted acid] as a reducing system can tolerate a wide range of functional groups.[6a,7c,8,9] Moreover, the mixture phenylsilane/*bis*(4-nitrophenyl)phosphate is known to reduce efficiently five-membered ring cyclic phosphine oxide at 60°C in toluene. Indeed, the 4-methyl-1-phenyl-2,3-dihydrophosphole **P1** catalyst proved to be very efficient in the synthesis of pyrrolo-indole and pyrrolizine derivatives (scheme 1a).[9]

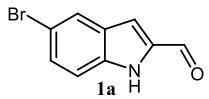
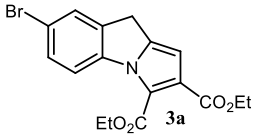
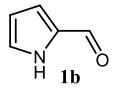
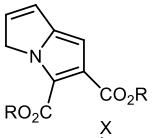
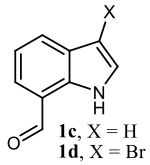
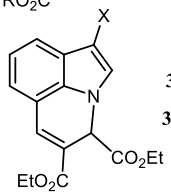
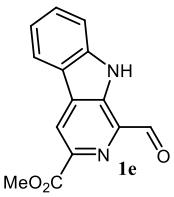
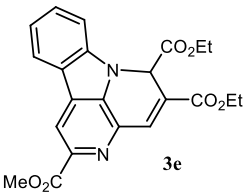
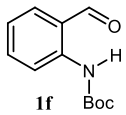
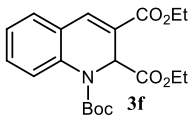
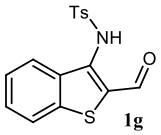
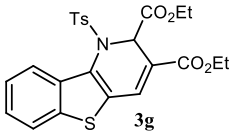
So, we decided to fully explore the substrate scope of this reaction, by using different amino-carbaldehydes (Table 1). Using the catalytic system {**P1** (5 mol %) as pre-catalyst, 5 mol % of *bis*(4-nitrophenyl)phosphate, phenylsilane (1 equiv.), for 16 hours at 60°C}, a wide range of umpolung addition/Wittig reactions was developed, giving access to a variety of *N*-containing condensed heterocycles. First of all, the diethyl 7-bromo-9*H*-pyrrolo[1,2-a]indole-2,3-dicarboxylate product **3a** was synthesized in 92% yield (Table 1, entry 1).[9] The structural assignment of this molecule was ascertained by single crystal X-ray analysis (Figure 2a), that verified the double bond migration after the intramolecular Wittig reaction (see the mechanism Scheme 2). Similarly, we were able to generalize the synthesis of dialkyl 3*H*-pyrrolizine-5,6-dicarboxylate derivatives **3ba-3bc** from **1b**. Starting from commercially available pyrrole-2-carbaldehyde and dimethyl, diethyl, and di-*tert*-butyl acetylene dicarboxylate **2a-c**, the corresponding 3*H*-pyrrolizines **3ba-3bc** were obtained in 83-90% yields (entries 2-4). It is worth noting that the structure of this bicyclic backbone was confirmed by X-ray diffraction study on crystals of **3ba** (Figure 2b). The more stable 3*H*-pyrrolizine isomer was isolated, contrary to the chemical structure of 1*H*-pyrrolizine, reported by Yavari *et al.*[10c] By ^1H and ^{13}C NMR analysis, we have the characteristic signals of the -NCH_2- moiety of **3ba** [δ 4.66 ($C\underline{H}_2$); 55.4 ($\underline{C}H_2$)] [δ 4.76 ($C\underline{H}_2$); 55.1

(C<u>H</u>$_2$)][10c] and **3bc** [δ 4.70 (C<u>H</u>$_2$); 55.1 (<u>C</u>H$_2$)] [δ 4.69 (C<u>H</u>$_2$); 55.1 (<u>C</u>H$_2$)].[10c]

Diethyl 4*H*-pyrrolo[3,2,1-*ij*]quinoline-4,5-dicarboxylate derivatives **3c,d** (entries 5,6) were obtained in 96% and 94% yield, respectively, from commercially available 1*H*-indole-7-carbaldehydes. Once more, the structure of **3c** was confirmed by X-ray diffraction studies (Figure 2c).

Table 1. Scope of different classes of *N*-containing condensed heterocycles.



Entry	Substrate **1**	Product **3**	Yield (%)[a] Δ[b]	MW[c]
1	 **1a**	 **3a**	92[d]	93
2	 **1b**	 **3ba**, R = Me	90	91
3		**3bb**, R = Et	83[d]	85
4		**3bc**, R = *t*Bu	89	89
5	 **1c**, X = H	 **3c**, X = H	96	99
6	**1d**, X = Br	**3d**, X = Br	94	99
7	 **1e**	 **3e**	86	n.r.
8	 **1f**	 **3f**	73	70
9	 **1g**	 **3g**	60	60

[a] Isolated yields. [b] Classical heating, using an oil bath, 60°C, 16h. [c] Microwave reactor, 100°C, 2h. [d] Results from ref. [9].

Moreover, a highly complex *N*-containing heterocycle **3e** could be obtained in 86% yield, starting from the 1-formyl-9*H*-pyrido[3,4-b]indole-3-carboxylate substrate **1e** (entry 7). In this case, some solubility problems of the starting material **1e** occurred, forcing the use of THF as a co-solvent to ensure a decent yield. Similarly, 1-Boc-2,3-diethyl quinoline-1,2,3(2*H*)-dicarboxylate **3f** was obtained in 73% yield (entry 8) and the tricyclic diethyl 1-tosyl-1,2-dihydrobenzo[4,5]thieno[3,2-*b*]pyridine-2,3-dicarboxylate **3g** in 60% yield (entry 9).

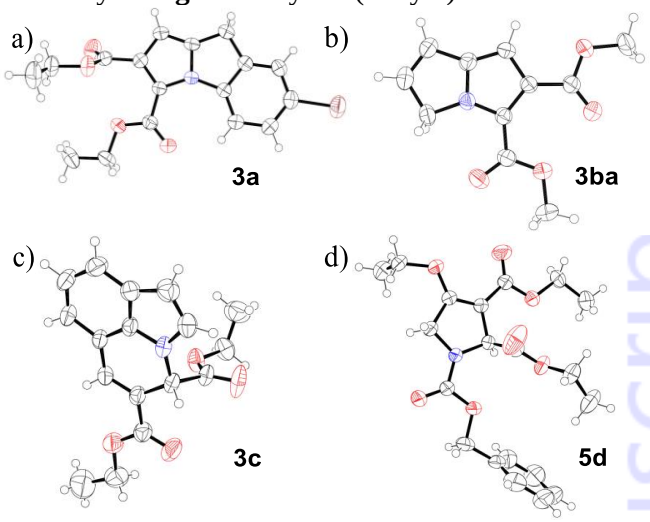


Figure 2. ORTEP-3 plot of a) **3a** (CCDC 1489491); b) **3ba** (CCDC 1489494); c) **3c** (CCDC 1489495) and d) **5d** (CCDC 1489493). Ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary radius.

Inspired by Werner and coworkers, who developed the first microwave-assisted catalytic Wittig reaction (CWR),[18] we decided to switch from classical heating conditions (oil bath, 60°C, 16h) to microwave heating (100°C, 2h). Keeping the reaction conditions developed previously, we studied the microwave-assisted performance of the addition/intramolecular CWR on the same substrates. Interestingly, all the reactions in table 1 (except for entry 7) were finished just after 2 hours while heating at 100°C, without decreasing the yields. On the contrary, the yields were even enhanced with some substrates (entries 3, 5, 6). Increasing the reaction temperature did not have any influences in the reaction time or in the reaction yields. The only disappointing result came from the substrate **1e** (entry 7), due to the low solubility of pyrido[3,4-*b*]indole-aldehyde substrate in toluene.

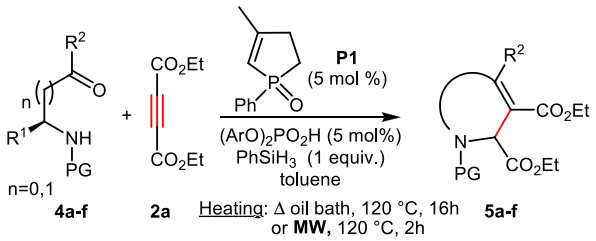
This catalytic system showed to be very efficient and allows an easy access to a wide library of different *N*-containing condensed heterocycles with very high yields and faster reaction rates.

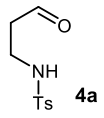
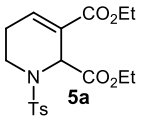
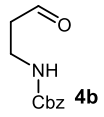
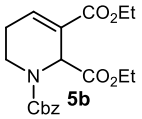
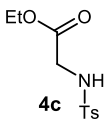
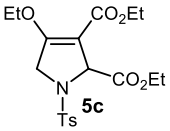
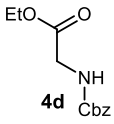
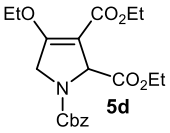
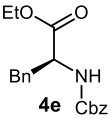
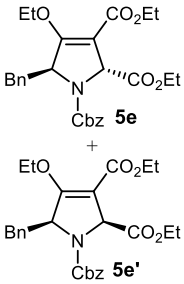
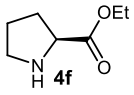
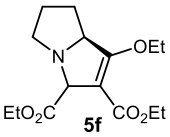
II) Phosphine-catalyzed synthesis of chiral tetrahydropyridine and 2,5-dihydro-1*H*-pyrrole derivatives.

Interestingly, this methodology can be also extended to acyclic amino-aldehyde and amino-ester substrates, as shown in Table 2, to prepare the

corresponding tetrahydropyridine and 2,5-dihydro-1*H*-pyrrole heterocycles.

Table 2. Synthesis of diverse *N*-containing heterocycles.



Entry	Substrate **4**	Product **5**	Yield (%)[a] Δ[b]	MW[c]
1	 **4a**	 **5a**	79[d]	81[e]
2	 **4b**	 **5b**	90[d]	92[e]
3	 **4c**	 **5c**	80	83
4	 **4d**	 **5d**	92	97
5	 **4e**	 **5e** + **5e'**	82 d.r. = 2/1	82 d.r. = 2/1
6	 **4f**	 **5f**	83	84

[a] Isolated yields. [b] Classical heating, using an oil bath, 120°C, 16h. [c] Microwave reactor, 120°C, 2h. [d] Classical heating, using an oil bath, 60°C, 16h. [e] Microwave reactor, 100°C, 2h.

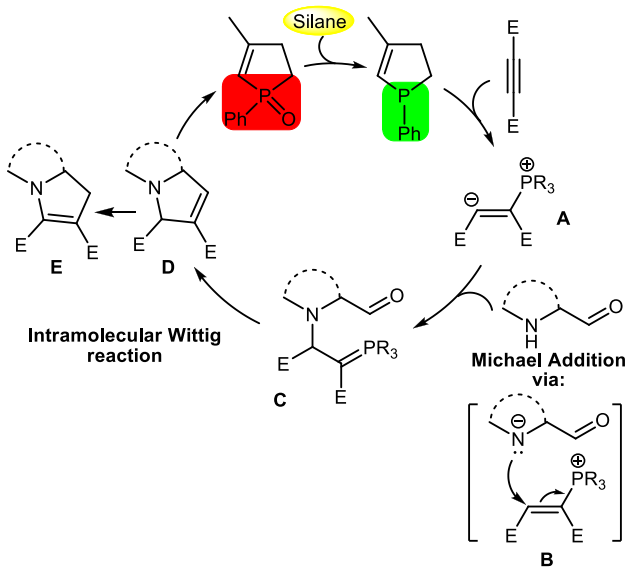
Diethyl tetrahydro-pyridine dicarboxylate derivatives with tosyl (**5a**) and Cbz (**5b**) protecting groups were obtained in 79% and 90% yields respectively, starting from *N*-protected 3-aminopropanal substrates (entries 1-2). Diethyl-4-ethoxy-2,5-dihydro-1*H*-pyrrole dicarboxylate with tosyl (**5c**) and Cbz (**5d**) as protecting groups were obtained in 80% and 92% yields, respectively, from protected commercially available amino-esters and DAAD (entries 3-4). In the latter case, the intramolecular Wittig reaction with ester group requires to increase the reaction temperature to 120°C, to obtain a total conversion.

We can note that **5d** was obtained as a mixture of two rotamers, due to the Cbz group. The structural assignment of this molecule was ascertained by single crystal X-ray analysis (Figure 2d). Finally, the higher reactivities of Cbz-protected substrates, compared to the tosyl-protected one can be explained by the lower nucleophilicity of the nitrogen atom in the case of NTs, compared to the NCbz substrate.

Diastereoselective reaction could be also performed, starting from enantiopure *D*-phenylalanine ethyl ester and DAAD (entry 5). A mixture of 2 diastereoisomers **5e** and **5e'** in 2:1 ratio was obtained, in 82% overall yield. With the *L*-proline ethyl ester substrate, only one diastereoisomer **5f** was synthesized in 83% yield (entry 6).

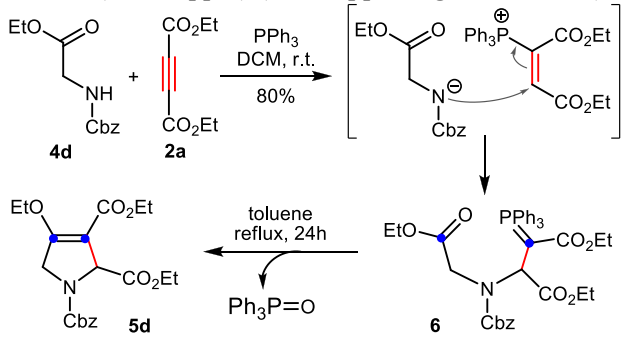
Moreover, the microwave-assisted reaction of the umpolung addition/CWR with acyclic amino-aldehydes worked properly at 100°C for 2 hours, to furnish **5a** and **5b** in 81-92% yield (entries 1-2). Concerning the use of amino-esters, the reaction temperature was at 120°C for 2h, giving access to the dihydropyrroles **5c-5f** in 82-97% isolated yields (entries 3-6). The microwave heating condition has not modified and/or altered the diastereomeric ratio in the case of products **5e** and **5f**.

As previously reported and according to the accepted mechanism,[10a-b] the trivalent phosphine adds to the DAAD to form the zwitterionic species **A** (Scheme 2).[19] The latter is subsequently protonated by the NH proton of the substrate, to give the corresponding vinylphosphonium salt **B**. The addition of the conjugate base of the substrate to **B** furnishes the ylide **C**, which undergoes an intramolecular Wittig reaction to form **D**. In some cases, migration of the double bonds formed the product **E**. Finally, the phosphine oxide generated by the Wittig olefination is reduced in situ by silane to the corresponding trivalent phosphine, to realize the $P^{V}=O/P^{III}$ redox cycling. Both trivalent phosphine or the corresponding phosphine oxide can be used indifferently at the beginning of the reaction. In the latter case the first step is the reduction of the P=O bond.



Scheme 2. Mechanism proposal for the phosphine-catalyzed addition/intramolecular CWR.

This mechanism was supported by the isolation of the stable phosphorus ylide **6** (Scheme 3). The reaction of ethyl 2-(benzyloxycarbonylamino)acetate **4d** and DAAD **2a** at room temperature, in presence of a stoichiometric quantity of triphenylphosphine, afforded the compound **6** in 80% yield. The ^{1}H and ^{31}P NMR spectra showed two series of signals ascribed to the respective two rotamers (see the Supporting Information).[20] Afterwards, the isolated phosphorus ylide **6** undergoes an intramolecular Wittig reaction with the carbonyl of the ester group, upon refluxing in toluene. The corresponding product **5d** and triphenyl phosphine oxide are formed quantitatively. The reaction can be followed by ^{31}P NMR: we observed the disappearance of the two peaks of **6** (δ = 26 and 27 ppm) and the formation of $Ph_3P{=}O$ (δ = 30 ppm) (See Supporting Information).

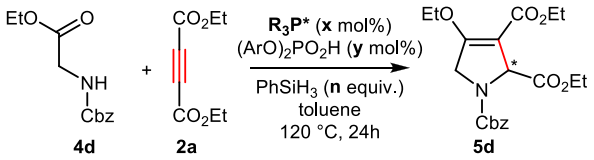


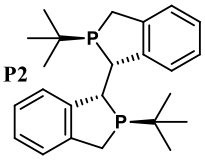
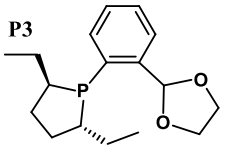
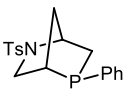
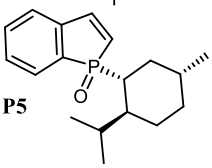
Scheme 3. Synthesis of the phosphorus ylide **6** and subsequent intramolecular Wittig reaction.

III) Catalytic and asymmetric umpolung addition/ intramolecular Wittig reaction.

In the following, one of our biggest interests, as well as the most challenging goal, was to develop a catalytic and asymmetric reaction, mediated by a chiral phosphine. At first, we screened several commercially available chiral phosphines to prove the concept of a catalytic and asymmetric tandem reaction. To the best of our knowledge, there is only one precedent in the literature of a catalytic and asymmetric Wittig reaction, with the use of (*S*,*S*)-Me-DuPhos (10 mol%) as chiral catalyst, in presence of $HSi(OMe)_3$. The conversion was less than 10%, but the enantiomeric excess was about 90% ee.[21] Contrary to this seminal example, where the enantioselective step occurred during the Wittig reaction, via a desymmetrisation reaction of a prochiral diketone substrate with the phosphorus ylide, in our case the enantioselective step is the addition of the nitrogen anion to the vinylphosphonium intermediate **B**, to furnish the ylide **C** (Scheme 2).[22] The best results are reported in Table 3.

Table 3. Asymmetric and catalytic process.



Entry	R_3P^*	x	y	n	Yield (%)[a]	ee (%)[b]
1	**P2** 	75	-	-	50	70
2	**P3** 	150	-	-	30	81
3	**P4** 	5	5	1	67	17
4	**P5** 	5	5	1	94	30

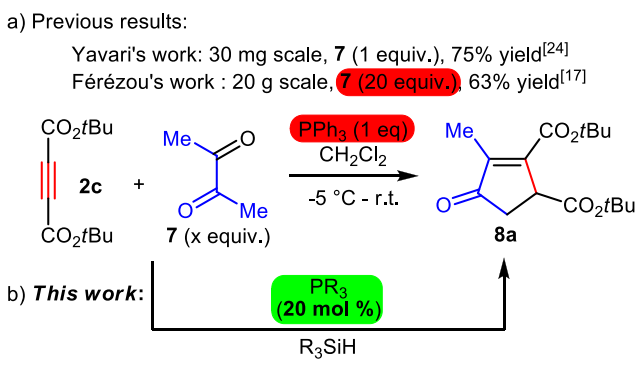
[a] Isolated yields. [b] Determined by HPLC on a chiral stationary phase.

(1*R*,1′*R*,2*S*,2′*S*)-DuanPhos **P2** and 2-{2-[(2*R*,5*R*)-2,5-diethyl-1-phospholano]phenyl}1,3-dioxolane **P3** (Table 3, entries 1 and 2) gave the best enantioselectivities with 70% and 81% ee, but in relatively low yields, in presence nevertheless of respectively 75 mol% and 150 mol% of phosphine (50% and 30% yields). Unfortunately, incorporation of 5-20 mol% of these chiral phosphines in the reaction mixture resulted in the formation of traces of the desired product **5d** after refluxing in toluene for 24 hours, and thereby does not allow the development of the catalytic and asymmetric reaction. That proved

the difficulties to find a chiral phosphine which is easily reducible, but also nucleophilic enough to catalyse the reaction. In general, cyclic phosphines, such as phenylphospholane oxide, are more easily reducible by silanes than acyclic phosphines. And this particularity of cyclic phosphine is especially true for the five-membered rings, such as catalyst **P1-5**. On the other hand, the steric hindrance around the phosphorus atom could explain the lower reactivity of **P2** and **P3**. Fortunately, the use of 5 mol% of (1*S*,4*S*,5*R*)-5-phenyl-2-tosyl-2-aza-5 phosphabicyclo [2.2.1]heptane **P4** (Kwon bicyclic phosphine catalyst)[23] gave the desired product in 67% yield, but with a moderate enantiomeric excess (17% ee, entry 3). Finally, the new chiral catalyst **P5**, a phosphindole-1-oxide bearing a chiral menthyl group, showed the best catalytic activity (94% yield, entry 4) and significant enantioselectivities (30% ee), with only a catalyst loading of 5 mol%. These interesting preliminary results showed the development of a catalytic and enantioselective tandem addition/CWR, previously known as racemic and stoichiometric in phosphine.

IV) Synthesis of 4-oxocyclopent-2-ene-1,2-dicarboxylate derivatives

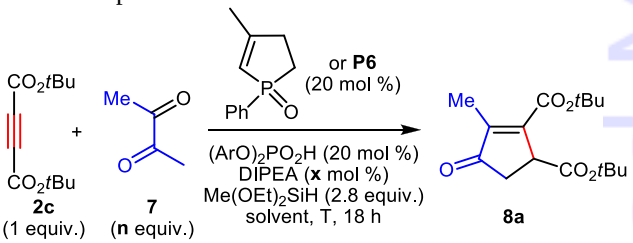
In the continuity of this work concerning the catalytic development of new reactions, we wondered whether it was possible to spread the reactivity of DAAD to other substrates, to obtain carbocycles. In 2004, Yavari et *al*. firstly reported the synthesis of di-*tert*-butyl 3-methyl-4-oxocyclopent-2-ene-1,2-dicarboxylate **8a** (Scheme 4a) using stoichiometric amount of PPh_3 as a promoter for the reaction between di-*tert*-butyl acetylene dicarboxylate **2c** and butane-2,3-dione **7**.[24] In the literature, **8a** proved to be an essential building block in the synthesis of natural products of trilobolide (see structure (**VI**) in Figure 1).[17] However, on bigger scale, Férézou et *al*. proved to have some difficulties to reproduce the synthesis of **8a**, following the Yavari's procedure. On 20g scale reaction, 1 equiv. of PPh_3 was used with 20 equiv. of **7** to obtain **8a** in 63% yield, as summarized in scheme 4a. Hence, large amounts of wastes were produced, and therefore developing a catalytic version of this reaction could be very interesting (Scheme 4b).



Scheme 4. Synthesis of cyclopentenone derivatives.

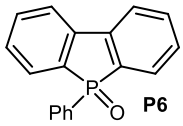
Initially, we examined the outcome of the reaction of acetylene dicarboxylate **2c** (1-3 equiv.) with butane-2,3-dione **7**, in the presence of sub-stoichiometric amounts of phosphine and silane. The reaction was conducted with 20 mol% of 4-methyl-1-phenyl-2,3-dihydrophosphole 1-oxide, 20 mol % of $(p\text{-}NO_2PhO)_2PO_2H$ and 2.8 equiv. of $Me(EtO)_2SiH$ for 16 hours at 70°C in toluene. Only traces of **8a** were observed with 1 equiv. of substrate **7**, independently of the concentration used (table 2, entries 1-2). To our delight, **8a** was formed in 33% yield, with the use of 2 equiv. of substrate **7** (entry 3). The use of other solvents (dioxane, dichloroethane; entries 4-5) did not improve the reaction rate. Surprisingly, the yield was increased to 48% while adding 20 mol% of DIPEA (entry 6), but the addition of 100 mol% of DIPEA had a negative effect on the catalytic activity (18% yield, entry 7). Enhanced yields were obtained at 90°C and 110°C (50% and 66% yields, respectively, entries 8-9). Traces of **8a** were produced by using PPh_3 as catalyst, and 54% yield was obtained with the P-phenyl-dibenzophosphole **P6** (entries 10-11). Interestingly, best reaction conditions were reached, as reported in entry 12, while using 3 equiv. of biacetyl **7**. The desired product **8a** was obtained in 83% NMR yield (77% isolated yield). Decreasing the amounts of $Me(EtO)_2SiH$ to two equivalents had a negative impact on the reaction rate (50% yield, entry 13).

Table 4. Optimization of the reaction conditions.



Entry	**7** (**n** equiv.)	DIPEA (**x** mol%)	solvent, [c]	T (°C)	Yield (%)[a]
1	1	-	Toluene, [0.1]	70	5
2	1	-	Toluene, [0.2]	70	5
3	2	-	Toluene, [0.2]	70	33
4	2	-	Dioxane, [0.2]	70	20
5	2	-	DCE, [0.2]	70	15
6	2	20	Toluene, [0.2]	70	48
7	2	100	Toluene, [0.2]	70	18
8	2	20	Toluene, [0.2]	90	50
9	2	20	Toluene, [0.2]	110	66
10[b]	2	20	Toluene, [0.2]	110	<5
11[c]	2	20	Toluene, [0.2]	110	54
12	3	20	Toluene, [0.2]	110	83 (77)[d]
13[e]	3	20	Toluene, [0.2]	110	50
14[f]	3	20	Toluene, [0.2]	110	39

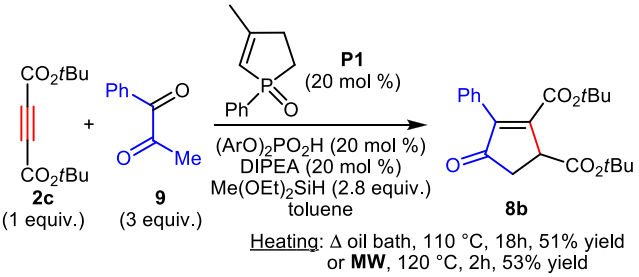
[a] NMR yields were determined using trimethoxybenzene as an internal standard. [b] Use of PPh_3 instead of phospholene catalyst. [c] Use of **P6** instead of phospholene catalyst. [d] Isolated yield. [e] $Me(OEt)_2SiH$ (2.0 equiv. instead of 2.8 equiv.). [f] Without $(ArO)_2PO_2H$. DIPEA = *N*,*N*-diisopropylethylamine; DCE = 1,2-dichloroethane.



Finally, the importance of *bis*(4-nitrophenyl) hydrogen phosphate in the reaction mixture was proved (only 39% yield without $(ArO)_2PO_2H$, entry 14). This result demonstrated the pivotal role of the phosphate in the P(V)/P(III) redox catalytic cycle. Under these reaction conditions, no better isolated yields were obtained with $PhSiH_3$ or Ph_2SiH_2.

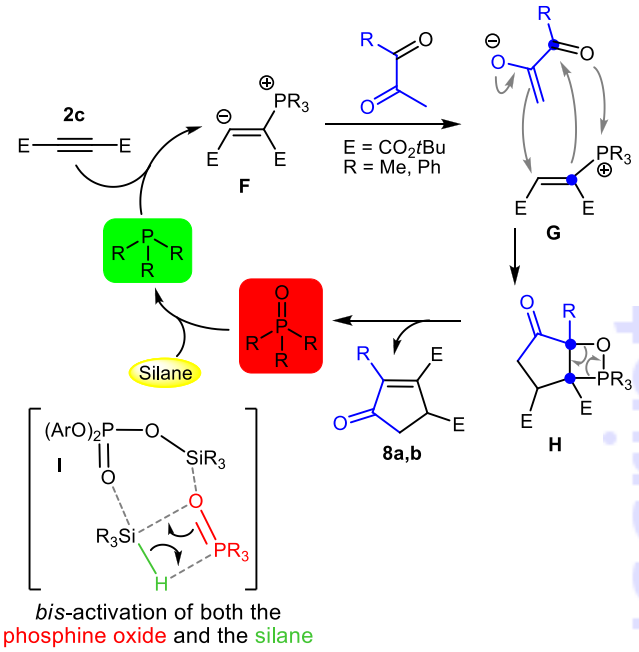
The practicability of our catalytic protocol was further demonstrated by a 2.2-mmol-scale synthesis of product **8a**. The desired product was obtained in 77% isolated yield (0.50 g). This scalability proves the robustness of our catalytic methodology and applications in the synthesis of key building blocks can be now envisaged.

This methodolgy was also extended to the synthesis of di-*tert*-butyl 4-oxo-3-phenylcyclopent-2-ene-1,2-dicarboxylate **8b** in 51% (Scheme 5). Moreover, **8a** and **8b** were obtained in 65% and 53% yields, respectively, while performing these reactions in microwave at 120°C for 2 hours.



Scheme 5. Application of the catalytic methodology to the synthesis of substrate **8b**.

Concerning the reaction mechanism (Scheme 6), nucleophilic addition of the phosphine to DAAD **2c** produces the zwitterionic species **F**, which reacts as a base to deprotonate the diketone substrate **7** or **9**. The enol intermediate subsequently adds on vinylphosphonium **G** to form the oxaphosphetane **H**, which produced the desired product **8a,b** and phosphine oxide as a concomitant by-product. In situ reduction of this phosphine oxide with silane such as phenylsilane allowed the regeneration of the active catalyst and close the catalytic cycle. During the phosphine oxide reduction, the phosphate proved to be necessary to facilitate this process (as showed in Table 4, entry 14). Thus, it is postulated that the in situ formed phosphoric silyl ester **I** (Scheme 6) acts as a bifunctional catalyst.[25] Both the oxygen atom of the phosphine oxide and the silane are activated by the Lewis acid/Lewis base properties of this organocatalyst. In this process the tertiary amine base DIPEA seems to have an important role by avoiding the protonation of the enol intermediate.



Scheme 6. Proposed mechanism for the synthesis of products **8a,b**.

Conclusion

The phosphine-catalyzed Michael addition/Wittig reactions tolerate a wide range of substrates, giving access to the corresponding heterocycles and cyclopentenone derivatives in good yields, either using classical heating or microwave conditions (17 examples, 60-99% yields). We are confident that our methodology could find applications in organic chemistry, particularly in medicinal chemistry, where people are interested in obtaining a large number of molecules, structurally varied, in minimum time. Finally, the use of a catalytic quantity of phosphine is even more relevant in the case of the use of a chiral phosphine. Given the prohibitive cost of these chiral catalysts, it is inconceivable to use in these reactions a stoichiometric quantity. The use of our method allows now to use of small quantity of catalyst, to obtain easily an enantioenriched product. Even if the results described here are preliminary, they are the first significant results in the domain. In the future, our work is going to concentrate on the discovery of new phosphine-catalyzed reactions, and in the development of asymmetric reactions. The synthesis of new chiral phosphines, especially designed to improve the current results will be reported in due course.

10.1002/adsc.201700313

Experimental Section

I. General information:

All non-aqueous reactions were run under a positive pressure of argon, by using standard techniques for manipulating air-sensitive compounds. Microwave assisted reactions were performed in Anton-Par Monowave 300 microwave in Borosilicate glass standard vial G10. Toluene was distilled over CaH_2 under an argon atmosphere. Tetrahydrofuran was distilled over sodium/benzophenone under an argon atmosphere. All other reagents and solvents were of commercial quality and used without further purification (substrates **1b**, **2**, **7**, **9** and chiral phosphines). Analytical thin-layer chromatography (TLC) was performed on plates precoated with silica gel layers. The developed chromatogram was visualized by UV absorbance and/or vanillin stain. Flash column chromatography was performed using a GraceResolv™ silica gel column on a Combi Flash® companion®. Nuclear magnetic resonance spectra (^{1}H, ^{13}C, ^{31}P) were recorded at 500 or 300 MHz spectrometers. Chemical shifts are reported in parts per million relative to an internal standard of residual chloroform (δ= 7.19 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) and time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode. HPLC was performed at a column temperature of 20°C on a Waters 2695 Separations Module equipped with a diode array UV detector. Data are reported as follows: column type, eluent, flow rate, retention time (t_r). Substrates 1*H*-indole-7-carbaldehyde **1c**,[26] 3-bromo-1*H*-indole-7-carbaldehyde **1d**,[26] methyl 1-formyl-9*H*-pyrido[3,4-b]indole-3-carboxylate **1e**,[27] *tert*-butyl (2-formylphenyl)carbamate **1f**,[28] 4-methyl-*N*-(3-oxopropyl)benzenesulfonamide **4a**,[29]benzyl (3-oxopropyl)carbamate **4b**,[30] ethyl tosylglycinate **4c**,[31] ethyl (benzyloxy)carbonyl)glycinate **4d**,[32] ethyl *L*-prolinate **4f**,[33] and **P5**,[34] were prepared according to literature. Synthesis of **1g** and 1-((2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)phosphindole 1-oxide are described in the supporting information.

II. Experimental Procedures:

General procedure for the reaction in Schlenk Line.
In a Schlenk tube, amino-aldehydes or amino-esters (0.15 mmol, 1 equiv.), phospholene (5 mol %) *bis*(4-nitrophenyl)phosphate (5 mol %), and freshly distilled degassed toluene (0.15 M) were added. Dialkyl acetylene dicarboxylate (0.15 mmol, 1 equiv.) and phenylsilane (1 equiv.) were then added using microsyringes and the reaction mixture was heated at 60°C for the aldehyde derivatives and 120°C for the ester derivatives for 16 hours. The crude reaction mixture was concentrated and purified by flash chromatography using 4g GraceResolv™ silica gel pre-packed column and EtOAc/heptanes as eluent (0 to 40% of EtOAc over 25 min, 18 mL/min).

General procedure for the Microwave assisted reaction.
In a Standard Vial G10, amino-aldehydes or amino-esters (0.15 mmol, 1 equiv.), phospholene (5 mol %) *bis*(4-nitrophenyl)phosphate (5 mol %), and freshly distilled degassed toluene (0.15 M) were added. Dialkyl acetylene dicarboxylate (0.15 mmol, 1 equiv.) and phenylsilane (1 equiv.) were then added using microsyringes. The vial was sealed by reusable snap-cap with PTFE coated silicone septum and the reaction mixture was then heated at 100°C for the aldehyde derivatives and 120°C for the ester derivatives for 2 hours. The crude reaction mixture was concentrated and purified by flash chromatography using 4g GraceResolv™ silica gel pre-packed column and EtOAc/heptanes as eluent (0 to 40% of EtOAc over 25 min, 18 mL/min).

Diethyl 7-bromo-9*H*-pyrrolo[1,2-a]indole-2,3-dicarboxylate (3a)[9] (52 mg, 92 % yield; Microwave: 53 mg, 93% yield). Yellow solid; mp 101–104°C; R_f 0.32 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.5 Hz, 1H), 7.50-7.46 (1H, m), 7.39 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.44-6.41 (m, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6 (*C*O), 161.2 (*C*O), 139.8 (*C*), 138.6 (*C*), 137.1 (*C*), 130.8 (*C*H), 128.7 (*C*H), 125.4 (*C*), 119.0 (*C*), 118.2 (*C*), 116.2 (*C*H), 104.6 (*C*H), 61.5 (CH_2), 60.8 (CH_2), 28.9 (CH_2), 14.3 (CH_3), 14.1 (CH_3); IR: ν_{max} = 2980, 1706, 1479, 1467, 1270, 1212, 1181, 1113, 1053, 751 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{17}BrNO_4$ $[M+H]^+$: 378.0341, found: 378.0312.

Dimethyl 3*H*-pyrrolizine-5,6-dicarboxylate (3ba) (29 mg, 90 % yield; Microwave: 30 mg, 91% yield). White solid; mp 63–65°C; R_f 0.41 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.55 (dt, *J* = 6.0, 2.1 Hz, 1H), 6.46 (dt, *J* = 6.0, 1.9 Hz, 1H), 6.35 (bs, 1H), 4.68-4.64 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9 (*C*O), 160.8 (*C*O), 143.6 (*C*), 132.6 (*C*H), 124.0 (*C*), 122.2 (*C*H), 120.4 (*C*), 102.3 (*C*H), 55.4 (CH_2), 51.8 (CH_3), 51.7 (CH_3); IR: ν_{max} = 2997, 2952, 1730, 1693, 1486, 1447, 1317, 1290, 1252, 1206, 1184, 1151, 1138, 1079, 1055, 951, 777 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}NO_4$ $[M+H]^+$: 222.0766, found: 222.0760.

Diethyl 3*H*-pyrrolizine-5,6-dicarboxylate (3bb) (31 mg, 83 % yield; Microwave: 36 mg, 85% yield). Yellow solid; mp 48–50 °C; R_f 0.39 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.56 (dt, *J* = 6.0, 2.1 Hz, 1H), 6.46 (dt, *J* = 6.0, 1.9 Hz, 1H), 6.35 (bs, 1H), 4.68-4.64 (m, 2H), 4.34-4.21 (m, 4H), 1.33-1.26 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7 (*C*O), 160.4 (*C*O), 143.5 (*C*), 132.4 (*C*H), 124.6 (*C*), 122.3 (*C*H), 120.3 (*C*), 101.9 (*C*H), 60.6 (CH_2), 55.3 (CH_2), 14.33 (CH_3), 14.30 (CH_3); IR: ν_{max} = 2982, 1725, 1688, 1487, 1442, 1286, 1250, 1210, 1151, 1077, 1054, 766 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{16}NO_4$ $[M+H]^+$: 250.1079, found: 250.1066.

Di-*tert*-butyl 3*H*-pyrrolizine-5,6-dicarboxylate (3bc) (41 mg, 89% yield; Microwave: 41 mg, 89% yield). Orange oil; R_f 0.82 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.61 (dt, *J* = 6.0, 2.1 Hz, 1H), 6.48 (dt, *J* = 6.0, 1.9 Hz, 1H), 6.31 (bs, 1H), 4.75-4.62 (m, 2H), 1.60 (s, 9H), 1.58 (s,

9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7 (*C*O), 159.4 (*C*O), 142.7 (*C*), 131.9 (*C*H), 126.2 (*C*), 122.4 (*C*H), 121.7 (*C*), 101.4 (*C*H), 81.3 (*C*), 80.4 (*C*), 55.1 (CH_2), 28.4 (CH_3), 28.2 (CH_3); HRMS (ESI) calcd. for $C_{17}H_{23}NNaO_4$ $[M+Na]^+$: 328.1525, found: 328.1522.

Diethyl 4*H*-pyrrolo[3,2,1-*ij*]quinoline-4,5-dicarboxylate (3c) (43 mg, 96 % yield; Microwave: 44 mg, 99% yield). Yellow solid; mp 93–95 °C; R_f 0.76 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 1.1 Hz, 1H), 7.48 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.22 (d, *J* = 3.4 Hz, 1H), 7.07-6.91 (m, 2H), 6.47 (d, *J* = 3.0 Hz, 1H), 6.04 (s, 1H), 4.30-4.20 (m, 2H), 4.19-4.01 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3 (*C*O), 165.3 (*C*O), 134.6 (*C*H), 133.4 (*C*), 126.2 (*C*H), 125.1 (*C*), 124.3 (*C*H), 122.1 (*C*), 121.5 (*C*H), 120.9 (*C*H), 116.0 (*C*), 103.7 (*C*H), 62.1 (CH_2), 61.1 (CH_2), 58.4 (*C*H), 14.3 (CH_3), 14.0 (CH_3); IR: ν_{max} = 2982, 2931, 1743, 1699, 1598, 1370, 1288, 1248, 1212, 1058, 1024, 1151, 794 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{18}NO_4$ $[M+H]^+$: 300.1236, found: 300.1223.

Diethyl 1-bromo-4*H*-pyrrolo[3,2,1-*ij*]quinoline-4,5-dicarboxylate (3d) (53 mg, 94 % yield; Microwave: 56 mg, 99% yield). Green solid; mp 67–70 °C; R_f 0.67 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 1.1 Hz, 1H), 7.40 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.24 (s, 1H), 7.10-6.98 (m, 2H), 5.96 (bs, 1H), 4.24 (qd, *J* = 7.2, 1.1 Hz, 2H), 4.19-4.03 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8 (*C*O), 165.0 (*C*O), 133.8 (*C*H), 132.8 (*C*), 125.1 (*C*H), 124.5 (*C*), 122.6 (*C*H), 122.4 (*C*H), 121.9 (*C*), 121.6 (*C*H), 116.2 (*C*), 92.7 (*C*), 62.3(CH_2), 61.4 (CH_2), 58.2 (*C*H), 14.2 (CH_3), 14.0 (CH_3); IR: ν_{max} = 2982, 2931, 1743, 1602, 1598, 1368, 1289, 1244, 1214, 1179, 1069, 1023, 790, 742 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{17}BrNO_4$ $[M+H]^+$: 378.0341, found: 378.0342.

5,6-diethyl 2-methyl 6*H*-indolo[3,2,1-*de*][1,5] naphthyridine-2,5,6-tricarboxylate (3e) (53 mg, 86 % yield; Microwave: no reaction). Yellow-orange solid; mp 167–170 °C; R_f 0.17 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (s, 1H), 8.14 (s, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 6.27 (s, 1H), 4.37-4.23 (m, 2H), 4.03-4.15 (m, 2H), 3.99 (s, 3H), 1.32 (t, *J* = 7.3 Hz, 3H), 1.08 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (*C*O), 166.3 (*C*O), 164.5 (*C*O), 141.0 (*C*), 139.4 (*C*), 135.9 (*C*), 135.6 (*C*), 135.2 (*C*H), 129.1 (*C*H), 128.4 (*C*), 125.9 (*C*), 122.8 (*C*H), 122.3 (*C*), 122.1 (*C*H), 119.8 (*C*H), 111.6 (*C*H), 62.5 (CH_2), 61.8 (CH_2), 57.3 (*C*H), 52.8 (CH_3), 14.1 (CH_3), 13.9 (CH_3); IR: ν_{max} = 2982, 2949, 1740, 1707, 1635, 1435, 1373, 1269, 1248, 1223, 1192, 1165, 1116, 1020, 767, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{21}N_2O_6$ $[M+H]^+$: 409.1400, found: 409.1389.

1-*tert*-butyl- 2,3-diethyl quinoline-1,2,3(2*H*)-tricarboxylate (3f) (41 mg, 73% yield (formation of a by-product (10%)); Microwave: 39 mg, 70% yield). White solid; mp 131–134 °C; R_f 0.76 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (bs, 1H), 7.57 (s, 1H), 7.39-7.33 (m, 1H), 7.30-7.26 (m, 2H), 7.13-7.08 (m, 1H), 6.31 (s, 1H), 4.42-4.29 (m, 2H), 4.15-3.99 (m, 2H), 1.58 (s, 9H) 1.39 (t, *J* = 7.0 Hz, 3H), 1.16 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3 (*C*O), 164.8 (*C*O), 152.4 (*C*), 136.7 (*C*), 134.1 (*C*H), 130.3 (*C*H), 128.6 (*C*H), 124.8 (*C*), 124.1 (*C*H), 123.8 (*C*H), 82.5 (*C*), 61.5 (CH_2), 61.1 (CH_2), 53.3 (*C*H), 28.2 (CH_3), 14.2 (CH_3), 13.9 (CH_3); IR: ν_{max} = 2980, 2936, 2908, 1744, 1710, 1368, 1290, 1247, 1230, 1202, 1156, 1128, 1025, 946, 856, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{25}NNaO_6$ $[M+Na]^+$: 398.1580, found: 398.1573.

Diethyl 1-tosyl-1,2-dihydrobenzo[4,5]thieno[3,2-*b*]pyridine-2,3-dicarboxylate (3g) (44 mg, 60% yield; Microwave: 44 mg, 60% yield). Yellow solid; mp 173–176 °C; R_f 0.67 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.69 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.48-7.31 (m, 2H), 7.19-7.13 (m, 2H), 7.02-6.89 (m, 3H), 6.05 (s, 1H), 4.26-4.09 (m, 2H), 4.03-3.85 (m, 2H), 2.27 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8 (*C*O), 163.7 (*C*O), 144.5 (*C*), 138.9 (*C*), 134.7 (*C*), 134.1 (*C*), 131.3 (*C*), 129.0 (*C*H), 128.1 (*C*), 127.2 (*C*H), 127.0 (*C*H), 126.5 (*C*H), 125.6 (*C*H), 125.3 (*C*H), 123.2 (*C*), 122.4 (*C*H), 62.1 (CH_2), 61.1 (CH_2), 57.4 (*C*H), 21.5 (CH_3), 14.3 (CH_3), 13.8 (CH_3); IR: ν_{max} = 3068, 2982, 2940, 1739, 1703, 1608, 1500, 1365, 1292, 1258, 1236, 1185, 1170, 1145, 1089, 1020, 769, 731 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{24}NO_6S_2$ $[M+H]^+$: 486.1045, found: 486.1037.

Diethyl 1-tosyl-1,2,5,6-tetrahydropyridine-2,3-dicarboxylate (5a) (45 mg, 79 % yield; Microwave: 46 mg, 81% yield). Colorless oil; R_f 0.5 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.13-7.04 (m, 1H), 5.43 (s, 1H), 4.30-4.17 (m, 2H), 4.14-3.97 (m, 2H), 3.89 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.30-3.19 (m, 1H), 2.42 (s, 3H), 2.39-2.28 (m, 1H), 2.26-2.14 (m, 1H), 1.29 (t, *J* = 7.3 Hz, 3H), 1.19 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8 (*C*O), 164.5 (*C*O), 143.6 (*C*), 139.3 (*C*H), 137.1 (*C*), 129.5 (2*C*H), 127.2 (*C*H), 127.1 (*C*), 61.6 (CH_2), 61.0 (CH_2), 54.2 (*C*H), 38.5 (CH_2), 24.5 (CH_2), 21.5 (CH_3), 14.1 (CH_3), 13.9 (CH_3); IR: ν_{max} = 2982, 2937, 2905, 1732, 1712, 1345, 1263, 1160, 1102, 1047, 1025, 996, 816, 716 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{24}NO_6S$ $[M+H]^+$: 382.1324, found: 382.1319.

1-benzyl 2,3-diethyl 5,6-dihydropyridine-1,2,3(2*H*)-tricarboxylate (5b) (49 mg, 90% yield; Microwave: 50 mg, 92% yield). Orange oil; R_f 0.53 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$, rotamers): δ = 7.46-7.28 (m, 5H), 7.12 (m, 1H), 5.63 (s, 0.4H), 5.52 (s, 0.6H), 5.34-5.08 (m, 2H), 4.37-4.08 (m, 5H), 3.23-2.92 (m, 1H), 2.52-2.18 (m, 2H), 1.36-1.14 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers): δ = 165.0 (*C*O), 139.1 (*C*H), 138.4 (*C*H), 136.4 (*C*), 128.5 (*C*H), 128.4 (*C*H), 128.1 (*C*H), 128.0 (*C*H), 127.7 (*C*H), 127.5 (*C*), 67.6 (CH_2), 67.5 (CH_2), 61.6 (CH_2), 60.9 (CH_2), 54.0 (*C*H), 53.8 (*C*H), 37.8(CH_2), 37.2 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 14.1 (CH_3), 14.0 (CH_3); IR: ν_{max} = 2982, 2937, 2902, 1736, 1706, 1657, 1422, 1367, 1337, 1285, 1236, 1210, 1192, 1108, 1051, 1024, 762, 699 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}NO_6$ $[M+H]^+$: 362.1604, found: 362.1605.

Diethyl 4-ethoxy-1-tosyl-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (5c) (49 mg, 80 % yield; Microwave: 51 mg, 83 % yield). Yellow oil; R_f 0.67 (40% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 4.92 (dd, *J* = 4.5, 1.5 Hz, 1H), 4.41 (dd, *J* = 15.1, 4.5 Hz, 1H), 4.26 (dd, *J* = 15, 1.7 Hz, 1H), 4.16-3.95 (m, 6H), 2.37 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.17 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3 (*C*O), 163.3 (*C*O), 161.6 (*C*O), 144.3 (*C*), 134.1 (*C*O), 129.9 (*C*H), 127.5 (*C*H), 101.0 (*C*), 68.3 (*C*H$_2$), 65.1 (*C*H), 61.5 (*C*H$_2$), 60.2 (*C*H$_2$), 52.1 (*C*H$_2$), 21.5 (*C*H$_3$), 15.2 (*C*H$_3$), 14.1 (*C*H$_3$), 14.0 (*C*H$_3$); IR: ν_{max} = 2984, 2943, 2908, 1741, 1644, 1369, 1333, 1211, 1163, 1090, 1027, 815, 764 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{26}NO_7S$ $[M+H]^+$: 412.1430, found: 412.1425.

1-benzyl 2,3-diethyl 4-ethoxy-1H-pyrrole-1,2,3(2H,5H)-tricarboxylate (5d) (54 mg, 92 % yield, Microwave: 57 mg, 97% yield). Light yellow solid; mp 95–98 °C; R_f 0.43 (40% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$, rotamers): δ = 7.37-7.20 (m, 5H), 5.18-4.96 (m, 3H), 4.54-4.27 (m, 2H), 4.19-4.01 (m, 5H), 4.00-3.82 (m, 1H), 1.37-1.28 (m, 3H), 1.25-1.14 (m, 4H), 1.02 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers): δ = 171.4 (*C*O), 171.1 (*C*O), 164.1 (*C*O), 163.9 (*C*O), 161.9 (*C*O), 153.7 (*C*), 136.0 (*C*), 135.8 (*C*), 128.5 (*C*H), 128.4 (*C*H), 128.3 (*C*H), 128.2 (*C*H), 128.1 (*C*H), 128.0 (*C*H), 100.9 (*C*), 100.7 (*C*), 68.0 (*C*H$_2$), 67.6 (*C*H$_2$), 64.0 (*C*H), 63.6 (*C*H), 61.4 (*C*H$_2$), 61.2 (*C*H$_2$), 60.0 (*C*H$_2$), 50.9 (*C*H$_2$), 50.6 (*C*H$_2$), 15.2 (*C*H$_3$), 14.2 (*C*H$_3$), 14.1 (*C*H$_3$), 13.9 (*C*H$_3$); IR: ν_{max} = 2983, 2934, 2908, 1737, 1717, 1640, 1410, 1354, 1240, 1212, 1113, 1059, 1028, 768 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{26}NO_7$ $[M+H]^+$: 392.1709, found: 392.1713.

(2*R*,5*S*)-1-benzyl 2,3-diethyl 5-benzyl-4-ethoxy-1*H*-pyrrole-1,2,3(2*H*,5*H*)-tricarboxylate (5e) (40 mg, 55% yield). Yellow oil; R_f 0.82 (40% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$, rotamers): δ = 7.35-7.19 (m, 5H), 7.18-7.01 (m, 4.2H), 5.24-4.99 (m, 2.8H), 4.76 (dd, *J* = 7.5, 3.8 Hz, 0.5H), 4.66-4.52 (m, 1.1H), 4.21-3.94 (m, 5.7H), 3.80 (q, *J* = 7.3 Hz, 1.1H), 3.36 (dd, *J* = 13.9, 4.1 Hz, 0.5H), 3.17 (dd, *J* = 13.6, 6.0 Hz, 0.5H), 3.04 (dd, *J* = 13.6, 6.8 Hz, 1.5H), 1.28-1.14 (m, 5.3H), 1.14-0.96 (m, 5H);^{13}C NMR (75 MHz, $CDCl_3$, rotamers): δ = 171.0 (*C*O), 170.8 (*C*O), 166.2 (*C*O), 165.4 (*C*O), 162.3 (CO), 154.2 (*C*), 153.6 (*C*), 137.8 (*C*), 137.6 (*C*), 136.2 (*C*), 135.9 (*C*), 129.7 (*C*H), 129.5 (*C*H), 128.4 (*C*H), 128.2 (*C*H), 128.0 (*C*H), 127.8 (*C*H), 126.4 (*C*H), 102.5 (*C*), 101.71 (*C*), 69.4 (*C*H$_2$), 69.2 (*C*H$_2$), 67.5 (*C*H$_2$), 67.3 (*C*H$_2$), 64.9 (*C*H), 64.7 (*C*H), 64.6 (*C*H), 64.0 (*C*H), 61.4 (*C*H$_2$), 61.3 (*C*H$_2$), 60.4 (*C*H$_2$), 41.3 (*C*H$_2$), 40.6 (*C*H$_2$), 15.0 (*C*H$_3$), 14.1 (*C*H$_3$), 13.9 (*C*H$_3$); IR: ν_{max} = 2981, 2934, 2905, 1739, 1711, 1634, 1407, 1345, 1270, 1213, 1109, 1062, 1027, 742, 700 cm^{-1};HRMS (ESI) calcd. for $C_{27}H_{32}NO_7$ $[M+H]^+$: 482.2179, found: 482.2199.

(2*S*,5*S*)-1-benzyl 2,3-diethyl 5-benzyl-4-ethoxy-1*H*-pyrrole-1,2,3(2*H*,5*H*)-tricarboxylate (5e') (20 mg, 27% yield). Yellow oil; R_f 0.75 (40% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$, rotamers): δ = 7.41-7.21 (m, 6.3H), 7.14-7.05 (m, 3.7H), 6.97-6.91 (m, 1.4H), 6.84-6.77 (m, 1H), 5.32-5.21 (m, 0.5H), 5.15-5.01 (m, 2H), 4.97-4.90 (m, 0.5H), 4.87-4.81 (m, 0.5H), 4.32-4.18 (m, 3.6H), 4.18-4.02 (m, 1.5H), 4.02-3.91 (m, 2.5H), 3.89-3.69 (m, 1.5H), 3.47 (dd, *J* = 13.8, 5.5 Hz, 0.5H), 3.17 (dd, *J* = 13.9, 5.3 Hz, 0.5H), 2.97-2.85 (m, 1.2H), 1.34-1.26 (m, 3.8H), 1.18 (t, *J* = 7.2 Hz, 2H), 1.13-1.05 (m, 3.8H), 0.95 (t, *J* = 7.16 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers): δ = 171.4 (*C*O), 171.1 (*C*O), 164.1 (*C*O), 164.0 (*C*O), 161.6 (CO), 153.6 (*C*), 153.2 (*C*), 136.0 (*C*), 135.9 (*C*), 135.3 (*C*), 135.1 (*C*), 129.8 (*C*H), 129.7 (*C*H), 128.6 (*C*H), 128.5 (*C*H), 128.4 (*C*H), 128.2 (*C*H), 128.2 (*C*H), 128.1 (*C*H), 127.9 (*C*H), 126.7 (*C*H), 126.1 (*C*H), 102.8 (*C*), 69.6 (*C*H$_2$), 69.3 (*C*H$_2$), 67.7 (*C*H$_2$), 67.2 (*C*H$_2$), 65.0 (*C*H), 64.6 (*C*H), 64.2 (*C*H), 63.8 (*C*H), 61.3 (*C*H$_2$), 61.1 (*C*H$_2$), 60.2 (*C*H$_2$), 36.8 (*C*H$_2$), 35.3 (*C*H$_2$), 15.4 (*C*H$_3$), 14.0 (*C*H$_3$), 13.8 (*C*H$_3$); IR: ν_{max} = 2982, 2936, 2905, 1742, 1710, 1639, 1404, 1338, 1312, 1215, 1198, 1118, 1062, 1027, 768, 700 cm^{-1}; HRMS (ESI) calcd. for $C_{27}H_{32}NO_7$ $[M+H]^+$: 482.2179, found: 482.2181.

(7*S*)-diethyl 7-ethoxy-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-5,6-dicarboxylate (5f) (35 mg, 83% yield; Microwave: 36 mg, 84% yield). Yellow oil; R_f 0.27 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.5 (s, 1H), 4.33-4.22 (m, 2H), 4.16-4.05 (m, 2H), 4.01 (dd, *J* = 14.0, 7.0 Hz, 2H), 3.42-3.33 (m, 1H), 3.29-3.17 (m, 1H), 2.22-2.11 (m, 1H), 2.05-1.88 (m, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8 (*C*), 167.3 (*C*O), 165.2 (*C*O), 151.4 (*C*), 86.8 (*C*H), 62.1 (*C*H$_2$), 61.4 (*C*H$_2$), 61.0 (*C*H), 59.3 (*C*H$_2$), 48.4 (*C*H$_2$), 30.5 (*C*H$_2$), 23.1 (*C*H$_2$), 14.4 (*C*H$_3$), 14.1 (*C*H$_3$), 13.8 (*C*H$_3$); IR: ν_{max} = 2981, 2935, 2901, 1736, 1692, 1574, 1434, 1378, 1339, 1269, 1219, 1182, 1140, 1093, 1045, 1022, 792 cm^{-1}.

Synthesis of ylide 6.

In a round bottom flask, **4d** (50 mg, 0.21 mmol) and PPh_3 (55 mg, 0.21 mmol) were dissolved in DCM. **2a** (0.21 mmol, 34 µL) was added and the reaction was stirred overnight at room temperature. The crude reaction mixture was concentrated and purified by flash chromatography using 4g GraceResolv™ silica gel pre-packed column and EtOAc/heptanes as eluent (0 to 70% of EtOAc over 25 min, 18 mL/min) to obtain 141 mg (80 %) of the ylide **6** in two geometrical isomers as a yellow oil.

^{31}P NMR (202 MHz, $CDCl_3$): δ = ppm 27.0, 26.0; HRMS (ESI) calcd. for $C_{38}H_{41}NaO_8P$ $[M+H]^+$: 670.2570 found: 670.2570.

General procedure for the synthesis of cyclopentan-2-ene-1-one derivatives.

In a Schlenk tube, biacetyl or 1-phenylpropane-1,2-dione (0.6 mmol, 3 equiv.), phospholene (20 mol %) *bis*(4-nitrophenyl)phosphate (20 mol %), DIPEA (20 mol%), and freshly distilled degassed toluene (0.2 M) were added. Di-*tert*-butyl acetylene dicarboxylate (0.2 mmol, 1 equiv.) and $Me(EtO)_2SiH$ (2.8 equiv.) were then added using microsyringes and the reaction mixture was heated at 110 °C for 18 hours. The crude reaction mixture was concentrated and purified by flash chromatography using 4g GraceResolv™ silica gel pre-packed column and EtOAc/heptanes as eluent (30 to 40% of EtOAc over 25 min, 18 mL/min).

Di-*tert*-butyl 3-methyl-4-oxocyclopent-2-ene-1,2-dicarboxylate (8a)[24] (46 mg, 77% yield; Microwave: 39 mg, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (m, 1 H) 2.75 (dd, *J*=18.9, 7.9 Hz, 1 H) 2.48 (dd, *J*=18.9, 2.4 Hz, 1 H) 2.07 (d, *J*=2.4 Hz, 3 H) 1.56 (s, 9 H) 1.46 (s, 9 H)

Di-*tert*-butyl 4-oxo-3-phenylcyclopent-2-ene-1,2-dicarboxylate (8b) (37 mg, 51 % yield; Microwave: 38 mg, 53% yield). Yellow oil; R_f 0.76 (30% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.29 (m, 3H), 7.27-7.20 (m, 2H), 3.93 (dd, *J* = 7.6, 2.8 Hz, 1H), 2.82 (dd, *J* = 18.9, 7.9 Hz, 1H), 2.65 (dd, *J* = 18.9, 3.1 Hz, 1H), 1.41 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.2 (*C*O), 170.4 (*C*O), 163.9 (*C*O), 155.8 (*C*), 146.2 (*C*O), 130.0 (*C*O), 129.1 (*C*H), 128.8 (*C*H), 127.8 (*C*H), 82.9 (*C*), 82.1 (*C*), 45.5 (*C*H), 38.8 (CH_2), 27.9 (CH_2), 27.7 (CH_2); IR: ν_{max} = 2979, 2928, 1722, 1368, 1251, 1146, 844, 764, 697 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{26}NaO_5$ $[M+Na]^+$: 381.1678, found: 381.1680.

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FULL PAPER

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