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Imino-Diels–Alder Reactions of 1-Aryl-3-(trialkylsiloxy)-1,3-butadienes in Solution and the Solid Phase

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Imino-Diels–Alder reactions between 1-aryl- or 1-heteroaryl-3-(trialkylsiloxy)-1,3-butadienes and imines derived from ethyl glyoxylate have been studied. When an achiral imine was used, the diastereoselectivity depended on the nature of the aryl or heteroaryl system; diastereoselectivities > 90 % were observed with methoxyphenyl or indolyl substituents, but were much lower for nitro substituents. High diastereoselectivities were also achieved if a chiral imine derived from methylbenzylamine was used as the dienophile. Solid-supported imine dienophiles yielded the *N*-deprotected cycloadducts by direct cleavage from the resin with no diastereoselectivity.

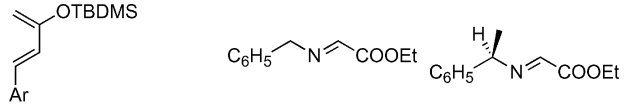
Introduction

The aza-Diels–Alder reaction of imines is a well-established procedure for obtaining differently substituted piperidines.[1] A large number of dienes that can be used in the Diels–Alder reaction with imines are described in the literature, among which Danishefsky's diene stands out due to its high reactivity, especially in the presence of Lewis acid catalysts. This diene has been employed in the synthesis of 2,3-dihydro-4-pyridones, which are starting materials for the synthesis of natural and non-natural products of interest.[2] According to this methodology, 2-phenyl-2,3-dihydro-4-pyridones have been synthesized from benzaldimines and analogues of Danishefsky's diene.[3] The asymmetric aza-Diels–Alder reaction of Danishefsky's diene with imines has also been performed by a number of different approaches, for example, with chiral imines,[4] chiral catalysts,[5] or chiral ionic liquids[6] as the chiral medium, to produce 2,3-dihydro-4-pyridones with regio-, diastereo-, and enantioselective control. The reaction has also been studied from a theoretical viewpoint.[7]

Among other applications of the aza-Diels–Alder reaction, the synthesis of enantiopure pipecolic acids and their derivatives continues to attract interest due to their important role in physiological processes.[8]

Based on the reactivity and utility of Danishefsky's diene, several years ago we designed a new series of dienes with the 1-aryl-3-(trialkylsiloxy)-1,3-butadiene structure, but with an aromatic substituent instead of the 1-methoxy group.[9] These compounds are interesting building blocks for the synthesis of polycyclic compounds and have been used in Diels–Alder reactions for the synthesis of analogues of anthracyclines and indolocarbazole alkaloids.[10] Recently, we started to study the imino-Diels–Alder (IDA) reactions of these dienes, which yield cycloaddition products; the reactivity of these products with different hydrazines has recently been published, although the details of the IDA reaction and the stereochemistry of the cycloadducts has not been discussed yet.[11]

In the study reported herein, the Diels–Alder reactions of the substituted dienes **1**–**6** with activated imines (Figure 1), obtained from ethyl glyoxylate, have been examined in order to explore its usefulness in the synthesis of new 6-aryl-4-oxopipecolic acid derivatives. The diastereoselectivity of the reaction between unsubstituted 1-phenyl-3-(trialkylsiloxy)-1,3-butadiene and different α-substituted alkylimines depends on the bulkiness of the α-substituent of the imine, the *trans* diastereomers being detected as the major reaction products in all cases.[12] The result of different substituents on the imine in the hetero-Diels–Alder reaction with 3-(*tert*-



1 Ar = 3,4,5-$(MeO)_3C_6H_2$
2 Ar = 2-$MeOC_6H_4$
3 Ar = 2-$O_2NC_6H_4$
4 Ar = 3-$O_2NC_6H_4$
5 Ar = *N*-methyl-3-indolyl
6 Ar = *N*-($C_6H_5SO_2$)-3-indolyl

7 **8**

Figure 1. Structure of 1-aryl- and 1-heteroaryl-3-(trialkylsiloxy)-1,3-butadienes **1**–**6** and imines **7** and **8**.

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butyldimethylsiloxy)-1-phenyl-1,3-butadiene has recently been investigated under Brønsted acid catalysis conditions.[13] Nevertheless, to the best of our knowledge, the effect on reactivity and diastereoselectivity produced by substituents on the phenyl group or the presence of other aromatic rings at the 1-position of the diene has not been studied so far.

During these studies on the IDA reaction an unexpected difficulty in *N*-deprotection was observed. Therefore, the use of solid-supported imines as dienophiles has been studied with the aim of determining their effect on the stereoselectivity of the reaction and their utility in the deprotection step. Finally, the chiral reaction with the imine obtained from α-methylbenzylamine and ethyl glyoxylate has been studied to determine its effect on the stereoselectivity of the process.

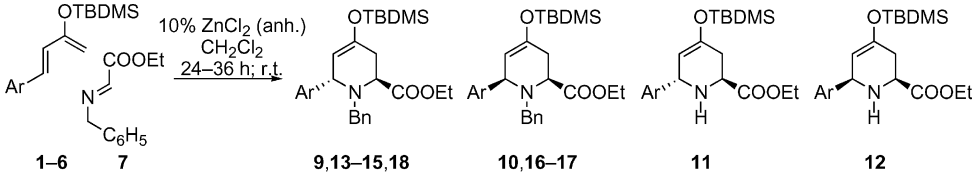
Results and Discussion

The influence of the aryl substituent on C-1 of the diene on the IDA reaction has been explored using dienes **1**–**4** with activating (methoxy) or deactivating (nitro) groups on the phenyl ring, and dienes **5** and **6** that have indolyl moieties in that position (Figure 1).

As has been described previously, the reactive imine **7**, activated by the electron-withdrawing carboxylate group on the carbon atom, has been used with simple dienes and TFA as catalyst,[14] yielding products from *endo* attack, although the reaction with Danishefsky's diene failed due to diene decomposition. Among other Lewis acid catalysts, $ZnCl_2$ is the most frequently used to promote this reaction.[15] Also the effect of various catalysts on the formation of cycloaddition versus Mannich-type products has been studied.[16]

We carried out the reaction between diene **1** and imine **7** in the presence of 10% anhydrous $ZnCl_2$ as catalyst (Scheme 1). A single diastereomer (**9**) was formed according to ^{1}H NMR spectroscopy. After isolation, the regiochemistry and *trans* relationship between the carboxylate and trimethoxyphenyl groups were unequivocally established by single-crystal X-ray analysis (Figure 2). A preferred pseudoequatorial disposition of the trimethoxyphenyl moiety and a pseudoaxial disposition for the ethyl carboxylate was observed.[17] The 1D and 2D NMR spectroscopic data for compound **9** were used for comparisons with other related products in order to assign their stereochemistries. In addition to **9**, the *cis* stereoisomer **10** and a 1:1 mixture of *trans* and *cis* debenzylated cycloadducts **11** and **12** were isolated in very low yields (Scheme 1). The ^{1}H and ^{13}C NMR spectra of the two diastereomers are very similar, the major difference being the shielding of the benzylic methylene carbon atom in the *trans* isomer ($\delta < 55$ ppm) in comparison to the *cis* isomer ($\delta > 57$ ppm).

Similar results (Scheme 1) were obtained with diene **2** and imine **7**. Cycloadduct **13** was isolated in a diastereomeric excess > 95%. In these reactions, no product from a Mannich-type addition was detected. The regiochemistry of the products was as expected for activated imines reacting with electron-rich 2-siloxydienes; the *trans* stereochemistry has been obtained for many related imino-Diels–Alder reactions.[12,18]



Diene	Ar	Time	(Crude ratio)	Isolated yield (%)
1	3,4,5-$(MeO)_3C_6H_2$	24 h	**9**/**10**/**11**/**12** (90:–:5:5)	**9** (73) **10** (<2) **11** (2) **12** (2)
2	2-$MeOC_6H_4$	24 h	**13** (*de* > 95)	**13** (72)
3	2-$O_2NC_6H_4$	36 h	**14**/**16** (60:40)	**14** (40) **16** (35)
4	3-$O_2NC_6H_4$	36 h	**15**/**17** (60:40)	**15** (30) **17** (28)
6	*N*-($C_6H_5SO_2$)-3-indolyl	24 h	**18** (*de* > 95)	**18** (55)

Scheme 1. Synthesis of **9**–**18**.

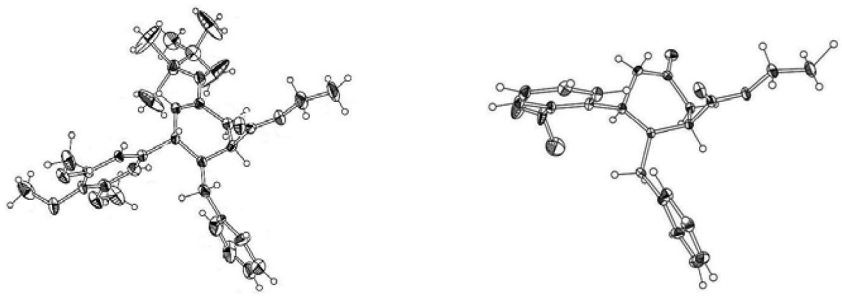


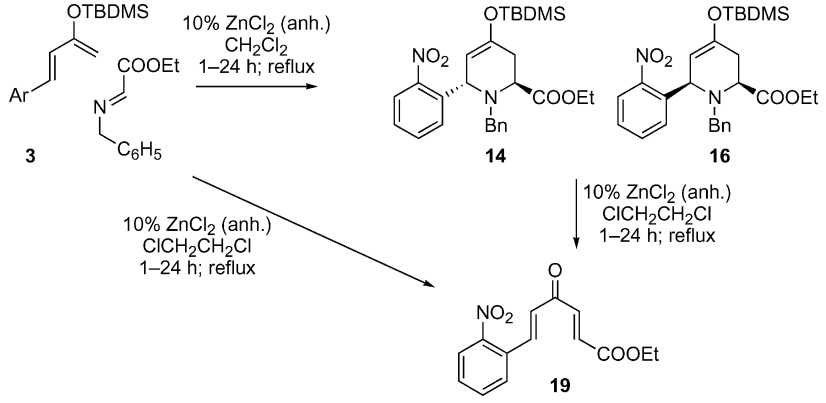
Figure 2. ORTEP drawing of crystal structures of **9** and **24**.

After the imino-Diels–Alder reaction of dienes **1** and **2**, reactions with siloxydienes **3** and **4** were carried out to determine the effect of the nitro group. In both cases, the reaction was slower than with dienes **1** or **2**, and longer reaction times were required for the diene to completely disappear. Interestingly, in these reactions the *trans* (**14** and **15**) and *cis* (**16** and **17**) cycloadducts were formed in a 6:4 ratio. They were separated and fully characterized by NMR spectroscopy, their relative stereochemistries being directly established by comparison with **9** and **10**. After the high diastereoselectivity (*trans* > 90%) observed for the cycloaddition reactions of aryl dienes **1** and **2**, no stereoselectivity was observed for the reactions of 1-(2-nitrophenyl)- and 1-(3-nitrophenyl)-3-(trialkylsiloxy)butadienes (**3** and **4**). Steric and electronic effects and reaction conditions can influence the second cyclization step, the step that is responsible for the relative stereochemistry of the product, and contribute to the loss of stereoselectivity.[19]

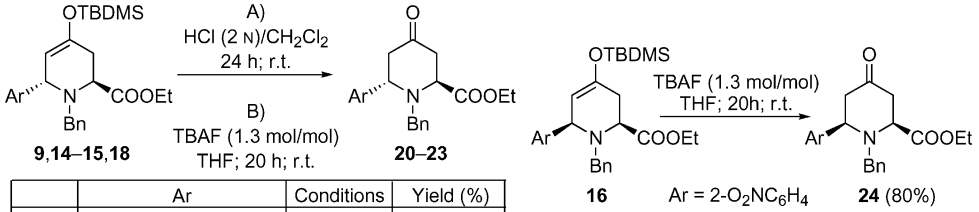
To determine the effect of temperature and other solvents on the reaction of diene **3** (Scheme 2), dichloromethane and dichloroethane were used at reflux. The evolution of the reaction was monitored by ^{1}H NMR spectroscopy for 24 h. No effect was produced on the stereochemical course of the reaction under the former conditions, and elimination to dienone **19** was observed in dichloroethane from the beginning of the reaction. If a mixture of cycloadducts (**14** and **16**) is maintained in dichloroethane under these reaction conditions, complete elimination reaction eventually takes place.

Deprotection of compound **9** to ketone **20** was carried out with 2 N hydrochloric acid in THF or with 1.3 equiv. of TBAF, which gave better yields. The other adducts were treated under the latter conditions to give the ketones **21**–**24** (Scheme 3). The structure of the *cis* compound **24** was confirmed by X-ray diffraction studies, which showed a semi-boat conformation with the ester group in a pseudoaxial disposition and the nitrophenyl in a pseudoequatorial disposition (Figure 2).

In order to investigate the effect of the indolyl group as a substituent at the 1-position in the siloxydiene, we prepared dienes **5** and **6**. Under the same conditions as those used in the previous reactions, diene **5** was transformed into the corresponding enone, and no signals corresponding to the formation of the cycloadduct could be detected by ^{1}H NMR spectroscopy. However, the presence of the withdrawing sulfonyl group stabilized the diene **6**, which does not decompose, and its total transformation into the cycloadduct was observed. The major reaction product (diastereomeric excess > 90%) was the *trans* isomer **18**, and its treatment with TBAF yielded the ketone **23**. These stereochemical results are similar to those obtained with dienes **1** and **2**, as commented above.



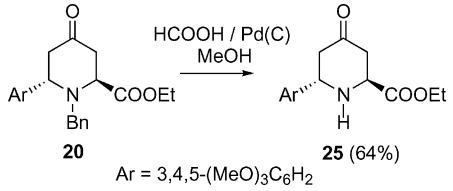
Scheme 2. Effect of solvent and temperature on the reaction products.



	Ar	Conditions	Yield (%)
9	3,4,5-$(MeO)_3C_6H_2$	A	**20** (30)
9	3,4,5-$(MeO)_3C_6H_2$	B	**20** (80)
14	2-$O_2NC_6H_4$	B	**21** (75)
15	3-$O_2NC_6H_4$	B	**22** (73)
18	*N*-($C_6H_5SO_2$)-3-indolyl	B	**23** (56)

Scheme 3. Deprotection of the adducts to yield ketones **20**–**24**.

Hydrogenolysis of the synthesized 1-benzyl-4-oxopiperidines was attempted under a variety of common conditions. Nevertheless, only **20** afforded the free amine **25** in a moderate yield with Pd/C in a mixture of formic acid and methanol (Scheme 4).[20] Taking into consideration the fact that solid-phase synthesis has been successfully applied to the preparation of pyridones using imines supported on polymers, we decided to extend the IDA study and to profit from the easy cleavage of the cycloadducts from the resin and also to study the diastereoselectivity of the reaction.[21]



Scheme 4. Formation of **25**.

The imine can be generated from a polymer-bound benzaldehyde or polymer-bound aryl/benzylamines.[22] In this work, the supported imine was prepared by mixing the polymer-bound benzylamine with ethyl glyoxylate and molecular sieves (4 Å) in CH_2Cl_2 at room temperature under different conditions (see Table 1 and the Experimental Section). The formation of the **7**-bound imine resins (**I**–**III** depending on the reaction conditions) was monitored by IR spectroscopy.[23] For the solid-phase IDA we used the same conditions as those employed in solution: $ZnCl_2$ as catalyst and CH_2Cl_2 as solvent (Scheme 5). First, the reaction between **I** and **3** was carried out at room temperature, but no evolution was detected. Next, the reaction was performed at reflux. The mixture was filtered, washed with CH_2Cl_2 and the filtrate concentrated. In this filtrate the cycloadduct **26** was isolated in 35% yield. Cleavage of the cycloadduct from the resin was attempted by treatment with different mixtures of TFA/CH_2Cl_2 or TBDMSOTf, but no further amounts of compound **26** were recovered.[24]

To test the reproducibility of the reaction and to improve the yields, different preparations of imine-resin, diene (**2** or **4**), imine-resin molar ratios, and reaction times were used. In all the experiments, deprotected cycloadducts (**27** or **28**) were obtained after filtration and concentration of the filtrate. It is noticeable that the yield of cycloadduct **27** was increased to 71%.

Under the conditions required for the solid-phase IDA reaction, no diastereoselectivity was observed. Heating of the CH_2Cl_2 at reflux was necessary for the evolution of the reaction, and this probably also had a strong effect on the stereochemical results. A mixture of stereoisomers of the 4-oxopipecolate derivative **29**, produced by treatment of **26** with TBAF, was also observed.

In this new contribution to solid-phase IDA reactions, it is especially noteworthy that all the cycloadducts were isolated as *N*-deprotected products, independent of the nature of substituents on the phenyl ring, and also good total yields were observed relative to those produced by a two-step process. The direct cleavage from the resin can be explained by the use of the crude product of the diene preparation, which contained an excess of TBDMSOTf in the medium, which has also been reported to catalyze the Diels–Alder reaction.[9b]

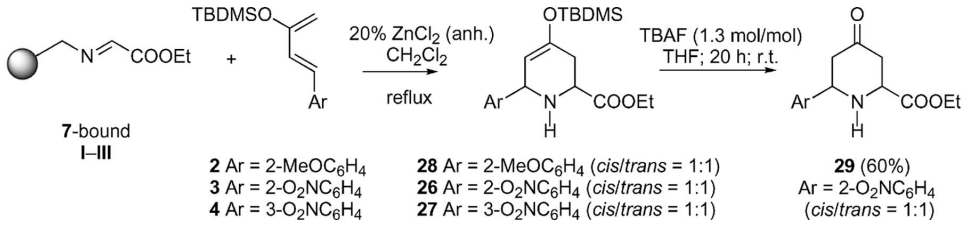
With the aim of determining the effect of chiral imines on the diastereoselectivity, we decided to study the reactions of the poorly diastereoselective (2-nitrophenyl)butadiene **3** and the highly diastereoselective indolylbutadiene **6** with chiral imines (Scheme 6). It is well established in the literature that a highly enantioselective synthesis of piperidines can be achieved by using chiral imines.[25] The reaction of chiral imines derived from chiral benzylamines has been studied with Danishefsky's diene under different conditions to determine their applicability in diastereoselective reactions.[26] Accordingly, we decided to prepare imine **8** from (*R*)-α-methylbenzylamine and ethyl glyoxylate.[27]

We applied the same reaction conditions as those used previously. However, after 30 h only a partial transforma-

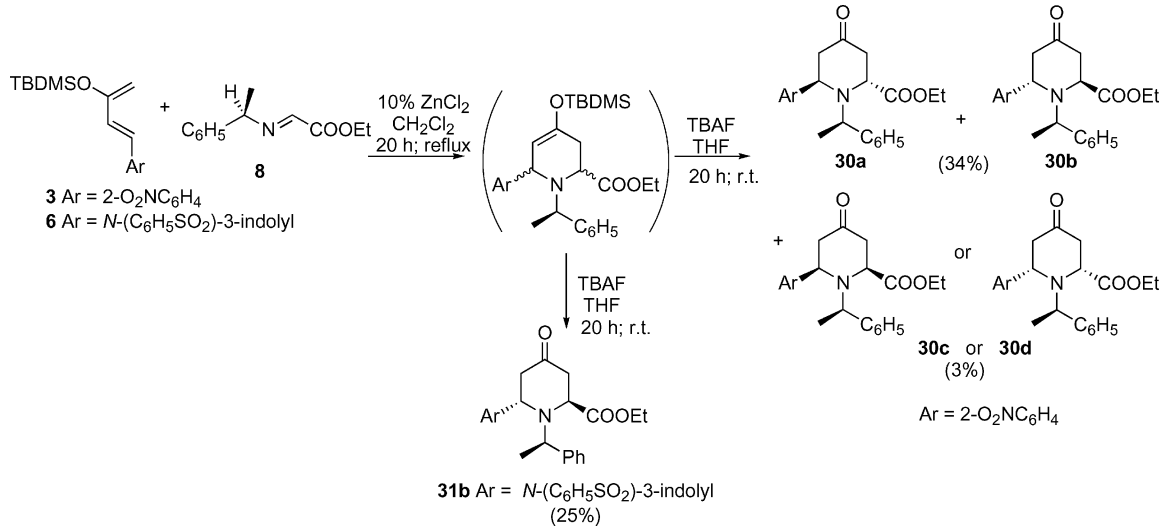
Table 1. Conditions used for the formation of imine resin and reaction conditions for the synthesis of **26**–**28**.

Ethyl glyoxylate [mmol]	Resin[a] [mmol]	*t* [h]	Imine-resin[b]	Imine-resin/diene (molar ratio)	*t* [h]	Product	Yield [%]
1.96	1.96	5	**I**	**I/3** (1:1)	24	**26**	35
1.96	1.96	24	**II**	**II/4** (1:1)	72	**27**	25
				II/2 (1:1)	72	**28**	48
2.50	1.67	5	**III**	**III/4** (2:1)	72	**27**	71

[a] Loading 4.0 mmol/g. [b] **7**-bound.



Scheme 5. IDA reactions with polymer-bound imine **7**.



Scheme 6. Diels–Alder reactions of dienes **3** and **6** with imine **8**.

tion of diene **3** was detected, although when the reaction was maintained at reflux a total transformation occurred. Greater crowding due to the presence of an additional methyl group on the benzylamine can explain the lower reactivity observed in this case. HPLC analysis showed the presence of three compounds in a ratio of 7:4.5:1. The reaction product was treated with TBAF and then purified to give *trans* and *cis* diastereomers **30a**,**b** and **30c** or **30d** in a 11:1 ratio.

Spectroscopic analysis of **30a**,**b** revealed a mixture of the corresponding diastereomers in a 6:4 ratio. The major spectroscopic differences between **30a** and **30b** correspond to the chemical shifts of the benzylic methyl groups (δ = 1.26 vs. 1.07 ppm), 5-H (δ = 3.32/3.18 vs. 2.51 ppm), and 3-H protons (δ = 2.85/2.76 vs. 2.73/2.51 ppm) in the ^{1}H NMR spectra.

Compound **30c** (or **30d**) showed signals in the ^{1}H and ^{13}C NMR spectra that correspond to a single stereoisomer. Taking into consideration the similarity between the NMR spectroscopic data for the related compounds **24** and **30c** (or **30d**), which indicates a close relationship between the conformations of the two piperidones, the *cis* structure was assigned to this isomer, although no stereochemical assignment could be made from NOE difference experiments (Table 2, Figure 3) because the observed effects can be produced in both diastereomers **30c** (2*S*,6*R*,1′*R*) and **30d** (2*R*,6*S*,1′*R*). The low yields of the *cis* cycloadducts and their ketones prevented the isolation or detection of the other *cis* diastereomer which would have allowed a definitive identification of the facial stereodifferentiation in this case.

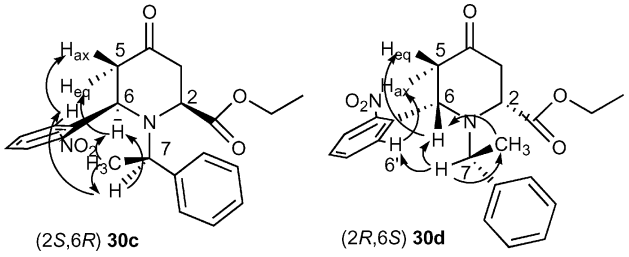


Figure 3. Representation of **30c** and **30d**, with the assignment of each of the observed NOEs.

These results confirmed the possible shift of the equilibrium for the *cis*/*trans* preference to a higher yield of the *trans* cycloadduct. For imine **7** a 6:4 ratio of *trans*-**14**/*cis*-**16** isomers was observed, whereas for chiral imine **8** a ratio of 11:1 for *trans*-**30a**,**b**/*cis*-**30c** (or **30d**) was produced due to the effect of the C-7 methyl group. The facial selectivity was, however, not highly affected by the presence of this stereodifferentiating element. These results agree with the absence of facial selectivity in other examples of the hetero-Diels–Alder reaction of imine **8**.[26d]

As we have described above, the reaction of the indolyldiene **6** with the nonchiral imine **7** gave *trans* cycloadduct

Table 2. Observed NOEs for compound **30c** (or **30d**).

Saturated[a]	Assignment	Observed[a]	Assignment
1.45	7-Me	3.83–3.86, 5.08, 7.2–7.4	2-H/7-H, 6-H, Ph
3.83–3.86	2-H/7-H	1.45, 2.77, 5.08, 7.2–7.4, 8.68	7-Me, 3-H, 6-H, Ph, 6′-H
5.08	6-H	1,45, 2.74, 3.83–3.86	7-Me, 5-H_{eq}, 2-H/7-H
8.68	6′-H	2.95, 7.2–7.4, 7.77	5-H_{ax}, Ph, 5′-H

[a] δ in ppm.

18. We therefore decided to study the stereochemical course of the reaction using the chiral imine **8** to determine whether diastereomeric discrimination occurred in this case. We carried out the reaction in CH_2Cl_2 at reflux, and the reaction product was treated directly with TBAF, yielding a major product that was purified by chromatography. This product (**31**) showed signals for a single compound, again corresponding to a *trans* disposition (**31a** or **31b**) of the indolyl and ester groups. The formation of only one *trans* diastereomer reflects the occurrence of facial discrimination. On this occasion, the absolute stereochemistry was assigned according to the NOEs observed, as shown in Figure 4 in which the key effects are depicted.

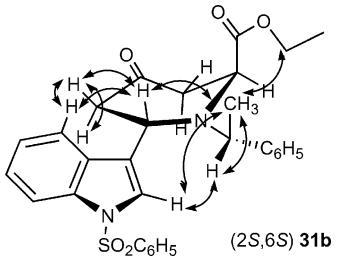


Figure 4. NOEs observed for **31b**.

The facial differentiation can be explained by the attack of the diene taking place through the less hindered face according to a Felkin–Anh model,[28] which corresponds to the approach of the diene to the imine closer to the benzylic hydrogen atom (*si*-facial selectivity) instead of the alternative approach, close to the benzylic methyl group (*re*-facial selectivity, Figure 5).

As the direction of the attack of the diene can explain the selectivity for the (*R*) absolute stereochemistry at C-2, the preference for the *trans* versus the *cis* diastereomer could be explained by the relative stabilities of the two products that result from the formation of the bond between the nitrogen atom and C-6 during the second step of the cyclization process.[29] In order to investigate the differences between the two possibilities, we minimized[30] the structures of the four diastereomers of the two cycloaddition products from imine **8** (silylenol ethers from diene **3**, which produce **30a**,**b**,**c**, or **d** upon deprotection, and silylenol ethers from diene **6**, which yield **31a**,**b**,**c**, or **d** by the deprotection reaction). The results are presented in Table 3.

For the 2-nitrophenyl derivatives, the differences between the *trans* and *cis* diastereomers with the same configuration at C-2 are smaller, which accounts for the appearance of a *cis* diastereomer as the reaction product. In the case of the enantioselective reaction that yields the indolyl derivatives **31** after deprotection, Figure 5 accounts for the (*S*) configuration at C-2. The final product must derive from the two possible diastereomers with this configuration, the *trans* diastereomer **b** and the *cis* diastereomer **c**. The difference in their stability (the *trans* compound is more stable by 12.63 kJ/mol) accounts for the observed presence and isolation of diastereomer **31b** as the unique reaction product in this case.

The whole process is presented in Scheme 7 starting with the activation of the imine by the zinc catalyst, followed by the Mannich addition, and finally by cyclization to the reaction products. This mechanism has previously been proposed for related imino-Diels–Alder reactions with activated dienes.[31]

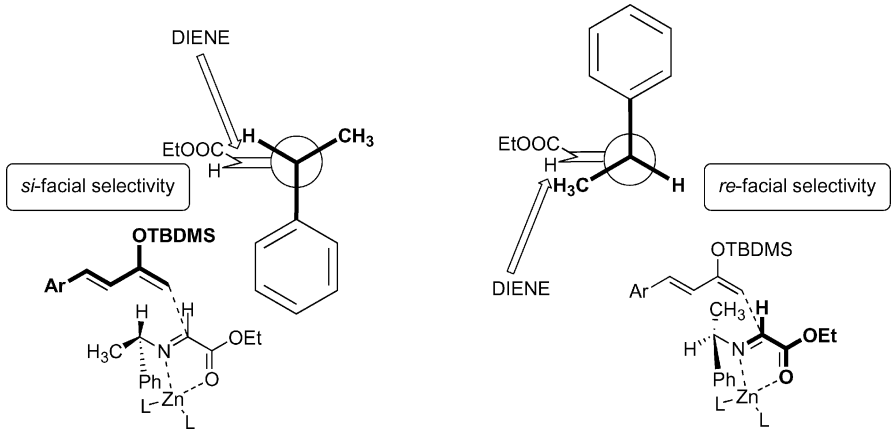
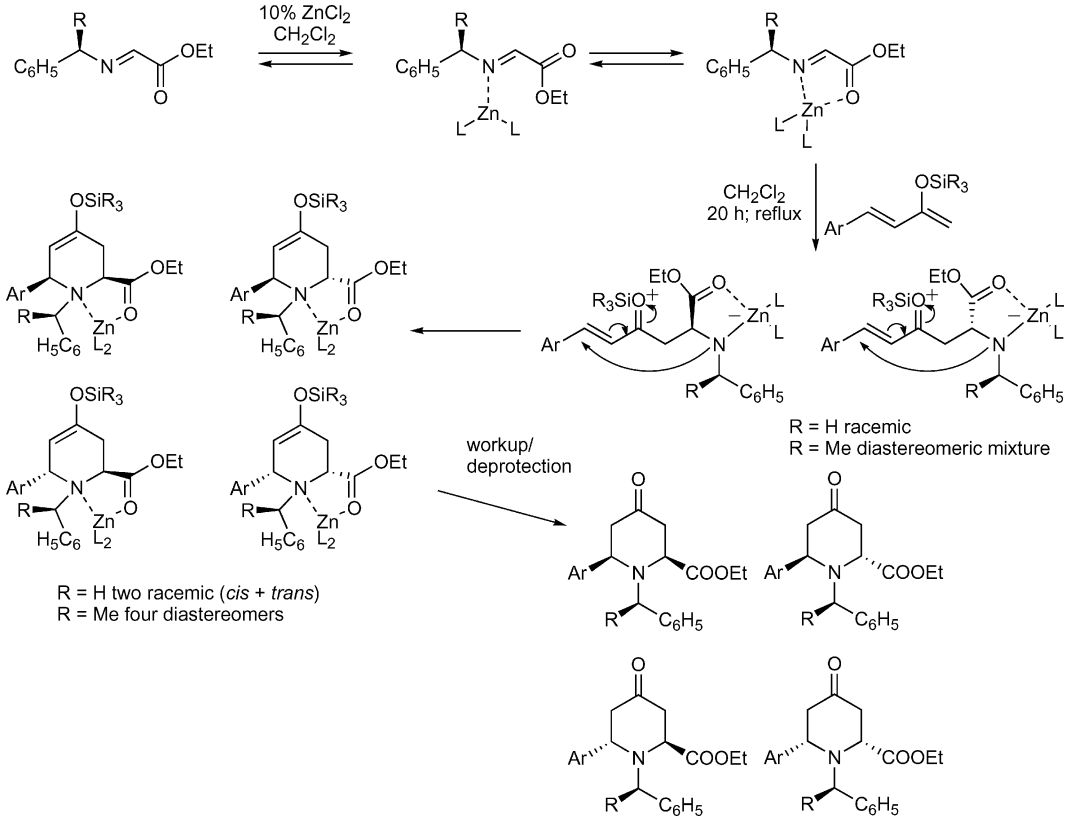


Figure 5. Facial selectivity leading to compound **31**.

Table 3. Calculated relative stabilities [kJ/mol] of the four possible diastereomeric cycloadducts (**a**–**d**) obtained from diene **3** and diene **6**.

OTBDMS, Ar, N, COOEt, C_6H_5	Ar	Ar N COOEt **a**	Ar N COOEt **b**	Ar N COOEt **c**	Ar N COOEt **d**
	2-$O_2NC_6H_4$	9.92	0.00	1.03	7.95
	N-($C_6H_5SO_2$)-3-indolyl	0.00	5.14	17.77	12.12



Scheme 7. Proposed mechanism for the stereochemical course of the reaction.

Conclusions

Reported in this work is a very attractive imino-Diels–Alder reaction that allows the preparation of 6-aryl(indolyl)-4-oxopipecolic acid derivatives with very high diastereoselectivity. The effect of different substituents on the 1-phenyl group of the butadienes on the diastereoselectivity of the reaction has been studied, with a loss of diastereoselectivity observed on replacing a methoxy by a nitro group. Furthermore, replacing the methoxyphenyl group with indolyl moieties maintains the diastereomeric effect observed in the former cases. A diastereoselective effect on the *trans*/*cis* ratio was also observed when the chiral imine derived from α-methylbenzylamine was used as the dienophile.

Attempts at adduct deprotection were sometimes unsuccessful. However, the use of a solid-supported imine as the dienophile has a remarkable effect on the cleavage of the *N*-protecting group, directly yielding the pipecolic acid derivatives in the free amino form.

Experimental Section

General: Melting points were determined with a Büchi 510 instrument and are uncorrected. NMR spectra were recorded with a Bruker 400 MHz DRX and/or a 200 MHz AC spectrometer in $CDCl_3$ as solvent with TMS as the internal standard. Mass spectra were obtained by the electrospray method with a VGTS-240 mass spectrometer. Flash chromatography was performed with Merck 60 silica gel (0.040–0.063 mm). Solvents of analytical grade were used as purchased and, when necessary, dried by using standard procedures.

Materials: Dienes **1**–**6** and imines **7** and **8** were prepared according to previously reported procedures.[9,26]

General Procedure for the Preparation of the Dienes: To the corresponding enone (1 mmol) in CH_2Cl_2 under Ar, Et_3N (5.4 mmol), and triisopropylsilyl triflate (4 mmol) were added dropwise. The reaction mixture was allowed to react at 50 °C for 2 h, and then Et_3N (1 mmol) was added. The mixture was diluted in CH_2Cl_2, washed with aqueous saturated $NaHCO_3$ solution and brine, dried, and the solvent evaporated.

Imino-Diels–Alder Reaction. General Procedure: $ZnCl_2$ (10%) was mixed with the imine (1 equiv.) in dry CH_2Cl_2 under argon. After stirring for 10 min, 1 equiv. of the diene was added, and the mixture was stirred at room temperature for 24 h (dienes **1**, **2**, **5**, and **6**) or 36 h (dienes **3** and **4**). The reaction mixture was washed with an aqueous saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with brine, and dried with anhydrous Na_2SO_4. The crude extract was concentrated to dryness and subjected directly to column chromatography (hexane/EtOAc, 8:2) to afford compounds **9**–**18**.

(±)-Ethyl (2*S*,6*S*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-6-(3,4,5-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (9): White solid (396 mg, 73%). M.p. 93–94 °C (hexane). ^{1}H NMR (400 MHz): δ = 7.27–7.20 (m, 5 H), 6.70 (s, 2 H), 4.80 (t, J = 2.4 Hz, 1 H), 4.65 (q, J = 2.3 Hz, 1 H), 4.18 (m, 2 H), 3.83 (s, 6 H), 3.82 (s, 3 H), 3.74 (s, 2 H), 3.66 (dd, J = 6.4, 2.3 Hz, 1 H), 2.64 (ddt, J = 16.8, 6.4, 2.3 Hz, 1 H), 2.35 (dt, J = 16.8, 2.3 Hz, 1 H), 1.29 (t, J = 7.2 Hz, 3 H), 0.90 (s, 9 H), 0.11 (s, 6 H) ppm. ^{13}C NMR

(100 MHz): δ = 172.6, 153.0, 146.3, 140.1, 139.5, 136.8, 128.4 (×2), 128.2 (×2), 126.9, 107.8, 104.9, 61.6, 60.3, 60.2, 55.9 (×2), 55.8, 54.0, 32.8, 25.6 (×3), 17.9, 14.3, –4.3 (×2) ppm. HRMS: calcd. for $C_{30}H_{43}NO_6Si$ [M + H]$^+$ 542.2960; found 542.2992.

(±)-Ethyl (2*S*,6*R*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-6-(3,4,5-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (10): Orange oil (11 mg, 2%). ^{1}H NMR (400 MHz): δ = 7.31–7.20 (m, 5 H), 6.52 (s, 2 H), 4.80 (d, *J* = 2.8 Hz, 1 H), 4.21 (d, *J* = 2.8 Hz, 1 H), 3.89 (m, 2 H), 3.83 (s, 6 H), 3.82 (m, 1 H), 3.80 (s, 3 H), 3.59 (m, 2 H), 2.65 (dd, *J* = 16.4, 7.2 Hz, 1 H), 2.30 (dd, *J* = 16.4, 4.8 Hz, 1 H), 1.05 (t, *J* = 7.7 Hz, 3 H), 0.94 (s, 9 H), 0.11 (s, 6 H) ppm. ^{13}C NMR (100 MHz): δ = 173.1, 155.6, 147.5, 138.9, 137.8, 136.7, 128.8 (×2), 127.8 (×2), 126.8, 105.8, 105.6, 62.7, 60.6 (×2), 60.4 (×2), 57.2, 55.9, 31.6, 25.6 (×3), 17.9, 13.8, –4.3 (×2) ppm.

(±)-Ethyl (2*S*,6*S*)/(2*S*,6*R*)-4-(*tert*-Butyldimethylsiloxy)-6-(3,4,5-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (11/12): Orange oil (18 mg, 4%). ^{1}H NMR (200 MHz): δ = 6.65/6.60 (s, 2 H), 5.47/5.15 (m, 2 H), 5.01/4.89 (m, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 4.50–4.20 (m, 2 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 2.0–2.7 (m, 2 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 0.95 (s, 9 H), 0.21 (s, 6 H) ppm. ^{13}C NMR (50 MHz): δ = 173.9, 153.0 (×2), 148.2, 136.7, 106.7, 106.1, 105.3/104.9, 77.8/74.1, 73.7/69.0, 61.7, 61.2, 56.0 (×2), 32.6/32.2, 25.6, 18.0, 14.4, –4.3 ppm.

(±)-Ethyl (2*S*,6*S*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-6-(2-methoxyphenyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (13): Orange oil (347 mg, 72%). ^{1}H NMR (200 MHz): δ = 7.69 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.24 (m, 5 H), 7.20 (m, 1 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 5.37 (q, *J* = 2.5 Hz, 1 H), 4.83 (t, *J* = 2.5 Hz, 1 H), 4.24 (m, 2 H), 3.83 (s, 3 H), 3.82 (d, *J* = 13.8 Hz, 1 H), 3.75 (d, *J* = 13.8 Hz, 1 H), 3.69 (dd, *J* = 6.2, 2.5 Hz, 1 H), 2.67 (ddt, *J* = 16.4, 6.2, 2.5 Hz, 1 H), 2.34 (dt, *J* = 16.4, 2.5 Hz, 1 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (50 MHz): δ = 172.9, 157.6, 146.1, 139.8, 132.3, 129.0, 128.7 (×2), 128.2 (×2), 127.7, 126.8, 120.7, 110.5, 107.8, 60.1, 55.9, 55.4, 54.2, 53.1, 33.2, 25.7 (×3), 18.0, 14.5, –4.1 (×2) ppm. HRMS: calcd. for $C_{28}H_{39}NO_4Si$ [M]$^{+\cdot}$ 482.2648; found 482.2688.

(±)-Ethyl (2*S*,6*S*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-6-(2-nitrophenyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (14): Orange oil (199 mg, 40%). ^{1}H NMR (400 MHz): δ = 8.01 (d, *J* = 7.9 Hz, 1 H), 7.70 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.59 (dt, *J* = 7.8, 1.0 Hz, 1 H), 7.35 (dt, *J* = 7.8, 1.0 Hz, 1 H), 7.25–7.15 (m, 5 H), 5.28 (q, *J* = 2.3 Hz, 1 H), 4.89 (t, *J* = 2.3 Hz, 1 H), 4.18 (m, 2 H), 3.82 (d, *J* = 13.7 Hz, 1 H), 3.65 (dd, *J* = 6.4, 2.0 Hz, 1 H), 3.57 (d, *J* = 13.7 Hz, 1 H), 2.70 (ddt, *J* = 16.4, 6.4, 2.3 Hz, 1 H), 2.35 (dt, *J* = 16.4, 2.0 Hz, 1 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 0.88 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR (100 MHz): δ = 172.4, 150.4, 147.2, 139.3, 138.5, 132.5, 130.4, 128.3 (×2), 128.0 (×2), 127.7, 127.1, 123.3, 106.7, 60.4, 56.3, 55.8, 54.8, 33.3, 25.5 (×3), 17.9, 14.3, –4.5 (×2) ppm. HRMS: calcd. for $C_{27}H_{36}N_2O_5Si$ [M]$^+$ 497.2466; found 497.2442.

(±)-Ethyl (2*S*,6*S*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-6-(3-nitrophenyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (15): Orange oil (149 mg, 30%). ^{1}H NMR (400 MHz): δ = 8.34 (t, *J* = 2.0 Hz, 1 H), 8.08 (ddd, *J* = 8.0, 2.0, 2.0 Hz, 1 H), 7.77 (dt, *J* = 8.0, 2.0 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.30–7.20 (m, 5 H), 4.85 (q, *J* = 2.8 Hz, 1 H), 4.75 (t, *J* = 2.8 Hz, 1 H), 4.20 (m, 2 H), 3.82 (d, *J* = 13.6 Hz, 1 H), 3.66 (dd, *J* = 6.4, 2.8 Hz, 1 H), 3.65 (d, *J* = 13.6 Hz, 1 H), 2.70 (ddt, *J* = 16.8, 6.4, 2.8 Hz, 1 H), 2.38 (dt, *J* = 16.8, 2.8 Hz, 1 H), 1.30 (t, *J* = 7.7 Hz, 3 H), 0.89 (s, 9 H), 0.09 (s, 6 H) ppm. ^{13}C NMR (100 MHz): δ = 172.5, 148.5, 147.8, 147.5, 138.7, 134.5, 129.3, 128.4 (×2), 128.0 (×2), 127.3, 123.3, 122.4, 106.7, 61.3, 60.5, 55.8, 54.4, 33.1, 25.6 (×3), 18.0, 14.4, –4.5 (×2) ppm. HRMS: calcd. for $C_{27}H_{36}N_2O_5Si$ [M + H]$^+$ 497.2466; found 497.2484.

(±)-Ethyl (2*S*,6*R*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-6-(2-nitrophenyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (16): Orange oil (174 mg, 35%). ^{1}H NMR (400 MHz): δ = 7.71 (d, *J* = 7.9 Hz, 1 H), 7.69 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.46 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.30 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.30–7.20 (m, 5 H), 5.03 (br. s, 1 H), 4.99 (d, *J* = 3.9 Hz, 1 H), 3.89 (d, *J* = 13.7 Hz, 1 H), 3.79 (d, *J* = 13.7 Hz, 1 H), 3.48 (t, *J* = 5.2 Hz, 1 H), 3.33 (m, 2 H), 2.51 (dd, *J* = 16.0, 5.2 Hz, 1 H), 2.21 (dd, *J* = 16.0, 5.2 Hz, 1 H), 1.10 (t, *J* = 7.2 Hz, 3 H), 0.94 (s, 9 H), 0.18 (s, 6 H) ppm. ^{13}C NMR (100 MHz): δ = 172.6, 150.1, 148.5, 138.0, 137.5, 131.8, 130.8, 129.0 (×2), 128.1 (×2), 127.5, 127.2, 123.7, 102.6, 60.6, 59.3, 58.0, 57.6, 28.3, 25.6 (×3), 17.9, 13.6, –4.3 (×2) ppm. HRMS: calcd. for $C_{27}H_{36}N_2O_5Si$ [M + H]$^+$ 497.2466; found 497.2436.

(±)-Ethyl (2*S*,6*R*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-6-(3-nitrophenyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (17): Orange oil (139 mg, 28%). ^{1}H NMR (400 MHz): δ = 8.16 (s, 1 H), 8.01 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.67 (d, *J* = 7.6 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.26–7.16 (m, 5 H), 4.73 (d, *J* = 2.0 Hz, 1 H), 4.36 (d, *J* = 2.0 Hz, 1 H), 3.85 (d, *J* = 14.4 Hz, 1 H), 3.76 (d, *J* = 14.4 Hz, 1 H), 3.72 (m, 2 H), 3.68 (dd, *J* = 7.2, 4.8 Hz, 1 H), 2.68 (dd, *J* = 16.8, 7.2 Hz, 1 H), 2.32 (dd, *J* = 16.8, 4.8 Hz, 1 H), 1.13 (t, *J* = 7.1 Hz, 3 H), 0.92 (s, 9 H), 0.15 (s, 6 H) ppm. ^{13}C NMR (100 MHz): δ = 172.4, 148.1, 148.0, 145.5, 137.7, 134.7, 128.7 (×2), 128.6, 128.0 (×2), 127.1, 123.6, 122.0, 104.5, 62.3, 60.7 (×2), 57.6, 31.8, 25.5 (×3), 17.9, 13.8, –4.3 (×2) ppm. HRMS: calcd. for $C_{27}H_{36}N_2O_5Si$ [M + H]$^+$ 497.2466; found 497.2448.

(±)-Ethyl (2*S*,6*S*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-6-[1-(phenylsulfonyl)-1*H*-indol-3-yl]-1,2,3,6-tetrahydropyridine-2-carboxylate (18): Brown oil (346 mg, 55%). ^{1}H NMR (200 MHz): δ = 7.96 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.2 Hz, 1 H), 7.70–7.10 (m, 11 H), 7.53 (s, 1 H) 4.94 (dd, *J* = 2.6, 2.6 Hz, 1 H), 4.77 (t, *J* = 2.6 Hz, 1 H), 4.18 (q, *J* = 7.3 Hz, 2 H), 3.78 (d, *J* = 13.5 Hz, 1 H), 3.71 (t, *J* = 4.9 Hz, 1 H), 3.66 (d, *J* = 13.5 Hz, 1 H), 2.65 (ddt, *J* = 6.8, 4.9, 2.6 Hz, 1 H), 2.46 (dd, *J* = 16.8; 4.8 Hz, 1 H), 1.28 (t, *J* = 7.3 Hz, 1 H), 1.02 (m, 18 H) ppm. ^{13}C NMR (50 MHz): δ = 172.6, 147.8, 139.2, 138.1, 136.1, 133.6, 130.0, 129.9 (×2), 128.6 (×4), 128.3 (×2), 127.0, 126.1, 124.9, 124.8, 123.0, 121.5, 113.8, 104.0, 60.4, 55.8, 54.1, 53.6, 32.2, 17.9/17.8 (×6), 14.4, 12.6/12.4 (×3) ppm.

Ethyl (2*E*,5*E*)-6-(2-Nitrophenyl)-4-oxohexa-2,5-dienoate (19): According to the previous imino-Diels–Alder procedure at reflux in dichloroethane, compound **19** (275 mg, 100%) was isolated. ^{1}H NMR (200 MHz): δ = 8.13 (d, *J* = 15.8 Hz, 1 H), 8.08 (d, *J* = 7.5 Hz, 1 H), 7.46 (d, *J* = 15.8 Hz, 1 H), 6.83 (d, *J* = 15.8 Hz, 2 H), 7.70–7.50 (m, 3 H), 4.28 (q, *J* = 7.0 Hz, 2 H), 1.33 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz): δ = 188.2, 165.4, 148.5, 141.0, 137.6, 133.8, 132.0, 130.9, 130.5, 129.5, 129.2, 125.2, 61.5, 14.2 ppm.

Deprotection of the Cycloadducts. Method A: Compound **9** (200 mg, 0.6 mmol), dissolved in CH_2Cl_2 (10 mL), was treated with 2 N HCl (5 mL) and then stirred for 24 h. The reaction mixture was washed with aqueous saturated $NaHCO_3$ solution, dried, and the solvents were evaporated. The residue was purified by column chromatography (hexane/EtOAc, 7:3) to afford **20** (46 mg, 30%). **Method B:** The corresponding compound (0.1 mmol) was dissolved in THF (5–10 mL), and TBAF (0.13 mmol in THF solution) was added to the solution. The reaction mixture was stirred at room temperature for 20 h, quenched with water, extracted with CH_2Cl_2, dried, and the solvents were evaporated. The reaction product was purified by chromatography on silica (hexane/EtOAc, 1:1) to give the pure compounds **20**–**24**.

(±)-Ethyl (2*S*,6*S*)-1-Benzyl-4-oxo-6-(3,4,5-trimethoxyphenyl)piperidine-2-carboxylate (20): Orange oil (342 mg, 80%). ^{1}H NMR (400 MHz): δ = 7.40–7.20 (m, 5 H), 6.71 (s, 2 H), 4.38 (dd, *J* = 9.6, 4.6 Hz, 1 H), 4.27 (m, 2 H), 3.92 (dd, *J* = 6.6, 2.2 Hz, 1 H), 3.86 (s, 6 H), 3.80 (d, *J* = 14.0 Hz, 1 H), 3.80 (s, 3 H), 2.77 (dd, *J* = 14.8, 6.6 Hz, 1 H), 2.69 (dd, *J* = 15.2, 4.6 Hz, 1 H), 2.59 (dd, *J* = 15.2, 9.6 Hz, 1 H), 2.51 (dd, *J* = 14.8, 2.2 Hz, 1 H), 3.31 (d, *J* = 14.0 Hz, 1 H), 1.32 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 205.8, 171.5, 153.6 (×2), 138.6 (×2), 137.3, 128.4 (×2), 128.3 (×2), 127.3, 103.9 (×2), 63.0, 60.8 (×2), 58.6, 56.1 (×2), 54.2, 49.2, 42.8, 14.4 ppm. HRMS: calcd. for $C_{24}H_{29}NO_6$ $[M + H]^+$ 428.2067; found 428.2055.

(±)-Ethyl (2*S*,6*S*)-1-Benzyl-6-(2-nitrophenyl)-4-oxopiperidine-2-carboxylate (21): Orange oil (286 mg, 75%). ^{1}H NMR (400 MHz): δ = 8.03 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 8.1 Hz, 1 H), 7.67 (t, *J* = 8.0 Hz, 1 H), 7.43 (t, *J* = 8.1 Hz, 1 H), 7.30–7.24 (m, 5 H), 4.99 (dd, *J* = 8.0, 5.6 Hz, 1 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 3.88 (dd, *J* = 6.4, 2.0 Hz, 1 H), 3.61 (d, *J* = 13.6 Hz, 1 H), 3.46 (d, *J* = 13.6 Hz, 1 H), 2.99 (dd, *J* = 15.6, 5.6 Hz, 1 H), 2.75 (dd, *J* = 14.8, 6.4 Hz, 1 H), 2.60 (dd, *J* = 14.8, 2.0 Hz, 1 H), 2.58 (dd, *J* = 15.6, 8.0 Hz, 1 H), 1.33 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 204.7, 171.2, 149.9, 137.5, 137.4, 133.2, 128.8, 128.6 (×5), 127.5, 124.1, 61.1, 58.2, 56.8, 55.0, 47.3, 42.7, 14.3 ppm. HRMS: calcd. for $C_{21}H_{22}N_2O_5$ $[M]^{+\cdot}$ 382.1529; found 382.1536.

(±)-Ethyl (2*S*,6*S*)-1-Benzyl-6-(3-nitrophenyl)-4-oxopiperidine-2-carboxylate (22): Orange oil (278 mg, 73%). ^{1}H NMR (200 MHz): δ = 8.43 (t, *J* = 1.8 Hz, 1 H), 8.17 (dd, *J* = 8.0, 2.1 Hz, 1 H), 7.83 (dt, *J* = 8.0, 2.1 Hz, 1 H), 7.58 (t, *J* = 8.0 Hz, 1 H), 7.25–7.30 (m, 5 H), 4.64 (dd, *J* = 9.5, 4.7 Hz, 1 H), 4.27 (m, 2 H), 3.93 (dd, *J* = 6.6, 2.6 Hz, 1 H), 3.67 (d, *J* = 13.5 Hz, 1 H), 3.37 (d, *J* = 13.5 Hz, 1 H), 2.70–2.40 (m, 4 H), 1.33 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (50 MHz): δ = 204.5, 171.5, 148.9, 146.0, 138.0, 133.4, 130.1, 128.6 (4), 127.7, 123.0, 122.5, 62.2, 61.1, 58.7, 54.8, 48.5, 42.8, 14.4 ppm. MS: calcd. for $C_{21}H_{22}N_2O_5$ 382.15; found 382.10.

(±)-Ethyl (2*S*,6*S*)-1-Benzyl-4-oxo-6-[1-(phenylsulfonyl)-1*H*-indol-3-yl]piperidine-2-carboxylate (23): Brown oil (289 mg, 56%). ^{1}H NMR (200 MHz): δ = 8.02 (d, *J* = 8.2 Hz, 1 H), 7.83 (d, *J* = 8.2 Hz, 1 H), 7.50–7.10 (m, 12 H), 7.60 (s, 1 H), 4.69 (dd, *J* = 10.0, 4.3 Hz, 1 H), 4.20 (m, 2 H), 3.89 (dd, *J* = 6.2, 2.5 Hz, 1 H), 3.72 (d, *J* = 13.5 Hz, 1 H), 3.39 (d, *J* = 13.5 Hz, 1 H), 3.00–2.50 (m, 4 H), 1.33 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (50 MHz): δ = 205.7, 171.3, 137.9 (×2), 137.9, 136.0, 134.0, 129.4 (×2), 128.9 (×2), 128.5 (×2), 127.4, 126.7 (×3), 126.7, 125.5, 124.4, 123.8, 123.5, 120.9, 114.1, 61.1, 58.3, 55.0, 54.0, 45.9, 42.3, 14.5 ppm. HRMS: calcd. for $C_{29}H_{28}N_2O_5S$ $[M]^{+\cdot}$ 516.1719; found 516.1723.

(±)-Ethyl (2*S*,6*R*)-1-Benzyl-6-(2-nitrophenyl)-4-oxopiperidine-2-carboxylate (24): Orange oil (305 mg, 80%). ^{1}H NMR (200 MHz): δ = 8.48 (d, *J* = 8.0 Hz, 1 H), 7.81 (d, *J* = 8.2 Hz, 1 H), 7.70 (t, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 8.2 Hz, 1 H), 7.24–7.20 (m, 5 H), 4.65 (dd, *J* = 9.6, 5.2 Hz, 1 H), 4.06 (q, *J* = 7.0 Hz, 2 H), 3.84 (t, *J* = 4.8 Hz, 1 H), 3.73 (d, *J* = 14.4 Hz, 1 H), 3.62 (d, *J* = 14.4 Hz, 1 H), 2.79 (m, 2 H), 1.21 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz): δ = 205.8, 173.4, 149.9, 137.8, 137.0, 133.5, 128.9 (×2), 128.8 (×3), 127.7, 127.4, 124.0, 61.4, 58.8, 58.6, 57.5, 46.1, 39.5, 14.1 ppm.

(±)-Ethyl (2*S*,6*S*)-4-Oxo-6-(3,4,5-trimethoxyphenyl)piperidine-2-carboxylate (25): Formic acid (1.0 mL) and Pd/C (10%, 22 mg) were added to a stirred solution of **20** (90 mg, 0.27 mmol) in MeOH (5.4 mL). The mixture was stirred under argon overnight, the Pd/C was filtered off, and the ethanol was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with aqueous saturated $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4, and the solvents were evaporated. The residue was purified by column chromatography (diethyl ether/EtOAc, 10:1) to afford **25** (215 mg, 64%) as a brown oil. ^{1}H NMR (400 MHz): δ = 6.63 (s, 2 H), 4.21 (q, *J* = 6.9 Hz, 2 H), 3.87 (s, 6 H), 3.84 (s, 3 H), 3.80–4.0 (m, 1 H), 3.72 (dd, *J* = 11.7, 3.6 Hz, 1 H), 2.75 (dd, *J* = 14.6, 3.7 Hz, 1 H), 2.60–2.40 (m, 2 H), 1.29 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 206.6, 170.9, 153.8 (×2), 137.6 (×2), 137.6, 103.4 (×2), 61.7, 60.8, 60.6, 57.9, 56.2 (×2), 50.4, 43.9, 14.8 ppm. HRMS: calcd. for $C_{17}H_{23}NO_6$ $[M]^{+\cdot}$ 337.1525; found 337.1555.

General Procedure for Imine Formation on a Solid Support: To a suspension of the polymer-bound benzylamine (1 mmol) (Aldrich, 473677) and molecular sieves (4 Å) (50 mg) in CH_2Cl_2 (15 mL) at room temperature under nitrogen was added ethyl glyoxylate in the molar proportion shown in Table 1. The corresponding imine-resin was filtered off and washed with CH_2Cl_2. The imine-resins (**I**, **II** or **III**) show an absorption at 1740 cm^{-1} in IR spectra.

General Procedure for the Imino-Diels–Alder Reaction on a Solid Support (see Table 1): Diene **2**–**4** (1 mmol) and dry $ZnCl_2$ (20%) were added to the resin (**I**, **II**, or **III**) (1–2 mmol) in dry CH_2Cl_2 (15–20 mL) under nitrogen. The reaction mixture was heated at reflux for 24 h or 72 h. After that, the resin was filtered off and washed with CH_2Cl_2. The filtrate was concentrated, and the reaction product purified by flash chromatography to give **26**, **27**, or **28**.

(±)-Ethyl (2*S*,6*S*)/(2*S*,6*R*)-4-(*tert*-Butyldimethylsiloxy)-6-(2-nitrophenyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (26): Brown oil (137 mg, 35%). ^{1}H NMR (200 MHz): δ = 8.0–7.1 (m, 4 H), 6.17/5.80 (m, 1 H), 5.04 (m, 1 H), 4.43 (m, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 2.7–2.0 (m, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 0.90 (s, 9 H), 0.12 (s, 6 H) ppm. ^{13}C NMR (50 MHz): δ = 170.8/170.3, 148.2/148.9, 147.9, 137.2/136.5, 133.7/132.7, 129.6/129.3, 128.6/128.4, 124.4/124.1, 105.6/103.5, 72.4/69.2, 73.6/70.8, 61.4, 32.6/31.5, 25.6, 18.0, 14.2, –4.5 ppm. HRMS: calcd. for $C_{21}H_{30}N_2O_5Si$ $[M + H]^+$ 419.1924; found 419.1976.

(±)-Ethyl (2*S*,6*S*)/(2*S*,6*R*)-4-(*tert*-Butyldimethylsiloxy)-6-(3-nitrophenyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (27): Brown oil (288 mg, 71%). ^{1}H NMR (200 MHz): δ = 8.3–7.4 (m, 4 H), 5.61/5.32 (m, 1 H), 5.02 (t, *J* = 2.8 Hz, 1 H), 4.84 (t, *J* = 2.8 Hz, 1 H), 4.5–4.2 (m, 1 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 2.7–2.2 (m, 2 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 0.90 (s, 9 H), 0.12 (s, 6 H) ppm. ^{13}C NMR (50 MHz): δ = 170.8/170.1, 148.9/148.7, 148.4, 143.5, 134.1/133.7, 129.5, 123.1, 122.8/122.6, 105.0/102.9, 77.7/73.0, 73.6/69.4, 61.4, 32.7/32.0, 25.6, 18.0, 14.2, –4.3 ppm.

(±)-Ethyl (2*S*,6*S*)/(2*S*,6*R*)-4-(*tert*-Butyldimethylsiloxy)-6-(2-methoxyphenyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (28): Yellow oil (195 mg, 48%). ^{1}H NMR (200 MHz): δ = 7.5–6.8 (m, 4 H), 6.00/5.68 (m, 1 H), 4.96/4.91 (m, 1 H), 4.5–4.3 (m, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 3.86/3.81 (s, 3 H), 2.8–2.2 (m, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 0.90 (s, 9 H), 0.12 (s, 6 H) ppm.

(±)-Ethyl (2*S*,6*S*)/(2*S*,6*R*)-6-(2-Nitrophenyl)-4-oxopiperidine-2-carboxylate (29): According to Method B described previously, **26** gave **29** as a brown oil (175 mg, 60%). ^{1}H NMR (200 MHz): δ = 8.2–7.3 (m, 4 H), 5.37 (dd, *J* = 11.4, 2.8 Hz, 1 H), 4.55 (dd, *J* = 11.0, 4.0 Hz, 1 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 3.1–2.4 (m, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H) ppm. HRMS: calcd. for $C_{14}H_{16}N_2O_5$ $[M]^{+\cdot}$ 292.1059; found 292.1096.

Imino-Diels–Alder Reaction and Deprotection: $ZnCl_2$ (10%) was mixed with the chiral imine **8** (1 equiv.) in dry CH_2Cl_2 (15 mL) under argon. After stirring for 10 min, diene **3** or **6** (1 equiv.) was added, and the mixture was stirred at reflux for 20 h. The resulting mixture was poured into aqueous saturated $NaHCO_3$ solution and

extracted with CH_2Cl_2, dried, and the solvents were evaporated. The reaction mixture was dissolved in THF (15 mL), and TBAF (1.3 equiv. in THF solution) was added to the solution. The mixture was stirred at room temperature for 20 h, quenched with water, extracted with CH_2Cl_2, dried, and the solvents were evaporated. The reaction product was purified by chromatography on silica (hexane/EtOAc, 1:1) to give the pure compounds **30** and **31**.

Ethyl (2*S*,6*S*)/(2*R*,6*R*)-6-(2-Nitrophenyl)-4-oxo-1-[(*R*)-1-phenylethyl]piperidine-2-carboxylate (30a and 30b): Orange oil (135 mg, 34%). ^{1}H NMR (400 MHz): δ = 7.92/7.95 (d, J = 8.0 Hz, 1 H), 7.80/7.70 (d, J = 8.0 Hz, 1 H), 7.43 (m, 1 H), 7.30 (m, 1 H), 7.22–7.40 (m, 5 H), 5.45 (m, 1 H), 4.20 (m, 2 H), 3.99 (m, 1 H), 3.99–3.89 (m, 1 H), 3.32 (dd, J = 15.6, 8.0 Hz, 1 H)/3.18 (ddd, J = 15.6, 6.4, 1.6 Hz, 1 H), 2.85/2.76 (ddd, J = 16.0, 7.6, 1.6 Hz, 1 H), 2.73/2.51 (dd, J = 16.0, 6.4 Hz, 1 H), 2.51 (dd, J = 16.0, 6.4 Hz, 2 H), 1.32/1.17 (t, J = 7.1 Hz, 3 H), 1.26/1.07 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 205.5, 174.3/173.5, 149.5, 141.6, 138.3, 132.9/133.0, 129.1/128.8, 128.5 (×2)/128.4 (×2), 127.5 (×2)/127.4 (×2), 127.0 (×2), 124.0/124.6, 61.2/60.9, 57.3/56.5, 55.4/54.8, 54.0, 47.6/46.8, 43.9, 21.3, 13.9/13.4 ppm. HRMS: calcd. for $C_{22}H_{24}N_2O_5$ [M + H]$^+$ 397.1685; found 397.1735.

Ethyl (2*S*,6*R*)/(2*R*,6*S*)-6-(2-Nitrophenyl)-4-oxo-1-[(*R*)-1-phenylethyl]piperidine-2-carboxylate (30c or 30d): Orange oil (12 mg, 3%). ^{1}H NMR (400 MHz): δ = 8.68 (d, J = 8.0 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.77 (d, J = 8.0 Hz, 1 H), 7.43 (t, J = 8.0 Hz, 1 H), 7.40–7.20 (m, 5 H), 5.08 (dd, J = 12.4, 3.6 Hz, 1 H), 3.98 (m, 2 H), 3.86 (q, J = 6.8 Hz, 1 H), 3.83 (t, J = 4.4 Hz, 1 H), 2.95 (dd, J = 17.6, 12.4 Hz, 1 H), 2.77 (d, J = 4.4 Hz, 1 H), 2.74 (dd, J = 17.6, 3.6 Hz, 1 H), 1.45 (d, J = 6.8 Hz, 3 H), 1.08 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 206.1, 174.4, 149.6, 141.5, 138.8, 133.4, 130.6, 129.1 (×2), 128.1 (×2), 127.7, 127.2, 123.6, 61.0, 57.6, 53.8, 52.7, 46.6, 41.8, 13.9, 11.2 ppm.

Ethyl (2*S*,6*S*)/(2*R*,6*R*)-4-Oxo-1-[(*R*)-1-phenylethyl]-6-[(1-phenylsulfonyl)-1*H*-indol-3-yl]piperidine-2-carboxylate (31b): Brown oil (132 mg, 25%). ^{1}H NMR (400 MHz): δ = 8.03 (d, J = 8.4 Hz, 1 H), 7.96 (d, J = 8.4 Hz, 1 H), 7.82 (d, J = 8.6 Hz, 2 H), 7.62 (s, 1 H), 7.49 (d, J = 8.2 Hz, 1 H), 7.48–7.10 (m, 9 H), 5.18 (dd, J = 9.6, 4.4 Hz, 1 H), 4.20 (q, J = 7.0 Hz, 2 H), 4.00 (q, J = 7.0 Hz, 1 H), 3.79 (dd, J = 6.7, 2.4 Hz, 1 H), 2.94 (dd, J = 15.2, 9.6 Hz, 1 H), 2.60 (dd, J = 14.8, 6.7 Hz, 1 H), 2.58 (dd, J = 15.2, 4.4 Hz, 1 H), 2.35 (dd, J = 14.8, 2.4 Hz, 1 H), 1.31 (t, J = 7.0 Hz, 3 H), 1.20 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 205.9, 174.1, 141.8, 137.9, 136.1, 133.9, 129.2 (×2), 128.6, 128.5 (×2), 127.8 (×2), 127.4, 127.2, 126.6 (×2), 125.4, 123.4 (×2), 120.8, 114.2, 60.9, 56.1, 54.8, 52.4, 46.6, 44.0, 13.9, 12.2 ppm. HRMS: calcd. for $C_{30}H_{30}N_2O_5S$ [M]$^{+\cdot}$ 530.1875; found 530.1915.

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