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Vinylogous Reactivity of Oxindoles Bearing Nonsymmetric 3-Alkylidene Groups

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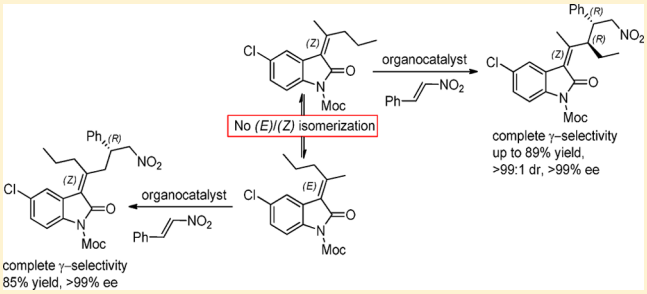
Supporting Information

ABSTRACT: The γ-functionalization of oxindoles bearing nonsymmetric 3-alkylidene groups via vinylogous Michael-type addition to nitroolefins was realized. The suppression of the interconversion between the *E* and *Z* isomers of the starting oxindoles allowed a site-specific diastereoselective and enantioselective transformation. Specific experiments allowed us to establish the rate-determining step of the reaction and to advance a robust hypothesis for the exclusive formation of an *s-cis* enolate as the only reactive intermediate.



INTRODUCTION

The rediscovery of old concepts and their application to novel strategies is a way of designing exceptional and successful chemical transformations. This is particularly true for organocatalysis[1] and vinylogous reactivity.[2] In fact, the application of vinylogous principles to the well-established aminocatalytic strategies of HOMO-raising and LUMO-lowering[3] allows for the synthesis of enantioenriched molecules, thus addressing the challenge of achieving enantioselective control at remote positions.[4] Recently, the vinylogous reactivity has been also successfully developed using organic base catalysis.[5] In this field, a noteworthy example is represented by the Michael addition reactions of alkylidene oxindoles with nitrostyrenes and β-CF_3-β-disubstituted nitroolefins, resepctively, developed by Casiraghi and co-workers[6] and Wang and co-workers.[7] These vinylogous reactions are important because they show new methods for the enantioselective functionalization of oxindole, an important scaffold found in many natural biological active compounds and pharmaceutical drugs.[8] In these reactions, the γ-positions of type **A**, **B**, and **C** oxindoles were functionalized with high regio- and stereoselectivity using a bifunctional cinchona alkaloid **I** or **II** as catalyst (Scheme 1).[9]

Despite the important results obtained in these reactions, several topics remain unexplored. First, the two protocols were limited to oxindoles having a single or at least two equivalent vinylogous γ and γ' sites of reaction.[10] Second, although the presence of an *s-cis* enolate as the only intermediate of the reaction was advanced by both Casiraghi's and Wang's research groups, no proof based on rational mechanism approaches was given for the site selectivity observed. For example, an oxindole of type **A** can furnish the same enantioenriched products through an *s-trans* nucleophilic intermediate (Scheme 2).[11] Indeed, as correctly pointed out by Casiraghi and co-workers, there is no shared idea about the way catalyst of type **I** promotes the reaction.[12,6b]

We report herein the site-, diastereo-, and enantioselective vinylogous Michael reactions of oxindoles having two nonequivalent reactive γ and γ' positions[13] taking on in particular the challenge of controlling the product distributions connected with the two nonequivalent sites of reaction (Scheme 3). Isotopic effect experiments were performed to elucidate the reasons for the observed γ-selectivity of this reactions, and we show how the thiourea moiety of catalyst **I** does not interact with the oxindole core but exclusively with the nitroalkene, thus furnishing important elements for the comprehension of the general reaction mechanism.

RESULTS AND DISCUSSION

Initially, we separately reacted oxindoles (*Z*)-**1a** and (*E*)-**1a** with *trans*-β-nitrostyrene **2a** at room temperature (Table 1, entries 1 and 2) using the thiourea derivatives of 9-*epi*-NH_2-hydroquinine **I** as catalyst in toluene at room temperature. In both reactions, we obtained a mixture of regioisomeric Michael adducts (*Z*)-**3a** and (*Z*)-**4a**, regardless of the double-bond configuration of the starting oxindoles. This result confirms that the product distribution is influenced by the isomerization equilibrium[14] and underlines the difficulties for the control of the vinylogous reaction of such substrates. In any case, the reaction occurred only at the γ-position, and each of the two regioisomers was obtained with high diastereo- and enantioselection.

By lowering the temperature to 0 °C, the isomerization rate was reduced in particular when (*Z*)-**1a** was used (entries 3 and 4). Finally, at −20 °C, the isomerization rate of both

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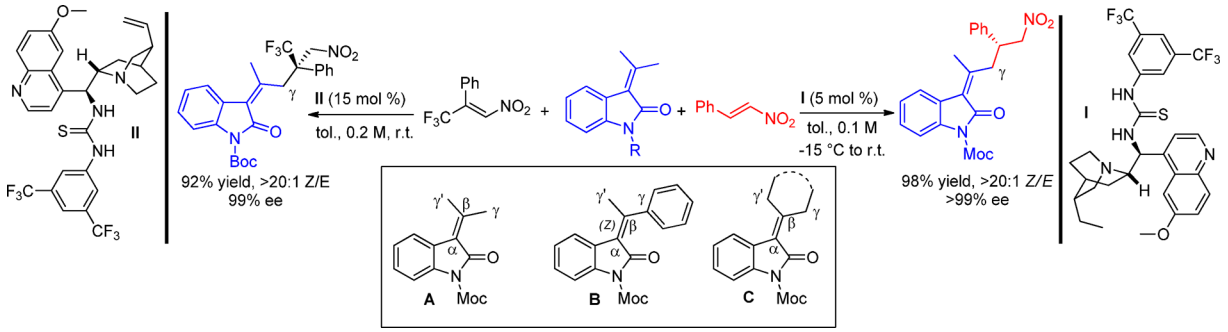
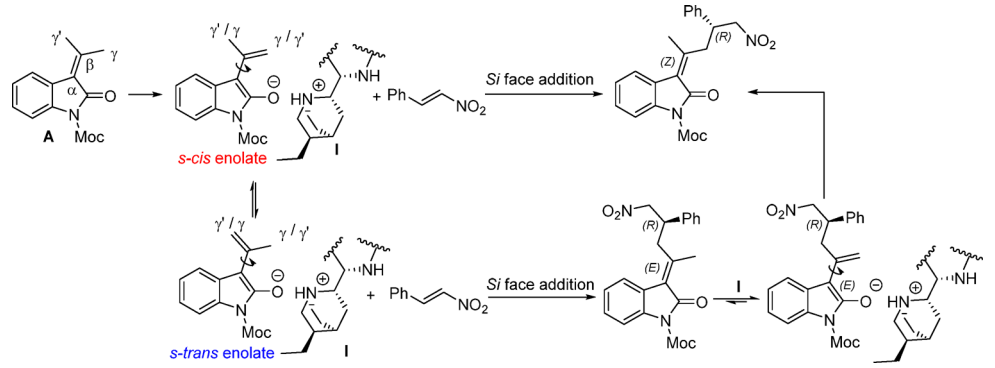
Scheme 1. Examples of Vinylogous Reactions of Oxindoles



Scheme 2. Vinylogous Reactions of Oxindoles



Scheme 3. Vinylogous Reactions of non Symmetric Alkylidene Oxindoles

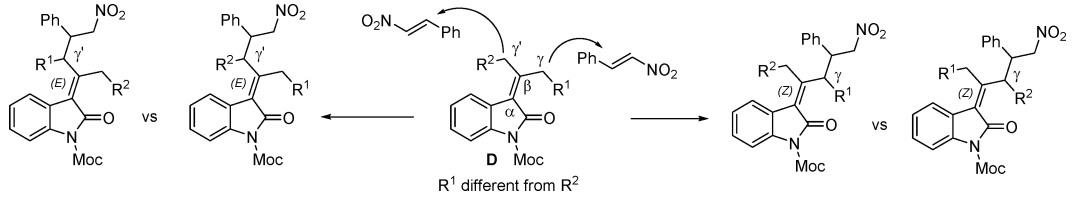
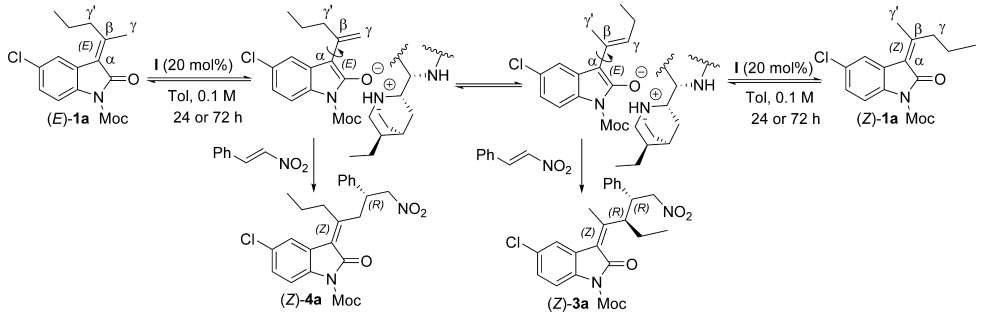


Table 1. Optimization of the Reaction Conditions[a]



entry	oxindole	T (°C)	time (h)	yield (%)	(Z)-3a/(Z)-4a[b]	dr of (Z)-3a[b]	ee (%)[c] of (Z)-3a	ee (%)[c] of (Z)-4a
1	(Z)-1a	25	24	67[d]	86:14	97:3	99	99
2	(E)-1a	25	24	60[d]	37:63	97:3	99	99
3	(Z)-1a	0	72	80[d]	95:5	>99:1	>99	nd
4	(E)-1a	0	72	75[d]	21:79	>99:1	>99	>99
5	(Z)-1a	−20	72	86[e]	>99:1	>99:1	>99	–
6	(E)-1a	−20	72	85[e]	1:>99	–	–	>99

[a]Unless otherwise noted, all reactions were performed using 0.2 mmol of (Z)-**1a** or (E)-**1a**, 0.2 mmol of **2a**, 20 mol % of **I**, and 2 mL of toluene. [b]Determined by ^{1}H NMR of the crude mixture. [c]Determined by chiral HPLC analysis. [d]Sum of (Z)-**3a** and (Z)-**4a**. [e]Isolated yield.

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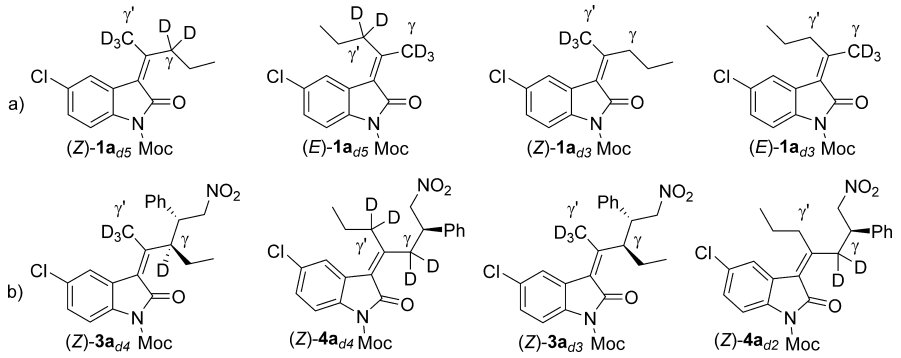

Figure 1. (a) Labeled oxindoles at γ- and γ'-positions. (b) Labeled vinylogous products expected from the reaction with deuterated oxindoles.

oxindoles was very slow, and single products were obtained for each reaction (entries 5 and 6).[15] Once we determined that the isomerization equilibrium could be inhibited and the product distribution controlled by lowering the temperature to −20 °C, we tried to investigate the origin for the high regioselectivity by preparing deuterated oxindole derivatives at both the γ- and γ'-positions (Figure 1).

We believed that, if present, an isotopic effect on the reaction rate could give us important information on the reaction mechanism and help us elucidate the reason for the γ-selectivity observed and if the deprotonation by catalyst **I** is the rate-determining step of the reaction. We reacted oxindoles (*Z*)-**1a**$_{d5}$ and (*E*)-**1a**$_{d5}$ with **2a** at −20 °C in toluene using **I** as catalyst. As depicted in Table 2, the reactions were particularly slow with

Table 2. Reaction of Deuterated Oxindole with 2a[a]

			conversion[b] (%)			
entry	oxindole	product	1 h	3 h	5 h	23 h
1[c]	(*Z*)-**1a**	(*Z*)-**3a**	6	22	32	85
2	(*Z*)-**1a**$_{d5}$	(*Z*)-**3a**$_{d4}$	nd[d]	nd[d]	nd[d]	6
3	(*Z*)-**1a**$_{d3}$	(*Z*)-**3a**$_{d3}$	8	23	31	80
4[c]	(*E*)-**1a**	(*Z*)-**4a**	22	54	70	93
5	(*E*)-**1a**$_{d5}$	(*Z*)-**4a**$_{d4}$	3	9	11	30
6	(*E*)-**1a**$_{d3}$	(*Z*)-**4a**$_{d2}$	15	37	50	75

[a]Reactions were performed using 0.2 mmol of oxindole, 0.2 mmol of **2a**, 20 mol % of **I**, and 2 mL of toluene. [b]Determined by ^{1}H NMR analysis. [c]Standard reaction conditions. [d]The conversion was too low to be accurately determined.

both oxindoles. A clear isotopic effect was observed with oxindole (*Z*)-**1a**$_{d5}$ having both γ- and γ'-positions deuterated, while oxindole (*Z*)-**1a**$_{d3}$, in which the only γ'-position is deuterated, was not subjected to isotopic effects and the rate of reaction of (*Z*)-**1a**$_{d3}$ and (*Z*)-**1a** were almost identical[16] (Table 2, compare entry 1 with entries 2 and 3).

Also with oxindole (*E*)-**1a**$_{d5}$ a clear isotopic effect was observed in fact only a 30% of conversion in (*Z*)-**4a**$_{d4}$ was obtained after 23 h (Table 2, compare entry 4 and 5). Moreover when only the γ-position was deuterated, as in oxindole (*E*)-**1a**$_{d3}$, an important reduction of the reaction rate was observed. After 24 h, a 75% conversion into the vinylogous product was recorded, while when (*E*)-**1a** was used the reaction was close to completion during the same reaction time (Table 2, compare entry 4 and 6). The results obtained support that the isotopic effect is observed during the deprotonation only when the γ-position of the oxindole is deuterated. Transferring this result to both (*Z*)- and (*E*)-**1a** oxindoles, it is possible to advance that the deprotonation by catalyst **I** occurs exclusively at the γ-vinylogous position and that is the rate-determining step of the process. The reasons for the regioselective deprotonation are not completely clear; however, a possible intramolecular activation of the C−H$_\gamma$ through a hydrogen-bond interaction by the oxygen of the amidic carbonyl group can be proposed. This interaction increases the acidity of the γ proton with respect to those in the γ'-position and assists catalyst **I** during the deprotonation path (Scheme 4).

The general scope of the reaction was then investigated by reacting (*Z*)- and (*E*)-alkylidene oxindoles with different *trans*-β-nitrostyrenes under the optimized conditions. The reactions of (*Z*)-oxindoles **1a**−**e** were found to be extremely stereoselective with most of the *trans*-β-nitrostyrenes employed (Table 3 entries 1−12). The corresponding adducts (*Z*)-**3a**−**l** were obtained as single diastereoisomers with excellent enantiocontrol that was independent of the electronic nature of the substituents on the benzene rings of both the oxindoles and the nitroalkenes. In particular, electron-rich, heteroaromatic-substituted, and halogenated nitrostyrenes were well tolerated (entries 2−8). Excellent enantioselectivity and poor yield were obtained with an aliphatic nitroalkene (entry 9). The reactions of nonsymmetric (*Z*)-oxindoles **1c**−**e** with different alkyl chains on the double bond did not affect the reactivity and stereoselectivity of the reaction, and the corresponding Michael adducts **3j**−**l** were formed with outstanding enantio- and diastereocontrol, albeit in slightly lower yields (entries 10−12).

Scheme 4. Intramolecular H$_\gamma$ Activation for Oxindole (*Z*)-1a and (*E*)-1a

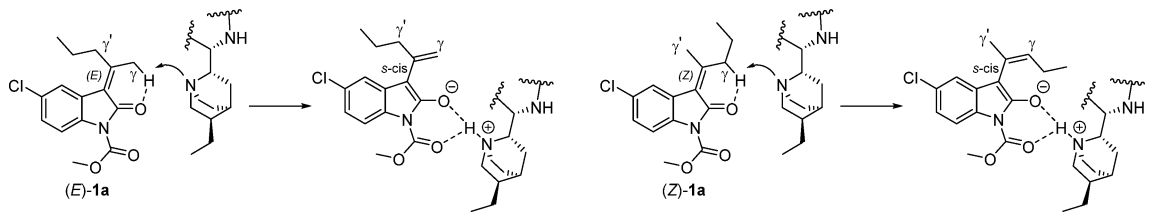

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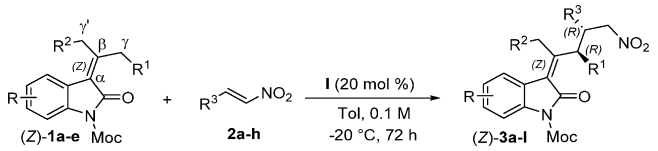
Table 3. Scope of the Reaction of (*Z*)-Alkylidene Oxindoles 1 with Nitroalkene 2[a]



entry	oxindole	R	R^1	R^2	nitroalkene	R^3	product	yield[b] (%)	dr[c]	ee[d] (%)
1	(*Z*)-**1a**	5-Cl	CH_2CH_3	H	**2a**	Ph	(*Z*)-**3a**	86	>99:1	>99
2	(*Z*)-**1a**	5-Cl	CH_2CH_3	H	**2b**	thienyl	(*Z*)-**3b**	89	>99:1	99
3	(*Z*)-**1b**	H	CH_2CH_3	H	**2a**	Ph	(*Z*)-**3c**	70	>99:1	>99
4	(*Z*)-**1b**	H	CH_2CH_3	H	**2c**	4-MeOPh	(*Z*)-**3d**	52	>99:1	>99
5	(*Z*)-**1b**	H	CH_2CH_3	H	**2d**	3-MeOPh	(*Z*)-**3e**	61	>99:1	>99
6	(*Z*)-**1b**	H	CH_2CH_3	H	**2e**	4-MePh	(*Z*)-**3f**	75	>99:1	>99
7	(*Z*)-**1b**	H	CH_2CH_3	H	**2f**	2-FPh	(*Z*)-**3g**	66	>99:1	>99
8	(*Z*)-**1b**	H	CH_2CH_3	H	**2g**	4-BrPh	(*Z*)-**3h**	62	>99:1	>99
9	(*Z*)-**1b**	H	CH_2CH_3	H	**2h**	isobutyl	(*Z*)-**3i**	20	>99:1	99
10	(*Z*)-**1c**	H	CH_2CH_3	CH_3	**2a**	Ph	(*Z*)-**3j**	44	>99:1	99
11	(*Z*)-**1d**	H	C_4H_7	H	**2a**	Ph	(*Z*)-**3k**	81	>99:1	>99
12	(*Z*)-**1e**	H	CH_2Ph	H	**2a**	Ph	(*Z*)-**3l**	50	>99:1	96

[a]All reactions were performed using 0.2 mmol of (*Z*)-**1**, 0.2 mmol of **2**, 20 mol % of **I**, and 2 mL of toluene. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis of the crude mixture. [d]Determined by chiral HPLC analysis.

The absolute configuration of (*Z*)-**3h** has been established as (3*Z*,3′*R*,4′*R*) by X-ray analysis.[17] The absolute configuration of similar products in Table 3 was assigned by analogy (Figure 2).

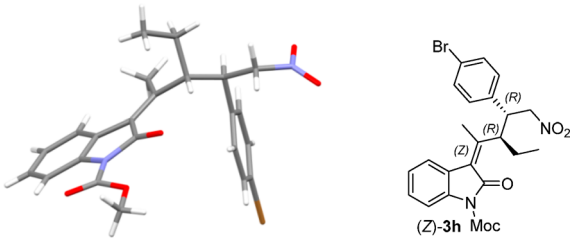


Figure 2. X-ray structure for compound (*Z*)-**3h**.

The reaction of (*E*)-**1a,c–e** afforded the desired vinylogous (*Z*)-adducts together with variable amounts of the (*E*)-isomers in moderate to high yields, with excellent enantioselectivity and exclusive *γ*-selectivity (Table 4, entries 1–14). The use of heteroaromatic and electron-rich substituted nitroalkenes is well tolerated (entries 2–6). Halogenated aromatic rings also provide access to the desired products with a high degree of stereocontrol. When 4-bromo-*trans*-*β*-nitrostyrene **2h** was used, no isomerization of the double bond was observed in the product. Interestingly, sterically demanding nitroalkene **2i** showed sufficient reactivity (entry 9). The reaction can be extended to aliphatic nitroalkenes without losing stereocontrol, albeit with a moderate yield (entry 10). Also for (*E*)-oxindoles, the presence of different alkyl chains on the double bond was studied. The reaction was found to be extremely enantioselective and regioselective (entries 11–13). When oxindole (*E*)-**1c** was employed, the reaction was also diastereoselective, and no *Z*/*E* isomerization was observed in the final product (entry 11). Indeed, good reactivity and enantioselectivity were still encountered when oxindoles (*E*)-**1d** and (*E*)-**1e**, containing isobutenyl and benzyl substituents, were employed. However, in these last examples, an increase in the yield of isomerization products was observed (entries 12 and 13).

The reaction tolerated the presence of a halogen substituent at a different position on the oxindole derivative (entry 14). The absolute configuration of (*Z*)-**4n** was determined to be (4′*R*) by comparison of the sign of the specific optical rotation ($[\alpha]_D^{20}$ −102.0) with the value reported for the similar product **6** in which R = 6-Cl, R^1 = R^2 = H, and R^3 = Ph ($[\alpha]_D^{20}$ −58.2).[6a] In addition, comparison of the experimental ECD spectrum of (*Z*)-**4n** with the experimental ECD spectrum of **6** confirmed that the absolute configuration was the same (Figure 3).[11]

Finally, the vinylogous Michael addition of asymmetric oxindoles can be easily extended to *β*,*β*-disubstituted nitroalkenes **7a** for the construction of quaternary stereocenters with four carbon substituents. In this last case, the reaction was completely *γ*-site selective and proceeded with complete enantio- and diastereoselectivity with both (*E*)-**1a** and (*Z*)-**1a** (Scheme 5).

One of the most important aspects of the studied reaction is the inhibition of isomerization at −20 °C and the subsequent absolute selectivity in the reaction products. We performed several experiments to gain more insight into the reaction mechanism, paying particular attention to the role played by the reagents and the catalyst. First, we considered the two units composing the catalytic system as two independent units having their proper catalytic mechanism of action in order to understand the specific role of the catalyst functionalities (Scheme 6). We then synthesized two catalysts (**III** and **IV**) having the same mechanism of action of the two units and tested their catalytic activity for the isomerization and vinylogous reaction. The results obtained have been compared with those of catalyst **I** in order to obtain the most reliable model for the reaction mechanism.

Reactions of (*Z*)-1a with Catalysts III and IV. In the absence of nitrostyrene catalysts, **III** and **IV** promoted the isomerization of (*Z*)-**1a** into (*E*)-**1a** independently but with different reaction rates. In particular, **IV** was shown to be the most active, and **III** was slightly slower than **I** (Table 5). These results would suggest that two different isomerization pathways might be operative (Scheme 6): (a) a faster pathway where the thiourea moiety of the catalyst associates with the oxindole via hydrogen bonding to promote the oxindole dienol formation and (b) a slower pathway where the quinuclidine moiety deprotonates the oxindole to promote the formation of the dienolate.

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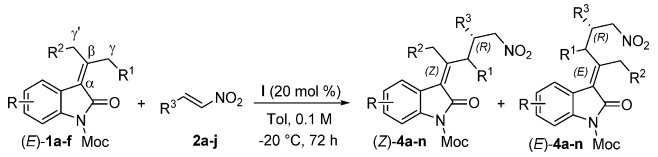
Table 4. Scope of the Reaction of (*E*)-Alkylidene Oxindoles with Nitroalkene[a]



entry	oxindole	R	R^1	R^2	nitroalkene	R^3	products	yield[b] (%)	Z/E[c]	ee[d] (%)
1	(*E*)-**1a**	5-Cl	H	CH_2CH_3	**2a**	Ph	(*Z*)-**4a** + (*E*)-**4a**	85	91:9	>99
2	(*E*)-**1a**	5-Cl	H	CH_2CH_3	**2b**	thienyl	(*Z*)-**4b** + (*E*)-**4b**	77	92:8	>99
3	(*E*)-**1a**	5-Cl	H	CH_2CH_3	**2c**	4-MeOPh	(*Z*)-**4c** + (*E*)-**4c**	78	96:4	>99
4	(*E*)-**1a**	5-Cl	H	CH_2CH_3	**2d**	3-MeOPh	(*Z*)-**4d** + (*E*)-**4d**	92	95:5	>99
5	(*E*)-**1a**	5-Cl	H	CH_2CH_3	**2j**	2-OBnPh	(*Z*)-**4e** + (*E*)-**4e**	93	93:7	>99
6	(*E*)-**1a**	5-Cl	H	CH_2CH_3	**2e**	4-MePh	(*Z*)-**4f** + (*E*)-**4f**	96	94:6	>99
7	(*E*)-**1a**	5-Cl	H	CH_2CH_3	**2f**	2-FPh	(*Z*)-**4g** + (*E*)-**4g**	87	95:5	>99
8	(*E*)-**1a**	5-Cl	H	CH_2CH_3	**2g**	4-BrPh	(*Z*)-**4h**	85	>99:1	>99
9	(*E*)-**1a**	5-Cl	H	CH_2CH_3	**2i**	2,6-ClPh	(*Z*)-**4i** + (*E*)-**4i**	80	92:8	>99
10	(*E*)-**1a**	5-Cl	H	CH_2CH_3	**2h**	isobutyl	(*Z*)-**4j**	50	>99:1	97
11[e]	(*E*)-**1c**	H	CH_3	CH_2CH_3	**2a**	Ph	(*Z*)-**4k**	44	>99:1	>99
12	(*E*)-**1d**	H	H	C_4H_7	**2a**	Ph	(*Z*)-**4l** + (*E*)-**4l**	92	80:20	>99
13	(*E*)-**1e**	H	H	CH_2Ph	**2a**	Ph	(*Z*)-**4m** + (*E*)-**4m**	63	80:20	>99
14	(*E*)-**1f**	6-Cl	H	CH_2CH_3	**2a**	Ph	(*Z*)-**4n** + (*E*)-**4n**	75	92:8	>99

[a]Reactions were performed at −20 °C using 0.2 mmol of (*E*)-**1**, 0.2 mmol of **2**, 20 mol % of **I**, and 2 mL of toluene. [b]Total combined yield of (*Z*)-**4** and (*E*)-**4**. [c]Determined by ^{1}H NMR of the crude mixture. [d]Determined by chiral HPLC analysis. [e]Product (*Z*)-**4k** was obtained as single diastereoisomer and the absolute configuration has been assigned (3′*R*,4′*R*) by analogy.

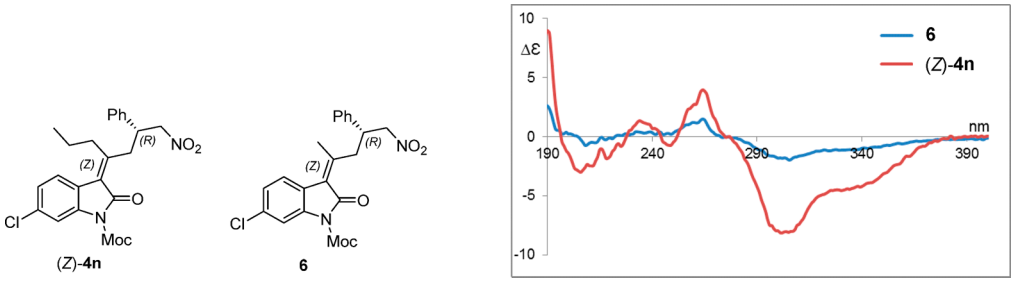
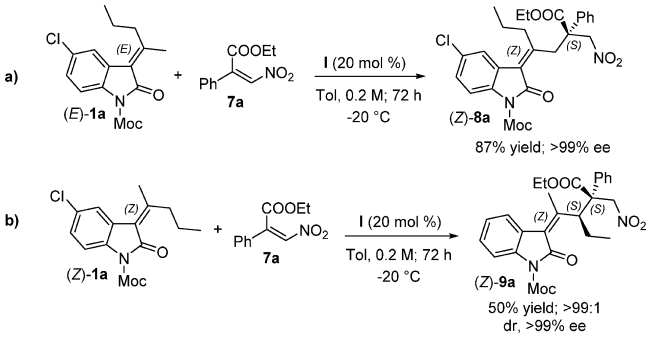


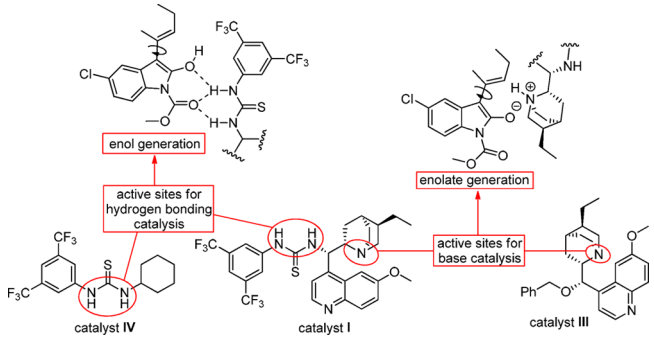
Figure 3. Experimental ECD spectra for (*Z*)-**4n** and **6**. The blue line corresponds to compound **6** (acetonitrile solution, 5×10^{-5} M, 0.2 cm path length, $\Delta\varepsilon$ in mol L^{-1} cm^{-1}), the red line is for (*Z*)-**4n** (acetonitrile solution, 5×10^{-5} M, 0.2 cm path length, $\Delta\varepsilon$ in Mol L^{-1} cm^{-1}).

Scheme 5. Synthesis of the All-Carbon Quaternary Stereocenter Derivatives



However, in the presence of nitrostyrene **2a** no vinylogous reaction with oxindole (*Z*)-**1a** was observed with either catalyst **III** or **IV** (Table 6). These experiments also show that **2a** inhibits the ability of catalyst **IV** to bring about the isomerization of (*Z*)-**1a**, while catalyst **III** maintains its ability to isomerize (*Z*)-**1a**. Therefore, it can be put forward that nitrostyrene associates to the thiourea moiety of the catalyst stronger than the oxindole, thus blocking the thiourea-promoted isomerization pathway.

Scheme 6. Activation Pathway of Catalyst I and New Catalysts That Simulate the Catalytic Activity of the Separate Unit of Catalyst I



Effect of the Concentration of (*Z*)-1a and 2a on the Reaction Rate. The reaction was furthermore studied using **I** and with a large excess of (*Z*)-**1a** and **2a** (Table 7 entries 1−3). Under standard reaction conditions, the conversion after 23 h is 85% but no isomerization was found in the remaining oxindole. With 2 equiv of (*Z*)-**1a**, the nitroalkene was totally consumed after 20 h, affording only product (*Z*)-**3a**. Thus, the reaction

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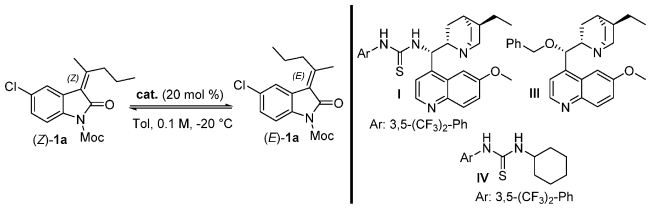
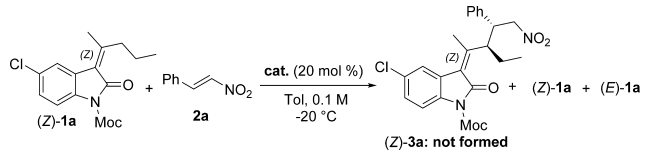
Table 5. Isomerization of (*Z*)-1a to (*E*)-1a in the Presence of Catalysts I, III, and IV[a]



	(*Z*)-1a/(*E*)-1a[b]			
catalyst	1 h	3 h	5 h	23 h
I	96:4	92:8	89:11	75:25
III	99:1	97:3	95:5	80:20
IV	89:11	80:20	74:26	66:34

[a]Reactions were performed using 0.2 mmol of (*Z*)-1a in 2 mL of toluene. [b]Determined by ^{1}H NMR analysis.

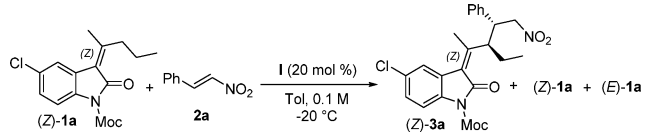
Table 6. Effect on the Isomerization Side Reaction with the Presence of 2a[a]



	(*Z*)-1a/(*E*)-1a[b]			
catalyst	1 h	3 h	5 h	23 h
III	99:1	98:2	97:3	80:20
IV	99:1	98:2	97:3	96:4

[a]Reactions were performed using 0.2 mmol of (*Z*)-1a and 0.2 mmol of 2a in 2 mL of toluene. [b]Determined by ^{1}H NMR analysis.

Table 7. Effect of the Concentration of (*Z*)-1a and 2a on the Reaction Rate[a]



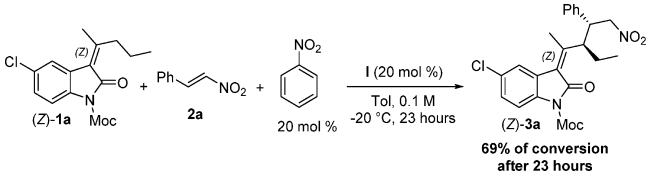
entry	(*Z*)-1a (M)	2a (M)	time (h)	conv to (*Z*)-3a (%)	(*Z*)-1a/(*E*)-1a[c]
1[b]	0.1	0.1	23	85	
2	0.2	0.1	20	full	96:4 (80:20)[d]
3	0.1	0.2	23	69	

[a]Reactions were performed using 20 mol % of catalyst I in 2 mL of toluene. [b]Standard reaction conditions. [c]Determined by ^{1}H NMR analysis. [d]After 44 h of reaction.

revealed to be faster than the standard conditions (entry 1) because of the increased concentration of the enolate intermediate, thus confirming that the deprotonation of (*Z*)-1a is the rate-determining step of the reaction. Interestingly, after 44 h, the unconverted oxindole was recovered as an 80:20 equilibrium mixture of isomerization (entry 2). This last observation indicated that when 2a disappears catalyst I is able to promote the isomerization of (*Z*)-1a, confirming our previous hypothesis and suggesting the presence of a complex between I and 2a that inhibit furthermore the isomerization. This idea was confirmed when 2 equiv of 2a was employed. In fact, the conversion to (*Z*)-3a was only 69% after 23 h (entry 3), and no isomerization was observed on the remaining oxindole during the course of the whole reaction. Thus, the concentration of the nitroalkene has a negative effect on the reaction rate, and this might be explained by the formation of an *unproductive* association between the catalyst and the nitroalkene. The higher the nitroalkene concentration the more catalyst is subtracted from the reaction as the catalyst−nitroalkene complex.

Since it is well-known that cinchona alkaloids of type I are able to give self-association in solution,[18] to exclude that isomerization can be influenced by this process, we repeated the reaction in the presence of 20 mol % of nitrobenzene.[19] We observed a conversion of only 67% exclusively for (*Z*)-3a after 23 h, indicating that effectively catalyst I is associated with the nitro group, giving rise to a complex that is not able to catalyze the reaction and effectively inhibits the isomerization process (Scheme 7).

Scheme 7. Effect on the Reaction Rate of the Presence of Nitrobenzene



A general scheme of the reaction can now be proposed (Scheme 8). The thiourea unit of catalyst I at −20 °C rapidly and strongly associates with 2a via hydrogen bonding ($k_1 > k_2 > k_3$), thus accounting for the formation of a complex between I and 2a. This associative process is faster than the associative process between the thiourea substituent and the oxindole ($k_1 \gg k_3$); as a main consequence, the enol intermediate probably is not involved in the reaction with the nitroalkene. The quinuclidine unit of catalyst I generates the enolate as the only reactive intermediate of the vinylogous reaction in what is the rate-determining step of the process ($k_1 > k_2$). Later, 2a reacts with the enolate with a reaction rate higher than the rate of isomerization at −20 °C ($k_4 \gg k_5$).

A transition state for the Michael addition step can be proposed. The high grade of diastereoselection observed is the result of the reaction of the (*E*)-*s*-*cis* enolate as the sole intermediate of reaction at −20 °C. The *E*-configuration of the terminal double bond has been assumed after the reaction between oxindole 1g with *tert*-butyldimethylsilyl trifluoromethanesulfonate in which only the (*E*)-silyl enol ether 10 was obtained (Figure 4).[20]

CONCLUSION

In summary, we have developed the organocatalyzed vinylogous Michael addition of nonsymmetric alkylidene oxindoles to nitroalkenes. The reaction proceeded at −20 °C with complete inhibition of the interconversion between the two (*E*)/(*Z*) isomers of the starting oxindole. The resulting products were obtained with high regio-, diastereo-, and enantiocontrol. The reaction proceeded only via a γ-site selective deprotonation by catalyst I, which exclusively interacts via hydrogen bonding only with the nitroalkene and not with the oxindole. The role of the nitroalkene is furthermore fundamental since the direct interaction with the catalyst via H-bonding that leads to a complex between the two species reinforces the effect of the temperature on the inhibition of the isomerization parasitic pathway.

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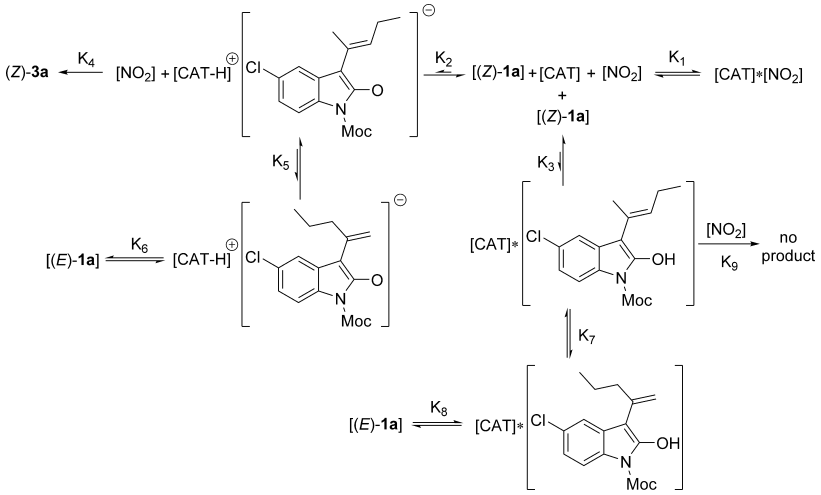
Scheme 8. Possible General Scheme of Reaction



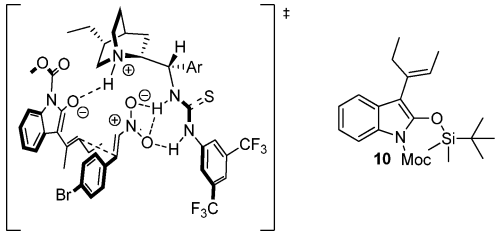


Figure 4. Proposed transition state for the reaction of (*Z*)-**1b**.

EXPERIMENTAL SECTION

The ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively, or at 600 MHz for ^{1}H and 150.8 MHz for ^{13}C, or at 300 MHz for ^{1}H and 75.4 MHz for ^{13}C. ^{19}F NMR spectra were recorded at 362 MHz. All the ^{1}H and ^{13}C signals were assigned by means of g-COSY, g-HSQC, and g-HMBC 2D-NMR sequences. NOE spectra were recorded using the DPFGSE-NOE sequence[21] with a mixing time of 1.0−2.0 s and "rsnob" 20 ÷ 50 Hz wide selective pulses, depending on the crowding of the spectra region. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$). Coupling constants are given in hertz. Carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230−400 mesh) according to the method of Still.[22] Organic solutions were concentrated under reduced pressure on a rotary evaporator. Optical rotations are reported as follows: $[\alpha]_D^{20}$ (*c* in g per 100 mL, solvent, % ee). Chiral thiourea catalyst **I** derived from 9-*epi*-9-amino-9-deoxydihydroquinine and *ent*-**I** derived from 9-*epi*-9-amino-9-deoxy-dihydroquinidine were prepared following the literature procedure.[23] Alkylidenoxindoles (*Z*)-**1a−e** and (*E*)-**1a,c−f** were synthesized following the literature procedure.[24] The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Chiral HPLC analysis was performed using amylose 2, cellulose 2, AD-H, AS-H columns, and OD-H with *i*-PrOH/hexane as the eluent. HPLC traces for compounds (*Z*)-**3a−m**, (*Z*)-**4a−m**, (*Z*)-**8a**, and (*Z*)-**9a** were compared to quasiracemic samples prepared by mixing the two antipodes obtained by performing the reaction with catalyst **I** and its pseudoenantiomer *ent*-**I** separately.

(*E*)-Methyl 5-Chloro-2-oxo-3-(pentan-2-ylidene)indoline-1-carboxylate ((*E*)-1a) and (*Z*)-Methyl 5-Chloro-2-oxo-3-(pentan-2-ylidene)indoline-1-carboxylate ((*Z*)-1a). Piperidine (40 mmol, 3.95 mL) was added to a 0.5 M solution of 5-chloroindolin-2-one (10 mmol, 1.67 g) in 0.5 M in ethanol/2-pentanone 1:1. The resulting solution was stirred overnight at room temperature. The reaction mixture was taken up with ethyl acetate, and the resulting organic solution was, respectively, washed with 20 mL of a 1 M solution of $KHSO_4$, water, and brine. The organic layer was made anhydrous over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was suspended in acetonitrile, and 4-(dimethylamino)pyridine (1 mmol, 122 mg) was added followed by the addition of dimethyl dicarbonate (12 mmol, 1.29 mL). After 30 min of stirring, the solvent was removed under reduced pressure and the crude products were obtained as a 45:55 mixture of (*E*)-**1a**/(*Z*)-**1a**. These were purified and separated from each other by flash column chromatography (hexane/ethyl acetate = 9:1) to give an overall yield of 75%. HRMS-ESI (+) of (*E*)-**1a**: calcd for $C_{15}H_{16}ClNaNO_3$ 316.0716, found 316.0718 $[M + Na]^+$, and of (*Z*)-**1a** calcd for $C_{15}H_{16}ClNaNO_3$ 316.0716, found 316.0717 $[M + Na]^+$. Mp: for (*E*)-**1a**, 105−108 °C; for (*Z*)-**1a**, 100−102 °C. ^{1}H NMR of (*E*)-**1a** (400 MHz, $CDCl_3$): δ (ppm) 7.93 (d, 1H, J = 8.6 Hz); 7.42 (d, 1H, J = 2.7 Hz); 7.24 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.7 Hz); 4.02 (s, 3H); 2.63 (t, 2H, J = 8.4 Hz); 2.57 (s, 3H); 1.68 (m, 2H); 1.11 (t, 3H, J = 7.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 165.0, 164.4, 151.7, 135.9, 129.5, 127.6, 124.8, 122.8, 120.2, 115.8, 53.8, 40.5, 22.9, 20.4, 14.3. ^{1}H NMR of (*Z*)-**1a** (400 MHz, $CDCl_3$): δ (ppm) 7.93 (d, 1H, J = 8.5 Hz); 7.53 (d, 1H, J_1 = 1.7 Hz); 7.25 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.6 Hz); 4.03 (s, 3H); 3.02 (t, 2H, J = 7.8 Hz); 2.38 (s, 3H); 1.59 (m, 2H); 1.04 (t, 3H, J = 7.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 164.4, 151.7, 135.9, 129.5, 127.6, 125.7, 123.3, 120.5, 115.7, 53.9, 38.9, 24.6, 21.5, 14.3.

Methyl (*Z*)-5-Chloro-2-oxo-3-(pentan-2-ylidene-*1,1,1,3,3-d*$_5$)-indoline-1-carboxylate ((*Z*)-1a$_{d5}$) and Methyl (*E*)-5-Chloro-2-oxo-3-(pentan-2-ylidene-*1,1,1,3,3-d*$_5$)indoline-1-carboxylate ((*E*)-1a$_{d5}$). DABCO (0.225 mmol, 25 mg) was added to a 60:40 mixture of oxindoles (*Z*)-**1a** and (*E*)-**1a** (0.5 mmol, 150 mg) in the minimum amount of deuterated chloroform, and then an excess of methanol-d_4 (2 mL) was added to the solution, which was left under magnetic stirring at 40 °C until ^{1}H NMR confirmed the complete deuteration of the γ and γ' positions. At this point, the solvent was removed at the rotary evaporator and the isomers were separated from each other by flash column chromatography (hexane/ethyl acetate = 9/1). MS-ESI (+): (*Z*)-**1a**$_{d5}$ 321 $[M + Na]^+$; (*E*)-**1a**$_{d5}$ 321 $[M + Na]^+$. ^{1}H NMR of (*Z*)-**1a**$_{d5}$ (400 MHz, $CDCl_3$): δ (ppm) 7.93 (d, 1H, J_1 = 9.0 Hz); 7.52 (d, 1H, J_1 = 2.0 Hz); 7.25 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.0 Hz); 4.02 (s, 3H); 1.59 (m, 2H); 1.03 (t, 3H, J_1 = 7.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 164.3, 164.2, 151.7, 135.9, 129.4, 127.5, 125.7, 123.2, 120.5, 115.7, 53.8, 21.3, 14.2. ^{1}H NMR of (*E*)-**1a**$_{d5}$ (400 MHz, $CDCl_3$): δ (ppm) 7.95 (d, 1H, J_1 = 9.2 Hz); 7.45 (d, 1H, J_1 = 2.1 Hz); 7.26 (dd, 1H, J_1 = 9.2 Hz, J_2 = 2.1 Hz); 4.02 (s, 3H); 1.67 (m, 2H); 1.11 (t, 3H, J_1 = 7.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 165.1, 164.3, 151.7, 136.0, 129.5, 127.6, 124.9, 122.8, 120.3, 115.8, 53.8, 20.2, 14.2.

Methyl (*Z*)-5-Chloro-2-oxo-3-(pentan-2-ylidene-*1,1,1-d*$_3$)-indoline-1-carboxylate ((*Z*)-1a$_{d3}$) and Methyl (*E*)-5-Chloro-2-oxo-3-(pentan-2-ylidene-*1,1,1-d*$_3$)indoline-1-carboxylate ((*E*)-1a$_{d3}$). DABCO (0.53 mmol, 59.0 mg) was added to a 60:40 mixture

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of oxindoles (*Z*)-**1a** and (*E*)-**1a** (1.2 mmol, 356 mg) in 7 mL of deuterated chloroform, and then methanol-d_4 (4.2 equiv., 170 μL, 150 mg) was added to the solution which was left under magnetic stirring overnight at room temperature. At this point, the solvent was removed via rotary evaporator, and the isomers were separated from each other by flash column chromatography (hexane/ethyl acetate = 9:1). From the ^{1}H NMR spectra we calculated the deuterium enrichment for each position of each isomer. Both isomers have a 50% deuterium enrichment on the methyl group and a 10% enrichment on the propyl group. MS-ESI (+): (*Z*)-**1a**$_{d3}$ 319 $[M + Na]^+$; (*E*)-**1a**$_{d3}$ 319 $[M + Na]^+$. ^{1}H NMR of (*Z*)-**1a**$_{d3}$ (400 MHz, $CDCl_3$): δ (ppm) 7.91 (d, 1H, J_1 = 9.4 Hz); 7.51 (d, 1H, J_1 = 2.2 Hz); 7.23 (dd, 1H, J_1 = 9.4 Hz, J_2 = 2.2 Hz); 4.02 (s, 3H); 3.00 (m, 1.8H); 2.36 (m, 1.45H); 1.60 (m, 2H); 1.04 (t, 3H, J_1 = 7.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 164.3, 164.2, 151.6, 135.8, 129.4, 127.5, 125.6, 123.2, 120.4, 115.7, 53.8, 38.7, 24.3, 21.3, 14.3. ^{1}H NMR of (*E*)-**1a**$_{d3}$ (400 MHz, $CDCl_3$): δ (ppm) 7.93 (d, 1H, J_1 = 8.8 Hz); 7.42 (d, 1H, J_1 = 2.2 Hz); 7.24 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.821 Hz); 4.02 (s, 3H); 2.63 (m, 1.78H); 2.54 (m, 1.51H); 1.67 (m, 2H); 1.11 (t, 3H, J_1 = 7.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 165.0, 164.4, 151.6, 135.9, 129.5, 127.6, 124.8, 122.8, 120.2, 115.8, 53.8, 40.4, 22.6, 20.3, 14.3.

(*Z*)-Methyl 2-Oxo-3-(pentan-2-ylidene)indoline-1-carboxylate ((*Z*)-1b). Piperidine (40 mmol, 3.95 mL) was added to a 0.5 M solution of indolin-2-one (10 mmol, 1.33 g) in 0.5 M in ethanol/2-pentanone 1:1. The resulting solution was stirred overnight at room temperature. The reaction mixture was taken up with ethyl acetate, and the resulting organic solution was washed, respectively, with 20 mL of a 1 M solution of $KHSO_4$, water, and brine. The organic layer was made anhydrous over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was suspended in acetonitrile, and 4-(dimethylamino)pyridine (1 mmol, 122 mg) was added followed by the addition of dimethyl dicarbonate (12 mmol, 1.29 mL). After 30 min of stirring, the solvent was removed under reduced pressure, and the title compound was obtained in a 45% yield after purification of the crude mixture by flash column chromatography (hexane/ethyl acetate = 9:1). HRMS-ESI (+): calcd for $C_{15}H_{17}NaNO_3$ 282.1106, found 282.1104 $[M + Na]^+$. Mp: 91−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.88 (d, 1H, J = 7.8 Hz); 7.43 (d, 1H, J = 7.7 Hz); 7.19 (m, 1H); 7.06 (m, 1H); 3.98 (s, 3H); 2.95 (t, 2H, J = 8.2 Hz); 2.27(s, 3H); 1.56 (m, 2H); 1.02 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 165.1, 162.3, 151.9, 137.6, 129.9, 127.9, 124.0, 123.3, 121.2, 114.7, 53.7, 38.7, 24.5, 21.5, 14.3.

(*E*)-Methyl 3-(Hexan-3-ylidene)-2-oxoindoline-1-carboxylate ((*E*)-1c) and (*Z*)-Methyl 3-(Hexan-3-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-1c). Piperidine (40 mmol, 3.95 mL) was added to a 0.5 M solution of indolin-2-one (10 mmol, 1.33 g) in 0.5 M ethanol/3-hexanone 1:1. The resulting solution was stirred overnight at room temperature. The reaction mixture was taken up with ethyl acetate, and the resulting organic solution was washed, respectively, with 20 mL of a 1 M solution of $KHSO_4$, water, and brine. The organic layer was made anhydrous over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was suspended in acetonitrile, and 4-(dimethylamino)pyridine (1 mmol, 122 mg) was added followed by the addition of dimethyl dicarbonate (12 mmol, 1.29 mL). After 30 min of stirring, the solvent was removed under reduced pressure, and the crude product was obtained as a 50:50 mixture of (*E*)-**1c**/(*Z*)-**1c**. These were purified by flash column chromatography (hexane/ethyl acetate = 9/1) to give an overall yield of 40% and separated from each other by preparative reverse-phase column chromatography. HRMS-ESI (+) of (*E*)-**1c**: calcd for $C_{16}H_{19}NaNO_3$ 296.1263, found 296.1261 $[M + Na]^+$ and of (*Z*)-**1c** calcd for $C_{16}H_{19}NaNO_3$ 296.1263, found 296.1261 $[M + Na]^+$. Mp for (*E*)-**1c**: 74−76 °C, for (*Z*)-**1c**: 60−61 °C. ^{1}H NMR of (*E*)-**1c** (400 MHz, $CDCl_3$): δ (ppm) 8.00 (d, 1H, J = 8.6 Hz); 7.47 (d, 1H, J = 8.4 Hz); 7.28 (m, 1H); 7.16 (m, 1H); 4.02 (s, 3H); 2.98 (*q*, 2H, J = 7.6 Hz); 2.63 (t, 2H, J = 8.5 Hz); 1.66 (m, 2H); 1.18 (t, 3H, J = 7.8 Hz); 1.11 (t, 3H, J = 7.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 168.3, 165.2, 151.9, 137.7, 127.9, 124.1, 123.6, 122.8, 120.4, 114.7, 53.7, 38.5, 28.7, 20.4, 14.5, 12.4. ^{1}H NMR of (*Z*)-**1c** (300 MHz, $CDCl_3$): δ (ppm) 8.01 (d, 1H, J = 9.0 Hz); 7.56 (d, 1H, J = 7.6 Hz); 7.30 (m, 1H); 7.18 (m, 1H); 4.03 (s, 3H); 2.94 (t, 2H, J = 8.1 Hz); 2.71 (*q*, 2H, J = 7.5 Hz); 2.38 (s, 3H); 1.59 (m, 2H); 1.26 (t, 3H, J = 7.6 Hz); 1.05 (t, 3H, J = 7.6 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 168.2, 165.3, 151.9, 137.7, 127.9, 124.2, 123.5, 122.9, 120.5, 114.7, 53.7, 37.0, 29.8, 21.7, 14.6, 11.2.

(*E*)-Methyl 3-(5-Methylhex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate ((*E*)-1d) and (*Z*)-Methyl 3-(5-Methylhex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-1d). Piperidine (40 mmol, 3.95 mL) was added to a 0.5 M solution of indolin-2-one (10 mmol, 1.33 g) in 0.5 M in ethanol/5-methyl-5-hexen-2-one 1:1. The resulting solution was stirred overnight at room temperature. The reaction mixture was taken up with ethyl acetate, and the resulting organic solution was, respectively, washed with 20 mL of a 1 M solution of $KHSO_4$, water, and brine. The organic layer was made anhydrous over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was suspended in acetonitrile, and 4-(dimethylamino)pyridine (1 mmol, 122 mg) was added followed by the addition of dimethyl dicarbonate (12 mmol, 1.29 mL). After 30 min of stirring, the solvent was removed under reduced pressure, and the crude product was obtained as a 40:60 mixture of (*E*)-**1d**/(*Z*)-**1d**. These were purified and separated from each other by flash column chromatography (hexane/ethyl acetate = 9:1) to give an overall yield of 58%. HRMS-ESI (+) of (*E*)-**1d**: calcd for $C_{17}H_{19}NaNO_3$ 308.1263, found 308.1265 $[M + Na]^+$ and of (*Z*)-**1d** calculated for $C_{17}H_{19}NaNO_3$ 308.1263, found 308.1262 $[M + Na]^+$. Mp for (*E*)-**1d**: 85−87 °C, for (*Z*)-**1d**: 66−69 °C. ^{1}H NMR of (*E*)-**1d** (300 MHz, $CDCl_3$): δ (ppm) 8.00 (d, 1H, J = 8.5 Hz); 7.50 (d, 1H, J = 7.6 Hz); 7.29 (m, 1H); 7.16 (m, 1H); 4.84 (d, 2H, J = 11.6 Hz); 4.03 (s, 3H); 2.82 (t, 2H, J = 8.4 Hz); 2.57 (s, 3H); 2.29 (t, 2H, J = 8.4 Hz); 1.83 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 165.6, 161.5, 151.8, 144.2, 137.6, 128.0, 124.2, 123.3, 122.6, 121.1, 114.7, 110.8, 53.6, 36.8, 34.3, 22.6, 22.5. ^{1}H NMR of (*Z*)-**1d** (300 MHz, $CDCl_3$): δ (ppm) 7.99 (d, 1H, J = 8.3 Hz); 7.59 (d, 1H, J = 7.2 Hz); 7.31 (m, 1H); 7.18 (m, 1H); 4.76 (bs, 2H); 4.03 (s, 3H); 3.19 (t, 2H, J = 8.1 Hz); 2.40 (s, 3H); 2.26 (t, 2H, J = 7.6 Hz); 1.83 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 164.9, 161.3, 151.8, 144.9, 137.6, 127.9, 124.2, 123.9, 123.3, 121.3, 114.6, 110.5, 53.7, 35.7, 35.3, 24.4, 22.3.

(*E*)-Methyl 2-Oxo-3-(4-phenylbutan-2-ylidene)indoline-1-carboxylate ((*E*)-1e) and (*Z*)-Methyl 2-Oxo-3-(4-phenylbutan-2-ylidene)indoline-1-carboxylate ((*Z*)-1e). Piperidine (40 mmol, 3.95 mL) was added to a 0.5 M solution of indolin-2-one (10 mmol, 1.33 g) in 0.5 M in ethanol/4-phenyl-2-butanone 1:1. The resulting solution was stirred overnight at room temperature. The reaction mixture was taken up with ethyl acetate, and the resulting organic solution was washed, respectively, with 20 mL of a 1 M solution of $KHSO_4$, water, and brine. The organic layer was made anhydrous over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was suspended in acetonitrile, and 4-(dimethylamino)pyridine (1 mmol, 122 mg) was added followed by the addition of dimethyl dicarbonate (12 mmol, 1.29 mL). After 30 min of stirring, the solvent was removed under reduced pressure and the crude product was obtained as a 40:60 mixture of (*E*)-**1e**/(*Z*)-**1e**. These have been purified and separated from each other by flash column chromatography (hexane/ethyl acetate = 9:1) to give an overall yield of 62%. HRMS-ESI (+) of (*E*)-**1e**: calcd for $C_{20}H_{19}NaNO_3$ 344.1263, found 344.1263 $[M + Na]^+$ and of (*Z*)-**1e** calculated for $C_{20}H_{19}NaNO_3$ 344.1263, found 344.1266 $[M + Na]^+$. Mp for (*E*)-**1e**: 111−113 °C, for (*Z*)-**1e**: 102−105 °C. ^{1}H NMR of (*E*)-**1e** (300 MHz, $CDCl_3$): δ (ppm) 8.03 (d, 1H, J = 8.4 Hz); 7.60 (d, 1H, J = 7.5 Hz); 7.35−7.20 (m, 7H); 4.04 (s, 3H); 3.00 (m, 4H); 2.55 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 165.7, 160.8, 151.9, 140.4, 137.7, 128.7, 128.3, 128.2, 128.1, 126.5, 124.2, 123.3.122.7, 121.4, 114.9, 53.8, 40.3, 32.8, 22.9. ^{1}H NMR of (*Z*)-**1e** (300 MHz, $CDCl_3$): δ (ppm) 8.01 (d, 1H, J = 8.0 Hz); 7.59 (d, 1H, J_1 = 8.00 Hz); 7.31 (m, 5H); 7.19 (m, 2H); 4.05 (s, 3H); 3.32 (t, 2H, J = 8.2 Hz); 2.87 (*q*, 2H, J = 8.2 Hz); 2.36 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 164.8, 160.7, 151.8, 141.2, 137.7, 128.5, 128.3, 128.0, 126.0, 124.1, 124.0, 123.4, 121.6, 114.7, 53.7, 39.3, 34.2, 24.8.

(*E*)-Methyl 6-Chloro-2-oxo-3-(pentan-2-ylidene)indoline-1-carboxylate ((*E*)-1f). Piperidine (40 mmol, 3.95 mL) was added to a 0.5 M solution of 6-chloroindolin-2-one (10 mmol, 1.67 g) in 0.5 M in ethanol/2-pentanone 1:1. The resulting solution was stirred overnight at room temperature. The reaction mixture was taken up with ethyl acetate, and the resulting organic solution was washed, respectively, with 20 mL of a 1 M solution of $KHSO_4$, water, and brine. The organic layer

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was made anhydrous over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was suspended in acetonitrile, and 4-(dimethylamino)pyridine (1 mmol, 122 mg) was added followed by the addition of dimethyl dicarbonate (12 mmol, 1.29 mL). After 30 min of stirring, the solvent was removed under reduced pressure, and the title compound was obtained in a 51% yield after purification of the crude mixture by flash column chromatography (hexane/ethyl acetate = 9:1). HRMS-ESI (+): calcd for $C_{15}H_{16}ClNaNO_3$ 316.0716, found 316.0717 $[M + Na]^+$. Mp: 100−101 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.05 (d, 1H, J = 2.1 Hz); 7.40 (d, 1H, J = 8.5 Hz); 7.15 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.1 Hz); 4.03 (s, 3H); 2.64 (t, 2H, J = 8.3 Hz); 2.56 (s, 3H); 1.67 (m, 2H); 1.10 (t, 3H, J = 7.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 165.3, 163.2, 151.7, 138.3, 133.6, 124.2, 123.5, 121.9, 120.3, 115.3, 53.9, 40.6, 22.8, 20.3, 14.3.

General Procedure for the Vinylogous Michael Addition of Nonsymmetric 3-Alkylidenoxindoles to Nitroalkenes. All of the reactions were carried out in undistilled toluene. In an ordinary vial equipped with a Teflon-coated stir bar were added 3-alkylidenoxindole derivative (0.2 mmol, 1.0 equiv), nitroalkene (0.2 mmol, 1.0 equiv), 9-*epi*-9-amino-9-deoxydihydroquinine **I** (0.04 mmol, 0.2 equiv), and 2 mL of toluene. The resulting solution was stirred at −20 °C for 72 h. The crude mixture was flushed through a short plug of silica using dichloromethane/ethyl acetate 1:1 as the eluent (100 mL). Solvent was removed in under reduced pressure, and the diastereomeric ratio (dr) was determined by ^1H NMR analysis of the crude mixture. The desired compound was isolated by flash column chromatography.

(*Z*)-Methyl 5-Chloro-3-((3*R*,4*R*)-3-ethyl-5-nitro-4-phenylpentan-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-3a) (Table 3, Entry 1). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8/2), (*Z*)-**3a** was obtained in 86% yield and >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, λ = 214 nm: τ_{major} = 14.10. $[\alpha]_D^{20}$ +117.1 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{23}H_{23}ClNaN_2O_5$ 465.1188, found 465.1188 $[M + Na]^+$. Mp: 133−134 °C. ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.87 (d, 1H, J = 8.7 Hz); 7.32 (d, 1H, J = 2.0 Hz); 7.23 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.0 Hz); 7.17 (m, 4H); 7.11 (m, 1H); 5.28 (ddd, 1H, J_1 = 10.7 Hz, J_2 = 4.2 Hz); 4.88 (dd, 1H, J_1 = 12.4 Hz, J_2 = 4.4 Hz); 4.66 (dd, 1H, J_1 = 12.5 Hz, J_2 = 10.5 Hz); 4.05 (s, 3H); 3.65 (ddd, 1H, J_1 = 10.6 Hz, J_2 = 4.7 Hz); 2.03 (s, 3H); 1.86 (m, 1H); 1.68 (m, 1H); 0.85 (t, 3H, J = 7.4 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 164.0 (C); 161.0 (C); 150.5 (C); 137.0 (C); 134.7 (C); 128.6 (C); 127.6 (CH); 127.1 (CH); 126.9 (CH); 126.7 (CH); 123.9 (C); 122.8 (CH); 114.7 (CH); 79.1 (CH_2); 53.0 (CH_3); 47.01 (CH); 42.4 (CH); 23.5 (CH_2); 17.25 (CH_3); 10.7 (CH_3).

(*Z*)-Methyl 5-Chloro-3-((3*R*,4*S*)-3-ethyl-5-nitro-4-(thiophene-2-yl)pentan-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-3b) (Table 3, Entry 2). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8/2), (*Z*)-**3b** was obtained in 89% yield and 99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, λ = 254 nm: τ_{major} = 17.31 min.; τ_{minor} = 25.85 min. $[\alpha]_D^{20}$ +72.9 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{21}H_{21}ClNaN_2O_5S$ 471.0752, found 471.0750 $[M + Na]^+$. Mp: 140−142 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.91 (d, 1H, J = 8.7 Hz); 7.42 (d, 1H, J = 2.0 Hz); 7.26 (dd, 1H, J_1 = 8.7 Hz, J_2 = 2.0 Hz); 7.07 (d, 1H, J = 5.2 Hz); 6.87 (d, 1H, J = 3.4 Hz); 6.80 (dd, 1H, J_1 = 5.0 Hz, J_2 = 3.6 Hz); 5.26 (ddd, 1H, J_1 = 10.4 Hz, J_2 = 4.3 Hz); 4.90 (dd, 1H, J_1 = 12.6 Hz, J_2 = 4.6 Hz); 4.65 (dd, 1H, J_1 = 12.6 Hz, J_2 = 10.4 Hz); 4.03 (m, 4H); 2.12 (s, 3H); 1.85 (m, 1H); 1.69 (m, 1H); 0.86 (t, 3H, J = 7.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 164.9, 161.17, 151.5, 140.2, 135.8, 129.6, 128.2, 126.8, 126.0, 125.0, 124.9, 124.2, 123.9, 115.7, 80.2, 54.0, 44.3, 42.8, 30.9, 24.4, 18.2, 11.6.

(*Z*)-Methyl 3-((3*R*,4*R*)-3-Ethyl-5-nitro-4-phenylpentan-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-3c) (Table 3, Entry 3). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8/2), (*Z*)-**3c** was obtained in 70% yield and >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, λ = 214 nm: τ_{major} = 17.7 $[\alpha]_D^{20}$+147.1 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{23}H_{24}NaN_2O_5$ 431.1577, found 431.1574 $[M + Na]^+$. Mp: 80−83 °C. ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.92 (d, 1H, J = 8.2 Hz); 7.36 (d, 1H, J_1 = 7. Eight Hz); 7.27 (m, 1H); 7.20 (m, 2H); 7.15 (m, 2H); 7.09 (m, 2H); 5.30 (ddd, 1H, J_1 = 10.7 Hz, J_2 = 4.1 Hz); 4.89 (dd, 1H, J_1 = 12.5 Hz, J_2 = 4.4 Hz); 4.61 (dd, 1H, J_1 = 12.4 Hz, J_2 = 10.4 Hz); 4.05 (s, 3H); 3.65 (ddd, 1H, J_1 = 10.4 Hz, J_2 = 4.5 Hz); 2.03 (s, 3H); 1.86 (m, 1H); 1.68 (m, 1H); 0.86 (t, 3H, J = 7.3 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 164.6 (C); 158.7 (C); 150.7 (C); 137.2 (C); 136.3 (C); 127.5 (CH); 127.4 (CH); 126.8 (CH); 123.6 (CH); 123.0 (CH); 122.8 (C); 122.6 (C); 113.6 (CH); 79.2 (CH_2); 52.9 (CH_3); 47.1 (CH); 42.2 (CH); 23.5 (CH_2); 17.1 (CH_3); 10.7 (CH_3).

(*Z*)-Methyl 3-((3*R*,4*R*)-3-Ethyl-4-(4-methoxyphenyl)-5-nitropentan-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-3d) (Table 3, Entry 4))-. The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8/2), (*Z*)-**3d** was obtained in 52% yield and 98% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, λ = 214 nm: τ_{major} = 19.9 min. $[\alpha]_D^{20}$ +200.0 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{24}H_{26}NaN_2O_6$ 461.1683, found 461.1677 $[M + Na]^+$. Mp: 130−134 °C. ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.93 (d, 1H, J = 8.2 Hz); 7.39 (d, 1H, J = 7.3 Hz); 7.28 (m, 1H); 7.11 (m, 3H); 6.68 (d, 2H, J = 8.5 Hz); 5.27 (ddd, 1H, J_1 = 10.6 Hz, J_2 = 4.3 Hz); 4.86 (dd, 1H, J_1 = 12.2 Hz, J_2 = 4.3 Hz); 4.61 (dd, 1H, J_1 = 12.1 Hz, J_2 = 10.8 Hz); 4.06 (s, 3H); 3.67 (s, 3H); 3.60 (ddd, 1H, J_1 = 10.9 Hz, J_2 = 4.6 Hz); 2.03 (s, 3H); 1.83 (m, 1H); 1.66 (m, 1H); 0.85 (t, 3H, J = 7.4 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 164.6 (C); 159.1 (C); 157.8 (C); 150.7 (C); 136.3 (C); 129.1 (C); 127.8 (CH); 127.4 (CH); 123.5 (C); 123.0 (CH); 122.8 (CH); 122.7 (C); 113.6 (CH); 112.9 (CH); 79.4 (CH_2); 54.0 (CH_3); 52.9 (CH_3); 46.4 (CH); 42.2 (CH); 23.6 (CH_2); 17.1 (CH_3); 10.7 (CH_3).

(*Z*)-Methyl 3-((3*R*,4*R*)-3-Ethyl-4-(3-methoxyphenyl)-5-nitropentan-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-3e) (Table 3, entry 5))-3-E. The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8:2), (*Z*)-**3e** was obtained in in 61% yield and >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, λ = 214 nm: τ_{major} = 21.39 min. $[\alpha]_D^{20}$ +105.4 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{24}H_{26}N_2O_6$ 461.1683, found 461.1677 $[M + Na]^+$. Mp: 72−75 °C. ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.92 (d, 1H, J = 8.1 Hz); 7.39 (d, 1H, J = 7.9 Hz); 7.27 (m, 1H); 7.10 (m, 1H); 7.05 (m, 1H); 6.76 (m, 2H); 6.63 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.6 Hz); 5.30 (ddd, 1H, J_1 = 10.5 Hz, J_2 = 4.1 Hz); 4.87 (dd, 1H, J_1 = 12.5 Hz, J_2 = 4.5 Hz); 4.65 (dd, 1H, J_1 = 12.4 Hz, J_2 = 10.3 Hz); 4.05 (s, 3H); 3.68 (s, 3H); 3.64 (ddd, 1H, J_1 = 10.7 Hz, J_2 = 4.8 Hz); 2.06 (s, 3H); 1.84 (m, 1H); 1.67 (m, 1H); 0.85 (t, 3H, J = 7.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 164.6 (C); 158.8 (C); 158.5 (C); 150.6 (C); 138.7 (C); 136.3 (C); 128.6 (CH); 127.4 (CH); 123.6 (C); 123.1 (CH); 122.8 (CH); 122.7 (C); 119.1 (CH); 113.6 (CH); 112.7 (CH); 112.0 (CH); 79.2 (CH_2); 54.0 (CH_3); 52.8 (CH_3); 47.1 (CH); 42.1 (CH); 23.5 (CH_2); 17.1 (CH_3); 10.7 (CH_3).

(*Z*)-Methyl 3-((3*R*,4*R*)-3-Ethyl-5-nitro-4-(*p*-tolyl)pentan-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-3f) (Table 3, Entry 6). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8:2) (*Z*)-**3f** was obtained in 75% yield and >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, λ = 214 nm: τ_{major} = 15.93 min. $[\alpha]_D^{20}$ +155.0 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{24}H_{26}NaN_2O_5$ 445.1734, found 445.1733 $[M + Na]^+$. Mp: 111−113 °C. ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.94 (d, 1H, J = 8.2 Hz); 7.39 (d, 1H, J = 7.8 Hz); 7.27 (ddd, 1H, J = 7.5 Hz); 7.09 (ddd, 1H, J = 8.0 Hz); 7.07 (d, 2H, J = 8.0 Hz); 6.69 (d, 2H, J = 7.8 Hz); 5.28 (ddd, 1H, J_1 = 10.5 Hz, J_2 = 4.0 Hz); 4.86 (dd, 1H, J_1 = 12.2 Hz, J_2 = 4.4 Hz); 4.62 (dd, 1H, J_1 = 12.2 Hz, J_2 = 10.6 Hz); 4.06 (s, 3H); 3.62 (ddd, 1H, J_1 = 10.4 Hz, J_2 = 4.4 Hz); 2.17 (s, 3H); 2.03 (s, 3H); 1.84 (m, 1H); 1.66 (m, 1H); 0.85 (t, 3H, J = 7.5 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.6 (C); 160.1 (C); 151.7 (C); 137.4 (C); 137.3 (C); 135.0 (C); 129.3 (CH); 128.3 (CH); 127.6 (CH); 124.4 (C); 124.0 (CH); 123.9 (CH); 123.8 (C); 114.6 (CH); 80.4 (CH_2);

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53.9 (CH_3); 47.8 (CH); 43.1 (CH); 24.6 (CH_2); 21.0 (CH_3); 18.2 (CH_3);11.7 (CH_3).

(*Z*)-Methyl 3-((3*R*,4*R*)-3-Ethyl-4-(2-fluorophenyl)-5-nitropentan-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-3g) (Table 3, Entry 7). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8:2), (*Z*)-**3g** was obtained in 66% yield and >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, λ = 214 nm: τ_{major} = 16.19 min. $[\alpha]_D^{20}$ +121.0 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{23}H_{23}FNaN_2O_5$ 449.1483, found 449.1472 $[M + Na]^+$. Mp: 71−76 °C. ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.92 (d, 1H, J = 8.1 Hz); 7.39 (d, 1H, J = 7.8 Hz); 7.28 (m, 2H); 7.09 (m, 2H); 6.97 (ddd, 1H, J_1 = 7.6 Hz, J_2 = 1.1 Hz); 6.89 (ddd, 2H, J_1 = 8.2 Hz, J_2 = 1.2 Hz); 5.31 (ddd, 1H, J_1 = 10.5 Hz, J_2 = 3.9 Hz); 4.90 (dd, 1H, J_1 = 12.8 Hz, J_2 = 4.7 Hz); 4.75 (dd, 1H, J_1 = 12.8 Hz, J_2 = 10.2 Hz); 4.09 (ddd, 1H, J_1 = 10.3 Hz, J_2 = 4.6 Hz); 4.05 (s, 3H); 2.08 (s, 3H); 1.87 (m, 1H); 1.70 (m, 1H); 0.86 (t, 3H, J = 7.4 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.4 (C); 160.3 (C, J = 246.5 Hz); 158.1 (C); 150.7 (C); 136.4 (C); 129.4 (CH, J = 8.3 Hz);129.1 (CH, J = 3.5 Hz); 128.5 (CH); 125.2 (C, J = 14.0 Hz); 123.6 (C); 124.4 (CH, J = 3.4 Hz); 123.1 (CH); 122.9 (CH); 122.6 (C); 115.6 (CH, J = 23.1 Hz); 114.5 (CH); 78.9 (CH_2); 53.9 (CH_3); 43.0 (CH); 24.6 (CH_2); 18.0 (CH) 17.9 (CH_3); 11.6 (CH_3).

(*Z*)-Methyl 3-((3*R*,4*R*)-4-(4-Bromophenyl)-3-ethyl-5-nitropentan-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-3h) (Table 3, Entry 8). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8:2), (*Z*)-**3h** was obtained in 62% yield and >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, λ = 214 nm: τ_{major} = 19.38 min. $[\alpha]_D^{20}$ +146.0 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{23}H_{23}BrNaN_2O_5$ 509.0683, found 509.0684 $[M + Na]^+$. Mp: 102−105 °C. ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.95 (d, 1H, J = 8.2 Hz); 7.39 (d, 1H, J = 7.9 Hz); 7.30 (m, 3H); 7.11 (m, 3H); 5.29 (ddd, 1H, J_1 = 10.6 Hz, J_2 = 4.0 Hz); 4.87 (dd, 1H, J_1 = 12.6 Hz, J_2 = 4.4 Hz); 4.61 (dd, 1H, J_1 = 12.5 Hz, J_2 = 10.7 Hz); 4.06 (s, 3H); 3.63 (ddd, 1H, J_1 = 10.6 Hz, J_2 = 4.4 Hz); 2.04 (s, 3H); 1.83 (m, 1H); 1.66 (m, 1H); 0.85 (t, 3H, J = 7.6 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 164.6 (C); 157.8 (C); 150.5 (C); 136.4 (C); 136.3 (C); 130.8 (CH); 128.5 (CH); 127.7 (CH); 123.8 (C); 123.2 (CH); 122.9 (CH); 122.5 (C); 120.9 (CH); 113.7 (CH); 79.0 (CH_2); 53.0 (CH_3); 46.5 (CH); 41.8 (CH); 23.5 (CH_2); 17.0 (CH_3); 10.7 (CH_3).

(*Z*)-Methyl 3-((4*S*)-3-Ethyl-6-methyl-4-(nitromethyl)hept-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-3i) (Table 3, Entry 9))-. The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 85:15), (*Z*)-**3i** was obtained in 20% yield and 99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 0.5 mL/min, λ = 254 nm: τ_{major} = 14.06 min.; τ_{minor} = 15.90 min. $[\alpha]_D^{20}$ +11.0 (*c* 0.25, $CHCl_3$). HRMS-ESI (+): calcd for $C_{21}H_{28}NaN_2O_5$ 411.1890, found 411.1891 $[M + Na]^+$. Mp: 120−122 °C. ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.03 (d, 1H, J = 8.1 Hz); 7.65 (d, 1H, J = 8.1 Hz); 7.37 (m, 1H); 7.23 (m, 1H); 4.79 (ddd, 1H, J_1 = 10.8 Hz, J_2 = 4.0 Hz); 4.51 (dd, 1H, J_1 = 13.6 Hz, J_2 = 6.0 Hz); 4.40 (dd, 1H, J_1 = 13.4 Hz, J_2 = 4.4 Hz); 4.04 (s, 3H); 2.53 (m, 1H); 2.26 (s, 3H); 1.73 (m, 1H); 1.49 (m, 1H); 1.32 (m, 2H); 1.01 (m, 1H); 0.83 (m, 6H); 0.77 (t, 3H, J = 7.3 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.5, 161.0, 151.8, 137.6, 128.6, 125.0, 124.2, 124.0, 123.9, 114.8, 78.5, 53.9, 45.0, 40.6, 38.0, 25.2, 23.8, 23.1, 21.3, 17.7, 11.7.

(*Z*)-Methyl 3-((4*R*,5*R*)-4-Ethyl-6-nitro-5-phenylhexan-3-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-3j) (Table 3, Entry 10). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8:2), (*Z*)-**3j** was obtained in 44% yield and 99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 0.5 mL/min, λ = 254 nm: τ_{major} = 19.11 min.; τ_{minor} = 24.48 min. $[\alpha]_D^{20}$ +185.8 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{24}H_{26}NaN_2O_5$ 445.1734, found 445.1732 $[M + Na]^+$. Mp: 145−148 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.92 (d, 1H, J = 8.5 Hz); 7.27 (m, 3H); 7.11 (m, 5H); 5.37 (ddd, 1H, J_1 = 10.6 Hz, J_2 = 3.6 Hz); 4.88 (dd, 1H, J_1 = 12.4 Hz, J_2 = 4.5 Hz); 4.65 (dd, 1H, J_1 = 12.6 Hz, J_2 = 10.2 Hz); 4.06 (s, 3H); 3.69 (ddd, 1H, J_1 = 10.3 Hz, J_2 = 4.5 Hz); 2.50 (m, 1H); 2.33 (m, 1H); 1.87 (m, 1H); 1.76 (m, 1H); 1.11 (t, 3H, J = 7.7 Hz); 0.94 (t, 3H, J = 7.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.1, 165.7, 151.7, 138.4, 137.3, 128.5, 128.4, 127.8, 127.7, 124.9, 124.2, 123.7, 122.4, 114.5, 80.6, 53.9, 48.2, 43.6, 24.2, 24.0, 12.8, 11.9.

(*Z*)-Methyl 3-((*R*)-5-Methyl-3-((*R*)-2-nitro-1-phenylethyl)hex-5-en-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-3k) (Table 3, Entry 11). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8:2), (*Z*)-**3k** was obtained in 81% yield and >99% ee. HPLC analysis on a cellulose-2 column: hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, λ = 214 nm: τ_{major} = 49.53 min. $[\alpha]_D^{20}$ +135.2 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{25}H_{26}NaN_2O_5$ 457.1734, found 457.1730 $[M + Na]^+$. Mp: 63−65 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.90 (d, 1H, J = 8.4 Hz); 7.34 (d, 1H, J = 8.4 Hz); 7.18 (m, 7H); 5.54 (m, 1H); 4.95 (dd, 1H, J_1 = 12.5 Hz, J_2 = 4.4 Hz); 4.73 (m, 3H); 4.05 (s, 3H); 3.70 (ddd, 1H, J_1 = 10.0 Hz, J_2 = 4.1 Hz); 2.47 (m, 2H); 2.01 (s, 3H); 1.74 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 164.5, 158.3, 150.6, 141.6, 136.8, 136.4, 127.5, 127.4, 126.9, 123.2, 123.0, 122.9, 122.7, 113.5, 112.2, 78.6, 52.9, 47.5, 39.8, 39.2, 21.2, 17.8.

(*Z*)-Methyl 3-((3*R*,4*R*)-3-Benzyl-5-nitro-4-phenylpentan-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-3l) (Table 3, Entry 12). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8:2), (*Z*)-**3l** was obtained in 50% yield and 96% ee. The ee was determined by HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 0.5 mL/min, λ = 254 nm: τ_{major} = 43.36 min.; τ_{minor} = 38.83 min. $[\alpha]_D^{20}$ +123.7 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{28}H_{26}NaN_2O_5$ 493.1734, found 493.1735 $[M + Na]^+$. Mp: 81−83 °C. ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.84 (d, 1H, J = 8.5 Hz); 7.18 (m, 12H); 7.02 (dd, 1H, J = 8.5 Hz); 5.76 (m, 1H); 4.83 (dd, 1H, J_1 = 12.4 Hz, J_2 = 4.2 Hz); 4.65 (dd, 1H, J_1 = 12.3 Hz, J_2 = 10.7 Hz); 4.05 (s, 3H); 3.82 (dd, 1H, J_1 = 10.2 Hz, J_2 = 4.2 Hz); 3.17 (dd, 1H, J_1 = 14.1 Hz, J_2 = 6.0 Hz); 2.92 (dd, 1H, J_1 = 14.1 Hz, J_2 = 9.0 Hz); 1.99 (s, 3H). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.3, 158.5, 151.5, 137.9, 137.3, 128.7, 128.6, 128.5, 128.4, 127.9, 127.8, 126.7, 124.3, 123.9, 123.7, 123.5, 114.5, 80.0, 53.8, 48.0, 42.9, 38.5, 18.9.

(*R*,*Z*)-Methyl 5-Chloro-3-(1-nitro-2-phenylhept-4-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-4a) (Table 4, Entry 1). The reaction was carried out following the general procedure to furnish the crude product **4a** as a 91:9 mixture of (*Z*)-**4a** and (*E*)-**4a**. The crude mixture was purified by flash column chromatography (hexane/ethyl acetate = 8:2) to give an overall yield of 85% and (*Z*)-**4a** in >99% ee. HPLC analysis on a OD-H column: hexane/*i*-PrOH 90:10, flow rate 0.75 mL/min, λ = 214 nm: τ_{major} = 20.79 min. $[\alpha]_D^{20}$ −120.0 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{23}H_{23}ClNaN_2O_5$ 465.1188, found 465.1188 $[M + Na]^+$. Mp for (*Z*)-**4a**: 87−90 °C. ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.95 (d, 1H, J = 8.8 Hz); 7.40 (d, 1H, J = 2.0 Hz); 7.30 (m, 6H); 4.79 (dd, 1H, J_1 = 13.1 Hz, J_2 = 9.9 Hz); 4.71 (dd, 1H, J_1 = 12.9 Hz, J_2 = 5.6 Hz); 4.07 (s, 3H); 4.03 (dd, 1H, J_1 = 12.2 Hz, J_2 = 8.2 Hz); 3.85 (m, 1H); 2.83 (dd, 1H, J_1 = 12.1 Hz, J_2 = 7.4 Hz); 2.64 (m, 1H); 2.23 (m, 1H); 1.54 (m, 2H); 1.05 (t, 3H, J = 7.3 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.1 (C); 163.3 (C); 151.4 (C); 139.2 (C); 136.3 (C); 129.9 (C); 129.0 (CH); 128.5 (CH); 128.0 (CH); 127.5 (CH); 124.1 (C); 123.4 (CH); 122.6 (C); 116.0 (CH); 79.4 (CH_2); 54.1 (CH_3); 43.7 (CH); 38.7 (CH_2); 38.4 (CH_2); 20.3 (CH_2); 14.3 (CH_3).

(s,*Z*)-Methyl 5-Chloro-3-(1-nitro-2-(thiophen-2-yl)hept-4-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-4b) (Table 4, Entry 2). The reaction was carried out following the general procedure to furnish the crude product **4b** as 92:8 mixture of (*Z*)-**4b** and (*E*)-**4b**. The crude mixture was purified by flash column chromatography (hexane/ethyl acetate = 8:2) to give an overall yield of 77% and (*Z*)-**4b** in >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 14.82 min. $[\alpha]_D^{20}$ −344.4 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{21}H_{21}ClNaN_2O_5S$ 471.0752, found 471.0750 $[M + Na]^+$. Mp for (*Z*)-**4b**: 82−85 °C. ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.96 (d, 1H, J = 8.9 Hz); 7.42 (d, 1H, J = 2.0 Hz); 7.31 (dd, 1H, J_1 = 8.9 Hz, J_2 = 1.9 Hz); 7.22 (dd, 1H, J_1 = 4.6 Hz, J_2 = 1.5 Hz); 6.94 (m, 2H); 4.75 (m, 2H); 4.18 (m, 1H); 4.06 (s, 3H); 3.99 (m, 1H);

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2.90 (dd, 1H, J_1 = 12.0 Hz, J_2 = 7.9 Hz); 2.67 (m, 1H); 2.23 (m, 1H); 1.55 (m, 2H); 1.06 (t, 3H, J = 7.3 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.0, 162.9, 151.3, 141.9, 136.3, 129.9, 128.5, 127.1, 125.6, 124.8, 124.0, 123.5, 122.6, 116.1, 80.1, 54.1, 39.7, 39.0, 38.5, 20.1, 14.3.

(*R*,*Z*)-Methyl 5-Chloro-3-(2-(4-methoxyphenyl)-1-nitrohept-4-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-4c) (Table 4, Entry 3). The reaction was carried out following the general procedure to furnish the crude product **4c** as a 96:4 mixture of (*Z*)-**4c** and (*E*)-**4c**. The crude mixture was purified by flash column chromatography (hexane/ethyl acetate = 8:2) to give an overall yield of 78% and (*Z*)-**4c** in >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 1 mL/min, λ = 214 nm: τ_{major} = 17.38. $[\alpha]_D^{20}$ −83.0 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{24}H_{25}ClNaN_2O_6$ 495.1293, found 495.1292 $[M + Na]^+$. Mp for (*Z*)-**4c**: 139−144 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.95 (d, 1H, J = 8.8 Hz); 7.40 (d, 1H, J = 2.1 Hz); 7.30 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.1 Hz); 7.22 (d, 1H, J = 8.6 Hz); 6.85 (d, 1H, J = 8.6 Hz); 4.74 (dd, 1H, J_1 = 12.6 Hz, J_2 = 9.9 Hz); 4.68 (dd, 1H, J_1 = 12.6 Hz, J_2 = 5.6 Hz); 4.06 (s, 3H); 3.97 (dd, 1H, J_1 = 12.2 Hz, J_2 = 7.9 Hz); 3.80 (m, 4H); 2.84 (dd, 1H, J_1 = 12.2 Hz, J_2 = 7.7 Hz); 2.64 (m, 1H); 2.24 (m, 1H); 1.55 (m, 1H); 1.05 (t, 3H, J = 7.4 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.1, 163.6, 159.2, 151.4, 136.2, 131.0, 129.9, 128.5, 128.4, 124.1, 123.4, 122.5, 116.0, 114.3, 79.7, 55.2, 54.1, 43.0, 38.7, 38.4, 20.2, 14.3.

(*R*,*Z*)-Methyl 5-Chloro-3-(2-(3-methoxyphenyl)-1-nitrohept-4-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-4d) (Table 4, Entry 4). The reaction was carried out following the general procedure to furnish the crude product **4d** as 95:5 mixture of (*Z*)-**4d** and (*E*)-**4d**. The crude mixture was purified by flash column chromatography (hexane/ethyl acetate = 8:2) to give an overall yield of 92% and (*Z*)-**4d** in >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 1 mL/min, λ = 214 nm: τ_{major} = 14.04 min. $[\alpha]_D^{20}$ −79.5 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{24}H_{25}ClNaN_2O_6$ 495.1293, found 495.1292 $[M + Na]^+$. Mp for (*Z*)-**4d**: 86−88 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.95 (d, 1H, J = 8.9 Hz); 7.41 (d, 1H, J = 2.2 Hz); 7.30 (dd, 1H, J_1 = 8.90 Hz, J_2 = 2.18 Hz); 7.24 (m, 1H); 6.90 (d, 1H, J = 7.8 Hz); 6.81 (m, 2H); 4.78 (dd, 1H, J_1 = 12.9 Hz, J_2 = 9.7 Hz); 4.69 (dd, 1H, J_1 = 12.9 Hz, J_2 = 5.7 Hz); 4.06 (s, 3H); 3.99 (dd, 1H, J_1 = 12.2 Hz, J_2 = 7.9 Hz); 3.81 (m, 4H); 2.85 (dd, 1H, J_1 = 12.1 Hz, J_2 = 7.4 Hz); 2.65 (m, 1H); 2.25 (m, 1H); 1.55 (m, 1H); 1.05 (t, 3H, J = 7.4 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.1, 163.3, 159.9, 151.4, 140.8, 136.2, 130.0, 129.9, 128.5, 124.1, 123.4, 122.6, 119.6, 116.0, 113.4, 113.1, 79.4, 55.2, 54.1, 43.7, 38.5, 38.4, 20.3, 14.3.

(*R*,*Z*)-Methyl 3-(2-(2-(Benzyloxy)phenyl)-1-nitrohept-4-ylidene)-5-chloro-2-oxoindoline-1-carboxylate ((*Z*)-4e) (Table 4, Entry 5). The reaction was carried out following the general procedure to furnish the crude product **4e** as a 93:7 mixture of (*Z*)-**4e** and (*E*)-**4e**. The crude mixture was purified by flash column chromatography (hexane/ethyl acetate = 8:2) to give an overall yield of 93% and (*Z*)-**4e** in >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 0.5 mL/min, λ = 254 nm: τ_{major} = 38.12 min. $[\alpha]_D^{20}$ −72.8 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{30}H_{29}ClNaN_2O_6$ 571.1606, found 571.1602 $[M + Na]^+$. Mp for (*Z*)-**4e**: 115−117 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.91 (d, 1H, J = 9.2 Hz); 7.37 (m, 6H); 7.24 (m, 3H); 6.93 (m, 2H); 5.08 (d, 1H, J = 11.2 Hz); 4.98 (m, 2H); 4.70 (dd, 1H, J_1 = 12.9 Hz, J_2 = 6.2 Hz); 4.36 (m, 1H); 4.03 (s, 3H); 3.83 (dd, 1H, J_1 = 11.2 Hz, J_2 = 8.4 Hz); 2.93 (m, 1H); 2.50 (m, 1H); 2.14 (m, 1H); 1.44 (m, 2H); 0.90 (t, 3H, J = 7.2 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 164.9, 164.3, 156.2, 151.4, 136.6, 136.1, 129.7, 128.8, 128.6, 128.2, 128.0, 127.4, 124.3, 123.3, 122.2, 121.3, 116.0, 112.2, 78.0, 70.4, 53.9, 38.3, 37.4, 29.7, 20.2, 14.2.

(*R*,*Z*)-Methyl 5-Chloro-3-(1-nitro-2-(*p*-tolyl)hept-4-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-4f) (Table 4, Entry 6). The reaction was carried out following the general procedure to furnish the crude product **4f** as a 94:6 mixture of (*Z*)-**4f** and (*E*)-**4f**. The crude mixture was purified by flash column chromatography (hexane/ethyl acetate = 8:2) to give an overall yield of 96% and (*Z*)-**4f** in >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 1 mL/min, λ = 254 nm: τ_{major} = 10.61 min. $[\alpha]_D^{20}$ −57.0 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{24}H_{25}ClNaN_2O_5$ 479.1344, found 479.1339 $[M + Na]^+$. Mp for (*Z*)-**4f**: 95−97 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.94 (d, 1H, J = 8.9 Hz); 7.40 (d, 1H, J = 1.9 Hz); 7.29 (dd, 1H, J_1 = 8.9 Hz, J_2 = 1.9 Hz); 7.19 (d, 1H, J_1 = 8.1 Hz); 7.13 (d, 1H, J_1 = 8.1 Hz); 4.76 (dd, 1H, J_1 = 12.7 Hz, J_2 = 10.0 Hz); 4.68 (dd, 1H, J_1 = 12.7 Hz, J_2 = 5.6 Hz); 4.06 (s, 3H); 4.01 (m, 1H); 3.81 (m, 1H); 2.81 (dd, 1H, J_1 = 12.1 Hz, J_2 = 7.5 Hz); 2.64 (m, 1H); 2.28 (m, 4H); 1.55 (m, 2H); 1.05 (t, 3H, J_1 = 7.2 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.0, 163.6, 151.3, 137.6, 136.2, 136.1, 129.8, 129.6, 128.4, 127.3, 124.1, 123.4, 122.5, 116.0, 79.5, 54.0, 43.3, 38.7, 38.3, 31.5, 22.6, 21.0, 20.2, 14.3, 14.1.

(*R*,*Z*)-Methyl 5-Chloro-3-(2-(2-fluorophenyl)-1-nitrohept-4-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-4g) (Table 4, Entry 7). The reaction was carried out following the general procedure to furnish the crude product **4g** as 95:5 mixture of (*Z*)-**4g** and (*E*)-**4g**. The crude mixture was purified by flash column chromatography (hexane/ethyl acetate = 8:2) to give an overall yield of 87% and (*Z*)-**4g** in >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 12.92 min. $[\alpha]_D^{20}$ −96.2 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{23}H_{22}ClFNaN_2O_5$ 483.1093, found 483.1089 $[M + Na]^+$. Mp for (*Z*)-**4g**: 104−106 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.95 (d, 1H, J = 8.9 Hz); 7.40 (bs, 1H); 7.28 (m, 3H); 7.08 (m, 2H); 4.91 (m, 1H); 4.76 (dd, 1H, J_1 = 12.5 Hz, J_2 = 5.5 Hz); 4.15 (m, 1H); 4.06 (s, 3H); 3.94 (m, 1H); 2.92 (m, 1H); 2.65 (m, 1H); 2.26 (m, 1H); 1.55 (m, 2H); 1.05 (t, 3H, J = 7.1 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.0, 162.9, 160.7 (d, J = 246.5 Hz), 151.4, 136.3, 129.9, 129.6 (d, J = 8.5 Hz), 129.3 (d, J = 4.4 Hz), 128.5, 126.0 (d, J = 13.6 Hz), 124.7 (d, J = 3.7 Hz), 124.1, 123.4, 122.7, 116.1, 116.0 (d, J = 22.1 Hz), 77.9, 54.0, 38.4, 37.9, 37.4, 29.7, 20.2, 14.3.

(*R*,*Z*)-Methyl 3-(2-(4-Bromophenyl)-1-nitrohept-4-ylidene)-5-chloro-2-oxoindoline-1-carboxylate ((*Z*)-4h) (Table 4, Entry 8). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8:2), (*Z*)-**4h** was obtained in 85% yield and >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 1 mL/min, λ = 214 nm: τ_{major} = 14.15 min. $[\alpha]_D^{20}$ −60.0 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{23}H_{22}BrClNaN_2O_5$ 543.0298, found 543.0295 $[M + Na]^+$. Mp: 150−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.95 (d, 1H, J = 8.8 Hz); 7.46 (d, 2H, J = 8.3 Hz); 7.41 (d, 1H, J = 2.0 Hz); 7.31 (dd, 1H, J_1 = 8.7 Hz, J_2 = 2.0 Hz); 7.20 (d, 2H, J = 8.4 Hz); 4.75 (dd, 1H, J_1 = 13.0 Hz, J_2 = 10.0 Hz); 4.68 (dd, 1H, J_1 = 13.0 Hz, J_2 = 5.5 Hz); 4.07 (s, 3H); 3.95 (dd, 1H, J_1 = 12.2 Hz, J_2 = 8.2 Hz); 3.83 (m, 1H); 2.84 (dd, 1H, J_1 = 12.2 Hz, J_2 = 7.4 Hz); 2.65 (m, 2H); 2.26 (m, 2H); 1.57 (m, 2H); 1.07 (t, 3H, J = 7.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 164.1, 161.5, 150.3, 137.3, 135.3, 131.2, 129.0, 128.2, 127.7, 123.0, 122.5, 121.9, 120.9, 115.1, 78.05, 53.1, 42.1, 37.5, 37.4, 19.3, 13.3.

(*R*,*Z*)-Methyl 5-Chloro-3-(2-(2,6-dichlorophenyl)-1-nitrohept-4-ylidene)-2-oxoindoline-1-carboxylate ((Z)-4i) (Table 4, Entry 9). The reaction was carried out following the general procedure to furnish the crude product **4i** as 92:8 mixture of (*Z*)-**4i** and (*E*)-**4i**. The crude mixture was purified by flash column chromatography (hexane/ethyl acetate = 8:2) to give an overall yield of 80% and (*Z*)-**4i** in >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 0.3 mL/min, λ = 254 nm: **4i** τ_{major} = 55.94 min. $[\alpha]_D^{20}$ −125.9 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{23}H_{21}Cl_3NaN_2O_5$ 533.0408, found 533.0410 $[M + Na]^+$. Mp for (*Z*)-**4i**: 110−113 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.96 (d, 1H, J = 9.6 Hz); 7.40 (m, 1H); 7.31 (m, 3H); 7.16 (m, 1H); 5.40 (m, 1H); 4.94 (m, 2H); 4.27 (m, 1H); 4.05 (s, 3H); 2.90 (m, 1H); 2.69 (m, 1H); 2.15 (m, 1H); 1.54 (m, 2H); 1.03 (t, 3H, J = 7.1 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 164.9, 162.4, 151.4, 136.9, 136.4, 134.8, 134.3, 130.2, 129.8, 129.4, 129.1, 128.5, 124.1, 123.4, 122.8, 116.0, 76.5, 54.1, 39.2, 38.6, 35.0, 29.7, 20.2, 14.3.

(s,*Z*)-Methyl 5-Chloro-3-(8-methyl-6-(nitromethyl)nonan-4-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-4j) (Table 4, Entry 10). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 85:15), (*Z*)-**4j** was obtained in 50% yield and 97% ee. HPLC analysis on a amylose-2 column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: **4aj** τ_{major} = 18.74 min; τ_{minor} = 14.2 min. $[\alpha]_D^{20}$ +155.0 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{21}H_{27}ClNaN_2O_5$ 445.1501, found 445.1501 $[M + Na]^+$. Mp: 72−75 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm)

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7.95 (d, 1H, J = 8.9 Hz); 7.45 (d, 1H, J = 1.7 Hz); 7.31 (dd, 1H, J_1 = 8.9 Hz, J_2 = 1.7 Hz); 4.42 (dd, 1H, J_1 = 12.7 Hz, J_2 = 7.2 Hz); 4.33 (dd, 1H, J_1 = 12.7 Hz, J_2 = 6.1 Hz); 4.04 (s, 3H); 3.48 (dd, 1H, J_1 = 12.2 Hz, J_2 = 9.2 Hz); 2.84 (dd, 1H, J_1 = 12.2 Hz, J_2 = 6.1 Hz); 2.72 (m, 2H); 2.57 (m, 1H); 1.69 (m, 4H); 1.35 (m, 1H); 1.14 (t, 3H, J = 7.2 Hz); 0.93(m, 6H). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.2, 164.1, 151.4, 136.1, 129.9, 128.4, 123.4, 122.9, 120.3, 116.0, 79.3, 54.0, 41.4, 38.2, 36.8, 35.0, 25.1, 22.6, 22.3, 20.6, 14.4.

(*Z*)-Methyl 3-((2*R*,3*R*)-3-Methyl-1-nitro-2-phenylhept-4-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-4k) (Table 4, Entry 11). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8:2), (*Z*)-**4k** was obtained in 44% yield and >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 0.5 mL/min, λ = 254 nm: τ_{major} = 22.36 min. $[\alpha]_D^{20}$ +145.5 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{24}H_{26}NaN_2O_5$ 445.1734, found 445.1732 $[M + Na]^+$. Mp: 59−61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.91 (d, 1H, J = 7.9 Hz); 7.25 (m, 1H); 7.15 (m, 5H); 7.09 (m, 2H); 5.45 (m, 1H); 4.85 (dd, 1H, J_1 = 12.2 Hz, J_2 = 4.3 Hz); 4.64 (dd, 1H, J_1 = 12.1 Hz, J_2 = 10.2 Hz); 4.06 (s, 3H); 3.70 (m, 1H); 2.43 (m, 1H); 2.32 (m, 1H); 1.47 (m, 2H); 1.34 (d, 1H, J = 6.5 Hz); 1.06 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 166.1, 165.8, 151.6, 138.2, 137.4, 128.6, 128.4, 127.8, 127.7, 124.2, 123.3, 122.9, 122.8, 114.5, 80.0, 53.9, 48.8, 36.4, 33.3, 21.4, 17.1, 14.6.

(*R*,*Z*)-Methyl 3-(7-Methyl-1-nitro-2-phenyloct-7-en-4-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-4l) (Table 4, Entry 12). The reaction was carried out following the general procedure to furnish the crude product **4l** as an 80:20 mixture of (*Z*)-**4l** and (*E*)-**4l**. The crude mixture was purified by flash column chromatography (hexane/ethyl acetate = 8:2) to give an overall yield of 92% and (*Z*)-**4l** in >99% ee. HPLC analysis on a cellulose-2 column: hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, λ = 214 nm: τ_{major} = 39.79 min. $[\alpha]_D^{20}$ −100.8 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{25}H_{26}NaN_2O_5$ 457.1734, found 457.1730 $[M + Na]^+$. Mp for (*Z*)-**4l**: 85−87 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.00 (d, 1H, J = 8.2 Hz); 7.49 (m, 1H); 7.27 (m, 6H); 4.77 (m, 4H); 4.07 (s, 3H); 3.87 (m, 1H); 2.76 (m, 1H); 2.41 (m, 1H); 2.14(m, 1H); 1.74 (s, 3H). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 164.5, 158.3, 150.6, 141.6, 136.8, 136.4, 127.5, 127.4, 126.9, 123.2, 123.0, 122.9, 122.7, 113.5, 112.2, 78.6, 52.9, 47.5, 39.8, 39.2, 21.2, 17.8.

(*R*,*Z*)-Methyl 3-(6-Nitro-1,5-diphenylhexan-3-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-4m) (Table 4, Entry 13). The reaction was carried out following the general procedure to furnish the crude product **4m** as an 80:20 mixture of (*Z*)-**4m** and (*E*)-**4m**. The crude mixture was purified by flash column chromatography (hexane/ethyl acetate = 8:2) to give an overall yield of 63% and (*Z*)-**4m** in >99% ee. HPLC analysis on a cellulose-2 column: hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, λ = 214 nm: τ_{major} = 49.28 min. $[\alpha]_D^{20}$ −92.5 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{28}H_{26}NaN_2O_5$ 493.1734, found 493.1735 $[M + Na]^+$. Mp for (*Z*)-**4m**: 101−104 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.02 (d, 1H, J = 8.7 Hz); 7.58 (d, 1H, J = 7.7 Hz); 7.26 (m, 12H); 4.79 (dd, 1H, J_1 = 12.8 Hz, J_2 = 9.8 Hz); 4.73 (dd, 1H, J_1 = 12.8 Hz, J_2 = 5.5 Hz); 4.07 (s, 3H); 3.99 (dd, 1H, J_1 = 12.2 Hz, J_2 = 7.6 Hz); 3.85 (m, 1H); 3.02 (m, 1H); 2.75 (m, 3H); 2.56 (m, 3H). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 164.6, 158.9, 150.5, 138.9, 138.4, 137.0, 128.2, 128.1, 128.0, 127.8, 127.0, 126.9, 126.5, 126.2, 125.6, 123.5, 122.8, 121.6, 114.1, 78.45, 53.0, 42.8, 37.7, 36.9, 31.4.

(*R*,*Z*)-Methyl 6-Chloro-3-(1-nitro-2-phenylhept-4-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-4n) (Table 4, Entry 14). The reaction was carried out following the general procedure to furnish the crude product **4n** as 92:8 mixture of (*Z*)-**4n** and (*E*)-**4n**. The crude mixture was purified by flash column chromatography (hexane/ethyl acetate = 8:2) to give an overall yield of 75% and (*Z*)-**4n** in >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 214 nm: τ_{major} = 24.60 min.; τ_{minor} = 16.69 min. $[\alpha]_D^{20}$ −102.0 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{23}H_{23}ClNaN_2O_5$ 465.1188, found 465.1188 $[M + Na]^+$. Mp for (*Z*)-**4n**: 78−80 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.04 (d, 1H, J = 1.7 Hz); 7.32 (m, 6H); 7.17 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.7 Hz); 4.80 (dd, 1H, J_1 = 12.6 Hz, J_2 = 9.8 Hz); 4.70 (dd, 1H, J_1 = 12.9 Hz, J_2 = 5.5 Hz); 4.07 (s, 3H); 4.03 (m, 1H); 3.85 (m, 1H); 2.80 (dd, 1H, J_1 = 12.2 Hz, J_2 = 7.3 Hz); 2.64 (m, 1H); 2.24 (m, 1H); 1.53 (m, 2H); 1.03 (t, 3H, J = 7.3 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.3, 161.9, 151.3, 139.3, 138.6, 134.6, 128.9, 127.9, 127.5, 124.5, 124.0, 122.7, 121.2, 115.5, 79.4, 54.1, 43.6, 38.6, 38.5, 20.2, 14.4.

(s,*Z*)-Methyl 5-Chloro-3-(1-ethoxy-2-(nitromethyl)-1-oxo-2-phenylhept-4-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-8a) (Scheme 6, Entry a). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8:2) (*Z*)-**8a** was obtained in 87% yield and >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 10.66 min.; τ_{minor} = 6.05 min. $[\alpha]_D^{20}$ +66.1 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{26}H_{27}ClNaN_2O_7$ 537.1399, found 537.1401 $[M + Na]^+$. Mp: 80−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.89 (d, 1H, J = 8.9 Hz); 7.39 (bs, 1H); 7.34 (m, 4H); 7.27 (m, 2H); 5.45 (d, 1H, J = 15.8 Hz); 5.16 (d, 1H, J = 15.8 Hz); 4.30 (m, 2H); 4.10 (d, 1H, J = 13.5 Hz); 4.04 (s, 3H); 3.81 (d, 1H, J = 13.5 Hz); 2.57 (m, 1H); 2.49 (m, 1H); 1.53 (m, 2H); 1.03 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 171.2, 164.6, 163.0, 150.3, 137.4, 135.0, 128.9, 127.8, 127.4, 127.1, 125.2, 123.2, 122.8, 122.7, 114.8, 78.0, 61.2, 54.2, 53.0, 39.1, 37.0, 28.7, 19.4, 13.3, 12.8.

(*Z*)-Methyl 3-((3s,4*S*)-5-Ethoxy-3-ethyl-4-(nitromethyl)-5-oxo-4-phenylpentan-2-ylidene)-2-oxoindoline-1-carboxylate ((*Z*)-9a) (Scheme 6, Entry b). The title compound was obtained as a single diastereosiomer. After purification by flash column chromatography (hexane/ethyl acetate = 8:2), (*Z*)-**9a** was obtained in 50% yield and >99% ee. HPLC analysis on an AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.5 mL/min, λ = 214 nm: τ_{major} = 15.16 min. $[\alpha]_D^{20}$ +13.0 (*c* 1.00, $CHCl_3$). HRMS-ESI (+): calcd for $C_{26}H_{28}NaN_2O_7$ 503.1789, found 503.1787 $[M + Na]^+$. Mp: 87−91 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.00 (d, 1H, J = 8.2 Hz); 7.58 (d, 1H, J = 7.3 Hz); 7.45 (d, 1H, J = 7.9 Hz); 7.34 (m, 5H); 7.16 (m, 1H); 5.76 (d, 1H, J = 15.5 Hz); 5.49 (dd, 1H, J_1 = 11.7 Hz, J_2 = 3.2 Hz); 5.19 (d, 1H, J = 15.4 Hz); 4.36 (m, 2H); 4.08 (s, 3H); 1.79 (m, 1H); 1.70 (m, 1H); 1.50 (s, 3H); 1.34 (t, 3H, J = 7.0 Hz); 0.71 (t, 3H, J = 7.2 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 171.2, 164.6, 163.0, 150.3, 137.4, 135.0, 128.9, 127.8, 127.4, 127.1, 125.2, 123.2, 122.8, 122.7, 114.8, 78.0, 61.2, 54.2, 53.0, 39.1, 37.0, 28.7, 19.4, 13.3, 12.8.

(Z)-Methyl 5-Chloro-3-((3*R*,4*R*)-3-ethyl-5-nitro-4-phenylpentan-2-ylidene-*1,1,1-d*$_3$)-2-oxoindoline-1-carboxylate ((Z)-3a$_{d3}$) (Figure 1). The title compound was obtained as an amorphous solid following the general procedure and was treated exactly like compound (Z)-**3a**. HRMS-ESI (+): calcd for $C_{23}H_{20}D_3ClNaN_2O_5$ 468.1484, found 468.1480 $[M + Na]^+$. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.87 (d, 1H, J = 8.9 Hz); 7.30 (bs, 1H); 7.23 (dd, 1H, J_1 = 12.9 Hz, J_2 = 2.1 Hz); 7.20−7.10 (m, 4H); 5.28 (m, 0.9H); 4.88 (dd, 1H, J_1 = 12.6 Hz, J_2 = 4.5 Hz); 4.66 (dd, 1H, J_1 = 12.6 Hz, J_2 = 10.4 Hz); 4.05 (s, 3H); 3.65 (m, 1H); 2.02 (m, 1.5H); 1.87 (m, 1H); 1.68 (m, 1H); 0.85 (t, 3H, J = 7.5 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.0, 161.8, 151.5, 138.0, 135.7, 129.6, 128.6, 128.1, 127.9, 127.7, 124.9, 123.9, 115.7, 80.1, 54.0, 48.0, 43.4, 24.5, 18.0, 11.7.

(*R*,*Z*)-Methyl 5-Chloro-3-(1-nitro-2-phenylhept-4-ylidene-*3,3,5,5-d*$_4$)-2-oxoindoline-1-carboxylate ((*Z*)-4a$_{d4}$) (Figure 1). The title compound was obtained as an amorphous solid following the general procedure and was treated exactly like compound (*Z*)-**4a**. HRMS-ESI (+): calcd for $C_{23}H_{19}D_4ClNaN_2O_5$ 469.1547, found 469.1560 $[M + Na]^+$. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.95 (d, 1H, J = 8.6 Hz); 7.40 (d, 1H, J = 2.0 Hz); 7.35−7.25 (m, 6H); 4.79 (dd, 1H, J_1 = 12.9 Hz, J_2 = 9.9 Hz); 4.71 (dd, 1H, J_1 = 12.9 Hz, J_2 = 5.5 Hz); 4.07 (s, 3H); 3.84 (m, 1H); 1.53 (m, 2H); 1.05 (t, 3H, J = 7.5 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.1, 163.1, 151.4, 139.2, 136.3, 129.9, 129.0, 128.5, 128.0, 127.5, 124.1, 123.4, 122.6, 116.1, 79.4, 54.1, 43.5, 37.9, 31.5, 20.1, 14.3.

(*R*,*Z*)-Methyl 5-Chloro-3-(1-nitro-2-phenylhept-4-ylidene-*3,3-d*$_2$)-2-oxoindoline-1-carboxylate ((*Z*)-4a$_{d2}$) (Figure 1). The title compound was obtained as an amorphous solid following the general procedure and was treated exactly like compound (*Z*)-**4a**. HRMS-ESI (+): calcd for $C_{23}H_{21}D_2ClNaN_2O_5$ 467.1421, found 467.1416 $[M + Na]^+$. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.95 (d, 1H, J = 8.9 Hz); 7.40 (bs, 1H); 7.35−7.25 (m, 6H); 4.79 (dd, 1H, J_1 = 12.9 Hz, J_2 = 9.9 Hz); 4.71 (dd, 1H, J_1 = 12.9 Hz, J_2 = 5.6 Hz);

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4.07 (s, 3H); 4.03 (m, 0.8H); 3.85 (m, 1H); 2.83 (m, 0.5H); 2.64 (m, 1H); 2.23 (m, 1H); 1.54 (m, 2H); 1.05 (t, 3H, J = 7.2 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ (ppm) 165.1, 163.3, 151.4, 139.2, 136.3, 129.9, 129.0, 128.5, 128.0, 127.5, 124.1, 123.4, 122.7, 116.1, 79.3, 54.1, 43.5, 38.4, 31.6, 20.3, 14.3.

■ ASSOCIATED CONTENT

Supporting Information

X-ray analysis, NOESY-1D experiments, ^{1}H, ^{13}C and ^{19}F NMR spectra, characterization data, and HPLC traces for compounds (*Z*)-**3a–l**, (*Z*)-**4a–n**, (*Z*)-**7a**, and (*Z*)-**8a**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01022.

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Notes

The authors declare no competing financial interest.

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(13) We arbitrarily defined the "γ-position" as the site occupied by the vinylogous carbon that, with respect to the double bond of the oxindole, is *cis* to the amide carbonyl group. Consequently, we arbitrarily defined the "γ'-position" as the site occupied by the vinylogous carbon that is *trans* to the same carbonyl.

(14) The presence of a 66:34 equilibrium ratio of isomerization in favor of (*Z*)-**1a** was confirmed by mixing oxindoles (*Z*)-**1a** and (*E*)-**1a** only with catalyst **I**. See the Supporting Information for details.

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(15) In the reaction of oxindole (*E*)-**1a** together with the desired product (*Z*)-**4a**, traces of the product of isomerization (*E*)-**4a** were detected. We confirmed that (*Z*)-**4a** when treated with **I** (20 mol %) at −20 °C in toluene isomerizes to (*E*)-**4a** with an equilibrium ratio of 95:5 after 72 h. See the Supporting Information for details

(16) The percentage of enrichment for (*Z*)-$\mathbf{1a}_{d3}$ and (*E*)-$\mathbf{1a}_{d3}$ was derived from the corresponding ^{1}H NMR spectra. We found 50% deuterium enrichment on the methyl group and 10% enrichement on the CH_2 of the propyl group for each isomer. In light of this findings, we can understand the reason for the small difference observed in the reaction rate between (*Z*)-$\mathbf{1a}_{d3}$ and the (*Z*)-**1a**.

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