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(E)-3-(Alkoxycarbonyl-2-Alkyliden)-2-Oxindoles: Multidentate Pronucleophiles for the Organocatalytic, Vinylogous Michael Addition to Nitroolefins

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(*E*)-3-(Alkoxycarbonyl-2-Alkyliden)-2-Oxindoles: Multidentate Pronucleophiles for the Organocatalytic, Vinylogous Michael Addition to Nitroolefins

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Abstract. We introduce 3-(alkoxycarbonyl-2-alkyliden)-2-oxindoles as pronucleophilic donors in the direct, vinylogous Michael addition to nitroolefins orchestrated by a chiral, bifunctional cinchona-thiourea organocatalyst. This reaction displays excellent levels of γ-site-, diastereo- and enantioselectivity delivering valuable enantioenriched functionalized oxindoles. Of note, the C-γ enolization of these pronucleophiles by the organocatalyst generates a multidentate, captodative dienolate that delivers vinylogous adducts with an unprecedented *Z*-selectivity through a peculiar interaction with the catalyst and the nitroolefin. The optimized procedure is operatively simple: the reaction is conducted in air, at room temperature, with low catalyst loading (up to 1 mol%). The synthetic versatility of these Michael adducts is demonstrated by several transformations leading to a valuable quaternary oxindolyl proline analogue and a chiral spirocyclic furoindolone structure. Finally, a mechanistic rationale and a suitable transition state accounting for the observed selectivities are proposed, which are supported by DFT calculations.

Keywords: asymmetric catalysis; density functional calculations; organocatalysis; oxindoles; vinylogous Michael reaction

Introduction

The last 15 years have witnessed the flourishing of asymmetric organocatalysis as a pivotal methodology for the stereoselective synthesis of natural products, chiral drugs and building blocks under mild and usually environment-friendly conditions.[1] In this field, cinchona alkaloid-based thioureas (Figure 1) emerged as powerful chiral organocatalysts for a large number of enantioselective transformations.[2] In fact, the thiourea hydrogen-bond donor ability linked to the quinuclidine basic character enable the coordination and activation of both the nucleophilic and the electrophilic partners of many reactions by non-covalent interactions. In addition, since these two acid/base cooperating moieties usually confer rigidity and tightness to the transition state, constraining it to a defined geometry, the transfer of the chiral information by the catalyst to the products often results successful.

In the field of organocatalysis, within the toolbox of synthetic transformations currently under scrutiny by the organic chemistry community, vinylogous reactions based on the reactivity of *in situ*-generated di- or polyenolates have become a topic of particular relevance.

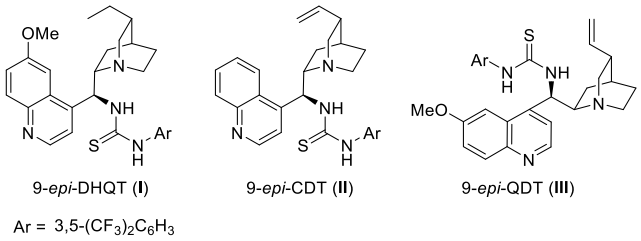
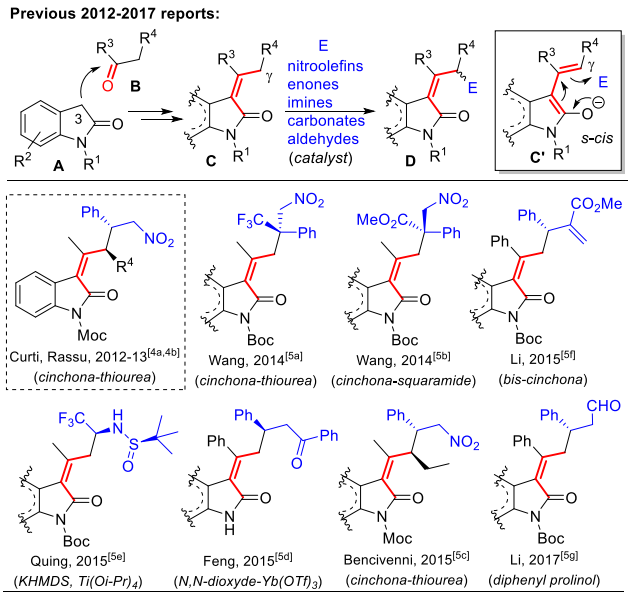


Figure 1. Representative bifunctional cinchona alkaloid-thiourea catalysts.[2]

Consequently, mastering the behaviour of these inherently polydentate vinylogous nucleophiles in a chemo-, regio-, and stereocontrolled way is of utmost importance to render vinylogy a really useful option in synthesis.[3]

In this context, we recently developed the first example of a direct, organocatalytic and enantioselective vinylogous Michael addition of 3-alkylidene oxindoles of type **C** (Scheme 1) to nitroolefins, nicely orchestrated by hydroquinine-derived bifunctional thiourea catalyst **I** (Figure 1).[4a,4b] Easily accessible by Knoevenagel condensation of 2-oxindoles **A** with suitable enolizable carbonyl acceptors **B**, these viable pronucleophiles afforded the corresponding γ-substituted 3-alkylidene oxindoles **D** with outstanding levels of regio- and stereocontrol (Scheme 1, dashed frame).



Scheme 1. Reactivity and scope of pronucleophilic 3-alkylidene oxindoles of type **C**: representative examples of up-to-date addition reactions. In parenthesis the catalytic system used.

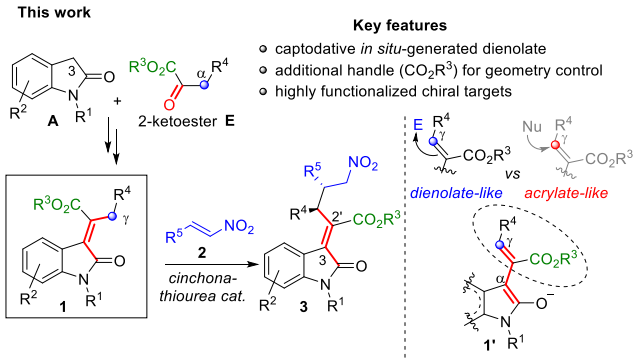
Since then, other groups have exploited similar pronucleophiles in the organo- or metal-catalyzed addition to various electrophilic partners such as nitroalkenes,[5a-c] enones,[5d] imines,[5e] Morita Baylis-Hillman (MBH) carbonates,[5f] and aldehydes,[5g] thus confirming the high viability and versatility of this class of vinylogous pronucleophiles in synthesis.

Interestingly, the selective C-γ homologation of all the tested 3-alkylidene oxindoles was achieved with high efficiency and stereoselectivity, invariably giving the corresponding oxindole products with geometrically defined, *cis*-disposed olefins (i.e. the newly installed chain is positioned on the same side with respect to the oxindole carbonyl), as detailed in Scheme 1.[6] In all instances, *s-cis* dienolate conformations of type **C′** are likely to be operative in the stereodetermining transition states, which dictate the final geometry of the products.

It is well known that the specific topology and geometry asset of olefins within unsaturated natural and unnatural bioactive molecules is of utmost importance in medicinal chemistry and biology, since in most cases it significantly affects the overall bioactivity of the molecule. In this context, the *Z/E* nature of the exocyclic double bond within scaffolds **D** is particularly relevant, since 3-alkylidene oxindoles are the core structure of a wide range of biologically and pharmaceutically relevant molecules.[7a] One notable example is sunitinib, an alkylidene oxindole multi-targeted receptor tyrosine kinase (RTK) inhibitor, which is highly active and stable only in its *Z*-configuration.[7b,c]

Continuing on this theme, we became interested in the chemistry of pyruvate-like structures of type **E** (Scheme 2), an appealing set of compounds that appear in most crucial steps of biochemical processes as either donor or acceptor components.[8] In particular, due to their high degree of functionalization, α-enolizable 2-ketoesters have raised wide interest in the field of organic synthesis, and in recent years their role as valuable d^2-synthons has been reconsidered and exploited.[9]

We envisioned that merging the 2-oxindole scaffold **A** with an enolizable 2-ketoester **E** would result in the formation of 3-(alkoxycarbonyl-2-alkyliden)-2-oxindole **1**, a vinylogous variant of **E** that retains its pronucleophilic character at C-γ, while significantly expanding its reactivity space. To date, several non-enolizable compound analogues are known and well exploited as electrophilic species in a vast array of transformations spanning from Michael-type reactions to one-pot or multistep cycloadditions;[10] however, the pronucleophilic character of such substrates remains elusive and substantially unexplored.



Scheme 2. Overview of the present work based on the exploitation of "*pyruvate-oxindole merger*" **1** as vinylogous pronucleophile.

Interestingly, the C-γ enolization of **1** would generate a multidentate dienolate **1'** embedding an exocyclic, captodative olefin,[11] whose dual nature is intriguing: in principle, it may act either as a vinylogous nucleophile in a "*dienolate-like*" fashion (Scheme 2, right) or, conversely, it may work as an "*acrylate-like*" moiety where the C-γ acts as an electrophilic site.

Moreover, we reasoned that the additional ester handle could play an active role in the interaction with the catalyst in the transition state, thus influencing the geometry outcome of the products.

Intrigued by the new opportunities these scaffolds could drive in terms of site-, geometry-, and stereoselectivity, we embarked in a project toward the exploitation of "*pyruvate-oxindole merger*" of type **1** as pronucleophilic donor in the direct and vinylogous Michael addition (VMcR) to nitroolefins **2** orchestrated by a chiral, bifunctional cinchona-thiourea organocatalyst (Scheme 2, left). The success of this endeavour is here reported, as demonstrated by the straightforward entry to a collection of multifunctionalized and highly enantioenriched oxindoles of type **3**. Also, the synthetic usefulness of these products was proven, by easy transformation of some representative compound into a quaternary oxindole-proline and a chiral spirocyclic furoindolone structure. Finally, several DFT analyses are reported to support a mechanistic rationale and a suitable transition state that account for the observed selectivities.

Results and Discussion

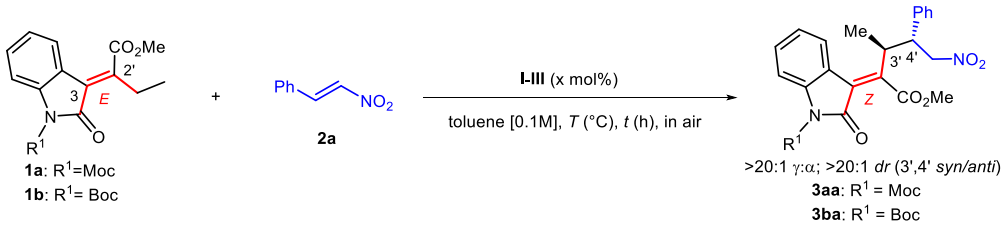
Viability and Optimization Survey

To test the viability of the planned VMcR, we chose *N*-Moc-3-(methoxycarbonyl-2-butylidene)-2-oxindole (**1a**) and *trans*-*β*-nitrostyrene (**2a**) as the model substrates (Table 1). Oxindole **1a**, in turn, could be easily obtained via a three-step sequence starting from 2-oxindole and methyl-2-oxobutanoate via Knoevenagel-type condensation chemistry (see the Supporting Information). Initially, several bifunctional organocatalysts, including cinchona-thiourea catalysts **I-III** (Figure 1), cinchona-squaramide and others were screened, as detailed in Table S1 in the Supporting Information.

In particular, starting from a readily available 3:1 (*Z/E*) mixture of **1a** and nitroalkene **2a** (2 equiv), the best hit was achieved with hydroquinine-derived 9-*epi*-DHQT (**I**), which afforded nitroalkylidene adduct **3aa** in an acceptable yield (53%) as a 1:1 *Z/E* mixture of geometric isomers, with complete γ-site selectivity, full 3′,4′-*syn* diastereoselectivity and almost complete enantioselectivity (Table 1, entry 1).

Despite these preliminary encouraging results, we soon noticed that the reaction was scarcely reproducible, and many attempts to improve its efficiency and *Z/E* selectivity met with only partial success. To better understand this unpredictable behaviour, we separately reacted either oxindoles (*E*)-**1a** or (*Z*)-**1a** with **2a**, using catalyst **I** as the promoter (entries 2 and 3). Surprisingly enough, we found that pure (*E*)-**1a** reacted efficiently with **2a**, affording **3aa** in a good 85% yield after only 3h reaction time and with complete enantiocontrol (>99% *ee*).

Table 1. Selected optimization studies for the direct, enantioselective VMcR between oxindoles **1a-b** and olefin **2a**.[a]



entry	**1**	**3**	Catalyst (mol%)	T [°C]	*t* [h]	Yield [%][b]	*Z:E*[c]	*ee*% [*Z/E*][d]
1	(*Z/E*)-**1a**	**3aa**	**I** (10)	40	12	53	1:1	98/99
2	(*E*)-**1a**	**3aa**	**I** (10)	40	3	85(69)	4.2:1	>99/99
3	(*Z*)-**1a**	**3aa**	**I** (10)	40	144	80(48)	1.5:1	99/99
4	(*E*)-**1a**	**3aa**	**I** (10)	–15	16	80(73)	10.6:1	>99/nd
5	(*E*)-**1b**	**3ba**	**I** (10)	–15	16	73(65)	8.3:1	>99/nd
6	(*E*)-**1b**	**3ba**	**II** (10)	–15	16	73(65)	11.5:1	>99/nd
7	(*E*)-**1b**	**3ba**	**II** (5)	–15	24	63(52)	11:1	>99/nd
8	(*E*)-**1b**	**3ba**	**II** (3)	–15	24	50(45)	9:1	>99/nd
9	(*E*)-**1b**	**3ba**	**II** (1)	40	48	33(30)	9:1	>99/nd
10[e]	**(*E*)-1b**	**3ba**	**II (3)**	**r.t.**	**16**	**98(93)**	**13:1**	**>99/nd**
11[e]	(*E*)-**1b**	**3ba**	**III** (3)	r.t.	16	50	10:1	>99/nd
12[e]	(*E*)-**1b**	**3ba**	**III** (10)	r.t.	24	70	8:1	–99/–98

[a] Unless otherwise noted, all reactions were carried out on a 0.2 mmol scale of **1a** or **1b** [0.1M] using **2a** (2 equiv), catalyst **I**, **II** or **III** in toluene at the reported temperature (°C) for the indicated period (h).

[b] Isolated combined yield after chromatographic purification. Isolated yield of major isomer (*Z*)-**3** in parenthesis.

[c] Determined by ^{1}H NMR of the crude.

[d] Determined by chiral HPLC analysis.

[e] 1.5:1 (**1b**:**2a**) molar ratio was used.

Of note, product **3aa** could be obtained as a separable 4.2:1 mixture of geometric isomers, the major isomer being the *Z*-configured **3aa**, featuring an unprecedented *trans* disposition between the nitroalkylidene side chain and the oxindole carbonyl (entry 2). Conversely, the reaction between pure (*Z*)-**1a** and **2a** proved to be much slower and less selective than the geometric isomer, yielding **3aa** in a 80% combined yield after 144 h reaction time as a 1.5:1 *Z/E* mixture of enantiopure isomers (entry 3). Aware that the fixed *E*-geometry of the starting oxindole could positively affect the efficiency and selectivity of the reaction, we continued our survey using pure (*E*)-**1a**.

Lowering the reaction temperature to −15 °C (entry 4) resulted in the formation of product **3aa** in a highly improved *Z/E* ratio (10.6:1) without loss of efficiency (80% yield), albeit requiring longer reaction time (16 h). *N*-Boc protected oxindole (*E*)-**1b** also proved a viable substrate under these conditions (entry 5), and the expected product **3ba** could be obtained in a good 73% combined yield, as an 8.3:1 *Z/E* mixture of isomers in an enantiopure format.

Subsequent optimization on this *N*-Boc-protected substrate (*E*)-**1b** revealed that an improved geometric selectivity in the product **3ba** could be achieved using cinchonine-derived thiourea catalyst **II** (entry 6, 11.5:1 *Z/E*); decreasing instead the catalyst loading to 5 mol% or 3 mol% (entries 7 and 8) resulted in a slight erosion of both efficiency and *Z/E* selectivity, and required longer reaction times (24 h). Of note, the reaction resulted viable also with a catalyst loading up to 1 mol%, though a substantial decrease of the reaction efficiency rendered these conditions less practical. In this case compound **3ba** was produced in a in a poor 33% yield while maintaining high *Z/E* selectivity (9:1) and excellent enantiocontrol (>99% *ee*) even at 40 °C (entry 9).

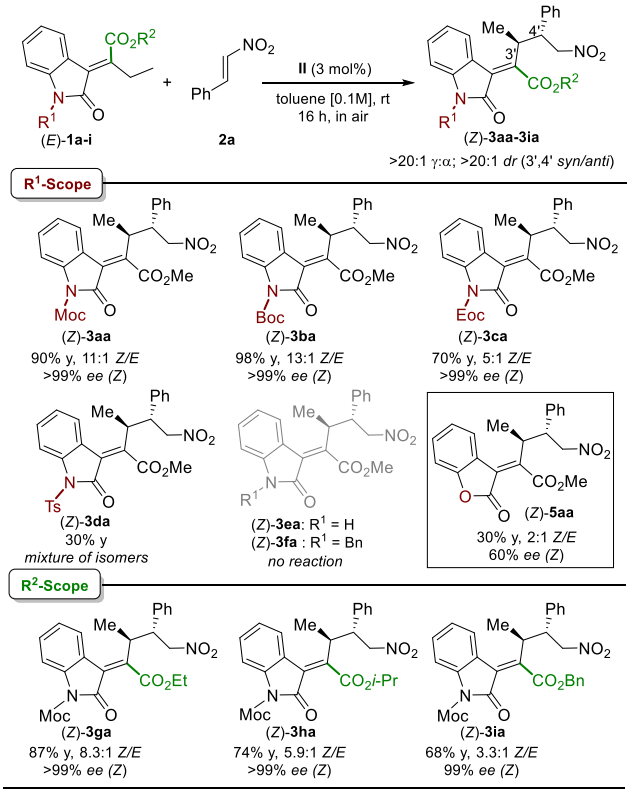
Willing to improve the reaction performance even more, we observed that longer reaction times associated with higher catalyst loadings produced a detrimental effect on the overall efficiency and selectivity of the process. We ascribed this behavior to an unproductive catalyst-mediated isomerization of (*E*)-**1** to the "slower" (*Z*)-**1** isomer.[12] Also, envisaging that similar isomerization equilibria might be operative on final adducts (*Z*)-**3**, we reasoned that longer reaction times would consequently end-up with lower *Z/E* ratios. To shorten reaction times while maintaining useful levels of "active" (*E*)-**1b** in solution, we performed the reaction at room temperature, with 3 mol% of **II**, and a slight excess of (*E*)-**1b** instead of **2a** (1.5/1 **1b**/**2a** molar ratio). This choice proved to be successful, and almost enantiopure (*Z*)-**3ba** could be obtained after 16 h in an almost quantitative yield (98%), and 13:1 *Z/E* ratio (entry 10).

To complete the survey, under the optimized reaction conditions, the pseudo-enantiomer quinidine-derived thiourea **III** (9-*epi*-QDT, 3 mol%) proved to be less efficient in promoting the title reaction, yielding the corresponding enantiomer *ent*-(*Z*)-**3ba** with only a 50% combined yield in a 10:1 *Z/E* ratio and >99% *ee* (entry 11). With this catalyst, a significant improvement was achieved using 10 mol% loading (70% yield), albeit with a slight decrease in selectivity (8:1 *Z/E*, entry 12).[13]

Reaction Scope and Limitations

With the optimal reaction conditions at hand (Table 1, entry 10), a careful insight into scope and limitations of this direct VMcR was investigated. We started by evaluating the role exerted by the nitrogen appendage R^1 on the reaction outcome (Table 2). Under the optimized reaction conditions, Moc-protected oxindole (*E*)-**1a** confirmed to be viable, yielding nitroalkylidene adduct **3aa** in a very good 90% isolated yield, a 11:1 *Z/E* ratio and an almost total *syn/anti* diastereocontrol (>20:1 3′,4′-*syn/anti* dr) and enantiocontrol (>99% *ee*).

Table 2. Substrate scope of the asymmetric VMcR: variation of R^1 and R^2 moieties.[a]



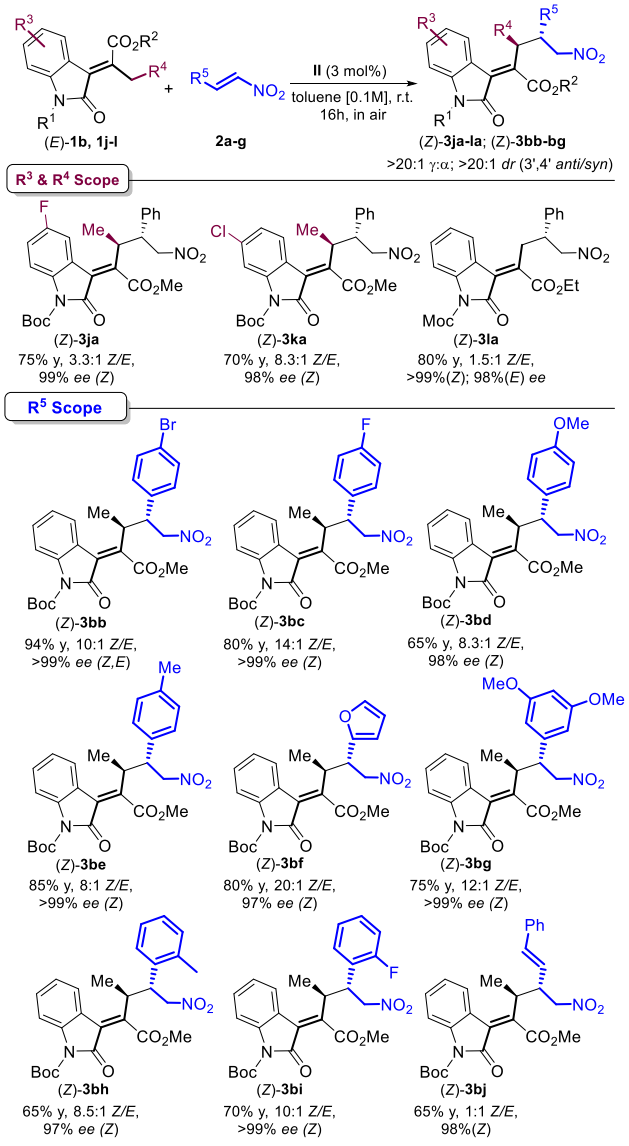
[a] Unless otherwise noted, all reactions were carried out on a 0.2 mmol scale of **2a** [0.1M] using **1**/**2a** (1.5:1 molar ratio), **II** (3 mol%) in toluene at r.t. in air, for 16 h. Yields (y) refer to isolated combined yields. *Z/E* ratio values were determined by ^{1}H NMR of the crude. *ee*% were determined by chiral HPLC analysis (see the Supporting Information for details).

Switching to ethyl carbamate derivative (*E*)-**1c**, a slightly inferior performance was recorded, in both efficiency (70% yield) and geometry control (5:1 *Z/E*). Furthermore, the presence of a multidentate moiety

such as the tosyl group in (*E*)-**1d** resulted highly detrimental for the reaction, affording a not-well-identified mixture of isomeric products.

Finally, protecting group-free oxindole (*E*)-**1e** and benzyl-protected derivative (*E*)-**1f** proved inert toward **2a** even under higher temperatures and with higher catalyst loadings. Interestingly, treating oxygenated 3-alkylidene coumaranone analogue (*Z*)-**4a** with **2a** under the same reaction conditions (Table 2, framed compound), gave the corresponding adduct **5aa** in a very modest 30% yield with poor stereocontrol (2:1 *Z/E* ratio, 60% *ee* for the *Z*-isomer).

Table 3. Substrate scope of the asymmetric VMcR: variation of R^3, R^4, and R^5 moieties.[a]



[a] Unless otherwise noted, all reactions were carried out on a 0.2 mmol scale of **2** [0.1M] using **1**/**2** (1.5:1 molar ratio), **II** (3 mol%) in toluene at r.t. in air, for 16 h. Yields (y) refer to isolated combined yields. *Z/E* ratio values were determined by ^{1}H NMR of the crude. *ee* % were determined by chiral HPLC analysis (see the Supporting Information for details).

These results confirm that the presence of a carbamate moiety installed at the oxindole nitrogen is pivotal for both the activation of pronucleophilic (*E*)-**1** and the stereocontrol of the whole process exerted by the dual cinchona-thiourea catalyst (*vide infra*).[4,14]

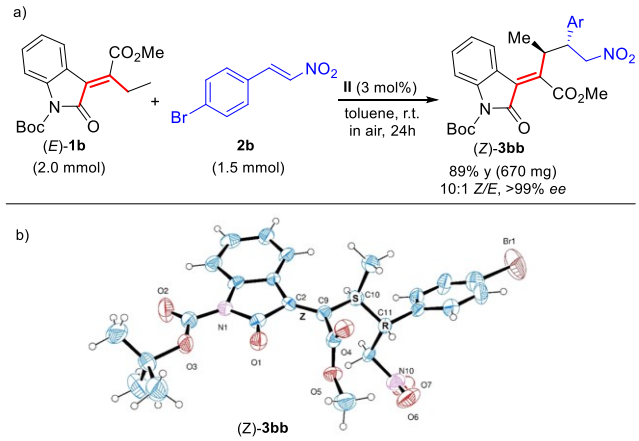
We next focused the attention on the ester appendage; in particular, the effects of ethyl- (**1g**), isopropyl- (**1h**), benzyl- (**1i**), and *tert*-butyl-ester derivatives were compared to the methyl ester analogue **1a** in terms of reaction efficiency and selectivity (Table 2, bottom). Of note, with the exception of the bulky *tert*-butyl ester derivative (not shown), which proved to be totally unreactive, the other oxindole scaffolds worked quite well, following a trend in which both yields and *Z/E* selectivity tended to worsen by the order methyl > ethyl > isopropyl > benzyl (Table 2, bottom).

This fact prompted us to conclude that the alkoxycarbonyl group moiety of the starting alkylidene – a peculiar structural motif of the title oxindoles – plays an important role in governing the reaction fate and regulating the geometry control of the products. Indeed, as anticipated in the premises of the work, it may function as a cardinal point of interaction with the catalyst concurring in the stabilization of the *s-trans* conformation of the *in situ*-formed dienolate species (*vide infra*).

Continuing the screening of the pronucleophilic substrates, evaluation of 5-fluoro- and 6-chloro-oxindole derivatives **1j** and **1k** was performed, giving the corresponding adducts **3ja** and **3ka** in good yields and modest-to-good stereoselectivities (Table 3, top). Interestingly, non-prostereogenic pyruvate-derivative **1l** proved a viable substrate under the optimized reaction conditions, consigning adduct **3la** in a good 80% yield and excellent enantioselectivity, albeit with a complete loss of *Z/E* selectivity, a fact that we ascribed to an increased rate of *Z/E* isomerization of the product operated by the catalyst during the reaction course. Several nitroalkene acceptors were also investigated (Table 3, bottom). Irrespective of the electronic and steric demand of the aromatic ring within nitroalkenes **2b-i**, all reactions worked efficiently, and the corresponding vinylogous adducts **3bb-3bi** were isolated in good yields (65-98%), good *Z/E* ratios (8:1-20:1), and excellent enantioselectivity (97->99% *ee*). Interestingly, the reaction between (*E*)-**1b** and extended diene **1j** afforded a 1:1 *Z/E* separable mixture of the sole *β*-adduct **3bj**, in an acceptable 65% yield and almost complete enantiocontrol.

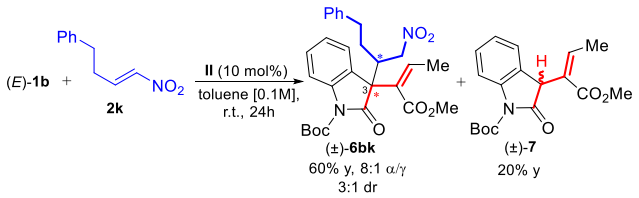
Also, 4-bromo nitrostyrene **2b** was successfully tested on a tenth-fold scale (1.5 mmol, Scheme 3, eq. a), confirming the high efficiency and selectivity of the optimized process from a preparative point of view; indeed, enantiopure (*Z*)-**3bb** could be isolated from a 10:1 *Z/E* mixture in a 89% yield. Moreover, compound (*Z*)-**3bb** turned out particularly useful for the determination of the absolute configuration and double bond geometry of nitroalkylidene adducts **3**. As shown in Scheme 3 (bottom), the absolute (3′*S*,4′*R*)-configuration of compound (*Z*)-**3bb** was unambiguously determined by X-ray structure

analysis. Therefore, the absolute configuration of all other major *Z*-configured nitroalkylidene adducts **3** was assigned in analogy, by assuming a similar reaction behaviour.[15]



Scheme 3. Preparative scale synthesis of enantiopure (*Z*)-**3bb** (a); X-ray crystal structure of (*Z*)-**3bb** (b).

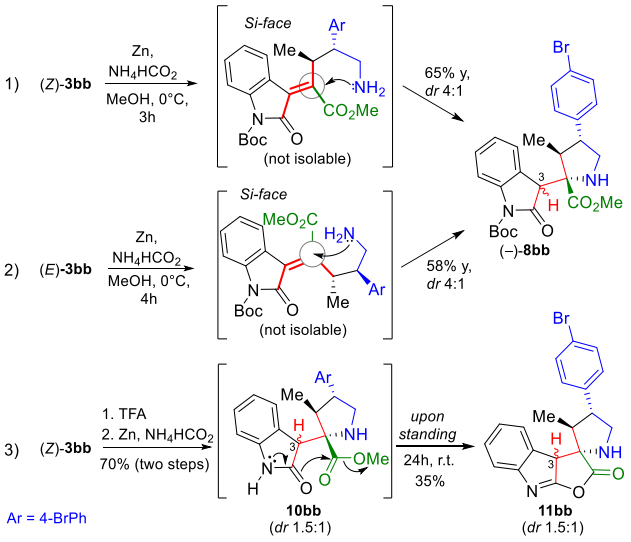
Regarding less reactive aliphatic nitroalkene acceptors, several candidates including cyclohexyl-, isopropyl-, and butyl-nitroalkenes were tested under the optimized or even harsher reaction conditions, without success. As an exception, 4-phenylnitrobutene (**2k**) smoothly reacted with oxindole (*E*)-**1b** at room temperature (10 mol% catalyst loading), affording a 3:1 diastereomeric mixture of racemic **6bk** (Scheme 4) resulting from a nonvinylogous α-attack (8:1 α/γ; 60% combined yield as a racemate), accompanied by a small amount (20%) of racemic (*Z*)-**7**, a tautomeric form of the starting material.



Scheme 4. Organocatalyzed Michael reaction between oxindole (*E*)-**1b** and aliphatic 4-phenyl-nitrobutene **2k**, affording α-adduct (±)-**6bk** and α-tautomer (±)-**7**.

An important feature of the present asymmetric VMcR is that it provides chiral multifunctional products in which the exocyclic C3-C2' double bond of the starting (alkoxy)alkylidene oxindole is preserved (and geometrically inverted), providing opportunities for further useful transformations. In this context, we envisaged that, upon chemoselective reduction of the terminal nitro group to an amine, an unprecedented merger oxindole-proline structure of type **8** could be accessed (Scheme 5, eq. 1), via intramolecular aza-Michael closure of the amine on the alkylidene olefin.

Pleasingly, treating enantiopure (*Z*)-**3bb** with Zn/ammonium formate couple in methanol, the quaternary proline methyl ester derivative (−)-**8bb** was obtained in a good 65% yield as a separable 4:1 mixture of epimers at C3, as certified by extensive 1D and 2D NMR studies (see the Supporting Information for details).[16]



Scheme 5. Transformations of 4-bromo-derivatives (*Z*)-**3bb** and (*E*)-**3bb** to indolyl-proline **8bb** and spirocyclic furoindolone **11bb**.

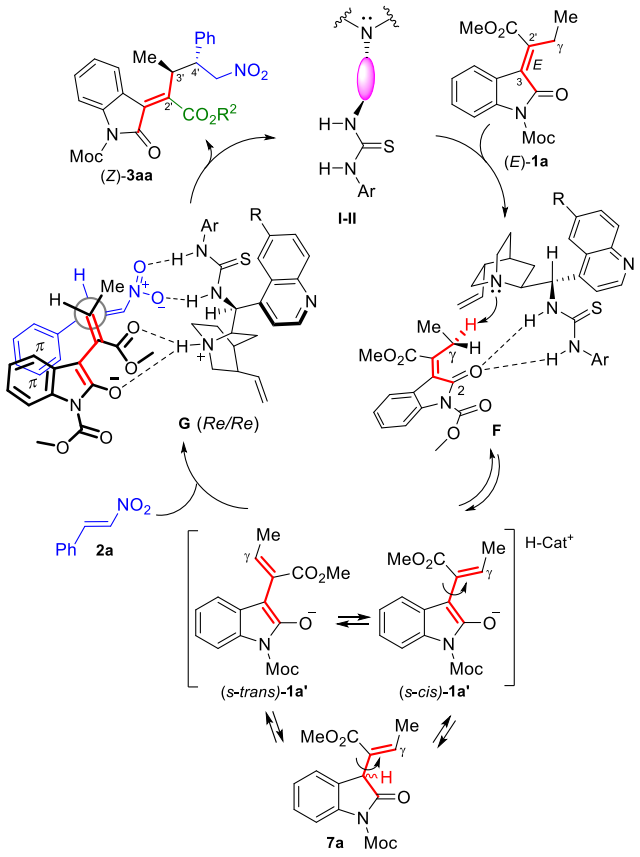
As a fine stereochemistry joke, the same oxindole-proline product **8bb** was afforded by starting from the geometric isomer (*E*)-**3bb** under the same reaction conditions, via the attack of the amine intermediate on the *Si*-face of the exocyclic C2′, as detailed in Scheme 5 (eq. 2). When the same reductive cyclization was performed on deprotected oxindole from (*Z*)-**3bb**, an unexpected yet quite interesting result was obtained. In fact, as shown in Scheme 5 (eq. 3), treating (*Z*)-**3bb** with trifluoroacetic acid (giving deprotected oxindole **9bb**, not shown) followed by Zn/formate reduction gave the expected *N*-deprotected oxindole-proline **10bb**, which spontaneously converted into furoindolone spirocycle **11bb** as an inseparable 1.5:1 diastereoisomeric mixture.[17]

Mechanistic Rationale and DFT Calculations

Capitalizing on previous activation models for cinchona-thiourea catalyzed reactions, and based on theoretical calculations for similar transformations,[18,1a,5c] a plausible mechanistic pathway is proposed to explain the stereochemical outcome of this asymmetric VMcR. As described in Scheme 6 for the synthesis of (*Z*)-**3aa**, we postulate that an initial hydrogen bonding interaction of the catalyst (**I** or **II**) with the highly reactive oxindole pronucleophile (*E*)-**1a** generates complex **F** in which the quinuclidine portion of the catalyst is spatially set

close to the acidic γ-methylene site positioned in *cis* to the lactam carbonyl C2. Subsequent deprotonation of this γ-site generates a dienolate (*Z*)-**1a'** that mainly reacts with nitrostyrene **2a** in a stabilized *s-trans* conformation after rotation of the ester moiety along the C3-C2' bond.

The catalyst ability to stabilize the active *s-trans* conformation of **1a'** may be due to the formation of H-bonding network involving the protonated quinuclidine, the oxy-anion at C2, and the ester moiety, as depicted in complex **G**.[19] According to this proposal, the observed inverse relationship between the hindrance of the ester substituent on the pronucleophile and the *Z/E* selectivity would be explained. More hindered esters might hamper the stabilizing H-bonding, allowing a higher degree of rotation along the C3-C2' bond.



Scheme 6. Proposed mechanism pathway for the asymmetric VMcR between 3-(alkoxycarbonyl)-propylidene oxindole (*E*)-**1a** and nitrostyrene **2a** promoted by catalyst **I** or **II**.

The high degree of stereoselectivity observed in the VMcR may thus be ascribed to the formation of the tight transition state **G** (Scheme 6) in which the interaction of the *Re* face of the *s-trans* dienolate **1a'** with the *Re* face of the activated nitroalkene is perfectly orchestrated by the dual catalyst, to afford (3'*S*,4'*R*)-configured (*Z*)-**3aa** almost exclusively. In addition, the synclinal approach as in **G** may be favoured by weak π–π interactions between the overlapping indole and the nitroalkene aromatic rings, an issue that may also account for the inertness observed for aliphatic nitroalkenes.

To support the proposed mechanistic rationale, we conducted some preliminary DFT calculations relative to *i*) the deprotonation step of oxindole (*E*)-**1a** and *ii*) the addition reaction catalyzed by 9-*epi*-CDT (**II**) with (*E*)-**2a**, giving product **3aa** (Table 2).[20,21] Concerning the deprotonation step (complex **F**, Scheme 6), two transition states, **TS_A** and **TS_B** (Figure 2), relative to the deprotonation of (*E*)-**1a** in complex with the organocatalyst **II**, were identified giving the corresponding dienolates (*Z*)-**1a'** and (*E*)-**1a'**, respectively.

Transition state **TS_A** was predicted to be more stable than **TS_B**, using both the 6-31G(d) basis set in the gas phase ($\Delta\Delta G^{\ddagger}$ = 4.62 Kcal/mol) and the triple-ζ def2-TZVPP basis set in toluene ($\Delta\Delta G^{\ddagger}$ = 4.58 Kcal/mol).[22]

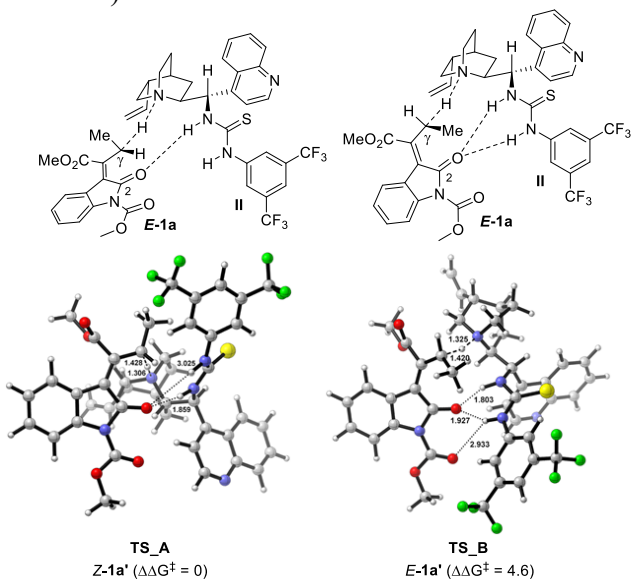


Figure 2. Transition states **TS_A** and **TS_B** relative to the deprotonation of (*E*)-**1a** with catalyst **II**. M06-2X/def2-TZVPP-IEFPCM(toluene)//M06-2X/6-31G(d); energies in Kcal/mol.

Thus, only the *Z*-configured dienolate **1a'** was selected for exploring the addition reaction step to nitrostyrene (*E*)-**2a**. Considering the approach of the s-*cis* and s-*trans* limit conformations of (*Z*)-**1a'**, two transitions states **TS_C** and **TS_D** (Figure 3) were identified for the two possible *Re/Re* approaches leading to the known absolute (3'*S*,4'*R*) configuration of the products. Once again, using both the less demanding 6-31G(d) basis set in the gas phase ($\Delta\Delta G^{\ddagger}$ = 7.8 Kcal/mol) and def2-TZVPP basis set in toluene ($\Delta\Delta G^{\ddagger}$ = 7.9 Kcal/mol), the transition state involving (*Z*)-(s-*trans*)-**1a'** (**TS_C**, Figure 3, left) was predicted to be considerably more stable than the (*Z*)-(s-*cis*)-**1a'** complex (**TS_D**, Figure 3, right). This difference can be explained by considering that in **TS_D**: *i*) no

stabilizing hydrogen-bond interactions are possible between the thiourea moiety or the protonated tertiary amine and the partially negative charged oxindole C2 oxygen, and *ii*) the substituents around the forming C3'-C4' bond are arranged in an almost eclipsed conformation.

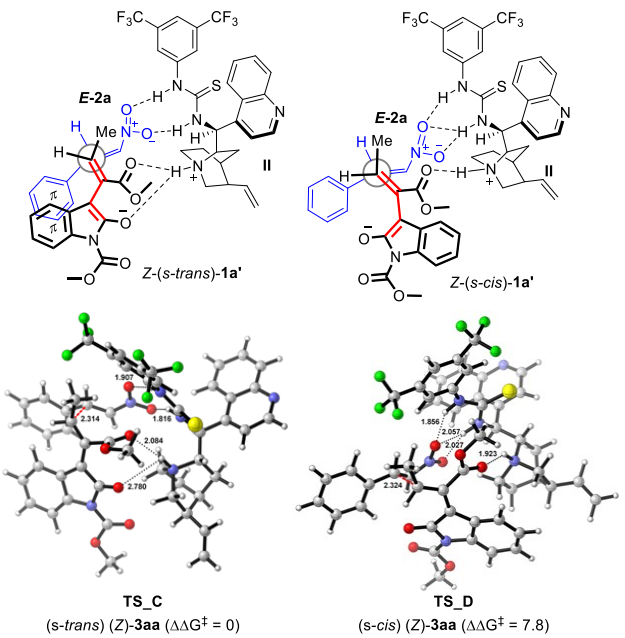


Figure 3. Transition states **TS_C** and **TS_D** relative to the addition step of (*Z*)-(s-*trans*)-**1a'** and (*Z*)-(s-*cis*)-**1a'** complexes with catalyst **II** and nitroolefin (*E*)-**2a**; the approach of (*Z*)-(s-*cis*)-**1a'** and (*E*)-**2a** corresponds to an almost eclipsed conformation, but was reported as staggered for the sake of clarity. M06-2X/def2-TZVPP-IEFPCM(toluene)//M06-2X/6-31G(d); energies in Kcal/mol.

In both TSs, the dual activation mode of the catalyst was in accordance to the one proposed by Takemoto,[18a] in which the thiourea activates the electrophile (**2a**) and the protonated tertiary amine activates the nucleophile (**1a'**) by hydrogen bonding. It is interesting to note that in both cases the ester group at Cβ is actively involved in the formation of stabilizing hydrogen-bond interactions with the protonated quinuclidine of catalyst **II**, thus playing an active role in determining the stereoselectivity of the process.

Conclusion

In summary, we exploited the d^4-reactivity of *in situ* generated prostereogenic, multidentate and captodative dienolates derived by C-γ enolization of (*E*)-3-(alkoxycarbonyl-2-alkyliden)-2-oxindoles in direct, enantioselective, vinylogous Michael addition to nitroolefins nicely orchestrated by chiral, bifunctional cinchona-thiourea organocatalysts. This reaction provided valuable and highly enantioenriched nitroalkylidene oxindole adducts in good isolated yields, complete γ-site and *syn/anti* diastereoselectivity, and showed tolerance for a wide range of functionality. Of note, an unprecedented *Z*-selective outcome was observed in many cases. In this context, experimental and DFT data highlight the crucial role exerted by the distinctive alkoxycarbonyl appendage in the stabilization of the active *s-trans* conformation of the *in situ*-formed dienolate species, via peculiar noncovalent interactions with the catalyst.

Finally, the synthetic versatility of the products was demonstrated by a couple of representative transformations leading to a quaternary oxyndolyl-proline analogue and a spirocyclic furoindolone structure.

Experimental Section

General Procedure for the Synthesis of 3-(Alkoxycarbonyl-2-Alkyliden)-2-Oxindoles of Type 1

Preparation of (*E*) and (*Z*)-3-(2-Methoxycarbonyl-2-propylidene)indolin-2-one (1e)

To a solution of commercial 2-oxindole (460 mg, 3.45 mmol, 1.0 equiv) in a 1:1 mixture of methyl-2-oxo-butanoate/MeOH (10 mL), vigorously stirred at 0 °C, piperidine was added (68 µl, 0.69 mmol, 0.2 equiv). The resulting solution was stirred at 0 °C for 3 h, and then warmed to r.t. for further 24 h. The resulting solution was concentrated under vacuum, and the crude was purified by silica gel flash chromatography (gradient mixture from 70:30 to 60:40 petroleum ether/EtOAc) to yield the corresponding aldol adduct (830 mg, 97% yield) as a 3:1 mixture of two diastereoisomers as a white solid. Recrystallization from a 2:1 water/MeOH mixture allowed the separation of the major isomer as a white, amorphous solid.

The previously prepared mixture of aldol adducts (830 mg, 3.33 mmol, 1.0 equiv) was suspended in water (30 mL) and to the resulting suspension 10% HCl (5 mL) was added dropwise at r.t. The solution was refluxed for 1 h at 100 °C. The resulting yellow solution was cooled to r.t., then extracted with EtOAc (3 × 30 mL) and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to yield a yellow-orange resin. The resulting crude was purified by silica gel flash chromatography (65:35 petroleum ether/EtOAc) to yield pure (*Z*)-**1e** (371 mg) as a yellow-orange solid and pure (*E*)-**1e** (167 mg, 70% combined yield) as a light yellow solid.

(*E*)-1e: ^{1}H NMR (400 MHz, chloroform-*d*): δ 9.10 (bs, 1H, NH), 7.19-7.25 (m, 2H, H4, H6), 6.96 (dd, *J* = 7.7, 7.7 Hz, 1H, H5), 6.86 (bd, *J* = 7.7 Hz, 1H, H7), 3.98 (s, 3H, $CO_2\underline{Me}$), 3.24 (q, *J* = 7.6 Hz, 2H, $\underline{CH_2}CH_3$), 1.22 (t, *J* = 7.6 Hz, 3H, $CH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, chloroform-*d*): δ 169.9 (Cq), 169.2 (Cq), 146.9 (Cq), 140.5 (Cq), 129.8 (CH), 124.5 (Cq), 122.4 (CH), 122.1 (CH), 121.0 (Cq), 110.2 (CH), 52.5 (CH_3, $CO_2\underline{Me}$), 22.8 (CH_2, C3'), 12.2 (CH_3, C4'); HR-MS: *m/z* = 232.0960, calcd. for $C_{13}H_{14}NO_3$: 232.0973 $[M+H]^+$.

(*Z*)-1e: ^{1}H NMR (400 MHz, chloroform-*d*): δ 9.26 (bs, 1H, NH), 7.49 (bd, *J* = 7.7 Hz, 1H, H4), 7.25 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H, H6), 7.02 (ddd, *J* = 7.7, 7.7, 0.8 Hz, 1H, H5), 6.89 (bd, *J* = 7.7 Hz, 1H, H7), 3.94 (s, 3H, $CO_2\underline{Me}$), 2.83 (q, *J* = 7.6 Hz, 2H, $\underline{CH_2}CH_3$), 1.31 (t, *J* = 7.6 Hz, 3H,

$CH_2\underline{CH_3}$); ^{13}C NMR (75 MHz, chloroform-*d*): δ 170.0 (Cq, C2), 168.6 (Cq, $\underline{C}O_2Me$), 146.2 (Cq, C7a), 141.8 (Cq, C3), 130.1 (CH), 125.4 (Cq, C2'), 124.4 (CH), 122.6 (CH), 121.9 (Cq, C3a), 110.8 (CH, C7), 52.8 (CH_3, $CO_2\underline{Me}$), 25.1 (CH_2, C3'), 11.3 (CH_3, C4'); HR-MS: *m/z* = 232.0957, calcd. For $C_{13}H_{14}NO_3$: 232.0973 $[M+H]^+$.

Preparation of (*E*)-1-(*tert*-Butoxycarbonyl)-3-(2-methoxycarbonyl-2-propylidene)indolin-2-one (*E*)-1b

To a solution of deprotected oxindole (*E*)-**1e** (150 mg, 0.64 mmol, 1.0 equiv) in CH_3CN (10 mL), kept under stirring at 0 °C (ice bath) under nitrogen atmosphere, di-*tert*-butyl dicarbonate $(Boc)_2O$ (209 mg, 0.96 mmol, 1.5 equiv) and DMAP (7.8 mg, 0.06 mmol, 0.1 equiv) were sequentially added and the solution turned from yellow to light yellow. After 30 min, an aqueous solution of $CuSO_4$ (0.5 N) was added dropwise to the reaction mixture. The crude was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to yield a yellow oil. The resulting crude was purified by silica gel flash chromatography (95:5 petroleum ether/EtOAc) to yield 170 mg of pure (*E*)-**1b** (80% isolated yield) as a yellow resin.

(*E*)-**1b**: ^1H NMR (400 MHz, chloroform-*d*): δ 7.87 (d, *J* = 8.2 Hz, 1H, H7), 7.33 (dd, *J* = 7.8, 7.8 Hz, 1H, H6), 7.22 (bd, *J* = 7.8 Hz, 1H, H4), 7.10 (ddd, *J* = 7.8, 7.8, 1.0 Hz, 1H, H5), 3.98 (s, 3H, $CO_2\underline{Me}$), 3.19 (q, *J* = 7.6 Hz, 2H, $\underline{CH_2}CH_3$), 1.67 (s, 9H, *t*-Bu, Boc), 1.22 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, chloroform-*d*): δ 169.4 (Cq, C2), 165.5 (Cq, $\underline{C}O_2Me$), 149.4 (Cq, Boc), 147.8 (Cq, C3 or C7a), 139.1 (Cq, C7a, or C3), 130.1 (CH, C4), 124.2 (CH, C6), 123.0 (Cq, C2'), 121.9 (CH, C5), 120.9 (Cq, C3a), 115.2 (CH, C7), 84.6 (Cq, *t*-Bu, Boc), 52.7 (CH_3, $CO_2\underline{Me}$), 28.3 (3C, Me, *t*-Bu, Boc), 23.6 (CH_2, C3'), 12.2 (CH_3, C4'); HR-MS: *m/z* = 332.1484, calcd. for $C_{18}H_{21}NO_5$: 332.1498 $[M+H]^+$.

General Procedure for the Synthesis of Vinylogous Michael Adducts of Type 3

Preparation of *(Z)*-(3′ *S*,4′ *R*)-1-(*tert*-Butoxycarbonyl)-3-(2-methoxycarbonyl-3-methyl-5-nitro-4-phenyl pentan-2-ylidene)-indolin-2-one (3ba)

To a solution of oxindole (*E*)-**1b** (100 mg, 0.3 mmol, 1.5 equiv) in toluene (2 mL) at r.t., *trans*-*β*-nitrostyrene **2a** (30 mg, 0.2 mmol, 1.0 equiv) and the thiourea-catalyst **II** (3.4 mg, 0.006 mmol, 0.03 equiv) were added in one portion. The reaction was kept under vigorous stirring at r.t. and monitored by TLC. After 16 h, the resulting solution was concentrated in vacuum and the crude was purified by silica gel flash chromatography (elution by gradient from 95/5 to 80/20 petroleum ether/EtOAc) to yield pure (*Z*)-**3ba** (99 mg) as a light yellow resin and (*E*)-**3ba** (6.7 mg, 98% combined yield) as a pink-yellow resin. The *dr* (*Z/E*) of the reaction was determined to be 13:1 by ^1H NMR analysis of the crude reaction mixture.

(***Z***)-**3ba**: ^1H NMR (400 MHz, chloroform-*d*): δ 7.98 (bd, *J* = 8.2 Hz, 1H, H7), 7.72 (bd, *J* = 7.8 Hz, 1H, H4), 7.42 (m, 3H, H6, Ph), 7.34 (m, 1H, Ph), 7.28 (m, 3H, H5, Ph), 5.02 (dd, *J* = 12.8, 3.7 Hz, 1H, H5'a), 4.62 (dd, *J* = 12.8, 11.3 Hz, 1H, H5'b), 4.04 (s, 3H, CO_2Me), 3.78 (dq, *J* = 11.3, 6.6 Hz, 1H, H3'), 3.57 (ddd, *J* = 11.3, 11.3, 3.0 Hz, 1H, H4'), 1.66 (s, 9H, *t*-Bu, Boc), 1.10 (d, *J* = 6.6 Hz, 3H, Me); ^{13}C NMR (100 MHz, chloroform-*d*): δ 167.7 (Cq, C2), 164.0 (Cq, CO_2Me), 148.9 (Cq, Boc), 146.5 (Cq, C3 or C7a), 140.9 (Cq, C7a or C3), 137.5 (Cq, Ph), 131.1 (CH, C6), 129.4 (2C, CH, Ph), 128.5 (CH, Ph), 128.2 (2C, CH, Ph), 125.4 (Cq, C2), 124.7 (CH, C5), 123.7 (CH, C4), 120.7 (Cq, C3a), 116.0 (CH, C7), 85.1 (Cq, *t*-Bu, Boc), 79.1 (CH_2, C5), 53.2 (CH_3, CO_2Me), 48.4 (CH, C4), 38.1 (CH, C3), 28.2 (3C, CH_3, *t*-Bu, Boc), 17.3 (CH_3, Me); HR-MS: *m/z* = 481.1961, calcd. for $C_{26}H_{28}N_2O_7$: 481.1975 $[M+H]^+$; $[\alpha]_D^{20}$=+124.0 (c 1.0, $CHCl_3$); chiral HPLC (Lux Amylose1, 90/10 Hexane/Ethanol, 1.0 mL/min, 254 nm): R*t* 5.84 min (minor), 6.43 min (major) (99.9:0.1 *er*).

Crystal Data

CCDC 1561942 contains the supplementary crystallographic data for (*Z*)-**3bb**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information

All synthetic procedures, characterization data, DFT calculations, copies of NMR spectra, and chiral HPLC chromatograms are presented in the Supporting Information

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[11] The "*captodative effect*" refers to the effect on stability of a carbon-centered radical by the combined action of electron-withdrawing (capto-) and electron-releasing (-dative) substituents attached to the radical center. In this work we apply this concept to dienolates **1'** featuring a C-γ site that in principle may assume a double connotation as either an electrophilic or nucleophilic site. For a comprehensive review on captodative aminoalkenes see: A. Y. Rulev, *Russ. Chem. Rev.* **2002**, *71*, 195-221, and references therein.

[12] Similar cinchona alkaloid-thiourea mediated *Z/E* isomerizations have been previously observed on nonsymmetric 3-alkylidene pronucleophiles. See *Ref.* 5c.

[13] Based on this result, all *ent*-(*Z*)-**3** adducts (necessary standard compounds for the evaluation of the *ee*% of the corresponding adducts (*Z*)-**3** by chiral HPLC), were usefully prepared by running the reaction under the conditions reported in Table 1, entry 12.

[14] For related works describing the influence of nitrogen appendages on the reactivity and selectivity of several heterocyclic vinylogous and hypervinylogous nucleophiles, see: a) C. Curti, A. Sartori, L. Battistini, N. Brindani, G. Rassu, G. Pelosi, A. Lodola, M. Mor, G. Casiraghi, F. Zanardi, *Chem. Eur. J.* **2015**, *21*, 6433-6442; b) C. Curti, B. Ranieri, L. Battistini, G. Rassu, V. Zambrano, G. Pelosi, G. Casiraghi, F. Zanardi, *Adv. Synth. Catal.* **2010**, *352*, 2011-2022.

[15] On these bases, furyl derivative **3bf** and β-adduct **3bj** feature a 4'*S* stereocenter instead of 4'*R*, due to CIP priority rules.

[16] For a recent review on the stereoselective synthesis of quaternary proline analogues, see: M. I. Calaza, C. Cativiela, *Eur. J. Org. Chem.* **2008**, 3427-3448.

[17] Interestingly, this tetracyclic derivative proved to be quite stable at r.t., and every effort to promote a rearomatization of the indole ring under acidic or basic conditions failed.

[18] a) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119-125; b) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151-13160.

[19] The peculiar role exerted by the catalyst in controlling the *s-trans* conformation of the dienolate in the transition state was also confirmed by several control experiments, in which Et_3N-promoted VMcR between (*E*)- and (*Z*)-**1b** and **2b**, without the assistance of the dual cinchona-thiourea catalyst, afforded the corresponding adduct with an inverted *E* selectivity (See Table S1 in the Supporting Information).

[20] The calculations were performed at the M06-2X/def2-TZVPP-IEFPCM(toluene)//M06-2X/6-31G(d) level of theory, using Gaussian 09 (see Supporting Information): a) J.-L. Zhu, Y. Zhang, C. Liu, A.-M. Zheng, W. Wang,

J. Org. Chem. **2012**, *77*, 9813–9825; b) M. N. Grayson, K. N. Houk, *J. Am. Chem. Soc.* **2016**, *138*, 9041−9044.

[21] The conformational preferences of the thiourea catalyst **II** by rotation about its C8−C9 and C9−C4' single bonds were also studied. It was found that open conformers (C8−C9 bond rotamers) were strongly favoured with respect to the closed ones, in accordance to what recently reported. See: A. Sengupta, R. B. Sunoj, *J. Org. Chem.* **2012**, *77*, 10525–10536. Moreover, *anti*-open conformer and *syn*-open conformers (C9−C4' bond rotamers) were similar in energy, but the *anti*-open arrangement causes less steric hindrance in the region where the reactions are supposed to occur, so only the *anti*-open conformer of the catalyst was considered for further calculations. See also *Ref.* 20b

[22] In addition to the reported computational analysis, the *Z*-geometry of the exocyclic double bond within **1a'** resulted in analogy with a *N*-Boc dienolsilane congener (*Z*)-**20** (not shown) obtained as a single isomer from isopropyl ester (*E*)-**1h** and whose configuration was certified by 2D-NOESY NMR analyses. See the Supporting Information for details.

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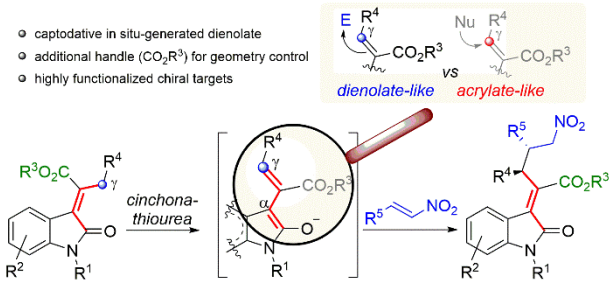
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