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Direct Regio-, Diastereo-, and Enantioselective Vinylogous Michael Addition of Prochiral 3-Alkylideneoxindoles to Nitroolefins

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Abstract: 3-Alkylidene-2-oxindoles represent a simple, yet enabling subfamily of indole alkaloids, and their ability to react as electron-poor acceptors has largely been investigated. In contrast, their utility as pronucleophilic synthons remains elusive. In this context, the present article describes the successful execution of the direct, organocatalytic asymmetric Michael addition of prochiral 3-alkylideneoxindoles to nitroolefins. A variety of γ-substituted alkylideneoxindoles carrying two stereocenters at both the γ- and δ-carbon sites was assembled with excellent stereoselectivity and without olefin isomerization or stereochemical ablation.

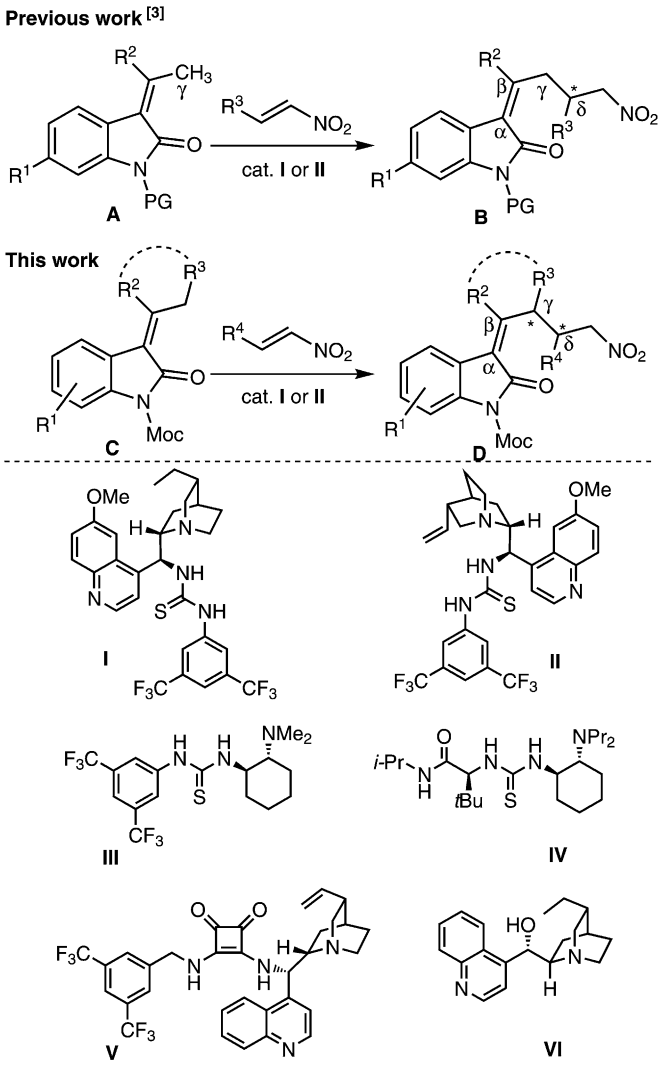
Keywords: asymmetric catalysis; *Cinchona* alkaloids; nitroolefins; organocatalysis; oxindoles; vinylogous Michael addition

Vinylogy and reactions inspired by this principle[1] are rapidly growing research themes that have significantly widened the organic synthesis landscape over the last decades.[2] In this context, our laboratory has recently described the direct regio- and enantioselective vinylogous Michael addition of β-substituted alkylideneoxindoles to prostereogenic nitroalkenes, a protocol that led to almost enantiopure γ-substituted nitro adducts bearing a δ-carbon stereocenter (compounds **B** in Scheme 1).[3] The key advance enabling this remarkable transformation was the use of the *Cinchona* alkaloid thiourea catalyst **I** (or **II**), a dual system where a Brønsted base and a proton donor moiety synergistically conspire to activate both the donor and acceptor reaction components.[4]

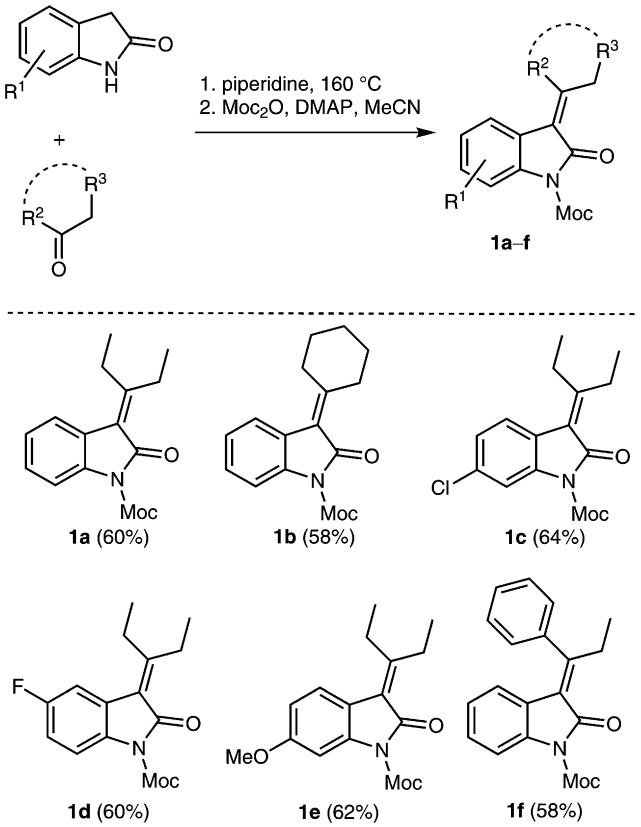
Continuing on this theme, we questioned whether this organocatalytic conjugate addition might be extended to the addition of 3-alkylideneoxindoles having a prostereogenic site at the γ-position, which could potentially proceed by an enantio- and diastereoselective process to deliver nitro adducts carrying two vicinal stereocenters at both the γ- and δ-positions (compounds **D** in Scheme 1). Herein we describe the first example of this transformation where indolinones of type **C** provide adducts **D** efficiently, with perfect regio- and geometry control and with outstanding levels of enantioselectivity and good diastereoselectivity.

We initiated our investigations by synthesizing a set of pronucleophilic oxindole candidates varying in shape and substitution (Scheme 2). The scaffold diversity encompassed "symmetrical" *N*-methoxycarbonyl-protected oxindoles **1a** and **1b**, benzo-ring substituted chloro, fluoro, and methoxy compounds **1c**, **1d**, and **1e**, as well as an "unsymmetrical" *E*-configured representative **1f**. From a synthetic point of view, it is noteworthy that these olefinic oxindoles are very stable compounds, which are readily synthesized from the parent oxindoles in two steps and in good yields (for procedures, see the Supporting Information).

The addition of 3-pentylideneindolinone **1a** to *trans*-β-nitrostyrene **2a** was selected as the model reaction to evaluate the ability of the dihydroquinine-derived catalyst **I** to control both the preference of the substitution site (γ *vs.* α) and the product topology



Scheme 1. Previous and current asymmetric vinylogous Michael approaches of oxindole pronucleophiles **A** and **C**.



Scheme 2. Pronucleophilic oxindole substrates used in this study. Moc = methoxycarbonyl.

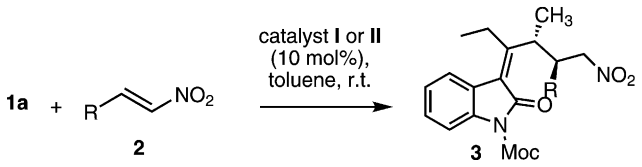
(*Z vs. E*; *anti vs. syn*), as well as the efficiency of the chirality transmittal from the catalyst to the product. Gratifyingly, the expected product **3aa** could be obtained in 97% isolated yield, with exclusive γ-site- and *Z*-selectivities, and with excellent stereocontrol after brief optimization studies [95:5 *anti/syn dr*; 99.9:0.1 *er* for the major (*R*,*R*)-configured diastereoisomer, Table 1, entry 1]. As expected, quasi-enantiomeric catalyst **II** derived from quinidine showed an equal reactivity profile and furnished the opposite enantiomer of **3aa** with quite similar *dr* and *er* values.

To clarify the role of the catalyst structure, we also checked, in addition to **I** and **II**, bifunctional thioureas **III** and **IV** as well as *Cinchona*-squaramide **V** and dihydroquinidine **VI**. Catalysts **IV**, **V**, and **VI** proved totally unproductive, while Takemoto's catalyst **III** resulted in very low conversion with only trace amount of adduct **3aa** recovered. We then performed a solvent screening, and the best results in terms of balance between yield and selectivity were obtained using toluene at 0.2 M substrate concentration. The transformation was productive in several polar and apolar solvents such as CH_2Cl_2, THF, Et_2O, and MeCN, but the stereochemical outcome was substantially less performing as compared to reactions conducted in toluene (see the Supporting Information for further details, Table S1).

With these results established, we next explored the generality of the reaction with regards to variation of the olefin acceptor using **1a** as a probe. All reactions were completed after 24 h at room temperature (18–20 °C) and returned the expected adducts in very good isolated yields, with excellent levels of γ-site selectivity, enantioselectivity, and diastereoselectivity with respect to the geometry of the exocyclic olefin linkage (Table 1).

Good *anti:syn* diastereoselectivities were also attained, favouring the (*R,R*)-configured isomers. In particular, for the use of β-aryl nitroolefins, the position and the electronic properties of the aromatic ring substituent did not alter the reaction performance significantly and, regardless of their nature, be the neutral, electron-withdrawing, or electron-donating groups, good yields and excellent enantioselectivities were uniformly attained. Nitroolefins bearing elec-

Table 1. Generality of the reaction with respect to the nitroolefin acceptor.[a]



Entry	R (**2**)	Product (**3**)	Yield [%][b]	*dr*[c]	*er*[d,e]
1	Ph (**2a**)	**3aa**	97	95:5	99.9:0.1 (98.5:1.5)
2	4-BrC_6H_4 (**2b**)	**3ab**	88	80:20	99.9:0.1 (98.5:0.5)
3	4-$MeOC_6H_4$ (**2c**)	**3ac**	98	80:20	99.9:0.1 (97.0:3.0)
4	2-FC_6H_4 (**2d**)	**3ad**	92	82:18	99.0:1.0 (98.5:1.5)
5	C_6F_5 (**2e**)	**3ae**	96	78:22	99.5:0.5[f] (98.5:1.5)[f]
6	4-MeC_6H_4 (**2f**)	**3af**	97	75:25	99.9:0.1 (99.7:0.3)
7	3,5-$(MeO)_2C_6H_3$ (**2g**)	**3ag**	94	80:20	99.0:1.0 (98.0:2.0)
8	2-furyl (**2h**)	**3ah**	97	88:12	99.0:1.0 (83.0:17.0)

[a] Unless otherwise specified, reactions were carried out using oxindole **1a** (0.19 mmol) and nitroolefins **2a–h** (0.19 mmol) in toluene (950 μL) with 10 mol% catalyst **I** (or **II**) at room temperature (18–20 °C) for 24 h.
[b] Yield of isolated **3** after chromatography.
[c] The *anti:syn* diastereomeric ratio was determined by integration of key signals in the ^{1}H NMR spectra of the reaction crude. No *E*-configured isomers or α-addition adducts were detected.
[d] Values in parentheses refer to reactions with catalyst **II**, with *S*,*S*-isomers as the major products.
[e] Determined by HPLC analysis using a stationary phase chiral column, for the major isomers.
[f] Determined on *N*-deprotected products.

tron-rich heteroaromatic groups, like 2-furyl derivative **2h**, also afforded the desired product with superb enantio- and geometry control and with a 88:12 *anti:syn* isomeric ratio. Interestingly, the reaction of **1a** with **2a** proved to be equally reliable on a 1.0 mmol scale, returning the product **3aa** in 98% yield, 95:5 *dr*, and 99.9:0.1 *er*.

Since the reactions could not be initiated by achiral amine catalysts, like Et_3N, DABCO, or pyrrolidine, all reactions were performed with equal success with both catalysts **I** and **II**, to obtain racemates of the products for use in the *er* measurements.

Disappointingly, alkyl nitroolefins such as β-cyclohexyl- and β-*n*-hexyl-1-nitroethenes, which have a modest repute as Michael acceptors under similar reaction conditions, did not give any clean conversion, even when forcing conditions or different catalysts **III**–**VI** were employed.[5]

Variation of the alkylidene donor was then surveyed in reactions with olefin **2a** (Figure 1). The presence of different indole substrates was compatible with this vinylogous reaction. Indolinones **1a** and **1b**, as well as benzo-ring substituted congeners **1c**, **1d**, and **1e** were found to be competent substrates, and returned the expected γ-substituted Michael adducts **3aa** and **3ba**, as well as **3ca**, **3da**, and **3ea** in high yields, with moderate to good *dr* and excellent *er* values, and with the same sense of stereoinduction as dictated by the *Cinchona* catalyst employed.

Alkylidene derivative **1f** bearing a phenyl group at the β-position could also be productively engaged in this asymmetric transformation, and afforded the corresponding adduct **3fa** with good results in terms of

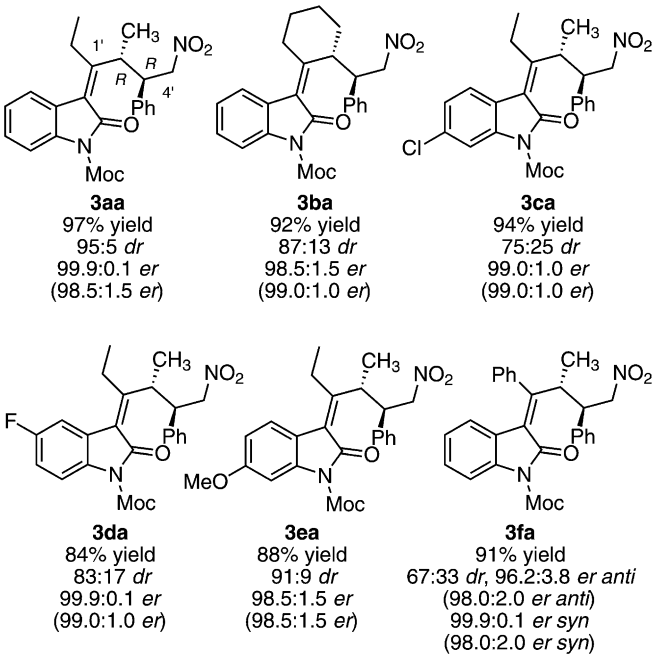


Figure 1. Products of the reactions with various indole substrates. Reactions were performed with 10 mol% catalyst **I** (or **II**). For all products site-selectivity (γ/α) was >99:1 and the geometry selectivity (*Z*/*E* or *E*/*Z*) was >99:1. Values in parentheses (*er*) refer to reactions with catalyst **II**, with *S*,*S*-isomers as the major products. For conditions and details, see Table 1 and the Supporting Information.

yield, enantioselectivity, and geometry control, albeit with modest diastereoselectivity (*ca.* 2:1 *anti/syn* ratio). The diminished diastereoselectivity for unsymmetrical oxindole **1f** could likely be ascribed to poor geometry control during the generation of the active dienolate by means of the catalyst employed, with both *Z*,*Z*- and *Z*,*E*-disposed dienolates competitively involved. That is, the ratio between the *Z*,*Z*- and *Z*,*E* dienolates would determine the *anti/syn* ratio of the products. As subjecting the major and minor stereoisomers of **3fa** to the reaction conditions did not result in any interconversion or epimerization, the low *dr* observed with this oxindole cannot be ascribed to thermodynamic equilibration of the products.

Protection-free NH oxindoles, as well as oxindoles having alkyl, allyl, or benzyl groups on the nitrogen did not exhibit any sign of reactivity toward the model substrates; and this suggests that a proper *N*-substituent able to engender a supplementary anchorage to the catalyst through hydrogen bonding is crucial for these organocatalytic conditions (*vide infra*).[6]

The relative and absolute configuration of **3ab**, bearing a heavy atom substituent, was unambiguously determined as 3*Z*,2′*R*,3′*R*[7] by resonant-scattering X-ray crystallographic analysis (Figure 2, *top*),[8] while that of *ent*-**3ac**, which was obtained with catalyst **II**, revealed the same 3*Z*-2′,3′-*anti* topology and, arguably, a 2′*S*,3′*S* absolute configuration (Figure 2, *bottom*).[9,10] The geometry of the exocyclic olefin linkages in both major and minor isomers was further corroborated by 2D NOESY NMR experiments (see Figure S3 in the Supporting Information). Assuming a uniform stereochemical outcome of the reactions, the configuration of the other Michael adducts in Table 1 and Figure 1 were assigned by analogy.

To explain the stereochemical outcome of this vinylogous addition, a plausible mechanistic pathway was proposed, taking into account the observed stereoselectivity of the reactions and capitalizing on previous proposals for *Cinchona* catalysts-promoted activation models, as well as theoretical calculations for similar transformations (Figure 3).

According to the general pathway proposed by Takemoto et al.,[4a,11] it is postulated that initial interaction of the quinuclidine base of the *Cinchona* catalyst with the oxindole pronucleophile, followed by deprotonation at the γ-methylene site, leads to the formation of the active dienolate species, which preferentially reacts in *s-cis* conformation and with a 2*Z*,1′*Z* geometry. The nucleophile is bonded to the protonated base *via* bidentate H-bonding, with both the hydroxy anion and *N*-carbamoyl groups involved. Meanwhile, the nitroalkene acceptor is recognized by the thiourea moiety of the catalyst through double H-bond interaction with its nitro functionality. In such a manner, the two reactants are independently, yet synergistically activated: the indole donor *via*

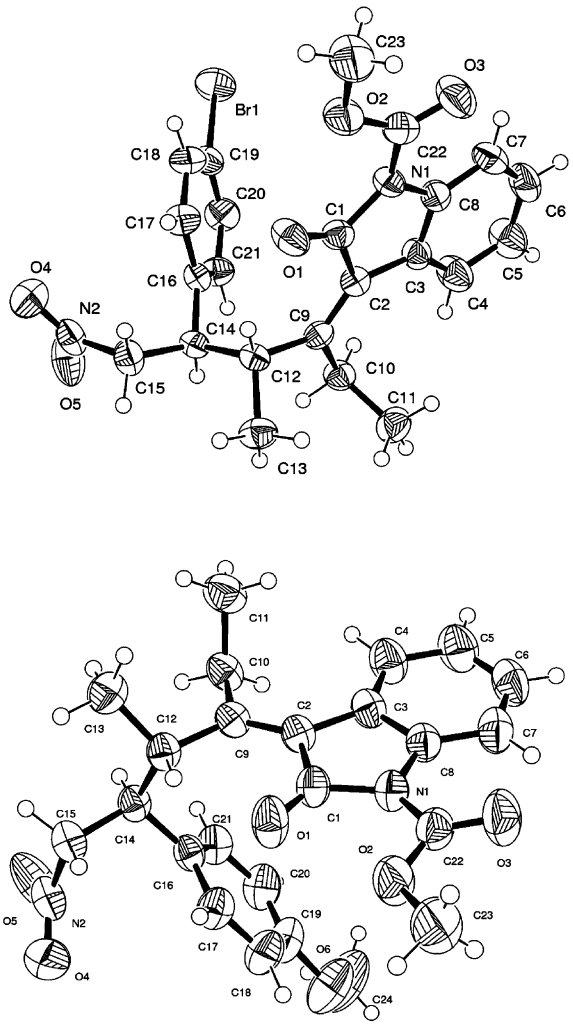


Figure 2. Relative and absolute stereochemistry of brominated product **3ab** (*top*) and relative stereochemistry of *ent*-**3ac** (*bottom*) as determined by single crystal X-ray analyses.

HOMO-raising activation and the nitroolefin acceptor *via* LUMO-lowering.[12]

Also, reactants are positioned in close spatial proximity within a chiral pocket, and this facilitates the vinylogous addition step along the *Si,Re*-face trajectory, through which (3*Z*,2′*R*,3′*R*)-configured (R^2 = alkyl), or (3*E*,2′*R*,3′*R*)-configured (R^2 = aryl)[13] oxindole products preferentially form. Moreover, the preferred 1′*Z*-geometry of the dienolate, which dictates the 2′,3′-*anti*-diastereoselectivity of the products, is likely due to a favourable steric disposition of the R^2 and R^3 substituents, as opposed to steric congestion of 1′*E*-configured dienolates (see Figure 3). This behaviour is in keeping with the experimental results.

Alternative dual activation channels cannot, however, in principle be excluded. As recently proposed by Wang et al. for similar *Cinchona*-thiourea-catalyzed transformations,[14] nucleophile activation is the result of dual H-bonding to both the protonated quinucli-

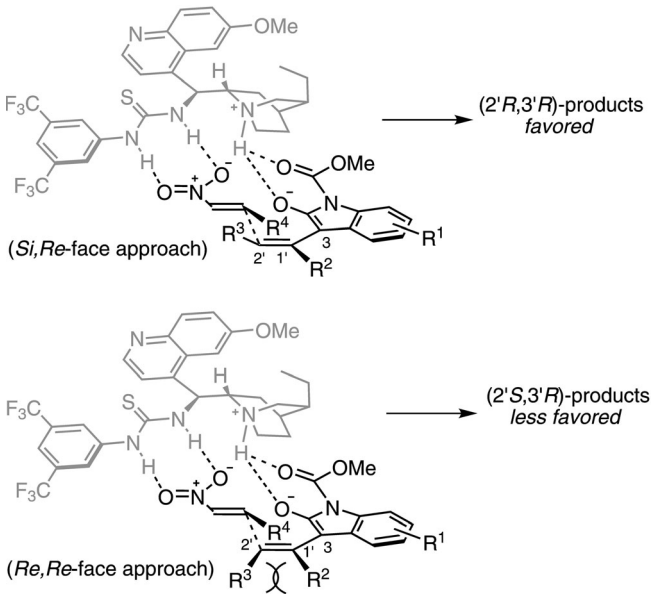


Figure 3. Possible pathways for the dual activation mechanism on the formation of the major and minor (2′*R*,3′*R*)- and (2′*S*,3′*R*)-configured diastereomeric products. The *s-cis* orientation of the indole dienolate dictates the geometry of the olefin linkage of the oxindole products. Simple diastereoselection (*anti* vs *syn*) is governed by the *Z/E* configuration of the remote olefin of the reacting dienolate. Facial selectivity is imparted by the catalyst environment.

dine nitrogen of the catalyst and one NH of the thiourea moiety, while the other thiourea NH activates the nitroolefin *via* bifurcate H-bonding. According to the proposal of Pápai[15] and Zhong[16] instead, the nucleophile is activated by the thiourea group of the catalyst, while the protonated quinuclidine nitrogen engenders a bifurcate H-bonding with the nitroolefin. In truth, an exact understanding of the mechanism of the present vinylogous transformation *via* DFT calculations and NMR determinations is desirable, and this issue is a current research theme in our laboratories.

In summary, to complement our previous results with methyl-substituted alkylideneoxindoles,[3] we have herein provided a limpid testimony to the unique capability of enolizable 3-alkylideneoxindoles to serve as pronucleophiles for the direct, asymmetric vinylogous Michael addition to nitroolefins. With prostereogenic oxindole substrates and employing the consecrated bifunctional *Cinchona* alkaloid-based thiourea catalysts, rigorous control of the regiochemistry and product geometry, as well as the stereochemistry in the addition reaction have been realized, where simultaneous discrimination of both the enantiofaces of the vinylogous enolate and the prochiral nitroalkene could be attained. We expect that the novel, functionality-rich oxindole products emerging from these studies will be valuable for those researchers involved in organic synthesis and pharmaceutical chemistry disciplines.

Experimental Section

General Comments

Survey of catalysts and conditions, compound characterization data of products **1** and **3**, HPLC traces, stereochemical assessment, and copies of ^{1}H and ^{13}C NMR spectra are given in the Supporting Information.

Representative Procedure. Synthesis of (*Z*)-1-Methoxycarbonyl-3-[(4*R*,5*R*)-4-methyl-6-nitro-5-phenylhexan-3-ylidene)indolin-2-one (3aa)

To a solution of oxindole **1a** (50 mg, 0.19 mmol) and nitrostyrene **2a** (28 mg, 0.19 mmol) in toluene (950 μL) at room temperature (18–20 °C), was added thiourea-catalyst **I** (11 mg, 0.019 mmol). The reaction mixture was kept under vigorous stirring at room temperature for 24 h. The reaction mixture was then concentrated in vacuum and the crude material was purified by silica gel flash chromatography (80:20 petroleum ether/EtOAc) to afford pure (3*Z*,4′*R*,5′*R*)-**3aa** as white crystals; yield: 71 mg (92%) ; mp 166–167 °C; $[\alpha]_D^{20}$: +249.2 (*c* 1.0, $CHCl_3$). Chiral HPLC (Chiralcel OD-H, hexane/EtOH 90:10, 1.0 mL min^{-1}, 254 nm): R_t 11.16 min (99.9:0.1 *er*).

Minor isomer (3*Z*,4′*S*,5′*R*)-**3aa′** was obtained as a colorless glass; yield: 3.9 mg (5%); $[\alpha]_D^{20}$: +72.4 (*c* 0.9, $CHCl_3$). Chiral HPLC (Chiralcel OD-H, hexane/EtOH 90:10, 1.0 mL min^{-1}, 254 nm); R_t 10.11 min (99.1:0.9 *er*).

Acknowledgements

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[8] For the *R,R*-configured enantiomer **3ab**, Flack parameter = 0.004(7).

[9] Based on the employed catalyst and chiro-optical measurements, the structure of *ent*-**3ac** in Figure 2 was drawn in an *S,S* configuration; however, lacking heavy atoms, this assignment, though reasonable, is not impeccable.

[10] CCDC 923455 [(*Z,R,R*)-**3ab**] and CCDC 923456 [(*Z,S,S*)-*ent*-**3ac**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K.; fax: (+ 44)-1223-336-033; or deposit@ccdc.cam.ac.uk].

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