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Light-Enabled Enantiodivergence: Stereospecific Reduction of Activated Alkenes Using a Single Organocatalyst Enantiomer

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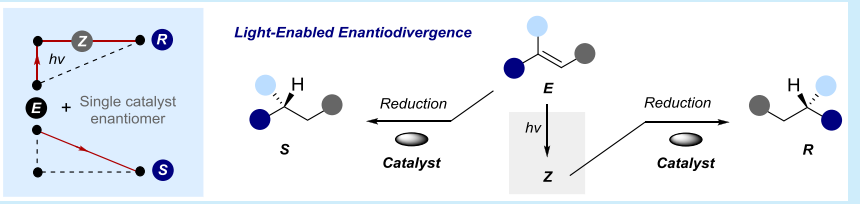
Supporting Information



ABSTRACT: Light-enabled enantiodivergence is demonstrated in which the alkene substrate configuration is manipulated (*E* → *Z*) prior to organocatalytic reduction with a chiral thiourea and Hantszsch ester. This allows stereodivergent reduction to be regulated at the substrate level with high fidelity and mitigates the need for a second, enantiomeric catalyst (up to 93:07 and 95:5 *er*). The synthetic utility of this strategy has been demonstrated in the synthesis of the weight-loss drug (*R*)-Lorcaserin (Belviq) and a potent AMPA modulator.

Enantioselective, catalytic hydrogenation of π-bonds remains an expansive strategy to access saturated, chiral building blocks from inexpensive feedstocks.[1] The importance of this technology in an industrial context remains a powerful impetus to explore new conceptual avenues to generate both chiral antipodes in an efficient, cost-effective manner.[2] Catalysis-based approaches are frequently reliant on chiral pool-derived stereoregulatory elements to encode enantioselection;[3] hence, availability is a precondition of enantiodivergence (Figure 1A). Often the *unnatural* enantiomer is prohibitively expensive or may have to be synthesized *de novo*, a persistent consideration for asymmetric catalysis in a broader sense.[4] Consequently, stereodivergent strategies[5,6] to access both products using a single catalyst enantiomer would be of significance, if the intrinsic directionality could be inverted by an external, physical stimulus such as light,[7] heat, or mechanical force. To validate this approach to alkene hydrogenation, it was envisaged that the directionality might be regulated at the alkene substrate level utilizing light. It was reasoned that *E* → *Z* geometric isomerization would provide a platform for divergence, when coupled to a stereospecific reduction of the alkene:[8,9] This would facilitate 2D to 3D translation of the stereochemical information. The renaissance of alkene photoisomerization,[10,11] together with advances in the hydrogenation of substituted nitrostyrenes[12] via organocatalytic strategies[13] provides a platform for concept validation (Figure 1B and C). This enantiodivergent, catalytic route to β-chiral amines conceptually complements the stereoconvergent, chemoenzymatic reduction of 2-phenyl maleic esters based on photocatalytic isomerization reported by Hartwig and coworkers.[14]

To explore the viability of an enantiodivergent reduction using light as the external stimulus, an efficient, catalyst-free isomerization of ***E*-1** was necessary to provide access to ***Z*-1** (Table 1). The ubiquity of *E*-α-substituted nitrostyrenes as precursors for asymmetric organocatalysis, and as masked β-chiral amines, has resulted in a rich variety of methods for their preparation. In contrast, *Z*-isomers continue to present a synthetic challenge. To address this, absorption spectra of both isomers (Table 1, insert) were measured, indicating that selective excitation of the *E*-isomer may be achievable, thereby generating the *Z*-isomer without an external photosensitizer. Gratifyingly, irradiation at λ = 402 nm in acetonitrile afforded ***Z*-1** with good selectivity (*Z*/*E* 89:11), albeit, with low yield due to competing degradation (Table 1, entry 1).

Changes to the reaction media were generally detrimental to selectivity, and only modest improvements to yield were observed (entries 2−4). A screen of concentration and reaction time (entries 5−9), followed by an increase in scale (entry 10) and reduction in reaction time, furnished ***Z*-1** in a synthetically useful yield and with a *Z*/*E* ratio of 92:08 (entry 11). Further improvement by the introduction of common photosensitizers was not possible (see Supporting Information). To that end, scope exploration was conducted on a 0.5 mmol scale (1.0 M in acetonitrile) for 7 h. To explore the scope of this photocatalyst-free isomerization of *E*-α-substituted nitrostyrenes, a series of derivatives were investigated (Figure 2).

In general, *para*-substituents were well tolerated irrespective of their electronic effect (***Z*-2**−***Z*-6**, up to *Z*:*E* 92:08), as were the *ortho*- and *meta*-derivatives ***Z*-7**−***Z*-9** (up to *Z*/*E* 95:05). Executing the reaction on a 2.5 mmol scale furnished *Z*-**9** in 82% isolated yield as a single geometric isomer (see Supporting Information). As a control series, the α-methyl

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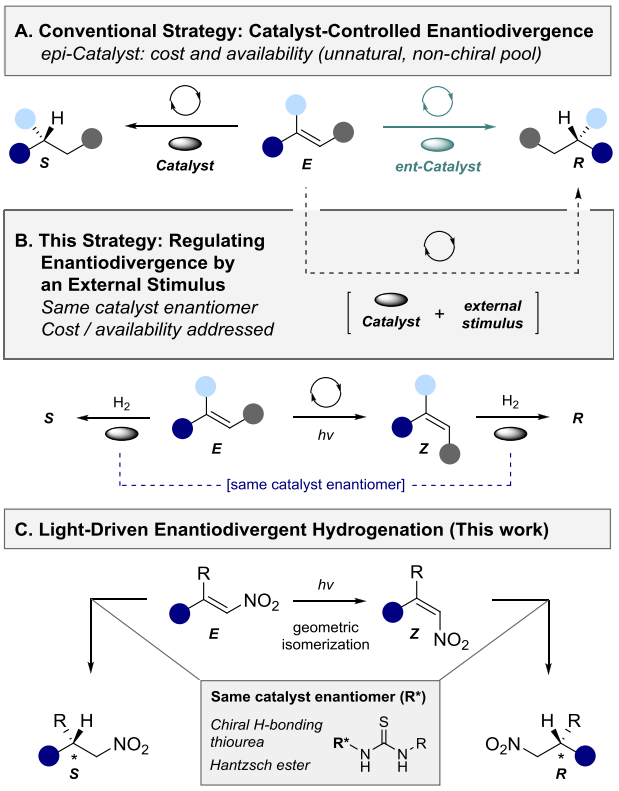


Figure 1. Catalysis-based strategies for enantiodivergence and a conceptual overview of this study.

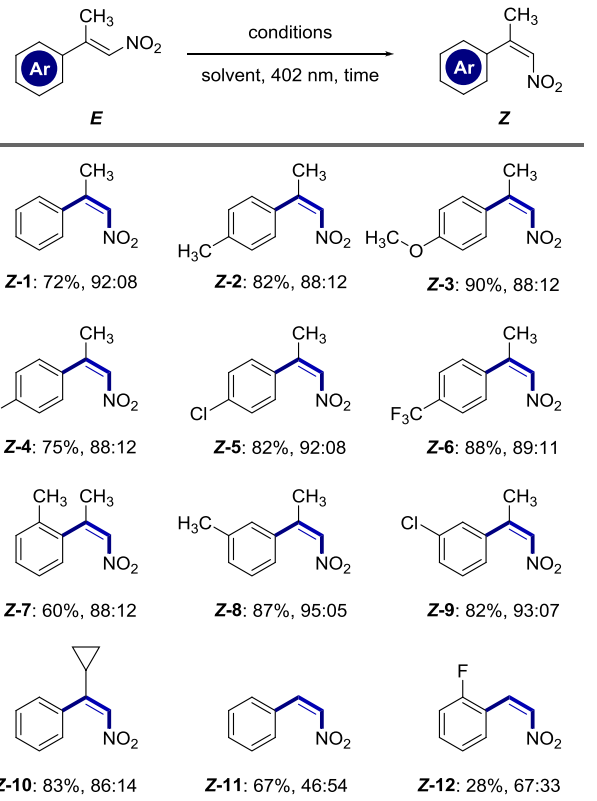
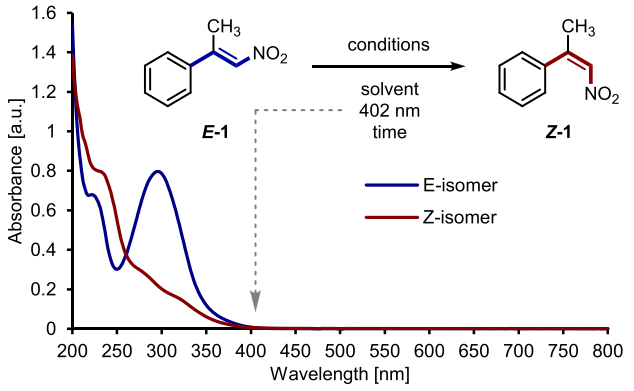


Figure 2. Exploring the scope of the isomerization. Reaction conditions: Substrate (0.5 mmol), MeCN (0.5 mL), 402 nm, 7 h.

Table 1. Photo-isomerization of *E*-1 to *Z*-1 Optimization



entry	solvent	scale (mmol)	molarity (M)	time (h)	yield (%)	Z/E^a
1	MeCN	0.2	0.1	16	33	89:11
2	1,4-dioxane	0.2	0.1	16	25	78:22
3	toluene	0.2	0.1	16	29	57:43
4	*c*-hexane	0.2	0.1	16	38	85:15
5	MeCN	0.2	0.1	4	60	80:20
6	MeCN	0.2	0.1	6	43	85:15
7	MeCN	0.2	0.2	16	34	86:14
8	MeCN	0.2	0.5	16	39	90:10
9	MeCN	0.2	1.0	16	47	89:11
10	MeCN	1.0	0.2	16	69	90:10
11	MeCN	0.5	1.0	7	72	92:08

[a]Determined by ^{1}H NMR spectroscopy.

group substituted by a cyclopropyl ring was investigated (**10**), together with *trans*-nitrostyrene (**11**). Although the latter is of no relevance to the subsequent asymmetric hydrogenation, it underscores the role of the methyl group in inducing 1,3-allylic strain in the α-substituted nitrostyrenes. This prevents reconjugation of the π-system chromophore and ensures directionality.[11d] Indeed, this manifestation of 1,3-allylic strain is evident from the subtle introduction of an *ortho*-fluoro substituent (***Z*-12**, Z/E = 67:33 versus 46:54). Having devised conditions for the photoisomerization of nitrostyrenes, organocatalytic hydrogenation strategies based on chiral thioureas derived from a natural amino acid were explored (Figure 3). The enantioselective hydrogenation of *E*-nitrostyrenes reported by List and co-workers using an unnatural *tert*-leucine derivative provided inspiration.[13a] However, to validate our concept of only requiring one (natural) enantiomer of the catalyst, a system based on inexpensive L-valine was conceived. Moreover, the diethylamino scaffold was replaced by a dimethylamino motif due to the negligible impact that these groups have on catalytic efficiency. Gratifyingly, these alterations to generate catalyst **A** had little impact on reaction efficiency with substrate ***E*-1** generating the *S*-configured product ***S*-13** (96% isolated yield and *er* 04:96 versus 97% conversion and *er* 02:98. See SI for full details).

Exposing ***Z*-1** to identical reaction conditions with catalyst **A** led to a marginal decrease in *er* (84:16), but the sense of enantioinduction was inverted to favor the *R*-enantiomer ***R*-13**. While these data constitute preliminary validation of concept, a slight matched−mismatched scenario was apparent. To improve the enantioselectivity of the *R*-series, further catalyst optimization was performed resulting in catalyst **B** (full details in the SI). Gratifyingly, stereospecific reduction was preserved, this time enhancing the yield (94%) and enantioselectivity to 93:07 ***R*/*S*-13**). The remainder of the scope was performed in

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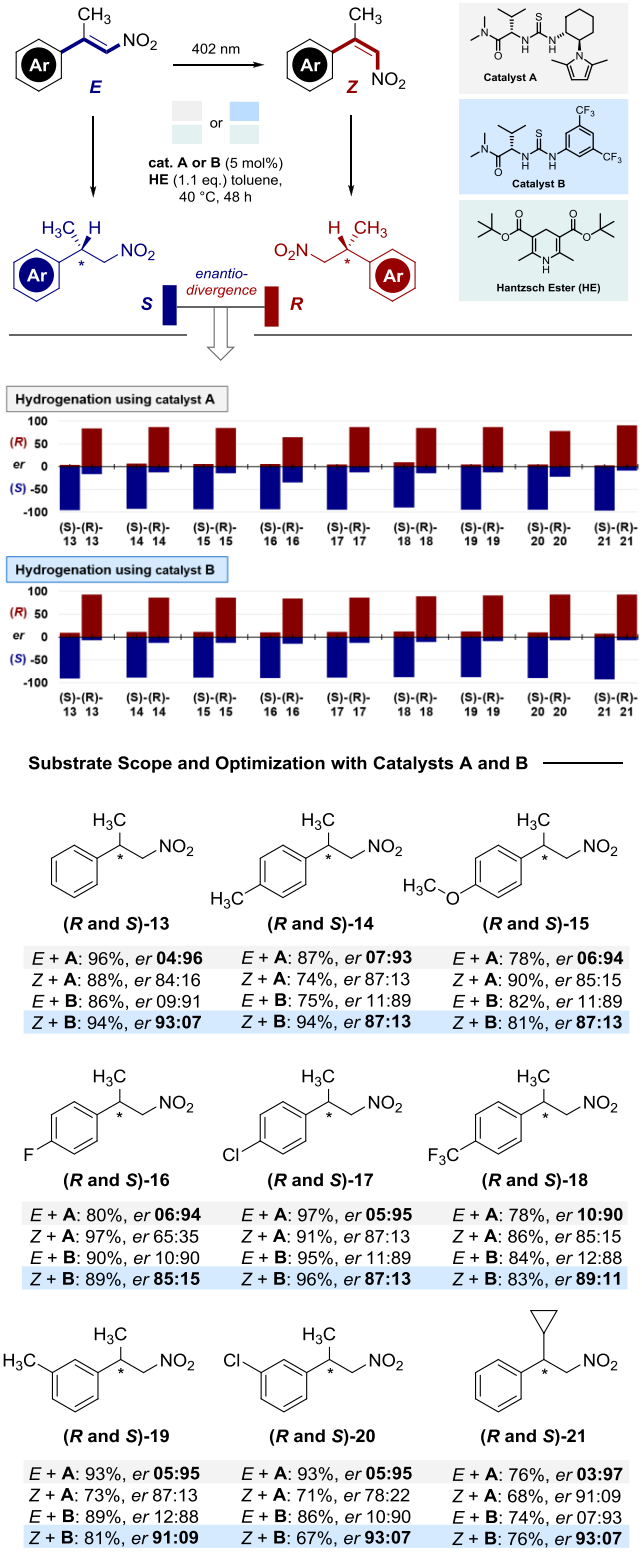

Figure 3. Establishing the scope of the stereospecific, enantiodivergent reduction of activated alkenes. Reactions conditions: (*E*) or (*Z*)-substrate (0.20 mmol, 1.0 equiv), **A** or **B** (0.01 mmol, 5 mol %), **HE** (0.22 mmol, 1.1 equiv), toluene (0.33 M), 40 °C, 48 h.

duplicate with both catalysts derived from L-valine, and it was demonstrated that *E* → *S* and *Z* → *R*. For each entry (compounds **13**−**21**) a series of four experiments were conducted to demonstrate enantiodivergency with these two discrete catalyst systems. From the perspective of optimization, it may be concluded that the highest levels of enantioselectivity with the *E*-substrates can generally be obtained with catalyst **A**, whereas, for *Z*-configured alkenes, catalyst **B** is optimum. However, exceptions were found with the *p*-CH_3 and *p*-Cl substituted substrates (**14** and **17**), whereby catalyst **A** gave similar or marginally higher *er* values for the *Z*-substrate.

Since the reduced products belong to a venerable class of *β*-chiral amine precursors, isomers ***E*-5** and ***Z*-5** were independently converted to **(*S*)-17** and **(*R*)-17**, respectively (Figure 4, top). These intermediates were processed to the corresponding sulfonamides, enabling a formal total synthesis of either the (*R*,*R*)- or (*S*,*S*)-configured dimer core of positive allosteric modulators of ionotropic glutamate receptors.[15] Finally, the *m*-Cl nitrostyrene ***Z*-9** was hydrogenated with catalyst **B** to generate **(*R*)-20**. The reaction was performed on a 2 mmol scale with no drop in enantioselectivity (*er* 93:07). The product was converted to the selective 5-HT2C receptor agonist and marketed drug (*R*)-Lorcaserin (Belviq) (**24**) via a known six-step procedure (Figure 4, bottom).[16] A one-pot protocol was also conducted as a proof of concept (Figure 5)

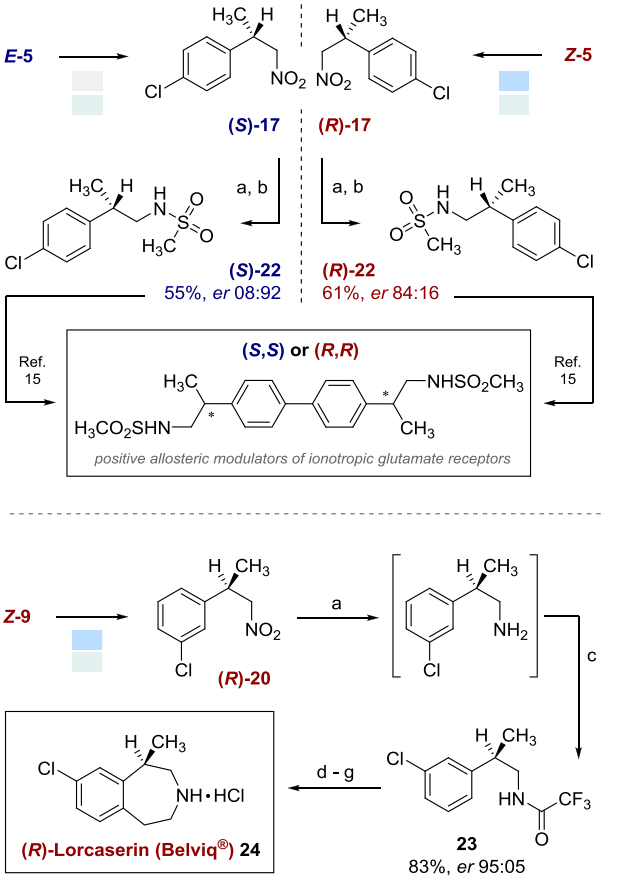

Figure 4. Application to the synthesis of selected bioactive small molecules. Reaction conditions: (a) Zn (5 equiv), AcOH (30 equiv), THF/MeOH (10:1), 0 °C−rt, 16 h; (b) NEt_3 (5.74 equiv), MsCl (1.50 equiv) CH_2Cl_2; (c) NEt_3 (1.13 equiv), TFAA (1.65 equiv), CH_2Cl_2, 0 °C−rt, 16 h, 83% (*er*: 95:05); (d) $HO(CH_2O)_nH$ (2 equiv), $AcOH/H_2SO_4$ (3:2), K_2CO_3 (3 equiv), 0 °C−rt, 16 h, 43%; (e) Boc_2O (1.1 equiv), NEt_3 (1.2 equiv), 16 h, 59% (*er* 95:05); (f) $TMSCHN_2$ (2.4 equiv), TEMPO *N*-oxoammonium BF_4 salt (1.5 equiv), CH_2Cl_2, 80 °C, 1 h, 33%; (g) $HSiEt_4$ (2 equiv), TFAA (7% v/v), HCl (30 equiv), CH_2Cl_2, rt, 2 h, 8% (*er* 81:19).

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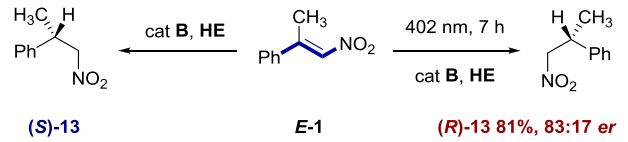

Figure 5. A one-pot enantiodivergent reduction of ***E*-1**.

thereby enabling the direct conversion of ***E*-1** to either chiral antipode. To enable this isomerization/*in situ* reduction sequence, a switch in solvent to cyclohexane was required which enabled access to ***R*-13** in 81% yield (83:17 *er*).

Light-enabled enantiodivergent hydrogenation of β-substituted nitrostyrenes using a single catalyst enantiomer derived from L-valine is disclosed. Unlike classical enantiodivergent catalysis strategies that proceed via energetically degenerate transition states, a bias exists in the diastereomeric transitions states that manifests itself in selectivity. This allows stereochemical regulation to be achieved via geometric isomerization of the substrate through an external stimulus, i.e. a photon. The need for the antipodal H-bonding catalyst derived from D-valine is mitigated, thus conferring operational simplicity and reducing catalyst preparation costs. Given the ubiquity of alkenyl substrates in asymmetric catalysis, manipulating π-bond configuration by light, prior to stereospecific functionalization, may constitute an expansive approach to enantiodivergence.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and NMR spectra (PDF). The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04263.

(PDF)

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Notes

The authors declare no competing financial interest.

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