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Organocatalytic Route to Dihydrocoumarins and Dihydroquinolinones in All Stereochemical Configurations

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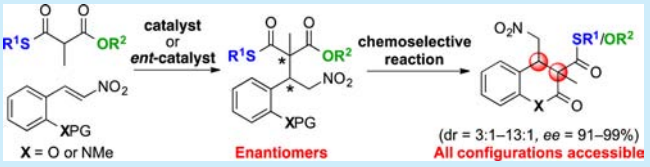
Supporting Information

ABSTRACT: A straightforward stereodivergent route to dihydrocoumarins and dihydroquinolinones based on cinchona alkaloid catalyzed addition reactions of monothiomalonates (MTMs) to functionalized nitroolefins followed by deprotection and chemoselective cyclization has been developed. The synthesis proceeds under mild conditions and yields heterocycles with adjacent quaternary and tertiary stereogenic centers in very high yields and stereoselectivities. Moreover, full control over the relative and absolute configuration is achieved by the use of (pseudo)enantiomeric catalysts and the difference in reactivity of thioester versus oxoester moieties.



Dihydrocoumarins and dihydroquinolinones are structural motives in nature that are found in numerous biologically active natural products (Figure 1).[1,2] Their stereochemistry

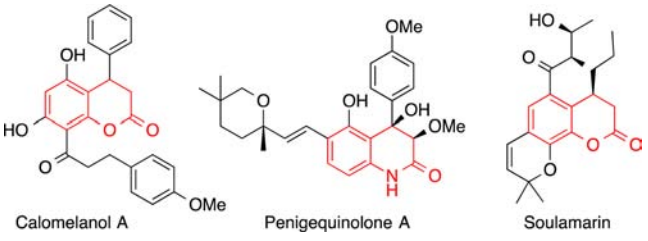


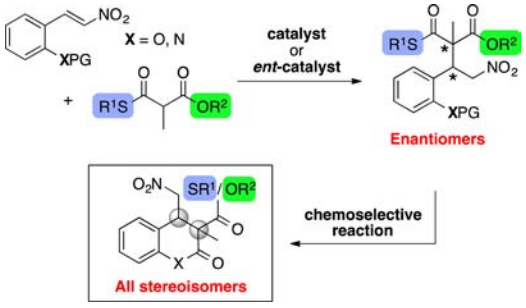
Figure 1. Examples of dihydrocoumarins and dihydroquinolinones.

varies among different derivatives and is often not yet known.[1,2] Straightforward stereoselective syntheses that allow access to dihydrocoumarins and dihydroquinolinones with different relative and absolute stereochemistries at C(3) and C(4) are therefore important.

Several stereoselective routes using transition-metal catalysts toward 3,4-disubstituted derivatives have been developed but typically provided racemic products.[3] Routes utilizing an organocatalytic key step were also developed.[4,5] These syntheses proceed often with good yields and enantioselectivities but offer access to only one specific stereoisomer. Moreover, many of them proceed via the respective hemiacetal and require an environmentally nonbenign chromium-mediated oxidation to provide the dihydrocoumarins.[5]

Recently, we showed that organocatalytic conjugate addition reactions of α-substituted monothiomalonates (MTMs) with nitroolefins or imines provide γ-nitrothioesters and β-aminothioesters, respectively, in high yields and stereoselectivities.[6,7] The synthetic utility of this method was, for example, highlighted by the stereoselective synthesis of substituted indolines.[8] We envisioned that this method should also provide facile access to chiral dihydrocoumarins and dihydroquinolinones via reaction of MTMs with *o*-hydroxy- or *o*-amino-β-nitrostyrenes followed by intramolecular cyclization (Scheme 1). We anticipated that an appropriate choice of the thio- and

Scheme 1. Stereodivergent Route to Dihydrocoumarins and Dihydroquinolinones[9]



oxoester moieties of the MTM should allow for a chemoselective reaction of either ester group with the internal nucleophile and thereby provide for access to diastereoisomers.[9] Combined with the use of (pseudo)enantiomeric catalysts, the method would enable the selective formation of dihydrocoumarins and dihydroquinolinones with all four possible configurations at the two newly generated stereocenters.[10]

We started by preparing β-nitrostyrene derivatives bearing a protected hydroxyl group in the *ortho*-position and reacted them with α-methyl MTM **1a** in the presence of cinchona alkaloid−(thio)urea catalysts under the previously established conditions.[6,11] Regardless of the protecting group on the phenolic hydroxyl group (PMB, allyl, MOM, or Ts), the desired conjugate addition products were obtained in excellent

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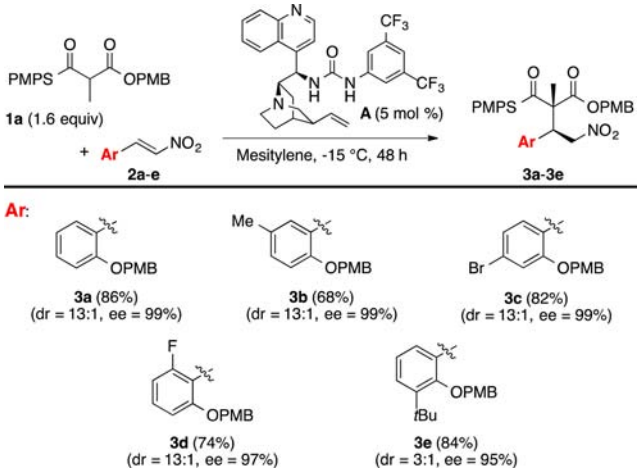
yields of >80%, enantioselectivities of 99% ee and high diastereoselectivities (≥6:1 dr) in the presence of 5 mol % of epicinchonine–urea **A** using mesitylene as solvent.[12,13] The highest diastereoselectivity of 13:1 dr was observed for the product bearing an easily removable *p*-methoxybenzyl (PMB) protecting group, which was therefore chosen for all further experiments. Reassuringly, also *o*-hydroxy-*β*-nitrostyrenes (**2a–e**) with different substitution patterns on the aromatic moiety reacted in the presence of **A** readily with MTM **1a** and afforded the desired addition products **3a–e** bearing adjacent tertiary and quaternary stereogenic centers in good yields and high stereoselectivities (Scheme 2). These results show that the

Scheme 2. 1,4-Addition Reactions between α-Methyl MTM 1a and Functionalized Nitroolefins 2a–e[a]



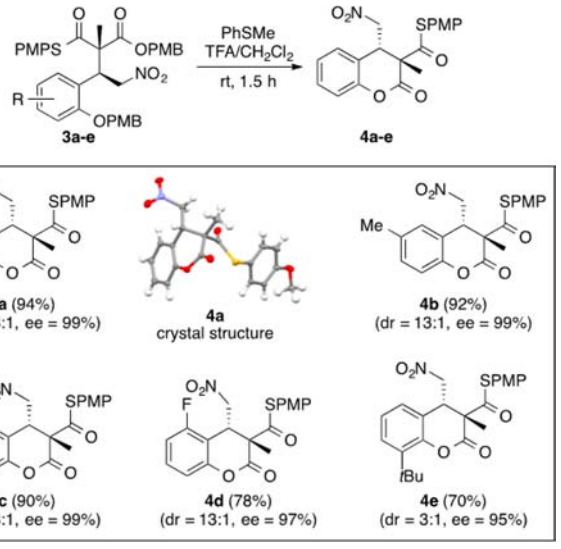
[a]Reactions were performed on a 0.2 mmol scale. Yields of isolated products. Enantioselectivities were determined by HPLC on a chiral stationary phase; dr values were determined by ^{1}H NMR of the crude product. The absolute configuration was determined by crystallization after deprotection and cyclization (see Scheme 3).

organocatalytic addition reaction between MTMs as thioester enolate equivalents and nitroolefins is robust and tolerates a broad scope of different substrates.

Next, we explored the conversion of the addition products **3a–e** into dihydrocoumarins. Whereas thioesters are ∼100 fold more reactive than oxoesters in basic environments and toward reactions with nucleophiles such as amines, they are comparatively stable in an acidic environment.[14,15] We therefore hypothesized that the thioester moiety within **3a–e** should withstand removal of the PMB protecting groups using trifluoroacetic acid (TFA). Deprotection of the phenolic hydroxyl and the carboxylic acid groups under acidic conditions was then envisioned to form the dihydrocoumarins by an intramolecular in situ Fischer esterification. Reassuringly, treatment of **3a–e** with TFA and thioanisole as a cation scavenger[16] provided the cyclized products **4a–e** in high yields and with retention of the excellent enantio- and diastereoselectivities (Scheme 3). Noteworthy, the thioester moiety remained fully intact under these reaction conditions. Crystallization of **4a** allowed for unambiguous assignment of the stereochemistry of the products (Scheme 3).

We then turned our attention to the synthesis of diastereoisomeric dihydrocoumarins with the same (*S*)-configuration at C(4) but opposite configuration at C(3). Because of the higher reactivity of thioesters compared to

Scheme 3. Deprotection and Cyclization of 3a–e[a]



[a]Reactions were performed on a 0.1–0.2 mmol scale. Yields of isolated products. Enantioselectivities were determined by HPLC on a chiral stationary phase; dr values were determined by ^{1}H NMR of the crude product.

oxoesters toward nucleophiles, the phenolic hydroxyl group was envisioned to react preferentially with the thioester under neutral or basic conditions and thereby provide the diastereoisomers of **4**.[9] To explore this alternative intramolecular lactone formation, we synthesized *α*-methyl MTM **1a′** bearing a benzyl (Bn) oxoester, which is stable under the acidic conditions used for deprotection of the phenolic hydroxyl group.[17] The conjugate addition of MTM **1a′** to nitroolefin **2a** under the same conditions as used before provided *γ*-nitrothioester **3a′** with the same absolute configuration as **3a** in good yield (89%) and stereoselectivity (dr 10:1, 99% ee, Scheme 4, upper half). The stereochemistry of **3a′** was confirmed by derivatization to **4a** of which the stereochemistry was previously unambiguously assigned by a crystal structure (Scheme 3, see the Supporting Information for details). As expected, the acid-promoted deprotection of **3a′** only liberated the phenolic hydroxyl group. Subsequent addition of Hünig's base facilitated the intramolecular cyclization, which only occurred at the thioester moiety and afforded dihydrocoumarin **4a′** with opposite configuration to **4a** at C(3) in 92% yield and retention of stereoselectivity (dr 10:1, 99% ee).[18]

To explore whether the enantiomers of **4a** and **4a′** are accessible via this route, we allowed *o*-hydroxy-*β*-nitrostyrene **2a** to react with MTMs **1a** and **1a′**, respectively, in the presence of the *epi*-cinchonidine derived urea catalyst ***Ψ-ent-A***, the pseudoenantiomer of catalyst **A**. In addition, these conjugate addition reactions proceeded smoothly to the desired products ***ent*-3a** and ***ent*-3a′**, which were obtained with slightly lower diastereoselectivities compared to the enantiomers **3a** and **3a′** but very high yields and enantioselectivities. The subsequent cyclizations to the enantiomeric dihydrocoumarins ***ent*-4a** and ***ent*-4a′** proceeded readily and in the same high yields as observed before (Scheme 4, lower half). Thus, the organocatalytic conjugate addition reactions between *α*-substituted MTMs and nitroolefins provide facile access to all possible stereoisomers[18] of dihydrocoumarins in excellent yields and stereoselectivities. These results illustrate the versatility of

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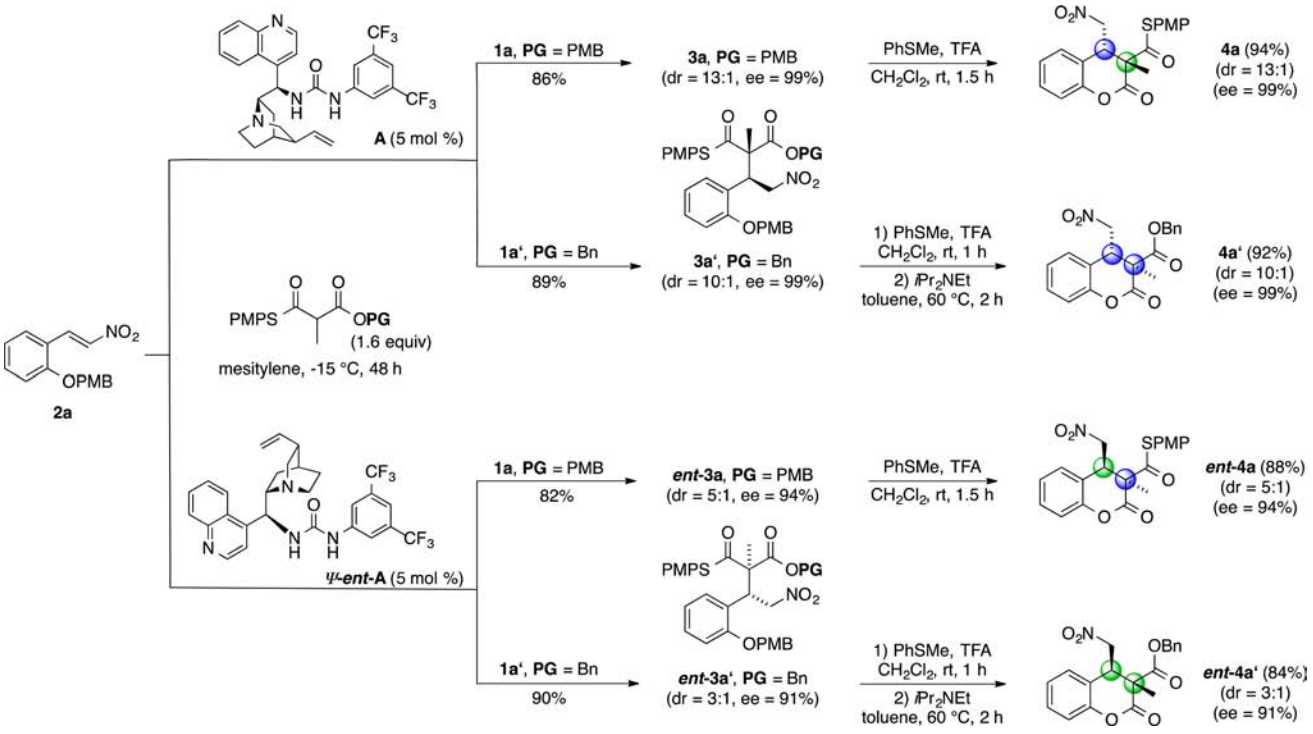
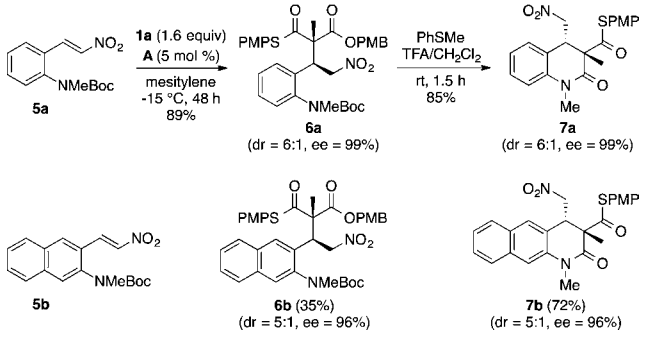
Scheme 4. Selective Formation of All Stereoisomers of Dihydrocoumarin 4a



MTMs as thioester enolate equivalents for accessing stereoisomers with all possible relative and absolute configurations.

Finally, we explored whether the methodology can also be expanded to the synthesis of 3,4-dihydroquinolinones[2] that contain a lactam instead of a lactone moiety. Toward this goal, *o*-amino-*β*-nitrostyrenes **5a** and **5b** bearing a protected anilinic moiety were prepared.[19] Both nitroolefins reacted readily with MTM **1a** under the organocatalytic conditions to provide the desired addition products **6a** and **6b** in moderate to good yields and high stereoselectivities (Scheme 5).[20]

Scheme 5. Synthesis of Dihydroquinolinones[a]



[a]Reactions were performed on a 0.2 mmol scale. Yields of isolated products. Enantioselectivities were determined by HPLC on a chiral stationary phase; dr values were determined by ^{1}H NMR of the crude product.

Subsequent simultaneous removal of the Boc and the PMB protecting groups of **6a** and **6b** with thioanisole and TFA led via an intramolecular cyclization to the 3,4-dihydroquinolinones **7a** and **7b** bearing adjacent quaternary and tertiary stereogenic centers in excellent yields (Scheme 5).

In conclusion, we have introduced a mild, organocatalytic route to access dihydrocoumarins and dihydroquinolinones containing adjacent tertiary and quaternary stereogenic centers in high yields and stereoselectivities. The method involves reaction of a substituted monothiomalonate with a functionalized nitroolefin and requires comparatively low catalyst loadings. The different reactivities of thio- and oxoesters combined with the use of pseudoenantiomeric catalysts allowed for full control over the absolute and relative configuration of adjacent quaternary and tertiary stereocenters. The results show that substituted MTMs are highly versatile thioester enolate equivalents for asymmetric, stereodivergent synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, electronic structure calculations, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) Since sulfur has a higher priority compared to oxygen following the IUPAC nomenclature, the absolute configuration, (*S*) versus (*R*), remains the same.

(10) For examples of stereodivergent syntheses, see: (a) Krautwald, S.; Sarlah, D.; Schafroth, M.; Carreira, E. M. *Science* **2013**, *340*, 1065−1068. (b) Luparia, M.; Oliveira, M. T.; Audisio, D.; Frøbault, F.; Goddard, R.; Maulide, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 12631−12635. (c) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768−769. For a recent highlight, see: (d) Oliveira, M. T.; Luparia, M.; Audisio, D.; Maulide, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 13149−13152 and references cited therein.

(11) Unprotected (*E*)-2-(2-nitrovinyl)phenol did not lead to the formation of the conjugate addition product, presumably due to the acidity of the phenolic hydroxyl group that might interfere with the cinchona alkaloid−(thio)urea catalyst.

(12) Optimization of the reaction conditions showed that the diastereoselectivities of the reaction were generally higher in mesitylene compared to toluene (e.g., dr 13:1 versus 6:1, for **3a**). See the Supporting Information for full details. For other examples of the beneficial role of mesitylene, see: (a) Maji, B.; Ji, L.; Wang, S.; Vedachalam, S.; Ganguly, R.; Liu, X.-W. *Angew. Chem., Int. Ed.* **2012**, *51*, 8276−8280. (b) Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *Chem. Commun.* **2009**, 1956−1958.

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(17) Derivatives with an allyl protecting group on the phenolic OH provided the addition products in high yields and stereoselectivities but Pd-catalyzed removal of the allyl group was unsuccessful.

(18) Following the CIP convention, sulfur has a higher priority compared to oxygen. Thus, the configurations of the stereoisomers are (*S,S*) **4a**, (*S,S*) **4a′**, (*R,R*) ***ent*-4a**, (*R,R*) ***ent*-4a′**.

(19) See the Supporting Information for details.

(20) A mono-Boc (NHBoc) protected derivative reacted sluggishly, further indicating that additional H bond donors disturb the organocatalytic transformation, ref 11.