Organic LETTERS

Letter

pubs.acs.org/OrgLett

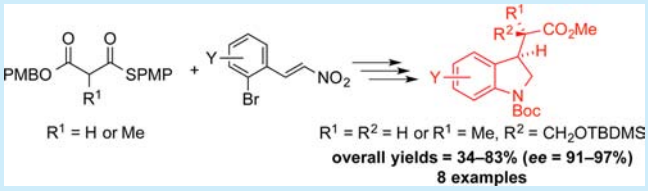
Stereoselective Synthesis of Indolines via Organocatalytic Thioester Enolate Addition Reactions

Andrej Kolarovic, Alexander Käslin, and Helma Wennemers*

ETH Zürich, Laboratorium für Organische Chemie, Vladimir-Prelog-Weg 3, CH-8093 Zürich, Switzerland

Supporting Information

ABSTRACT: A straightforward stereoselective synthesis route to indolin-3-yl acetates has been developed using organocatalytic addition reactions of monothiomalonates to *ortho*-bromo nitrostyrenes as the key step. The addition products of this highly stereoselective one-pot addition–deprotection–decarboxylation sequence were easily further converted to the target indolin-3-yl acetates, via an intramolecular Buchwald–Hartwig coupling reaction. The route provided indolin-3-yl acetates bearing tertiary and exocyclic quarternary stereogenic centers in excellent stereoselectivities and overall yields of 34–83%.



Indolines are common structural motifs in natural products and therapeutically active compounds and are also valuable as organocatalysts and ligands for stereoselective synthesis (Figure 1).[1−3]

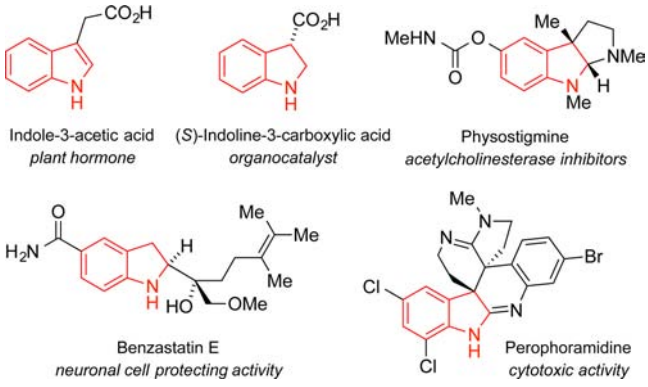
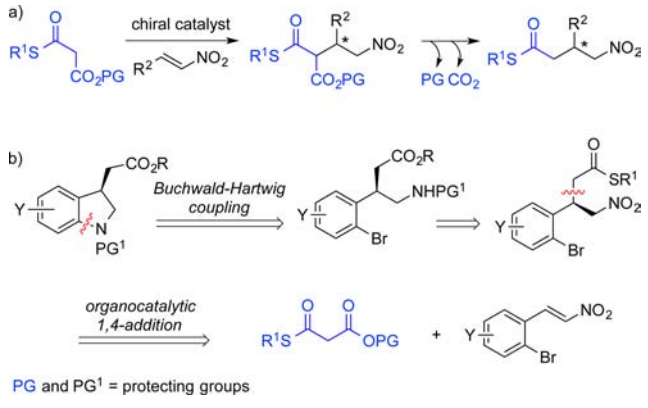


Figure 1. Examples of indolines and closely related derivatives.

The development of straightforward enantioselective synthetic routes toward substituted indoline derivatives is therefore important. Known stereoselective syntheses of indolines with substituents at C(3) rely on either enantioselective catalytic hydrogenations or hydrosilylations of indoles,[4,5] enantioselective catalytic or stoichiometric intramolecular cyclizations of aniline derivatives with chiral ligands,[6,7] ring closure of enantioenriched precursors by radical or metal-catalyzed cyclizations,[8,9] or diastereoselective conjugate additions.[10,11] Whereas many of these approaches provide the target indolines in good yields and stereoselectivities, the substrate scope and the accessible substitution patterns are typically limited. Alternative stereoselective routes to, e.g., functionalized indolin-3-yl derivatives are therefore important. Herein we present a method that relies on an organocatalytic, highly enantioselective addition reaction of thioester enolates to *o*-bromo-nitrostyrenes followed by an intramolecular Buchwald–Hartwig cyclization as key steps. The route offers access to indolin-3-yl derivatives in high yields and stereoselectivities. In addition, we present the first synthesis of an indoline bearing an exocyclic all-carbon quaternary stereogenic center.

Recently, we introduced monothiomalonates (MTMs) as robust thioester enolate equivalents that allow for stereoselective addition reactions with electrophiles under mild organocatalytic conditions.[12−14] We showed that MTMs react in the presence of catalytic amounts of cinchona alkaloid-urea derivatives with nitroolefins or imines to provide access to γ-nitrothioesters and β-aminothioesters, respectively, in high yields and stereoselectivities (Scheme 1a).[12−14] The efficiency of these asymmetric reactions intrigued us to expand their synthetic utility for organic synthesis. We envisioned that

Scheme 1. (a) One-Pot Conjugate Addition–Deprotection–Decarboxylation with MTMs and (b) Retrosynthetic Analysis towards Indolines



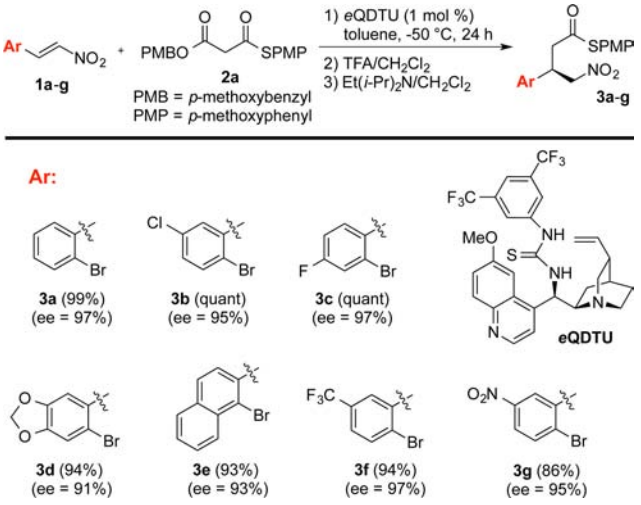
Received: July 3, 2014
Published: August 7, 2014

   dx.doi.org/10.1021/ol501936n | *Org. Lett.* 2014, 16, 4236–4239

1,4-addition reactions of MTMs with nitroolefins bearing an *o*-Br-aryl functionality would furnish *γ*-nitrothioesters that could be easily converted via a Buchwald–Hartwig cyclization to indolin-3-yl acetates (Scheme 1b).

To probe the value of the envisioned route we started by preparing seven differently functionalized *o*-bromo-*β*-nitrostyrenes (**1a–g**)[15,16] and reacted them with MTM **2a** in the presence of cinchona alkaloid-urea derivatives under the previously established conditions (Scheme 2).

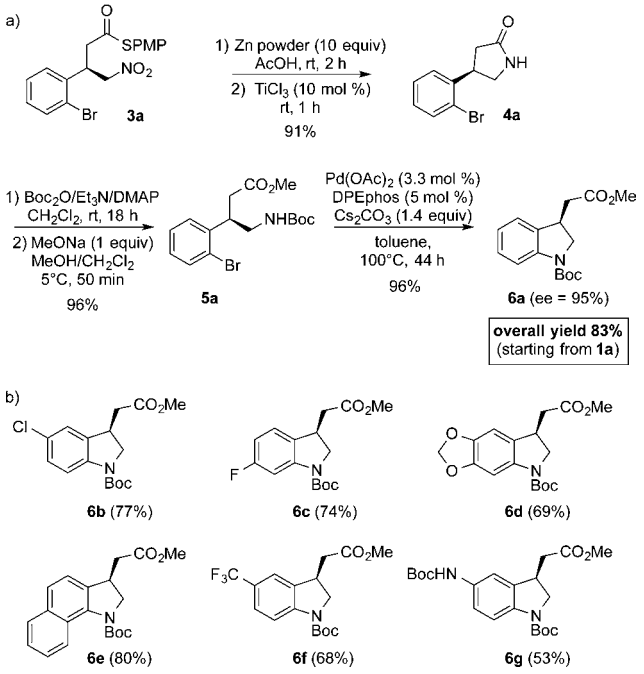
Scheme 2. 1,4-Addition Reactions between Nitrostyrenes 1a–g and MTM 2a, Catalyzed by *e*QDTU



We were pleased to find that *o*-bromo-*β*-nitrostyrenes **1a–g** reacted smoothly with MTM **2a** in the presence of as little as 1 mol % of epiquinidine thiourea catalyst (*e*QDTU)[17] at −50 °C. Also removal of the *p*-methoxylbenzyl (PMB) protecting group followed by base-induced decarboxylation proceeded cleanly. Regardless of the substitution pattern and the nature of the substituent at the nitrostyrene, the *γ*-nitrothioesters **3a–g** were obtained in very high yields and enantioselectivities (Scheme 2). These results underline that this organocatalytic transformation of thioester enolate equivalents is very robust and tolerates a broad range of substitution patterns on the nitroolefin.

Next, the route from the *γ*-nitrothioesters **3a–g** to indolin-3-yl acetates **6a–g** was explored. Scheme 3a exemplifies the route that proved to be best for the synthesis of indoline **6a**. Reduction of the nitro group under traditional conditions using zinc in acetic acid, followed by intermolecular cyclization to lactam **4a**, proved to be problematic due to the formation of high amounts of the corresponding hydroxamic acid (30–35%).[18] We solved this issue by developing an efficient catalytic system based on substoichiometric amounts of $TiCl_3$[19] that was concurrently regenerated by a small excess of zinc (3.3 equiv with respect to the electron demand). These conditions enabled the *in situ* reduction of the undesired hydroxamic acid intermediate and formation of the lactams in excellent yields of e.g. 91% for **4a**. Activation of the lactam group by Boc-protection facilitated a subsequent base-mediated ring opening to furnish *γ*-amino acid derivative **5a**. Finally, cyclization by an intramolecular Buchwald–Hartwig coupling[20] provided indolin-3-yl acetic acid derivative **6a** in an excellent yield of 96% and uncompromised stereochemical integrity. Overall, indoline **6a**

Scheme 3. (a) Synthetic Route towards Esters of Indolin-3-yl acetic acids; (b) Overall Yields of Indolines 6a–g



was obtained in an overall yield of 83% starting from nitroolefin **1a**.

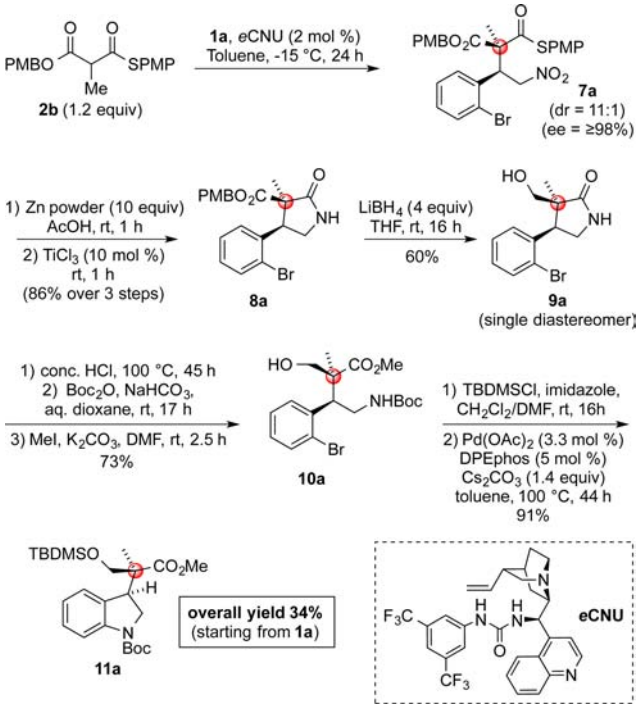
Also the other *γ*-nitrothioesters **3b–g** were converted via this synthetic route into the indolin-3-yl acetates **6b–g**. They were obtained in excellent overall yields of 53–80% starting from nitroolefins **1b–g**, which illustrates the efficiency of the syntheses (Scheme 3b).

Finally we investigated whether the described method can be expanded to the synthesis of indoline derivatives bearing an exocyclic all-carbon quaternary stereogenic center. The construction of such acyclic quaternary stereocenters under mild conditions is challenging.[21] Whereas several syntheses of indolines and indolinones with C(2) or C(3) as quaternary stereocenters have been accomplished, not a single example for an enantioselective synthesis with an exocyclic all-carbon quaternary stereogenic center has been reported.[22] We were therefore pleased when *o*-bromo-*β*-nitrostyrene **1a** reacted readily with a slight excess (1.2 equiv) of the *α*-methyl substituted MTM **2b** in the presence of 3 mol % of epicinchonine urea catalyst *e*CNU (Scheme 4). Addition product **7a** with adjacent quaternary stereocenters was obtained with a diastereoselectivity of 11:1 in favor of the *syn* product and an excellent enantioselectivity of ≥98%.

The crude addition product **7a** was sufficiently pure to be directly reduced to the amine. Under the previously established conditions ($Zn/AcOH/TiCl_3$) the amine formed and cyclized immediately to lactam **8a** that was isolated in a yield of 86% over three steps. Reduction of the *p*-methoxybenzyl ester with $LiBH_4$ yielded alcohol **9a**, which was isolated after column chromatographic purification as a single diastereoisomer. This lactam proved to be significantly less reactive compared to the analogues bearing a tertiary stereocenter. For example, activation of the lactam by Boc-protection followed by base mediated lactam ring opening was dismissed after numerous unsuccessful attempts.[23] Hydrolysis of the lactam was finally achieved with concentrated hydrochloric acid, and the resulting

dx.doi.org/10.1021/ol501936n | *Org. Lett.* 2014, 16, 4236–4239

Scheme 4. Synthesis of Indolin-3-yl Acetate 11a Bearing a Quarternary Stereocenter



amino acid was converted to the *N*-Boc-protected methylester **10a**. The Buchwald–Hartwig coupling[20] reliably furnished then indolin-3-yl acetate **11a** that was obtained in an excellent overall yield of 34% for 8 steps starting from nitroolefin **1a**.

In conclusion, we have developed an efficient synthetic route to access indolin-3-yl derivatives with high enantio- and diastereoselectivity. Key steps are an organocatalytic addition reaction of monothiomalonates to *o*-bromo-nitrostyrene and an intramolecular Buchwald–Hartwig cyclization. Both steps are robust and furnished the indolines on gram scales in overall yields of 34–83% starting from the nitrostyrenes. The route provides not only access to indolines with tertiary but also all-carbon quaternary stereogenic centers. The results also underscore the value of monothiomalonates as versatile thioesterenolate equivalents.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Helma.Wennemers@org.chem.ethz.ch.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A.K. is grateful to SCIEX for the postdoctoral fellowship 12.158.

■ REFERENCES

(1) (a) *Modern Alkaloids*; Fattorusso, E., Taglialatela-Scafati, O., Eds.; Wiley-VCH: Weinheim, 2008. (b) *Natural Products*; Ramawat, K. G., Mérillon, J.-M., Eds.; Springer-Verlag: Heidelberg, 2013.
(2) Pietruszka, J.; Simon, R. C. *ChemCatChem* **2010**, *2*, 505–508.
(3) Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4165–4173.
(4) (a) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614–7615. (b) Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* **2004**, *6*, 2213–2215. (c) Kuwano, R.; Kashiwabara, M.; Sato, K.; Ito, T.; Kaneda, K.; Ito, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 521–535. (d) Kuwano, R.; Kashiwabara, M. *Org. Lett.* **2006**, *8*, 2653–2655. (e) Li, C.; Chen, J.; Fu, G.; Liu, D.; Liu, Y.; Zhang, W. *Tetrahedron* **2013**, *69*, 6839–6844.
(5) Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10661–10664.
(6) (a) Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G.; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2012**, *134*, 15331–15342. (b) Hashimoto, T.; Yamamoto, K.; Maruoka, K. *Chem. Commun.* **2014**, *50*, 3220–3223.
(7) (a) Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 6787–6788. (b) Gil, G. S.; Groth, U. M. *J. Am. Chem. Soc.* **2000**, *122*, 6789–6790. (c) Bailey, W. F.; Luderer, M. R.; Mealy, M. J. *Tetrahedron Lett.* **2003**, *44*, 5303–5305. (d) Mealy, M. J.; Luderer, M. R.; Bailey, W. F.; Sommer, M. B. *J. Org. Chem.* **2004**, *69*, 6042–6049.
(8) (a) Curran, D. P.; Chen, C. H.-T.; Geib, S. J.; Lapierre, A. J. B. *Tetrahedron* **2004**, *60*, 4413–4424. (b) Petit, M.; Geib, S. J.; Curran, D. P. *Tetrahedron* **2004**, *60*, 7543–7552. (c) Guthrie, D. B.; Curran, D. P. *Org. Lett.* **2009**, *11*, 249–251. (d) Shirakawa, S.; Liu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 916–919.
(9) (a) Pineschi, M.; Bertolini, F.; Crotti, P.; Macchia, F. *Org. Lett.* **2006**, *8*, 2627–2630. (b) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485–1488. (c) Rudolph, A.; Rackelmann, N.; Turcotte-Savard, M.-O.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 289–297.
(10) Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 6630–6631.
(11) For a recent example describing organocatalytic asymmetric synthesis of related indolin-2-yl acetic acids, see: Miyaji, R.; Asano, K.; Matsubara, S. *Org. Lett.* **2013**, *15*, 3658–3661.
(12) Clerici, P.; Wennemers, H. *Org. Biomol. Chem.* **2012**, *10*, 110–113.
(13) Arakawa, Y.; Fritz, S. P.; Wennemers, H. *J. Org. Chem.* **2014**, *79*, 3937–3945.
(14) Bahlinger, A.; Fritz, S. P.; Wennemers, H. *Angew. Chem., Int. Ed.* **2014**, DOI: 10.1002/acie.201310532.
(15) Nitrostyrenes **1a–g** were prepared by a procedure adapted from: Chang, C.-F.; Huang, C.-Y.; Huang, Y.-C.; Lin, K.-Y.; Lee, Y.-J.; Wang, C.-J. *Synth. Commun.* **2010**, *40*, 3452–3466. For details, see the Supporting Information.
(16) Note that purification of the nitrostyrenes **1a–g** by crystallization from CH_2Cl_2/hexanes was generally sufficient. Several of them, *e.g.*, nitrostyrene **1e**, had to be purified additionally by flash chromatography to allow for high and reliable enantioselectivities in the asymmetric catalytic reaction with MTM **2a**.
(17) For original reports on cinchona alkaloid urea derivatives, see: (a) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967–1969. (b) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603–606. (c) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481–4483. (d) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367–6370.
(18) For another example of undesired hydroxamic acid formation, see: Kimmel, K. L.; Weaver, J. D.; Lee, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 11828–11828.
(19) $E°(TiO^{2+}/Ti^{3+}) = +0.10$ V, $E°(Zn^{2+}/Zn^{0}) = -0.76$ V. For work describing the reduction of hydroxamic acids with stoichiometric amounts of $TiCl_3$ (2 equiv), see: Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1980**, *45*, 410–415.

(20) (a) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35−37. For a related nonenantioselective route to 2-indolines that also uses an intramolecular Buchwald−Hartwig coupling, see: (b) Anderson, J. C.; Noble, A.; Tocher, D. A. *J. Org. Chem.* **2012**, *77*, 6703−6727.
(21) For recent reviews, see: (a) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 2682−2694. (b) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593−4623.
(22) The only previously described example relies on chiral resolution, see: Kost, A. N.; Romanova, N. N.; Budylin, V. A.; Grishina, G. V.; Potapov, V. M.; Bundel', Y. G.; Ben, A.; Vrubel', E.; Tyaglov, B. V. *Chem. Heterocycl. Compd.* **1983**, *19*, 638−641.
(23) For details, see the Supporting Information.